

SPOTLIGHT ON RESEARCH

ACL Intervention Initiative



FALL 2013

Preventing Osteoarthritis

The Arthritis Foundation's ACL Intervention Initiative is a comprehensive endeavor to investigate early joint and cartilage changes after an anterior cruciate ligament injury; identify chemical and magnetic imaging biomarkers that signal the presence of early osteoarthritis; provide a means to measure OA over time; and develop interventions to halt disease progression.

Osteoarthritis (OA), a degenerative joint disease, is the most common form of arthritis, affecting more than 27 million Americans—more than any other joint disease. The destruction of the joints in OA is so profound, causing chronic pain and stiffness, it is the leading cause of disability in the U.S., resulting in 632,000 joint replacements each year and costing the economy a staggering sum of over \$185 billion annually.

Despite the personal and societal toll of the disease, little is known about the exact causes of OA, although a joint exposed to any type of physical injury, including an anterior cruciate ligament (ACL) tear or a meniscus tear, has about a 50 percent chance of developing OA within ten years. Obesity, advancing age—about half of those over age 65 have osteoarthritis—and diseases like diabetes are also contributing risk factors for disease onset.

In 2012, the Arthritis Foundation launched the 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 therapies for the disease. And this year, the Foundation announced the ACL Intervention Initiative (ACLII), a comprehensive endeavor to explore ways to investigate early joint and cartilage changes after an ACL tear; test compounds to stop or slow the changes; determine chemical biomarkers and develop new magnetic resonance imaging se-

quencing technology to detect onset of OA at its earliest stage, before joint damage takes place; and develop treatment interventions to stop disease progression.

The first phase of ACLII was launched in July 2013 with a \$1 million gift from Marsha Laufer, PhD, and Henry Laufer, PhD. This phase of the initiative includes patient validation studies in new quantitative imaging sequencing technologies, called T2 mapping and T1 rho imaging, and chemical biomarkers to identify and measure breakdown in the extracellular cartilage matrix in an injured joint, and then determine whether the use of a compound to stabilize the joint will prevent OA onset.

Finding the cause of OA and more effective therapies to treat it are especially important to Marsha Laufer, who has suffered from the effects of OA for more than 30 years (see “A Patient’s Story on page 4”).

The studies are taking place at three institutions across the country: Hospital for Special Surgery (HSS) in New

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York City; University of California, San Francisco; and Mayo Clinic in Rochester, Minnesota. The following pages introduce you to the research team from the Hospital for Special Surgery: Scott Rodeo, MD, Co-Chief of the Sports Medicine and Shoulder Service; Steven R. Goldring, MD, Chief Scientific Officer; and Hollis G. Potter, MD, Chief, Magnetic Resonance Imaging, Director of Research in the Department of Radiology & Imaging.

“All three institutions have outstanding orthopedic surgical services and enormous experience caring for

people with ACL tears, so we couldn't have a more capable group of researchers to work on ACLII,” says John Hardin, MD, Managing Scientist for Osteoarthritis at the Arthritis Foundation. “The challenge of ACLII is very straightforward: identify young, healthy people who tear an ACL and get them into the study very quickly after their injury, collect fluid from the injured knee joint and blood and urine samples to identify biomarkers of early onset OA, and provide a way to measure OA progression over time.”



Scott Rodeo, MD

Co-Chief of the Sports Medicine and Shoulder Service, Hospital for Special Surgery; Professor of Orthopaedic Surgery, Weill Cornell Medical College; and Co-Principal Investigator of the Arthritis Foundation's ACL Intervention Initiative (ACLII)

A former competitive swimmer, Scott Rodeo, MD, has devoted his medical career to researching the biology of cartilage, tendon and ligament healing, meniscal allograft transplantation, and rotator cuff repair, and treating anterior cruciate ligament (ACL) and meniscus tears in the knees. He also treats joint injuries to the shoulder, ankle, and elbow, especially those that occur as a result of sports activities. In his clinical practice, Dr. Rodeo cares for both professional and amateur athletes and is the Associate Team Physician of the New York Giants Football Team and has also served as the Team Physician for the USA Olympic Swimming Team in 2004, 2008, and 2012.

