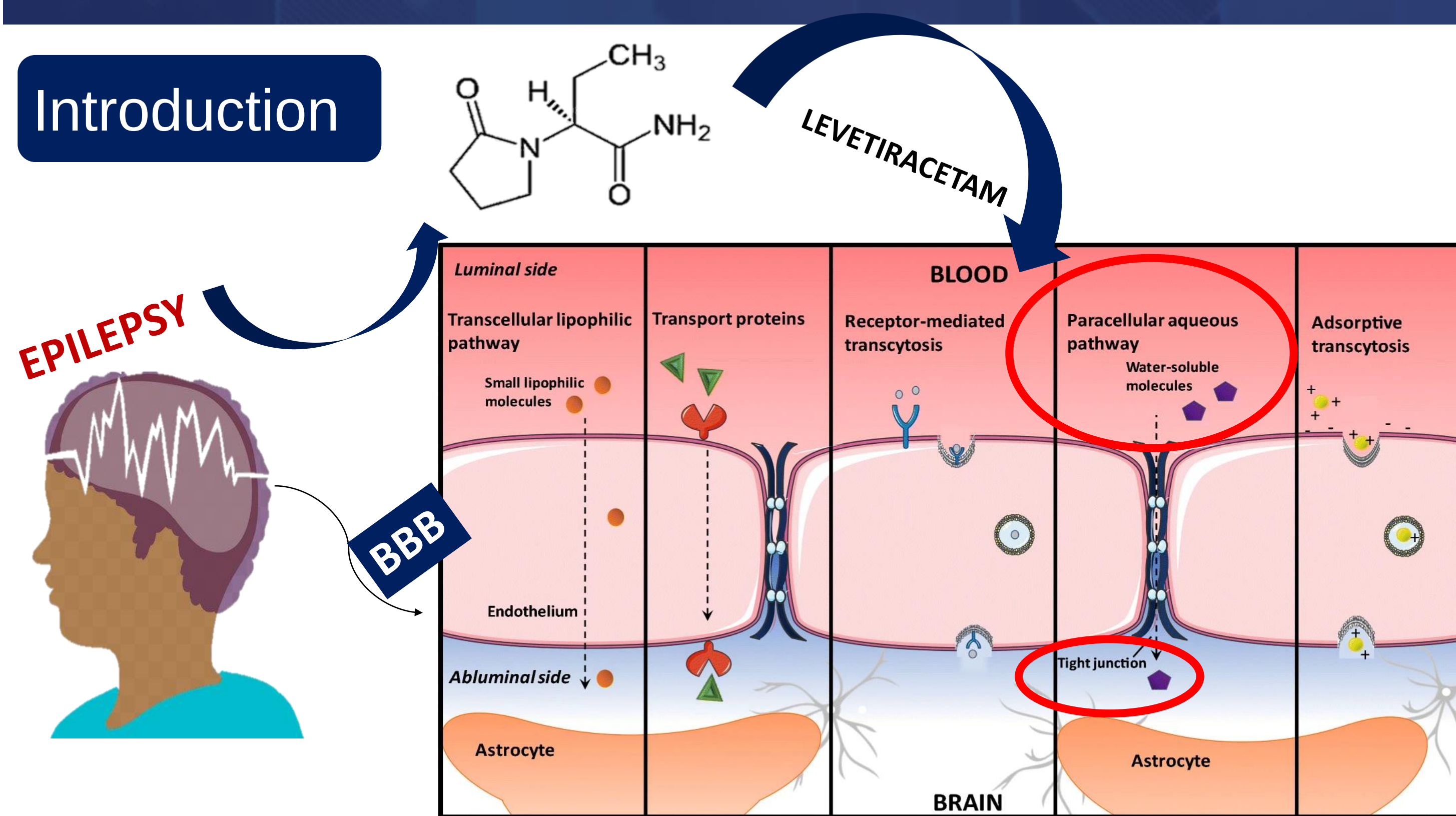


Application of interspecies PBPK-PD modeling to characterize BBB permeability and assess target site exposure-response using levetiracetam as model drug



