UCLA Innovation Fund #1701: A Platform for Spatiotemporal Control of Drug Delivery

### Achievements to Date
- **In vivo** biocompatibility and biodistribution
- Visualization and externally controlled release of cargo *ex vivo*

### Upcoming Milestones
- **In vivo** proof of concept in KPC murine pancreatic cancer model

### Problem
- Limited ability to target therapeutics to diseased tissue increases chance of untoward effects in normal tissue
  - e.g., systemic toxicity of chemotherapy

### Solution
- Mesoporous silica nanoparticles (MSNs) loaded with therapeutic cargo of choice, that only release cargo upon stimulation
- HIFU (high intensity focused ultrasound) for externally controlled cargo release
- Incorporation of dual-contrast MRI materials allows real-time imaging of MSNs and diseased tissue

---

**Completed**
- HIFU-responsive NP optimization
- Targeted cargo release *ex vivo*

**In Progress**
- *In vivo* safety evaluation
- Targeted cargo release *in vivo*

---

Jeffrey Zink, PhD  
Dist. Professor, Chemistry and Biochemistry

Holden Wu, PhD  
Assoc. Professor, Radiology, Bioengineering

Caius Radu, MD  
Professor, Molec. & Medical Pharmacology
UCLA Innovation Fund #1705:
Next-Generation Selective Estrogen Receptor Degrader

Problem
- Patients with ER+ breast cancer commonly develop resistance to ER antagonists or estrogen deprivation
- Faslodex is an approved selective ER down-regulator (SERD), but has poor bioavailability

Solution
- Leverage steroid backbone to design potent SERDs, but modify for bioavailability and elimination of agonist effects
- Orally available lead compound shows enhanced \textit{in vivo} tumor reduction and limits estrogen-induced MDSC expansion that can foster immune escape

ACHIEVEMENTS TO DATE
- Novel SERDs augment PD-L1 inhibitors to block tumor growth \textit{in vivo}
- Preliminary \textit{in vitro} ADME and tox data collected for top SERD compound

UPCOMING MILESTONES
- Eurofins SafetyScreen
- Formulation development
- \textit{In vivo} PK

Completed
- SAR, MOA investigation
- Preliminary \textit{in vitro} ADME

In Progress
- SafetyScreen
- Formulation dev., \textit{in vivo} PK
UCLA Innovation Fund #1802:
NPEPPS Enhancers for Tau-Induced Neurodegeneration

**ACHIEVEMENTS TO DATE**
- SAR ongoing
  - Novel compounds generated with improved oral availability and CNS penetration

**UPCOMING MILESTONES**
- *In vivo* POC in mouse model of human tauopathy (hTau.P301S)

**Problem**
- >5M US patients affected by Alzheimer’s Disease (AD) and other tau-associated neurodegenerative diseases (e.g., frontotemporal dementia, progressive supranuclear palsy)
- β-amyloid-targeting treatments have not lived up to expectations

**Solution**
- Puromycin-sensitive aminopeptidase (NPEPPS/PSA), identified as tau modulator by unbiased cross-species screen
- Suppresses neurodegeneration via direct tau degradation
- Orally available small molecules directly engage and enhance NPEPPS activity

**Completed**
- MOA investigation
- Preliminary *in vitro* ADME
- Preliminary PK & BBB penetration
- Animal model validation

**In Progress**
- SAR ongoing (100+ new analogues)
- *In vivo* POC

Additional support from: AMGEN

Michael Jung, PhD
Dist. Professor, Chemistry

Dan Geschwind
MD, PhD
Dist. Professor, Genetics, Neurol., and Psychol.
UCLA Innovation Fund #1803: Novel Excipient for Biotherapeutics Stabilization

ACHIEVEMENTS TO DATE

- Conjugated polymer improves insulin PK; does not alter PK as excipient
- No evidence of acute toxicity \textit{in vivo}
- Lack of immune response (alone) and hapten effect (with ovalbumin) in mice

UPCOMING MILESTONES

- \textit{In vivo} biodistribution (PET study)
- Effect of excipient on viscosity of an antibody solution

Problem

- Antibodies require cold-storage for stability, which adds cost and creates logistical supply chain challenges
- PEG is immunogenic in some patients, which hinders efficacy and can cause adverse side-effects

Solution

- Novel trehalose polymer for stabilization of biotherapeutics
  - Provides thermal and mechanical stabilization
  - Eliminates the need for cold-storage
  - Non-toxic and non-immunogenic (unlike PEG)

Completed

- Stabilization to various stressors
- PK of insulin with polymer as excipient and conjugate

In Progress

- \textit{In vivo} tox studies (acute)
- Safety / immunogenicity

- Viscosity and shelf-life stability

Heather Maynard, PhD
Professor, Chemistry & Biochemistry
UCLA Innovation Fund #1804:
Small Molecules Targeting RNA Regulators in Cancer Stem Cells

