OA Preclinical Landscape - DRAFT

Organization Name	Contact PI / Project Leader	Project Title	OniX Summary
BRIXTON BIOSCIENCES, INC.	SIDOTI, CHARLES	Injectable Ice Slurry Cooling Technology for Treatment of Postoperative Pain	**Research question:** Can a newly developed injectable ice-slurry method be used for cryoneurolysis to reduce post-operative pain following total knee arthroplasty (TKA) surgery, thereby reducing opioid dependence? **Stage:** Early development (Phase I) **Methods:** • Develop a commercial prototype device to create a sterile, injectable ice-slurry on-demand. • Test the design for syringes to generate the ice-slurry and measure heat extraction. • Evaluate the feasibility of injection through a standard needle and in-vivo tissue cooling using a rat model. **Drug development:** Not applicable (non-pharmaceutical intervention)
CASE WESTERN RESERVE UNIVERSITY	ZHOU, GUANG	Jab1-BMP signaling interaction in chondrocyte differentiation	**Research question:** How does Jab1, a transcriptional cofactor, interact with BMP signaling during the process of chondrocyte differentiation (cartilage cell development)? **Stage:** Early investigation (uses in vitro and in vivo with animals) **Methods:** • Analyze the molecular mechanisms of Jab1-BMP interaction in chondrocytes (Aim 1). • Use genetic engineering to manipulate Jab1 expression in chondrocytes and assess its effect on BMP-driven cartilage formation in developing embryos (Aim 2). • Identify Jab1 target genes through RNA sequencing and chromatin immunoprecipitation sequencing (Aim 3). **Drug development:** Not applicable (focuses on understanding a biological process)

UNIVERSITY OF PENNSYLVANIA	SCANZELLO, CARLA ROSE	Modulation of Inflammation in Osteoarthritis via CD14-mediated pattern recognition	**Research question:** Does CD14, a molecule involved in inflammation, directly contribute to both the pain and pathology (bone remodeling and inflammation) observed in osteoarthritis (OA)?
			Stage: In vivo (using mice) and in vitro
			Methods:
			• Use a mouse model of OA (DMM) to assess the impact of CD14 deficiency on inflammation and bone remodeling (Aim 1).
			  ○ Techniques include examining bone marrow chimeric mice to understand the role of myeloid cells.
			  ○ Investigate how CD14 affects the development of bone-remodeling cells and inflammatory mediators.
			• Evaluate the effects of CD14 on nerve cell activation and pain response using TLR stimulation (Aim 2).
			  ○ Compare responses of normal and CD14-deficient cells in vitro.
			  ○ Analyze pain response in mice after joint injection with TLR stimulants.
			• Test the effectiveness of a drug targeting CD14 in reducing OA progression and pain in mice (Aim 3).
			Drug development: Potential application (investigating a potential therapeutic target)

KYTARO, INC.	GAITAS, ANGELO	Novel single cell disease markers with a hybrid AFM scanning piezo-thermal probe	**Research question:** Can a new microscopic imaging tool using piezo-thermal probes distinguish between healthy and diseased cells based on mechanical and thermal properties? **Stage:** Early development (Phase I SBIR) **Methods:** • Design and develop micromachined scanning piezo-thermal probes for use in liquids (aqueous environments). • Build an interface circuit and specialized software to operate the probes. • Demonstrate the system's ability to create thermal and topographical images of cells. • Test if the system can differentiate between healthy and diseased cells based on thermal and mechanical properties. **Drug development:** Not directly applicable, but the technology has the potential to be used in drug discovery (exploring single cell disease markers).

CORNELL UNIVERSITY	REESINK, HEIDI	Engineering recombinant lubricin to combat orthopedic infection	**Research question:** Can lubricin, a protein with both adhesive and anti-adhesive properties, be used to prevent and treat biofilms on orthopedic implants?
			Stage: Early investigation (applying for funding to continue research after K08 award)
			Methods:
			• Investigate how lubricin inhibits biofilm formation and disrupts existing biofilms (Aim 1)
			  ○ Test in different environments (growth media, synovial fluid, titanium alloy)
			• Determine if specific sugar molecules (O-glycans) on lubricin are important for its anti-biofilm effects (Aim 2)
			  ○ Engineer lubricin molecules with different O-glycan structures
			Drug development: Potential application (investigating a new use for an existing molecule)
			Additional notes:
			• This research could lead to new treatments for orthopedic implant infections.
			• The applicant has expertise in veterinary orthopedics and is collaborating with specialists in glycoengineering and biofilm research.

