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

Master Thesis 2017 - 2018

Department of Drug Design and Pharmacology

Index

Projects

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.

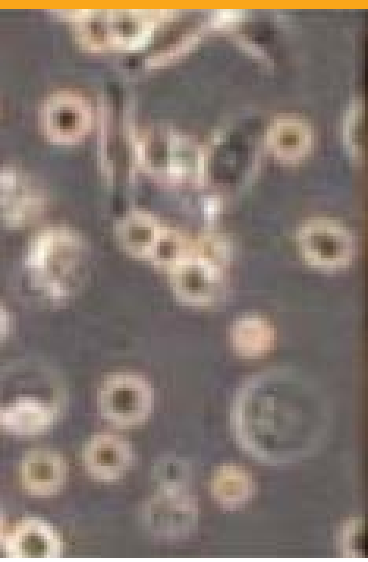
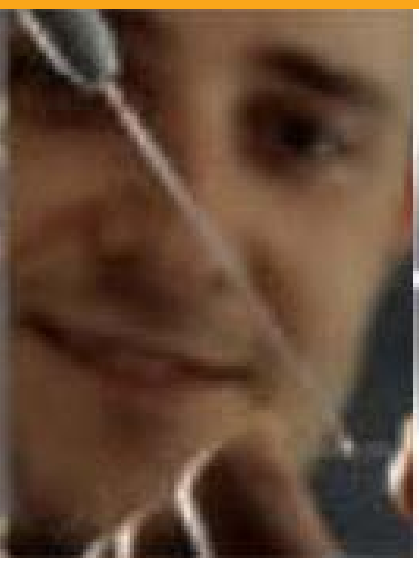
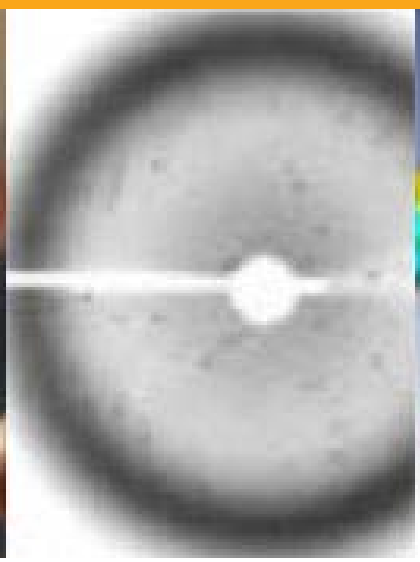
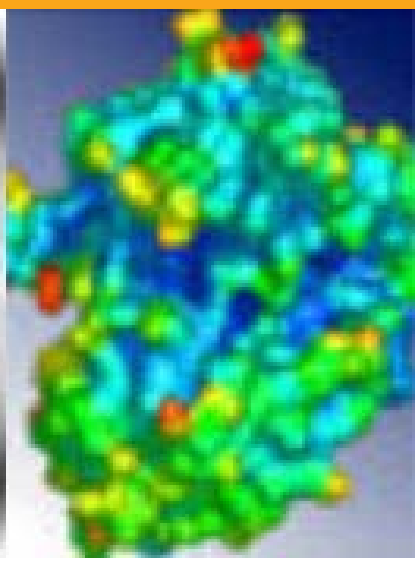
Please, note that as your thesis project is often part of a larger ongoing project, research in the coming 1 ½ year may lead to thesis-projects changing from the descriptions in this catalogue.

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
Anna Jäger
Chair of Teaching Board, DDP

Biostructural Research

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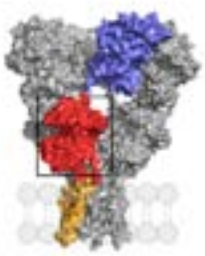
Master project: Within ionotropic glutamate receptors or nicotinic acetylcholine receptors

Are you interested in some of these research areas?

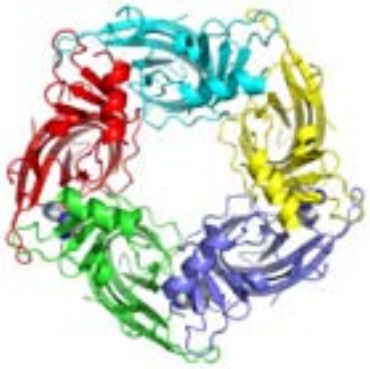
- Important receptors in our central nervous system and diseases such as Alzheimer's disease and epilepsy
- How potential new drugs bind to the receptors
- Drug design and how receptor selectivity is achieved



Structure of the ionotropic glutamate receptor GluA2. The ligand-binding domain is marked red.

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.



Structure of acetylcholine binding protein.

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

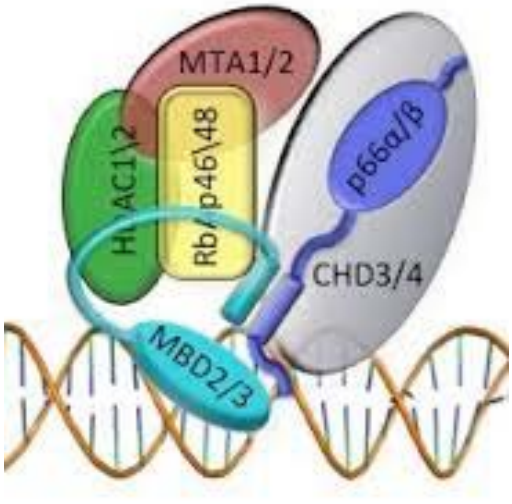
Contact person: Professor Jette Sandholm Kastrup, jsk@sund.ku.dk
Potential co-supervisors: Karla Frydenvang, karla.frydenvang@sund.ku.dk, Lars Olsen, lo@sund.ku.dk, Michael Gajhede, mig@sund.ku.dk

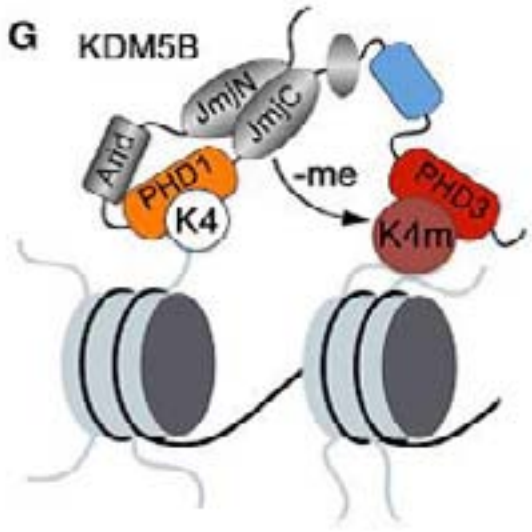
Interactions between nucleosomes, NuRD and the histone demethylase KDM5B

The histone demethylase KDM5B (Kristensen et al., 2012) is known to be involved in 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 seeked 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

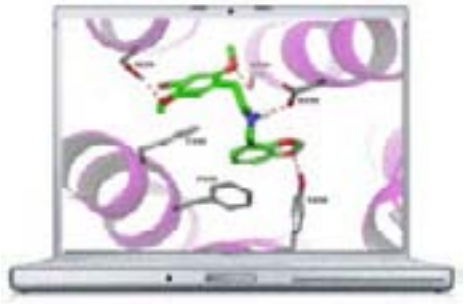
Computational Drug Design
Identify and optimise receptor ligands; Keys to physiological functions & drug design

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



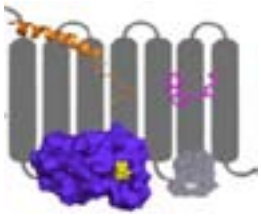
Docking of a ligand into the binding site of a receptor target structure provides a model of their molecular interactions, guiding further medicinal chemistry optimisation and pharmacological validation by mutagenesis.

