

# Specialization Drug Disposition and Safety Assessment

## Study programme

### General description

In the specialization Drug Disposition and Safety Assessment (Molecular Toxicology) you will study the causes and effects of unwanted and sometimes toxic properties of drugs and substances. The research focuses on elucidating enzymes involved in bio-activation and on reactive metabolites responsible for toxicity of drugs and drug candidates. These studies will make it possible to develop safer drugs and to identify patient risk groups which may develop adverse drug reactions. Among various techniques you will use biochemical and analytical approaches.

### Programme components

The Master's programme in Drug Discovery and Safety is a two-year programme starting in September. The specialization Drug Disposition and Safety Assessment contains the following components (EC):

- Compulsory courses (36)
- Major research project (42)
- Literature thesis and colloquium (12)
- Ethics and academic skills (6)
- Elective: minor research project; traineeship abroad/company; optional courses (24)

### Course overview

Period	Month	Course (EC)	Category
1	Sep – Oct	Chemical biology (6) ADME processes and toxic side effects (6) Principles of pharmacology (6)	Compulsory course Compulsory course Introductory course*
2	Nov – Dec	Drug induced stress and cellular response (6)	Compulsory course
3	Jan	Drug action (6)	Compulsory course
4	Feb – Mar	Computational design and synthesis of drugs (6)	Compulsory course
5	Apr – May	Advanced course on drug disposition and safety assessment (6)	Compulsory course
6	Jun		

**More information: [www.vu.nl/dds](http://www.vu.nl/dds)**

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. Jan Commandeur**

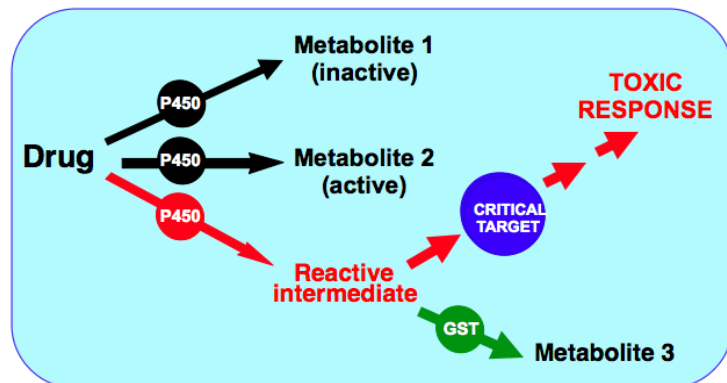
Phone: +31 20 59 87595 E-mail: [j.n.m.commandeur@vu.nl](mailto:j.n.m.commandeur@vu.nl)

\*Compulsory course only for students without prior background in pharmaceutical sciences

Prof. Dr. Nico Vermeulen; Dr. Jan Commandeur; Dr. Chris Vos

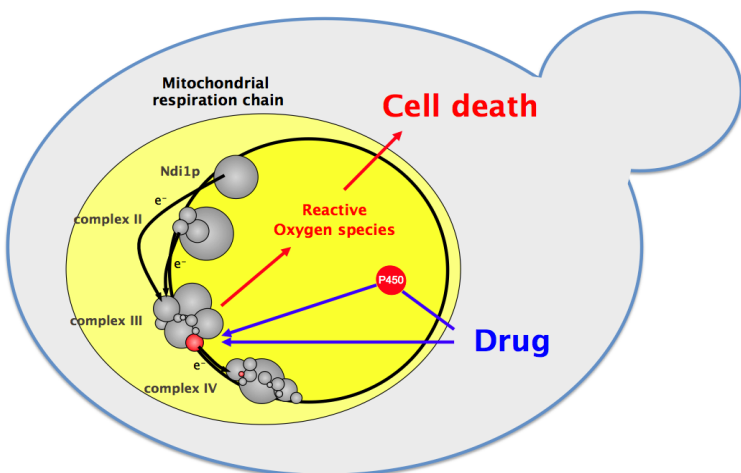
## Identification of molecular mechanisms and risk factors underlying rare adverse drug reactions

Idiosyncratic drug reactions are very rare and severe adverse drug reactions. It is hypothesized that reactive intermediates formed by hepatic cytochrome P450 enzymes are initiating this process, leading to severe drug-induced liver injury. We are currently developing analytical methods for the identification of reactive intermediates and their target proteins. Furthermore, we investigate whether genetically-determined enzymes (e.g. glutathione transferases (GSTs)) are involved in the formation and/or inactivation of reactive intermediates. These studies might explain which patient is susceptible to these life-threatening side-effects.



## Development of novel *in vitro* models to study the mechanism of drug-induced toxicity

To study the cellular responses caused by reactive drug metabolites, we are developing novel cellular toxicity model systems. We express different cytochromes P450s in these systems which may be involved in production of reactive drug metabolites. By studying the cellular responses caused by reactive metabolites, we want to characterize the affected cellular targets. Using yeast as an eukaryotic model, we recently identified specific components of the mitochondrial respiration chain as a target of hepatotoxins. These studies will be extended in human cell systems. By co-expressing individual GSTs we are studying their role in protection against cytotoxicity.



## Novel biocatalysts for the production of human drug metabolites and other fine-chemicals

Drug metabolites produced by cytochrome P450s can possess very potent pharmacological or toxicological activity. Because metabolites are often difficult to obtain by organic synthesis, we are developing novel biocatalysts which produce high levels of metabolite products. We use a combination of site-directed mutagenesis and random mutagenesis to create a library of catalytically diverse mutants of bacterial cytochrome P450 BM3. These mutants are capable to oxidize drugs and other fine-chemicals with high activity and with high regio and stereo selectivity. These studies are aiming to obtain more fundamental insight into the mechanism of action of this highly important class of enzymes.

