

A high-angle, close-up photograph of a surgeon in a sterile operating room. The surgeon is wearing a surgical cap, glasses, a face mask, and a clear protective shield. They are wearing white scrubs and surgical gloves, and are focused on a task. The lighting is dramatic, highlighting the surgeon's face and hands against a dark background.

UPMC LIFE
CHANGING
MEDICINE

Department of Orthopaedic Surgery | Highlights 2015

About the Department

Founded in 1953 as a separate department of the University of Pittsburgh School of Medicine, the Department of Orthopaedic Surgery is committed to delivering the highest quality of diagnostic and therapeutic patient care to both adults and children for a diverse spectrum of orthopaedic disorders. To this aim, the department seeks to meet the needs of 21st century orthopaedic care not only by integrating the latest biological and technological advancements in

orthopaedic science, but equally by leading the development of novel treatment modalities through distinguished basic science and clinical research programs. In addition, the Department of Orthopaedic Surgery seeks to be a leader in educating the next generation of orthopaedic surgeons through its residency and fellowship training programs, which include comprehensive, in-depth exposure to all specialties of orthopaedic care and advanced surgical experience.

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A Message from the Chairman

In our 106th year at the Department of Orthopaedic Surgery, we continue our mission of providing excellent care for our patients, the best education for medical students, residents, and fellows, and extensive basic science and clinical research that translates to improved care and outcomes.

Our commitment to advancing orthopaedic care at every level is evident in ongoing projects like our work with total joint replacement, where we are evaluating the cost of care and developing strategies for quality management and enhancement; our program to capture quality metrics via a tablet computer platform to provide the basis for the analysis of quality measures; and in our multidisciplinary collaboration on clinics such as the UPMC Total Care-Musculoskeletal Health, which utilizes a patient-centered medical home approach for patients with musculoskeletal pain, including a focus on low back pain.

In 2015, our sports medicine program also expanded with the opening of the UPMC Lemieux Sports Complex. One of the first-of-its-kind, this 185,000 square foot complex includes UPMC Sports Medicine's orthopaedic, primary care, physical therapy, concussion, imaging, and sports performance services, and is the primary practice and training facility for the NHL's Pittsburgh Penguins®.

We take great pride in our clinical care and research, as well as for teaching and developing the next generation of orthopaedic surgeons and researchers. Our residency and fellowship programs continue to attract a diverse group of promising individuals, and we are one of only a few programs in the United States that offers residents the opportunity to engage in one year of dedicated research.

In this year's report, I am pleased to feature exciting, ground breaking work from a number of our dedicated researchers and surgeons. Their efforts, talent, and ingenuity are what help make our program a national and international leader.

Sincerely,

A handwritten signature in black ink that reads "Freddie Fu". The signature is fluid and cursive, with a long horizontal stroke at the end.

Freddie H. Fu, MD, DSc (Hon), DPs (Hon)

Professor and Chairman, Department of Orthopaedic Surgery
University of Pittsburgh School of Medicine



Dr. Irrgang is vice chairman of clinical outcomes research in the Department of Orthopaedic Surgery. His background in physical therapy and educational and psychological measurement techniques (the focus of his PhD studies) inform his current research efforts in the development, collection, and validation of patient-reported outcome measures. His past work has included the development of two separate outcomes measures — the Knee Outcome Survey, and the International Knee Documentation Committee Subjective Knee Forum (IKDC), one of the most widely used patient-reported outcome measures for a variety of knee problems that range from ligament and cartilage injury to meniscus injury, and early arthritis.

In 1996, while serving as vice president for Clinical Outcomes and Quality with UPMC Centers for Rehab Services, his team designed a system to collect patient-reported data at the start of physical therapy and then follow-up data every week, with a final data capture at discharge. While the challenges of that project were numerous, and the data collected not ideal, the process and findings proved valuable. “We were trying to collect way too much data. The logistical things really truly got in the way and we weren’t able to collect data like we wanted to,” says Dr. Irrgang. Logistical challenges aside, the need to collect patient outcomes throughout treatment was still seen as immensely important as it can, and will, inform how care is managed in order to achieve an optimal outcome.

Patient-Reported Outcomes: Integrating Data Collection Into Clinical Practice

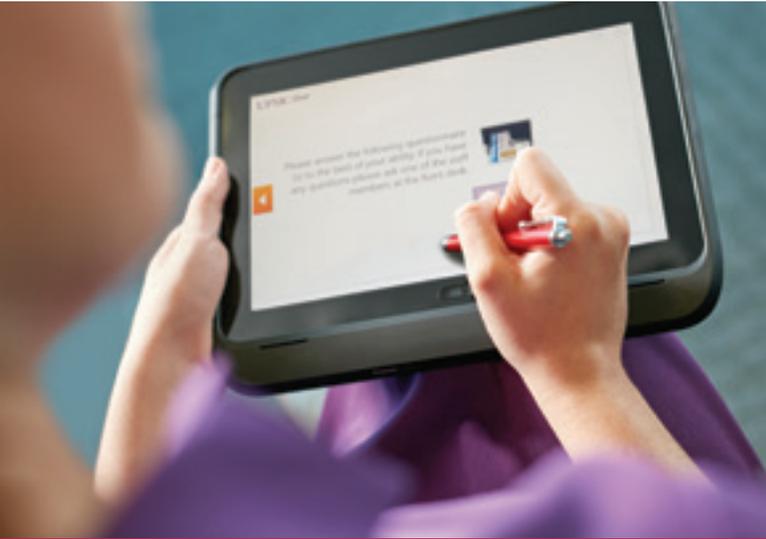




Led by James Irrgang, PT, PhD, a data collection and analytics system — the computerized clinical data repository (CCDR) — is being implemented to capture, assess, and integrate patient-reported outcomes (PRO) data into orthopaedic surgery at UPMC. The goals are to improve patient care, enhance patient-provider communication, and develop quality improvement and value-based care initiatives.

Toward an Integrated Data Collection System

The Department of Orthopaedic Surgery has committed significant resources, and has prioritized the development of its computerized clinical data repository. “Within the last several years the electronic health record was implemented in orthopaedic surgery and has enabled the collection of outcomes data as part of patient care,” says Dr. Irrgang.



Data collection can be accomplished at follow-up visits to the clinic, with prompts in the scheduling system to alert staff, or if patients do not come back they can receive an email alert through MyUPMC, an information portal available to all UPMC patients.

To facilitate the capture of PRO data in the clinic, Dr. Irrgang’s team has adapted the UPMC Patient-Reported Information Clinical Intake System, also known as PRICis. Originally developed at Magee-Womens Hospital of UPMC, the system allows a patient to complete outcome surveys via a touch screen tablet while they are waiting to see

their physician. “Basically it takes 5 to 10 minutes to complete these surveys, and the physician has that data immediately available to them in the EMR,” says Dr. Irrgang, along with the typical clinical exam, diagnostic, and surgical data. For patients who undergo surgery, data will be collected at three, six, and 12 months post-surgery.

