C D M I

CENTER FOR DISRUPTIVE MUSCULOSKELETAL INNOVATIONS

High-throughput screening for osteocyte-mediated bone remodeling (OMBRE) regulatory compounds

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Bone Fragility – beyond osteoporosis

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Healthy bone

Osteoporotic bone

At least half of fragility fractures occur in individuals with normal bone mass.

- Wainwright, JCEM 2005

Osteocyte-Mediated Bone Remodeling (OMBRE)

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Clinical Need and Industrial Relevance

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Agents that control OMBRE have therapeutic potential for treating skeletal diseases.

DMI HTS for OMBRE regulatory compounds

PROPRIETARY INFORMATION



Knowledge Gaps: role of OMBRE in skeletal disease, OMBRE therapies

- 1. Are there current FDA-approved **drugs that can be repurposed** as OMBRE-regulators for treating skeletal diseases?
- 2. What are the **side effects of currently used medications** that regulate OMBRE on skeletal health?
- 3. Advance **fundamental understanding of OMBRE** to develop improved therapies for skeletal diseases.



This project aims to screen a library of FDA-approved small molecule compounds to identify agents that regulate OMBRE in vitro.

Aim 1: Validate functional OMBRE assays in a highthroughput screen (HTS) format.

- currently, there is no validated in vitro PLR assay

Aim 2: Perform high throughput screen for OMBRE regulatory compounds.

Aim 3: Identify and validate lead OMBRE-regulatory compounds for in vitro analysis.

CDMI HTS for OMBRE regulatory compounds



Validate in vitro OMBRE HTS assay

Aim 1: Functional pHi assay Gene expression screening

Identify OMBRE regulatory compounds

Aim 2: FDA-approved drug screening *Aim 3:* Validate OMBRE-regulatory compounds

Deliverables

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Validate in vitro OMBRE HTS assay Aim 1: Functional pH Assay

Gene expression screening



Change in intracellular pH will be visually and quantitatively evaluated.

Secondary Screen- Gene Expression

In vitro OMBRE assay

Aim 1: Functional pH Assay

Gene expression screening



Using OCY454, Taqman array plates will screen genes known to be involved in OMBRE in vivo.

CDMI HTS for OMBRE regulatory compounds

PROPRIETARY INFORMATION

Deliverables

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Validate in vitro OMBRE HTS assay

Aim 1: Functional pHi assay Gene expression screening



Progress Update

Hired Nick Szeto for needed personnel efforts

Progress Update

Recruiting 2 post-docs for needed personnel efforts

Identify OMBRE regulatory compounds

Aim 2: FDA-approved drug screening *Aim 3:* Validate OMBRE-regulatory compounds

Progress Update

Anticipate new results in next quarterly meeting

Milestones & Timeline

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December 2017 Spring 2018 March 2018

June 2018 August 2018

September 2018

November 2018

Conference Call Spring Symposium @ UT Validate HTS OMBRE assays & Screening plan for FDA approved compound library Conference Call *List of lead OMBRE regulatory* compounds for in vitro validation Fall Symposium @ UCSF Validate list of OMBRE regulatory compounds for in vitro and in vivo analysis Final Report

DMI HTS for OMBRE regulatory compounds

Clinical Need and Industrial Relevance

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DMI OMBRE: Osteocyte-Mediated Bone Remodeling Core