NewYork-Presbyterian
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ADVANCES IN RHEUMATOLOGY

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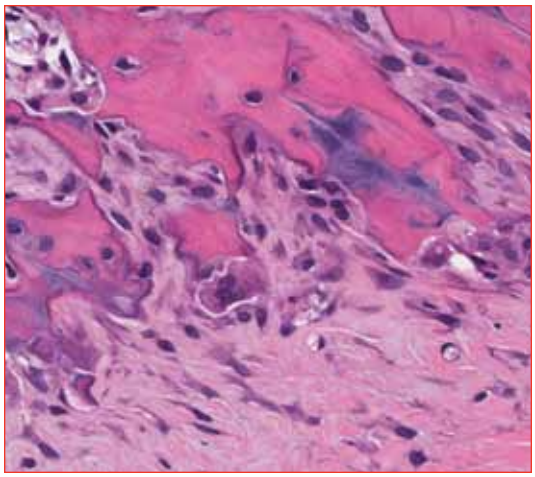
SPECIAL EDITION

Osteoimmunology Research Yields Significant Findings Affecting Diverse Group of Diseases

Weill Cornell Medical College, a teaching affiliate of NewYork-Presbyterian Hospital, is among the top-ranked clinical and medical research centers in the country. The advanced research at Weill Cornell Medical College furthers medical science and improves clinical practice, and many of the physicians with academic appointments at the College also practice medicine at NewYork-Presbyterian/Weill Cornell Medical Center. Here, the Dean of Weill Cornell Medical College discusses research that explores both the immune and skeletal systems, with wide-ranging implications.



Osteoclasts lining scalloped edges of bone.

"We are undertaking advanced research in areas such as inflammatory arthritides and lupus, and are engaged in important research in skeletal biology, particularly as it relates to inflammatory diseases, cancer, osteoporosis, and osteoarthritis," Laurie H. Glimcher, MD, said.

She added, "At Weill Cornell Medical College, we have a very vigorous rheumatology research group. I think it is very important for the academic community to realize that we are fully committed to strengthening our research even further, and one way we will do that is through additional recruits."

As Stephen and Suzanne Weiss Dean of Weill Cornell Medical College, where she is also Professor of Medicine, Dr. Glimcher is clearly well positioned to state these goals, but she also happens to be an example of this commitment herself. Dr. Glimcher was recruited a year ago from her position as the Irene Heinz Given Professor of Immunology at the Harvard School of Public Health, where she was Director of the Division of Biological Sciences. She was also Professor of Medicine at Harvard Medical School, directing its immunology program, and Senior Physician and Rheumatologist at Brigham and Women's Hospital, in Boston.

Dr. Glimcher's research laboratory has made several notable discoveries, many of which have centered on the pathophysiologic immune responses affecting autoimmune, infectious, and malignant diseases. In an emerging field that has been called osteoimmunology, the interrelationships between cells of the immune and skeletal systems are explored, which has led to discoveries that increase understanding of the basic science and eventually may lead to advanced therapeutics for a range of disorders.[1] Such discoveries have led to her election into several prominent scientific institutions, including the National Academy of Sciences and the Institute of Medicine.

Osteoimmunology centers on the fact that the skeleton is continually engaged in osteoclast-mediated bone resorption coupled with osteoblast-mediated bone deposition. "The osteoblast has been shown to be the niche where hematopoietic stem cells emerge within the bone marrow," Dr. Glimcher explained. "The osteoblast creates factors and provides the environment that allows hematopoietic stem cells to differentiate, and supports the immune system. Correspondingly, the cells of the immune system—T and B cells and macrophages—secrete inflammatory cytokines that activate the osteoclast and lead it to resorb bone. So, for example, in rheumatoid arthritis you find activated macrophages that differentiate into osteoclasts under inflammatory signals as well as signals from osteoblasts, which cause bony erosive lesions."

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Robotic Applications and Operating Room Technology Are Transforming the Post-Op Surgical Experience

Building on the concept of minimally invasive procedures, robotic surgical approaches performed at NewYork-Presbyterian Hospital are vastly improving the patient experience. Real-time imaging in the operating suite combined with continually advancing robotic systems offer the potential for greater precision with less trauma, less scarring, less blood loss, and quicker healing. Surgeons are driving the advances, and there are programs at both NewYork-Presbyterian/Columbia University Medical Center and NewYork-Presbyterian/Weill Cornell Medical Center that create an environment that encourages their rapid implementation.