Currently, a major focus of Dr. Rodeo's clinical practice and area of research is in ACL injuries and their potential long-term effects on knee joints, including the development of osteoarthritis (OA). According to studies, a torn ACL leads to OA in more than half of affected knees five to 15 years after the injury occurred.

“We can fix ACL and meniscus tears, but we are not very good at preventing arthritis and degenerative changes in the joints,” says Dr. Rodeo. As Co-Principal Investigator of the Arthritis Foundation's ACLII study, Dr. Rodeo hopes to change that dynamic by identifying chemical biomarkers that signal OA onset before symptoms arise.

The study, launched in July of 2013, is currently recruit-

ing patients aged 18 to 50 who suffered an ACL injury within two weeks of their enrollment into the study. The patients will be followed for five years. At the time of enrollment, fluid will be removed from the injured knee joint, and blood and urine samples will be taken to look for diagnostic and prognostic osteoarthritis biomarkers that show early disease presence and provide a means to measure OA progression over time. The patients will also undergo quantitative magnetic resonance imaging (MRI) evaluation to detect early changes to the cartilage in the knee joint.

“The ACLII study is a good way to investigate the development of arthritis because we will know the exact date of the injury and we will be able to follow the patients over a long period of time,” says Dr. Rodeo. “In some cases, you see a patient six months after an injury and by then the biomarkers in the joint may be altered. At that point, it is also impossible to reverse structural changes in the joint. One of the difficulties in the study—and in the treatment—of OA is that we have not found a perfect marker of the disease. If we can detect very early changes in the joint cartilage, we have the potential to change the natural history of OA, because alterations in articular cartilage are some of the earliest changes in arthritis.”

If the ACLII study is successful at identifying common biomarkers involved in OA onset and progression, it will allow physicians not only to track response to treatment

but will spur the development of more effective therapies as well. “Our whole goal is to identify OA biomarkers of early injury so that when we have a magic-bullet therapy,

whether it is stem cells, an injectible synthetic molecule to reduce wear on joint cartilage, or an oral drug, we’ll have a way of halting OA,” says Dr. Rodeo.

Steven R. Goldring, MD

Richard L. Menschel Research Chair and Chief Scientific Officer, Hospital for Special Surgery; Professor of Medicine at Weill Cornell Medical College; Participating Investigator of the Arthritis Foundation’s ACL Intervention Initiative (ACLII)



In his role as Chief Scientific Officer at the Hospital for Special Surgery (HSS) in New York City, Steven R. Goldring, MD, oversees both basic and translational research focusing on diseases affecting the musculoskeletal system, including osteoporosis and arthritis. Dr. Goldring’s research investigations have included the evaluation of the effects of orthopedic implant biomaterials used for joint replacement to determine the molecular mechanisms and cell-associated signaling pathways by which these foreign materials modulate cell and tissue responses. The goal of his research is to develop more effective treatment strategies for arthritis.

As part of the research team at HSS involved in the Arthritis Foundation’s ACL Intervention Initiative (ACLII), Dr. Goldring’s main focus is evaluating potential biomarkers for the earliest development of knee osteoarthritis (OA) following an anterior cruciate ligament (ACL) tear. Dr. Goldring will oversee the collection of synovial fluid from the injured knee joint as well as blood and urine samples from the participants

enrolled in the ACLII study. All study volunteers will have experienced an ACL injury within two weeks of their enrollment into the study.

“The biospecimens are products that are being generated by the joint tissues either as a function of breakdown or attempts at repair,” says Dr. Goldring. “Our goal is to create a biobank with the expectation that as we learn more about the natural history and progression of OA that data can be mined for the validation of existing biomarkers and the discovery of new ones.”

If successful, the study findings, says Dr. Goldring, could have applications in providing more effective interventions in preventing or slowing progression of OA following not just ACL injuries but meniscus tears and other ligament injuries and joint instability as well. “In two to five years, the results from ACLII could be a game changer in the understanding of OA onset and progression and in the assessment of effective therapeutic medical interventions,” says Dr. Goldring.