To date, Dr. Irrgang, with the support of the spine and foot and ankle surgeons, including MaCalus Hogan, MD, whom he credits as an instrumental and driving force, has fully integrated the collection of patient-reported outcomes data across the entire UPMC system for spine and foot and ankle patients. Now the team is focused on integrating the collection of PRO data for joint replacement services. As a matter of priority, collecting data on joint replacement surgeries has numerous benefits that go well beyond informing better care and facilitating improved doctor-patient communication. In November 2015, the Centers for Medicare and Medicaid (CMS) released final rules for a bundled payment model for joint replacement to include financial incentives and penalties based on quality indicators, making PRO data collection prior to surgery and nine to 12 months post-surgery, crucial for UPMC and the department of orthopaedic surgery. “Dr. Hogan and I have spent quite a bit of time in the last several months working with the PRICis team to implement this data collection for patients undergoing joint replacement,” says Dr. Irrgang. “The ability to collect this data is going to be tied directly to our reimbursement from CMS, and we expect to have the process to collect PROs for patients undergoing joint replacement in place early in 2016.” Dr. Irrgang expects that further out in 2016 sports medicine and one other area, possibly hand and upper extremity or trauma, will come online. Eventually all of orthopaedics will be included in the initiative to collect PROs. The totality of efforts to implement this system in the short term are great, but the results and data collected will provide invaluable information for many years to come.

The Data Collection of Today Will Not Be the Data Collection of Tomorrow

Currently spine and foot and ankle patients receive traditional patient-reported outcomes measures, like the Oswestry Low Back Pain Disability Index or the Foot and Ankle Ability Measure. While instruments such as these are powerful tools, and provide useful findings for clinicians, for Dr. Irrgang there are inherent flaws in the process. “If we are looking at a patient with a lumbar issue we collect an outcome instrument called the Oswestry Low Back Disability Index. There are perhaps four or five, maybe 10 other possible instruments that we could use. If we look at somebody with neck pain it’s the Neck Disability Index. For foot and ankle problems it’s the Foot and Ankle Ability Measure.

There are multiple measures, and that really becomes a problem system-wide because there is no consistency,” he says. And for many patients, numerous questions in the existing surveys have no relevance to their current condition. They are one-size-fits-all applications that are increasingly becoming old technologies in today’s patient-centric, individualized approach to care.

For Dr. Irrgang, these have been very interesting and crucial parts of the process — how to individualize the surveys for patients, and how to standardize the measurements. These are the next steps in the project, and something Dr. Irrgang has, for the last several years, investigated and incorporated into several existing research projects within the department.



Refining the Surveys to Obtain More Meaningful Data

Meaningful, actionable, comparable data requires that patients be asked relevant questions and an understanding that the relevance of the questions can change over time as the patient progresses through treatment and recovery. There also exists a requirement that the outcomes measures have a common scale or metric regardless of the condition so that comparisons of the quality and value of care provided to every patient can be assessed on a similar scale.

“For example, if we have a 65-year-old patient with osteoarthritis of the knee, the first question we may ask is how much difficulty do you have walking a city block? And if they say they are unable to do that very well, we do not then ask them if they can walk a mile. The next question might be how much difficulty do you have walking across your living room? If they say no difficulty, then it might go to something in between walking a block and walking across the living room, like going up and down a flight of steps,” says Dr. Irrgang.

The computer algorithm selects perhaps six to seven questions that are best for that patient and can give them a score instead of administering all of the more than 100 questions in the item bank. It picks the most relevant items for the patient at that time. This has the effect of reducing the length of time to complete the surveys, and it improves efficiency. As the patient changes or progresses over time, their next survey may contain five or six different questions, but they will be measured on the same scale. Individualized data becomes available, and depending on the patient, it is captured longitudinally across their entire length of care. “Ultimately, our goal is to put all the measures on the same metric or scale, which has the advantage of consistency of measurement and really facilitates the study of comparability,” says Dr. Irrgang.

“ The integration of patient-reported outcomes collection across all phases of musculoskeletal care will be essential as we use data to drive our clinical care re-design and optimization. Jay’s expertise and passion for this critical work is truly second-to-none. ”

MaCalus Hogan, MD
*Assistant Professor of
Orthopaedic Surgery
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Leveraging a Collective Wisdom

In September 2015, Dr. Irrgang facilitated a day-long retreat with patients, orthopaedic surgeons, primary care physicians, physical medicine physicians, physical therapists, occupational therapists, leaders in quality improvement, and the UPMC Health Plan. “We had measurement experts attend, and we asked them what they thought was important to measure, how to use that information, and what the best technology to collect that information looks like. It was interesting because we had all parties together and it became evident that from the patient’s perspective, they don’t mind completing the outcome measures, but they get frustrated when the outcome measures are not relevant for them or they cannot answer the question because they don’t understand it,” says Dr. Irrgang.

If a patient has a low back problem and the outcome measure asks them how much difficulty they have writing, it really makes no sense. “So what we’ve realized is that even using these item banks we now need to make them specific for the individual’s type of problem. Do they have a problem with their upper quarter including the neck and shoulder and hand and arm? Or is it a problem with their lower quarter because they use their arms and their legs to do different types of activities. Depending on where they are on the scale, you don’t want to ask questions that represent high-level activities to somebody who is at a very low level of function. This is the next avenue for us. We want to create forms that can be administered with the computer that are individualized to a particular patient’s condition.”

The current lack of consistency across measures has led Dr. Irrgang and the department to investigate the use of algorithms that can tailor the outcome instrument to a specific patient by using computer adaptive testing that contains question banks that use common measurement scales. For the last several years, Dr. Irrgang and his collaborators have worked to test the reliability and relevancy of certain computer adaptive measurement systems, most notably the Patient-Reported Outcome Measurement Information Systems (PROMIS), an NIH funded initiative begun in 2004 to create computer adaptive tests to measure PROs.

“About three or four years ago there was a request for proposals to integrate the use of the PROMIS computer adaptive tests into ongoing clinical research projects. We wrote a grant in which we proposed to collect evidence that supports the interpretation and use of two of the PROMIS tools, one related to physical function and the other related to pain interference,” says Dr. Irrgang. The PROMIS tools were integrated into four studies in the department. One was a trial, funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), designed to compare patients undergoing single versus double-bundle anterior cruciate ligament (ACL) reconstruction. The other studies included investigating manual therapy for patients with knee osteoarthritis, a registry of patients undergoing ACL reconstruction, and a study looking at treatment of degenerative meniscus tears.

“In our NIAMS-funded Knee CAT study we were seeking evidence for interpretation and use of the PROMIS computer adaptive tests for patients with a variety of knee complaints.” Specifically, Dr. Irrgang and his collaborators sought to determine three key metrics: were the questions relevant for patients with knee problems; was the data reliable and responsive; and how did the computer adaptive tests compare to the standard outcome measures used traditionally, such as the IKDC Subjective Knee Form.