CLEVELAND CLINIC LERNER COM-CWRU	SUBHAS, NAVEEN	MRI Predictors of Outcome after Arthroscopic Partial Meniscectomy	**Research question:** Can preoperative magnetic resonance imaging (MRI) be used to predict which patients over 45 years old will benefit from arthroscopic partial meniscectomy (APM) surgery for knee pain and dysfunction? **Stage:** Data analysis (using existing data set) **Methods:** • Analyze data from a large existing cohort of patients (over 1000) who underwent APM surgery. • Patients were all over 45 years old and have preoperative MRI scans and patient-reported outcome measures (PROMs) at baseline and 1 year after surgery. • Use statistical modeling to identify preoperative MRI features that are associated with improvement in pain and function after surgery. • Develop tools to predict which patients are unlikely to benefit from APM surgery based on these MRI features. **Drug development:** Not applicable **Additional notes:**

			• This study could help improve decision-making about APM surgery for older patients with knee pain. • The researchers plan to use the results of this study to design a future randomized controlled trial.

RUSH UNIVERSITY MEDICAL CENTER	MILLER, RACHEL ELIZABETH	Biomechanical Pathways Associated with Osteoarthritis Pain	**Research question:** How does mechanical stress contribute to pain in osteoarthritis (OA)?
			Stage: Early investigator career development
			Methods:
			• Dr. Miller will receive training in techniques to study nerve cells, calcium signaling, and the application of mechanical stress to tissues.
			• The research will use a mouse model of OA to investigate:
			  ○ Responses of nerve endings in the joint to mechanical stimulation (Aim 1).
			  ○ How mechanical stress affects the production of pain-inducing molecules by cartilage cells (Aim 2).
			  ○ The types of ion channels present in cartilage cells and their response to mechanical stress (Aim 3).
			Drug development: Not directly applicable, but the research could lead to improved treatments for OA pain.
			Additional notes:
			• This is a proposal for a career development award to support Dr. Miller's research on OA pain.
			• The research will be conducted at Rush University Medical Center, which has a strong research environment for studying arthritis.

OKLAHOMA MEDICAL RESEARCH FOUNDATION	JAMES, JUDITH A	Oklahoma Rheumatic Disease Research Cores Center (Overall Application)	**This is a proposal for a Rheumatic Disease Research Cores Center (ORDRCC) grant renewal.** **What the ORDRCC does:** • Connects researchers who study rheumatic diseases (like arthritis and lupus). • Maintains a large biorepository with samples from patients with these diseases. • Provides resources and training to junior investigators new to this field. • Offers pilot project funding and helps researchers write grant applications. **Goals of the ORDRCC:** • Improve collaboration between researchers.

			• Understand the causes and treatments of rheumatic diseases. • Identify subgroups of patients who might respond better to specific treatments (precision medicine). • Develop new investigators in this field. **Key resources:** • Clinical Characterization and Biorepository Core (CCBC): manages the biorepository and associated data. • Human Phenotyping Core (HPC): helps researchers perform advanced tests on patient samples. • Administrative Core: oversees the entire ORDRCC and provides support services. **Outcomes:** • Launched the careers of 27 new investigators. • Provides infrastructure for clinical trials at a lower cost.
WASHINGTON UNIVERSITY	SANDELL, LINDA J	The Dynamic Range of Site-1 Protease Functions in Skeletal Development	**Research question:** How does a protein called S1P influence the development and function of cartilage and bone? **Stage:** Early investigation (using genetically modified mice) **Methods:** • Analyze the effects of S1P deficiency on lipid composition and function of the endoplasmic reticulum (ER) in cartilage cells (Aim 1). • Investigate whether S1P is required to process a protein called Adamts3, which is important for cartilage development (Aim 2). • Study the role of Adamts3 in cartilage development using mice with a cartilage-specific Adamts3 deficiency. • Examine how S1P deficiency in cartilage and bone cells contributes to spinal abnormalities (hunchback and curvature of the spine) (Aim 3). **Drug development:** Not applicable (focuses on understanding a biological process) **Additional notes:** • S1P is known to be involved in fat metabolism and the stress response in the ER. • This research may provide insights into the causes of skeletal diseases like chondrodysplasia (abnormal cartilage development) and spinal deformities.

