



CENTER FOR DISRUPTIVE
MUSCULOSKELETAL INNOVATIONS

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

Cristal Yee, Ph.D.
Alliston Lab

University of California San Francisco

WWW.NSFCDMI.ORG

Bone Fragility – beyond osteoporosis

CENTER FOR DISRUPTIVE
MUSCULOSKELETAL
INNOVATIONS



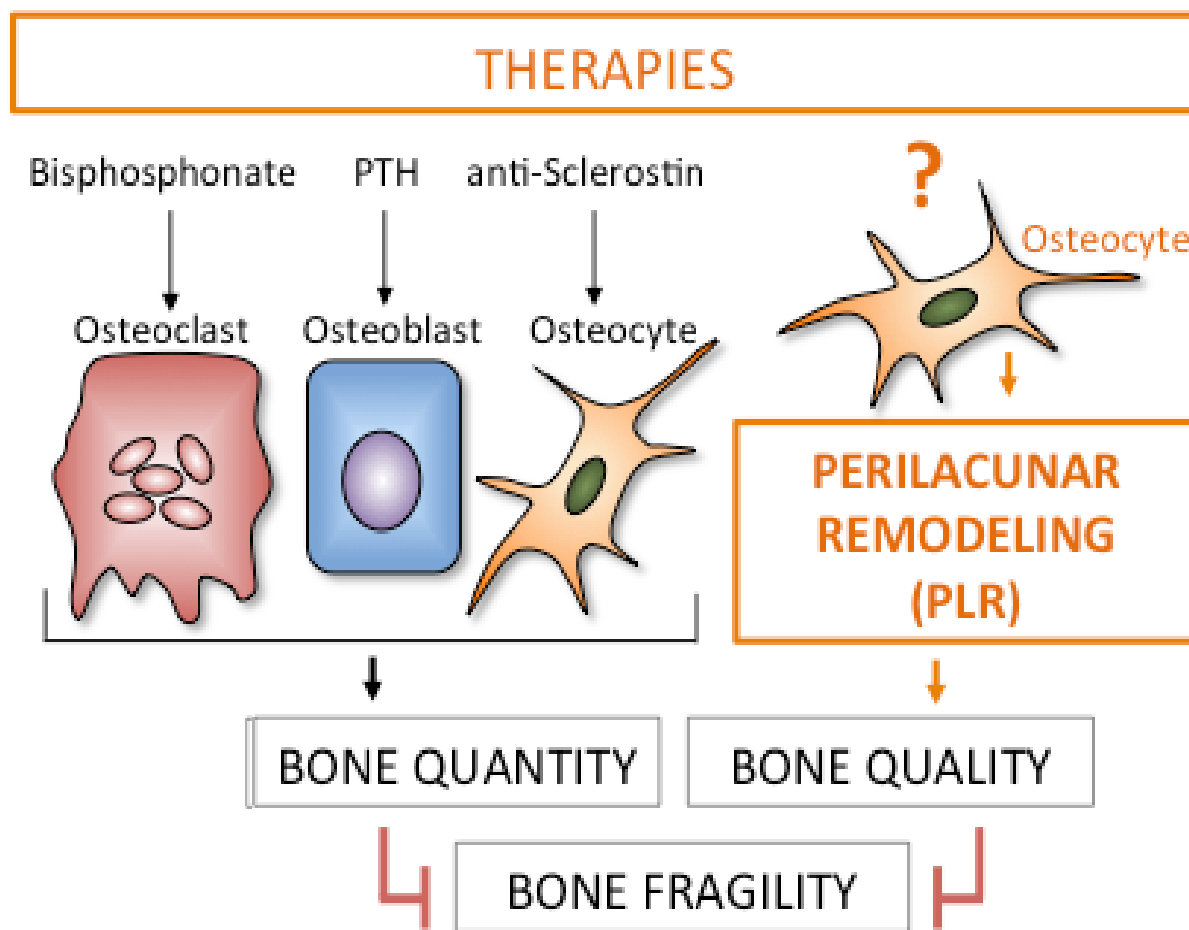
Healthy bone

Osteoporotic bone

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

- Wainwright, JCEM 2005

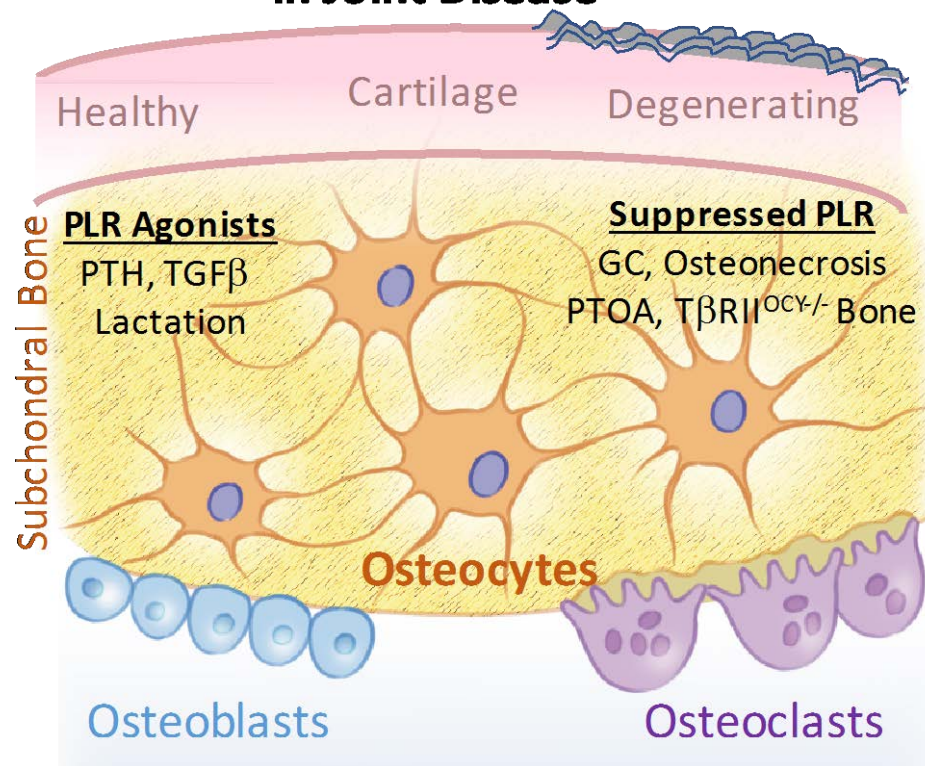
Osteocyte-Mediated Bone Remodeling (OMBRE)



Clinical Need and Industrial Relevance

CENTER FOR DISRUPTIVE
MUSCULOSKELETAL
INNOVATIONS

Osteocytic Perilacunar Remodeling (PLR) in Joint Disease



