Osteoporosis Preclinical Landscape - DRAFT

Organization Name	Project Leader	Project Title	OniX Summary
UNIV OF MASSACHUSETTS MED SCH WORCESTER	SHIM, JAE-HYUCK	A novel bone-targeting AAV-mediated gene therapy to promote bone formation in osteoporosis	**Research Question:** Can RNA interference (RNAi) gene therapy using a modified adeno-associated virus (rAAV) be used to treat osteoporosis by targeting sclerostin (SOST) and schnurri-3 (SHN3)? **Stage:** In vivo (using mice) **Methods:** • Engineered rAAV9 vector with bone-specific delivery will be used to silence SHN3 or SOST genes. • Mouse models of osteoporosis (ovariectomized (OVX) and aged mice) will be used to test the therapeutic effects. • Whole transcriptome analysis and proteomics will be used to identify novel osteogenic and/or angiogenic factors regulated by the SHN3/SOST pathway. **Drug Development:** RNAi-based gene therapy, targeting SHN3 and SOST for promoting bone formation. **Key Points:** • This approach targets bone formation (anabolic) rather than resorption (like current osteoporosis drugs). • The rAAV9 vector is designed to minimize side effects by delivering the therapy specifically to bone cells. • The study aims to identify new factors involved in bone formation regulated by SHN3 and SOST, which could lead to future drug targets. This abstract describes a pre-clinical study (in mice) developing a novel gene therapy for osteoporosis.
MAINEHEALTH	ESTELL, EBEN GRANT	The Myokine Irisin Modulates Bone Resorption via Stimulation of Osteoclastogenesis	**Research Question:** How does irisin, a muscle-derived hormone, influence bone remodeling and how does it interact with different bone cells (osteocytes, osteoblasts, osteoclasts)? **Stage:** In vitro (cell cultures) and in vivo (using mice) **Methods:** • Genetically modified mice with altered irisin production will be used to assess its effects on bone formation and resorption. • Cell cultures of osteocytes, osteoblasts, and osteoclasts will be treated with irisin to study its direct effects.

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			• The role of integrin receptors in mediating irisin's effects on these cells will be investigated. • The influence of mechanical loading (fluid shear) on these cells and their response to irisin will be examined. **Drug Development:** Not directly mentioned, but the research could inform future therapeutic strategies targeting irisin or its signaling pathway to influence bone health. **Key Points:** • Irisin has complex effects on bone, potentially stimulating both bone formation and resorption depending on the context. • The study focuses on the cellular and molecular mechanisms by which irisin interacts with bone cells. • The role of mechanical forces on bone cells and how they interact with irisin signaling will be explored. This abstract describes a pre-clinical study investigating the mechanism of irisin's action on bone remodeling in mice and cell cultures. The findings could help develop future therapies targeting irisin for bone health.
UNIVERSITY OF ARIZONA	HAUSSLER, MARK R	Vitamin D Hormone Signaling in Bone Mineral Homeostasis	**Research Question:** How does the vitamin D hormone (1,25(OH)2D3) regulate bone mineral levels and prevent bone diseases like osteoporosis? **Stage:** In vitro (cell cultures) **Methods:** • Cell cultures representing target tissues (bone, intestine, kidney) will be used to study the effects of 1,25(OH)2D3. • Techniques like ChIP assays and promoter analysis will be used to identify genes regulated by the vitamin D receptor (VDR). • The role of VDR in different signaling pathways related to bone formation, mineral transport, and phosphate regulation will be investigated. **Drug Development:** The study aims to understand the mechanism of action of vitamin D, which could lead to the development of improved vitamin D analogs for treating osteoporosis. **Key Points:**

