

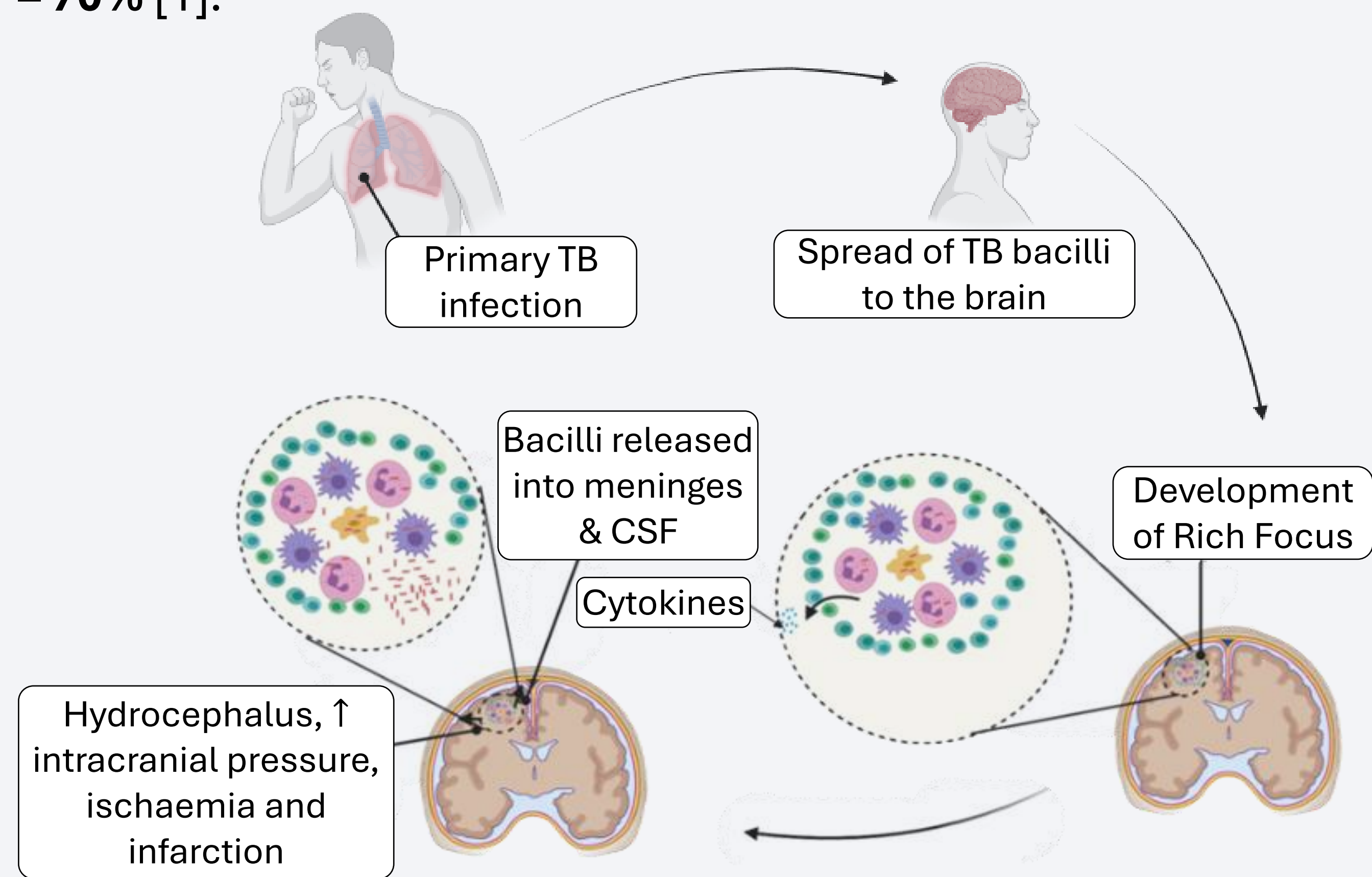


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Introduction

Tuberculous meningitis (TBM) is the most critical form of extrapulmonary tuberculosis (TB) with **mortality rates between 20 – 70%** [1].



TBM Treatment

Standard of care [2]:

- Rifampicin
- Isoniazid
- Pyrazinamide
- Ethambutol

Moxifloxacin

Achieves **high cerebrospinal fluid (CSF) concentrations**.

Strongly recommended in the context of **rifampicin-resistant TBM** [2,3].