Preliminary findings by Dr. Irrgang indicated that in the bank of 140 questions, 30 to 35 items were not relevant for patients with a knee problem, and about 20 were questions patients could not understand how to answer. “This led us to rewrite some of the questions and we are now testing them,” he says. The next part of the project looked at the reliability or consistency of measurement and the responsiveness compared to traditional outcomes measures. “Now, on that front, we have very preliminary data and have not completely finished the analysis. Directionally, it appears the computer adaptive tests may be good enough to replace some of the measures that are traditionally used. And again, the advantage is that we can place all patients on the same metric regardless of the body region in question.”

Analytics and the Future

The sheer size of the clinical orthopaedics services at UPMC, in excess of 25,000 patients a year, means a tremendous amount of data is and will be collected on patients and patient outcomes. Long term, this trove of knowledge will be put to use to better direct patient care, to facilitate communication among a patient’s entire care team, and to understand patient perceptions of the quality of care provided, as well as to understand the value of that care relative to patient outcomes. And, of course, the intelligence gathered can be mined for additional clinical research studies, or put to use to validate treatment regimens and develop quality improvement initiatives. “We’ve done a good job getting data, but now the next step is to access it and put it to work. This is the next horizon, to go beyond just the collection,” says Dr. Irrgang. ■

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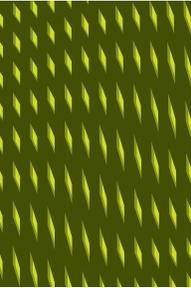
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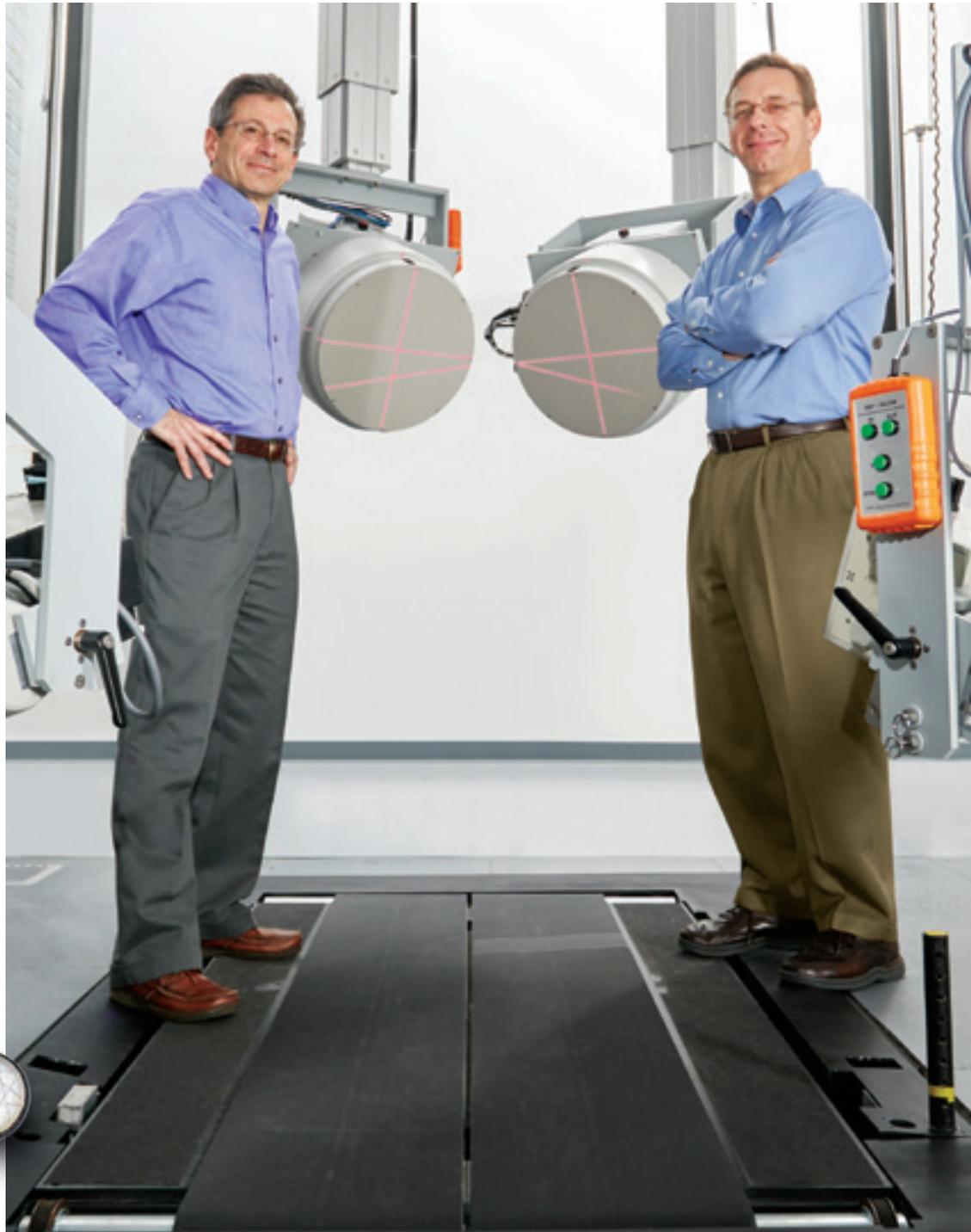
A Dynamic System for Imaging the Invisible



Employing a custom-designed, patented biplane radiography system to study in vivo joint mechanics under dynamic loading conditions, **Scott Tashman, PhD**, and **William Anderst, PhD**, are visualizing aspects of musculoskeletal function with a precision and depth that is leading to exciting changes in how joint motion is perceived and understood.



Reflective markers placed externally to capture body motion.





The BioDynamics laboratory, under the direction of Scott Tashman, PhD, associate professor of orthopaedic surgery, is peering into a world that is traditionally unseen through imaging techniques such as MRI and fluoroscopy. Three-dimensional modeling and visualization of joint function while in motion and under specific loading or movement conditions is shedding new light on a range of orthopaedic conditions.

The BioDynamics lab is engaged primarily in the study and elucidation of the relationships between dynamic joint function and joint disease and injury, and treatments to improve the diagnosis and care of orthopaedic conditions. There are several ongoing studies, including those devoted to degenerative joint disease in the knee, mechanisms by which adjacent segment disease in the cervical spine manifests after arthrodesis, and evaluation of anterior cruciate ligament reconstruction techniques, as well as other musculoskeletal disorders including rotator cuff tears and temporomandibular joint dysfunction.

The lab and principal investigators conducting research have at their disposal cutting-edge imaging technology that allows for the creation and analysis of three-dimensional models capable of visualizing the motion of joints under functional load. This ability to see and interpret joint mechanics in three-dimensional space with sub-millimeter clarity and precision is producing a wealth of knowledge for researchers and clinicians. "We can rotate the three-dimensional bone model any way we want to in our computer and make measurements on all aspects of the bones or joint, from any angle," says Dr. Tashman.



