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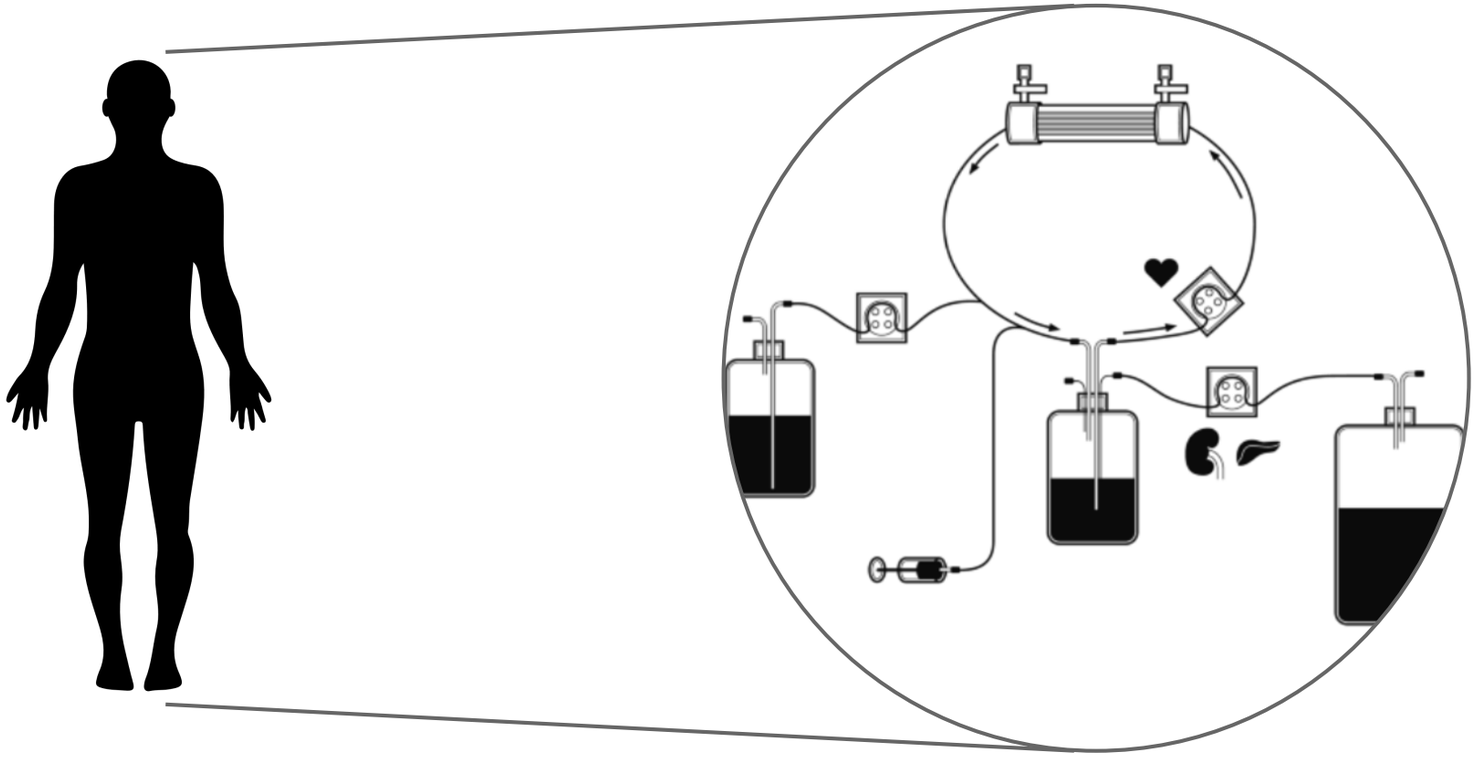
Hollow Fibre System at Evotec