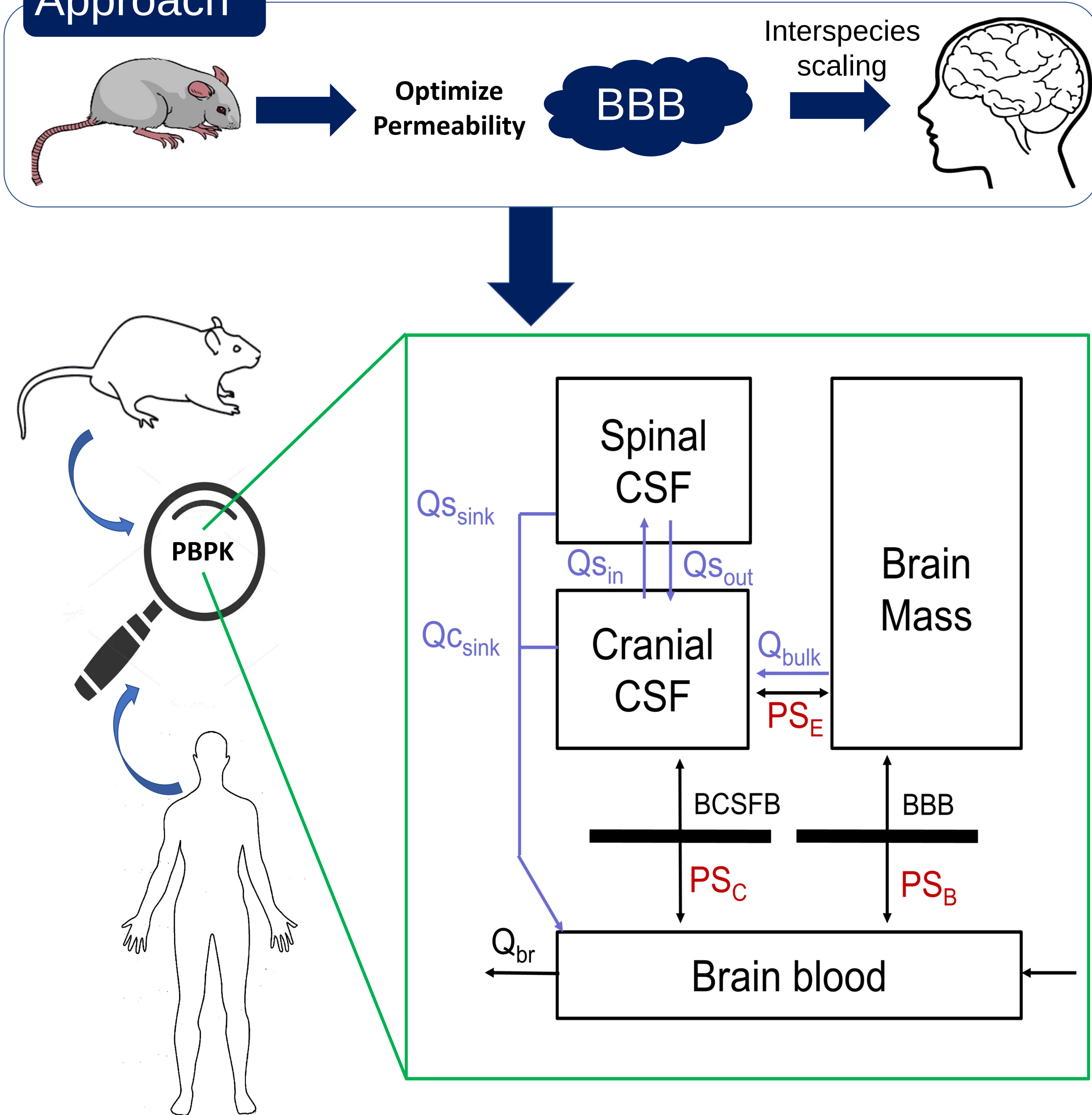
AIMS

- Characterize the permeability across the BBB using PBPK model in rats
- Evaluate the drug disposition at target site linking it to PD-Response