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



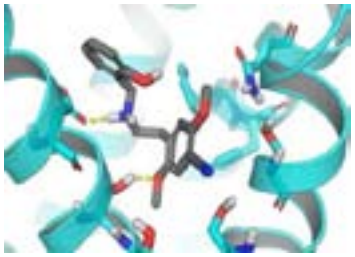
We use computational methods to identify; endogenous ligands (orange) that link the receptor to a physiological system, tool compounds (pink) for pharmacological characterisation, and G protein inhibitors (yellow) for dissection of intracellular signalling pathways.

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

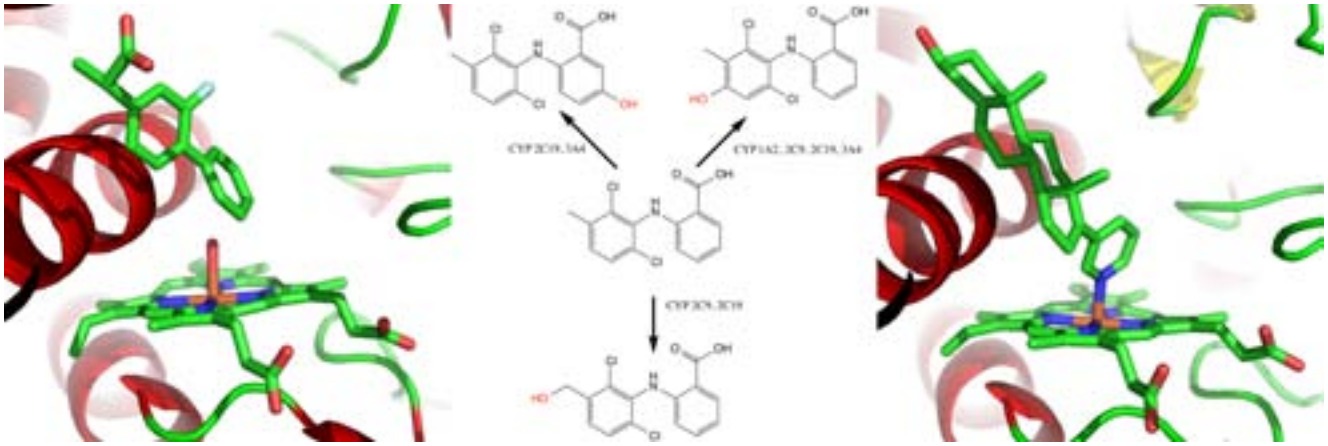
Aim: To study how drugs compounds are metabolized by or inhibit cytochromes P450 (CYP) enzymes.

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).



Left: Binding of an ibuprofen analogue to a CYP enzyme. Center: Several P450 enzymes are involved in the metabolism of meclofenamic acid. Right: Binding of Abiraterone (a prostate cancer drug compound), to a CYP enzyme, inhibiting its function.

Involvement in Cancer

Cytochrome P450 enzyme are involved in the formation of several hormones and is therefore a potential drug target in cancer. Arbiraterone (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

Cytochrome P450 topic	*Understanding of cytochrome P450 drug metabolism: What metabolites are generated*	*Design of new inhibitors of cytochrome P450 enzymes*
Methods used in the project	*Methods in computational chemistry like docking, molecular dynamics, quantum mechanics*	*X-ray crystallography, testing of potential inhibitors in assays*

to the project.

We can offer

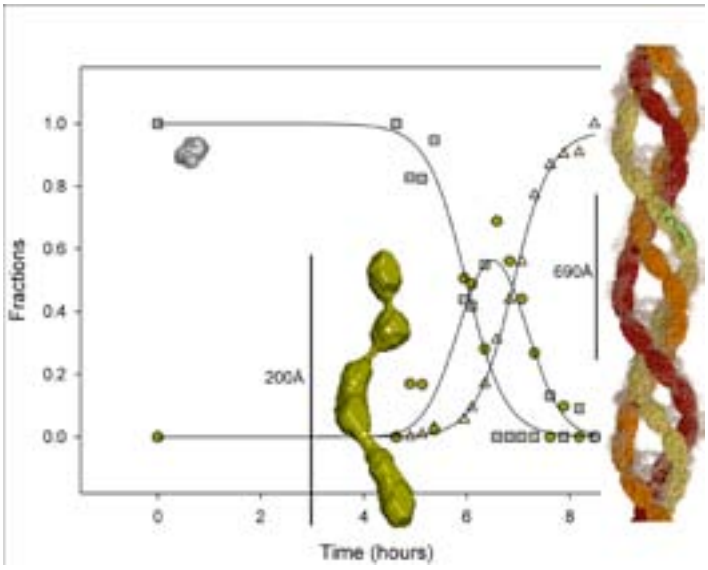
A research project with international collaborations, both in academia and industry. The group also develops the SMARTCyp software for predictions of CYP metabolism.

Contact information: Lars Olsen (lo@sund.ku.dk)

Protein fibrillering – strukturel indsigt som basis for nye lægemidler?

Problemstilling:

Proteiners 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 protein-baserede 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.



Figur 1: Oversigt over de strukturelle enheder der dannes når insulin fibrillerer. Grafen viser det procentvise indhold og strukturerne er observeret med metoden SAXS: Først er der monomerer i opløsning (grå overflade, grå firkanter), dernæst en oligomer nukleus (grønne) og sidst dannes meget store fibriller (gule trekanter og rød/gul/orange model) hvor 3 gentagne symmetriske enheder er vist i figuren. Vestergaard et al. (2007) PLoS Biology.

Lidt flere detaljer:

Komplekse systemer:Det aktive foldede protein er i ligevægt med delvist udfoldede proteiner. Nogle af disse kan gå sammen og danne et kim, et såkaldt nucleus for fibrilleringsprocessen, hvorefter en polymerisering startes, hvor større og større fibriller dannes. Alle disse enheder har meget forskellige størrelse (nanometer til micrometer) og eksisterer i både forskellige mængder og på forskellige tidskalaer. Det er meget vanskeligt at lave strukturelle undersøgelser på sådanne ligevægte, og hvis man forsøger at isolere enkeltkomponenter indstiller der sig nye ligevægte. Det er den udfordring vi tager op i vores gruppe.

