A physiologically based pharmacokinetic (PBPK) model of the leukotriene receptor antagonist montelukast

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1. BACKGROUND

In this project, we develop a physiologically based pharmacokinetic (PBPK) model of montelukast. The aim is to improve our understanding of interindividual variability in montelukast pharmacokinetics, including the effects of hepatic metabolism, CYP2C9/CYP3A4 variability, drug-drug interactions, food-effect, and weight-related differences in adult populations.

2. METHODS

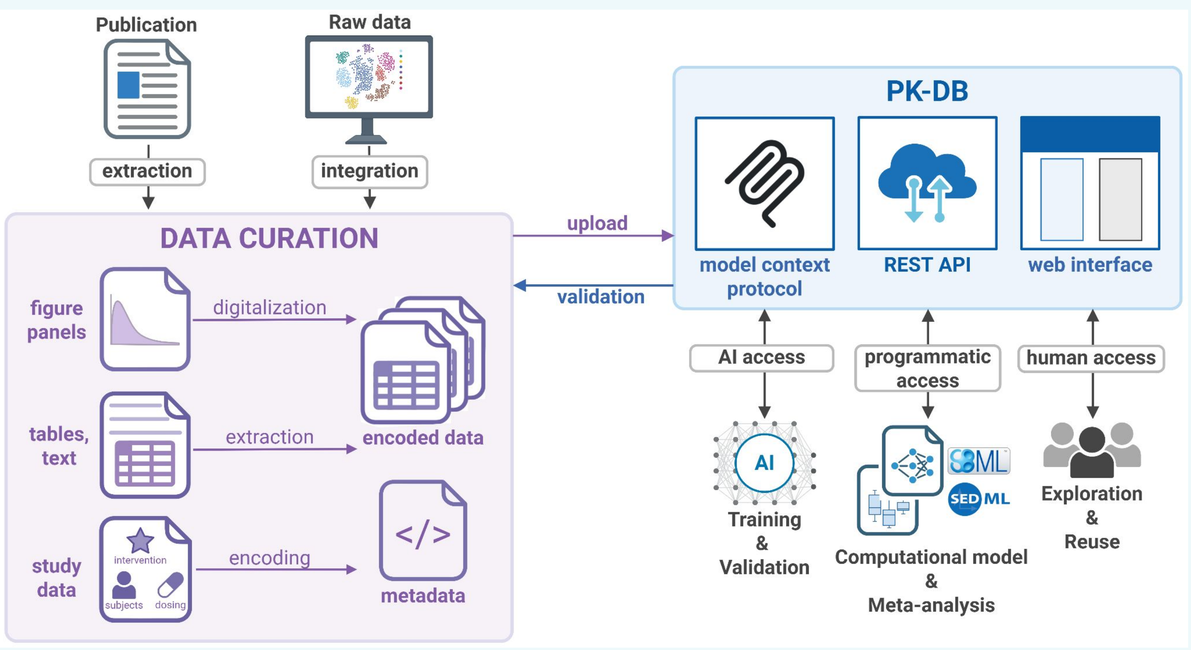

Figure 1. PK-DB overview. Schematic overview of the PK-DB data curation process. Figure panels, datasets, metadata and study information on subjects, interventions and dosing are curated from the publications. The uploaded study information can be accessed either programmatically via the REST API or via the web front-end.

