UCLA Technology Development Group

UCLA Innovation Fund

Therapeutic Track
Portfolio Update Newsletter

June 2020

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

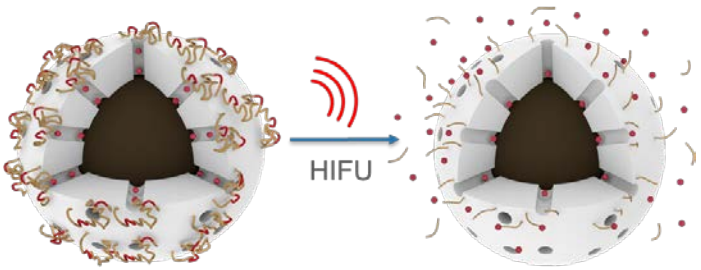
- *In vivo* proof of concept in KPC murine pancreatic cancer model

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 vitro evaluation

In vivo biodistribution

In Progress

In vivo safety evaluation

Targeted cargo release *in vivo*

UCLA Technology Development Group

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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

ACHIEVEMENTS TO DATE

- Novel SERDs augment PD-L1 inhibitors to block tumor growth *in vivo*
- Preliminary *in vitro* ADME and tox data collected for top SERD compound

UPCOMING MILESTONES

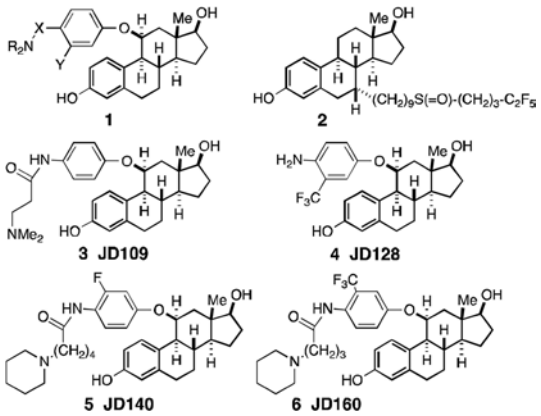
- Eurofins SafetyScreen
- Formulation development
- *In vivo* PK

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 *in vivo* tumor reduction and limits estrogen-induced MDSC expansion that can foster immune escape



Completed

SAR, MOA investigation

Preliminary *in vitro* ADME

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In vivo efficacy, combination studies

Preliminary *in vitro* tox

In Progress

SafetyScreen

eurofins

Formulation dev., *in vivo* PK

UCLA Technology Development Group

Michael Jung, PhD
Dist. Professor, Chemistry

Rich Pietras, MD, PhD
Professor, Chemistry & Biochemistry

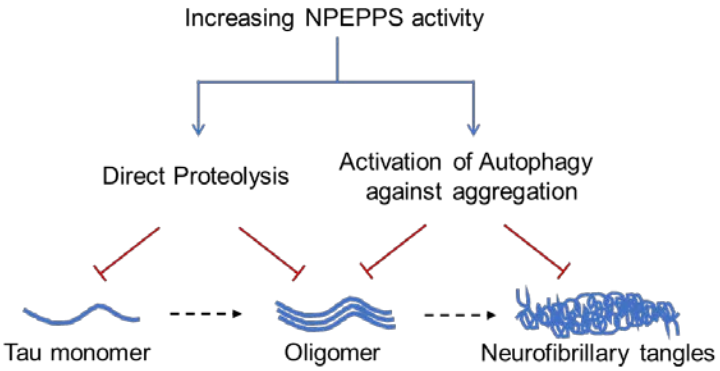
UCLA Innovation Fund #1802:
NPEPPS Enhancers for Tau-Induced Neurodegeneration

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 PK & BBB penetration

Preliminary *in vitro* ADME

Animal model validation

In Progress

SAR ongoing (100+ new analogues)

In vivo POC

Additional support from: AMGEN

UCLA Technology Development Group

Michael Jung, PhD
Dist. Professor, Chemistry

Dan Geschwind MD, PhD
Dist. Professor, Genetics, Neurol., and Psychol.

