Master's programme in Drug Discovery and Safety

# Drug Disposition and Safety Assessment

Study programme

## General description

The specialization of Drug Disposition and Safety Assessment, directed by the Division of Molecular and Computational Toxicology, deals with the understanding of how chemicals are processed in the body and can interfere with cellular and biological processes. This includes biological systems involved in biotransformation and transport of xenobiotics, adaptive stress response pathways and toxicity mechanisms. The course also deals with biological and analytical tools and the application of this information to safety assessment of chemicals. The ultimate aim is to develop better and safer drugs and to identify patients at particular risk for certain outcomes.

## Programme components (EC)

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 (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

| Period | Month | Course (EC) | Category |
|---|---|---|---|
| **1** | Sep – Oct | Chemical biology (6)<br>ADMET (6)<br>Principles of pharmacochemistry (6) | Compulsory core course*<br>Compulsory core course*<br>Introductory course** |
| **2** | Nov – Dec | Drug induced stress and cellular response (6) | **Compulsory course** |
| **3** | Jan | Ethics and academic skills courses (6 total) | |
| **4** | Feb – Mar | Computational design and synthesis of drugs (6),<br>Drug action (6) | Compulsory core course*<br>Compulsory core course* |
| **5** | Apr – May | Advanced course on drug disposition and safety assessment (6) | **Compulsory course** |
| **6** | Jun- | Traineeship, literature study, optional course | |

## More information: www.vu.nl/dds

* At least 3 out of 4 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.

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VU UNIVERSITY AMSTERDAM | Faculty of Sciences

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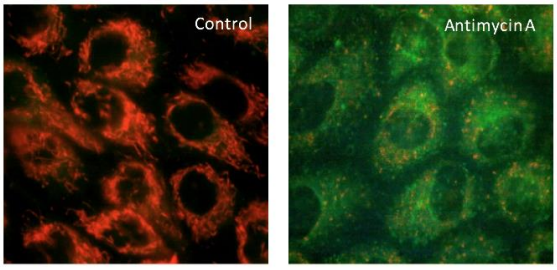
# Drug Disposition and Safety Assessment

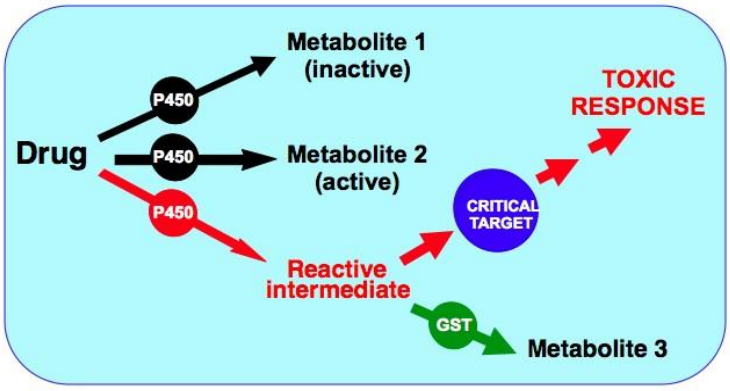
Research topics

Prof. Paul Jennings, Dr. Jan Commandeur, Dr. Chris Vos, Dr. Anja Wilmes

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

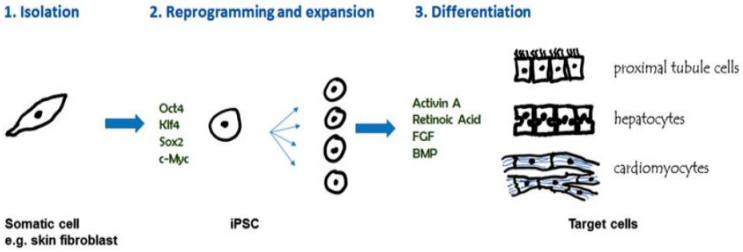
Idiosyncratic drug reactions are rare and severe adverse drug reactions. It is hypothesized that reactive intermediates formed by hepatic cytochrome P450 enzymes are initiating this process, leading to severe drug-induced liver injury. In our laboratory we use analytical methods for the identification of reactive intermediates and their target proteins. Furthermore, we investigate whether polymorphic enzymes (e.g. cytochrome P450 or glutathione transferases ) are involved in the formation and/or inactivation of reactive intermediates. These studies aim to determine if a particular individual is susceptible to potential life-threatening toxicities. Similar analytical procedures are used in combination with cellular systems for biokinetic analysis (cellular uptake and metabolism rates), for application to hazard identification and physiologically based pharmacokinetic (PBPK) modeling.




## Biological perturbations of chemical exposure, omics, imaging and mitochondrial respiration

Parenchymal cells of the kidney and liver are pretty resistant to chemical-induced injury and can adapt to cellular perturbations by activating numerous **stress responses**. Determination of the activation of these stress responses is particularly helpful to understand the original insult (molecular initiating event) and to predict the consequences in real life exposure scenarios. We utilise cultured human cells (cell lines and induced Pluripotent derived cells) in combination with 'omic' methodologies to characterise stress responses. Also, using **high content imaging**, we can monitor chemical effects in real time on a cellular and subcellular level. Additionally, chemicals can adversely affect **mitochondrial function**, a frequent off-target effect of chemical-induced organ toxicity. We utilize the Seahorse bioanalyzer to measure oxygen consumption rates and extracellular acidification rates in intact cells. With the use of modulators of oxidative phosphorylation, we can gain insight on key parameters of cell metabolism.




## Development of novel *in vitro* models

We are utilizing primary cells and cell lines representing the human liver, kidney and endothelial cell culture models. Also a major activity is the development of induced pluripotent stem cells (iPSC) to create patient derived biological systems for chemical safety evaluation and identification of susceptible traits.

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