A study of drug metabolism in zebrafish larvae using MALDI-MS Imaging

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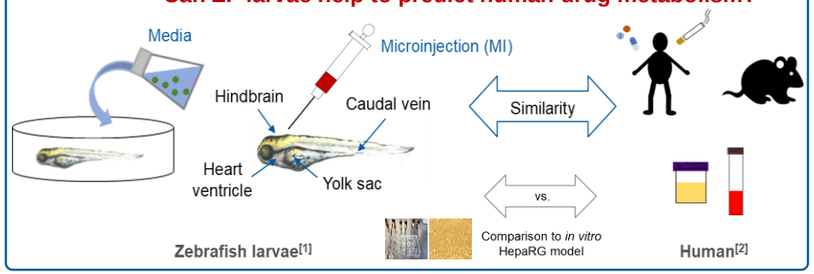
Introduction

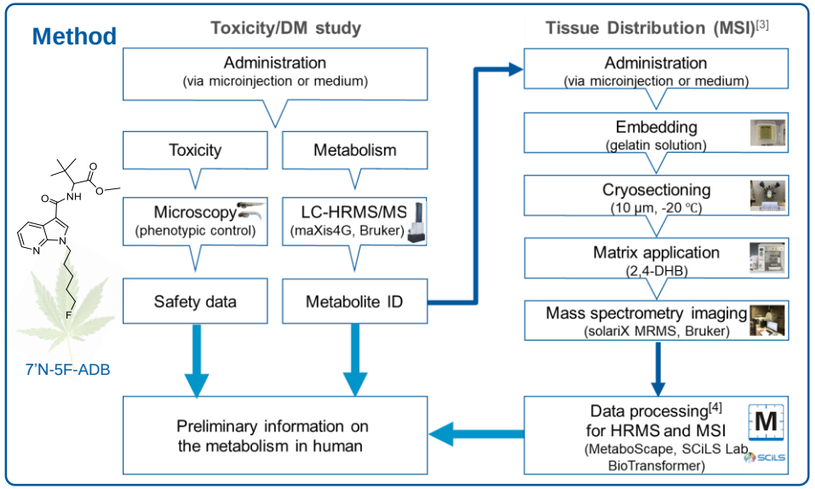
In this study we identified metabolites of a drug and the distribution of its metabolites in zebrafish larvae using LC-MS/MS and MALDI-MSI. Zebrafish (*Danio rerio*, abbr. ZF) larvae have been investigated as a promising vertebrate model to study drug metabolism (DM) due to their easy handling in high-throughput *in vivo* metabolite identification workflows. Mass spectrometry imaging (MSI) is a powerful technology allowing for visualization and analysis of the spatial distribution of molecules without labelling or staining. Matrix-assisted laser desorption/ionization (MALDI)-MSI has previously been proven to be suitable for the analysis of small molecules such as drugs and their metabolites in tissue samples.

New approach of ZF larvae to study *in vivo* DM

Can ZF larvae help to predict human drug metabolism?

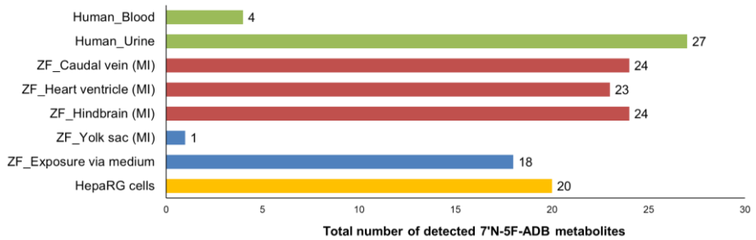


Method

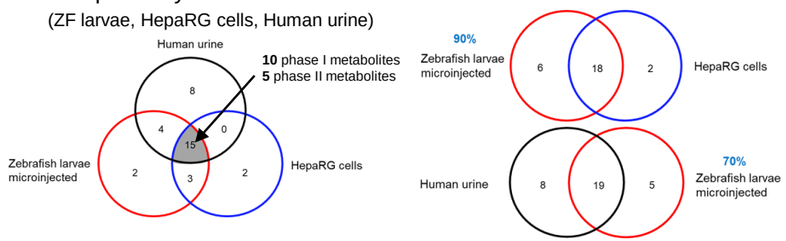


Results

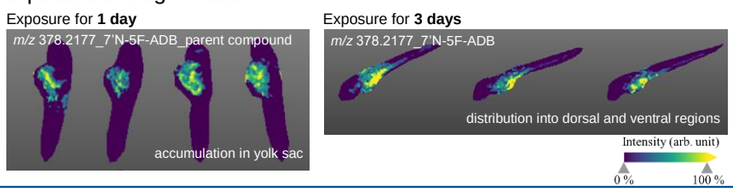
- Comparison of the detected metabolites following different administrations

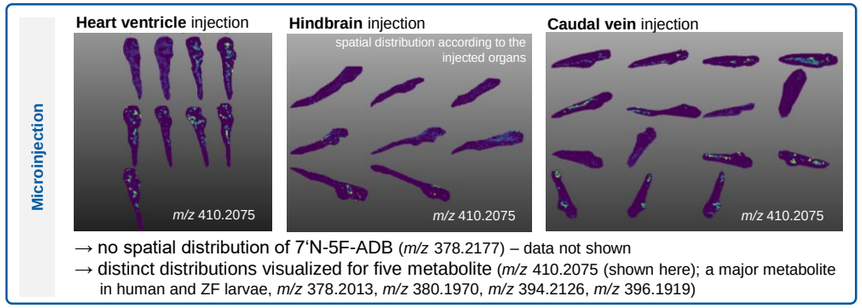


- Comparability of the metabolites detected in three models (ZF larvae, HepaRG cells, Human urine)



- Visualization of the spatial distribution of the parent drug in ZF larvae after exposure through medium (All images show different sections of one larva in each condition)





→ no spatial distribution of 7'N-5F-ADB (*m/z* 378.2177) – data not shown
→ distinct distributions visualized for five metabolite (*m/z* 410.2075 (shown here); a major metabolite in human and ZF larvae, *m/z* 378.2013, *m/z* 380.1970, *m/z* 394.2126, *m/z* 396.1919)

Summary

- Metabolites were compared among three different models (i.e., ZF larvae, HepaRG cells, human urine)
- Microinjection in different organs was applied in ZF drug metabolism model
- The distribution of 7'N-5F-ADB and its metabolites was studied using MSI

Conclusions

- ZF larvae model is a promising tool to study human drug metabolism
- MSI can help to optimize compound administration in DM model of ZF larvae

On-going works

- Application of new drugs to MSI method in ZF larvae
- Optimization of MSI method in zebrafish larvae
- Data interpretation integrated by DM and MSI results

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Ref. [1] Richter LHJ et al., Drug Test Anal 2019, 11, 305-317, [2] Richter LHJ et al., Toxicol Lett 2019, 305(1), 73-80, [3] Kirla KT et al., Toxicol Sci 2016, 154(1), 183-193, [4] Djoumbou Feunang Y et al., J Cheminform 2019, 11 (1), 2.