CPRIT-funded Preclinical Development Core for Large Molecular Therapeutics

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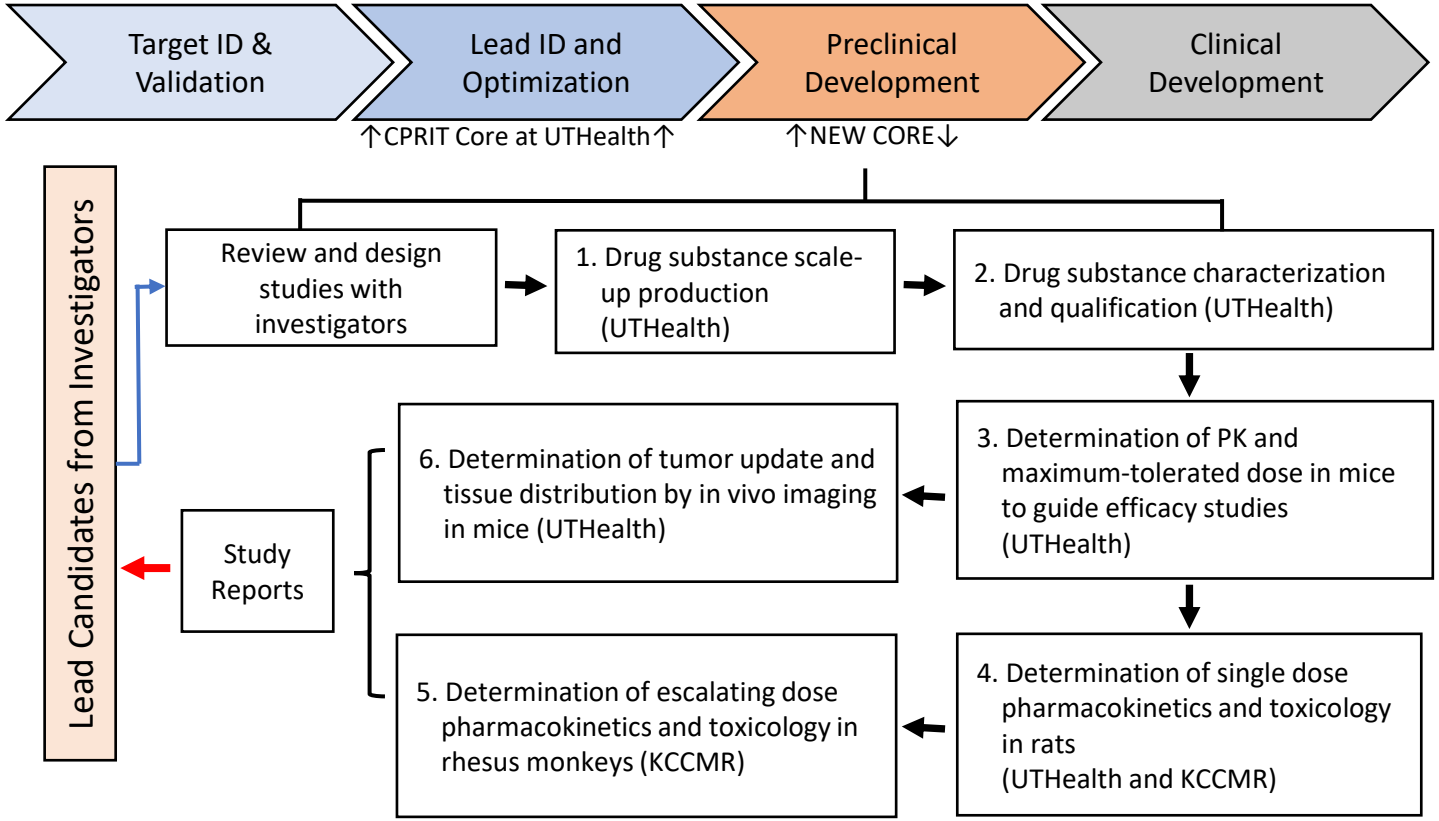
CPRIT-Funded Core for Preclinical Development of Large Molecule Therapeutics



- UTHealth-Houston: University of Texas Health Science Center at Houston.
- KCCMR: Keeling Center for Comparative Medicine and Research, The University of Texas MD Anderson Cancer Center.

Co-investigators and Responsibilities of the Core

- Dr. Qingyun “Jim” Liu @UTHealth:
  - PI and overall responsibility
- Dr. Zhiqiang An @UTHealth and Dr. Ningyan Zhang @UTHealth:
  - Scale-up production and characterization.
- Dr. Kendra Carmon @UTHealth:
  - PK and Tox study in mouse and rats.
- Dr. Rich Finch @KCCMR and Dr. Kathryn Shelton @KCCMR:
  - PK and Tox study in rhesus monkeys.
- Dr. Ali Azhdarinia @UTHealth
  - In vivo imaging in tumor-bearing mice.

