ccCTA 2023 Scientific Days

Precision medicine: The role of CYP2C19 in pharmacokinetic variability

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Precision Medicine

Innovative approach

Tailoring medical treatments

Subpopulation Focus

Differences in susceptibility

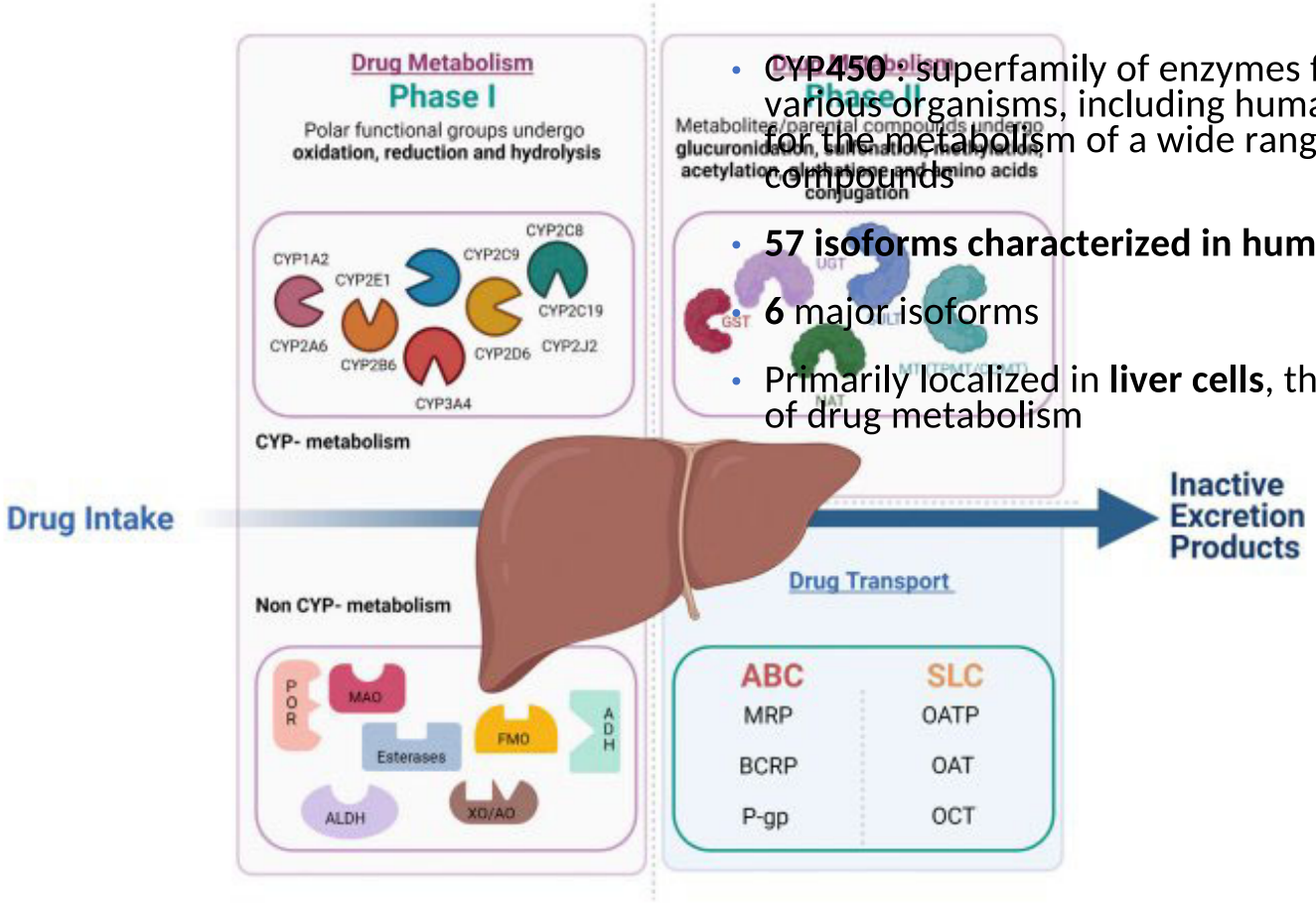
Genetic, environmental and lifestyle factors

