Orthopaedic Research & Education Foundation

IMPACT

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Room for Many More

Investigating the Value of Creating Space for New Cells to Grow and for More Successful Meniscus Transplants

Replacing the structure in the knee responsible for stability and cushioning may become easier with longer-lasting results because of research conducted by **Cristin M. Ferguson, M.D.**, funded in part by a Clinician Scientist Award through OREF.

OREF named Dr. Ferguson a 2007 recipient of the award, which provides an annual stipend of $100,000 for three years to compensate for the loss of income associated with devoting more time to research than to clinical practice. In return, OREF Clinician Scientists are asked to devote extensive time to research; serve as role models for orthopaedic residents, interns, and medical students; and organize and participate in conferences.

Dr. Ferguson's award will be funded by a contribution to OREF from ***The Journal of Bone and Joint Surgery***.

"It is very easy to have all your research time taken up by clinical practice," Dr. Ferguson said. "You add on a surgery. You add on a clinic. It's very hard to carve out research time, and that's what this award enables someone to do. It helps develop the research part of a career and frees up time to serve as a mentor to people who have similar interests."

Getting to the Center

Dr. Ferguson's research concerns the meniscus, a C-shaped cartilage cushion that acts as a shock absorber and stabilizes the knee. One of the

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The meniscus tissue engineering research team
(Standing, left to right): ***Mark Van Dyke, Ph.D.*** *(collaborator at the Wake Forest Institute for Regenerative Medicine),* ***Cristin Ferguson, M.D.*** *(Department of Orthopaedics). (Seated, left to right):* ***Mr. Devin Odom*** *(first-year medical student, Wake Forest University School of Medicine),* ***Kathryne Stabile, M.D., M.S.*** *(research resident, Department of Orthopaedics),* ***Ms. Julie Steen*** *(graduate student, School of Biomedical Engineering). Not pictured:* ***Tom Smith, Ph.D.*** *and* ***Beth Smith, Ph.D.*** *(Department of Orthopaedics).*

Brought to Their Knees: How a Study That Began With OREF Funding Is Changing the Way Orthopaedists Think About ACL Reconstruction

Nearly 275,000 anterior cruciate ligament (ACL) reconstructions are performed in the United States each year. Hoping to improve patient outcomes, **Kurt P. Spindler, M.D.** is leading a clinical follow-up study, initially funded by OREF, to assess what makes some reconstructed ACLS last longer than others.

"I really want to know the answer to what happens to these ACLs, to know what predicts their failure or success so that we can improve our outcomes," he said. "OREF gave us the seed money to design a study that proved we could follow up with patients years after their operations."

From Patient to Orthopaedist

Dr. Spindler, whose interest in orthopaedics and sports medicine resulted from his experience as a patient, after sustaining an injury during high school football practice, said he first became interested in research when he was asked to participate in a scientific investigation as a college student.

"I became hooked on evaluating things in a scientific way. I think that colors the way you look at things. You begin to wonder, 'How do I want to experiment?' 'What is factual?' 'What is true?'"

Research remained a significant part of Dr. Spindler's training as he continued

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most common procedures performed by orthopaedists, according to Dr. Ferguson, is knee arthroscopy to manage damaged cartilage structures. And the majority of these, Dr. Ferguson said, involve the trimming of torn menisci instead of repair, which has long-term implications for the knee.

"One of the more difficult things to see in your practice is a young, active person whose knee is, overall, very healthy, but they have a cartilage tear that can't be fixed. Often a substantial portion of the injured meniscus needs to be taken out because it is biologically and mechanically unable to heal," Dr. Ferguson said. "While current meniscus transplants with cadaver tissue are good, there are certain biological aspects that lead to earlier failure. They do not all appear to function as well as the original meniscus and they do not appear to last as long."

Dr. Ferguson is seeking a solution to this problem, which she believes is caused by the nature of the cadaver transplant tissue.

"Studies show that the recipient of the transplant, or host's, cells cannot grow into the central portion of the transplant, which is a dense tissue. Ultimately there are no cells living in the central portion of the transplant to help maintain its structure and strength, so it wears out."

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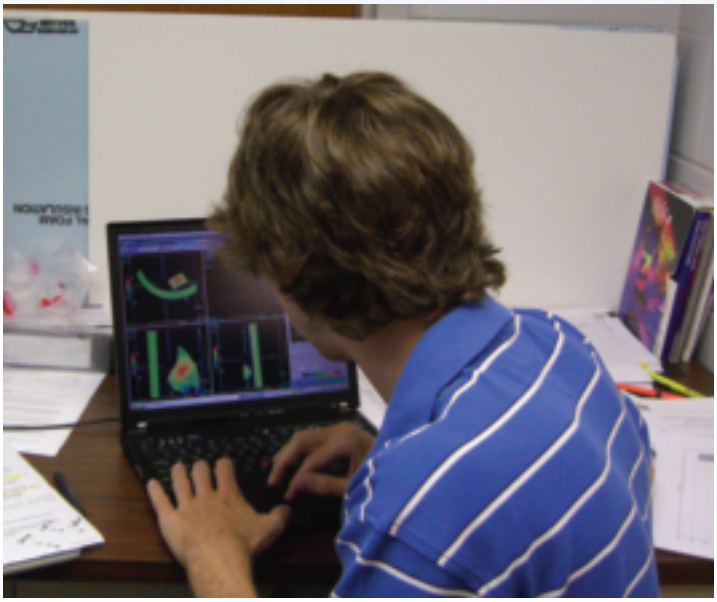
> *— Cristin M. Ferguson, M.D.*

To prevent this problem, Dr. Ferguson is investigating a way to transplant menisci with living cells in the center. Her research involves chemically processing a cadaver meniscus to not only remove the cadaver cells, but also create spaces (porosity) for new cells to grow. This should give the host's cells room to grow into the center of the transplant tissue, or allograft.