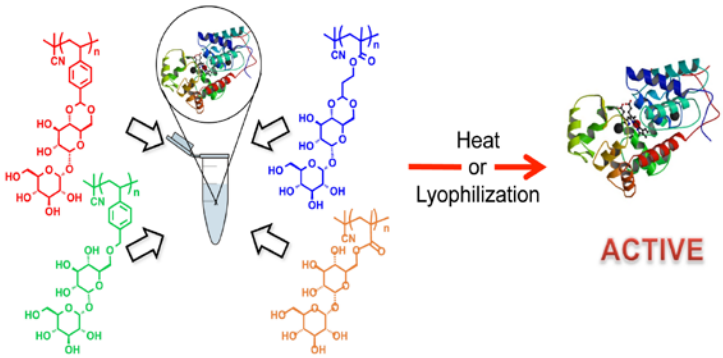
UCLA Innovation Fund #1803:
Novel Excipient for Biotherapeutics Stabilization

ACHIEVEMENTS TO DATE
- Conjugated polymer improves insulin PK; does not alter PK as excipient
- No evidence of acute toxicity *in vivo*
- Lack of immune response (alone) and hapten effect (with ovalbumin) in mice

UPCOMING MILESTONES
- *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 vivo tox studies (acute)

Safety / immunogenicity

In Progress

In vivo biodistribution

Viscosity and shelf-life stability

UCLA Technology Development Group

Heather Maynard, PhD
Professor, Chemistry & Biochemistry

UCLA Innovation Fund #1804:

Small Molecules Targeting RNA Regulators in Cancer Stem Cells

ACHIEVEMENTS TO DATE

- Composition of matter IP generated
- Lead identification in progress for LIN28B inhibitor program

UPCOMING MILESTONES

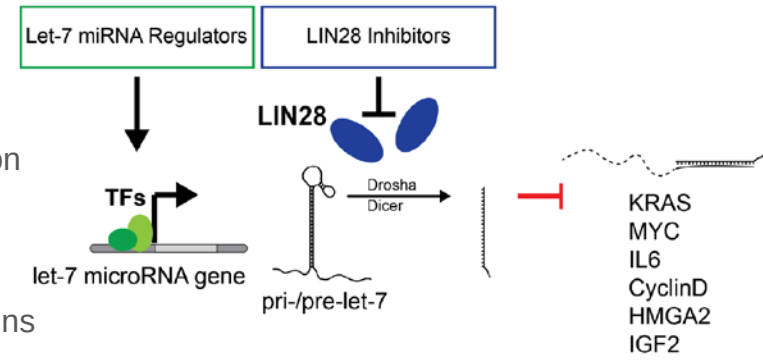
- Lead ID
- Evaluating POC model

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

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In Progress

Lead identification

Evaluating POC model

UCLA Technology Development Group

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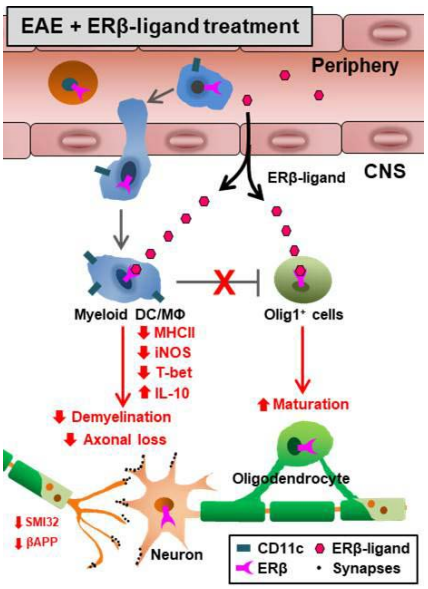
UCLA Innovation Fund #1805:
Estrogen Receptor Ligands to Treat Multiple Sclerosis