Hollow Fibre Infection Model

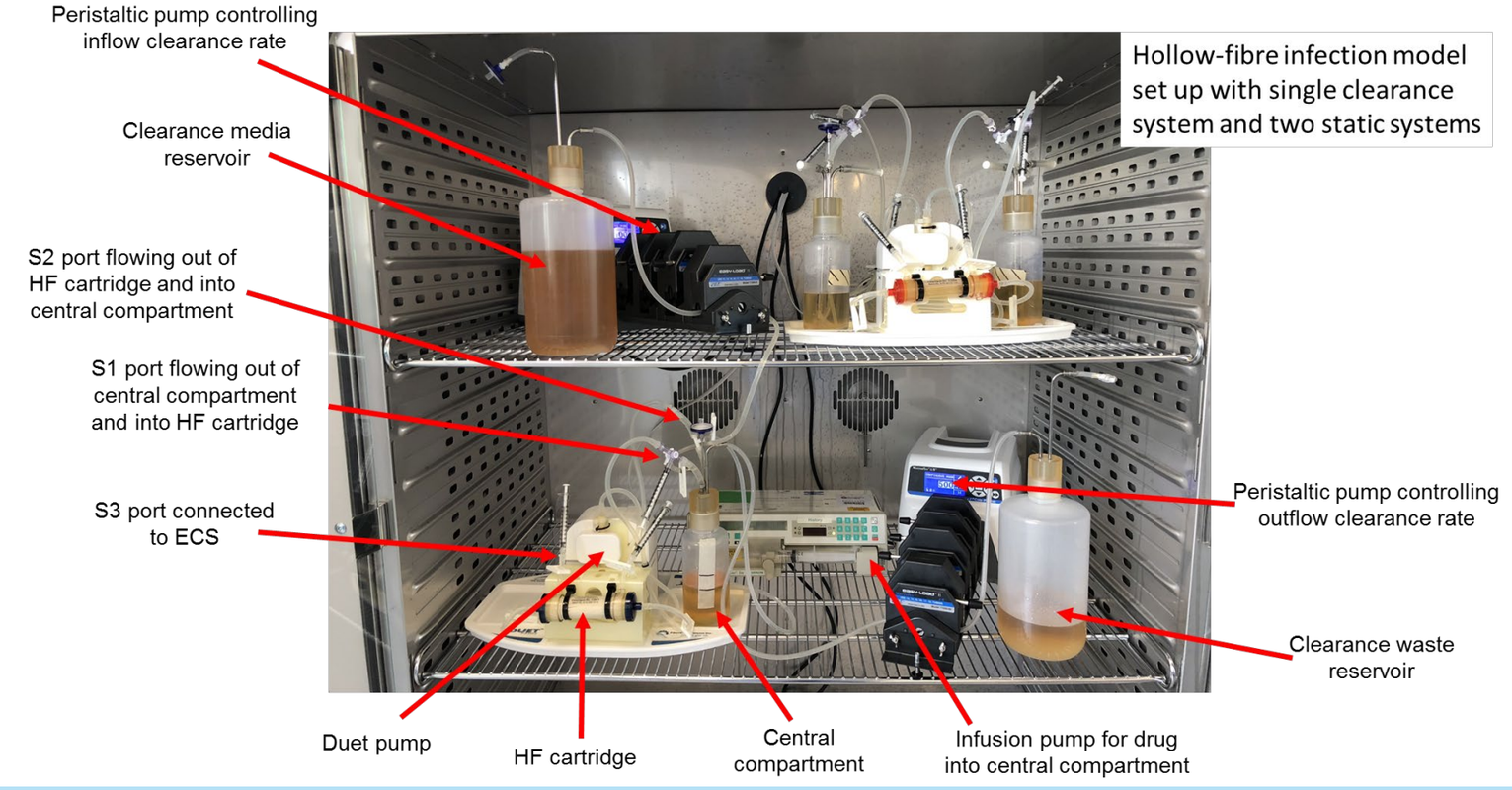
Understanding the PK/PD relationship

The Hollow Fibre Infection model is a system of pumps, tubing and microfibers that mimics the body (animal or human) and allows *in vitro* assessment of *in vivo* processes