STANFORD UNIVERSITY	AIRAN, RAAG D	Clinical Translation of Ultrasonic Ketamine Uncaging for Non-Opioid Therapy of Chronic Pain	**Research question:** Can a non-invasive technique using ultrasound to release the drug ketamine specifically in the brain's anterior cingulate cortex (ACC) be a safe and effective treatment for chronic pain?
			Stage: Early clinical development (first-in-human trial)
			Methods:
			• Preclinical (UG3 phase):
			  ○ Scale up production of nanoparticles to meet human dosing standards and good manufacturing practices (GMP).
			  ○ Conduct additional animal studies for regulatory approval of a clinical trial.
			• Clinical trial (UH3 phase):
			  ○ Evaluate the safety and efficacy of the technique in patients with chronic osteoarthritis pain.
			  ○ Measure the amount of ketamine released based on the ultrasound dose.
			  ○ Assess if the released ketamine reduces pain sensitivity and emotional response to pain.
			Drug development: This is an application to develop a new method for delivering an existing drug (ketamine).
			Additional notes:
			• This approach aims to avoid the side effects of systemic ketamine administration by delivering it directly to the ACC, a part of the brain involved in pain processing.
			• Ultrasound is used to trigger the release of ketamine from tiny biocompatible carriers implanted in the brain.
			• If successful, this could be a new non-opioid treatment for chronic pain.

UNIVERSITY OF ALABAMA AT BIRMINGHAM	LI, YI-PING	Transcriptional Regulation of Osteoclast Lineage Commitment and Differentiation	**Research question:** How does the transcription factor C/EBPβ regulate the development and function of osteoclasts (cells that break down bone)? **Stage:** Early investigation (using genetically modified mice and cell cultures) **Methods:** • Analyze the effects of C/EBPβ deficiency on osteoclast development and function in mice (Aims 1 & 2). • Use genetic techniques to manipulate C/EBPβ expression in cultured osteoclast precursors (Aim 3).

