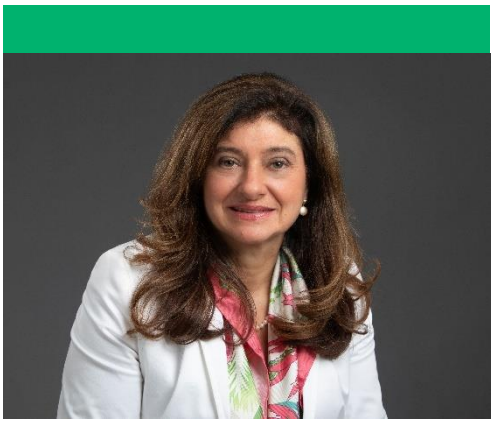
RUSH

Anna Spagnoli, MD

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



Advancement of Medicine

In 2024, the John W. and Helen H. Watzek Endowment was a vital source of support for my research in bone and joint health and diseases at Rush.

My primary research interest is in developing new therapies to treat joint and bone diseases, with a specific focus on osteoarthritis, fracture repair, bone health and osteoporosis.

This past year, the endowment provided me with the resources necessary to support our studies identifying innovative ways to discover novel targets for developing therapies to treat osteoarthritis, promoting healing in fractured bones, and assessing fracture risk in patients undergoing weight-management surgery. Our goal is to develop novel therapies to treat osteoarthritis and fractures due to osteoporosis, two conditions that affect more than 42 million Americans.

Research

Our studies on osteoarthritis have led to the submission of a multi-year grant to the National Institutes of Health that was submitted in February 2025. Our studies have led to the identification of a novel drug called interleukin 36 receptor antagonist — or IL-36Ra — that we have shown to be capable of protecting the joints from the degenerative effects of osteoarthritis and to treat the joint pain associated with osteoarthritis. Specifically, we have shown that when IL-36Ra is locally injected into the joints, it can treat the joint damage and the pain associated with osteoarthritis. Our goal is to develop a novel, long-acting joint-injectable drug that, without causing systemic side effects, can prevent the progression and treat the pain of osteoarthritis, a disease that affects more than 30 million Americans.

Our studies on fracture healing and fracture risk have led to the characterization of the function of two critical molecular factors. One is the growth factor known as insulin-like growth factor, or IGF, which we have shown is essential for maintaining bone density and promoting fracture healing. The

other molecular factor is the gene PRRX1. We have demonstrated its critical role in fracture healing and skeletal growth, particularly its functional relationship with the most common form of genetic short stature, SHOX deficiency, which affects at least 1 in 1,000 people. As a result of these studies, we are in the process of submitting a multi-year grant to the NIH.

In our studies assessing the effects of weight-loss surgeries on bone health, we have evaluated the effects of sclerostin, an FDA-approved treatment for osteoporosis, after bariatric surgery. Specifically, in pre-clinical studies, we found that bariatric surgery has a detrimental impact on bone health, and this effect is not reversed by sclerostin treatment, leading to the discovery of unexpected sclerostin resistance and potentially an interplay between sclerostin and GLP-1 signaling. GLP-1 signaling has been the target of the new class of effective weight-control and diabetes-control drugs that have reached global attention and clinical use. According to some polls, 12% of the U.S. adult population has used or is currently using GLP-1 medications.

Recognition and Leadership

In the 2024-2025 period, thanks to the support of the John W. and Helen H. Watzek endowment, the research community of professional societies and federal agencies have recognized me. I have served as an ad hoc member of the National Institutes of Health's Skeletal Biology Development and Disease Study Section. I was appointed the liaison officer between the American Society for Bone and Mineral Research and the World Health Organization WHO; a member of the Ambassador Sub-Committee of the American Society for Bone and Mineral Research; and a member of the Annual Meeting Program Committee of the American Society of Bone & Mineral Research Society. I continue to serve as co-editor of *Current Osteoporosis Reports*.

Grants

I have submitted a proposal for an R01 grant from the NIH titled "Sustained Intra-Articular Release of IL-36Ra-HGC, a Novel DMOAD for Treating and Controlling Pain in Post-Traumatic Osteoarthritis." The overall goal of the grant is to determine, in pre-clinical animal and human studies, the therapeutic efficacy of IL-36Ra-HCG as a disease-modifying osteoarthritis drug to treat joint degeneration and ameliorate pain in post-traumatic osteoarthritis, including in exercise-active joints. I serve as the principal investigator.

I am in the process of submitting a multi-year NIH grant by November 2025 related to the work on fracture repair and skeletal growth.

Poster Presentations — Abbreviated

- Mishra PK, Meka SRK, Klüppel M, **Spagnoli A.** Understanding novel-tissue parameters in single-cell RNA sequencing through novel and systematic pipelines. Poster presentation ASBMR Annual Meeting 2024
- Mishra PK, Meka SRK, Klüppel M, Hakimiyan A, Chubinskaya S, Wimmer M, **Spagnoli A.** Role of IL-36RA on human chondrocyte homeostasis in osteoarthritis and post-traumatic osteoarthritis models. Poster presentation ASBMR Annual Meeting 2024
- Meka SRK, Mishra PK, Klüppel M, **Spagnoli A.** Limb-specific Prrx1 expression in postnatal skeletal morphogenesis. Poster presentation ASBMR Annual Meeting 2024
- Mishra PK, Meka SRK, Klüppel M, Ozkan H, Ozkan E., **Spagnoli A.** Singling Out Sources of Error in Novel-Tissue Single-Cell RNA Sequencing. Annual Meeting Orthopaedic Research Society (ORS 2024) Poster presentation.

The Year Ahead: 2025 and Beyond

In the year ahead, I will continue to expand my multifaceted clinical and translational research program on fracture repair, the mechanisms underlying bone fragility and the development of a long-acting injectable drug to treat osteoarthritis. I will also expand my role as the liaison officer between the American Society for Bone and Mineral Research and the WHO by contributing to the definition of the new guidelines for defining osteoporosis and participating in the Artificial Intelligence for Bone Health working group. I interviewed with the nominating committee of the American Society of Bone & Mineral Research Society for inclusion on the ballot for president of the society. It has been an honor to have been selected by the committee, and I look forward to the next steps in the election process.

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With Gratitude

I would like to express my immense gratitude and thoughts to John W. Watzek Jr. and his family, who established this endowed professorship in memory of his parents, John W. and Helen H. Watzek. Without the support of the endowment, this exciting breakthrough research would not be possible.