“ Capturing the x-ray images at high speed is essential for reconstructing 3-D joint motion with sub-millimeter accuracy during rapid movements. ”

Scott Tashman, PhD

The Engineering Inside

The technological centerpiece of the BioDynamics Lab is a custom-built dynamic biplane radiography system. Designed by Dr. Tashman and built to his specifications, the system captures synchronized x-ray images at multiple angles using low-dose, high-energy, short duration pulses facilitating the capture of up to 180 frames per second, with each frame taken at 1/1000 of a second using pulsed x-ray generators and high-speed digital cameras. "Capturing the x-ray images at high speed is essential for reconstructing 3D joint motion with sub-millimeter accuracy during rapid movements," says Dr. Tashman.

The x-ray imagers are outfitted onto independently moveable arms that pivot on enormous bearings similar to those used on gun turrets. This flexibility allows the researchers to position the cameras at virtually any angle to obtain the necessary images. "We can position the cameras at just about any angle, down to approximately 40 degrees from one another, and still obtain good accuracy for creating the three-dimensional models," says Dr. Tashman.

Incorporated into the imaging apparatus is a duel-belt, computer-controllable treadmill that allows, for example, the impact forces generated by a person running to be measured independently for each limb, thereby enabling comparisons between normal limb function and that of an injured or repaired one.

Beyond the conceptual approach and design of the system, Dr. Tashman selected the high-speed digital cameras used to capture the x-ray images, created the couplings between the cameras, assembled the electronics and computer interface, and developed aspects of the software the lab uses to render the three dimensional models and recreate the motion. Dr. Anderst explains, "A big advantage of the system is it is very user independent. We don't rely on somebody being able to identify specific landmarks on a bone to tell us how much it is moving. We have an automated computer algorithm that does much of the matching process. It gives us almost exactly the same result every single time, whereas if you have a person trying to identify points on a bone, you are going to have large variability in your measurement."

Creating the Three-Dimensional Models and Motion

The process by which Drs. Tashman and Anderst are able to create their models and motion studies involves a number of steps. The capture of synchronized, multiple angle, high-speed x-ray images is the crucial first part. In some instances, depending on the structures to be imaged, separate measurements are taken using reflective markers positioned on a subject to provide an overall model of body motion for a particular type of movement that is incorporated into the modeling. "This is an important step. We need to know how the joint is affected by the mechanics of the entire body while performing a specific and coordinated movement," explains Dr. Tashman.

To this, researchers are able to incorporate other analytical tools, such as electromyography to collect data on muscle function relative to the imaged motion which enables an understanding of the associated specific muscle activation patterns and intermuscular coordination known to change after an injury as Dr. Tashman points out.

The second part of the process requires the researchers to collect a subject-specific computed tomography (CT) scan of each participant's anatomy. The CT scan is used to create three-dimensional bone models that are then placed into a computer-generated reproduction of the x-ray system. A computer algorithm that optimizes the correlation between the digitally reconstructed radiographs and the edge-enhanced radiographs, determines bone position and orientation. "We simulate shooting x-rays through the 3D bone model and visualize what the radiographs would look like in a given position. By moving the bones around in 3D space at some point they will match both radiographs simultaneously. When it matches, we have the bone in the correct position. The process is repeated for the entire movement that we collect, whether it's a flexion extension or head rotation, or a knee bending," explains Dr. Anderst.



Electromyography is used in specific studies to detail muscle activation patterns and intermuscular coordination.

The Cervical Spine in Motion

In collaboration with William F. Donaldson III, MD, and Joon Y. Lee, MD, Dr. Anderst is investigating patients who undergo single or double-level arthrodesis of the cervical spine, and how the kinematics of the vertebra and intervertebral discs changes post surgery. “Ten years after surgery, approximately 25% of patients who have had cervical spine fusion need additional surgery as a result of adjacent segment disease (ASD). So a thrust of our research is in understanding what is normal cervical spine motion, how do the mechanics of the cervical spine change as part of the natural aging process, and how does surgery affect these normal mechanics. Ultimately, we would like to identify the mechanical mechanisms behind disc degeneration so that treatments and long-term outcomes can be improved,” says Dr. Anderst.

“Dr. Anderst’s work is exceptional in dissecting cervical spine motion. He is able to analyze human motion in continuous real time, making it much more applicable to a clinical setting. With his work, we can analyze post-surgical motion of the spine with “millimeters” of precision. His data is helping to improve upon our current surgical techniques to give our patients better outcomes.”

Joon Y. Lee, MD

Associate Professor of Orthopaedic Surgery

In order to understand what is normal cervical spine motion, Dr. Anderst’s studies have imaged young, healthy individuals between the ages of 20 and 35 to model the mechanics of a healthy cervical spine, establishing a baseline for what normal motion looks like, how the cervical spine segments perform during motion, and in what ways the intervertebral discs act under load.

“It’s important for us to be able to first define how much motion we expect people to lose as they age before we start to make comparisons,” he says. “This is why we are in the process of building a database of different age ranges. Next we will be working on a group of 20-30 year olds, and a group of 40-50 year olds,” all with the goal of developing a repository of knowledge of how cervical spine mechanics change relative to age.

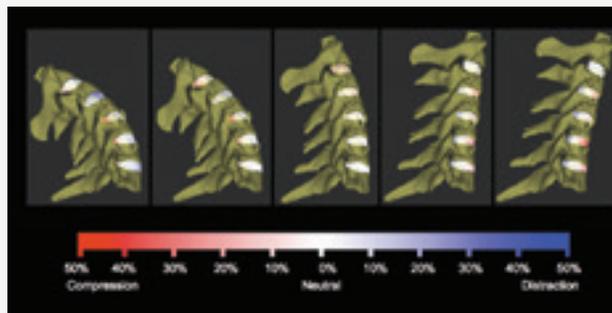
To that, they have collected three-dimensional models from a set of healthy 35 to 55 year old individuals who are asymptomatic, with no previous neck problems. This group of individuals has served as a control for the recent studies on cervical spine arthrodesis and ASD. “One of the theories behind adjacent segment disease is that aging is a cause; it doesn’t matter if they had surgery or not, the adjacent disc in question will degenerate because of the patient’s inherent genetics.”

Preliminary findings in Dr. Anderst’s ASD study show that two-years post-surgery, “as far as range of motion, it doesn’t seem to be affected by the surgery. They have a certain amount of motion six months after surgery, and that motion remained the same two years later. Dr. Anderst explains that this group of subjects who did not experience any change in adjacent segment range of motion from six months to two years after were almost identical to age-matched control subjects without any history of spine disease.

The control group for the study consisted of patients who did not have surgery and were healthy and free from pain over a five-year period. Interestingly, Dr. Anderst notes, “This subset of patients lost range of motion during that time. And that is to be expected; as you age, you lose some range of motion in your neck. So the fact that the adjacent segment motion didn’t increase in the arthrodesis patients is not the whole story; it’s that you would have expected it to decrease a little bit because they got older. And that didn’t happen.”