Strukturelle undersøgelser: Vi benytter en kombination af strukturelle og biofysiske metoder til at studere processen. Vi arbejder både med våde eksperimenter og med computer-baseret modellering. Vi benytter SAXS (small angle X-ray scattering), protein krystallografi, fiber diffraktion, TEM (transmission electron microscopy) og fluorescence microscopy, og kombinerer dermed både højt- og lavt-opløste data. Vi udvikler analysemetoderne i samarbejde med nogen af verdens førende specialister. Vi kombinerer med fluorescence målinger og andre biofysiske metoder som f.eks. kalorimetri og cirkulær dichroisme.

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:
Hvis du indgår i et af de konkrete projekter, vil du for det første være en del af en gruppe, der har ekspertise med alle de anvendte metoder (gruppen består pt af 1 lektor, 1 post-doc, 4 PhD-studerende, 1 projekt-studerende og ½ laborant). Du vil være tilknyttet et projekt hvor en eller flere PhD-studerende og/eller post-docs arbejder med noget stærkt beslægtet, så du er sikker på at kunne få god og konkret vejledning. Du vil opleve et miljø med mange internationale samarbejder, og komme med ud til disse miljøer i forbindelse med data-indsamling og/eller konferencer. Projekt-gruppen ledes af lektor Bente Vestergaard.

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Center for Biopharmaceuticals

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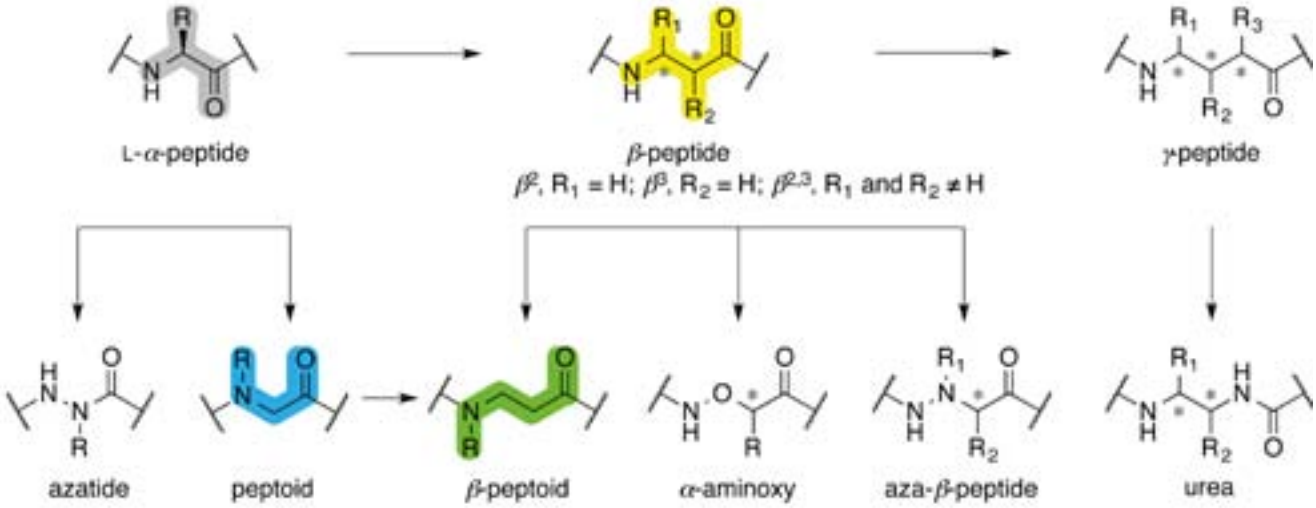
Novel types of Peptidomimetic Foldamers

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.

[1] J. S. Laursen, J. Engel-Andreasen, C. A. Olsen.β-Peptoid Foldamers at Last. Acc. Chem. Res. 2015, 48, in press (doi: 10.1021/acs.accounts.5b00257).

[2] J. S. Laursen, P. Harris, P. Fristrup, C. A. Olsen. Triangular Prism-Shaped beta-Peptoid Helices as Unique Biomimetic Scaffolds. Nat. Commun. 2015, 6, 7013 (doi: 10.1038/ncomms8013).

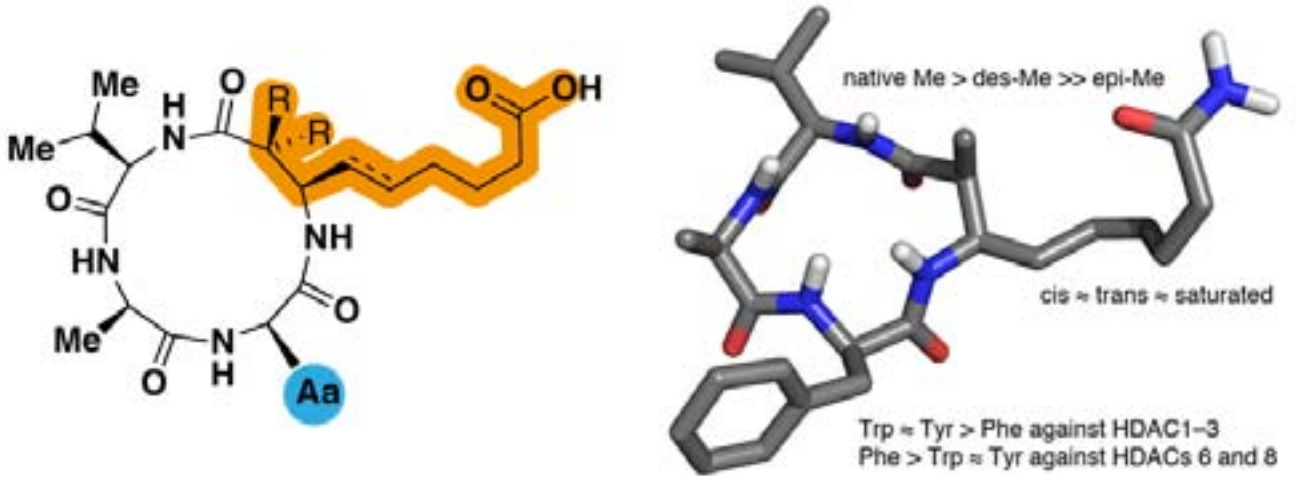
Contact information: Christian Adam Olsen, cao@sund.ku.dk

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).

[1] A. S. Madsen, H. M. E. Kristensen, G. Lanz, C. A. Olsen. The Effect of Various Zinc Binding Groups on Inhibition of Histone Deacetylases 1–11. ChemMedChem 2014, 9, 614–626.

[2] J. S. Villadsen, H. M. Stephansen, A. R. Maolanon, P. Harris, C. A. Olsen. Total Synthesis and Full Histone Deacetylase Inhibitory Profiling of Azumamide A–E as well as beta2-Epi-Azumamide E and beta3-Epi-Azumamide E. J. Med. Chem. 2013, 56, 6512–6520.

