IMPACT

Orthopaedic Research and Education Foundation

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Zimmer/OREF partnership supports research that lessens pain, enhances healing in bone loss patients

Kristy L. Weber, M.D. works with mice near the Faxitron X-ray machine

Patients who suffer from bone loss due to trauma or disease, such as cancer, may find help through research studies conducted by recipients of the OREF/Zimmer Career Development Award.

Each year Zimmer supports six $50,000 awards through OREF. According to **Ray Elliott**, Zimmer Chairman, President, and CEO, "When we realized that young, practicing clinicians did not have the resources that are available to residents or veteran clinicians, we decided to help these young researchers by providing funding through OREF for a new grant program. Since then, we've granted to OREF more than a quarter of a million dollars each year to help these younger surgeons pursue additional research, education, travel, or any legitimate endeavor to help them advance orthopaedic science or care."

The work of two current Zimmer recipients — **Kristy L. Weber, M.D.** and **Robert L. Satcher, M.D., Ph.D.** — demonstrates how **research** can be used **to help patients whose bones are affected by disease or trauma.**

Study gives new hope of less suffering to bone cancer patients

Cancer is a dreaded diagnosis for any patient. Though not always fatal, it can be debilitating, which leads researchers to investigate ways to prevent complications from the disease.

Kristy L. Weber, M.D., chief of the Division of Orthopaedic Oncology and associate professor at Johns Hopkins School of Medicine, is investigating how kidney cancer metastasizes, moving from the kidney into the bone. She hopes that her research will lead to new treatments for metastatic kidney cancer.

"We're not so bold as to be looking for a cure for kidney cancer," Dr. Weber said. "We are really just trying to make a small step forward in how these patients' lives are lived. We're trying to stop some of the suffering due to bone metastasis."

From kidneys to the bone

Kidney cancer, unlike breast and prostate cancers, does not respond well to chemotherapy, radiation, or hormone treatments. According to Dr. Weber, once kidney cancer is in the bone, there is currently no method that can reliably stop it. As kidney cancer spreads into the bone, it can cause destructive holes that result in fractures and, if it enters the spine, even paralysis. Orthopaedic surgeons can surgically repair some of the damage and prevent future fractures by placing hardware in the bone

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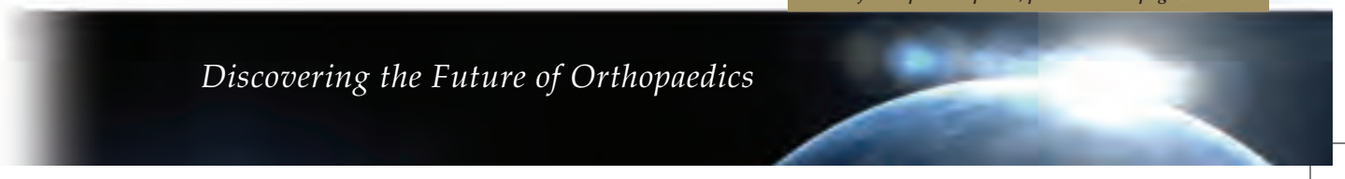
In this Issue

Robert L. (Bobby) Satcher Jr., M.D., Ph.D., mission specialist astronaut candidate, floats freely aboard a KC-135 aircraft as part of his early training.

To read about Dr. Satcher's studies of how bone reacts to the forces placed upon it, please turn to page 10.



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prophylactically, but Dr. Weber would like to find a way to prevent kidney cancer from moving into the bone, or stop it from growing if it does.

"We're looking for a way to help the bone specifically. Once kidney cancer is spread in the bloodstream, it's incurable, so to treat it, we need to find a way to stop it from spreading from the kidney."

To find out how to stop it from spreading, first Dr. Weber must learn how and why kidney cancer metastasizes, or moves, into the bone. With permission, Dr. Weber obtained kidney cells from one of her patients whose cancer had spread to his arm. As Dr. Weber placed a metal rod in the patient's arm to prevent a fracture, she scraped out some tumor cells.

