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Farshid Guilak, PhD, named Kappa Delta Elizabeth Winston Lanier Award recipient for research in functional cartilage engineering for total joint resurfacing

ROSEMONT, Ill. (February 12, 2021)—The 2021 Kappa Delta Elizabeth Winston Lanier Award was presented to Farshid Guilak, PhD and his co-authors, Bradley T. Estes, PhD, and Franklin T. Moutos, PhD, for their research and development of technology to grow bioartificial cartilage using a patient's own donor cells and seeding them on a novel scaffold that can be molded to match the shape of a patient's joint. Following a successful preclinical trial on canines with hip osteoarthritis (OA), the research is soon expected to begin a Phase I clinical trial. Additionally, Dr. Guilak's work in gene therapy to protect against joint inflammation has the potential to advance the treatment of patients with arthritis and some orthopaedic conditions. The Kappa Delta Awards recognize research in musculoskeletal disease or injury with great potential to advance patient care.

OA is a debilitating and costly disease affecting more than 32 million Americans and totaling approximately $65 billion in direct medical fees annually in the United States.[i] It occurs when the articular cartilage (smooth white tissue that covers the end of bones where they meet to form joints) gradually degenerates, contributing to the degeneration of the joint. Approximately 2.8 million patients with OA are between the ages of 40-65 and seek medical treatment for hip OA.[ii] [iii] Of these, 840,000 (about 30%) suffer from activity limiting hip OA, and these patients are typically recommended for hip replacement surgery.

"Due to injuries sustained from increased athletic activity and, conversely, a high prevalence of obese patients, we're seeing more hip osteoarthritis in younger patients," said Dr. Guilak, lead author, Mildred Simon Professor of Orthopaedic Surgery at Washington University and director of Research at Shriners Hospitals in St. Louis.

A hip replacement is an ideal surgery for patients in their 70s and 80s to relieve pain and restore function. However, a younger patient who receives a hip replacement will likely need a revision surgery since the life span of the prosthesis is typically 15-20 years.

"This is not ideal," said Dr. Guilak. "It is traumatic to tear out an old prosthesis and the risk of infection and complications increase tremendously. We wanted to find a way to restore hip joint function in the short term (5-10 years) until the time was right for a hip replacement."

Drs. Guilak, Estes, and Moutos, along with numerous collaborators and colleagues, spent more than 15 years developing a scientific approach for extracting cells from the patient's fat or bone marrow, combining them with a biomaterial scaffold and establishing an optimal environment for the cells to multiply and form a living joint replacement. "Our goal from the beginning has been to help patients afflicted with debilitating arthritic disease. We have progressed to the point that we are now on the verge of bringing a product into the clinic. We are excited about

that," said Dr. Estes, who is currently the President and Chief Operating Officer at Cytex Therapeutics, Inc.

While there had been progress in tissue engineering to repair focal defects, there was nothing available to biologically replace an entire joint surface. The challenge, however, was developing an anatomically sized and functional cartilage, and ensuring that the inflammatory environment within an arthritic joint didn't stymie the continued growth of the cartilage once implanted.

"It is easier to fill a pothole rather than repave an entire road," said Dr. Guilak. "With a background in bioengineering, we knew success was contingent upon a biomaterial scaffold that could not only hold cells but have the strength and durability to withstand joint loading after covering the entire joint surface."

Over the years, the team tried hydrogels and nonwoven fabrics (mesh of fine materials) as the base for the scaffold. However, the weak mechanical properties of these substances didn't withstand the joint loading, which can often be 10 times a person's body weight.

"At this point, we theorized that if we wove our own fabric using individual fibers of a material that was safe and resorbable, such as a dissolvable suture, we could create a scaffold that was porous enough to seed the stem cells directly into the fabric, but strong enough to withstand loading compression."

After initial studies demonstrated the exciting potential of this new approach, Drs. Guilak, Estes, and Moutos formed a startup company, Cytex Therapeutics, Inc., so that this promising technology could ultimately be translated to the clinic to treat young patients with joint disease.

Dr. Moutos, who is now the Vice President of Technology Development at Cytex Therapeutics Inc. in Durham, N.C., previously worked in the textile industry and understood the intricacies of textile construction. His expertise was instrumental in developing a loom that could weave 600 sutures into a 3-D pattern, entwining multiple fiber layers in three orthogonal directions to form a one-piece scaffold structure with regular, interconnected pores that could be molded into the shape of a patient's joint. Tuning and perfecting this process took nearly two years.

To develop the cartilage, Dr. Estes worked to create optimal conditions to isolate the stem cells from either fat or bone marrow and then treat them with a cocktail of growth factors and supplements that allowed them to form into bone or cartilage-forming cells on the scaffold.

The result is a living joint replacement that can restore the function of an osteoarthritic hip joint. By implanting regrown cartilage started in a laboratory into the body to resurface a damaged joint, the stem cells continue to grow on a tough yet flexible scaffold which will eventually disintegrate once the cartilage is fully developed.