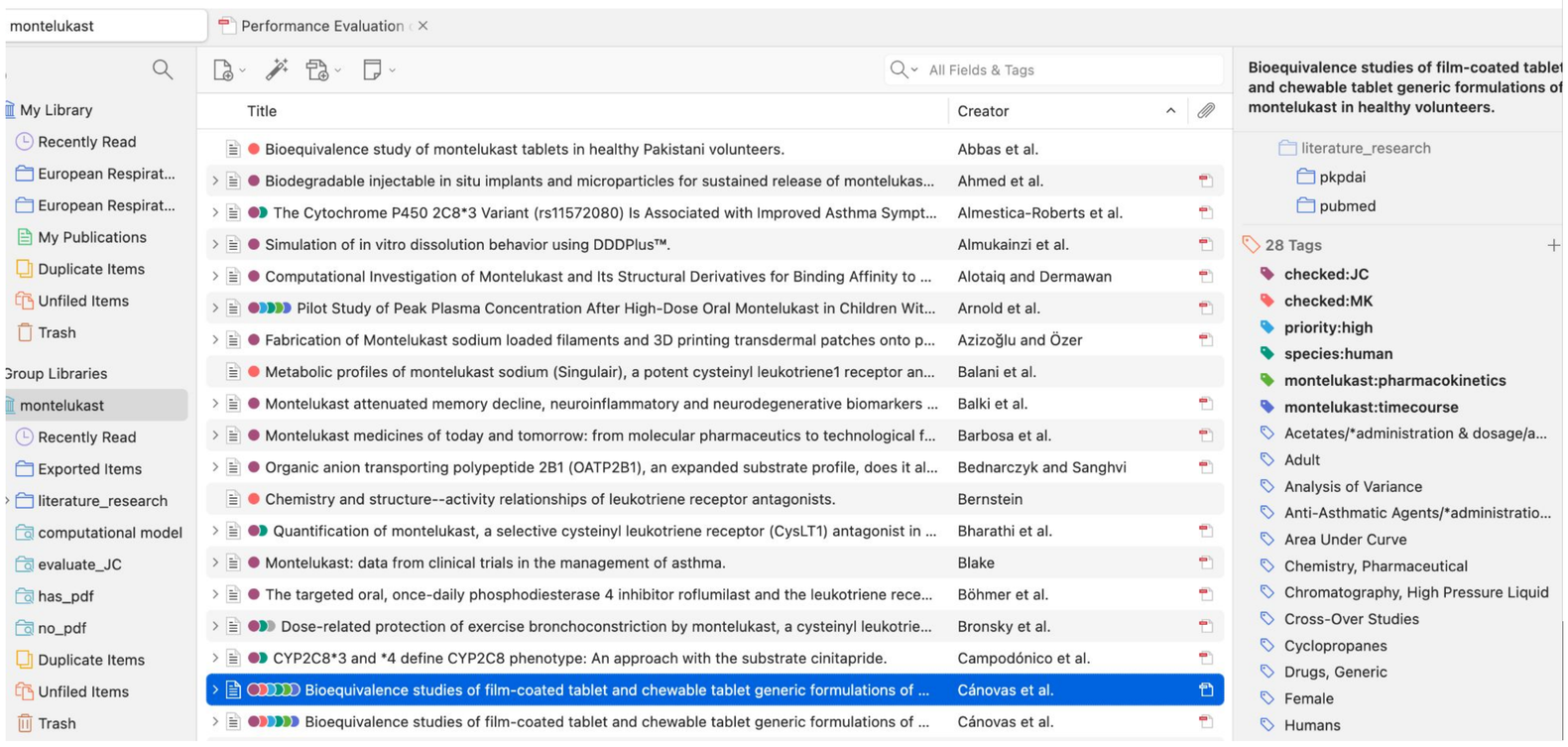

Figure 2. Montelukast literature search. A systematic literature search was performed in PubMed and PKPDAI for publications related to pharmacokinetics AND montelukast. All publications were manually evaluated, tagged according to the information found in the article, and sorted by priority for curation in PK-DB [1].

3. RESULTS

Zotero was used to review over 100 articles and extract relevant information. Studies were prioritized for curation in PK-DB (Figure 1) based on predefined criteria (Figure 2, colored tags). Studies were excluded if they involved non-human species, children, or if neither pharmacokinetic or pharmacodynamic data were available for montelukast. Examples of pharmacokinetic data of interest are shown in Figure 3. Based on the curated data the PBPK model will be developed (Figure 4).

