

## 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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participating in projects as a medical student and resident, and is still central to his work with the current generation of young orthopaedists. Today, Dr. Spindler is professor and vice-chairman of the department of orthopaedics and rehabilitation at Vanderbilt University Medical School where he is also director of the Vanderbilt Sports Medicine Center and Orthopaedic Patient Care Center, and serves as head team physician for Vanderbilt University's NCAA Division I varsity athletes.

"By going through scientific inquiring and using the best evidence-based medicine, you can be assured that you're applying the best care to your patients," he said, explaining his penchant for research. "And what being an orthopaedist really comes down to is taking excellent care of patients."

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— Kurt P. Spindler, M.D.*

### First Funding

Dr. Spindler first became involved with OREF when he applied for and received funding for a basic science project that examined the role played by bone growth factors in the normal healing process. He wanted to know if they could be applied clinically to accelerate and seal healing in joints. The *Journal of Orthopaedic Research* published papers on his work in which he concluded that the

growth factors did not speed healing enough to warrant their use in clinical practice.

Still interested in the healing process, however, he searched for someone who shared his passion for research, looking outside Vanderbilt when he didn't find anyone at his own university.

"I found Martha Murray, who had received some OREF funding and now has an R01 NIH grant. I decided to collaborate with her and continue in the supporting role with that research."

With **Martha M. Murray, M.D.**, an assistant professor in orthopaedic surgery at Children's Hospital of Boston, Dr. Spindler continued to investigate what inhibits joint healing. Currently their studies show that platelets might play a significant role.

Dr. Spindler, however, was also interested in research beyond basic science, particularly in terms of ACL reconstruction.

"When you perform surgery on someone, you want to know what predicts their result. I think of result as being function. You want to know how well they function, what their activity level is, and what's the risk of them developing arthritis."

### Survey Says

Adding to a database he had already developed as a fellow at Cleveland Clinic, Dr. Spindler collected prospective data from ACL reconstructions at Vanderbilt and from **Jack T. Andrish, M.D.** and **Richard D. Parker, M.D.** at Cleveland Clinic Foundation. With this data, he applied for and received an OREF Prospective Clinical Research Grant in 2002. The OREF funding allowed him to amplify the prospective data by contacting patients a few years after their operations. The study proved not only that a high percentage of follow-up was possible two to five years after ACL reconstruction, but also that valid information could be obtained from the previously validated questionnaires patients completed themselves.

"The forms are supposed to be interpreted and completed only by the patient and they are not to be changed by anyone," Dr. Spindler explained. "Their design is to be independent of any interviewer — physician or anyone else — so that the patient can interpret the questions reliably and accurately."

At two years after surgery, orthopaedists taking part in this study asked patients to answer four standardized questionnaires designed to gather outcome data.

The study used two general forms. Short Form 36 (SF36) contains 36 questions to measure health-related quality of life for all medical disciplines, and the Western Ontario MacMaster (WOMAC) form asks 24 questions about pain, disability, and joint stiffness to evaluate pain and function in knees and hips affected by osteoarthritis.

Dr. Spindler's research also used two sports-specific forms; the International Knee Documentation Committee (IKDC) form and the Knee Injury Outcome Osteoarthritis Score (KOOS) form, both of which measure activity level by asking such questions as, "Do you have problems with your knee in everyday life?" and "Do you limit your sports and recreational activities because your knee bothers you?"

## Challenging the Status Quo

The research conducted under the OREF grant changed the way in which outcomes were evaluated. Before the OREF study, Dr. Spindler indicated, the standard methods to measure ACL reconstruction were based on structural factors, such as knee stability, range of motion, and laxity. Dr. Spindler's study did not measure structural changes, but relied instead on the questionnaires in which patients expressed how their knees felt years after their procedures. The questionnaires evaluated physical and mental health, function in sports, symptoms of arthritis, and overall quality of life. In August of 2005 *The Journal of Bone and Joint Surgery (JBJS)* published a paper on the study, highlighting validated questionnaires as a means to measure ACL reconstruction. Consistent with this, *JBJS* now recommends the WOMAC as the best form to evaluate osteoarthritis.



Kurt P. Spindler, M.D.

"Prior to the *JBJS* paper, everyone evaluated an ACL reconstruction by how stable your knee was. We said, 'we don't have that information, but we can tell you how well it's functioning by some valid sports-specific forms. We can tell you whether they have symptoms of arthritis,'" Dr. Spindler said.

