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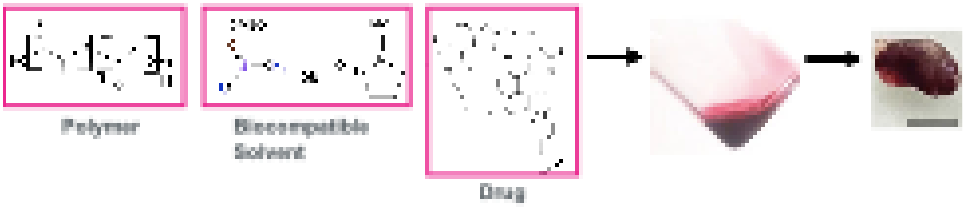
Long-acting formulations based on ISFIs for TB

"LA rifabutin was our first foray into the TB field."

In situ forming implant (ISFI) technology

Process is simple and scalable:

- Prepare a liquid suspension comprising three key components (pink).
- The suspension forms a solid after injection into the body.



Many clinical examples of long, efficacious drug release.

- Successful delivery of single, double, and triple drug combinations for HIV has inspired development for TB.

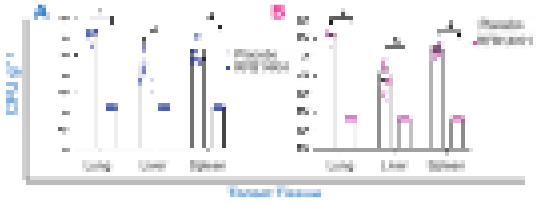
Multiple parameters are easily modified for any given drug to generate a formulation with desired drug delivery.

- Polymer molecular weight (MW). Higher MW increases or decreases the initial burst release of hydrophilic or hydrophobic drugs, respectively.
- Polymer concentration. Lower concentration increases the initial burst release.
- Drug load. Higher load increases initial burst release.
- Polymer composition, polymer end group, solvent type, and additives. Affect the release profile of any formulation.

Previous work on LA RFB formulations

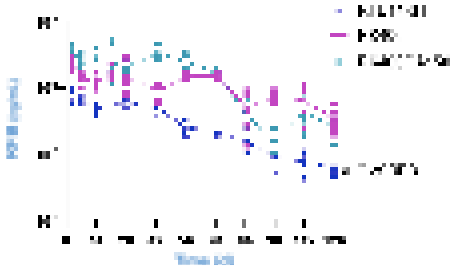
Preclinical studies of initial formulations (RFB14 and RFB14KH).

- Long duration *in vivo* drug release.
  - Both formulations release RFB and maintain plasma concentrations above the MIC for Mtb ≥16 weeks.
- Efficacy of RFB14KH for *Mtb* prevention and treatment in mice.
  - Pre- **(A)** and post-exposure **(B)** dosing demonstrate significant bactericidal activity in Mtb tissue targets at day 28 vs placebo.



RFB14KH modification generates new formulations with improved PK (RK400, RK400OA150).

- Increased drug delivery enables preclinical PK translation from NHPs to humans.
- **RK400OA150** > **RK400** > **RFB14KH**.
  $AUC_{RK400OA150} > AUC_{RFB14KH}$ (5.2-fold; p<0.0001)
  $AUC_{RK400} > AUC_{RFB14KH}$ (3.5-fold; p<0.0001)
  $AUC_{RK400OA150} > AUC_{RK400}$ (1.5-fold; p=0.0003)



LA Delamanid formulations

Rationale for delaminid (DEL).

- Effective anti-TB agent developed for MDR-TB (FDA approval in Aug 2017). Inhibits synthesis of mycobacterial cell wall components.
- Low MIC for *Mtb* (12.5 ng/mL).

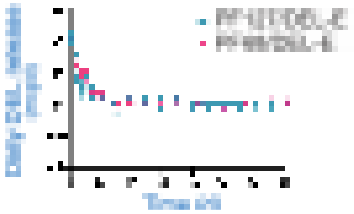
- PK studied in three species (mouse, rat, and dog).

Prepared several DEL formulations.

- Liquid suspensions are transportable and all form solid implants.

Favorable in vitro drug release (PF127/DEL-E and PF68/DEL-E).

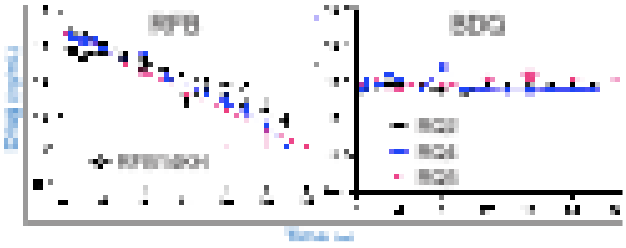
- Both formulations release delaminid and sustain conc >100-fold above the MIC for *Mtb* for ≥ 98d.



LA multi-drug delivery systems

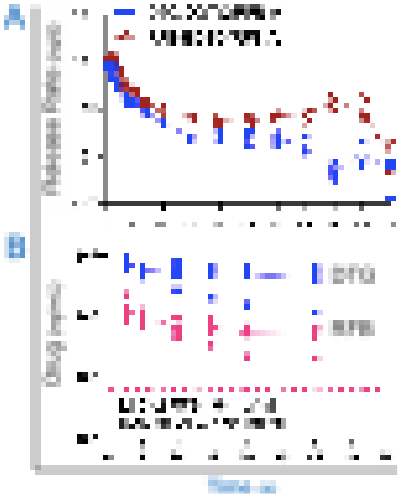
Two-in-one drug formulation for TPT and TB treatment.

- Considerations for pairing RFB and BDQ.
  - Different mechanisms of action. RFB inhibits bacterial RNA synthesis; BDQ inhibits mycobacterial ATP synthase.
  - Different MIC, half-life, logP, and solubility. DMSO is the best solvent for RFB; NMP is the best solvent for BDQ.
- Prepared several RFB/BDQ co-formulations (RQ1, RQ2, RQ3, RQ4, RQ5).
  - Liquid suspensions form solid implants.
- Individual drug release (*in vivo*).
  - RFB was released. PK was similar to the single-drug formulation (RFB14KH).
  - BDQ was not released. Failed drug release drug was observed with initial delaminid formulations and is fixable.
  - Further formulation work is needed. To modify drug release properties.



Two-in-one drug formulation for TB and HIV prevention.

- Considerations for pairing RFB and Dolutegravir (DTG).
  - DTG is a second generation INSTI with a lot of clinical experience and is expected to come out of patent in a couple of years.
  - There is a theoretical concern that RFB could interfere with DTG concentrations.
- DTG/RFB co-formulation (DTG/RFB-A).
  - Liquid suspension is injectable with a 19G needle and forms a solid implant.
- Individual drug release.
  - *In vitro* (A).
    - Both drugs are released from the polymer.
    - RBT and DTG have similar release kinetics.
  - *In vivo* (B).
    - DTG and RFB remained >64 ng/mL ≥42 days.
    - **RFB did not impact DTG concentration.**
    - Individual drug release from the co-formulation matched published PK data for the single-drug formulations (RFB14KH and ULA-DT).



Acknowledgements:

Manse Kim engineered all formulations; UNC shared the technology; CSU is the partner institution.