Need of drug response variability understanding and management

Variability in drug response

Drug response = efficacy at the therapeutic target (**PD**) **+** drug disposition in the body (**PK**)

Drug Metabolism



- CYP**450** : superfamily of enzymes found in various organisms, including humans , essential for the metabolism of a wide range of compounds
- **57 isoforms characterized in humans**
- **6** major isoforms
- Primarily localized in **liver cells**, the main site of drug metabolism

CYP450 Variability

CYP450 Phenotyping at HUG

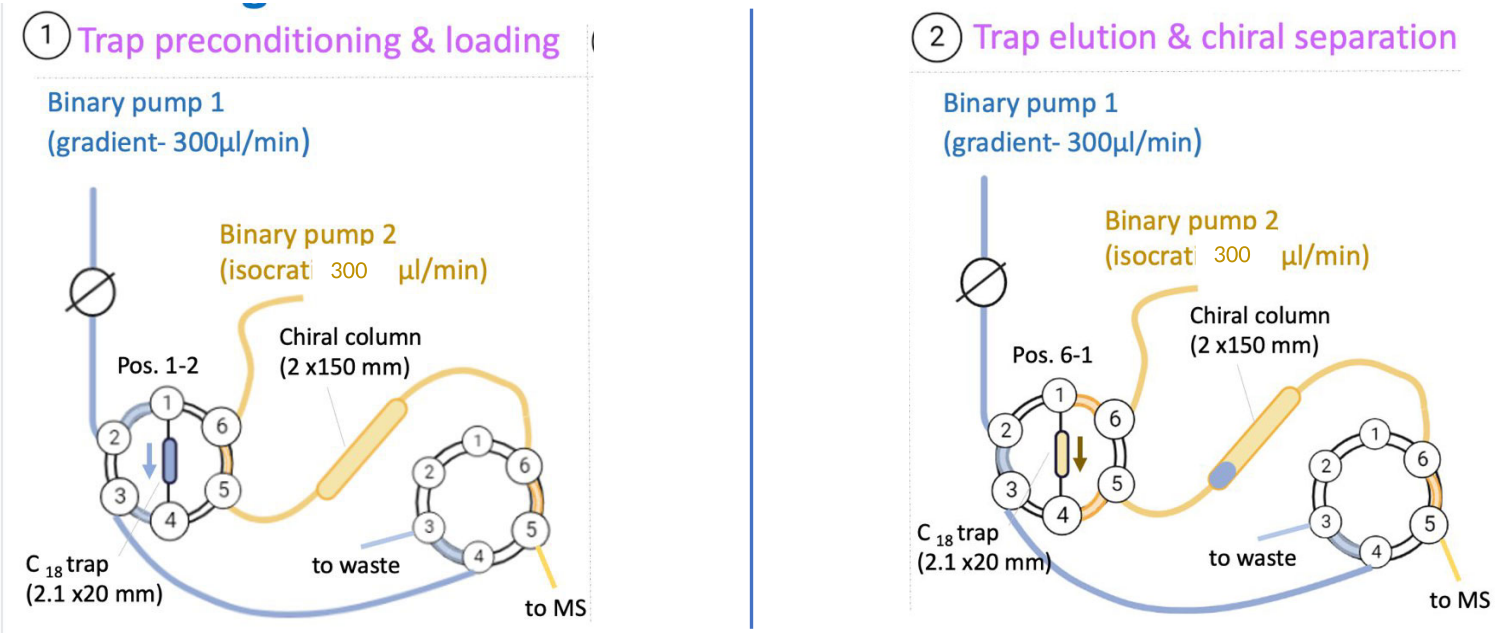
Omeprazole

Omeprazole (OME): first proton pump inhibitor (PPI) irreversibly blocking the (H^+/K^+) ATPase enzymes

OME is indicated in treatment of all acid-related diseases : ↘ gastric acid secretion

