Andrew Owen, Director of CELT at University of Liverpool
Progress and challenges in development of LA medicines for TB treatment and prevention

LONGEVITY is developing solid drug nanoparticles for IM injection.

Overview of LAI TB drug development

Targets.

- TPT is the most plausible short-term goal. Single-dose LAIs are feasible.
  - Evidence supports shortened regimens and monotherapy: BRIEF-TB trial (1HP non-inferior to 9H) and ASTERoiD trial (Rifampicin alone).
- TB treatment is complex, but potential LA benefits are profound.
  - Long (>6m), multi-drug regimens are required, particularly for DR-TB.
  - Incomplete adherence is a major obstacle to TB elimination – Increased time to culture-negative conversion; Increased resistance; Longer treatment.

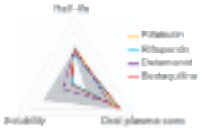
LAT selection for TB.

- Certain LATs may be more appropriate in certain populations. **Prenatal, perinatal, adolescent, and pediatric populations should be prioritized.**
- Key comparators:

IM Injection	SC Injection	Transdermal MAP	Subdermal Implant
• Higher dose/volume • Clinic Visit required. • Example: CAB LA	• Lower dose/volume • Possible Clinic Visit • Example: LEN	• Lowest dose • No Clinic Visit required. • Example: None	• Lower dose • Clinic Visit required. • Example: Contraception

- Unique aspects of LAI approaches, independent of route.
  - Most leverage flip-flop kinetics. When the rate of absorption is slower than rate of elimination, half-life becomes dependent on drug release (i.e., “drug release-dependent half-life extension”).
  - High metabolic stability for long exposures (LEN).
  - Unprecedented potency for very long duration (ISL).

TB drug selection for LAI delivery is based on similarity to existing LAI products (Int J Tuberc Lung Dis 2018).



- Identified key API components for LAI delivery.
  Water solubility; Half-life; and Target concentration.
- Used triangles to map the range for successful LAIs. **Grey shaded area.**
- Screened all available TB drugs. **Rifamycin, delaminid, and BDQ are compatible.**
- Developed a PBPK model to simulate the release rate required to achieve a LAI target (Advanced Drug Delivery Reviews 2016). **Defined release rates for LAI delaminid, INH, rifabutin.**

LAI solid drug particle suspensions

Characteristics of successful LAIs.

- Large API mass can be loaded into a small aqueous volume.
- Dosage form is syringeable using an appropriately sized needle.
- **Low aqueous solubility is the key to half-life extension**.
  - Low solubility rarely means no solubility: Drug particles are suspended in a saturated drug solution, which has implications for drug release.
  - Particle suspension leads to slow drug dissolution, which manifests release-dependent half-life (Ka < Ke).

Particle suspensions cannot be developed for drugs with high solubility (forms drug in solution).

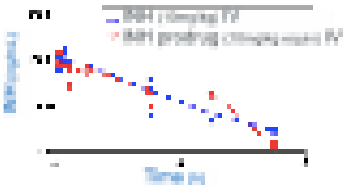
Challenges in development of LAIs

<u>Drugs with higher aqueous solubility.</u> Need methods to optimize LAIs based on drug particle suspensions.

- Preclinical example of prodrug derivatization to optimize LAI ARVs for HIV.

- FTC prodrug nanoparticle suspensions achieved 20-fold half-life extension and fully protected humanized mice from HIV exposure for 14d.
- Rapid hydrolysis is highly desirable when repositioning existing oral drugs.

- ***Prodrug strategy may work for INH.***
  - Initial studies of a novel INH prodrug (developed by JHU-CHAI under LONGEVITY) confirm rapid hydrolysis of unformulated prodrug to release INH.
    - Prodrug fully converted to INH within 10 min in rat, mouse, and rabbit plasma (*in vitro*).
    - Prodrug was undetectable in mice after IV dosing.
    - Kg-scale synthesis has been optimized (CELT); Preclinical evaluations are underway.



<u>Inactive ingredients.</u> Even though FDA GRAS excipients are used, LAIs require higher doses than approved products (to stabilize the large API mass needed).

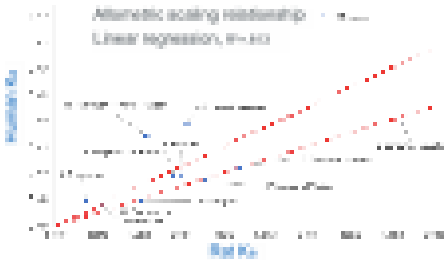
- Toxicity of a novel LAI RBT formulation is attributed to an inactive ingredient.
  - Severe ISRs were observed in rats after RBT-LAI.
  - A novel primary muscle cytotoxicty assay implicates an inactive ingredient.
- ***HuSKMC cytotoxicity assays may offer a rapid tool for excipient selection.***

<u>Reliable in vitro-in vivo correlation (IVIVC) for LATs</u> is needed to accelerate development and reduce animal use.

- A priori predictions of *in vivo* exposure profiles for nine LA materials did not reliably match PK studies, revealing a knowledge gap (e.g., FTC).
  - IVIVC was based on convoluting *in vitro* release kinetics with IV PK disposition.
  - *IVIVC accurately predicted the ranked-release rate and PK exposure of FTC in rats; No scaling factor was identified for robust in vitro-in vivo extrapolation across LATs.*
- ***Need to further develop in vitro methods for better in vivo prediction.***

<u>Animal-to-human scaling of LAI PK</u> is needed to better predict human dosing, guide decision-making, and accelerate P1 development.

- Half-life of IM LAIs differs across species (e.g., CAB and RPV).
  - We sourced matched rat and human data for 11 IM LAIs (publications and in-house studies) and determined release rates from flip-flop kinetics.
  - PK half-life in mice < rats < humans.
  - Implications for paucibacillary mouse model.
- ***Species-specific algorithms are needed for scaling preclinical PK.***
  - Combined dataset enabled initial investigation of two approaches:
    - Linear regression (human Ka vs rat Ka).
    - Allometric scaling of Ka by body size (predicted human Ka = rat Ka x 0.255).
  - Found reasonable concordance of human PK projections for CAB & RPV (Assuming 50% and 100%F, respectively).
  - Validation requires a priori application for a novel LAI.



Forward implementation of learnings:

LEAP Modeling and Simulation Core services.
(https://www.leapresources.org/content/use-our-services).

TEORELER web based PBPK modeling application.
(https://www.liverpool.ac.uk/centre-of-excellence-for-long-acting-therapeutics/teoreler/).