[3] A. R. Maolanon, J. S. Villadsen, N. J. Christensen, C. Hoeck, T. Friis, P. Harris, C. H. Gotfredsen, P. Fristrup, C. A. Olsen. Methyl Effect in Azumamides Provides Insight Into Histone Deacetylase Inhibition by Macrocycles. J. Med. Chem. 2014, 57, 9644–9657.

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 a 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 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.

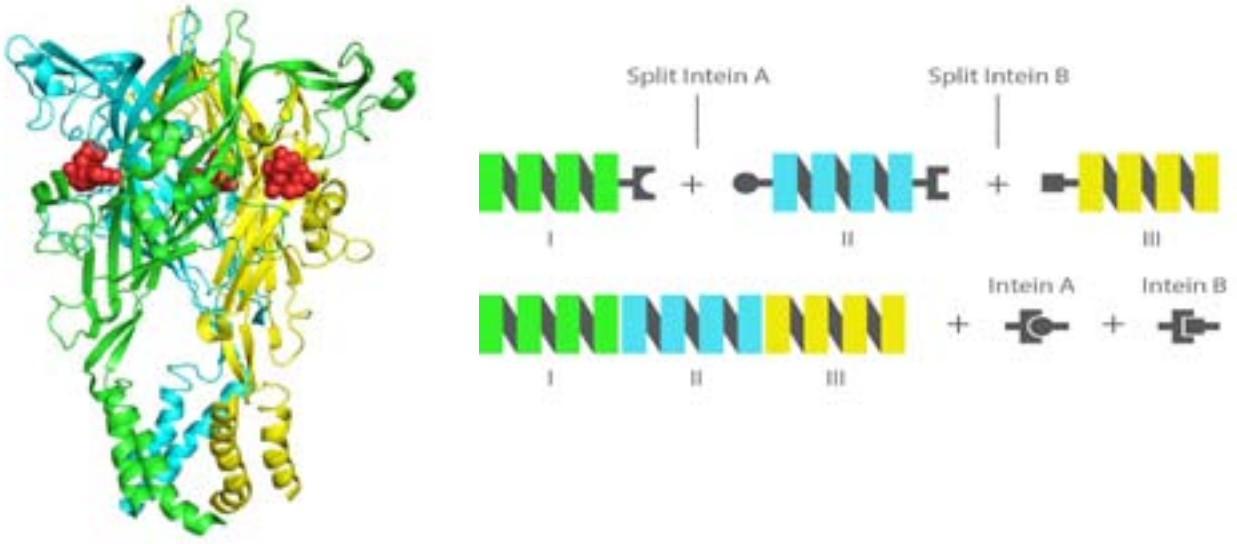


Fig 1: Left: Example of the structure of a trimeric LGIC with subunits indicated by different colors and the ligand shown in red ; Right: cartoon illustrating the use of (split)inteins in order to create a trimeric protein in which a defined number of subunits can be individually manipulated

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.

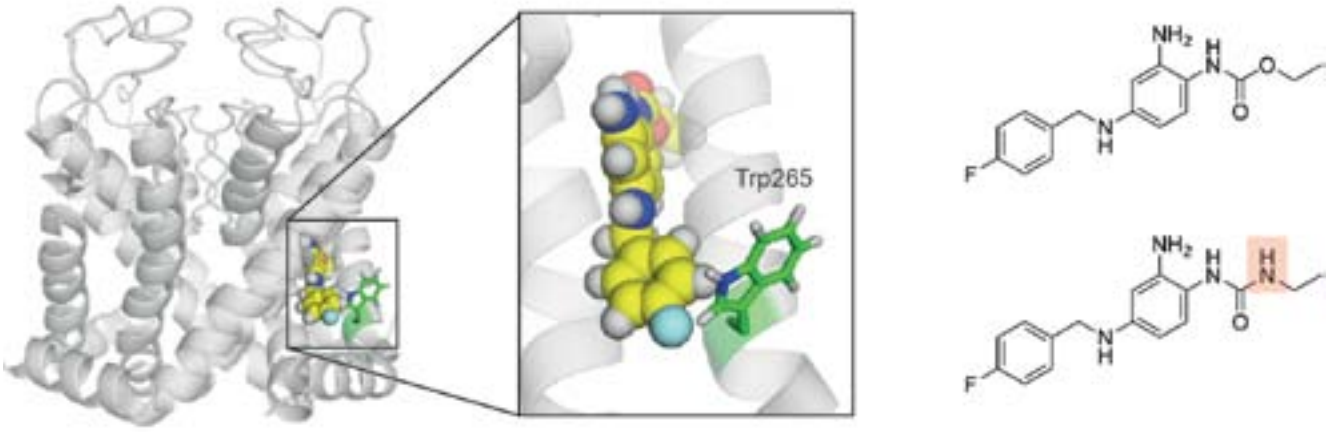


Fig 1: Left: Hypothetical model of the potassium channel bound to retigabine; Right: Retigabine (top) and one of its analogues (bottom) containing a single-atom change (highlighted in red), as an example of a analogue that will be used to determine the atomic details of the drug-channel interaction.

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

Experimental Pharmacology

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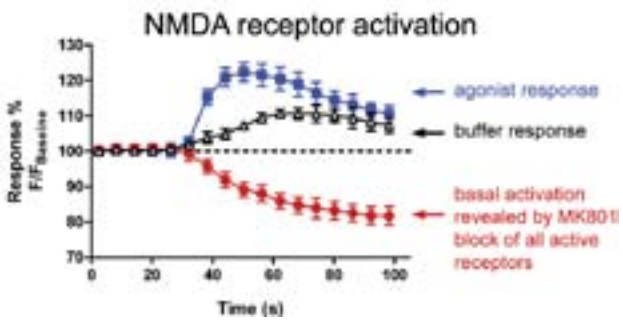
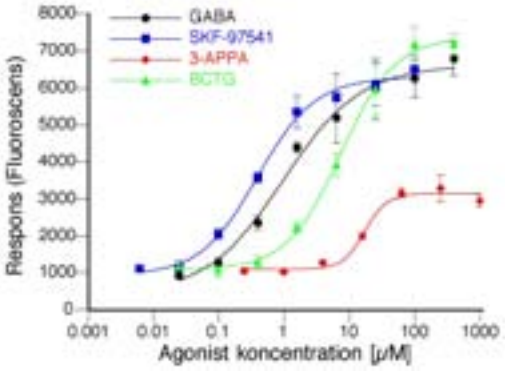
Molecular pharmacology

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 parmacological assays (e.g. concentration-response curves and development of novel assays).