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			• The research focuses on the molecular mechanisms by which vitamin D signaling regulates bone mineralization. • The study investigates how vitamin D interacts with other signaling pathways in bone cells, intestine, and kidney. • The findings could inform the development of new drugs targeting the vitamin D pathway for bone health. This abstract describes a basic science study using cell cultures to understand how vitamin D signaling regulates bone health. This knowledge could be used to develop new drugs for osteoporosis in the future.
UNIVERSITY OF ARIZONA	HAUSSLER, MARK R	Vitamin D Hormone Signaling in Bone Mineral Homeostasis	**Research Question:** How does the vitamin D hormone (1,25(OH)2D3) regulate bone mineral levels and prevent bone diseases like osteoporosis? **Stage:** In vitro (cell cultures) **Methods:** • Cell cultures representing target tissues (bone, intestine, kidney) will be used to study the effects of 1,25(OH)2D3. • Techniques like ChIP assays and promoter analysis will be used to identify genes regulated by the vitamin D receptor (VDR). • The role of VDR in different signaling pathways related to bone formation, mineral transport, and phosphate regulation will be investigated. **Drug Development:** The study aims to understand the mechanism of action of vitamin D, which could lead to the development of improved vitamin D analogs for treating osteoporosis. **Key Points:** • The research focuses on the molecular mechanisms by which vitamin D signaling regulates bone health. • The study investigates how vitamin D interacts with other signaling pathways in bone cells, intestine, and kidney. • The findings could inform the development of new drugs targeting the vitamin D pathway for bone health. This abstract describes a basic science study using cell cultures to understand how vitamin D signaling regulates bone health. This knowledge could be used to develop new drugs for osteoporosis in the future.

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UNIV OF MASSACHUSETTS MED SCH WORCESTER	SHIM, JAE-HYUCK	Novel approaches to promote healing of bone loss in inflammatory arthritis	**Research Question:** Can targeting the protein Schnurri-3 (SHN3) promote bone formation and prevent bone loss in rheumatoid arthritis (RA)? **Stage:** In vivo (using mice) **Methods:** • Mice with SHN3 deficiency will be used in models of RA to assess bone health. • The effects of RA-associated cytokines (TNF, IL-17A) on SHN3 expression and osteoblast function will be investigated. • A bone-specific adeno-associated virus (rAAV) designed to silence SHN3 will be tested for its ability to prevent bone loss in RA models. • Molecular mechanisms by which SHN3 regulates bone formation in RA will be explored. **Drug Development:** The study focuses on SHN3 as a potential therapeutic target for developing new drugs to treat bone loss associated with RA. **Key Points:** • SHN3 suppresses bone formation and is increased in RA patients. • Blocking SHN3 in mice promotes bone growth and protects from inflammation-induced bone loss. • The study investigates how SHN3 is regulated by inflammatory signals and its role in osteoblast function during RA. • A bone-targeted gene therapy approach using rAAV to silence SHN3 is being explored for future treatment. This abstract describes a pre-clinical study investigating SHN3 as a target for treating bone loss associated with RA in mice. The findings could inform the development of new therapies for RA patients.
RLR VA MEDICAL CENTER	ROBLING, ALEXANDER G	Neurogenic bone loss after SCI: skeletal rehabilitation via Wnt and exercise interactions	**Research Question:** Can a combination antibody therapy targeting sclerostin and Dkk1, combined with exercise, be an effective long-term treatment for bone loss caused by spinal cord injury (SCI)? **Stage:** In vivo (using animals) **Methods:** • Mice with SCI will be treated with a low-dose combination antibody therapy targeting sclerostin and Dkk1.

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			• The effects of this therapy on bone density, size, and strength will be evaluated. • The ability of this therapy to improve the effectiveness of exercise on bone health after SCI will be investigated. • The long-term effects of stopping the antibody therapy and relying on continued exercise for bone health will be examined. • Motor neuron and muscle recovery, along with functional outcomes, will be assessed to evaluate the overall impact of the therapy. **Drug Development:** Develop a safer and more effective treatment for bone loss after SCI by combining a low-dose sclerostin/Dkk1 antibody therapy with exercise rehabilitation. **Key Points:** • Standard osteoporosis drugs are not suitable for treating bone loss after SCI due to safety concerns. • This study proposes a combination therapy with a lower dose of sclerostin antibody to reduce side effects while maintaining bone-building effects. • The therapy aims to improve bone health after SCI by combining the antibody treatment with exercise to create a long-lasting effect. • The study will also assess the potential benefits of this approach for motor neuron and muscle recovery after SCI. This abstract describes a pre-clinical study in mice investigating a new therapeutic approach for bone loss after SCI. The approach combines a low-dose antibody therapy with exercise rehabilitation and could potentially lead to a safer and more effective treatment for SCI patients.
UNIVERSITY OF CALIFORNIA, SAN DIEGO	PILZ, RENATE B	PKG Regulation of Sirtuin 1 as a Novel Treatment Strategy for Age-related Osteoporosis	**Research Question:** Can activating the PKG and SIRT1 signaling pathways together be a more effective treatment for age-related osteoporosis than current options? **Stage:** In vivo (using mice) **Methods:** • The study will investigate how PKG signaling increases SIRT1 expression in bone cells. • The effects of PKG activation on bone health in mice with reduced SIRT1 function will be examined.