She placed the cells in a dish in the laboratory and with the right ingredients, the cell line continued to grow. Repeating this procedure with other patients, Dr. Weber now has six to eight kidney cancer cell lines that she uses to test different drugs and to investigate the various molecular pathways the cells take when specific growth factors are added.

In addition to the cell line studies, when Dr. Weber performs surgery on a patient with kidney cancer in his or her bone, she removes a slice of tissue and extracts the DNA or RNA: the building blocks of the cancer.

Through this research, Dr. Weber is trying to answer several questions. She wants to know how the cells respond to different drugs and different growth factors; what proteins the cells secrete along the molecular pathway; how the kidney cancer that lives in the kidney differs from the kidney cancer that lives in the bone and what causes the difference.

"We try to figure out what had to happen for someone's kidney cancer to move into his or her bone, and what growth factors are turned on in the bone versus in the kidney environment," she said.

Stopping cancer's destruction

Dr. Weber is also studying bone metastasis from kidney cancer in an animal model. The cells from her patients are placed in a mouse's leg bone where they grow. Using a small, digital X-Ray machine, she can view how much of the bone is destroyed.

> *"Many of the current advances in orthopaedics are due to research performed using OREF funds."*
> *— Kristy L. Weber, M.D.*

She and her research team experiment, testing specific drugs or modifying the cells in some way, such as by blocking a certain growth factor receptor, to see if they can stop cancer growth and bone destruction.

"One drug doesn't really cure anybody's cancer anymore. Cancer cells are really smart, and if you block one pathway for growth, they will find a way around it," said Dr. Weber. "So you've got to hit cancer with a few different agents at the same time. Just when we think we've made progress in one area we find another whole area that's more difficult to solve."

In addition, Dr. Weber said, the right drug probably hasn't been developed yet. Because of this, she also looks for natural methods of blocking cancer cell growth, such as antibodies or small molecule inhibitors.

"When we discover a successful biological treatment in our mouse model, we can work that into actual treatment of patients in the clinic. We're testing different ways to block growth factors, and if any of them look incredibly promising, then we'll work with a company to develop the drugs that can reproduce the effect. If we can stop kidney cancer from moving into or growing in the bone, we can prevent patients from breaking their bones and living in such misery," she said.

Supporting research

Dr. Weber began her research with funding from an OREF/Zimmer Orthopaedic Career Development Award, and without the award she doesn't think her bone metastasis research would have gone as far.

"The OREF/Zimmer award was one of the first grants I received for the bone metastasis research, which has become the main focus of our laboratory. Without that support, we wouldn't be going forward as we are," she said.

Dr. Weber also thinks supporting OREF is important to advance orthopaedic care. She became a member of OREF's highest recognition society, the Shands Circle, in 2004, and has given to the annual campaign at the *Order of Merit* level — $1,000 or more — since 2001. "Without OREF funding, I probably wouldn't be able to conduct any research today, because I wouldn't have had the money to get the experiments off the ground. We are now applying at the NIH level and hopefully we will receive additional support, but OREF helped me in the beginning."

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Dr. Weber also thinks that doctors who are not researchers, as well as the general public, could also support OREF. "People who don't have such an interest in research may understand what I'm trying to do for bone cancer patients and want to support OREF, too. Many of the current advances in orthopaedics are due to research performed using OREF funds," she said.

Researcher looks at ways to replace destroyed bone

Bone loss can occur after trauma, diseases such as cancer, and surgical procedures, prompting researchers to study ways to replace the loss.

Upon conducting his post-doctoral work, **Robert L. Satcher, M.D., Ph.D.** became interested in how bone responds as a whole to the various stresses thrust upon it and, conversely, how it responds to the absence of those stresses. In 2002 he received an OREF/Zimmer Career Development Award to begin that study.