ACHIEVEMENTS TO DATE
- New ER-beta ligands generated
- Pilot PK study in progress

UPCOMING MILESTONES
- Formulation development to solubilize compounds in a more suitable vehicle for *in vivo* dosing in progress

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

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



Completed

PK (plasma, brain, spinal cord)

SAR to improve solubility

ABSORPTION SYSTEMS

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Prelim *in vivo* efficacy in EAE mouse model

PK of new analogues

In Progress

Formulation dev., PK (plasma, brain, spinal cord)

ABSORPTION SYSTEMS

PD, *in vivo* efficacy with MRI*

* *Industry sponsored research*

Michael Jung, PhD
Dist. Professor, Chemistry

Rhonda Voskuhl, MD
Professor, Neurology

UCLA Technology Development Group

UCLA Innovation Fund #1814:

Acoustofluidic Platform for High Throughput Cell Transfection

ACHIEVEMENTS TO DATE

- Initial POC data demonstrating successful transfection of primary human cells published in *PNAS*

UPCOMING MILESTONES

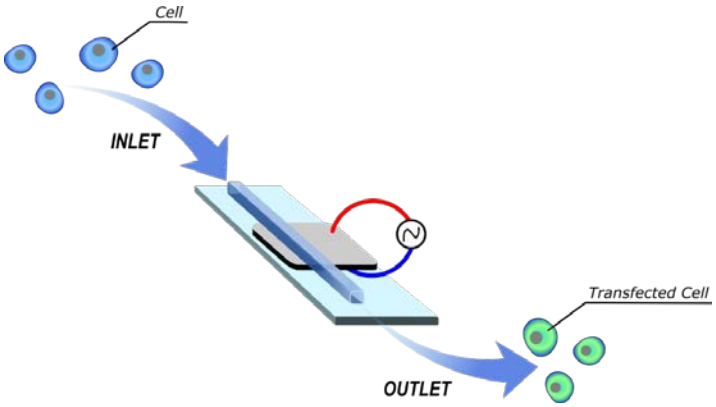
- Optimization of transfection efficiencies based on cargo and cell type while maintaining high cell viability

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



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

UCLA Technology Development Group

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Professor, Heme/Onc, Immunology & Molecular Genetics

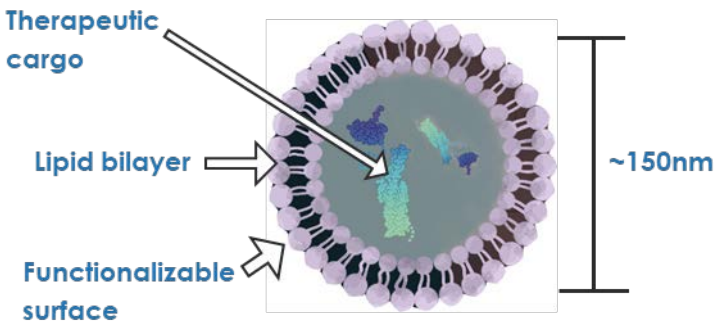
UCLA Innovation Fund #1902:
Synthetic Exosomes for CNS Drug Delivery

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

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



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

In vivo POC in MPS I mouse model

Platform expansion: CRISPR/Cas9 delivery to CNS

Additional support from: AMGEN, KAIROS VENTURES, UCLA Technology Development Group

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Jesus Campagna, MS
Staff Researcher, UCLA Drug Discovery Lab