Pharmacological testing

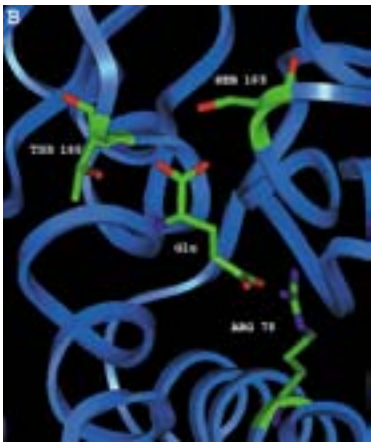
Most receptors and transporters belong to families of targets for which the endogenous ligand activate several subtypes. For example, 24 glutamate receptors and 5 glutamate transporters have been identified. Therapeutically, it is often desired to only activate/inhibit one or few of the subtypes to e.g. 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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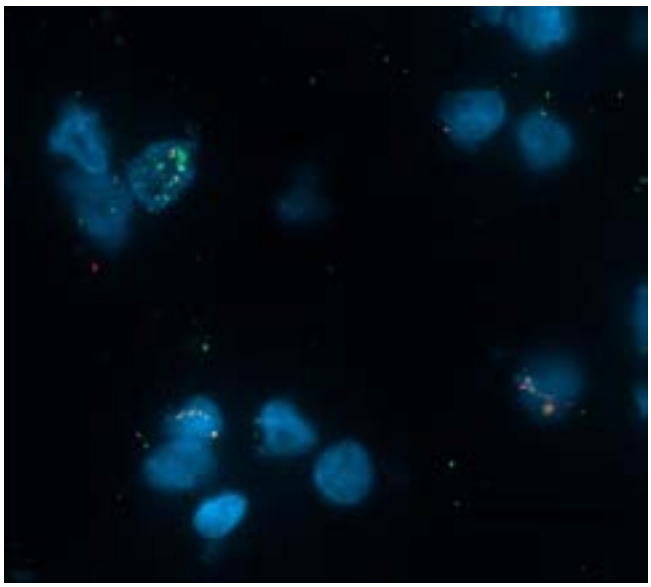
Anders A. Jensen (aaj@sund.ku.dk)
Petrine Wellendorph (pw@sund.ku.dk).

Website: http://drug.ku.dk/research/ep/molecular_pharmacology/

Translational neuropharmacology

We study mechanisms underlying chronic pain states, cognitive dysfunction & emotional disturbances, as well as the mechanism of action of compounds used to treat these conditions. Animal models of human CNS disorders are limited in terms of their ability to replicate or resemble human conditions. An integral part of our research is therefore to study the human conditions directly as well as developing animal models that more closely replicate symptoms associated with human disease.



Staining of mRNA in a spinal cord slice from a cancer-inoculated rat. It was found that mRNA from the P2X7 receptor (orange) was expressed with mRNA from a microglia marker (Iba1: red) and an astrocyte marker (GFAP: green) around cell nuclei (DAPI: blue).

We employ a range of experimental techniques to address these scientific questions from different levels of complexity, the main focus being on bridging the gap between in vitro and in vivo studies as well as the gap between animal and human studies. Our approach is therefore largely interdisciplinary, and involves close collaborations with medicinal chemists and clinical researchers.

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Medicinal Chemistry Research

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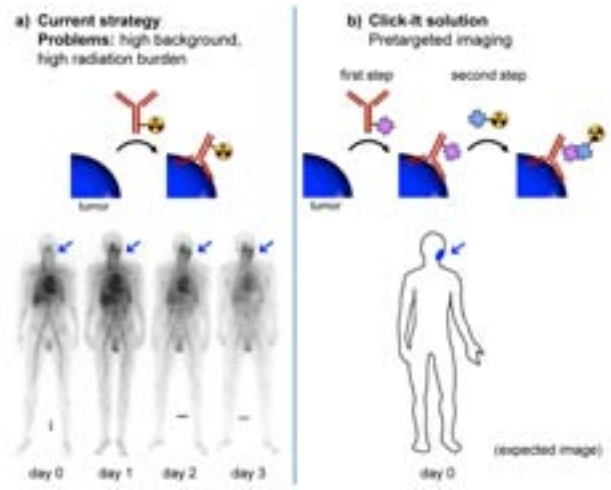
Pretargeted chemistry: Organic chemistry in man

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.

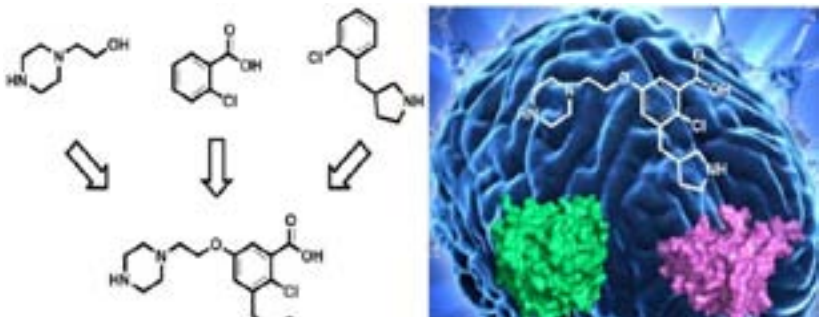
Figure 1: a) Single-photon emission computed tomography (SPECT) images of a patient with a carcinoma in the left parotic region after the administration of a radiolabeled mAb (^{186}Re-bivatuzumab). The dark background and the contrast in the heart and in major blood vessels demonstrate the effect of 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[1]. b) General scheme of a pretargeting in vivo click imaging approach. First step tumor pretargeting (days); second step pretargeted chemistry (hours)[2]. 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)

References: 1. Postema, E. J. et al. J Nucl Med 44, 1690 (2003) 2. Rossin, R. et al.. Angew Chem Int Ed Engl 49, 3375 (2010)

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.

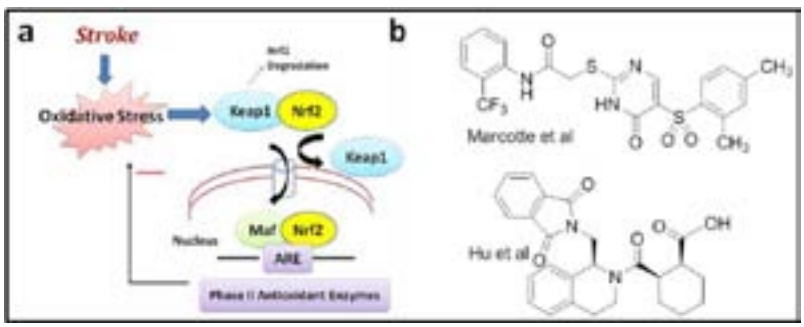


We apply fragment-based drug discovery on proteins involved in CNS diseases. We screen fragments and optimize hits by chemical synthesis in order to identify novel chemical probes and therapeutic principles.