Steroid Use
Osteonecrosis
Osteoarthritis
Bone Fragility-
Aging
Diabetes

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

Clinical Need and Industrial Relevance

CENTER FOR DISRUPTIVE
MUSCULOSKELETAL
INNOVATIONS

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.

Project Aims

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 high-throughput 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.

Validate in vitro OMBRE HTS assay

Aim 1: Functional pHi assay

Gene expression screening

Identify OMBRE regulatory compounds

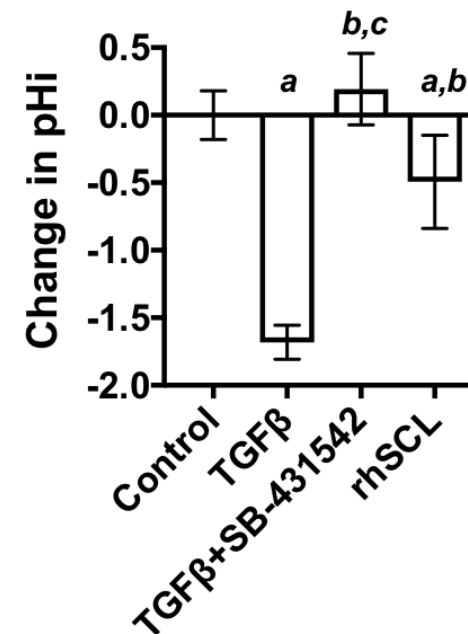
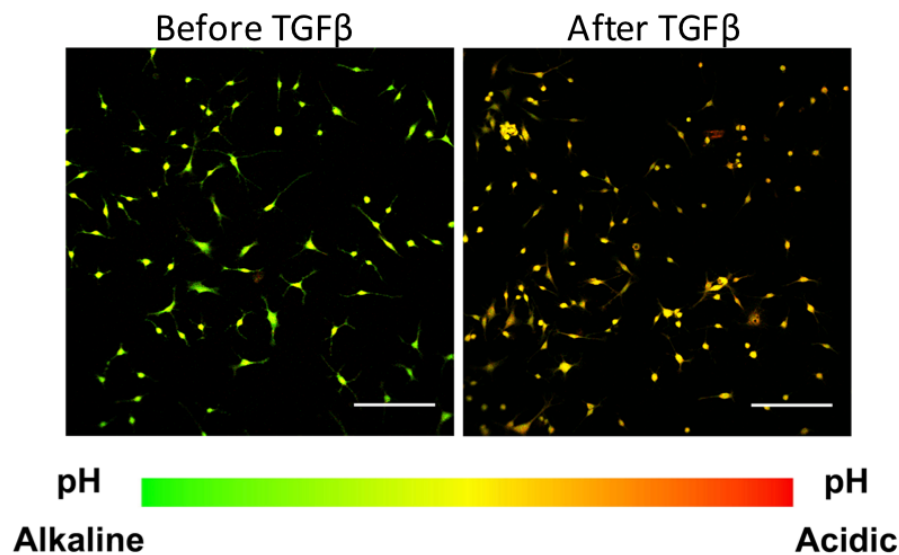
Aim 2: FDA-approved drug screening