Drug candidate Application and Selection

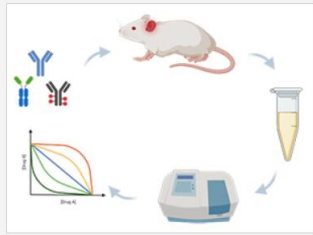
- **Selection Criteria:**
  - Large molecule therapeutic leads that have demonstrated robust efficacy in tumor models.

- **Candidate Application:**
  - Website outlining capabilities and detailed selection criteria. (https://www.uth.edu/imm/core-facilities/lmpd-core/index.htm)

- **Candidate Selection:**
  - Applications will be reviewed by the core co-investigators and selected in discussion with applicants.

Welcome to the Preclinical Development Core for Large Molecule Therapeutics (LMPD Core)

Large molecule therapeutics, such as antibodies and other protein-based drugs, has become the major modality of oncology treatments. Discovery and development of drug candidates require detailed characterization of the candidates in pharmacokinetics (PK) and potential toxicity (Tox, also known as safety assessment) in designated animal species, a process called preclinical development. Understanding of PK and Tox is essential for the advancement of the candidates intoclinical trials.



The LMPD core, funded by the Cancer Prevention and Research Institute of Texas (CPRIT) is a joint operation of the Brown Foundation Institute of Molecular Medicine (IMM) of the University of Texas Health Science Center at Houston (UTHealth) and the Michale E. Keeling Center for Comparative Medicine and Research (KCCMR) of the University of Texas MD Anderson Cancer Center. Our mission is to provide preclinical development support free of charge to cancer researchers at Texas, including scale up production and characterization of drug candidates, PK and Tox analysis in two animal species, and in vivo imaging and biodistribution.

See our services

Study Implementation, Deliverables and Cost

- **Study Implementation**
  - Confirm funding and commitment from investigators
  - Establish confidentiality agreement with investigators if necessary.
  - Design studies and establish go-no-go criteria with investigators
  - Define timeline and deliverables

- **Deliverables:**
  - Study reports and clinical findings with investigators

- **Cost:**
  - Free for accepted candidates from investigators inside Texas, either academic or commercial entities.
  - Investigators may need to cover certain material cost, such as antibody-drug conjugation.

Scale-up Production and Characterization of Drug Candidates

- Candidates entering PK and Tox studies in large animals must be produced in large quantities with high purity and endotoxin at a minimum level.
- Will use transient transfection of freeStyle™ or Expi293F™ cells to purify sufficient quantity of protein drug candidates.
- Drug conjugation or other modifications if necessary will be completed by by the PI of the candidate.
- Purified drug candidates will be analyzed for purity, solubility, aggregation, stability, and glycosylation using SDS-PAGE, FPLC, and/or LC-MS, as well as antigen binding affinity by receptor binding, ELISA and/or BLI (bio-layer interference) assays.
- Endotoxin will be removed to levels below the limit of monkey tolerance (<5EU/kg).
- Large molecule drugs are generally soluble in PBS and they will be formulated in PBS and sterilized before in vivo use.

PK and MTD (Maximum-Tolerated Dose) Determination and In vivo Imaging

- **PK and MTD determination in mice**
  - Develop specific assay to measure drug candidate concentration.
  - Drug candidate will be administered into host animals of tumor models (e.g. athymic nude mice) and blood will be collected at 1hr, 2hr, 4hr, 24hr, 2d, and 4d for PK analysis.
  - Animals will be observed for body-weight and adverse clinical signs
  - The dose without severe toxicity judged by body weight loss (<10% or specified otherwise) and adverse clinical signs will be considered MTD.
  - Drug levels (total ADC and free antibody if it is ADC) in the blood will be determined using the developed assays.
  - PK and MTD data will be provided to the investigators timely for the design of efficacy studies in dose selection and dosing frequency.

- **In vivo Imaging in tumor models**
  - Drug candidates will be labeled with radionuclides used for positron emission tomography (PET) or single-photon emission computed tomography (SPECT)
  - Whole-body imaging will be performed up to 7 days post-injection to determine uptake levels of the labeled drug candidates in target and off-target tissues.

Standard 2-week Non-GLP Toxicology Study in Rats

- Drug candidates will be dosed into rats by IV at three levels (exact doses are to be determined), 6 animals (3M/3F) per level, plus a vehicle control group.
- Animals will be monitored for body weight and general well-being.
- Blood will be collected at Day -1 (pre-dosing and at termination for drug level, blood cell count, clinical chemistry (liver enzyme, etc.).
- At termination (Day 14), all major organs will be collected and fixed, followed by sectioning and histopathology examination by veterinary pathologies.
- All PK data and Tox findings as well as the NOAEL (No Observed Adverse Effect Level) will be provided to investigators in detailed study reports.

Non-GLP PK and Toxicology in Non-Human Primates (NHP)

- Drug candidates that passed the safety test in rats will be considered for PK and toxicology study in rhesus monkeys.
- Monkey study will be carried out at the Keeling Center for Comparative Medicine and Research (KCCMR), the University of Texas MD Anderson Cancer Center.
- Drug candidates will be dosed by IV in 2 animals (1M/1F) in an escalating fashion (dose level to be determined) and monitored for body weight and adverse clinical signs. Blood will be collected for drug level, CBC, and clinical chemistry.
- If no major adverse effects are observed, the animals will be dosed at 2x of the first dose and measurement will be repeated, and this will be repeated by another 2x dose.
- If animals are terminated due to adverse effect, all major organs will be collected for histopathology examination.

