

SPOTLIGHT ON RESEARCH

Advances in OA Drug Discovery 

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Collaborations Accelerate Progress

This is a very exciting and challenging time in the study of osteoarthritis (OA) and the search for DMOADs (Disease Modifying Osteoarthritis Drugs),” said Dr. John Hardin, Professor of Medicine, Orthopaedic Surgery, and Microbiology and Immunology at Albert Einstein College of Medicine and Director of ACL Research for the Arthritis Foundation. “You might say we’re at an OA tipping point.”

Many scientists and institutions are independently investigating various aspects of the OA disease process, trying to discover how cell biology and outside forces, like injuries and repetitive stress, lead to OA so they can find ways to treat or prevent it. “We must coordinate these efforts by fostering collaborations to establish standards for OA measurement, thereby accelerating drug discovery,” Dr. Hardin explains.

This issue of *Spotlight on Research* features an update of local collaborative efforts, plus the work of regional investigators in the field of OA research—Dr. George Dodge of the University of Pennsylvania along with his colleague, Dr. Robert Mauck; and Dr. Lawrence Bonassar of Cornell University in Ithaca, NY.

The most common form of arthritis and the leading cause of disability in the U.S., OA affects more than 27 million Americans. Caused by the breakdown of cartilage in one or more joints, OA is

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a serious quality of life and economic issue. It costs the U.S. economy more than \$128 billion annually in medical expenses and lost earnings and is responsible for over 632,000 joint replacements a year.

The Centers for Disease Control and Prevention (CDC) estimates that by 2030, 67 million adults or 25 percent of Americans aged 18 years or older will have doctor-diagnosed arthritis. And the number of patients undergoing OA-related joint replacement surgery will quadruple! Currently there are no OA drugs that are capable of intervening and altering the course of the disease.

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New Synthetic Compound Mimics Natural Joint Lubricant

Lawrence Bonassar, PhD, and his research group at Cornell's Department of Biomedical Engineering have developed an exciting new synthetic compound that mimics an essential, naturally occurring lubricant in human joints. In tests on laboratory animals, the compound has retarded, or stopped, the progression from joint injury to osteoarthritis (OA). Dr. Bonassar and his team are working closely on this project with Cornell polymer chemist, David Putnam, PhD, and Hospital for Special Surgery orthopaedic surgeon, Scott Rodeo, MD.

Cartilage is smooth, shiny tissue that covers the bone surfaces of our joints so bones can glide easily when we move. Lubrication on and around cartilage is essential to healthy, pain-free movement within the joint. Insufficient lubrication increases friction between cartilage causing damage or erosion, often leading to painful OA. The two main lubricating molecules in our joints are hyaluronic acid and lubricin. While hyaluronic acid is a thick substance which surrounds cartilage, lubricin chemically interacts with the surface of the cartilage and has the ability to hold fluid which it uses as a protective layer or buffer.

"When a joint is injured, the level of natural

lubrication drops dramatically," Dr. Bonassar explained. "While the natural lubrication levels will eventually recover over time, sometimes it takes months. Our goal was to focus on supplementing the lubricant in that acute stage after injury to prevent any damage from setting in until the natural lubrication has recovered."

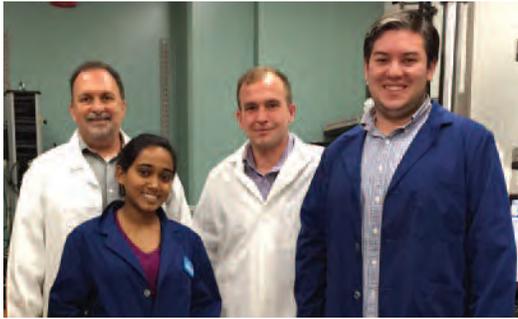
Today, hyaluronic acid injections are commonly used for knee pain and cartilage damage related to OA. But Dr. Bonassar and his colleagues have focused on lubricin as a new and possibly better way, not only to alleviate joint pain, but to retard or stop the progression to OA.

"We arrived at the engineered form of lubricin through a combination of hard work and serendipity," Dr. Bonassar explained. "After studying natural lubricin for several years and working on replicating it in our lab, I observed a presentation of an engineered molecule that a colleague's student was making in an adjacent chemistry lab. The molecule looked a lot like lubricin and we were able to apply the knowledge in creating that molecule towards our lubricin project as well."

After testing the compound in vitro with his colleague Dr. Putnam, Dr. Bonassar worked with Dr. Scott Rodeo at the Hospital for Special Surgery to test the efficacy of the compound on rats with induced OA. The synthetic lubricin was injected into the rats' OA joints once a week for three weeks. The research team observed the rats for two months and they found that the development of OA was greatly inhibited or stopped in the injected rats. The next step is to test the synthetic lubricin on larger animals before clinical trials on humans.

"We may see veterinary application of the new compound within the next couple of years," Dr. Bonassar said. "Hopefully, it won't be ten years, but maybe four to five years before its human application."

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From left to right: Dr. George Dodge, Bhavana Mohanraj, Dr. Robert Mauck and Greg Meloni in their lab at UPenn.

University of Pennsylvania

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Adjunct Associate Professor of Orthopaedic Surgery

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Associate Professor of Orthopaedic Surgery

New Device Speeds Up Discovery Process

A cartilage biologist from the University of Pennsylvania, George R. Dodge, PhD, and his colleague, bioengineer Robert Mauck, PhD, are embarking on an exciting four-year project funded by the **Department of Veterans Affairs** at the **Philadelphia VA Medical Center**. They are working in collaboration with a team of other bioengineers, molecular scientists, orthopaedic and trauma surgeons, and rheumatologists in the new VA Translational Musculoskeletal Research Center.