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			• The role of SIRT1-induced NO synthesis and PKG activation in bone health will be explored. • The researchers will test if combining PKG and SIRT1 activators has a synergistic effect on bone formation in aged mice. **Drug Development:** The study aims to develop a new treatment strategy for osteoporosis by targeting the PKG and SIRT1 signaling pathways. **Key Points:** • Current osteoporosis drugs with bone-building effects have limitations. • This study focuses on activating PKG and SIRT1 signaling, which have been shown to improve bone health in mice. • The research explores how these pathways interact and how they might be used together for treatment. • The study tests a novel drug (nitrosyl-cobinamide, NO-Cbi) that activates both PKG and has antioxidant effects. This abstract describes a pre-clinical study investigating the potential of activating PKG and SIRT1 signaling for treating osteoporosis in mice. This approach could lead to the development of new and more effective drugs for age-related osteoporosis.

NATIONAL HUMAN GENOME RESEARCH INSTITUTE	COLLINS, FRANCIS S.	Hutchinson-Gilford Progeria syndrome--a model for the genetics of aging.	**Research Question:** How can we develop effective treatments for Hutchinson-Gilford progeria syndrome (HGPS)?
			Stage: In vivo (using mice)
			Methods:
			• The study investigates different approaches to target the progerin protein or LMNA gene mutation that causes HGPS.
			• This includes using a mouse model with the human LMNA G608G mutation.
			• The researchers are testing:
			  ○ MTOR inhibition (using a genetic approach) to reduce progerin levels.
			  ○ Antisense oligonucleotide therapy to block the abnormal splicing of LMNA pre-mRNA.
			  ○ Base editing to correct the LMNA gene mutation.

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			• They are also investigating the effects of HGPS on bone cells and signaling pathways. **Drug Development:** The study aims to develop new therapies for HGPS based on different strategies: • MTOR inhibitor drug (already in clinical trials). • Antisense oligonucleotide therapy (in preparation for IND application). • Base editing gene therapy (in pre-clinical development). **Key Points:** • HGPS is a fatal genetic disease causing premature aging in children. • The study explores multiple approaches to target the underlying cause of HGPS. • Promising results have been achieved with MTOR inhibition, antisense oligonucleotide therapy, and base editing using gene delivery systems. • The research also investigates how HGPS affects bone health. This abstract describes a comprehensive study in mice investigating different therapeutic approaches for HGPS. The findings hold promise for developing new treatments that could significantly improve the lives of children with this devastating disease.
UNIV OF MASSACHUSETTS MED SCH WORCESTER	SHIM, JAE-HYUCK	Identification of novel regulators governing osteoclast-osteoblast coupling	**Research Question:** Can targeting the protein CHMP5 in osteoclasts (OCs) help develop new treatments for bone loss disorders like osteoporosis and Paget's disease of bone (PDB)? **Stage:** In vivo (using mice) with some in vitro studies planned **Methods:** • Mice with OC-specific CHMP5 deletion will be used to investigate its role in bone remodeling. • The effects of CHMP5 deficiency on human osteoclasts will also be examined. • Researchers will explore how CHMP5 regulates signaling pathways and protein degradation in OCs. • They will identify and validate factors secreted by CHMP5-deficient OCs that stimulate osteoblast activity.

