Screening for lipophilic drugs in human plasma with lipidomics

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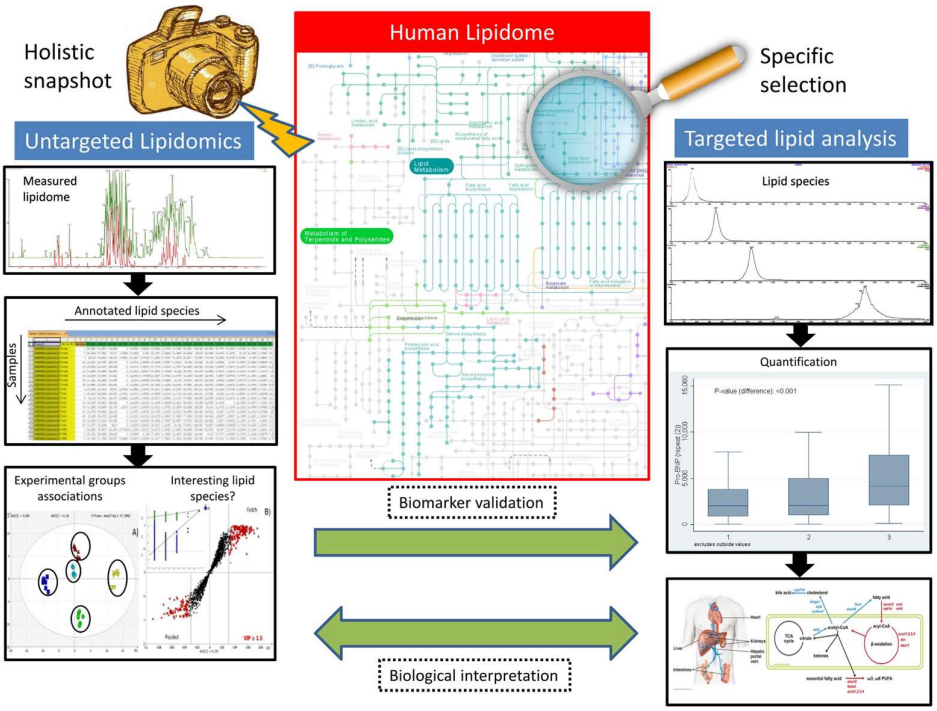
Project background

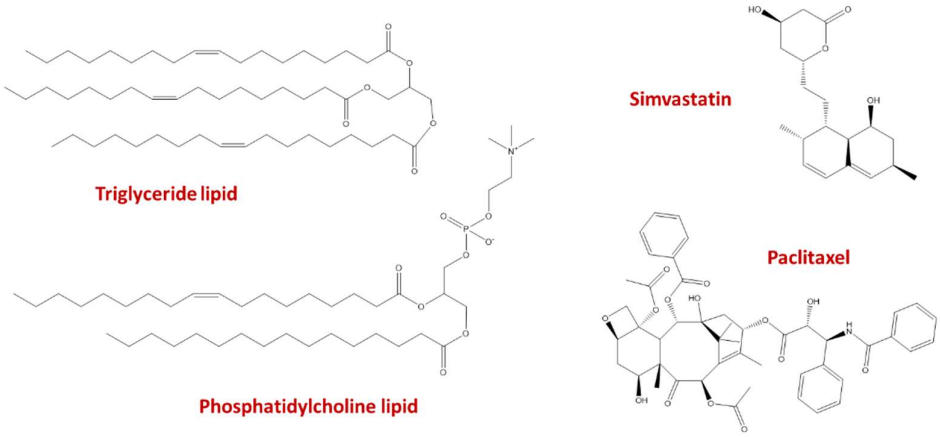
Quantitative analysis of metabolites and drugs is commonly performed by liquid chromatography (LC) coupled to mass spectrometry (MS). Lipids constitute a specific class of hydrophobic metabolites whose major role is the formation of membranes but they also serve as signal molecules and for energy storage. Lipidomics is an LC-MS-based analytical technique to study the complete lipid composition of a sample, such as plasma or tissue [1].



Lipidomics analysis using high-resolution mass spectrometry allows differential analysis of hundreds of lipids, although complete annotation is not straightforward because many lipids have multiple isomeric species. Fragmentation using high resolution MS/MS provides important additional information for lipid species assignment. Quantification in lipidomics, as with most omics techniques, is typically done by relative quantification, resulting in per-compound fold changes between samples.

While most drugs are relatively hydrophilic, lipophilic drugs such as simvastatin and paclitaxel are also widely used. They are usually measured with targeted LC-MS methods, focusing only on specific drugs and their metabolites. This provides accurate and sensitive quantitative data, but ignores information on all other components of the sample. Untargeted analyses provide

a comprehensive overview of the entire sample extract. In this project we want to evaluate whether the existing lipidomics workflow [2] can be used to also measure lipophilic drugs in human plasma, in an unbiased manner. You will use our standard extraction and chromatography (LC) protocols and will explore various untargeted MS/MS methods for drug and lipid detection. The goal is to have a unified method for analysis of the lipophilic fraction of plasma, measuring both endogenous lipids as well as therapeutic or xenobiotic compounds, such as pharmaceutical drugs.



Project tasks & goal

In this Master's project you will apply data-dependent and data-independent untargeted LC-MS/MS strategies in order to improve the detection and annotation of lipophilic drugs in lipid extracts. You will use extracts of human plasma and plasma spiked with known lipophilic drugs. The LC-MS/MS fragmentation strategies will be optimized for the concurrent detection of both the pharmaceutical drugs and the major lipid classes.

The practical work will involve sample preparation in the form of lipid extraction, and hands-on LC-MS/MS analysis. A substantial amount of data analysis using available mass spectrometry software packages will be performed, for annotation of the lipid and drug spectra and creating and/or curating a combined database including potential drug targets.

You will then use the best method to analyze a clinically relevant plasma sample set and/or tissue extracts to evaluate their compositions and relate those to biological questions.

[1] One- vs two-phase extraction: re-evaluation of sample preparation procedures for untargeted lipidomics in plasma samples. Andres Gil, Wenxuan Zhang, Justina Wolters, Hjalmar Permentier, Theo Boer, Peter Horvatovich, Rebecca Heiner-Fokkema, Dirk-Jan Reijngoud, Rainer Bischoff. Analytical and Bioanalytical Chemistry, 2018.

[2] Omics technology: Lipidomics and its pitfalls during the preanalytical stage. Andres Gil, Wenxuan Zhang, Justina Wolters, Hjalmar Permentier, Peter Horvatovich, Rebecca Heiner-Fokkema, Dirk-Jan Reijngoud, Rainer Bischoff. In: Encyclopedia of Analytical Science, 3rd edition, Elsevier, 2018.