An Amenable Allograft

In addition to making room for the host's cells, Dr. Ferguson is working on another process to help the transplant patient accept the allograft. By deriving stem cells from the host's own blood or bone marrow and inserting them into the transplant tissue, Dr. Ferguson hopes to create a meniscus that is already populated by the patient's own cells before the transplant takes place.



Mr. Devin Odom, a first-year summer medical student, works on meniscus scaffold image analysis.

"I think the one thing that's attractive about this method is that the fundamental structure of the meniscus — the natural arrangement, structure, and composition of collagen fibers — is maintained. We're not trying to synthetically reproduce the meniscus. It is a complex tissue that would be very difficult to accurately recreate with synthetic materials. Instead, we're preserving the natural structure, but making it more biologically compatible for the body's cells to grow in and take over. The ingrowing cells can also take cues from the surrounding collagens and proteins to guide them to grow into the desired tissue. We're capitalizing on the complex structure and biology of the meniscus scaffold that's already there by making the allograft tissue more amenable for our bodies to incorporate and maintain it."

The idea behind this, according to Dr. Ferguson, is that the living host cells that grow into the center of the tissue upon implantation should be better able to maintain the collagen and surrounding matrix proteins and, therefore, maintain the structural integrity of the meniscus tissue transplant. The fact that the host cells are added to the allograft also helps the recipient's body accept the tissue because it already seems like the patient's own.

These studies could have additional implications for older patients. As people age, the meniscus degenerates, and Dr. Ferguson would like to further her research by studying the processes of aging in the meniscus.

"Concurrent with meniscus degeneration, we also see the development of arthritis, and while the articular cartilage research that's currently being done is very important, I think we're missing information on another very important structure within the knee that contributes to the development of arthritis: the meniscus," said Dr. Ferguson. "We need to understand the biology that is happening in the meniscus with aging and development of degenerative changes."

Hope for Healthier Knees

If the biological studies show promise, Dr. Ferguson would like to move on to human clinical trials, comparing the new meniscus replacement to what she terms the current gold standard: allograft transplantation. If this new meniscus replacement shows promise, she hopes that it could someday be used to help patients who've experienced more extensive cartilage and arthritic injury than what is currently managed with standard meniscus allograft transplantation.

"I'm trying to work on the current technique to make it better so that patients will have better results with better long-term function. By creating a healthier knee, patients can stay more active longer, especially in their younger years, doing all of the activities that they like to do instead of giving them up."

"I'd like to understand why people tear their meniscus. I'd like to understand why the meniscus wears out. Research allows me the opportunity to ask these questions and, over time, answer them. I think the ultimate goal is to expand our knowledge so we can better treat patients."
— Cristin M. Ferguson, M.D.

Dr. Ferguson believes research is important, not only because she is herself a clinician scientist, but also to advance orthopaedics.

"There are so many things that I do every day that seem to work in clinical practice, but I don't really understand them. I'd like to understand why people tear their meniscus. I'd like to understand why the meniscus wears out. Research allows me the opportunity to ask these questions and, over time, answer them. I think the ultimate goal is to expand our knowledge so we can better treat patients."

Dr. Ferguson has focused her medical career around orthopaedic clinical training, sports medicine fellowship training, and basic-science orthopaedic research. She spent more than two years conducting orthopaedic research during her training, first at the University of California, San Francisco, and then at the University of Rochester. In 1999 she received an OREF Resident Research Grant for her study of the process of cartilage maturation. Currently, Dr. Ferguson is an assistant professor at Wake Forest University where she divides her time among teaching, clinical practice, and research. In addition to OREF, Dr. Ferguson will receive funding to support her meniscus transplant research from the Musculoskeletal Transplant Foundation and National Football League Charities. ■

(left to right) Beth Smith, Ph.D., Cristin Ferguson, M.D., and Tom Smith, Ph.D. review data in the orthopaedic research lab at Wake Forest University.

OREF Clinician Scientist Award Now in Its Fifth Year

The OREF Clinician Scientist Award was established by **Dr. Zachary B. and Mrs. Kathleen Friedenberg** in 2003 to encourage young orthopaedic surgeons to pursue careers as clinician scientists, with a special emphasis on continued research. After the creation of the first award, **Dr. Dane and Mrs. Mary Louise Miller** and ***The Journal of Bone and Joint Surgery*** also established Clinician Scientist Awards. ***The Journal of Bone and Joint Surgery*** will support Dr. Ferguson's Clinician Scientist Award.

Clinician Scientist Awards provide an annual stipend of $100,000 for three years to compensate for the loss of income associated with devoting more time to research, and less time to clinical practice. In return, OREF Clinician Scientists are asked to devote extensive time to research; serve as role models for orthopaedic residents, interns, and medical students; and organize and participate in conferences.