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			Drug Development: The study aims to understand how CHMP5 regulates osteoclast activity and its coupling with osteoblast function. This knowledge could be used to develop new therapies for bone loss disorders. **Key Points:** • Balanced activity of osteoclasts (bone breakdown) and osteoblasts (bone formation) is crucial for healthy bone remodeling. • Current osteoporosis treatments can disrupt this balance. • CHMP5 dampens a signaling pathway important for OC activity and its coupling with osteoblasts. • The study investigates how CHMP5 deficiency affects bone remodeling in mice and humans. • Identifying factors that stimulate osteoblast activity from CHMP5-deficient OCs could lead to new treatments for bone loss. This abstract describes a pre-clinical study investigating the role of CHMP5 in osteoclasts and its potential for developing new treatments for bone disorders characterized by bone loss.
WEILL MEDICAL COLL OF CORNELL UNIV	TUNG, CHING-HSUAN	Novel approach to promote bone formation in osteoporosis using bone-homing mesenchymal stem cells	**Research Question:** Can targeting the protein Schnurri-3 (SHN3) promote bone formation and treat osteoporosis? **Stage:** In vivo (using mice) **Methods:** • The study will investigate the use of mesenchymal stem cells (MSCs) with reduced SHN3 function for bone repair in osteoporosis models. • Researchers will optimize methods to label and deliver these modified MSCs to bone tissue. • They will assess the effectiveness of these cells in restoring bone loss in mice with osteoporosis caused by estrogen deficiency or aging. • The study will also identify factors secreted by SHN3-deficient MSCs that stimulate bone formation. **Drug Development:** The study aims to develop a new approach for treating osteoporosis by transplanting bone-homing MSCs with reduced SHN3 function. This approach could potentially stimulate bone formation without the side effects associated with current osteoporosis drugs.

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			Key Points: • Imbalance between bone formation and breakdown leads to osteoporosis. • Most osteoporosis drugs target bone breakdown, but new drugs that stimulate bone formation are needed. • SHN3 suppresses bone formation. Mice lacking SHN3 have increased bone mass. • The study explores transplanting MSCs with reduced SHN3 function to promote bone healing in osteoporosis models. • Researchers will also identify factors secreted by these modified MSCs that could be future drug targets. This abstract describes a pre-clinical study investigating the use of genetically modified MSCs as a potential new treatment for osteoporosis. The approach targets the SHN3 protein to stimulate bone formation and could offer advantages over current osteoporosis drugs.
UNIV OF MASSACHUSETTS MED SCH WORCESTER	GRAVALLESE, ELLEN M	Novel approaches to the treatment of bone loss in rheumatoid arthritis	**Research Question:** Can targeting the protein Schnurri-3 (SHN3) promote bone formation and prevent bone loss in rheumatoid arthritis (RA)? **Stage:** In vivo (using mice) **Methods:** • Researchers will investigate SHN3 deficiency in mesenchymal stem cells (MSCs) to promote bone formation in RA models. • They will examine if SHN3 deficiency protects against systemic bone loss caused by inflammatory factors. • The study will explore the molecular mechanisms by which SHN3 affects bone formation and how it might be regulated by inflammatory signals. • The researchers will also assess the effectiveness of transplanting SHN3-deficient MSCs to promote bone healing in RA models. **Drug Development:** The study aims to develop a new approach for treating bone loss in RA by targeting SHN3 in MSCs. This could potentially stimulate bone formation and offer advantages over current therapies. **Key Points:** • RA causes bone erosion and systemic bone loss, contributing to pain and disability.

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			• SHN3 suppresses bone formation. Mice lacking SHN3 have increased bone mass. • Inflammatory factors in RA increase SHN3 expression in bone-forming cells. • SHN3 deficiency protects these cells from the suppressive effects of inflammatory molecules. • The study explores using SHN3-deficient MSCs to promote bone formation and prevent bone loss in RA models. This abstract describes a pre-clinical study investigating the potential of targeting SHN3 in MSCs as a new treatment for bone loss associated with RA. This approach could lead to improved bone health for RA patients.
UNIVERSITY OF MARYLAND BALTIMORE	CHELLAIAH, MEENAKSHI A	L-plastin: a novel target for intervention in the treatment of osteoporosis	**Research Question:** Can targeting the protein L-Plastin (LPL) help develop new treatments for osteoporosis with fewer side effects? **Stage:** In vivo (using mice) with some in vitro studies planned **Methods:** • Researchers will investigate the role of LPL in osteoclast (OC) function, which is important for bone breakdown. • They will focus on LPL phosphorylation, a process regulated by TNF-α signaling. • Mice with LPL deficiency will be used to assess its impact on bone remodeling. • The effects of inhibiting LPL phosphorylation on bone loss in models of aging and estrogen deficiency will be examined. **Drug Development:** The study aims to identify LPL as a target for new osteoporosis drugs that specifically inhibit OC function without affecting bone formation by osteoblasts. This could address limitations of current osteoporosis medications. **Key Points:** • Osteoporosis is a major public health problem, especially for postmenopausal women. • Current osteoporosis drugs target OCs but may also suppress bone formation.