Patricia Spilman, PhD
Sr. Staff Scientist, UCLA Drug Discovery Lab

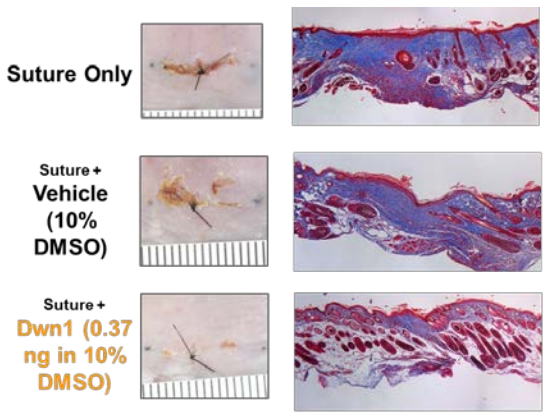
UCLA Innovation Fund #1903:
Small Molecule *Npas2* Suppressors for Scar Prevention

ACHIEVEMENTS TO DATE
- Additional studies to support proposed disease mechanism
- Over-expression studies for target ID in progress

UPCOMING MILESTONES
- CRISPR KO studies for target validation
- Targeted screen to identify additional repurposing candidates

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 Technology Development Group

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UCLA Innovation Fund #1904:

Ketohexokinase Inhibitors for Targeted Cancer Therapy

ACHIEVEMENTS TO DATE

- Additional *in vitro* target validation studies

UPCOMING MILESTONES

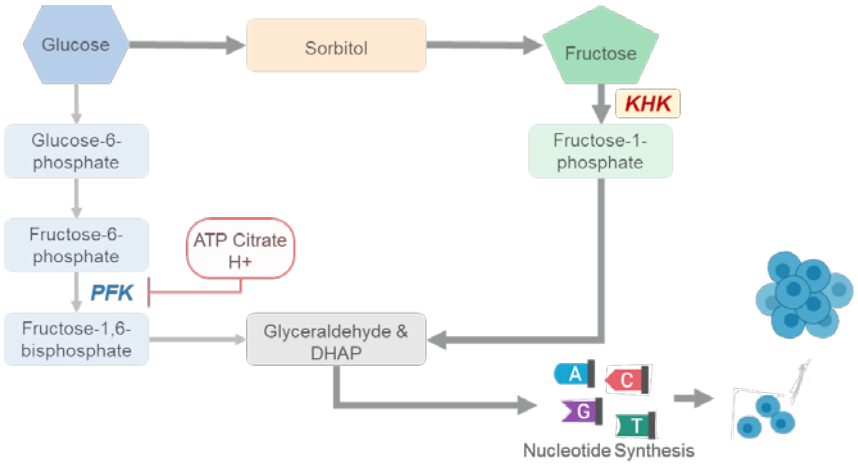
- Assess xenograft tumor growth in KHK WT vs. KHK KO mice

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

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eurofins

Kinase screen, MOA investigation

In vivo efficacy

UCLA Technology Development Group

Michael Jung, PhD
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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

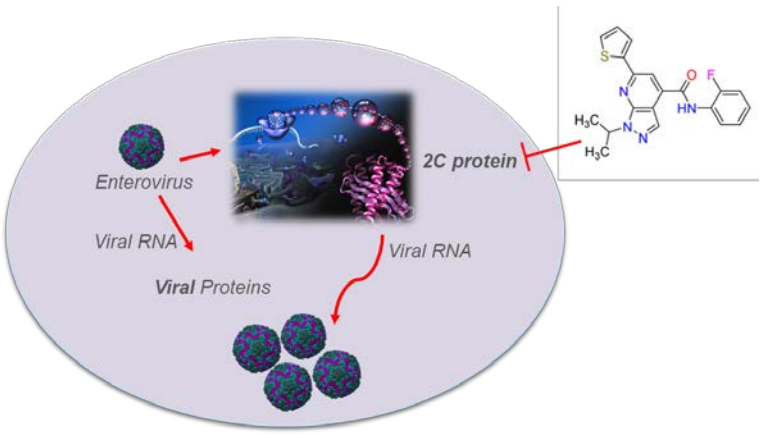
- Lead identification

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

UCLA Technology Development Group

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Thank You

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