ACHEEVMENTS TO DATE
• Composition of matter IP generated
• Lead identification in progress for LIN28B inhibitor program

UPCOMING MILESTONES
• Lead ID
• Evaluating POC model

Problem
• Chemotherapy harms healthy tissue and quiescent cancer stem cells (CSCs) survive
• Single-target-directed therapy harms healthy stem cells; CSCs evolve and evade selective pressure of targeted therapy

Solution
• Targeting RNA regulators enables simultaneous suppression of multiple CSC oncogenes
• 2 screening platforms enabling identification of small molecules that
  1. Upregulate tumor suppressor microRNAs
  2. Inhibit oncogenic RNA-binding proteins

Completed
HTS screen, hit identification
SAR studies
In vitro and in vivo hit validation, MOA studies
In vivo PK

In Progress
Lead identification
Evaluating POC model
UCLA Innovation Fund #1805:
Estrogen Receptor Ligands to Treat Multiple Sclerosis

**Problem**
- >2.3M patients affected WW by Multiple Sclerosis (MS)
- Current treatment regimens are anti-inflammatory, but fail to reverse cognitive impairment or stimulate remyelination

**Solution**
- Mimic aspects of late-stage pregnancy, where natural disease remission is well-documented (attributed to ER-beta ligand)
- NCEs generated (ER-beta agonists) with greater CNS penetration and persistence

<table>
<thead>
<tr>
<th>ACHIEVEMENTS TO DATE</th>
<th>UPCOMING MILESTONES</th>
</tr>
</thead>
</table>
| • New ER-beta ligands generated
• Pilot PK study in progress | • Formulation development to solubilize compounds in a more suitable vehicle for *in vivo* dosing in progress |

**ACHIEVEMENTS TO DATE**

<table>
<thead>
<tr>
<th>Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK (plasma, brain, spinal cord)</td>
</tr>
<tr>
<td>SAR to improve solubility</td>
</tr>
</tbody>
</table>

**In Progress**

<table>
<thead>
<tr>
<th>In Progress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation dev., PK (plasma, brain, spinal cord)</td>
</tr>
<tr>
<td>PD, <em>in vivo</em> efficacy with MRI*</td>
</tr>
</tbody>
</table>

Michael Jung, PhD
Dist. Professor, Chemistry

Rhonda Voskuhl, MD
Professor, Neurology

* Industry sponsored research
UCLA Innovation Fund #1814:
Acoustofluidic Platform for High Throughput Cell Transfection

Problem
• The use of viral vectors for delivery in gene therapy is costly and can result in off-target activity
• Alternative techniques, such as electroporation, have technical limitations and toxicity concerns

Solution
• Acoustofluidic platform which transiently renders target cells porous via acoustic waves
• Specialized microchannels allow for high-throughput, high-efficiency delivery of biomolecular payloads

ACHIEVEMENTS TO DATE
• Initial POC data demonstrating successful transfection of primary human cells published in *PNAS*

UPCOMING MILESTONES
• Optimization of transfection efficiencies based on cargo and cell type while maintaining high cell viability

Completed
- Alpha prototype device
- Scale-up to multi (10) channel device
- Transfection of Jurkat cells, human T-cells, CD34+ HSPCs

In Progress
- Optimization of transfection efficiencies
- Partnering to validate platform with diverse cell types / cargo

Paul Weiss, PhD
Professor, Chemistry, Engineering

Steve Jonas, MD, PhD
Professor, Pediatrics, Heme/Onc

Ali Khademhosseini, PhD
Professor, Bioengineering

Don Kohn, MD
Professor, Heme/Onc, Immunology & Molecular Genetics
UCLA Innovation Fund #1902: Synthetic Exosomes for CNS Drug Delivery

<table>
<thead>
<tr>
<th>ACHIEVEMENTS TO DATE</th>
<th>UPCOMING MILESTONES</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Optimization of SE-IDUA synthesis in progress; to be completed when labs reopen</td>
<td>• Iterative PK to demonstrate IDUA enzyme delivery to CNS and uptake in cells</td>
</tr>
<tr>
<td></td>
<td>• Delivery of CRISPR/Cas9 construct to CNS</td>
</tr>
</tbody>
</table>

**Problem**

- Inability to penetrate the blood-brain barrier (BBB) is a major impediment to the delivery of potential therapeutics for central nervous system diseases
  - Most small molecules and virtually all large molecule therapeutics do not cross the BBB

**Solution**

- Synthetic exosomes (SEs) encapsulating biomolecules as a linkage-free nanoparticle drug delivery system to cross the BBB
- Delivery of diverse biomolecular cargo
- Tunable size (~50-500nm), zeta potential, and structural flexibility enable permeation of the BBB