The stresses bones face

To gain a better understanding of how various forces affect bones, Dr. Satcher, then an assistant professor of orthopaedic surgery at the Feinberg School of Medicine, a researcher at The Robert H. Lurie Comprehensive Cancer Center of Northwestern University, and an orthopaedic surgeon at Northwestern Memorial Hospital, investigated bone at the cellular level. Bone is made up partly of living tissue and partly of an inorganic and organic matrix. Proteins make up the organic portion, while calcium and phosphates constitute the inorganic part. It is the living portion, however, that reacts to stress placed upon it.

"It's been known for a long time that if you subject bone to physical stress, such as loading it, the bone will become larger in size," Dr. Satcher said. "What that means is that the bone cells — the smallest living units that make up the bone — are helping to build up that bone to make it stronger in response to that physical stress."

Dr. Satcher, a mission specialist candidate in NASA's 2004 astronaut class, poses with a T-38 jet trainer aircraft at Ellington Field.

> *"As people age, most will need orthopaedic care, even if it's not operative... If orthopaedics is going to continue to improve, it is going to be through research that is carried out intelligently and effectively. Supporting research is essential to the continuing improvement and evolution of orthopaedics."*
> *— Robert L. Satcher, M.D., Ph.D.*

Using bone cells harvested from rats, Dr. Satcher and a team of researchers were able to study how bone reacts to different physical forces using several methods. In

photos and captions courtesy of NASA

Dr. Satcher gets a closeup look at one of the agency's T-38 jet trainer aircraft.

one method, Dr. Satcher observed flowing fluid across the bone cells to see how they were affected. The side of the cell exposed to the flowing fluid represented how a physical force would impact bone.

Dr. Satcher was also able to grow cells on a deformable membrane. "When you deform the membrane that the cell is growing on, it subjects that cell to the same deformation, which is equivalent to a physical stress that would cause deformation in the bone."

This allowed Dr. Satcher to test the cells' response to controlled loading. "We can specify how much straining the cells experience, or the deformation they experience because we artificially input the load. This lets us observe the patterns of response."

These initial studies that began with the OREF/Zimmer award led Dr. Satcher to his more recent investigation of designing materials that promote bone growth and that could be used to reconstitute areas of bone lost due to trauma, surgery, or cancer.

"We took what I had learned from working on the more fundamental process of how physical stresses affect bone and applied it to practical applications."

Research beyond Earth

Dr. Satcher may have the opportunity to study this process in a completely different setting. He was selected as a NASA astronaut candidate last year. He is currently completing a nearly two-year basic training course that involves everything from classroom training, which teaches the specifics of the space shuttle and international space station, to training in a large pool that simulates weightlessness.

"We also have a trip that involves leadership training, where we are put in scenarios of hostile environments and have to work together as a team to solve the problem under stressful situations," Dr. Satcher said.

Once his training is finished and he has completed a technical assignment to support ongoing activities at NASA, Dr. Satcher will be eligible to be assigned to either a space shuttle mission or a research project on the international space station. In either case, at least part of Dr. Satcher's role will be that of researcher.

"There have been some NASA experiments that have specifically studied how bone cells respond to a low gravity environment, but I won't necessarily be conducting orthopaedic research," Dr. Satcher said. "NASA has a review process similar to the NIH or OREF, where they accept research proposals, and select which experiments are going to be flown on the space shuttle and on the space station. Most likely I'll be a proxy scientist for the principle investigator, doing some experiments that were selected by the peer review process."

Discovering the future of orthopaedics

Dr. Satcher stresses, however, that it is important to support orthopaedic research. "Orthopaedics as a whole has been expanding throughout the years and the capabilities of the surgeries have become better as technology has improved," Dr. Satcher said. "As people age, most will need orthopaedic care, even if it's not operative. Our joints are going to start to bother us, or our back is going to give us problems. If orthopaedics is going to continue to improve, it is going to be through research that is carried out intelligently and effectively. Supporting research is essential to the continuing improvement and evolution of orthopaedics."