'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 Nfr2 and transcription of antioxidant enzymes.*



b) *Non-covalent Keap1 inhibitors (examples).*

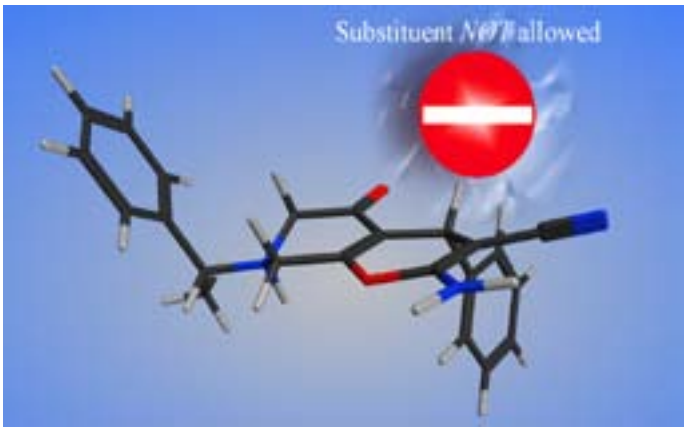
Project Aims: The goals of this project are: 1) Synthesize known non-covalent inhibitors of Keap1; 2) Defragment known inhibitors, i.e. split the larger inhibitors into fragments, in order to evaluate the binding efficiency of these.
- The results from this project will lead to useful tool compounds 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

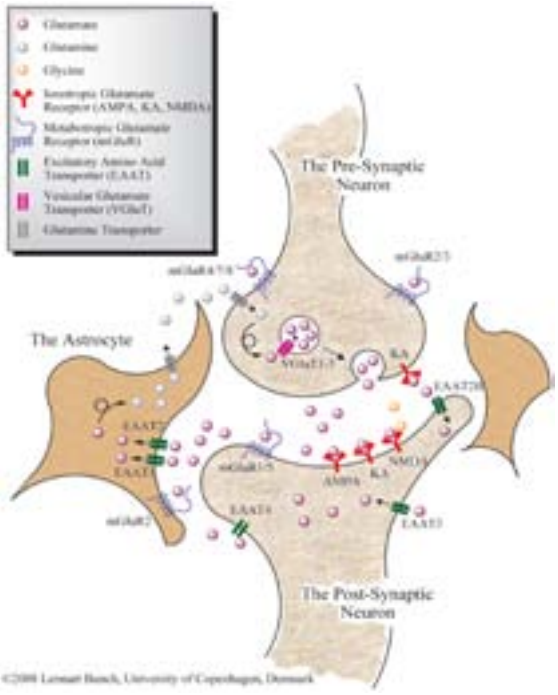
Q: Are you interested in organic / medicinal chemistry?
A: Join us to uncover the diseases of the brain!

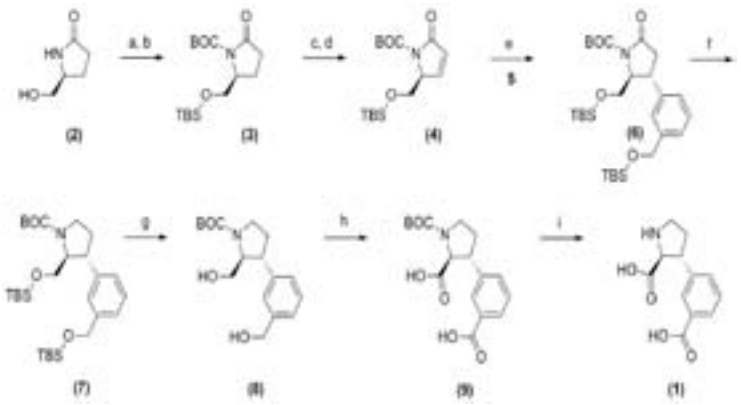
Q: Why target the glutamatergic neurotransmitter system?
A: The neurotransmitter glutamate (Glu) is involved in important neuro-physiological processes such as memory and learning, motor functions, and neural plasticity and development. Therefore, it is believed that brain diseases such as Alzheimer's 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

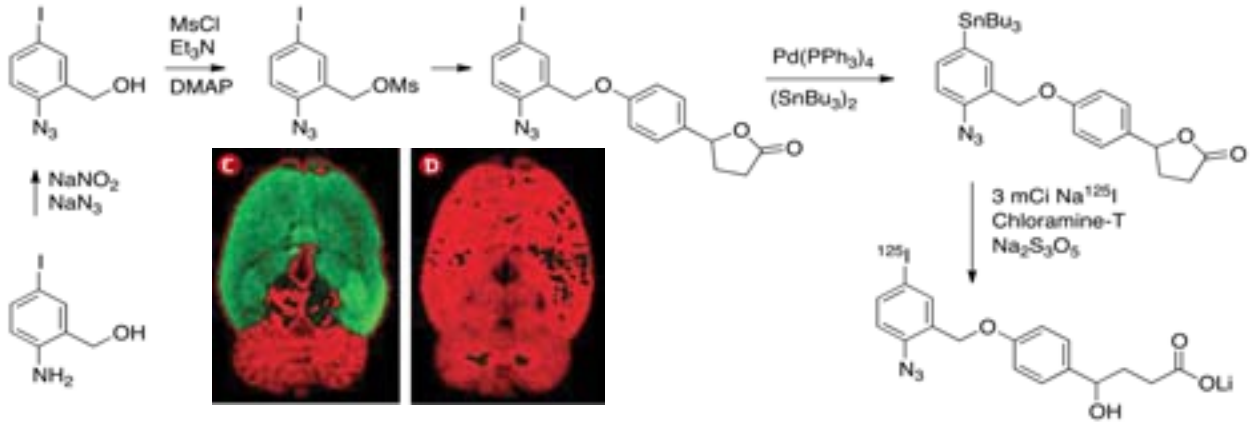
Project outline:
Retro-synthetic analysis
Literature study
Experimental organic chemistry
Report writing / publication

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 (Xyrem^{TM}) for treatment of narcolepsy and alcoholism (Alcover^{TM}). 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 $GABA_B$ 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 $GABA_A$ 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 $GABA_AR$, 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.



Ref: *Sabbatini et al, J.Med.Chem., 2010, 6506–6510, Villumsen et al, 2011, Lægemiddelforskning, Absalom et al, PNAS, 2012, 13404–13409, Vogensen et al, J.Med.Chem., 2013, 56, 8201-8205.*

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 $GABA_{A/C}$ 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 ionotropic 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 $GABA_A$ and $GABA_C$ 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:
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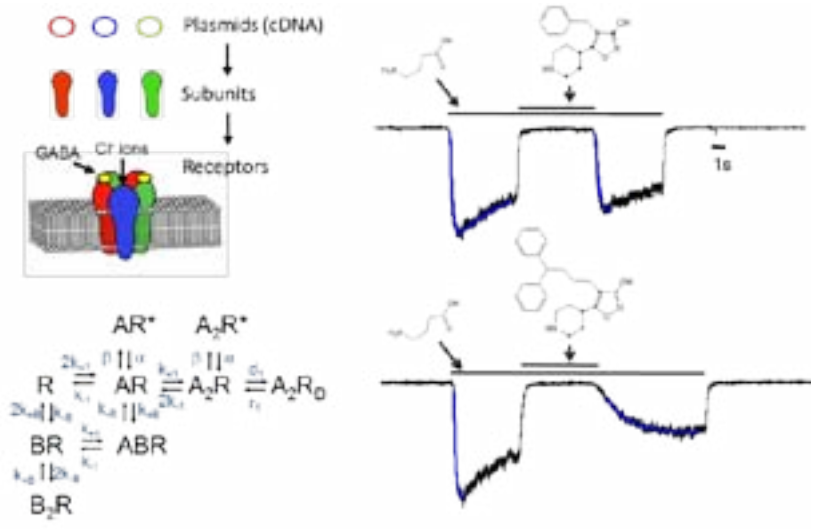
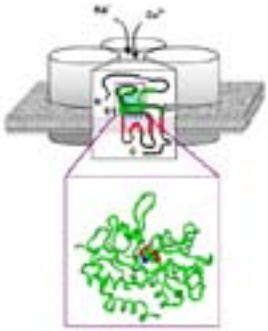
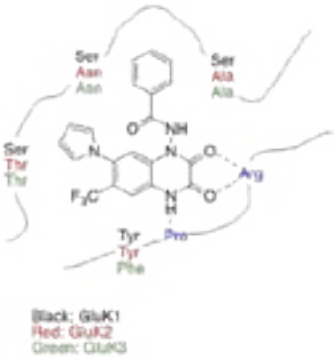


