Enabling Tyrosine Kinase Inhibitor Precision Medicine through PET-Guided Physiologically-Based Pharmacokinetic Modeling

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Background

Non-small-cell lung cancer (NSCLC) remains the predominant cause of cancer-related deaths globally, often driven by mutations in **the epidermal growth factor receptor** (EGFR)[1]. Current treatments, including tyrosine kinase inhibitors (TKIs) like osimertinib, target these mutations but face challenges due to variable drug resistance and patient response[1]. This study utilizes **PET-scans** with microdosed radiolabeled TKIs to map drug distribution and uptake in tumor tissues. To enhance precision in dosing and efficacy, a **whole-body physiology-based pharmacokinetic (PBPK) model** was developed. This model predicts both micro- and therapeutic dose pharmacokinetics, aiming to optimize treatment through **personalized dosing strategies**.

Objective: Develop a **PBPK-model** to predict the tissue and plasma distribution of ^{11}C-Osimertinib.

Methods

- A published whole-body PBPK model *Figure 1A)*[2] was extended focusing on NSCLC, including immune tumor deprivation, tumor perfusion, tumor environment acidity *(Figure 1B)*, and EGFR binding characteristics *(Figure 1C)*[3].
- Four patients underwent dynamic PET scans following the intravenous administration of a microdose of [11C]C-osimertinib (*Figure 2A*). Additionally, three of these patients also participated in a whole-body static PET scan one hour post-injection (*Figure 2B*).

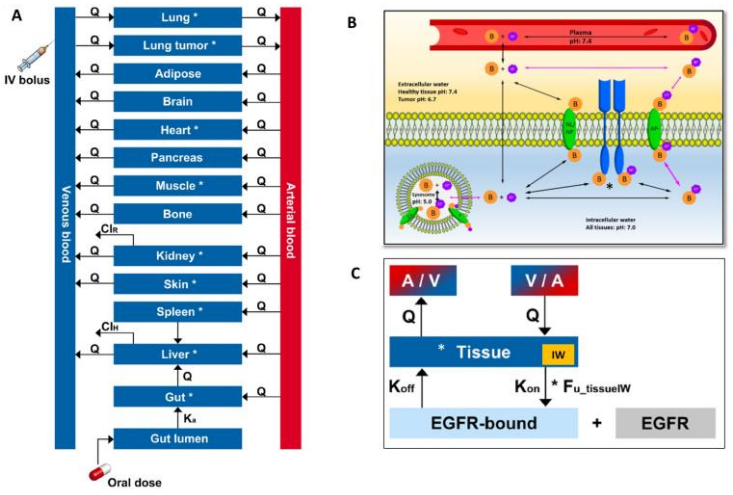

Figure 1: Schematic overview of the PBPK model. A: various compartments with respective blood flow (Q), clearance (CL). * Represents compartments expressing EGFR. **B: drugs dis(associate) with EGFR with constants kon/koff. Only the unbound fraction of drug in intracellular water can bind to EGFR.**

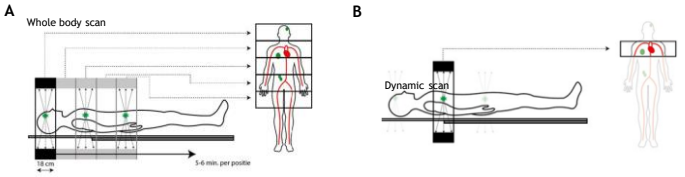

Figure 2: PET scan imaging of osimertinib distribution. A: Whole-body static PET scan image demonstrating drug distribution one hour post-injection. **B:** Dynamic PET scan image showing area scanned continuously over 60 or 120 minutes.

References
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3. Bartelink IH, van de Stadt EA, Leeuwerik AF, Thijssen VLJL, Hupsel JRI, van den Nieuwendijk JF, et al. Physiologically Based Pharmacokinetic (PBPK) Modeling to Predict PET Image Quality of Three Generations EGFR TKI in Advanced-Stage NSCLC Patients. Pharmaceuticals 2022;15(7):796.

Results

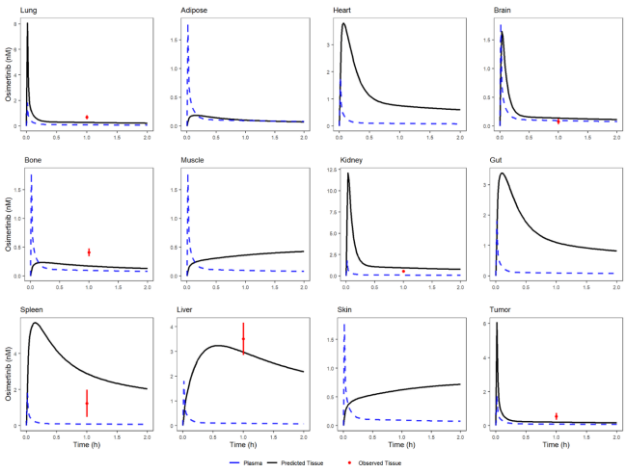

Figure 3: Microdose (16µg) tissue concentration-time profiles for osimertinib across various organs. Each panel represents a different tissue type. Solid black lines indicate predicted tissue concentrations based on the PBPK model, while dashed blue lines show plasma concentrations. Red arrows mark observed tissue concentrations, confirming the model's predictive accuracy at the 1hr time point.

Time post-injection (hours)	Dose	Tissue	Concentration-predicted (nM)	Concentration-observed (nM)	PE (%)*
7	80mg	Vein	232.15	167.8	32.18
72	80mg	Vein	68.4	68.4	0

Table 1: Therapeutic dose (80µg) vein concentration profile at 7h and 72h after a single dose of osimertinib. The model shows low prediction error for therapeutic dose vein concentrations at Cmax and 72h post-PO administration (~2x the half-life of osimertinib).

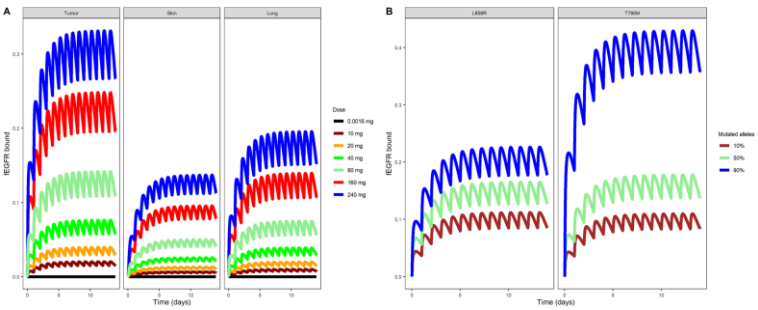

Figure 4: Steady state (24h) tissue concentration-time profiles for osimertinib at various doses and tumor mutation ratios. A: Tissue concentrations in tumor, skin, and lung over 10 days for different oral doses of osimertinib (20 mg to 320 mg) **B:** Tissue concentrations in tumor under different mutant allele statuses (L858R and T790M) with colors indicating the proportion of mutant alleles, demonstrating how genetic variations affect drug distribution and retention in the tissue.

Conclusion

The research demonstrates that PET-guided PBPK modelling effectively predicts the pharmacokinetic behaviour of tyrosine kinase inhibitors across various tissues (inside three-fold error range), a first step towards precision dosing strategies tailored to individual genetic profiles and enhancing targeted therapy outcomes in cancer treatment.