Master’s programme in Drug Discovery and Safety

Drug Discovery and Target Finding

General description
In the specialization Drug Discovery and Target Finding (Molecular Pharmacology) you will investigate the interaction of biological active molecules (small molecule or an antibody (biological)) with their target. The research focuses on ligand-receptor interactions, modulation of signal transduction pathways, and novel concepts like ligand-independent receptor signaling, biased signaling and receptor dimerization. You will learn concepts of molecular biology and pharmacology and use innovative imaging and biophysical approaches.

Programme components (EC)
The Master’s programme in Drug Discovery and Safety is a two-year programme starting in September. The specialization Drug Discovery and Target Finding contains the following components (EC):

- Compulsory (core) courses (30-36)
- Major research project (42-60)
- Literature thesis and colloquium (12)
- Ethics and academic skills (6)
- Elective: minor research project; traineeship abroad/company; optional courses (6-30)

Course overview

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<thead>
<tr>
<th>Period</th>
<th>Month</th>
<th>Course (EC)</th>
<th>Category</th>
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<tbody>
<tr>
<td>1</td>
<td>Sep – Oct</td>
<td>Chemical biology (6)</td>
<td>Compulsory core course*</td>
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<td></td>
<td></td>
<td>ADMET (6)</td>
<td>Compulsory core course*</td>
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<td>Principles of pharmacochemistry (6)</td>
<td>Introductory course**</td>
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<td>2</td>
<td>Nov – Dec</td>
<td>High-throughput screening (6)</td>
<td>Compulsory course</td>
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<td>Signal transduction in Health and Disease (6)</td>
<td>Compulsory course</td>
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<td>3</td>
<td>Jan</td>
<td>Ethics and academic skills courses (6 total)</td>
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<td>4</td>
<td>Feb – Mar</td>
<td>Computational design and synthesis of drugs (6), Drug action (6)</td>
<td>Compulsory core course*</td>
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<td>5</td>
<td>Apr – May</td>
<td>Traineeship, literature study, optional course</td>
<td>Compulsory core course</td>
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<td>6</td>
<td>Jun-</td>
<td>Traineeship</td>
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More information: www.vu.nl/dds

* At least 2 out of 3 compulsory core courses are obligatory.
** Principles of pharmacochemistry only compulsory for students without prior background in pharmaceutical sciences.

This overview can be subjected to alterations.

Every part of the programme, including the choice of optional courses, has to be discussed and agreed upon with the Master’s coordinator and approved by the examination board.

Master’s coordinator: Dr. Marco Siderius
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**Molecular Pharmacology : Prof. Rob Leurs, Dr. Henry Vischer**

Multidisciplinary research on the medicinal chemistry interface in close collaboration with chemists from the Drug Design and Synthesis group in e.g. projects looking for new anticancer or antiparasitic drugs or the development of new photoswitchable GPCR ligands.

**Novel concepts in drug discovery**

Our molecular receptor pharmacologists study -the kinetics of ligand (drug) interactions with G protein-coupled receptors (GPCRs), signal transduction events, and novel concepts like biased agonism, ligand-independent signaling and receptor dimerization. We utilize molecular biology, pharmacology, BRET- and FRET-based biosensors, innovative imaging and biophysical approaches. These studies aim on elucidating the role of GPCRs (histamine and chemokine receptors) in health and disease and ultimately to validate their potential as future drug targets.

**Photopharmacology: controlling cell function with light**

We have launched a research line addressing the design and synthesis of novel photo-responsive GPCR ligands acting on histamine or chemokine receptors. Upon irradiation with light, these molecules change their 3D-shape and consequently their physiochemical and biological properties, giving the potential to optically modulate biochemical processes. This in turn allows for the exciting opportunity to modulate cellular processes with spatial and temporal precision by simply using light.

**Parasitic PDEs as targets for Neglected Infectious Disease**

To target Neglected Parasitic Diseases, we aim at nucleotide phosphodiesterase (PDEs) from different parasites (Kinetoplastids (T. brucei, cruzi), Helminths (S. mansoni)) building on insights and technologies that have been developed in the successful therapeutic targeting of various members of the 11 human PDE families in the human genome (e.g. Viagra®, Daxas® or Otezla®). PDEs make such good drug targets because these enzymes have a unique architecture at their active site, allowing the development of selective inhibitors. PDEs are ideal for target-centric approaches, since most state-of-the-art drug discovery technologies (e.g. computer-aided drug design, biophysical screening, structural biology) are applicable to PDEs.
Human and viral chemokine receptors as novel targets for therapeutic intervention of cancer

G protein-coupled receptors (GPCRs) play a key role in cellular communication. In the ‘Receptor Biochemistry and Signaling’ research group, we examine the role of chemokine receptors (CXCR4 and CXCR7/ACKR3) in inflammation and cancer using in vitro (cell-based signaling assays) and in vivo (xenograft mouse) model systems. Moreover, genomes of herpesviruses contain genes encoding GPCRs, which show homology to chemokine receptors. Interestingly, these viral chemokine receptors display oncogenic properties and induce tumor formation in vivo. These viral GPCRs may therefore play a role in cancer after viral infection and are considered as novel drug targets. We aim to modulate these (viral) chemokine receptors using novel antibody technology; llama-derived nanobodies/VHHs.

Network-based drug discovery to find new targets of cancer

To elucidate the role of GPCRs in pathological signaling, we use a systems biology approach to map key signaling events and components. We investigate the role of (viral) GPCRs in pathology (cancer, inflammatory disease) using genome and proteome wide analyses. These studies unveil the intricate organization and interplay of signaling pathways involved.

Modulation of 14-3-3 interactions; PPIs involved in oncogenic signaling

Dynamic interactions between 14-3-3 proteins and their targets (e.g. estrogen receptor, GPCRs) is studied using biochemical, genetic and electrophysiological techniques. We aim to characterise relevant interactions and modulate these using natural compounds (like the fungal compound Fusicoccin) and small molecules to therapeutically target these important regulatory elements in oncogenic signaling.
Drug Discovery and Target Finding

Research topics

Organic and Protein Chemistry: Dr. Sven Hennig, Prof. Dr. Tom Grossmann

Biophysical characterization of ligand-receptor interactions
The characterization of interactions between our designed ligands (peptides and peptidomimetics) and their biological targets (proteins and RNA) is central for the follow-up design of improved inhibitors. For this purpose, the following techniques are used: fluorescence polarization assays, isothermal titration calorimetry (ITC) and cellular pull-down assays (among others).

Heterologous expression of proteins
The expression and purification of proteins also in complex with binding partners is the starting point of our projects. Standard, state of the art molecular biology techniques are our core expertise and usually result in the large scale, heterologous protein expression in bacteria. Diverse subsequent purification steps (FPLC) including affinity, size exclusion and/or ion exchange chromatography lead to mg amounts of pure protein that can be used in further studies.

Protein X-ray crystallography for structural elucidation
The determination of protein structures and of their corresponding complexes with ligands is central to the design of novel bioactive agents. For that purpose, we obtain protein crystals with can be analyzed using X-ray diffraction. The resulting high-resolution atomic coordinates provide the basis for our subsequent synthesis and can also foster new biological insights.