*"Without OREF there is no NIH grant. You can think of the NIH as a car race. No one is going to give you a Ferrari to race at first . . . The OREF allows you to race safely and appropriately at your level to build your skills set so that you have the opportunity to advance to the NIH, to get that Ferrari and win." —*

*Kurt P. Spindler, M.D.*

"We changed the paradigm and said that measuring success in this way was equally important to the patient. *JBJS* agreed and this is the kind of shift the OREF paper made. Now people don't just focus on knee stability, they focus on stability but also on patient-reported outcomes."

## To the MOON

Based on the success of the OREF-funded study, Dr. Spindler and his research partners established the Multicenter Orthopaedic Outcomes Network (MOON), a consortium of seven hospitals and universities throughout the United States, each of which adds ACL patient outcome data to the database.

In the first three years the members of MOON collected data on 1,600 patients, approaching a 90% follow-up rate. The high percentage of follow-up is due to the competitive nature of orthopaedists, Dr. Spindler indicated.

"We print out every surgeon's percent follow-up so that everyone else in the group sees, and it becomes them versus the rest of their friends. Since we're all at the same level and most of us run large sports medicine centers, we don't want to lose to each other. I don't want to lose to the guy in Cleveland, and the guy in Iowa doesn't want to lose to the orthopaedist at Vanderbilt or Cleveland."

Dr. Spindler explained that a high follow-up percentage is necessary because the minimum follow-up for Level 1 evidence-based medicine is 80%. Because some data,

such as revisions, must be excluded, the goal has to remain even higher to ensure percent follow-up remains above the minimum threshold.

## From Hondas to Ferraris

After four years of collecting data and a little more than two years of writing grants, Dr. Spindler received, as the principal investigator, a \$1.2 million NIH R01 grant to continue the MOON cohort study.

According to Dr. Spindler, OREF funding was instrumental to the beginning of this long-term, follow-up research, and without it, NIH funding would have been impossible to obtain.

"Without OREF there is no NIH grant. You can think of the NIH as a car race. No one is going to give you a Ferrari to race at first. You're going to have to race cars that are more appropriate for your level. So you race Hondas for a while before you get good enough to go race with the big cars. That's exactly what OREF is. The OREF allows you to race safely and appropriately at your level to build your skills set so that you have the opportunity to advance to the NIH, to get that Ferrari and win."

## Sophisticating MOON

The NIH funding will enhance data for the study. The four forms that the MOON members were using as follow-up are now used pre-operatively as well. Since the patients are asked the same questions before

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surgery as they are at follow-up, Dr. Spindler said, the data paint a more accurate picture of how well reconstructed ACLs are functioning.

“We use the same valid outcome measures that we apply to patients at the time of their surgery, so when we follow up with the same measures our results are more powerful because we’re able to control for their initial baseline account.”

The database used by MOON affiliates has also become more sophisticated, having been customized by the Vanderbilt biostatistics department, headed by **Frank E. Harrell Jr., Ph.D.** and having received epidemiological support from **Robert S. Dittus, M.D., M.P.H.** at Vanderbilt’s Health Services Research Center.

In addition to improving the data aspects of the study, the NIH funding will allow further investigation. The members of MOON will take structural measurements. While the cost would be too great to have every patient in the database return to the MOON universities and hospitals to have their reconstructed ACLs structurally measured, a randomized sub-set of patients can act as a model for the whole group. Among other structural indicators, on follow-up the patient sub-set will be tested for laxity and function, and will have their ACLs X-rayed to measure joint space width.

### **Patient Patients**

About 99% of MOON patients agree to participate in the cohort study. Dr. Spindler believes this is partly because patients realize that as subjects of the study they will receive the best possible care. But there are other benefits as well.

“When does a surgeon operate on you and then call you two years later to ask you to fill out a form to see how you’re doing? I think that patients realize that there’s no down side, other than the time it takes to fill out the form, but there’s a definite upside because you can improve ACL reconstruction for other people, and they may find improvements for themselves.”

In fact, Dr. Spindler said, much can be learned by evaluating the patient-reported data. The information will show whether patients are modifying sports and

*“I think the insurance companies are going to have to take notice. Good clinical research can not only help the patients but it can also help you as physicians show that you’ve improved the quality and the efficacy of what you do and, therefore, should be reimbursed.”*  
— Kurt P. Spindler, M.D.

recreational activities due to knee-related pain, and how well their reconstructed ACLs are functioning compared to other patients who’ve had the same procedure. This data can be assessed to learn why some outcomes are better than others.

For example, Dr. Spindler said, a poor outcome could be the result of the partial loss of the meniscus. If they find this to be the case, orthopaedists would seek help from engineers to develop a meniscus substitute that could be implanted during the ACL reconstruction, hoping for a longer-lasting ACL graft.