In their laboratories in the Department of Orthopaedic Surgery, Drs. Dodge and Mauck have created a unique device capable of simultaneously testing the impact of thousands of potentially therapeutic molecules on articular cartilage found in joints. “This device, using a technique known as ‘high throughput screening,’ can greatly accelerate the discovery of new therapies to treat post-traumatic injuries and the crippling and painful osteoarthritis (OA) that may develop,” Dr. Dodge explained. “Once these therapeutic compounds are identified, they might be designed as medical interventions to treat soldiers on the battlefield, or the injured at the scene of an automobile accident, and administered on site to prevent the development of post-traumatic OA.”

Cartilage has some unique qualities that present interesting challenges to investigators seeking treatments for joint disorders. Unlike other human tissue, cartilage lacks the restorative benefits of a blood supply, making it difficult to repair and regenerate. It also has fewer cells than other tissue and functions in a pressurized, or loaded, environment. Drs. Dodge and Mauck and their team developed a “compression simulator” device to replicate the loaded environment of human cartilage, thereby simulating a wide range of natural movements as well as joint injuries. Using uniform engineered cartilage tissue samples, they test them to see their reaction to damaging compression.

Because the device has up to 96 wells where the cartilage samples are placed, the lab team can introduce many potentially therapeutic molecules into the wells and simultaneously monitor the reactions of several sets of cartilage and molecules. This high throughput screening method cuts down on time-consuming individual trial-and-error laboratory tests and can identify molecules that may have the greatest therapeutic benefit and thereby qualify for more sophisticated study.

Dr. Dodge’s interest in articular cartilage began while he was growing up and observed his mother suffering from severe OA. He developed a curiosity about medicine and science and specialized in cartilage biology. He feels that, given the many new approaches being explored, the field is prime for progress in the discovery of therapies to treat cartilage damage and OA. “Today we have a better understanding of where OA comes from,” he said. “We suspect that even small joint injuries as well as larger traumatic events can occur early in life and later progress into OA. Scientists and drug companies are also taking new approaches and recognizing that joints function in a loaded environment and there is a definite need to add biomechanics to the equation for new OA drug discovery.”

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—George R. Dodge, PhD

ACCELERATING PROGRESS

Update on Arthritis Foundation Research Collaborations

SNOW VI—6th Segal North American Osteoarthritis Workshop

More than 100 osteoarthritis (OA) experts registered for the 6th Segal North American Osteoarthritis Workshop held from Friday to Sunday, October 24-26, 2014 in Chicago. Named after workshop funders Gordon and Carole Segal and hosted by the Arthritis Foundation, the event featured arthritis investigators from North America and Europe who presented new OA research that could lead to better ways to detect, treat, prevent, and cure OA. The title of this year's workshop was "Anterior Cruciate Ligament Injury as a Model for Post-traumatic Arthritis and Drug Discovery in Osteoarthritis." The goal was to consider options and set standards for the design of an ACL intervention study, working towards the development of industry standards and protocols for setting up OA clinical trials in the near future.

Arthritis Foundation Co-sponsors Einstein Symposium

The Arthritis Foundation was a sponsor of the 3rd Annual Musculoskeletal Repair and Regeneration Symposium held on October 2, 2014 at the Albert Einstein College of Medicine. Designed to expand the knowledge base within the field of musculoskeletal repair and regeneration, the symposium featured an elite group of scientific investigators who shared their findings and enthusiasm with a packed amphitheater of colleagues and students. This is the second year the Foundation supported this collaborative effort which emphasized recent advances in translational research in three exciting areas: (1) mechanisms and treatments for musculoskeletal disorders, cancer, and diseases; (2) tissue remodeling and interactions in musculoskeletal and other systems; and (3) stem cell, tissue repair, and regeneration.

NIH Establishes Accelerating Medicines Partnership (AMP) Network

In May, 2014 the Arthritis Foundation became a member of the Accelerating Medicines Partnership, a venture that joins the National Institutes of Health (NIH), biopharmaceutical companies and several nonprofits in a mission to identify and validate the most promising biologic targets of disease for new diagnostics and drug development. In September, the NIH awarded grants to 11 research groups across the U.S. to establish the Accelerating Medicines Partnership in Rheumatoid Arthritis and Lupus Network. Among the 11 network sites are the following in the area served by the Arthritis Foundation, Northeast Region: in **Rochester, NY** at the University of Rochester; in **New York City** at New York University School of Medicine, Albert Einstein College of Medicine, Rockefeller University, and Hospital for Special Surgery; and in **Manhasset, NY** at the Feinstein Institute for Medical Research.

Inspired Science from Arthritis Foundation-Funded Young Investigators

On April 23rd, the Arthritis Foundation, Northeast Region will host a forum at the Joan and Joel Smilow Research Center of NYU Langone Medical Center in New York City featuring the research of three Arthritis Foundation grant recipients. In addition to the young investigators, speakers include Stephen I. Katz, MD, PhD, Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, and Jose Scher, MD, Assistant Professor of Medicine, NYU Langone, Hospital for Joint Diseases. For additional information, contact Kristin Gardner at kgardner@arthritis.org or visit www.afresearchforum.org.