Aim 3: Validate OMBRE-regulatory compounds

Validate *in vitro* OMBRE HTS assay

Aim 1: Functional pH Assay

Gene expression screening



Change in intracellular pH will be visually and quantitatively evaluated.

Validate in vitro OMBRE HTS assay

1

Progress Update

Recruiting new hire for needed personnel efforts

Evaluating top candidates and will make an offer this week

Aim 1: Functional pHi assay

Gene expression screening

Identify OMBRE regulatory compounds

Aim 2: FDA-approved drug screening

Aim 3: Validate OMBRE-regulatory compounds

2

Progress Update

Scheduling meeting with UCSF Small Molecule Development Center (SMDC)

Secondary Screen- Gene Expression

CENTER FOR DISRUPTIVE
MUSCULOSKELETAL
INNOVATIONS

In vitro OMBRE assay

Aim 1: Functional pH Assay

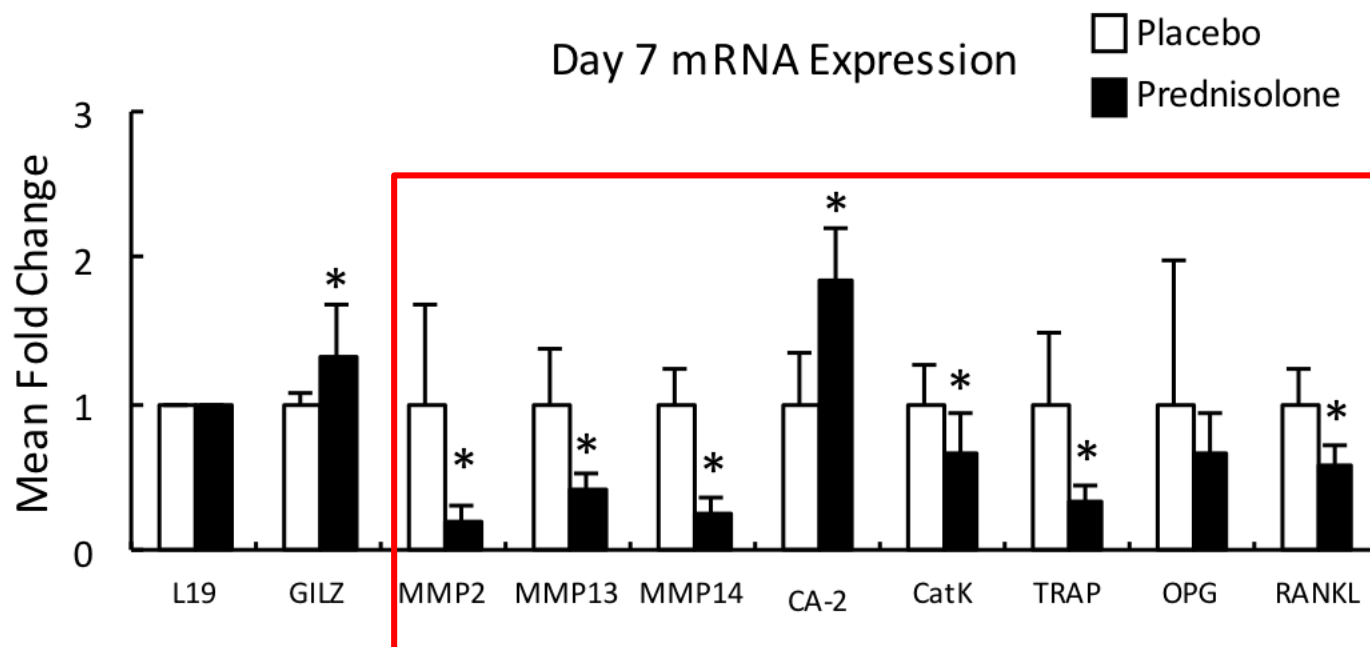
Gene expression screening

3

Progress Update

Explore new gene expression array reader for Taqman arrays

core resource at the VA



