Rodney Ho, PI at Univ of Washington

"Targeted Long-acting combination Antiretroviral Therapy (TLC-ART) Program – update"

TLC-ART program transforms multiple oral HIV drugs into an all-in-one LAI drug combination product for HIV treatment.

Approach.

- Defined *synchronized tissue and cell drug targets* (lymph nodes and lymphocytes) for sustained viral suppression (TPP).
- Developed *fit-for-purpose, enabling technology* to combine multiple HIV drug substances into a stable, injectable drug-combination suspension product (multiple HIV drugs are required for sustained viral suppression).
- Created *innovative strategies* to accelerate research and development.
- Sought *Preferred User Characteristic* studies to understand national and international differences among patients, payors, implementers, and healthcare providers.
- Developed *private-public partnerships* to support the program (donating API, funding, project participation).

Innovations.

- Drug-combination nanoparticle (DcNP) platform discovery: DcNP technology enables APIs with disparate physicochemical characteristics to be packaged in a stable all-in-one suspension product for an injectable dosage form (e.g., enables LPV, RTV, and TFV to be packaged into a single SC injection).
- Regulatory pathway: We leverage current HIV drugs with bracketed safety and efficacy data and early FDA input to accelerate IND-enabling planning.

First proof of principle – TLC-ART 101 (LPV/RTV/TFV) is in Phase 1.

DcNP technology enabled production of a stable, injectable LPV/RTV/TFV dosage form.

- Innovation needed to combine LPV (hydrophobic), RTV (hydrophobic), and TFV (hydrophilic).
- We developed the know-how to make a unique multidrug domain matrix (MDM) via spray drying technology and facilitated by lipid excipients.
    - Chemical/physical interactions form stable LPV/RTV/TFV compositions in a dry powder.
    - After re-suspension and size reduction at high temperature, the cooled nano sized product is well-suspended and stable *in vitro* and *in vivo.*

We leveraged IND-enabling strategies to accelerate development.

- FDA-guided regulatory pathway; DAIDS-supported safety and toxicity studies; and TLC-ART 101 manufacturing under cGMP.

P1 study in healthy volunteers (NCT06850728).

- Safety, tolerability, and LA mechanism of single-dose SC TLC-ART 101 (LPV 15.6/RTV 4.1/TFV 9.2mg in 1.5mL); reference is QD oral dose (LPV 800/RTV 200/TFV 300mg).
- Initial 57-day study (n=4): no safety signals; good tolerability; and LA PK properties.
- Study lengthened; dose-escalation cohort is ongoing.

NextGen products – GLAD project is focused on transforming QD oral TLD to QM injectable TLD (TLC-ART 301) for HIV treatment in LMICs.

TLC-ART 301 (Tenofovir/Lamivudine/Dolutegravir) combines first-line HIV drugs of global interest.

- We leveraged the same DcNP injection platform used to produce TLC-ART 101, with slight modifications, to package TFV (hydrophilic), 3TC (hydrophilic), and DTG (hydrophobic) into a stable nanoparticulate product (AIDS 2023).
- A single SC injection replaces the monthly pill burden of daily oral TLD (30 pills, 19.5g TLD).
- The DcNP formulation allows a synchronized fixed-dose combination for collective drug exposure, instead of producing different PKs intrinsic to each API (e.g., Cabenuva [LAI CAB + LAI RPV] produces different PKs for CAB and RPV).

Accelerated regulatory pathway.

- Treatment indication is drug combination repositioning, not repurposing.
- Existing safety data for each API allows quick advancement through the regulatory process and standard safety studies.

PBPK modeling approach to advance TLC-ART 301 into clinical studies – scaling from NHP models to humans and children across different age brackets.

Developed and validated a PBPK model to understand the unique physiologic and PK mechanisms of DcNP LA products.

- Modeled the cell and tissue targets of DcNP products (lymphocytes, lymph nodes, and lymph system).
- Defined characteristics of different LA mechanisms for PBPK modeling (CROI poster #947).
  - Class 1 (LAI CAB and LAI RPV): Depot sustained release at injection site with fast uptake to blood.
  - Class 2 (LPV/RTV/TFV in DcNP SC injectable): Fast uptake to tissues, slower lymphatic distribution, then to blood.
- Validated the model in NHPs using TLC-ART 101 (LPV/RTV/TFV) IV and SC.
  - DcNP product remains associated with water-soluble (TFV) and insoluble drugs (LPV/RTV) *in vivo.*
  - Unbound drug removal unnecessary for DcNP manufacturing.

The validated PBPK model supports pediatric dosing across age brackets.

- Modeling across age bands accounts for differential development of the liver and kidney and flow rate.
- PBPK dosing vs weight-band dosing.
  - PBPK predicted doses of LPV, RTV, and TFV in TLC-ART 101 tend to be lower than purely weight-based doses, particularly in younger children.
- May get closer to finding the most suitable fixed-combination formulations for pediatrics and drive development.

Summary

- DcNP technology has advanced TLC-ART 101 and 301 – provides a scalable, simplified, validated process to produce drug combination products for HIV.
  - TLC-ART 101 (LAI LPV/RTV/TFV) has progressed to P1 – multi-dose, dose-escalation studies are ongoing.
  - TLC-ART 301 (LAI TFV/3TC/DTG) is proceeding at accelerated pace – TLC-ART 301 in NHPs supports SC dosing.
- Treatment indication of repositioning accelerates development.
  - Current HIV drugs may be developed through a 505b2-like pathway.
- PBPK model development and validation may help accelerate pediatric drug development and access.