SPOTLIGHT ON RESEARCH

Post-Traumatic Osteoarthritis

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Preventing Joint Disability

New research in image sequencing and biomarker identification may alter the course of the development of post-traumatic arthritis, one of the leading causes of joint disability in the U.S.

BY JO CAVALLO

Osteoarthritis (OA), a degenerative joint disease in which cartilage is worn away, is the most common form of arthritis, affecting as many as 27 million Americans, and a leading cause of disability in the U.S.—resulting in 632,000 joint replacements each year—and a hit to the economy of upwards of $60 billion a year. Post-traumatic osteoarthritis (PTOA), a prevalent subtype of OA, is caused by the wearing out of a joint that has been exposed to any kind of physical injury, including an anterior cruciate ligament tear (ACL) or a meniscus tear, and can lead to OA development years after the initial joint trauma. PTOA causes nearly 12 percent of OA of the hip, knee, and ankle—affecting approximately six million people.

While participation in sports activities increases the risk of joint injuries that can lead to PTOA, having misaligned joints, being overweight or obese, or being female can increase the chances of developing the ailment. For example, female athletes have a two to ten times greater risk of injuring their ACL than their male counterparts, due in part, say researchers, on their reliance on using their quadriceps muscles in the front of the thigh to stabilize their knee during play, rather than the stronger hamstring muscles that support the back of the thigh, making women more vulnerable to joint injury and PTOA.

But perhaps the population at greatest risk of developing PTOA—and suffering long-term disability—is military personnel. "People in the military are exposed to high-demand efforts, including carrying 150 pounds of gear or jumping from powerful vehicles. And all you have to do is step in a hole or turn an ankle the wrong way to sustain an injury that can lead to PTOA," says Lt. Col. Steven J. Svoboda, MD, an orthopedic surgeon at Keller Army Community Hospital at West Point and a researcher investigating the viability of using blood biomarkers to predict who may be predisposed to ACL tears (see page 4).

Since its inception over 62 years ago, the Arthritis Foundation has funded over $400 million in research—$150 million in osteoarthritis research alone—to find the causes of arthritis, more effective therapies to treat the disease, and early diagnostic methods to prevent disease progression. In 2012, the Foundation launched an Osteoarthritis Flagship Initiative to outline goals over the next decade to determine predictors and causes of OA; identify who is at risk for developing the disease; find methods for detecting OA at its earliest stage before disease effects are felt; and develop targeted treatments. This year, the Foundation committed $1 million to launch the ACL Intervention Initiative (ACLII) to explore ways to investigate early joint and cartilage changes after an ACL tear; test compounds to stop or slow the changes; and provide tools for drug developers to bring potential therapies to the market faster.

"The first step of ACLII is to validate the fact that some of the new imaging technologies and potentially some of the new biochemical technologies can actually measure the breakdown in the extracellular cartilage matrix in an injured joint. And then determine whether we can prevent the emergence of OA by using a compound that will stabi-

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lize the injured joint," says John Hardin, MD, Vice President for Research for the Arthritis Foundation.

To prove the effectiveness of a new type of magnetic resonance imaging (MRI) sequence to detect early changes in joint cartilage and test a novel bisphosphonate to thwart OA progression, the Foundation awarded an Innovative Research Grant to Thorsten Kirsch, PhD, whose work is profiled below. A third researcher featured in this issue is Mary B. Goldring, PhD, who is investigating the first molecular indicators of OA in an injured or compromised joint, and whether it is possible to stop disease progression.

Thorsten Kirsch, PhD

Professor of Orthopedic Surgery and Cell Biology, Vice Chair for Research, New York University School of Medicine; Director, Musculoskeletal Research Center, Hospital for Joint Diseases at NYU Langone Medical Center, New York City, New York

Being able to detect cartilage destruction at its earliest stages to ward off the development of osteoarthritis (OA) and post-traumatic osteoarthritis (PTOA) and finding therapies to halt disease progression, preventing the need for joint replacement surgery, is the focus of Thorsten Kirsch's current research. The recipient of a two-year, $100,000 per year, Arthritis Foundation Innovative Research Grant in Novel Imaging Biomarker and Treatment for Osteoarthritis, Dr. Kirsch's research is following two tracks: the investigation of a new type of magnetic resonance imaging (MRI) sequence to detect the very early changes in joint cartilage and a novel bisphosphonate to slow OA progression.

Bisphosphonates are antiresorptive medicines that are commonly used in the treatment of osteoporosis to slow the rate of bone thinning and the risk of broken bones. However, the type of bisphosphonate Dr. Kirsch is studying has different chemical properties than the bone-building drugs currently on the market and does not affect the osteoclasts, the cells that degrade bone and are responsible for bone resorption.

"The type of bisphosphonate we are investigating appears to protect cartilage cells against catabolic (breakdown) events," says Dr. Kirsch. "We now have to determine whether this compound can inhibit cartilage destruction during OA progression using OA animal models. Since this bisphosphonate does not affect osteoclasts, it is not expected to have any major unwanted side effects on the overall bone structure."

The MRI sequence Dr. Kirsch is investigating also differs from the conventional type of MRI currently in use because current sequences can only detect changes in one of the two main extracellular matrix components of cartilage, collagen or proteoglycans, and, therefore, cannot detect very early signs of cartilage deterioration. Based on Dr. Kirsch's findings, the new MRI sequence has great potential to detect early stages of OA and PTOA. Using animal OA models the research team will determine how early this novel MRI sequence can detect changes in the cartilage extracellular matrix.