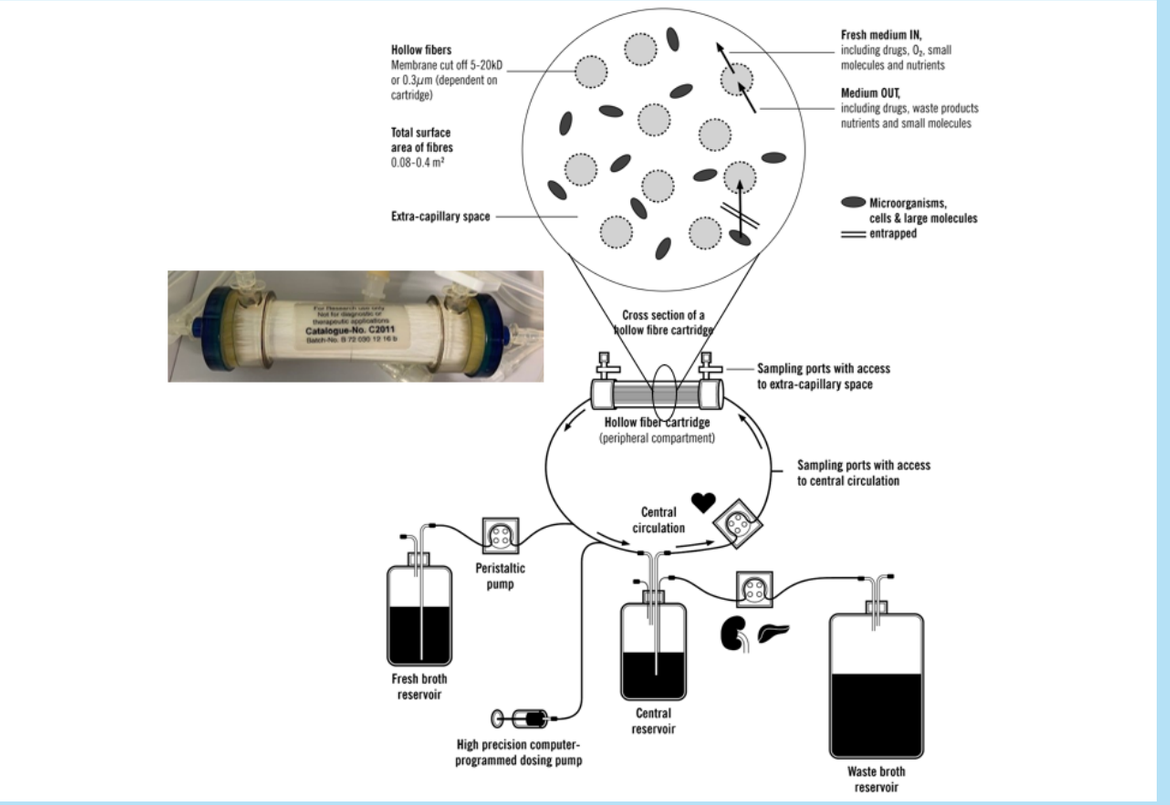
Hollow Fibre Infection Model

- Dynamic *in vitro* method to assess impact of time course of drug exposure(s) on a cell
  - Evaluation of PK/PD indices
  - Optimisation of dosing regimens for bacterial killing and suppressing the amplification of drug resistant mutants
- Can be adapted to range of organisms including strains that cannot be used for *in vivo* studies.
  - *Mycobacterium tuberculosis H37Ra*
  - *Acinetobacter baumannii*
  - *Klebsiella pneumoniae*
  - *Escherichia coli*
  - *Pseudomonas aeruginosa*
  - *Aspergillus fumigatus*



Hollow Fibre Infection Model

- Two principal compartments:
  - Central reservoir and tubing as circulating system
  - Hollow fibre cartridge with thousands of permeable capillaries
  - The extracapillary space (ECS) outside the fibres but within the cartridge housing contains the target organism
- Drug-infused growth medium in the central reservoir is continuously pumped to the hollow fibre cartridge
  - Rapidly passes through the capillaries into ECS
  - Nutrients and oxygen are continuously refreshed
  - Waste products are removed
- Drug clearance is simulated by addition of fresh medium into the central reservoir effectively diluting the drug from the system
- Balance of drug addition and drug clearance simulates PK profile