**Achievements to Date**

- Optimization of SE-IDUA synthesis in progress; to be completed when labs reopen

**Upcoming Milestones**

- Iterative PK to demonstrate IDUA enzyme delivery to CNS and uptake in cells
- Delivery of CRISPR/Cas9 construct to CNS

**Completed**

- Prelim *in vitro* characterization
- Prelim *in vivo* demo of BBB penetration, TE

**In Progress / Planned**

- Optimization of SE-IDUA synth.
- PK, biodistribution, cellular uptake
- Platform expansion: CRISPR/Cas9 delivery to CNS

**In vivo POC in MPS I mouse model**

**Additional support from:**

- Varghese John, PhD
  - Prof., Neurology; PI, UCLA Drug Discovery Lab
  - Completed: Prelim *in vitro* characterization
  - Prelim *in vivo* demo of BBB penetration, TE

- Jesus Campagna, MS
  - Staff Researcher, UCLA Drug Discovery Lab
  - In Progress / Planned: Optimization of SE-IDUA synth.
  - Platform expansion: CRISPR/Cas9 delivery to CNS

- Patricia Spilman, PhD
  - Sr. Staff Scientist, UCLA Drug Discovery Lab
  - In Progress / Planned: Prelim *in vitro* characterization
  - Prelim *in vivo* demo of BBB penetration, TE

**Platform Expansion**

- CRISPR/Cas9 delivery to CNS

**Technology Development Group**

- UCLA

**KV KAIROS VENTURES**

**Amgen**
Problem

- Unmet need for scarless wound healing therapeutics that are both safe and effective
  - ~100 M patients globally develop scars from elective and trauma operations each year
- Therapeutics targeting “fetal-like” wound healing and inflammation have had limited success

Solution

- Small molecule suppressors of clock gene Npas2 promote accelerated wound healing and scar reduction
  - Novel target Npas2 identified from genomic screen
  - Npas2 modulators identified in HTS of approved drugs
  - Potential expansion to other applications related to tissue fibrosis

Completed

Hit ID and in vitro validation

Prelim in vivo efficacy in split wound model

In Progress / Planned

Target validation / MOA investigation

Validate trans-dermal delivery in vivo

Targeted screen of approved compounds to ID more selective leads
**UCLA Innovation Fund #1904:**
Ketohexokinase Inhibitors for Targeted Cancer Therapy

**ACHIEVEMENTS TO DATE**
- Additional *in vitro* target validation studies

**UPCOMING MILESTONES**
- Assess xenograft tumor growth in KHK WT vs. KHK KO mice

---

**Problem**
- Cancer cells reprogram metabolism to activate anabolic processes essential for tumor survival and growth
- Existing strategies for targeting cancer metabolism produce deleterious effects in healthy cells

**Solution**
- Novel ketohexokinase inhibitors selectively "starve" cancer cells by blocking key enzyme involved in fructose metabolism
- KHK is not essential in humans, presenting an opportunity for selective inhibitors with minimal impact on healthy cells

---

**Completed**
*In vitro and in vivo* target validation
- Hit ID, preliminary SAR studies

**In Progress / Planned**
- Additional target validation studies
- Continued SAR, ADME/PK
- Kinase screen, MOA investigation
- *In vivo* efficacy

---

Michael Jung, PhD
Dist. Professor, Chemistry

Heather Christofk, PhD
Professor, Biological Chemistry
# UCLA Innovation Fund #1905: Broad Spectrum Antivirals to Treat Enteroviruses

## Achievements to Date
- Screening of top compounds against SARS-CoV-2 in progress

## Upcoming Milestones
- Lead identification

## Problem
- No approved antiviral therapeutics have activity against enteroviruses (10 - 15 M infections each year in US)
  - Serious complications and death can occur, particularly in vulnerable patients (infants, immunocompromised individuals)

## Solution
- Novel small molecule derivatives of pyrazolopyridine carboxamide (PPC) with broad spectrum activity against enteroviruses
  - Targets highly conserved viral protein (2C) for RNA replication
  - Low toxicity in preliminary mouse studies and favorable in vivo PK profile

## Completed
- SAR, MOA investigation
- Preliminary in vivo PK

## In Progress / Planned
- Lead identification
- In vivo PK with multiple doses
- Potency shifts in human serum in vitro
- In vivo efficacy

---

**Problem**

- No approved antiviral therapeutics have activity against enteroviruses (10 - 15 M infections each year in US)
  - Serious complications and death can occur, particularly in vulnerable patients (infants, immunocompromised individuals)

**Solution**

- Novel small molecule derivatives of pyrazolopyridine carboxamide (PPC) with broad spectrum activity against enteroviruses
  - Targets highly conserved viral protein (2C) for RNA replication
  - Low toxicity in preliminary mouse studies and favorable in vivo PK profile
Thank You