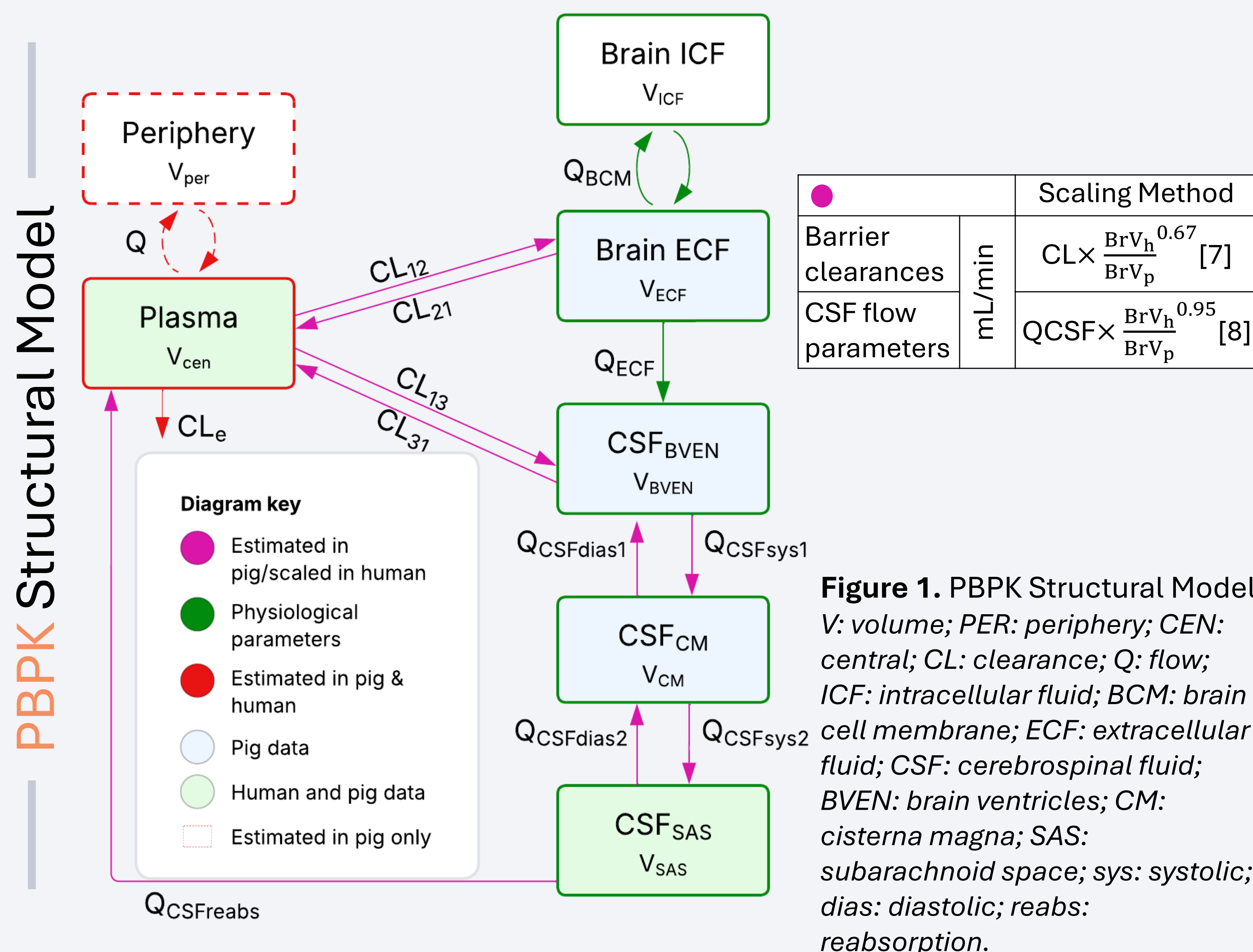
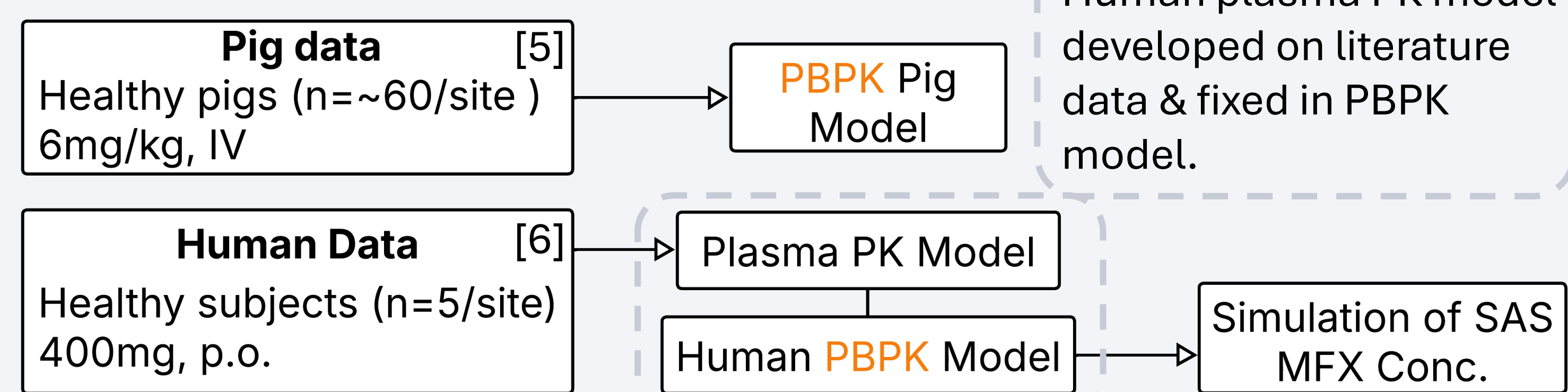
Knowledge regarding moxifloxacin central nervous system (CNS) pharmacokinetics (PK) in TBM is limited [4].