Chiral drug but used as a racemic mixture and pure enantiomer

Heart cutting 2D-LC method development



Sample preparation: DPS spots extracted with 100 µL of MeOH and diluted 2-fold with H2O

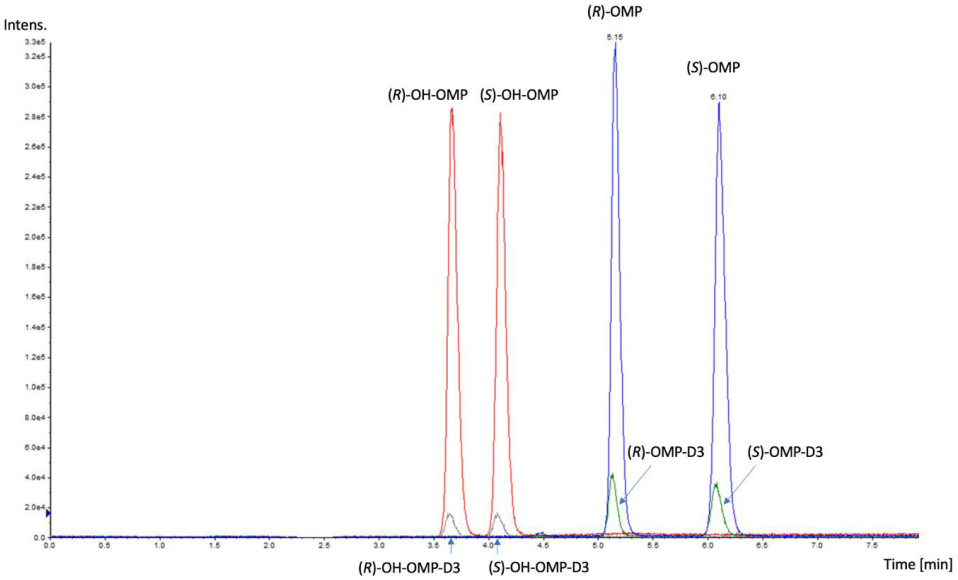
Separation:

- **First dimention :** achiral Discovery C18 trapping column for purification
- **Second dimention :** cellulose-based chiral column (lux-cellulose-4)

Detection: MRM after electrospray ionization using an AB Sciex Qtrap® 6500 mass spectrometer

Heart cutting 2D-LC method development

Analyte	Configuration	Theoretical added concentration (ng/mL)	Accuracy (%)	Repeatability (% CV_w)	Intermediate precision (% Cv_{ip})
OME	(S)-OME	2	89.8	4.0	5.1
		10	92.0	6.2	9.2
		50	96.8	5.3	9.0
		150	95.6	3.6	11.4
	(R)-OME	2	89.5	4.6	5.5
		10	92.8	6.0	10.3
		50	97.1	5.0	9.9
		150	96.4	2.9	11.5
OH-OME	(S)-OH-OME	2	88.2	4.7	4.9
		10	92.0	5.8	12.2
		50	95.6	5.5	11.4
		150	96.2	3.4	13.7
	(R)-OH-OME	2	87.9	4.4	4.8
		10	91.6	5.7	11.7
		50	96.6	5.3	11.3
		150	97.1	3.2	13.1
			93 %	5 %	10 %



All substances were stable at room temperature for at least 14h, at 4°C for at least 24h
Matrix effect was lower than 10% for all of the substances.

Application of the 2D-LC method to clinical samples

Set of data extracted from a previous study (Trial registered under NCT01731067)
10 healthy male volunteers that received 5 mg OME