The data assessment could also indicate other factors that lead to poor outcomes. Orthopaedists could then counsel their patients before and after surgery to teach them how to help their own recovery and maintain their reconstructed ACL.

This principle, based on the Framingham Study that showed high cholesterol, high blood pressure, family history, lack of exercise, and smoking to be the risk factors for cardiovascular diseases, is what Dr. Spindler would like to apply to knees and ACL reconstruction.



*Dr. Spindler examines an ACL reconstruction patient.*

"We're going to find out what the most important factors are in someone developing poor ACL function and we're going to see if we can modify them in the future to improve the outcome," he said. "Perhaps people who gain 50 pounds are doomed after surgery, for example. Weight may be a big thing, I don't know. That's what this study will tell us."

### Satisfaction for Orthopaedists and Patients Both

Assessment of follow-up data has already led the surgeons involved in MOON to a few conclusions. They now know, for example, that the risk of tearing the graft in the reconstructed ACL is exactly the same as tearing the ACL in the knee that hadn't needed surgery. They have also found that body mass index, smoking status, arthritis on the medial femoral condyle, and pre-surgical activity level can predict how active a patient is two years after ACL reconstruction.

And the MOON cohort study could also directly benefit orthopaedists by changing insurance practices, Dr. Spindler indicated, since demonstrating that ACL reconstruction makes a difference in a patient's quality of life proves the effectiveness of the treatment.

"I think the insurance companies are going to have to take notice. Good clinical research can not only help the patients but it can also help you as physicians show that you've improved the quality and the efficacy of what you do and, therefore, should be reimbursed."

Dr. Spindler said he hopes that orthopaedists realize that clinical studies are research and development for orthopaedics and that supporting the research is critical, not only to prove the efficacy of orthopaedic procedures, but to improve patient care, which is, after all, why he became an orthopaedist.

"The most satisfying thing about being an orthopaedist is when a patient says 'thank you' for taking care of him or her. They don't have to thank me. I'm paid very well to take care of them, but they go out of their way to say 'thank you.'" ■

# OREF...

## Helping Residents Explore New Possibilities in Orthopaedics

### OREF Resident DEVELOPMENT

The Orthopaedic Research and Education Foundation (OREF) has developed several resources we want to share, designed to help orthopaedic residents sharpen their skills and build a firm foundation for a rewarding career.

LEARNING FROM PEERS... Top-rated work (winning research abstract and poster submissions) from our Spring 2007 Resident Research Symposia competition are now posted on the OREF Resident Resources Web page: [www.oref.org/residents](http://www.oref.org/residents).



#### GRANTS, WORKSHOPS & MORE...

OREF shared the work of 2007 Resident Research Symposia and 2007 State Society competition winners online and in print, through a call-for-grants poster, distributed to residents and candidates with the July 2007 issue of *The Journal of Bone and Joint Surgery*. Requests for extra copies of the poster, which also features the opportunities OREF provides for residents, may be sent to [communications@oref.org](mailto:communications@oref.org).

RELATING TO INDUSTRY... Demand has been exceptionally high for *Essential Guidelines, Regulations and Ethical Considerations: The Evolving Relationship between Orthopaedists and Industry*, an article commissioned by OREF to help orthopaedic surgeons address health care compliance issues.

#### Congratulations

2007 Resident Research Symposia Winners

#### Midwest

Todd A. Irwin, M.D.,  
William Beaumont  
Hospital, Royal Oak, MI  
Harold Schock, M.D.,  
Loyola University  
Patrick O'Leary, M.D.,  
Loyola University  
Alvin Detterline, M.D.,  
Rush University  
Medical Center

#### New England

Peter G. Passias, M.D.,  
Tufts University  
Keith Monchik, M.D.,  
Brown University,  
Rhode Island Hospital  
Matthew Plante, M.D.,  
Brown University,  
Rhode Island Hospital

#### New York

Lawrence Gulotta, M.D.,  
Hospital for Special  
Surgery  
Samuel Cho, M.D.,  
Columbia University  
Jordan Kerker, M.D.,  
North Shore/Long  
Island Jewish  
Julie Keller, M.D.,  
Columbia University  
Shawn Trokhan, M.D.,  
Columbia University  
James Voos, M.D.,  
Hospital for Special  
Surgery

2007 State Society  
Resident Research  
Award Recipients

#### California Orthopaedic Association

Robert Grumet, M.D.,  
University of California,  
Irvine

#### Mid-Central States Orthopaedic Society

Joshua Nelson, M.D.,  
University of Kansas  
Chad A. Waits, M.D.,  
University of Kansas