Aims

- To characterise the **CNS PK of moxifloxacin (MXF)** in **healthy pigs** using CNS PBPK modeling.
- To **translate the CNS PK of MXF from pigs to humans**.

Methods

Workflow



Conclusions

- The PBPK model provides a new **physiologically accurate** computational tool for **predicting moxifloxacin concentrations** in pigs.
- The suboptimal pig to human translation indicates **species differences** in the **flow of CSF** through the brain and **moxifloxacin transport**.

References:

[1] Dodd *et al.* PLOS Global Public. 1, 12 (2021); [2] WHO, Guidelines on Tuberculosis, (2020); [3] Lin, Front. Immunol. 15 (2025); [4] Alfenaar *et al.* Antimicrobial Agents and Chemotherapy. 52 2293–2295 (2008); [5] Mariager *et al.* Journal of Antimicrobial Chemotherapy. 79, 1313–1319 (2024); [6] Kanellakopoulou *et al.* Journal of Antimicrobial Chemotherapy. 61, 1328–1331 (2008); [7] Westerhout, Doctoral Thesis. (2014); [8] Seymour, J Exp Biol. 218, 2631–2640 (2015).

Results

Pig Model

Table 1. Pig PBPK Model Parameters

	Parameter	Estimate	RSE (%)	IIV	RSE (%)
mL	V_{CEN}	113582.81	13.8	--	--
	V_{PER}	269159.64	15.7	0.33	33.2
mL/min	Q	5088.91	30.7	0.67	37.4
	CL_e	161.67	39.7	0.55	65.0
	CL_{12}	4.26	18.9	0.33	32.4
	CL_{21}	2.98	13.2	--	--
	CL_{13}	2.27	20.0	0.42	30.0
	CL_{31}	0.78	12.6	--	--
	$Q_{CSFdias1}$	0.19	8.37	--	--
	$Q_{CSFsys1}$	0.85	21.9	0.4	30.4
	$Q_{CSFdias2}$	1.66	20.1	--	--
	$Q_{CSFsys2}$	2.42	21.0	0.37	31.5
	$Q_{CSFreabs}$	0.33	21.0	--	--

RSE: relative standard error; IIV: interindividual variability.

The 7-compartment pig PBPK model adequately describes the *in vivo* data with good precision as seen from the parameter estimates and visual predictive checks.