This approach was tested in dogs with hip OA and the implants showed success in all measured outcomes. The dogs who received the engineered implant returned to normal gait, activity

levels and behavior by six months, whereas the control cohort did not return to these levels by the end of the study. The study demonstrated that the engineered implant restored the contour and functional properties of the femoral head to its native condition, providing the needed large animal data to advance this technology to the clinic. As a result, the team expects to begin a Phase I clinical trial for use in humans in the near future.

Dr. Guilak and his team continue to study the complexities of optimal cellular growth to advance the next generation of tissue engineering. They are currently conducting laboratory research utilizing gene editing and gene therapy to change the genetic makeup of the cell and program them to fight off inflammation that can inhibit cartilage growth. This includes:

- The development of a virus to create an anti-inflammatory drug that will rewrite a cell's DNA by inserting a gene into the stem cells. This virus is coated on the scaffold, so it doesn't go anywhere else in the body. When the stem cells are added to the scaffold, they take on that viral construct. In inflamed joints, inflammatory cytokines (signaling molecules) such as TNF and Interleukin-1 cause inflammation and arthritis. The virus was developed to make biologic inhibitors (similar to those used in rheumatoid arthritis drugs) and the gene can be turned on and off simply by adding or removing a harmless compound to the cells in the laboratory or to the diet of the animals undergoing testing.
- Utilizing the same genetic program that will turn on an anti-inflammatory drug, the team created self-regulating SMART cells (Stem Cells Modified for Autonomous Regenerative Therapy) by using CRISPR-Cas9 (removing, editing or altering sections of the DNA sequence). They edited the cells to cut out the signaling pathway in the cytokine that breaks down the cartilage, and in its place, inserted the biologic drug to shut off inflammation. Instead of remotely adding or removing inhibitors, these cells can turn on the drug when it senses inflammation and turn on and turn off when the inflammation stops. This approach is currently being tested in mouse models with rheumatoid arthritis.

"We're hopeful that as we work through this next chapter in our research, we can increase the efficacy of the joint replacement, so eventually it has a longer life span and one day could provide permanent regeneration and replacement option," said Dr. Guilak.

Dr. Guilak previously received the Kappa Delta Young Investigator Award in 1998 for "The Biomechanics of the Chondrocyte in Articular Cartilage" and was part of the team who received the 2015 Kappa Delta Ann Doner Vaughn Award for "Early Inhibition of Proinflammatory Cytokines Prevents Post-Traumatic Arthritis: Insights from the Natural History of Arthritis Developing after Intra-Articular Fracture."

About the Kappa Delta Awards

In 1947, at its golden anniversary, the Kappa Delta Sorority established the Kappa Delta Research Fellowship in Orthopaedics, the first award ever created to honor achievements in the field of orthopaedic research. The first annual award, a single stipend of $1,000, was made available to the Academy in 1949 and presented at the AAOS meeting in 1950. The Kappa Delta

Awards have been presented by the Academy to persons who have performed research in orthopaedic surgery that is of high significance and impact.

The sorority has since added two more awards and increased the award amounts to $20,000 each. Two awards are named for the sorority national past presidents who were instrumental in the creation of the awards: Elizabeth Winston Lanier, and Ann Doner Vaughn. The third is known as the Young Investigator Award. For more information about the manuscript submission process, please visit aaos.org/kappadelta.

Kappa Delta Foundation

Kappa Delta Sorority is a national organization for women with nearly 260,000 members, more than 500 chartered alumnae chapters and 169 active collegiate chapters. Established in 1981, the Kappa Delta Foundation is a 501(c)3 organization whose mission is to secure funds for the educational, leadership and charitable purposes of Kappa Delta Sorority. The foundation is supported by member donations and bequests that fund programs and initiatives such as scholarships, internships, grants and more. Kappa Delta National Headquarters is in Memphis, Tennessee. For more information, visit www.kappadelta.org/foundation/.

About the AAOS

With more than 39,000 members, the American Academy of Orthopaedic Surgeons is the world's largest medical association of musculoskeletal specialists. The AAOS is the trusted leader in advancing musculoskeletal health. It provides the highest quality, most comprehensive education to help orthopaedic surgeons and allied health professionals at every career level best treat patients in their daily practices. The AAOS is the source for information on bone and joint conditions, treatments and related musculoskeletal health care issues and it leads the health care discussion on advancing quality.

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Disclosure

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Conflicts of Interest

Drs. Guilak, Estes, and Moutos have received patents that cover the technology described in this work. The patents have been licensed to a startup company Cytex Therapeutics, Inc. The authors are employees and shareholders of Cytex Therapeutics, Inc.

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[ii] Gunther KP, Puhl W, Brenner H, et al. 2002. [Clinical epidemiology of hip and knee joint arthroses: an overview of the results of the "Ulm Osteoarthrosis Study"]. Z Rheumatol 61:244-249.

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