"Our surgeons are the ones driving robotic applications. My goal is simply to ensure we are setting up our operating rooms [ORs] to facilitate these innovations," said John C. Evanko, MD, MBA, who is Medical Director of Perioperative Services at NewYork-Presbyterian/Columbia and a gynecologic surgeon. Dr. Evanko—whose expertise with the da Vinci Surgical System includes a minimally invasive approach to treat uterine fibroids, as well as other gynecologic surgeries—reported that real-time imaging has been fundamental to creating the modern OR, which is capable of offering minimally invasive endovascular procedures, as well as radiologic-guided interventional, cardiothoracic hybrid, and robotic procedures.

"ORs for minimally invasive endovascular procedures provided a head start because they were set up for real-time imaging and had the structure and size to accommodate the equipment and connectivity that we need for robotic procedures," explained Dr. Evanko, who works to assist OR innovation at NewYork-Presbyterian/Columbia. "Minimally invasive surgery overall and robotics in particular are now being used effectively across specialties, including gynecology, urology, otolaryngology, and thoracic and general surgery."

Urology

In urology, Ashutosh K. Tewari, MD, led much of the pioneering work in robotics at NewYork-Presbyterian/Weill Cornell. Dr. Tewari, who is Director of the Prostate Cancer Institute and the LeFrak Center for Robotic Surgery, has performed more than 5,000 robotic-assisted urologic procedures, and is widely recognized for this work. Data from a recently published meta-analysis of 79 studies suggested robotic-assisted prostatectomies are at least as effective by essentially any measure, particularly in regard to the proportion of patients who achieve cancer-free margins, but generate fewer complications.[1]

"Robotic surgery was initially attractive because of the visualization," Dr. Tewari explained. "While the precision of robotic excisions is an important advantage, the ability to visualize the anatomy in the structural context that can be lost in an open approach has been the most important attribute. There is also significantly less bleeding, which can also obscure the anatomy when performing a reconstruction." However, other advantages, such as reduced blood loss, have followed.

The work by Dr. Tewari has greatly advanced the use of robotic procedures for a broad array of urologic surgical procedures, including resection of benign hypertrophy, and he has now assembled one of the most important facilities in the world for this approach. NewYork-Presbyterian/Weill Cornell's LeFrak Center for Robotic Surgery has several unique features. In addition to a large endowment that has permitted the Center to upgrade imaging capabilities and to employ multiple robotic systems, a comprehensive therapeutic program includes a multidisciplinary team to focus on recovery with emphasis on sustaining a good quality of life.

"There are several exciting developments that will generate further evolution in the field," Dr. Tewari said. "For example, I think there will be synergy between the technological advances made in robotics and genomic advances, which will allow us to provide individualized

NewYork-Presbyterian Hospital is improving its patient care by implementing new, advanced robotic systems that help to improve the patient experience.

care to the characteristics of the malignancy. However, robotic-assisted surgery in urology is a mature platform at our Center. Our outcomes validate that this approach provides advantages over an open approach."

Oncology

"A major focus for us at Weill Cornell Cancer Center is working to improve the quality of our patients' lives, leaving them with less morbidity from our treatments so they go on to live fruitful lives without any long-standing detriment. I think in that regard, robotics plays a major role," said Kevin Holcomb, MD, Director of Minimally Invasive Surgery of the Department of Obstetrics and Gynecology, NewYork-Presbyterian/Weill Cornell. He added that his team is studying robotic-assisted surgery, which involves the use of the da Vinci Surgical System, in gynecologic cancers other than those for which it has already demonstrated benefit, such as in endometrial cancer. "We've been performing many robotic surgeries for recurrent ovarian cancer, and really pioneering this," said Dr. Holcomb, who instructs other surgeons on the technology. "Recently I was able to debulk a patient's ovarian cancer robotically. She was rendered in complete clinical remission with a surgery that lasted about 2 hours and she didn't have to stay in the hospital overnight. I think that is a huge benefit and it isn't being offered in many places."

Orthopedic, Gastrointestinal, Neurologic

At NewYork-Presbyterian/Columbia, robotic-assisted surgery is now being employed for some common orthopedic diseases, for resections of a vast array of malignancies, and for gastrointestinal diseases, including resections of the bowel. The precision of robotic-assisted surgery has long made it attractive for neurologic applications, but the expansion to such a broad array of organ systems is attributed primarily to its role in taking minimally invasive surgery to the next step. Although the laparoscope brought momentum to minimally invasive surgery, modern imaging systems allow visualization without a scope. It is a new approach that demands ORs with different capabilities.

"Imaging was once a preoperative device to plan surgery," Dr. Evanko said. "Increasingly, imaging such as CT [computed tomography] scanning is an intraoperative tool to guide the procedure. The modern OR has to be large enough to accommodate the imaging systems, the displays, the robotic devices, as well as the monitoring equipment that would be found in a conventional OR. This requires planning and the infrastructure that allows the OR to function efficiently." Simply running the wires to an increasingly complex and sophisticated array of devices limits the degree to which the OR can be retrofitted as needs evolve.