Validation of Human Model

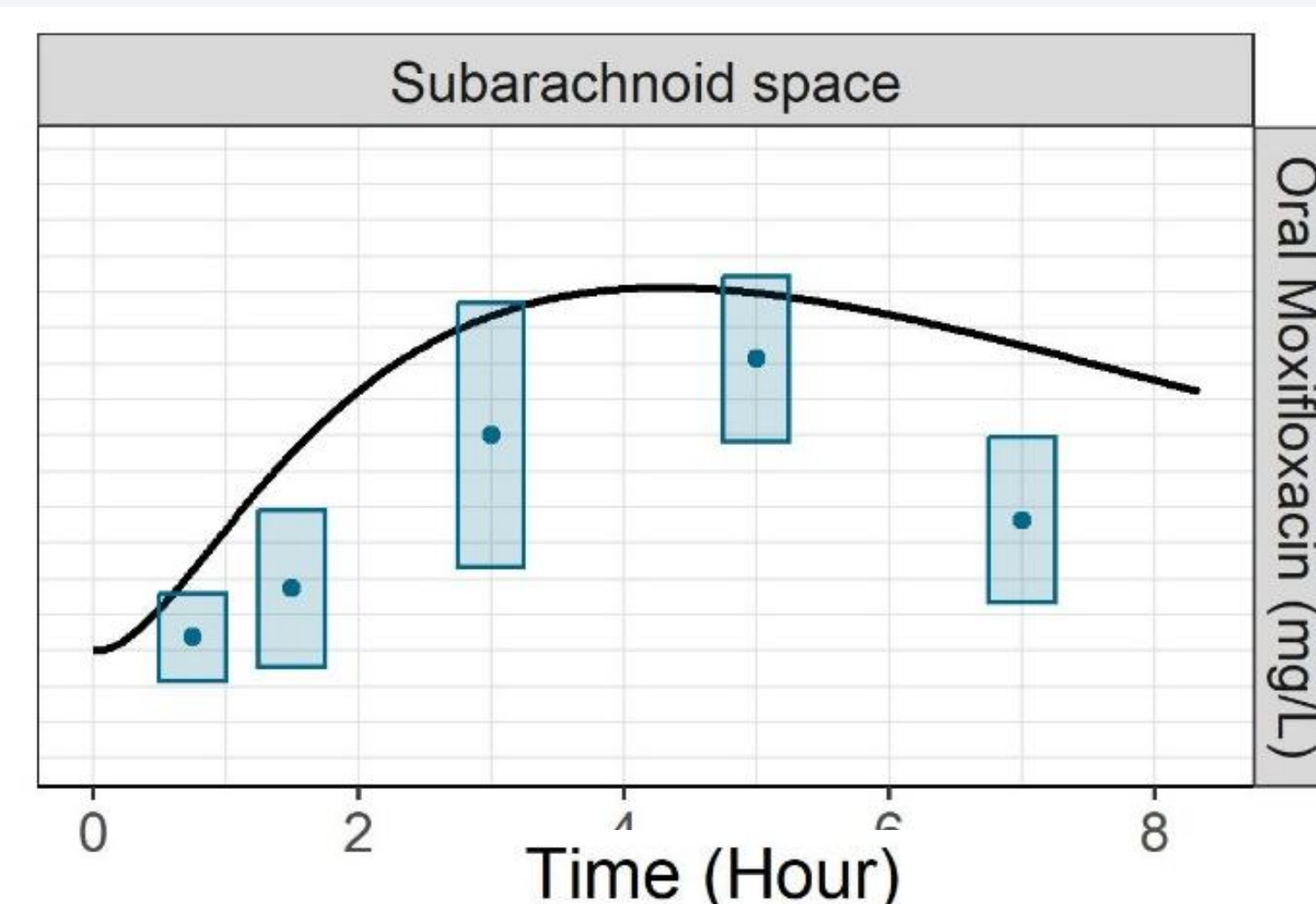


Figure 3. Prediction of PK in the subarachnoid space using the human semi-PBPK model.

The human PBPK model overpredicted CSF MXF concentrations in the SAS likely due to interspecies differences.

Pig Model Visual Predictive Checks

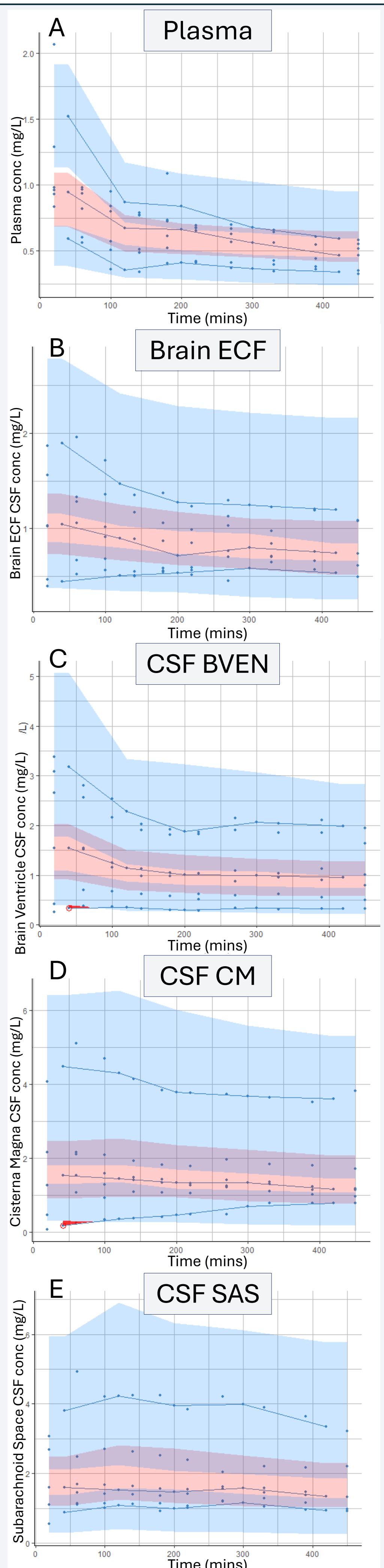


Figure 2. Confidence interval visual predictive check of the pig PBPK model in (A) plasma, (B) brain extracellular fluid, (C) brain ventricle CSF, (D) cisterna magna CSF, (E) subarachnoid space CSF