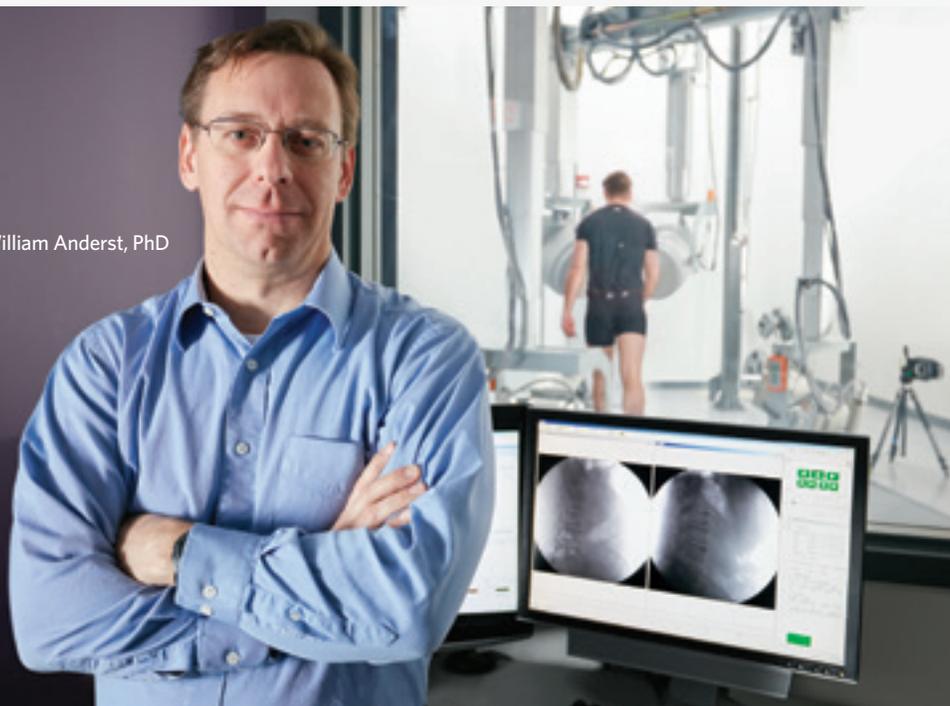
Informing the Surgical Procedures to Potentially Alter Outcomes

Another outcome of Dr. Anderst’s research is the possibility to help inform orthopaedic surgeons who perform cervical spine fusions. A factor in post-surgery adjacent segment mechanics, and perhaps adjacent segment disease, is the orientation of fusion during arthrodesis. Dr. Anderst explains, “How much curvature is going to be in the spine at the fused segments depends upon the surgeon performing the procedure, and if you alter this dramatically during the surgery it may greatly affect the mechanics of the adjacent segments.” This is a difficult decision for surgeons in large part due to the huge variability in the natural curvature of the spine, and one factor that could be altered during surgery to affect the long-term health of the adjacent segments. Changes in segment loading conditions may be a contributing factor to ASD, and something Dr. Anderst and his colleagues are interested in investigating in the future by studying patients before and after arthrodesis.



For Dr. Anderst, studying the cervical spine will continue to be the focus of his research efforts. “There are a lot of opportunities to pursue computational modeling in order to facilitate an understanding of tissue loading in the spine. A predominant theory is that mechanical loading is a primary factor that drives disc degeneration, but we have no idea what normal loading is because we can’t place loading measurement devices inside of a live person. We need to develop computational models that can give us an accurate estimate of the dynamic loads in a variety of circumstances.”

William Anderst, PhD



“ Bill and his lab, directed by Scott Tashman, have developed a way to quantify the motions of the cervical spine in actual patients to better understand the normal and abnormal motions in control subjects and patients whom we have performed surgery upon. This is ground-breaking research that will soon be extended to the lumbar spine. ”

William F. Donaldson III, MD
Executive Vice Chairman for Clinical Services
Chief, Division of Orthopaedic Spinal Surgery

Understanding Osteoarthritis of the Knee

For Dr. Tashman, one of his primary research interests is elucidating the factors that lead to degenerative joint disease after injury, in particular that of the knee. “Technology isn’t a universal solution to things, but there are targeted applications where I think we can use engineering skills to really improve the quality of care by understanding the function of joints, how they are affected by injury, and how the treatments work to restore normal motion,” indicates Dr. Tashman.

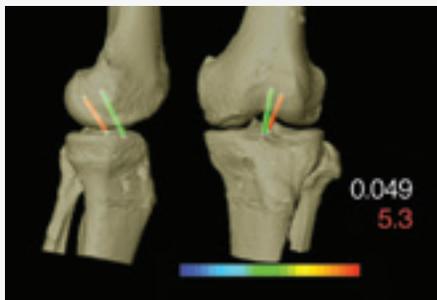
In current collaborative studies with Freddie Fu, MD, and James Irrgang, PhD, Dr. Tashman is studying dynamic knee function after ACL injury, and its contribution to long-term osteoarthritis, with the goals of informing treatment protocols and surgeries to limit or reduce the incidence and effect of osteoarthritis. “Visualizing the motion, and interpreting how changes in mechanics of the knee after injury contribute to degenerative changes in cartilage leading to osteoarthritis is of great interest,” says Dr. Tashman.

In the NIH study that Dr. Tashman and colleagues are finishing on ACL reconstruction, the question at hand is whether there is a difference between single and double repairs. He indicates, “We are able to address this question, and at the same time we are able to look at serial changes from cartilage in MRI that we are obtaining, and the detailed mechanics of joint motion we can get from the imaging system in our lab”. Dr. Tashman is able to investigate aspects of abnormal motion that may predict whether there will be degenerative changes in cartilage over time leading to osteoarthritis. “I can get at the basic question of why do people get arthritis after this knee injury? Why doesn’t the surgery fix them? What are the small differences in knee

function post-surgery that are not completely fixed, and how do they relate to arthritis in the future?” says Dr. Tashman.