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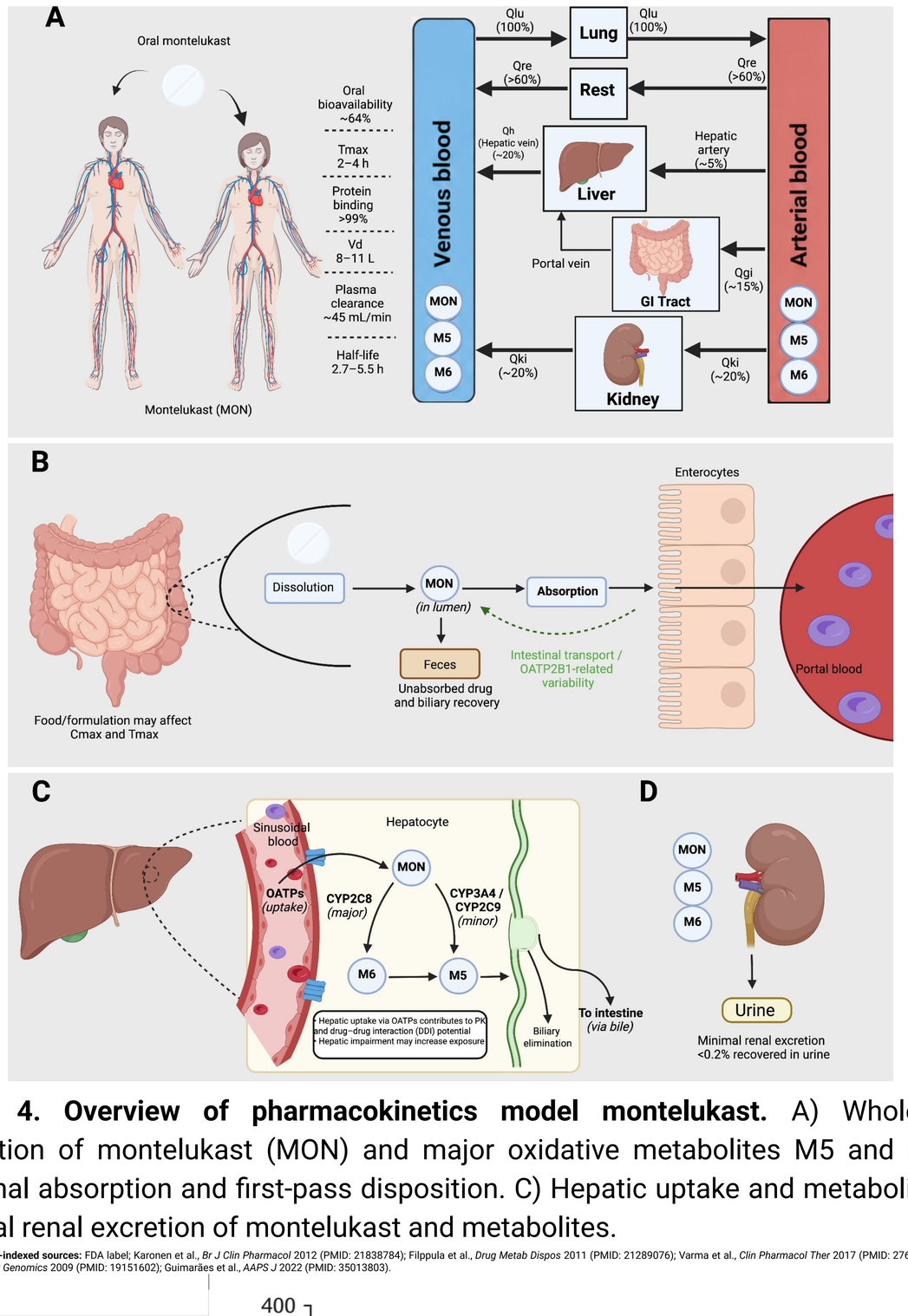