Hollis G. Potter, MD

Chief, Magnetic Resonance Imaging; Director of Research in the Department of Radiology & Imaging, Hospital for Special Surgery in New York City; and Site Leader on the Arthritis Foundation’s ACL Intervention Initiative (ACLII)

For more than two decades, Hollis G. Potter, MD, has dedicated her medical career in radiology to developing magnetic resonance (MR) imaging applications for

orthopedic conditions like arthritis. Dr. Potter’s research at the Hospital for Special Surgery (HSS) has led to the development and application of advanced imaging technology called T2

mapping and T1 rho imaging. These new pulse-sequencing technologies provide cartilage assessment at an ultrastructural level, particularly in the detection of early biochemical alterations in the extracellular matrix. The extracellular matrix is composed of water, collagen fibers and proteoglycan, the scaffolding necessary to hold tissues together. T2 mapping and T1 rho imaging technology provide a noninvasive way to assess loss of cartilage and other changes in the joint after a traumatic chondral injury, such as anterior cruciate ligament (ACL) tear, which can lead to the development of osteoarthritis (OA).

In addition to the collection of chemical specimens, such as synovial fluid from the injured knee joint and blood and urine

samples from patients enrolled in the Arthritis Foundation's ACL Intervention Initiative (ACLII), the patients will also undergo quantitative MR evaluation at different points during the five-year study to detect early changes to the cartilage and ACL destruction over time.

"These new MR technologies allow us to evaluate traumatic chondral injury from an ACL tear noninvasively without having to biopsy the cartilage tissue and further to assess the longitudinal loss of cartilage as well as changes in its microstructure," says Dr. Potter. "If we can identify OA biomarkers we may be able to prevent or delay OA onset through physical therapy, a drug, or an injection of a synthetic material."

A PATIENT'S STORY

Marsha Laufer, PhD

Scientist and philanthropist, Marsha Laufer, PhD, was used to living an active lifestyle, exercising nearly every day while working in her private practice in speech-language pathology, teaching at Stony Brook University on Long Island, New York, and engaging as a political activist in local, county, state, and national Democratic arenas. But in the late 1980s and



through the '90s, pain in her knees, followed by mild scoliosis and osteoarthritis (OA) in her hips and spine threatened to curtail those activities. Despite prescriptions of anti-inflammatory medications to reduce joint inflammation and pain and arthroscopic surgery on her right knee to repair torn cartilage, the discomfort increased. Over the last year, Marsha developed OA in her hips and was diagnosed with avascular necrosis, bone tissue death due to a lack of blood supply, necessitating right hip replacement surgery in April 2013.

"The pain became so debilitating, I went from a highly functional individual in terms of my level of physical activity to having to use a walker," says Marsha.

Wanting to find a solution to halt further OA progression Marsha consulted with Jonathan Lee, MD, an orthopedic surgeon and family friend. It was Dr. Lee who introduced Marsha and her husband, Henry, to Dr. John Hardin, who presented the proposal for the Arthritis Foundation's ACL Intervention Initiative (ACLII).

"The ACLII study sounded so well designed, exciting and has the potential to offer such a huge breakthrough in the discovery of biomarkers that can detect OA at its earliest stages and predict progression, we decided to fund it," says Marsha.

While waiting for more effective therapies for OA to become available, Marsha is taking a holistic approach to her disease, practicing mindfulness-based stress reduction (MBSR) meditation almost every day to help with pain management, resuming swimming, playing golf, exercising, and losing weight to reduce the pressure on her knees and hip. Although Marsha occasionally takes

anti-inflammatory medications when necessary, staying physically active and practicing MBSR has had a profound impact on both her physical and mental health.

As a result of the hip surgery, "I no longer need a walker and I have a heightened consciousness about the importance of leading an active healthy lifestyle," says Marsha.

Although retired from her private practice, faculty position at Stony Brook University, and grassroots political activities in New York, Marsha remains active in the Democratic Party, and currently sits on the Board of Planned Parenthood South Florida and the Treasure Coast.

As a researcher, Marsha is keenly aware of the importance of continuing funding for innovative studies that will further the understanding of the pathology of complex and diverse diseases like arthritis and the development of more effective therapies for the disease. "While government support for research is very important, what our grant represents is a public/private partnership that is critical to helping advance progress in arthritis," says Marsha. "I do believe that we will find better solutions in the treatment of OA and relieve pain in so many affected individuals that will allow them to significantly improve their quality of life."

To make a donation to the Arthritis Foundation, go to Spotlightnewsletter.kintera.org. To make a comment about this newsletter, e-mail us at Spotlight@arthritis.org.