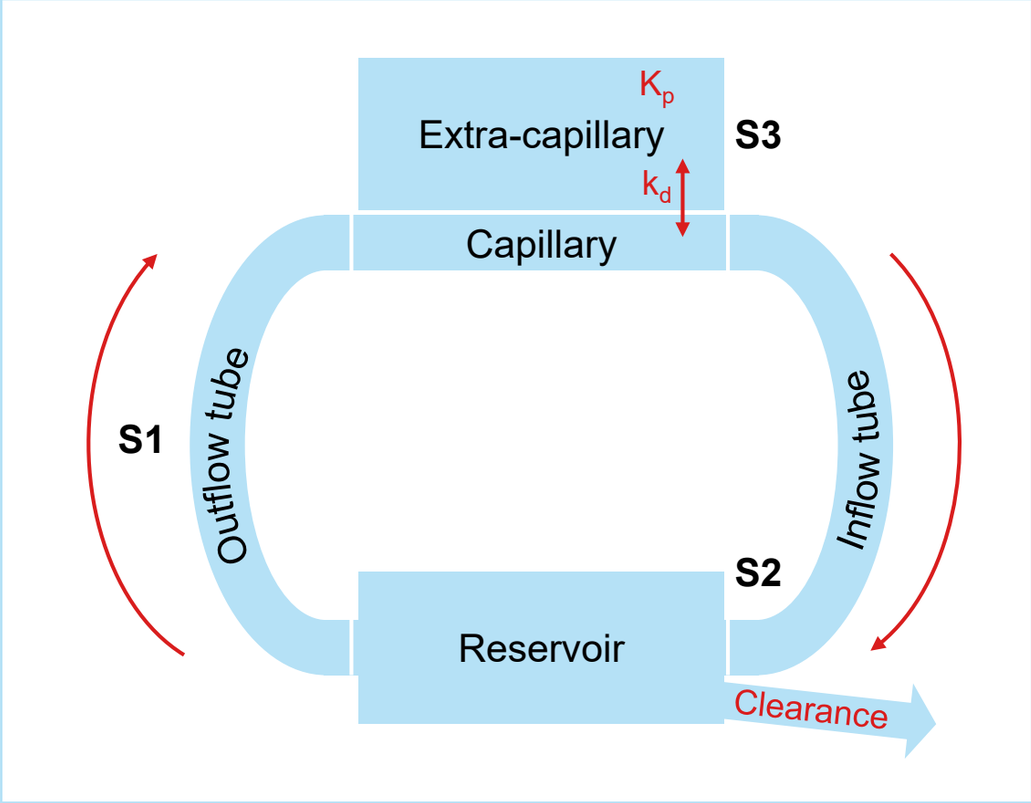


Hollow Fibre Systems

Mathematical modelling overview

Mathematical modelling support to Hollow Fibre systems provides:

- Experimental design for single- and multiple-drug experiments
  - Generation of infusion parameters (duration, rates, frequency) to reproduce specific PK profile
- Mathematical models for interpretation of pharmacokinetic and pharmacodynamic data
- PK/PD analysis



Parameters of the model

- Parameters related to physical system
  - Volumes – determined by set-up
  - Flow-rate
  - Clearance – variable, dependent on experiment
- Parameters related to the compound – optimised using experimental data
  - Partition coefficient (K_p)
  - Diffusion constant (k_d) for partitioning between capillary and extra-capillary compartments

Hollow Fibre Infection Model (HFIM)

Facilities at Evotec

- BSL 2 laboratory space dedicated to running HFIM studies
- Up to 34 cartridges[1)] can be run in parallel for different organisms, variable drug infusion and clearance rates with study duration from hours to 6 weeks
- Additional CO_2 incubator for intracellular infection
- Bioanalysis facilities for LC-MS analysis of PK samples
- Full range of microbiology support, e.g.
  - alternative endpoints
  - whole-genome sequencing and bioinformatics services to support resistance characterisation studies
  - mechanism of action determination

[1)] Depending on model type and duration

HFIM

When to use hollow fibre and what for?

1	Early screening can de-risk future experiments • Determining compatibility of HFS and novel compounds • Study PK profile characteristics of individual drugs • Early resistance studies
2	Studies at pre-clinical stage (pre-IND) to better understand the PK/PD relationship • Use animal PK profile or generate a human concentration-time profile derived from allometric scaling • Assess drugs individually as monotherapies followed by combination therapy • Dose fractionation to determine PK driver of efficacy • Resistance generation/ mutant prevention window studies by modelling multiple dose regimens
3	During clinical trials to inform trial design or build on what is already known • Perform or re-do HF studies based on human data • Collect additional data for small target population or special populations e.g. critically ill, children • Identify/confirm optimal doses and combinations for Phase II and III studies

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