Structure-based medicinal chemistry towards subtype-selective kainate receptor ligands



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?**



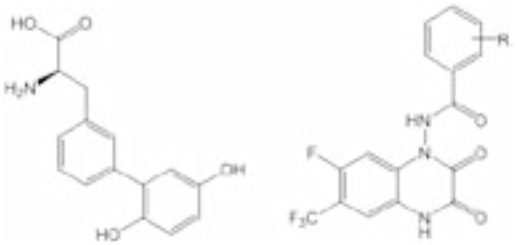
Structure-based design

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

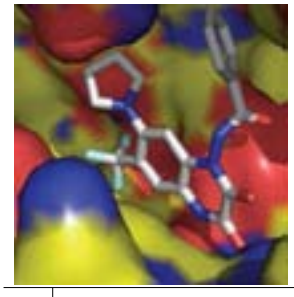


R	Native AMPA*	GluK1 *	GluK2 §	GluK2 *
H	0.95	0.15	-	0.33
o-OH	0.96	0.62	-	0.09
m-OH	0.72	0.52	-	0.10
p-OH	2.1	2.1	-	0.56

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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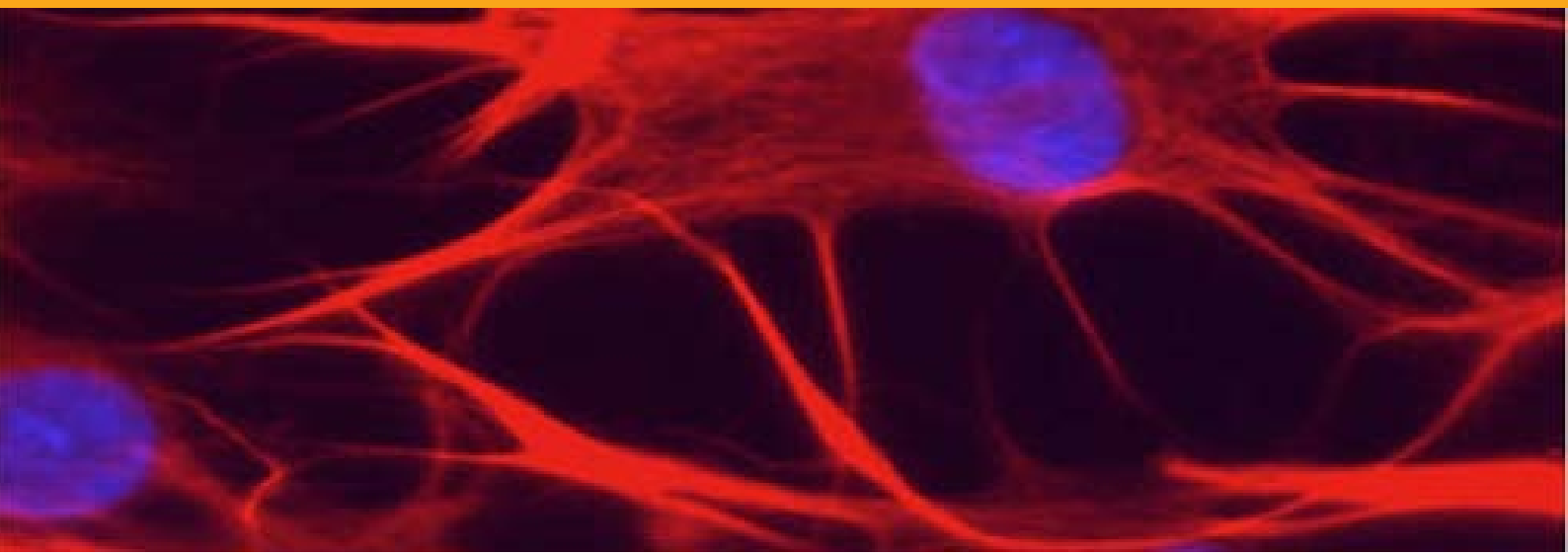

Molecular and Cellular Pharmacology

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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 neuropathological 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. Futhermore, 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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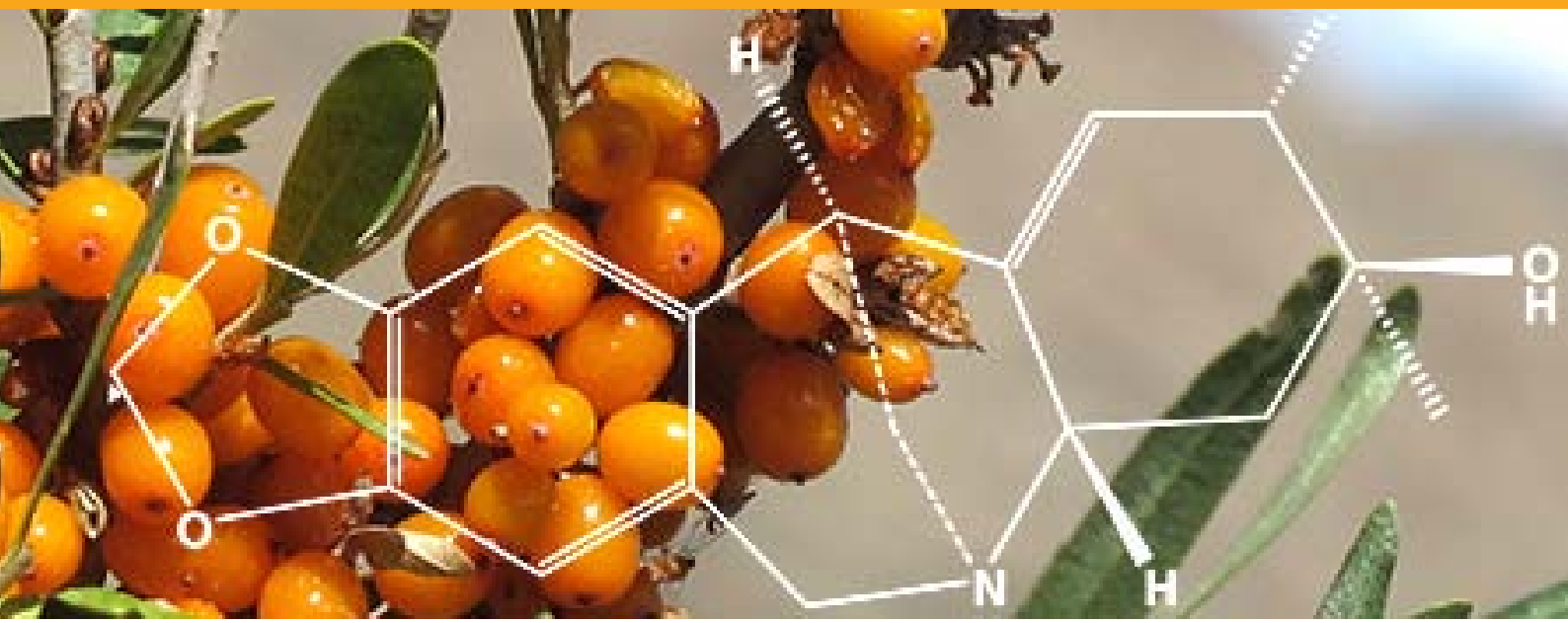