"We have been deeply involved in attempting to anticipate these changes and to approach the development of a modern OR with a prospective approach. This has allowed us to stay at the front of the curve in expanding robotic-assisted surgery where it has advantages for the patient," Dr. Evanko said.

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A focus of Dr. Glimcher's research is this fundamental skeletal biology and the interplay between the immune and skeletal systems, which necessarily touches on diseases as diverse as osteoporosis, osteoarthritis, inflammatory arthritides, and cancers, such as multiple myeloma. Dr. Glimcher pointed out that some of the same therapeutics are used across some of these disease states, including the bisphosphonates, whose major target is the osteoclast, and denosumab, FDA-approved for prevention of skeletal-related events in patients with solid tumor bone metastases. Denosumab is a receptor activator of nuclear factor κ-B ligand (RANKL) inhibitor, which is the major factor that stimulates osteoclastogenesis.

"The most important point I want to emphasize is that these diseases are vastly undertreated," Dr. Glimcher said. "One out of 2 women over the age of 55 years has low bone mass, whether it is from the tendency to resorb bone with age, or from a rheumatoid arthritis bony erosion caused by inflammation, or from cancer.… We need to figure out how to make more bone. We have ongoing research at Weil Cornell that is dedicated to doing just that."

Indeed, Dr. Glimcher and her colleagues discovered a gene that controls bone mass, finding that if the gene is inhibited there will be a vast increase in bone mass and protection from age-related bone loss.[2]

> **"We very much need to enhance and expand the research we are doing on those diseases that arise from dysregulation of bone formation."**
>
> —Laurie H. Glimcher, MD

"There are two ways to do that. Several researchers at Weill Cornell Medical College and the Hospital for Special Surgery are targeting the osteoclast and working to inhibit it. Another approach is to make the osteoblast produce more bone.

Schnurri-3 (*Shn3*) is a large zinc finger protein that, among other functions, is an adapter protein within the immune system. Very few genes have been found to regulate postnatal osteoblast-mediated

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bone remodeling; one such gene is the transcription factor *Runx2*. Dr. Glimcher and her colleagues found that mice that were developed with a null mutation of the *Shn3* gene, with no *Shn3* mRNA or protein, were born healthy without gross abnormalities, but at maturity showed increased bone mass at various points along the skeleton. They found that *Shn3* controlled protein levels of *Runx2*, and discovered that it is a "central regulator of postnatal bone mass."

"The most attractive route for research is to activate the osteoblast because you need to form new bone," Dr. Glimcher observed. "Halting bone resorption by targeting the osteoclast is a very good first step, but ultimately bone resorption and bone formation are coupled, so if you decrease osteoclast activity you will eventually decrease osteoblast activity as well. However, if you increase osteoblast activity it is possible that there are circumstances where you will not also increase osteoclast activity, or, if you do, there is still a net positive."

Indeed, Dr. Glimcher's laboratory found that *Shn3* concurrently activates the osteoblast and inhibits the osteoclast.[3] Their research confirmed that mice lacking *Shn3* display heightened osteoblastic bone formation. They also found that mesenchymal cells lacking the protein were defective in promoting osteoclastogenesis, and that *Shn3* controls the expression of RANKL, the key osteoclastogenic cytokine, in mesenchymal cells.

This finding is very promising, and research is ongoing. "You can imagine that when you have inflammatory immune cells that are making RANK ligand, or tumor necrosis factor, then that is going to cause osteoclastic activation and bone resorption, and that is of course what we see," Dr. Glimcher said. "You can preserve bone mass if you can block inflammation in these inflammatory diseases, and the gold standard for testing whether new therapeutic agents can do that is radiographic evidence that erosive lesions have been halted. So inflammation is a key part of regulating the skeletal system, which in turn can regulate and mediate the consequences of inflammation."

Dr. Glimcher is very optimistic about the research program at Weill Cornell Medical College, although she noted, "the field of skeletal biology in general is very underpopulated with talented scientists." She had invited a number of those talented people to join her when she accepted the position of Dean at the College, and several did, and she continues to actively work to further strengthen research, in rheumatology as well as other areas. "There is a lot of cross-talk between the immune system and the skeletal system and between the skeletal system and the endocrine system," she said. "We very much need to enhance and expand the research we are doing on those diseases that arise from dysregulation of bone formation, which happens, for example, in inflammatory arthritis, patients who take steroids, women after menopause, in the setting of cancer, and in some inherited diseases."

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