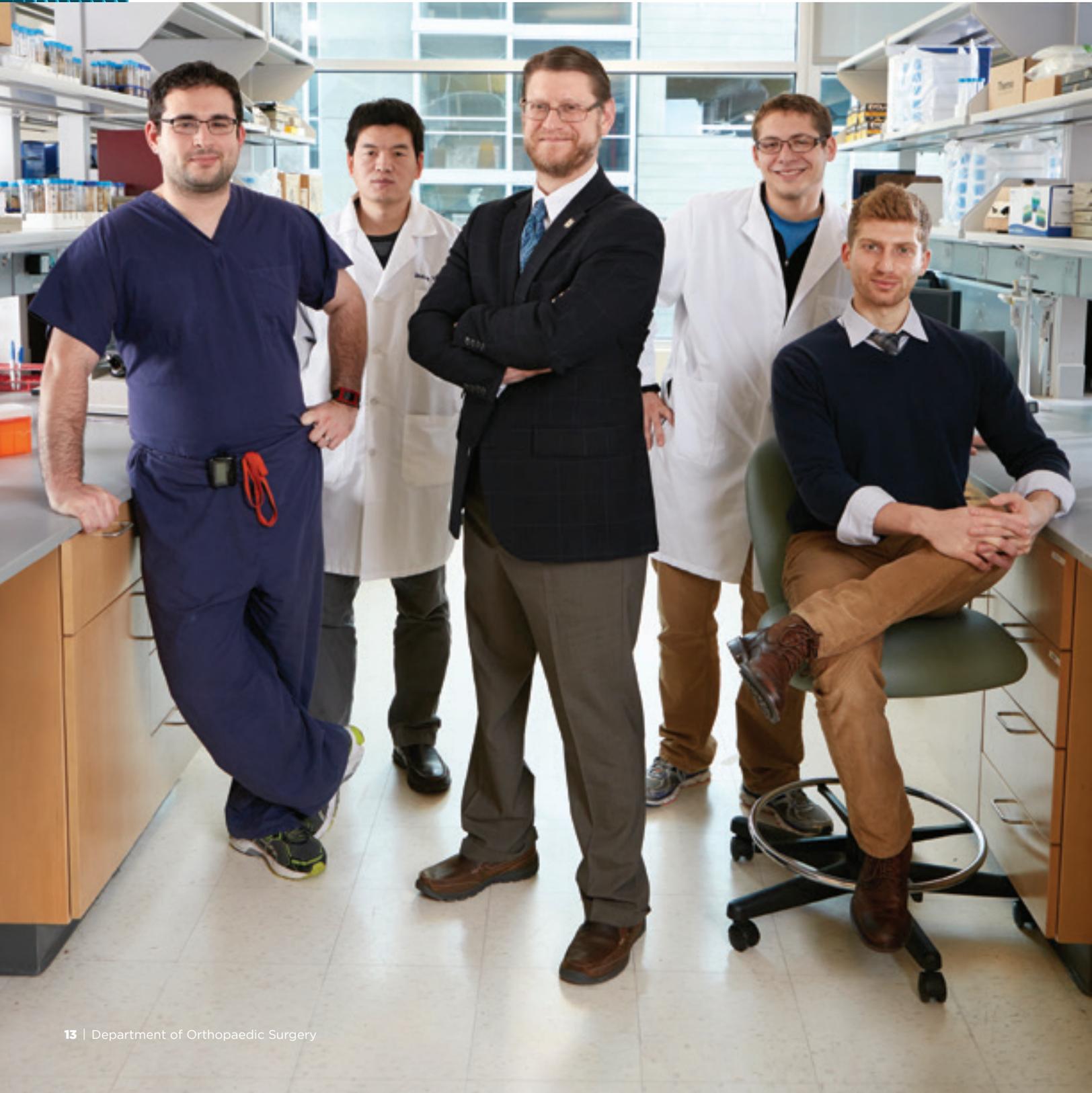
In preliminary findings the researchers have noted some changes in cartilage in areas of the joint related to the differences in strain or how much the cartilage is being compressed relative to the uninjured knee. “We have two years of data and are finding interesting relationships that suggest perhaps abnormal motions of the knee may actually be detrimental to the cartilage. We need to keep studying these people long enough to see if they develop more damage so we can determine whether there are definitive relationships,” says Dr. Tashman.

“I like the idea that I can actually have a direct influence on patient care. I love working with surgeons and clinicians. They’re the ones who really know what’s going on with patients, and I get some of my best ideas from them. Being in this kind of environment, I can work to develop technology and at the same time interact with clinicians and patients and be at the front line of care. This is what drives me and my work,” says Dr. Tashman. ■



CT-derived bone models with the ACL grafts represented as lines that are color-coded based on the amount they are being stretched.

Stripping Away the **Secrets of Sarcoma**



Sarcomas of the bone and connective tissues are some of the most rare and least understood of all cancers. Orthopaedic surgeon Kurt Weiss, MD, who specializes in musculoskeletal oncology, is pursuing the secrets of sarcomas in an effort to develop new treatments and save lives.



An Intense Determination

For Dr. Weiss, understanding the origins and complexities of sarcoma development is a life's work borne out of his own personal experiences as a sarcoma patient, diagnosed and successfully treated as a teenager. He has a single-mindedness of purpose in his work to understand the basic science, developmental pathways, and metastatic properties of these cancers, and to share this information with other scientists in order to push the field of study forward.

The rarity of sarcomas — an umbrella name for more than 60 different types of bone and connective tissue cancers — and the even rarer incidence of many of the subtypes leaves a dearth of knowledge and research funds to study tumor properties and develop new treatments. About 1% of all diagnosed malignancies are sarcomas. The small number of cases makes it exceptionally difficult to conduct research and clinical trials due to the low volume of patients for a given diagnosis.

Lab team (left to right):

Mitch Fourman, MD - Orthopaedic Surgery Resident

Shibing Yu, MD, PhD - Research Associate

Kurt R. Weiss, MD - Assistant Professor and Director,
Cancer Stem Cell Lab

Jon Mandell - Research Technician

Adel Mahjoub - University of Pittsburgh
Medical School Student

Not pictured:

Jessica Tebbets - Lab Manager

David Hirsch, MD - Orthopaedic Surgery Resident

Stuti Patel - University of Pittsburgh
Medical School Student

Daniel Brynien - University of Pittsburgh
Medical School Student



“ We may be the only group out there that is working to understand how cachexia manifests in sarcoma patients, and how to stop it. ”

Kurt Weiss, MD

A Shared Repository of Knowledge

The foundational centerpiece of Dr. Weiss' research into sarcomas and their underlying properties is the Musculoskeletal Oncology Tumor Registry and Tissue Bank started in 2011 with Mark A. Goodman, MD, and Richard L. McGough III, MD, to study the basic biology of sarcoma tumors and how and why they metastasize. "The tumor registry and tissue bank has changed everything. It changes the questions I can ask, the grants we can apply for, and my collaborations with other scientists and surgeons," says Dr. Weiss.

The sarcoma tumor registry and tissue bank currently contains close to 50 viable cell lines that are available to researchers at UPMC and the University of Pittsburgh. These cell lines are used in animal models to investigate, among other processes, osteosarcoma metastasis, cachexia, and gene regulatory factors in tumor growth.



The large-scale clinical practice at UPMC, coupled with the ability to investigate basic science questions and facilitate translational studies using the cell lines, combined with the derived data, has put Dr. Weiss and his colleagues at the forefront of sarcoma research. The volume and diversity of cell lines enables researchers to seek answers to numerous lines of inquiry. In 2015, Dr. Weiss and his lab began sharing cell lines and data with researchers at a number of institutions including Stanford and Ohio State universities. "There are many eminent researchers at other institutions who, because they do not have a big clinical practice, are lacking direct access to this kind of basic, cellular data for their investigations," says Dr. Weiss. He goes on to say that because the sarcoma community is small, relative to other

Sarcoma and Cachexia

An oft-occurring condition seen in patients with soft tissue sarcomas and other types of cancer is cachexia; a syndrome characterized by muscle wasting and weight loss that is refractory to nutritional supports. In cancer patients, cachexia correlates with poor survival, a diminished ability to bounce back from the physical tolls that treatments such as radiation and chemotherapy inflict, and a diminished quality of life. "If you get it, it's a big problem. It makes the treatment of these patients that much more difficult," says Dr. Weiss.

