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The John W. and Helen H. Watzek
Professor of Biochemistry



Advancement of Medicine

In 2025, the John W. and Helen H. Watzek Endowment continued to play a central role in supporting my research on bone and joint health at Rush. My work is focused on finding better ways to prevent and treat conditions such as osteoarthritis, fractures, osteoporosis, genetic bone disorders, and the bone complications that can follow weight management-related loss.

Over the past year, the endowment allowed my research team to pursue new approaches to understanding how bones heal and grow, how joints are protected from degeneration and why these natural processes sometimes fail. We are identifying key signals and mechanisms inside bone and joint tissues that can be targeted with future therapeutics to slow joint damage, reduce pain, improve fracture recovery, and preserve bone strength and growth. These efforts are especially important because osteoarthritis and osteoporosis together affect more than 42 million Americans and remain leading causes of chronic pain, disability and loss of independence.

Research

Osteoarthritis and Joint Protection

Our laboratory has made significant progress toward developing a new treatment for osteoarthritis. We have identified a naturally occurring protein, interleukin-36 receptor antagonist, or IL-36Ra, that can protect joint tissue from damage and lessen pain. In pre-clinical studies, we showed that injecting IL-36Ra directly into affected joints reduces cartilage degeneration and improves comfort and mobility. We also discovered that part of this protective effect occurs through a related pathway known as SIGIRR.

Our long-term goal is to create a long-acting injectable therapy that can slow or stop the progression of osteoarthritis without causing unwanted side effects elsewhere in the body. To move this work closer to patients, we submitted a multi-year grant to the National Institutes of Health in June 2025.



The proposal received a positive scientific review and was considered competitive, and we are preparing a strengthened resubmission this year. Building on these discoveries, we also filed a U.S. non-provisional patent application to protect this novel technology and support its future development.

Fracture Healing and Skeletal Growth

Another major focus of our research is understanding how bones repair themselves after injury and why this regenerative capacity declines or fails in many patients. We have been studying a gene called PRRX1, which plays a critical role in bone growth and development and in cartilage health. Our studies demonstrate that when PRRX1 is absent in the stem cells of bones and joints, fractures fail to heal properly, growth is impaired, and cartilage becomes fragile and degenerative.

Using advanced technologies such as single-cell RNA sequencing and spatial transcriptomics, we found that PRRX1 helps regulate the body's response to oxidative stress—an important driver of tissue damage, failure of repair and aging. We are also exploring how this pathway relates to SHOX deficiency, the most common genetic cause of short stature, which affects at least 1 in 1,000 people. These discoveries have laid the foundation for a new NIH grant that we are preparing to submit.

Bone Health After Weight-Management-Related-Loss

We also investigated how bariatric surgery and drug-induced weight loss affect bones and glucose metabolism. In pre-clinical studies, we tested sclerostin — an FDA-approved treatment for osteoporosis — and found unexpected benefits beyond the skeleton. After bariatric surgery, sclerostin improved insulin sensitivity and glucose control while also strengthening bone. However, it increased bone porosity, underscoring the complexity of treating patients who face both metabolic disease and skeletal fragility.

Our data suggests that these effects are linked to GLP-1 signaling, the same pathway targeted by widely used medications for diabetes and weight control. With approximately 12% of U.S. adults now using GLP-1 therapies, understanding how these drugs influence bone health has become an urgent public health priority.



Recognition and Leadership

Thanks to the support of the John W. and Helen H. Watzek Endowment, I have been able to contribute to the broader scientific and medical community. In 2025, I served as liaison between the American Society for Bone and Mineral Research, or ASBMR, and the World Health Organization, helping shape global strategies to improve the diagnosis and prevention of osteoporosis. I also served on the board of the International Federation of Musculoskeletal Research Societies and on the ASBMR Ambassador Sub-Committee. I was invited to participate as an expert in the WHO Policy Brief on modernizing health information systems to better detect fracture risk and osteoporosis. I was deeply honored to be nominated for and placed on the ballot for president of ASBMR, one of the highest recognitions of leadership in our field. I continue to serve as co-editor of *Current Osteoporosis Reports*, supporting the communication of new discoveries to clinicians and scientists worldwide.

Grants

I am the principal investigator of an NIH R01 proposal titled “Sustained Intra-Articular Release of IL-36Ra-HGC, a Novel Disease-Modifying Therapy for Post-Traumatic Osteoarthritis.” The project seeks to determine whether this new treatment can slow joint deterioration and relieve pain in both animal models and human tissues. The application was reviewed in December 2025 and received encouraging feedback; we plan to resubmit an improved version this year.

In addition, as principal investigator, I am developing a second multi-year NIH proposal focused on PRRX1 and fracture repair, with planned submission in June 2026.

Patent Filed

To advance our research work toward real-world therapies, a U.S. non-provisional patent application, based on International Application No. PCT/US2024/039664, has been filed by Rush University Medical Center; Inventor: Anna Spagnoli. The patent, titled “*Novel Chitosan-IL-36Ra Conjugates for Adjustable, Sustained Release and Tissue Distribution*,” describes a new technology designed to deliver IL-36Ra to joints in a controlled and long-lasting manner. This approach aims to extend the therapeutic benefits of IL-36Ra while minimizing the need for repeated injections and reducing the risk of side effects, bringing this potential osteoarthritis treatment closer to clinical use.