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			• LPL is essential for sealing ring formation, which is crucial for OC function. • LPL-deficient mice have impaired bone resorption but normal bone formation. • The study explores how LPL phosphorylation by TNF-α affects sealing ring formation and bone loss. • Inhibiting LPL phosphorylation might be a strategy for developing new osteoporosis drugs with improved side effects. This abstract describes a pre-clinical study investigating LPL as a potential target for new osteoporosis treatments. By focusing on a protein specific to OC function, this approach could offer advantages over current medications.
UNIV OF MASSACHUSETTS MED SCH WORCESTER	SHIM, JAE-HYUCK	Identification of novel regulators governing osteoclast-osteoblast coupling	**Research question**: Investigating the role of CHMP5 in osteoclast (OC) and osteoblast (OB) coupling and its implications for bone remodeling disorders, particularly Paget's disease of bone (PDB). **Stage**: In vitro and in vivo with animals. **Methods**: The study aims to determine the effects of OC-specific deletion of CHMP5 on PDB-like phenotypes in mice through hematopoietic stem cell transfer experiments. Additionally, biochemical studies will be conducted to elucidate the mechanisms by which CHMP5 regulates NF-κB signaling and ubiquitin-mediated proteasomal degradation in OCs. Proteomic analysis and validation studies will be employed to identify and characterize CHMP5-regulated proteins involved in NF-κB signaling and osteoclastogenesis. Furthermore, the study will investigate OC-derived factors promoting OB activity using mass spectrometry and functional assays. **Drug development**: Understanding the role of CHMP5 in OC/OB coupling may lead to the development of novel therapies for bone remodeling disorders such as PDB by targeting pathways that enhance bone formation while mitigating excessive bone resorption.
Hokkaido University	Terukawa Hendo	Exploring therapeutic effects of anti-inflammatory and resolving factors in	**Research Question:** Can annexin A1, a protein with anti-inflammatory properties, be used to treat osteoporosis? **Stage:** In vivo (using mice) **Methods:**

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		osteoporosis model mice	• Mice with osteoporosis will be divided into two groups: one receiving annexin A1 and a control group that does not. • Researchers will compare bone mass between the two groups to assess the effectiveness of annexin A1 treatment. **Drug Development:** The study aims to determine if annexin A1 can be a new treatment for osteoporosis by targeting inflammation associated with bone loss. **Key Points:** • Osteoporosis is a disease characterized by decreased bone mass. • Annexin A1 has anti-inflammatory effects. • The study investigates whether annexin A1 can prevent bone loss in a mouse model of osteoporosis. • Researchers will compare bone mass in mice treated with annexin A1 to a control group. This abstract describes a pre-clinical study to investigate the potential of annexin A1 as a new treatment for osteoporosis. By targeting inflammation, this approach could offer a novel strategy for managing this bone loss condition.
Toho University	Kaichi Kaneko	Elucidation of the pathogenesis of glucocorticoid-induced osteoporosis targeting newly identified circulating osteoclast precursor cells	**Research Question:** How do steroids contribute to osteoporosis by affecting osteoclast precursor cells (OPCs)? **Stage:** In vitro (using human blood samples) **Methods:** • Researchers will analyze OPCs from the blood of patients with collagen disease before and after steroid treatment. • They will compare changes in these cells to understand how steroids might influence their differentiation into osteoclasts, the cells responsible for bone breakdown. **Drug Development:** The study aims to improve understanding of how steroids affect OPCs, which could be a target for new treatments to prevent steroid-induced osteoporosis. **Key Points:** • Steroid use can cause osteoporosis by increasing bone breakdown by osteoclasts. • OPCs differentiate into osteoclasts.

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			• The study investigates changes in OPCs from patients with collagen disease before and after steroid treatment. • Understanding how steroids affect OPCs could lead to new treatments for steroid-induced osteoporosis. This abstract describes a study using blood samples to investigate the role of OPCs in steroid-induced osteoporosis. This research could provide valuable insights for developing new therapies to prevent bone loss caused by steroid medications.