Recent research and findings in Dr. Weiss' lab has led his team to explore grants to specifically study cachexia in sarcoma patients. "If you look at the literature, you will find virtually nothing about cachexia in sarcoma patients. We may be the only group out there working to understand how cachexia manifests in sarcoma patients, and how to stop it," says Dr. Weiss.

Investigators in the lab working on an animal model of metastatic osteosarcoma noticed that the mice models were losing weight — both muscle mass and fat. The animal models showed a chronic, systemic inflammation — a factor researchers believe drives the incidence of cachexia. "This inflammatory state caused by cancer stays turned on for too long, it starts to catabolize muscle, and leads to this wasting effect."

The goal is to understand the basic biological processes, the genetic factors regulating cachexia, and work towards interventions.

cancer types and research volume, this type of collaboration and data sharing is essential to the entirety of investigative efforts into soft tissue cancers. "We share our knowledge with the broader research community to further the collective goal of cracking the code of sarcoma."

Dr. Weiss acknowledges that not all researchers and institutions can do everything needed to study sarcoma, so collaborative studies between scientists investigating sarcomas and their properties are going to be exceptionally important. With rare diseases like sarcoma, "Nobody has 1,000 cell lines that they're sitting on or thousands of patients, so we really need to collaborate and cooperate. This tissue bank is a great way to do that," he says.

Implicating the Notch Developmental Gene

Recent lab findings in animal models have shown that there is a higher level of Notch in the tumors and the muscles of the experimental animals compared to the controls.

"The interesting thing was that when we grew tumor cells with muscle-derived stem cells, it stopped them from differentiating. The Notch gene keeps them in that locked in state," remarks Dr. Weiss, "And when we added in a Notch inhibitor, the muscle grew normally again."

Having the tissue bank and cell lines at their disposal has allowed Dr. Weiss and his co-investigators to look at patients who have presented with cachexia (defined as unintended weight loss greater than or equal to 5%). Within the registry, approximately a third of patients presented with this finding. Now, Dr. Weiss is interested in studying these cell lines to see if they can reverse the muscle wasting process in a manner similar to what they have seen in their animal model. "We'll be able to generate xenografts with cancer cells from our patients and see what happens. It's very exciting, and the only reason why we can even ask these questions is because of all of the cell lines we've collected from our patients," says Dr. Weiss.



“Based on the data, not only is the chronic inflammation happening in our model, which cachexia investigators have been talking about for a long time, but this developmental gene, Notch, is important to the development of the syndrome.”

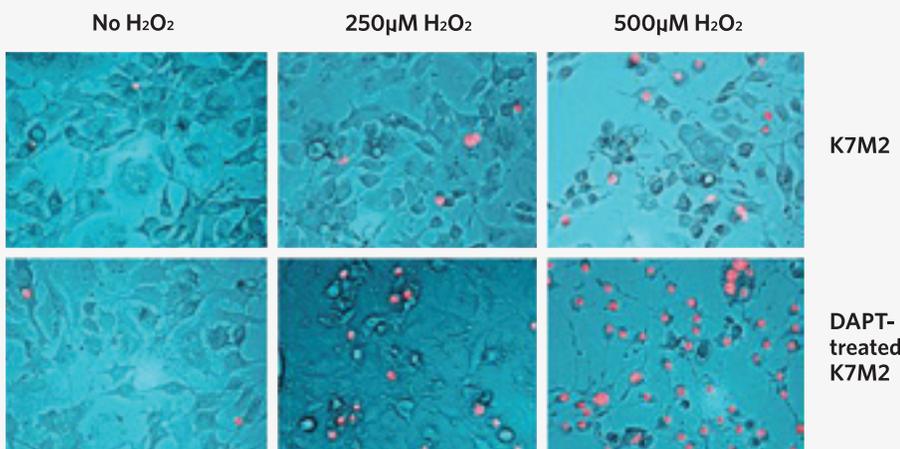
Understanding the Metastatic Pathways of Sarcoma

For Dr. Weiss, the core of sarcoma research and treatment ultimately comes back to metastases. "Nobody dies because of a tumor on their arm or their leg. Surgically, we can address that with good success. The real troublemaker is the metastatic path sarcoma usually follows." If a sarcoma metastasizes, 95% of the time it travels to the lungs of the patient. There are many different variants of sarcoma but they all exhibit this same pattern. "There are some that go to lung and lymph nodes, but they all end up traveling to the lung," says Dr. Weiss.

journey. "I think and I hope that we're going to find these conserved pathways that all sarcomas follow. I don't think nature would be wasteful enough to invent 60 different ways for cells to do that. I think we will find variations and themes, but overall we will find that sarcoma cells all kind of do the same thing to fulfill that goal." Dr. Weiss explains that in order to ask these kinds of questions and study these pathways, you need to explore them in rigorous, in vivo animal models. "And this brings us back to our cell lines," he says.

labor intensive, and few institutions are positioned to do these kinds of patient-derived xenografts. The infrastructure needed for surgical and laboratory support is challenging. It requires having someone on call who can be on standby in the operating room who will then quickly transport and place the tumor into an animal model.

From a research perspective, Dr. Weiss is pursuing an understanding of what advantages patient-derived xenografts may have over traditional xenografting using the cultured cells from the lines in his bank. "Right now, this is an unanswered question. Researchers believe that PDX works better because of its purity, but nobody has tested that hypothesis for sarcoma," says Dr. Weiss. Future work by he and his lab will explore cell line and direct tumor implantation from the same patient in animal models.

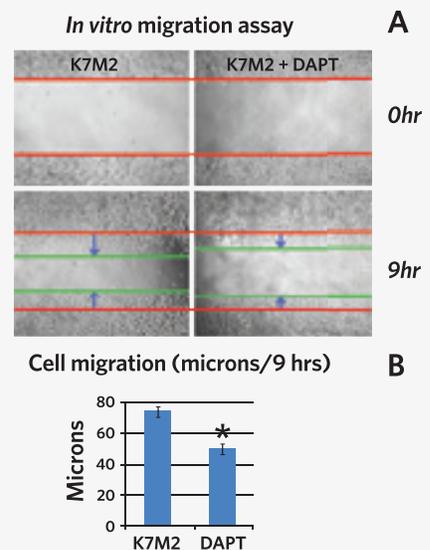


K7M2 mouse osteosarcoma cells are resistant to oxidative stress with hydrogen peroxide. This resistance can be abrogated with a Notch inhibitor.