Natural Product Research

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Drug discovery from nature using advanced bioanalytical chemistry

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 wil 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 wil 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.

- Collecti
  lowed 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.

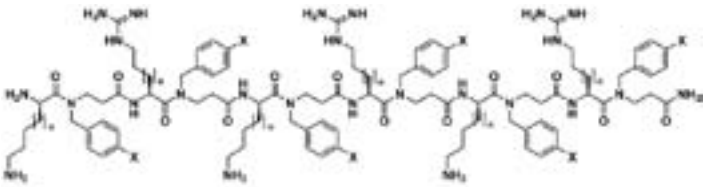
Antimicrobial nanomedicine: Focus will be design and synthesis of an array of AMPs followed by formulation of these into a drug delivery system intended for preventing or treating infections. The aim is to understand the mechanisms of interaction with and transport through eukaryotic and/or prokaryotic 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).

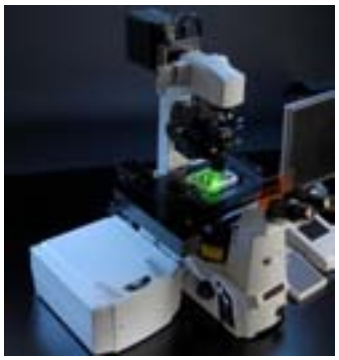
Introduction to CPPs: Certain peptides enable transport of therapeutic peptides or even large macromolecules and particles (delivery systems) across cell membranes. These are known as cell-penetrating peptides (CPPs).

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.

Apparatus for SPPS



Examples of peptidomimetics



Microscopy of CPP uptake.

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Master Project 2017: Peptide-Based Antibiotics

WHO has predicted that within a decade, it will be common to encounter pathogenic bacteria resistant to all known antibiotics. Especially worrying is the growing resistance among Gram-positive and Gram-negative pathogens that cause infection in the hospital and in the community.
Therefore it is essential that research efforts focus on antimicrobial agents with alternative modes of action.
Antimicrobial peptides are produced by all living organisms as part of their natural first line of defense against pathogens. General features of antibacterial peptides are a positive overall charge and an amphiphilicity due to positioning of basic and hydrophobic amino acids.

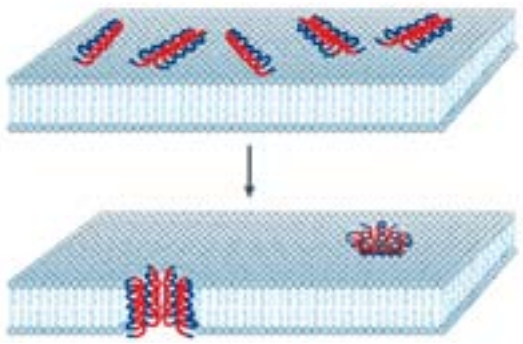

Figure: Antimicrobial peptides kill bacteria by disrupting the membrane

In contrast to most traditional antibiotics which block a biochemical process within the bacterial cell, antimicrobial peptides affect the bacterial membrane which results in cell death within minutes. One hypothesis states that the initial interaction is an electrostatic attraction between the positively charged peptide and the negatively charged outer-membrane of bacteria, and once a threshold concentration has been reached, they penetrate the hydrophobic lipid-bilayer and disrupt the local environment enough to cause cell death. Antimicrobial peptides are considered promising lead structures in the development of new antibiotics, primarily because of their membrane-specific mode of action, but also because it is anticipated that bacteria will be less capable of developing resistance to such peptides than to traditional antibiotics.

The aim of this Master Project will be to improve the antimicrobial activity and proteolytic stability of an antimicrobial peptide lead compound.
You will first perform i) structure-activity studies and then ii) optimize the activity by inserting N-substituted glycine units (peptoids) in selected positions. The derivatives will be synthesized by solid-phase peptide synthesis, purified by preparative HPLC, characterized by MALDI-TOF-MS/LC-MS and concentration determined by NMR.
You will test the antimicrobial activity of the derivatives against both human and veterinary pathogens. With our collaborators at Danish Centre for Antibiotic Research and Development you will test against resistant strains.
You will also test the hemolytic activity and proteolytic susceptibility.

Reference:
Alberto Oddo, Thomas T. Thomsen, Susanne Kjelstrup, Ciara Gorey, Henrik Franzyk, Niels Frimodt-Møller, Anders Løbner-Olesen, Paul R. Hansen (2016). An all-D undecapeptide shows promising activity against colistin-resistant strains of Acinetobacter baumannii. Antimicrobial Agents and Chemotherapy. doi: 10.1128/AAC.01966-15.

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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 reasearch 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 occurence 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 reseachers 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 pharmcokinetics 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

Possible projects will be announced in fall 2017 and spring 2018.

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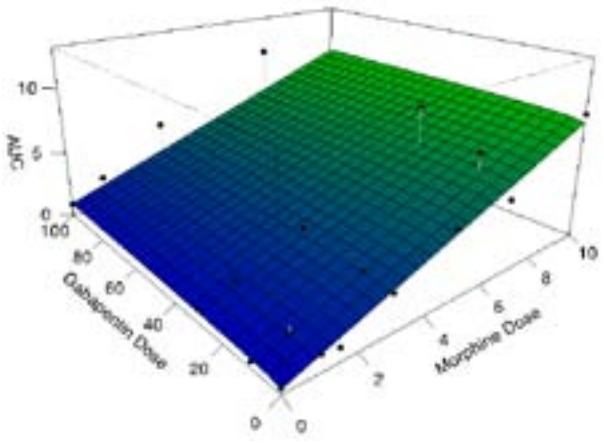
Population pharmacokinetic/pharmacodynamic (PK/PD) modelling

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
- Population pharmacokinetic modeling on Itraconazol. Collaboration with Lundbeck, 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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