TNO.NL

HepMetPro

- HEPATIC METABOLITE PRODUCTION-

TNO innovation for life

TNO HEALTHY LIVING

TNO initiates technological and societal innovation for healthy living and a dynamic society.

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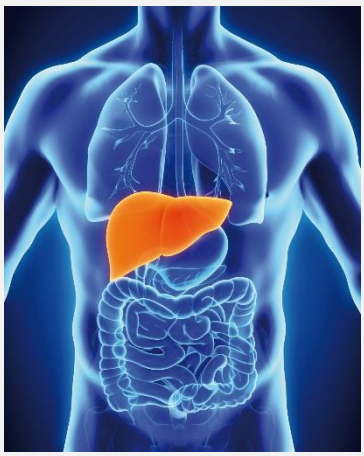
INTRODUCTION

- Drug metabolites are needed during various phases of drug development of small molecules.
- Current production platforms produce low amounts of metabolites (in vitro/chemical), are difficult to scale, and often require long timelines (weeks to months).



SOLUTION

- Normothermic perfusion of slaughterhouse porcine livers to produce (human-like) hepatic kinetic & metabolite profile and production of (multiple) metabolites .

REFERENCES

[1]***Stevens et al.***, *Evaluation of Normothermic Machine Perfusion of Porcine Livers as a Novel Preclinical Model to Predict Biliary Clearance and Transporter-Mediated Drug-Drug Interactions Using Statins;* ***Drug Metab Dispos 49:780–789, 2021***

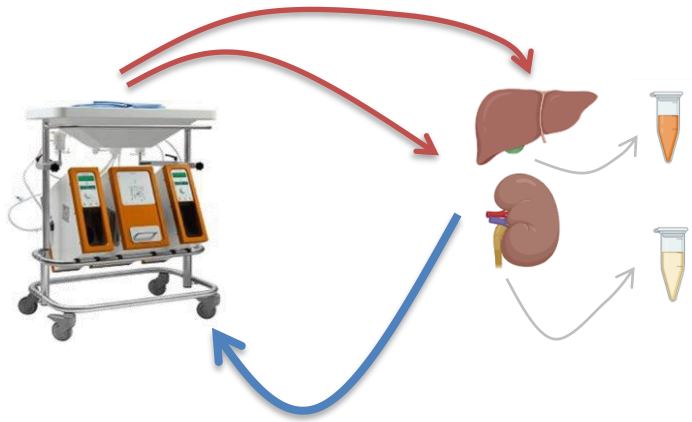


***Figure** 1. Graphical representation of ex vivo liver perfusion with the option to connect a kidney as well, thereby generating perfusate, bile and urine fractions.*

PROCEDURE

1. Shipment of compound
2. Feasibility of hepatic metabolite production in human and porcine liver microsomes
3. Upon go: perform normothermic liver perfusion experiment with continuous (increasing) dose of test compound
4. Optional: combined liver-kidney perfusion
5. Collection of perfusate (plasma), bile (and urine) samples over period of approximately 6h
6. Shipment of perfusate, bile (and urine)
7. Optional next step: isolation and purification of metabolites

EXAMPLE

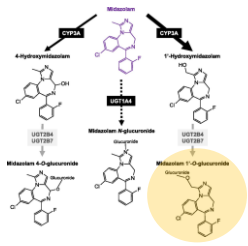


***Figure 2**. Metabolism of midazolam in the liver by CYP3A4/5 and UGTsv*

In a single normothermic liver perfusion experiment ~3,5 mg of Midazolam 1'-O-glucuronide was produced

YOUR BENEFITS

- Fast production of hepatic metabolites in mg range
- All hepatic metabolites formed in 1 run
- Fast production & short run time (within 1-2 weeks)
- Option to combine with kidney perfusion in order to produce/isolate renal metabolites