PCDH7 Antibody Rat Tox Study

Project Investigators:

Dr. Kathryn O'Donnell, UT-Southwestern

Dr. Ningyan Zhang: UTHealth-Houston

Study Overview

- SD rats, 4 groups: 0, 10, 25, and 50 mpk; 3M/3F per group
- Pre-bleed on day 0 for CBC and serum chemistry.
- Single dose by IV.
- Staggered dosing: 0, 50, 25, 10 mpk
- Observations on Days 1, 4, 8, 11, 15.
- Final bleed and necropsy on Day 15.
- Serum and whole blood samples were sent to MD Anderson Lab Medicine at Houston for serum chemistry and complete blood count.

Clinical Chemistry and Blood Count

- Clinical chemistry and complete blood count (CBC) were carried out by MD Anderson Lab Medicine in Houston.
- All blood samples were analyzed successfully.
- Detailed data and analysis were reported to the Investigators.

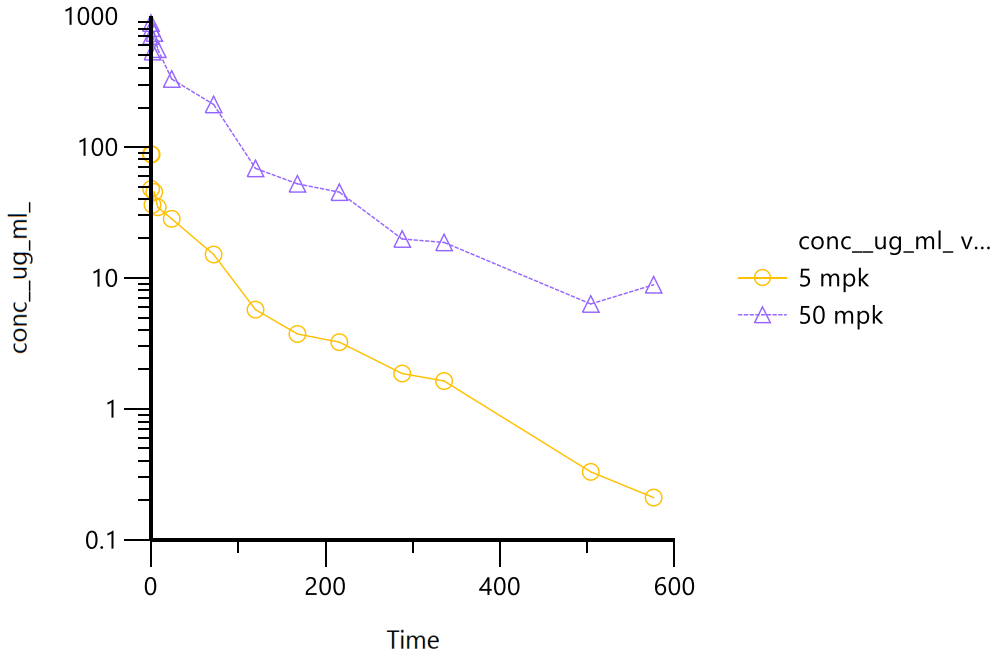
Tissue Collection and Pathology Report

- A total of 25 tissues (all major organs) were collected, weighed, and fixed
- Tissues were processed by KCCMR for histopathology
- Drs. Carolyn Hodo and Martha Hensel, both board-certified pathologists, completed the examination and generated final report

PCDH7 Antibody Study Acknowledgement

- Drs. Wei Xiong and Ningyan Zhang at UTHealth-Houston
  - Antibody production and characterization, and drug exposure analysis.
- Drs. Mingxin Zuo and Qingyun Liu at UTHealth
  - In-life study and data analysis.
- Drs. Rick Finch, Cathryn Shelton, Carolyn Hodo, and Martha Hensel at KCCMR, M.D. Anderson Cancer Center
  - Histopathology analysis and report.

An Example of Antibody PK Study in the Rat



Group	N_Samples	Dose (mg/kg)	Half-life (hours)	Cmax (ug/ml)	AUClast	AUCINF_obs
5 mpk-Ave-all (N = 5)	15	5	88.5	88.1	3251.6	3278.5
50 mpk-Ave-all (N = 6)	15	50	135.3	883.1	43156.7	44885.9

Summary

- The CPRIT-funded Core for Preclinical Development of Large Molecule Therapeutics (LMPD) is a fully supported PK and Toxicology service core for Cancer Researchers in Texas.
- Projects/candidates are accepted based on applications reviewed by the core investigators.
- Services include drug candidate production, PK and Toxicology study mice, rats, and rhesus monkeys.
- Services are free for accepted projects.
- The core is in full operation.
- More information can be found at the LMPD website (https://www.uth.edu/imm/core-facilities/lmpd-core/index.htm)