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

Milestones & Timeline

CENTER FOR DISRUPTIVE
MUSCULOSKELETAL
INNOVATIONS

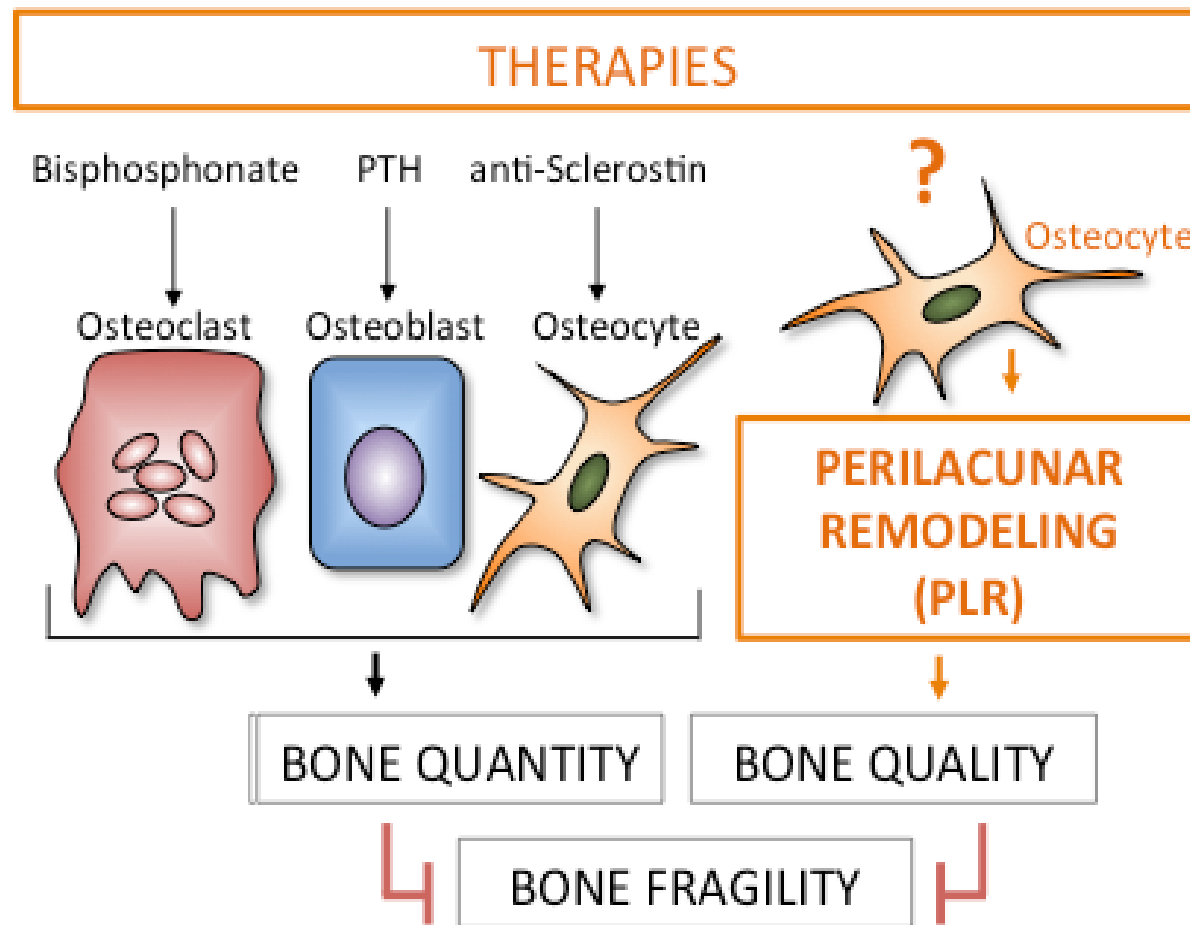
<i>December 2017</i>	<i>Conference Call</i>
<i>Spring 2018</i>	<i>Spring Symposium @ UT</i>
<i>March 2018</i>	<i>Validate HTS OMBRE assays & Screening plan for FDA approved compound library</i>
<i>June 2018</i>	<i>Conference Call</i>
<i>August 2018</i>	<i>List of lead OMBRE regulatory compounds for in vitro validation</i>
<i>September 2018</i>	<i>Fall Symposium @ UCSF</i> <i>Validate list of OMBRE regulatory compounds for in vitro and in vivo analysis</i>
<i>November 2018</i>	<i>Final Report</i>

Clinical Need and Industrial Relevance

CENTER FOR DISRUPTIVE
MUSCULOSKELETAL
INNOVATIONS

Contributors

Justin Lopez
Neha Dole
Cristal Yee
JJ Woo
David Monteiro
Courtney Mazur
Claire Acevedo
Tristan Fowler
Jackie Nguyen



Steroid Use
Osteonecrosis
Osteoarthritis
Aging
Diabetes