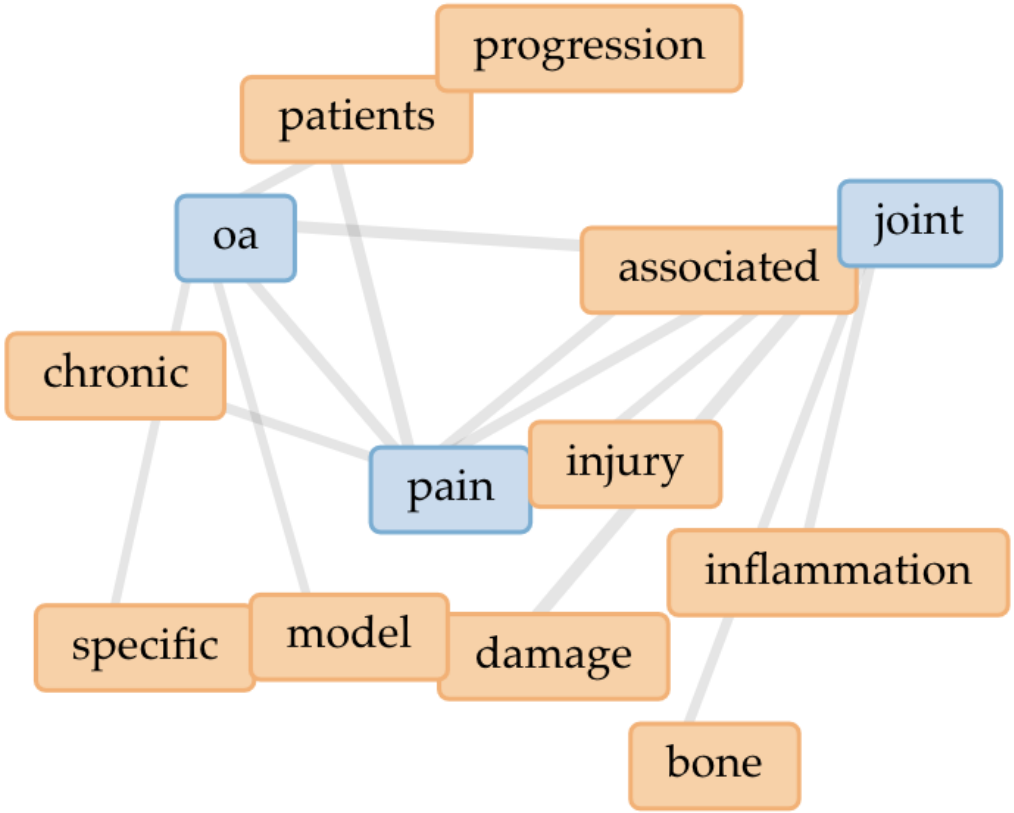
			• Identify the other proteins that C/EBPβ interacts with and the genes it regulates in osteoclasts (Aim 4). **Drug development:** Not directly applicable, but the research could lead to new treatments for bone diseases like osteoporosis and bone cancer. **Additional notes:** • C/EBPβ is a protein that binds to DNA and helps control gene expression. • Understanding how C/EBPβ works in osteoclasts could help develop new drugs to target these cells. • Current osteoporosis drugs may have side effects, so there is a need for new treatments.
UNIVERSITY OF PITTSBURGH AT PITTSBURGH	WOO, SAVIO L-Y.	Non-Contact ACL Injuries in Females: an In-Vivo and Robotic Study	**Research question:** Why are females more prone to non-contact ACL injuries than males? **Stage:** Data collection and analysis **Methods:** • Measure the forces and distribution of forces on the ACL during landing from a jump (Aim 1). • ○ In vivo (living subjects): Use high-speed X-ray imaging to track knee movements. • Ex vivo (dead bodies): Apply the measured movements to human knee specimens and measure ACL forces using a robotic testing system. • Investigate if an ACL injury prevention program reduces ACL forces in females (Aim 2). • Analyze the relationship between ACL forces, strains, and leg anatomy (Aim 3). • Use computer models to estimate stress and strain in the ACL (Aim 3). **Additional notes:** • This research could help explain why ACL injuries are more common in females and inform the development of better prevention strategies.
UNIVERSITY OF ROCHESTER	OVERBY, CLYDE THOMAS	Development of Anti-Fouling Peptide-Nanoparticle Conjugates for the Delivery of siRNA to Fractures	**Research question:** How can we improve the delivery of small interfering RNA (siRNA) drugs throughout the body (systemically)? **Problem:** Naked siRNA drugs degrade quickly and have trouble entering cells. Nanoparticles (NPs) can protect siRNA, but they get stuck in the immune system and don't reach target tissues well. **Current solutions:**

			• **PEGylation:** Coating NPs with a molecule (PEG) to reduce protein sticking, but this can also make the NPs less effective. **Proposed solution:** Coating NPs with specially designed **semi-randomized Zwitterionic Peptides (srZIPs)**. These peptides should reduce protein sticking while allowing the NPs to function effectively. **Methods:** • Develop a library of different srZIPs and test which ones prevent NPs from clumping together in blood serum (Aim 1). • See how well srZIP-coated NPs deliver siRNA into target cells and avoid uptake by immune system cells (Aim 2). • Test if srZIP-coated NPs carrying siRNA that helps bone healing can accumulate in fractured bones in mice (Aim 3). **Expected outcome:** Identify effective srZIPs for coating NPs, which could lead to new ways to deliver siRNA drugs throughout the body for various diseases, including bone problems.
UNIVERSITY OF FLORIDA	SHARMA, BLANKA	Nanoparticle targeting within the joint for site-specific delivery of osteoarthritis therapeutics	**Research question:** Can nanoparticles be designed to deliver drugs to specific locations within a joint to treat osteoarthritis (OA)? **Stage:** Early investigation (using animal models) **Problem:** OA damages cartilage and synovium (joint lining) but existing drugs don't stay in the right places long enough to be effective. **Proposed solution:** Develop nanoparticles that can deliver two different drugs: • **Chondroprotective drug (kartogenin) to protect cartilage** (Aim 1). • **Immunomodulatory drug (CD200) to reduce inflammation in the synovium** (Aim 2). **Methods:** • Design nanoparticles that stick to and enter cartilage to release kartogenin (Aim 1). • Design nanoparticles that target inflamed synovium and deliver CD200 (Aim 2). • Test if delivering both drugs together is more effective than either one alone (Aim 3). • Use laboratory models of OA to assess the effects of these nanoparticle therapies on joint health (cartilage structure, inflammation, pain, movement). **Expected outcome:** This research could lead to new treatments for OA that target multiple disease processes simultaneously and improve long-term joint health.