Figure 4. Overview of pharmacokinetics model montelukast. A) Whole-body circulation of montelukast (MON) and major oxidative metabolites M5 and M6. B) Intestinal absorption and first-pass disposition. C) Hepatic uptake and metabolism. D) Minimal renal excretion of montelukast and metabolites.
Based on PubMed-indexed sources: FDA label; Karonen et al., *Br J Clin Pharmacol* 2012 (PMID: 21838784); Filppula et al., *Drug Metab Dispos* 2011 (PMID: 21289076); Varma et al., *Clin Pharmacol Ther* 2017 (PMID: 27648490); Mougey et al., *Pharmacogenet Genomics* 2009 (PMID: 19151602); Guimarães et al., *AAPS J* 2022 (PMID: 35013803).

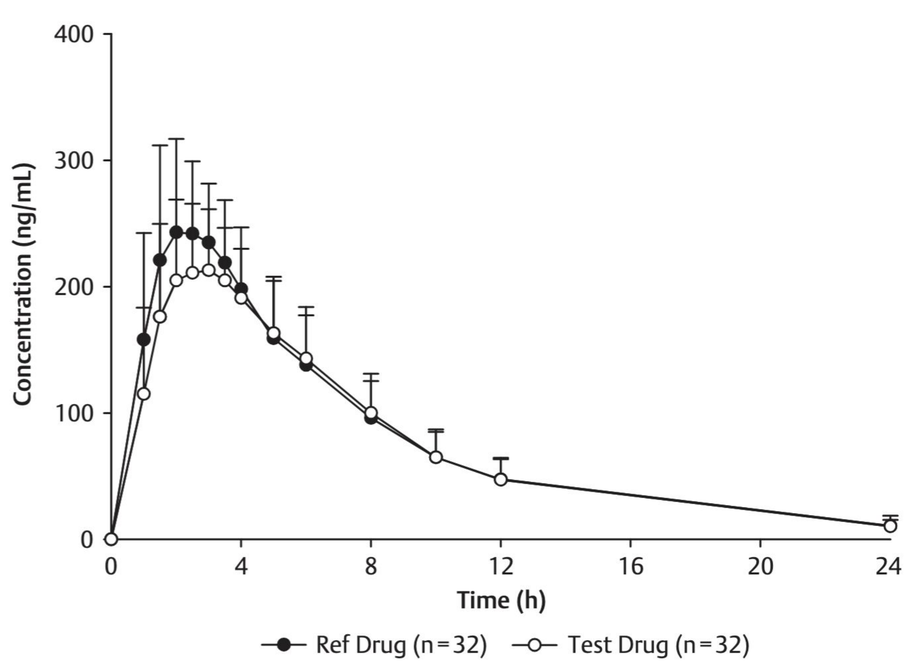

Figure 3. Example data. Mean (SD) plasma concentration-time plots of montelukast after a single oral administration of montelukast 5-mg [2].

4. NEXT STEPS

- Dataset digitization and curation
- Integration into PK-DB
- Development of montelukast PBPK model
- ODE model implementation in SBML
- Model simulations and variability analysis
- Model evaluation using published clinical data
- Manuscript draft preparation

5. HIP EXPERIENCE

Although I have only been in the internship for two weeks, it has already been a highly enriching experience. As a medical doctor, I was mainly accustomed to the hospital environment, work with patients, being in the operating room and always working actively but now I am learning how to use different computational tools and be very careful and precise with every detail. I am enjoying this new phase during the first semester of my master degree although sometimes I do miss my patients.

[1] PK-DB: pharmacokinetics database for individualized and stratified computational modeling. Grzegorzewski et al., Nucleic Acids Res. 2021, 10.1093/nar/gkaa990.
[2] Cánovas M, Arcabell M, Martínez G, Canals M, Cabré F. Bioequivalence studies of film-coated tablet and chewable tablet generic formulations of montelukast in healthy volunteers. Arzneimittelforschung. 2011;61(11):610-616. doi:10.1055/s-0031-1300563.