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Long-acting rifapentine is efficacious in a mouse model of TB prevention

Rationale of LAI RPT for TPT

RPT is the basis for the shortest oral TPT regimens.

- WHO-recommended 1HP (1-month QD INH + RPT).
- RPT as monotherapy (6-week QD RPT) is being evaluated in the ASTERoiD trial.

RPT physicochemical properties are suitable for a LAI.

- High potency (Low MIC for *Mtb*: 0.06 mcg/mL); Low solubility (0.02 mg/mL); and Low clearance (0.03 L/h/kg).

Review of data from a paucibacillary TPT model in BALB/c mice

The model represents a stable, low-level Mtb lung infection.

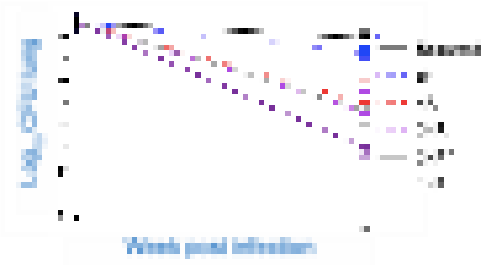
- Model generation.
  - Immunization via aerosol infection with *M. bovis* (rBCG30), followed by challenge via aerosol infection with *Mtb* (H37Rv) at 6 weeks.
  - rBCG30 immunization helps mice contain the subsequent low-dose aerosol infection with virulent *Mtb*.
- Treatment regimen is initiated at 6 weeks post *Mtb* infection.

Untreated mice inform the course of LTBI in humans (i.e., stalemate between bacteria & human host with likely reactivation in 1 to 2 years).

- Mice maintain a stable, low bacterial burden for months.
  - Bacteria exist in compact granulomas inside foamy macrophages from 6 weeks to 5.5 months post Mtb challenge.
- As mice age, some reactivate and develop more progressive disease.
  - Larger lesions with more chronic and diffuse inflammation at 7.5 months post Mtb challenge.

Treated mice inform clinical translation.

- Ranked WHO-recommended TPT regimens by bactericidal effect.
  - Informed the order of WHO recommendation: 1HP>3HP>3HR>4R>9H.
  - Provided the preclinical rationale for the BRIEF TB trial (1HP vs 9H; Swendels et al, 2019), which supports TPT shortening (1HP non-inferior to 9H).
- PKPD modeling of daily TPT regimens.
  - 1HP vs 6wP indicates INH has minimal impact on the RPT exposure-response curve.
  - Provided further rationale for the ASTERoiD trial of RPT as monotherapy (6wP).



Understanding PKPD relationships of potential LAI RPT formulations

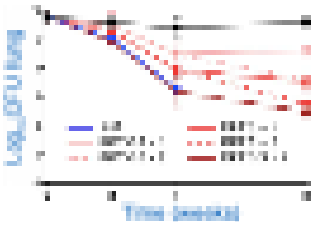
PK modeling without an available LAI formulation.

- Leveraged dynamic oral RPT dosing to simulate multiple LAI exposure profiles over 4 or 8 weeks.
  - Used de-escalating 7/7 oral dosing (7 days a week, twice per day) to simulate a LAI.
  - Modeled several dose levels administered as a SD or two doses given 28 days apart.
- Selected high, middle, and low concentration targets:

Target (day 28 and 56)	Rationale
3.5 mcg/mL	Cavg in humans receiving 1HP.
2.0 mcg/mL	In between high and low targets.
0.6 mcg/mL	Predicted day 28 conc for simulated SD RPT (750mg) IM.

- Compared predicted (RPT LAI) vs observed (1HP) exposure profiles.
  - The model overpredicted exposures somewhat and underestimated the degree of autoinduction with oral dosing.
  - SC or parenteral route might be better than oral.

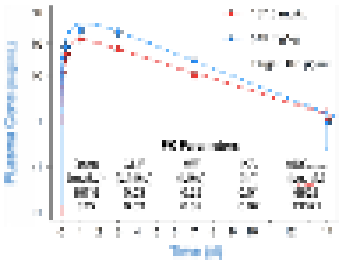
Simulated efficacy of LAI RPT exposure profiles in a TPT mouse model.



- Bacterial burden at 4 and 8 weeks (simulated LAI RPT vs 1HP).
- Identified RPT exposure profiles that may be efficacious as TPT:
  - **Two highest RPT dose levels** had similar bactericidal activity as 1HP.
  - **Two-dose schedule** sustained longer duration bactericidal activity than single dose (8w vs 4 w).

Preclinical studies of a novel RPT solid drug NP formulation

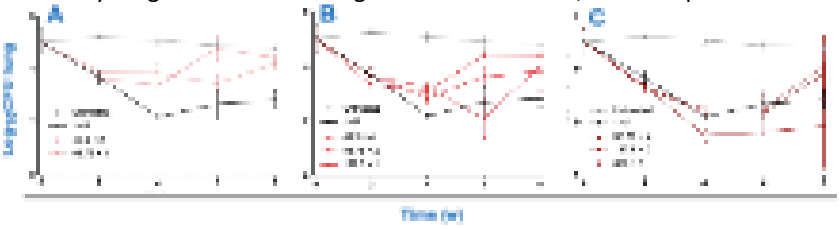
PK of single-dose RPT IM in rodents.



- Longer plasma exposure duration in rats vs mice (≥ 21 vs 14 d).
  Expect slower clearance in humans vs rats.
- Dose-linear PK (187.5 and 375 mg/kg) and terminal release-dependent,
- flip-flop kinetics in mice (see Figure).

Efficacy studies in a TPT mouse model.

- Dose-escalation and fractionation study design (LAI RPT vs 1HP or 1P).
  - Selected three total dose levels bracketing the median cAUC for 1HP (7000 mg*h/L):
    (A)93.75 mg/kg; **(B)** 187.5 mg/kg, and **(C)** 375 mg/kg.
  - Each total dose was divided into one, two, and four doses over 4 weeks.
  - Bi-weekly lung CFU counts through week 8 and in-life/terminal plasma PK sampling.



- Key findings:
  - **Dose-dependent bactericidal activity.**
  - **Trend towards superior efficacy with divided dosing** (Weekly > Bi-weekly > SD).
  - **Several regimens achieved an Emax similar to 1HP in humans.**
    Weekly LAI RPT (187.5 mg/kg); Single-dose LAI RPT (375 mg/kg); and Bi-weekly LAI RPT (375 mg/kg).
  - **Repeat, weekly doses had lower exposures than expected** (based on initial simulations).
  - Repeated injections into the mouse thigh may disrupt tissue architecture and affect drug release. PK study was repeated and PKPD modeling is underway.

Conclusions and next steps

- **Provided proof of concept** for a LAI RPT formulation to achieve efficacy comparable to 1HP in a validated TPT mouse model**.**
- **Preliminary scaling data** suggest the feasibility of achieving effective RPT exposures in humans for ≥28 days after a single dose of LAI RPT**.**
- **Work is underway** to further characterize the PK for repeat dosing in mice and enable PKPD modeling and human dose projections**.**
- **GLP toxicology studies** are planned to support first-in-human studies.