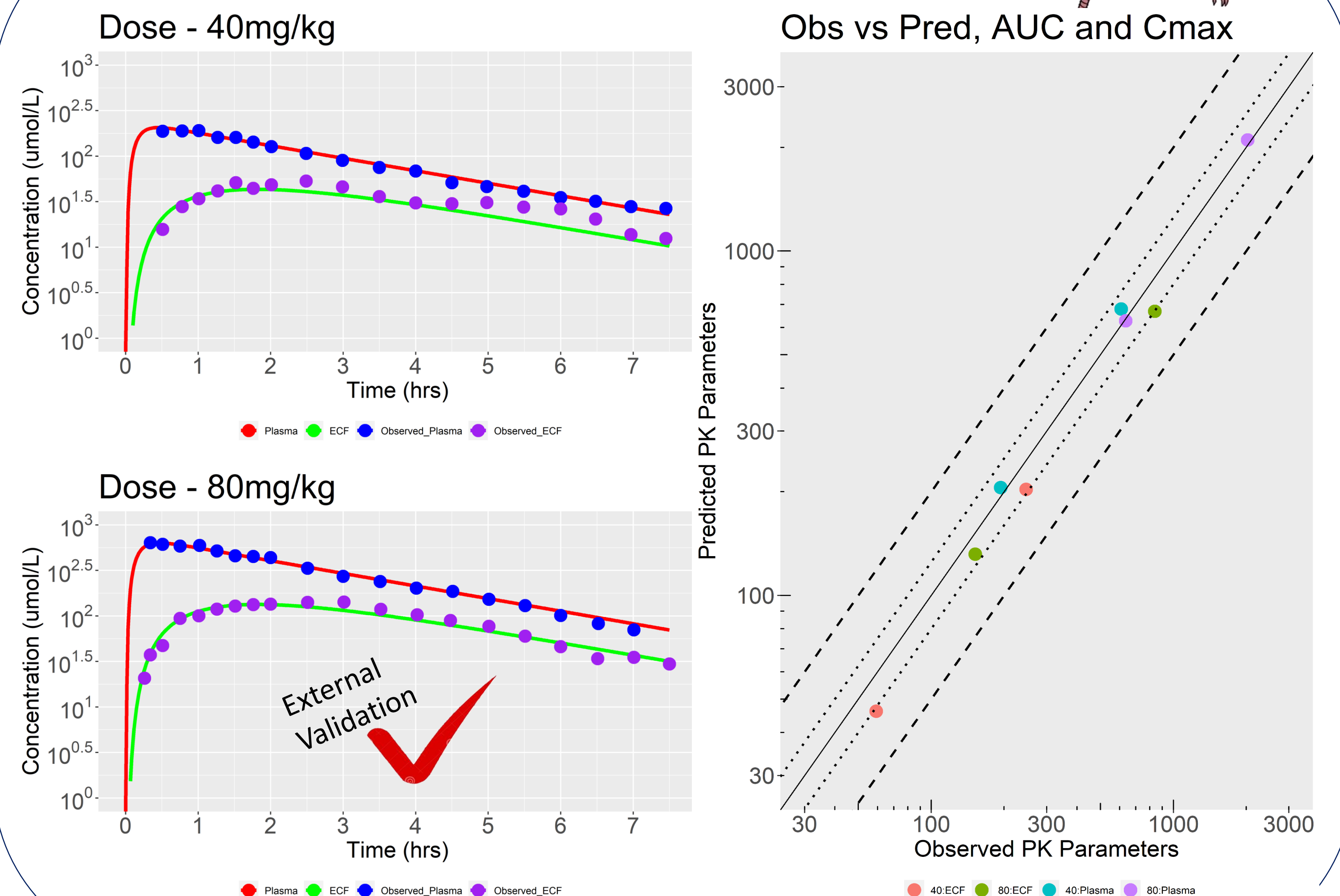
VS

Caco-2 cell permeability

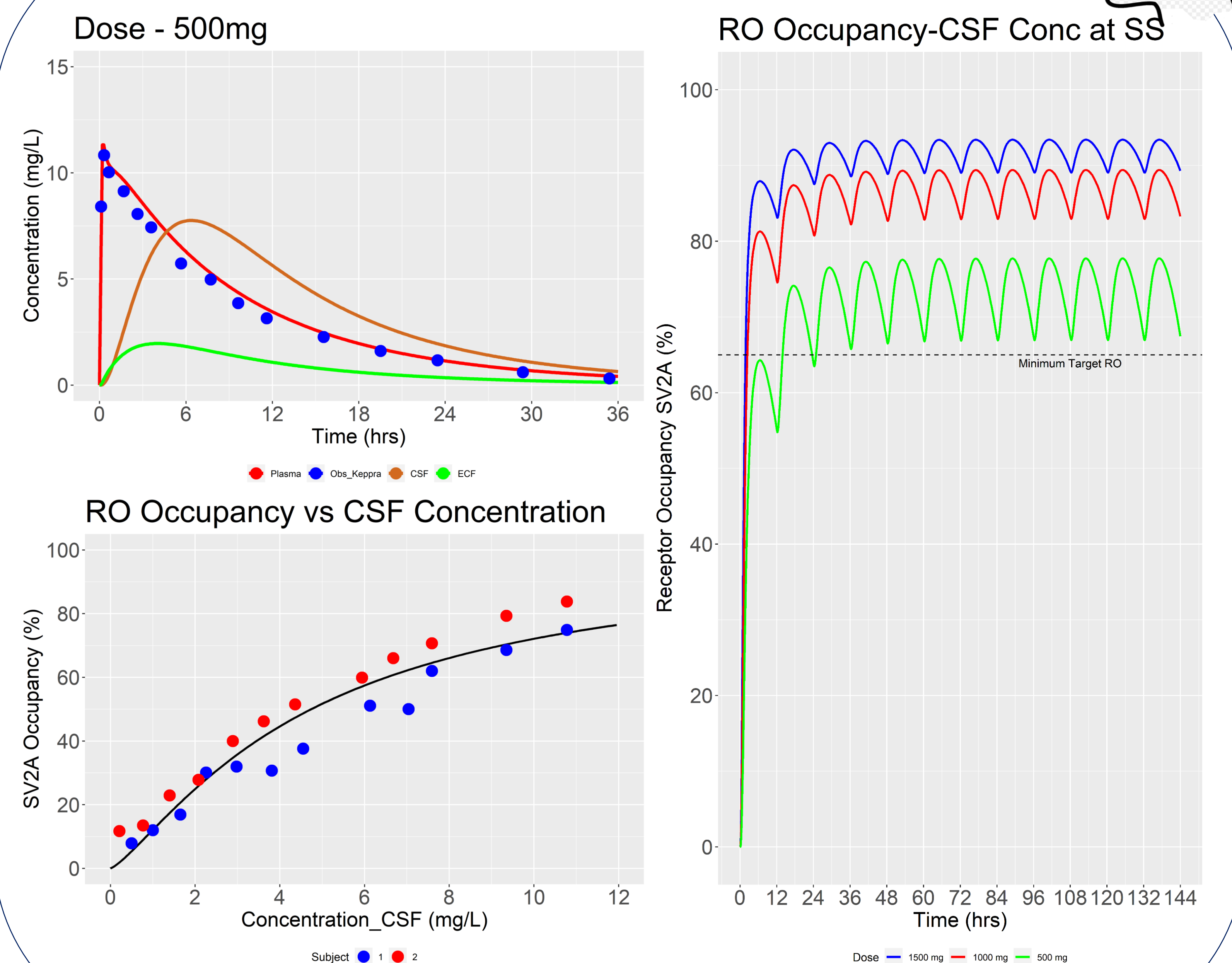
Approach



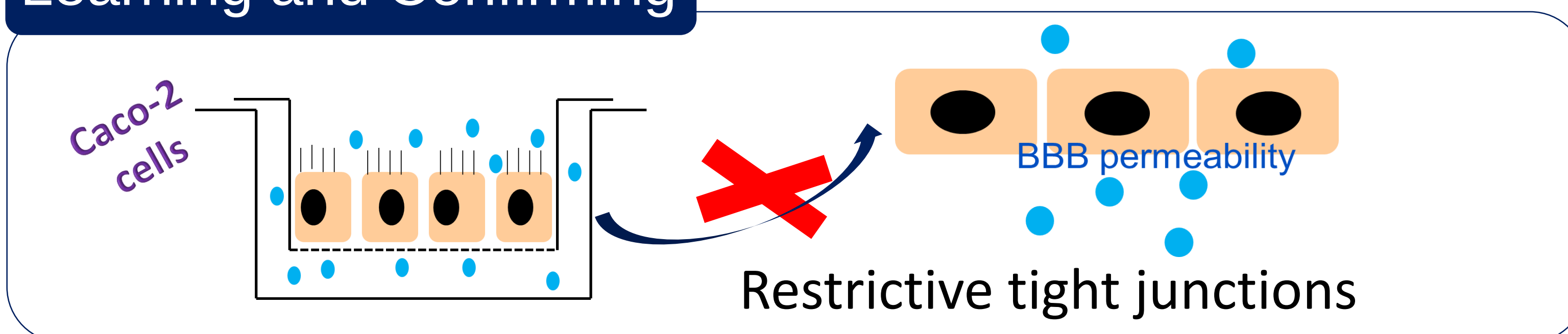
Model Development & Validation



Model Application



Learning and Confirming



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Conclusion

- Delay in CNS Concentrations -> Permeability limited model
- Caco-2 cells permeability is not indicative of BBB paracellular permeability, because BBB has tight restrictive junctions delaying levetiracetam passage
- Linking of CNS PK with the drug-target binding kinetics helps understand clinical effectiveness of various posology's
- The minimal effective dose for RO is better achieved by a dose of 1000 mg.