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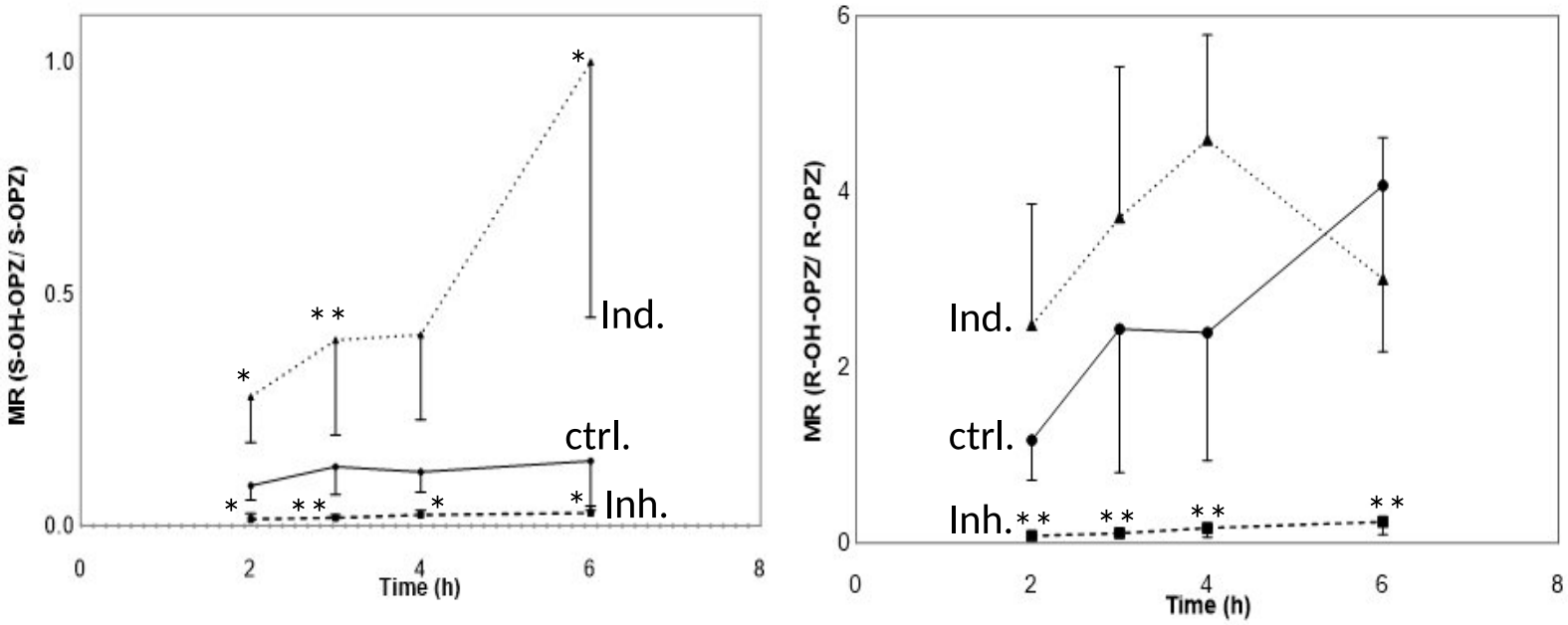

S-isomer better candidate … but analytical limitation !

Clinical trial CYP2C19

- New genotype dosing guidelines have been published for substrate drugs of CYP2C19 (August 2020)
- The influence of genotype on the magnitude of drug-drug interactions (DDIs) involving this isoenzyme remains uncertain
- Interest when a substrate of CYP with narrow therapeutic window is given concomitantly with an inhibitor of its metabolism pathway

Aim of the study

To assess the impact of genotype on the vulnerability to DDIs involving CYPs

Next steps

To treat the Switch19 data

Aim :

- **To compare CYP2C19 activity at baseline in the 3 study groups.**
- **To assess the risk of phenotype switch in three genetically defined CYP2C19 activity groups**
- **To evaluate the need of prospective dose adjustment of CYP2C19 substrates based on patient CYP2C19 phenotype /genotype**
- **To check that the chiral separation method results are comparable to the results obtained from the 10 volunteers in the cocktail study.**

In a nutshell

- We developed a **sensitive** and **accurate bioanalytical** method for OME and OH-OME determination .
- **S- OME** isomers is a better candidate to **CYP2C19 phenotype determination**
- **CYP2C19** genotype impact on the **vulnerability to DDI** is being analyzed …

Back-up slides