Selected Presentations to Scientific Meetings

- **Distinct Expression and Heme Homeostasis Patterns of Prrx1+ Chondroprogenitors in Limb Growth Plates: Conditional Ablation of Prrx1 Elucidates Mechanisms Underlying Chondrodysplasia** Sai Rama Krishna Meka, Michael Klüppel, Pranav K. Mishra, Tanishka Khurana, Alfonso Torquati, Anna Spagnoli. Presented at the Annual Meeting of the Orthopedic Research Society - February 2025.
- **Unexpected Effects of Sclerostin Antibody (SOST-Ab) on Bone Health in Ovariectomized Mice Undergoing Bariatric Surgery: New Insights on Bone Loss** . Adrian E. Rodrigues, Katrien Corbeels, Pranav Kumar Mishra, Michael Klüppel, Sai Rama Krishna Meka, Tanishka Khurana^{1,2}, Alfonso Torquati, and **Anna Spagnoli**. Presented at the Annual Meeting of the American Society for Bone and Mineral Research - September 2025.
- **The PRRX1-SHOX axis is a novel regulator of chondrocyte hemoglobin and growth plate maturation with implications for mitochondrial homeostasis: Lessons learned from Prrx1^{cko}** Sai Rama Krishna Meka, Michael Klüppel, Pranav Mishra, Tanishka Khurana, Adrian E. Rodrigues, Alfonso Torquati, and **Anna Spagnoli**. Presented at the Annual Meeting of the American Society for Bone and Mineral Research - September 2025.
- **Growth plate cell annotations from scRNA-seq: a transfer learning model for murine developmental tissues** Pranav Mishra, Sai Rama Krishna Meka, Michael Klüppel, Tanishka Khurana, Adrian E. Rodrigues, Alfonso Torquati, and Anna Spagnoli. Presented at the Annual Meeting of the American Society for Bone and Mineral Research - September 2025.
- **Roux-en-Y Gastric Bypass Followed by Sclerostin Inhibition Improves Murine Bone Mechanical Competence** Adrian E. Rodrigues, Katrien Corbeels, Pranav Kumar Mishra, Michael Klüppel, Sai Rama Krishna Meka, Tanishka Khurana, Brittany M. Wilson, Alfonso Torquati, and **Anna Spagnoli**. Accepted for presentation to the Annual Meeting of the American Society for Metabolic and Bariatric Surgery (ASMBS)
- **Creation of a longitudinal bariatric biobank to explore the Bone-Fat-Glucose Interface using next-generation multiomics** Pranav K. Mishra, Adrian E. Rodrigues, Michael Klüppel, Tanishka Khurana, Nicholas Skertich, Philip Omotosho, Alfonso Torquati, and **Anna Spagnoli**. Accepted for presentation to the Annual Meeting of the American Society for Metabolic and Bariatric Surgery (ASMBS)

Manuscripts submitted or in preparation for publication

- **Roux-en-Y Gastric Bypass Followed by Sclerostin Inhibition Improves Murine Bone Mechanical Competence and Metabolic Parameters** Adrian E. Rodrigues, Katrien Corbeels PhD, Pranav Kumar Mishra, Michael Klüppel, Tanishka Khurana, Philip A. Omotosho, Brittany M. Wilson, Alfonso Torquati, and **Anna Spagnoli** Manuscript in preparation to be submitted to *Annals of Surgery*
- **Reimagining Health Management Information Systems to Detect Osteoporosis and Fracture Risk: a policy brief from the World Health Organisation (WHO).** Marc Sim, Amy Vassallo, Germain Honvo, Bo Abrahamsen, Sandra Bartein, Ching Lung Cheung, María Diehl, Gustavo Duque, Ghada El-Hajj Fuleihan, Noushin Fahimfar, Claus Gluer, Ceclia Celia L Gregson, Namki Hong, Muhammad Kassim Javaid, Flavia Matovu Kiweewa, William D Leslie, Kebba Marenah, Lisa Micklesfield, Kyoung Min Kim, Lee Nedkoff, John T Schousboe, Anna Spagnoli, Kate Ward, Ling Wang, Jotheeswaran Amuthavalli Thiyagarajan, Joshua R Lewis. In preparation

The Year Ahead: 2026 and Beyond

In the coming year, I will continue to expand our translational research program aimed at helping patients maintain healthy, pain-free movement throughout life. Our priorities include advancing IL-36Ra therapy toward clinical development as a potential treatment for osteoarthritis, deepening our understanding of how bones regenerate after injury and clarifying how new weight-loss medications influence skeletal health. We will also build on our discoveries related to PRRX1, with the goal of developing new strategies to improve fracture repair and to address forms of genetic short stature that affect children and adults worldwide.

At the same time, I will continue my collaboration with the World Health Organization and the American Society for Bone and Mineral Research to help define updated global guidelines for osteoporosis, contribute to initiatives on artificial intelligence in bone health and support international strategies for earlier detection of fracture risk. Together, these efforts aim to translate scientific discoveries into practical advances that improve quality of life for patients at all ages.



With Gratitude

I remain deeply grateful to John W. Watzek, Jr. and his family for establishing this professorship in honor of his parents, John W. and Helen H. Watzek. Their generosity makes it possible for my team to pursue innovative research that has the potential to ease suffering and improve the lives of millions. I am honored to carry forward their legacy through this work.