Once the research is completed and the preliminary results confirmed, says Dr. Kirsch, the new MRI sequence will not only be an effective new screening tool in detecting early changes in the extracellular cartilage matrix in people who have suffered an injury to a joint—the precur-

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sors to the development of PTOA—it will also be a useful monitoring device to show the treatment effectiveness of novel compounds in the prevention of OA and PTOA.

"We are very optimistic that our novel MRI sequence will be available in the clinic soon. We could then tell a young person who has had an ACL injury or a meniscus injury, for example, that he is at high risk for developing PTOA and it would be recommended to have an annual or biennial MRI scan with our novel sequence to spot early cartilage changes in his injured joint," says Dr. Kirsch. .

Mary B. Goldring, PhD

Senior Scientist and Director of the Tissue Engineering Regeneration and Repair Program, Hospital for Special Surgery, Professor of Cell and Developmental Biology, Weill Cornell Medical College, New York City, New York

The exploration of the structure and evolution of living systems has interested Mary B. Goldring, PhD, from the time she was an undergraduate student at the University of Oregon several decades ago. After graduation, a two-year stint as a Peace Corp volunteer in Peru teaching biology to secondary school teachers solidified that interest and eventually led her to pursue a doctorate degree in a biomedical setting with a focus on rheumatology and cartilage research.

Today, Dr. Goldring's research is focused on identifying the molecular mechanisms at work in the onset and progression of osteoarthritis (OA) and how cartilage cells, or chondrocytes, respond to inflammatory cytokines, the proteins that act as mediators between the cells. Among the questions Dr. Goldring hopes to answer are, what are the first molecular indicators of OA in the injured or compromised joint, and do they develop at the cellular level; and is it possible to stop the process?

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To identify the key regulatory molecules involved in disease onset, Dr. Goldring is using several laboratory strategies, including genetically modified mouse models of OA that can be followed over the course of the disease, culture models of primary human and mouse chondrocytes and cell lines, and human cartilage samples to validate the mechanisms linked to risk factors for developing OA, including biomechanical instability, injury, inflammation, obesity, and genetic susceptibility.

Dr. Goldring's laboratory studies have been successful in identifying some of the transcription factors and signaling kinases that contribute to stress or inflammation in cartilage cells, which can lead to both OA onset and irreversible joint damage. Dr. Goldring is also using human tissue samples from patients undergoing joint replacement surgery to investigate genes that play a role in the regulation of cartilage degradation and repair.

Once the critical molecules at play in OA onset and progression are identified in the mouse models, Dr. Goldring hopes to compare her genomic (gene) datasets against the genomic as well as the existing proteomic (protein) datasets from human OA samples to determine the clinically relevant therapeutic targets.

"By understanding the basic cellular mechanisms involved in cartilage injury and repair, we may be able to define cellular targets for treatment at every stage of OA, which may be used to develop effective therapies," says Dr. Goldring. "We are hoping that our mouse models can give us the answers."

Lt. Col. Steven J. Svoboda, MD

Orthopedic Surgeon, Keller Army Community Hospital, Head Team Physician for the Army Football Team, West Point, New York

Although Lt. Col. Steven J. Svoboda, MD, concedes that an ACL injury he incurred while playing football for the U.S. Military Academy at West Point more than two decades ago influenced his decision to become an orthopedic surgeon, his main reason was he wanted to make patients whole again after sustaining a joint injury. He also wanted to prevent the debilitating effects of post-traumatic osteoarthritis (PTOA), the likely outcome of an ACL tear or major joint injury.

Of special concern to Dr. Svoboda are military members, especially young soldiers who suffer disproportionate rates of arthritis. According to a study published in *Arthritis and Rheumatism,* service members ages 20 to 24 have a 26 percent higher rate of developing arthritis than people in the general population and troops over the age of 40 are more than twice as likely to develop the disease than civilians.

"We know from the literature over the last ten years that one of the biggest burdens of injury to military personnel is a major joint injury such as an ACL tear. ACL tears can be related to injuries from carrying heavy tactical gear or walking on rough terrain in war zones. Oftentimes, soldiers don't get medical attention immediately and as a result they have substantial long-term quality of life issues from the development of PTOA," says Dr. Svoboda.

Although individuals with ACL injuries are seven to eight times more likely to develop PTOA, currently there is no way to identify who will actually get the disease or accurately detect disease onset at its earliest stage when there is a chance to potentially alter its clinical course. According to Dr. Svoboda's research, blood biomarkers—the biologic molecules that are used to measure the presence or progression of disease—involved in cartilage turnover and metabolism following an ACL injury may be good predictors in determining not just who is likely to get PTOA following an ACL injury, but who may be predisposed to having an ACL tear.

In an analysis of blood taken from West Point cadets at different times over the course of their enrollment, Dr. Svoboda examined changes in four serum biomarkers in both the pre-injury and post-injury state in a group of ACL injured patients and in an uninjured control group. He found that three of the four biomarkers in the pre-injury blood samples were associated with subsequent ACL injury and three biomarkers in the post-injury samples that may indicate early arthritis development.

"We found changes in CPII markers (a product of type II collagen synthesis) in the post-injury cadets as well as changes in the C2C biomarker (a breakdown product of type II collagen) that were different from the uninjured control subjects. Ratios of these biomarkers suggest an adverse effect by ACL injuries on the normally well-balanced synthesis and degradation of type II collagen and may be an early indicator of arthritis," says Dr. Svoboda. While the results from Dr. Svoboda's research look promising, he cautions that more studies need to be done before it can be determined whether biomarkers are accurate predictors of the risk for an ACL tear or PTOA onset.

"There are some challenges we have to overcome before we can say that biomarkers will tell us who is vulnerable for an ACL injury or who is going to get arthritis. But they will help us understand the early stages of arthritis and possibly present us with ways to mitigate impact of the disease," says Dr. Svoboda.

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