# Systems pharmacokinetic models to the prediction of local CNS drug concentrations in human

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Propositions to the thesis

**"SYSTEMS PHARMACOKINETIC MODELS TO THE PREDICTION OF LOCAL CNS DRUG CONCENTRATIONS IN HUMAN"**

1. Integration of multiple factors is needed for the prediction of target-site drug concentrations in the central nervous system (CNS). (This thesis)
2. Microdialysis, to measure local and temporal unbound drug concentrations, is an essential tool in systems pharmacokinetic modeling. (This thesis)
3. Drug distribution into and within the CNS differs between drugs and must be accounted for when developing systems pharmacokinetic models. (This thesis)
4. The relative contributions of paracellular and transcellular passive diffusion and of active transport to the total drug transport at the blood-brain barrier and the blood-cerebrospinal fluid barrier vary between individual drugs as well as between CNS conditions. (This thesis)
5. Systems pharmacokinetic models support the refinement, the reduction and ultimately the replacement, of animal experiments in drug development. (This thesis)
6. Systems pharmacology models are the next frontier of pharmacokinetic and pharmacodynamics models, in which mechanistic detail is added to every step on the path from dose to exposure to response. (PH van der Graaf et al., Clin. Pharmacol. Ther. 94: 379-381, 2013)
7. Understanding disease related alterations in the drug concentrations at the target-site, is a prerequisite for successful drug development. (MN Pangalos et al., Nature Reviews, 6: 521-532, 2007; AK Deo et al., Mol Pharmaceutics, 10: 1581-1595, 2013)
8. The development of rational drug treatment modalities for traumatic brain injury requires a systems pharmacology model approach.
9. The major threat to CNS drug discovery and development is the tendency to oversimplify relevant factors underlying CNS disease and drug effects.
10. Everything should be made as simple as possible, but not simpler when developing systems pharmacokinetics models. (modified from Albert Einstein)
11. Today's best is not the best tomorrow: sciences have to create tomorrow's best tomorrow. (modified from Konosuke Matsushita)

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