VALITOR, INC.	JACKSON, WESLEY MICHAEL	Anti-inflammatory bioconjugates for sustained inhibition of post-traumatic osteoarthritis following joint injury	**Research question:** Can a new drug delivery system be developed to provide long-lasting anti-inflammatory effects in joints after injury, potentially preventing post-traumatic osteoarthritis (PTOA)? **Stage:** Preclinical development (using animal models) **Problem:** • Existing anti-inflammatory drugs for PTOA need frequent injections because they are cleared from the joint too quickly. • Frequent injections increase the risk of side effects. **Proposed solution:** Develop a new drug delivery system that uses clusters of anti-inflammatory drugs. The size of the clusters can be controlled to determine how long the drug stays in the joint. **Methods:** • Develop and test drugs with different cluster sizes to see how long they stay in the joint (compared to existing drugs) (Aim 1). • Use a model of joint injury in animals to see if the longer-lasting drugs prevent PTOA from developing (Aim 1). **Expected outcome:** This research could lead to a new treatment for PTOA that requires fewer injections and has fewer side effects.

NATIONAL INSTITUTE ON AGING	LING, SHARI M.	Delineating Early Events Osteoarthritis of the Knee	**Research question:** How do body characteristics, gait mechanics, blood and urine proteins, muscle function, and inflammation contribute to osteoarthritis (OA) development?
			Stage: Early investigation (observational studies and animal models)
			Methods:
			• Epidemiological studies (BLSA):
			  ○ Following a group of people over time to see how body fat, muscle function, gait mechanics, and blood/urine protein levels are linked to OA risk.
			  ○ Looking at relationships between hand OA and arterial stiffness.
			• Clinical trials:
			  ○ Studying muscle strength, mass, and function in people with and without knee OA.
			  ○ Investigating how weight loss through exercise programs affects inflammatory markers in knee OA.
			• Animal models:

			○ Studying muscle properties in response to OA and physical inactivity. **Drug development:** Not directly mentioned, but the research aims to better understand OA to inform future treatment strategies.
UNIVERSITY OF TEXAS HLTH SCI CTR HOUSTON	MILEWICZ, DIANNA M	Mutations in Smooth Muscle Contractile Proteins: Pathways to Vascular Diseases	**Research question:** How do mutations in smooth muscle cell (SMC) genes cause vascular diseases? **Stage:** Preclinical development using animal models **Methods:** • Lab studies (Projects 1 & 2) will use cells in vitro to investigate how mutations affect SMC protein function. • Project 3 will use mouse models with the mutations to study how SMC function changes with age and how blood vessels respond. • Project 4 will use the same mouse models to study cellular processes leading to aneurysms and arterial blockages. **Drug development:** Not directly mentioned, but the research could inform the development of new treatments for vascular diseases.
FLORIDA ATLANTIC UNIVERSITY	BREW, KEITH	TIMP Engineering and Application to Arthritis	**Research question:** Can tissue inhibitors of metalloproteinases (TIMPs) be engineered to selectively block enzymes that degrade cartilage, potentially treating arthritis? **Stage:** Preclinical development (using animal models and cells) **Methods:** • Study how TIMPs interact with enzymes that break down cartilage (aggrecanases and MMPs) (Aim 1 & 4). • Design and create TIMP variants that target specific enzymes (Aim 2 & 3). • Test the effectiveness of these TIMP variants in lab models (cartilage explant system) (Aim 5). • Test the effectiveness of TIMP variants in animal models of arthritis (Aim 6). • Identify the enzymes involved in human cartilage breakdown (Aim 7). **Drug development:** Yes, this research directly aims to develop new drugs (TIMP variants) to treat arthritis.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