Once the sarcoma cells metastasize to the lungs, their growth behavior is remarkably similar in nature. They tend to grow on the pleura but not in spiculated masses the way lung cancer generally behaves. "They grow in perfectly little round blobs. They don't act like lung cancer at all and they're also very refractory to treatment, which isn't so surprising because the cell has already proven itself to be very capable of making the journey from the patient's extremity into the lungs while undergoing chemotherapy," he says.

For Dr. Weiss, this is the biggest question he and his collaborators in the lab are trying to answer with the knowledge and data being acquired in the tumor registry and tissue bank — how does a sarcoma cell make that

Cancer researchers have used xenografting for a long time, taking human cancer cells and injecting them into their animal models to study the effects. And while this approach certainly yields results, Dr. Weiss and his lab are positioned to undertake a different approach — patient-centered xenografts or PDXs. Tumors are taken directly from an operating room and implanted into an animal model — bypassing the traditional cell propagation techniques. "I can operate on a sarcoma patient, harvest their tumor, and take it directly from the operating room to my laboratory where a piece of that tumor is placed directly into an animal model. It goes from one biologic microenvironment to another. It never sees the artificial pressures, the artificial conditions of cell culture," says Dr. Weiss. The process is very



Notch inhibition decreases the motility of osteosarcoma cells in an in vitro scratch assay.

"If we look at a patient derived xenograft and it metastasizes just the same as the human did, but the cell line model doesn't, then clearly PDX is the way to go. However, if they both metastasize like the patient did it makes much more sense to use the cell line because it's easier, faster, and many more researchers are capable of doing so," he says.

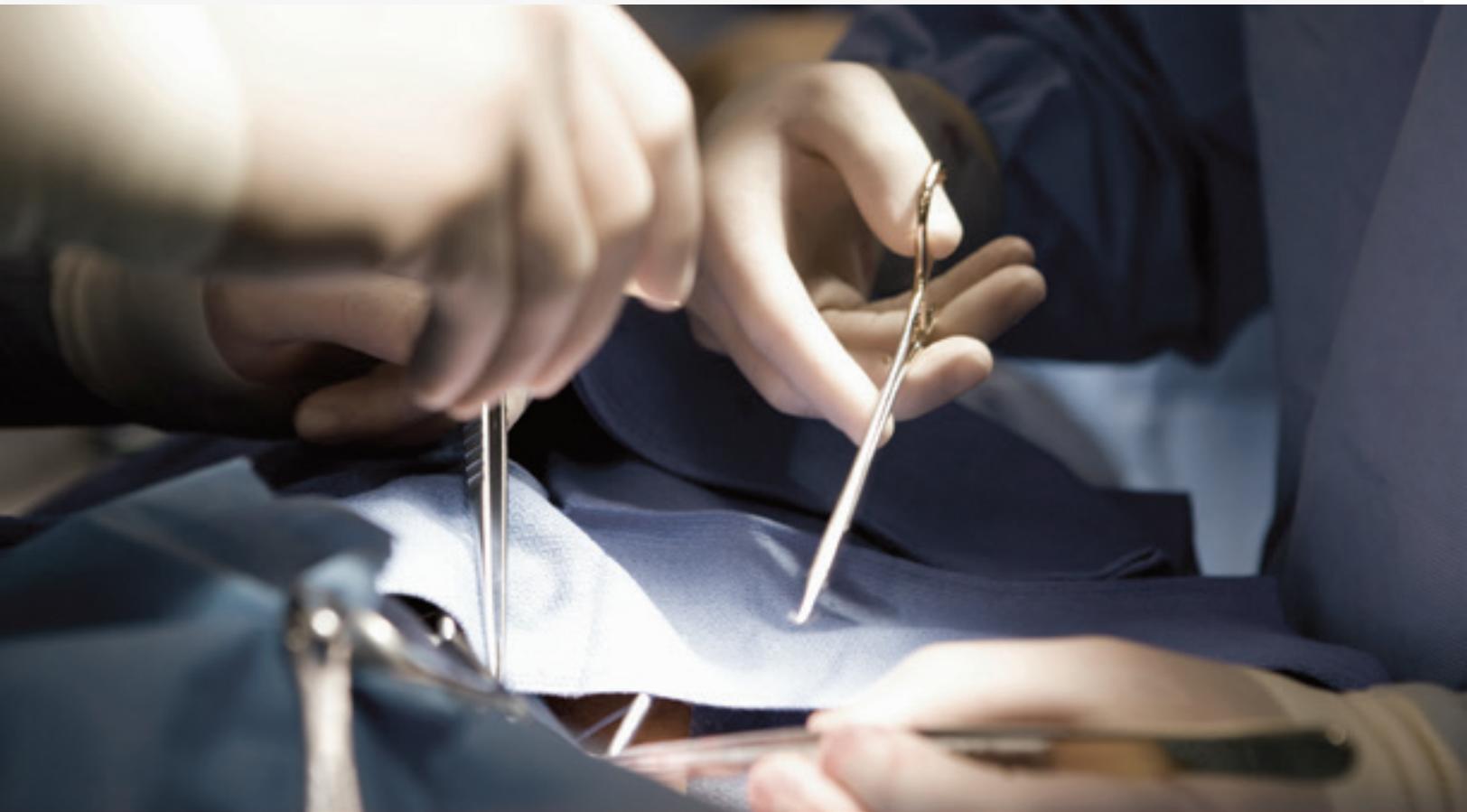
Translational Application of the Tumor Registry and Tissue Bank

A core principle held by Dr. Weiss and his lab is collaboration. Collaboration not only with other sarcoma researchers, but also with those who are investigating other lines of cancer research. At present, Dr. Weiss is involved in a collaboration with Steffi Oesterreich, PhD, professor of pharmacology and chemical biology at the University of Pittsburgh Cancer Institute, who is investigating breast cancer metastases. "We're taking the idea of sarcoma and putting it on its head, talking about a tumor that starts in the breast and then infiltrates bone."

Dr. Weiss explains that frequently "a woman gets breast cancer and she has surgery, chemotherapy, and radiation and she does great. And the cancer stays away for about 10 to 12 years. But then it just comes roaring back. Breast cancer is very, very sinister in that regard.

Oftentimes, these women will come back with late metastases, and a common place for breast cancer to go is the bone. I'm trying to figure out how sarcoma cells spread, and Dr. Oesterreich is attempting to understand how breast cancer cells spread, why they go the places that they go and the molecular and biological processes driving them. What is it about bone that makes breast cancer cells want to go there? These are the same sort of questions that I'm asking about sarcoma, but about a different disease system."

These collaborations, and those that will exist in the future, are because of Dr. Weiss' ability to capture, collect, and share his knowledge from the cell lines in the tumor registry and tissue bank. ■



“ I know that there are going to be continued advances in surgery and that we're going to be able to do wonderful things in 10 years that we can't do now. But it's not going to change survival. The way you change survival is by doing a better job with metastatic disease. That's what I'm consumed with. That is my most important job. ”

Kurt Weiss, MD

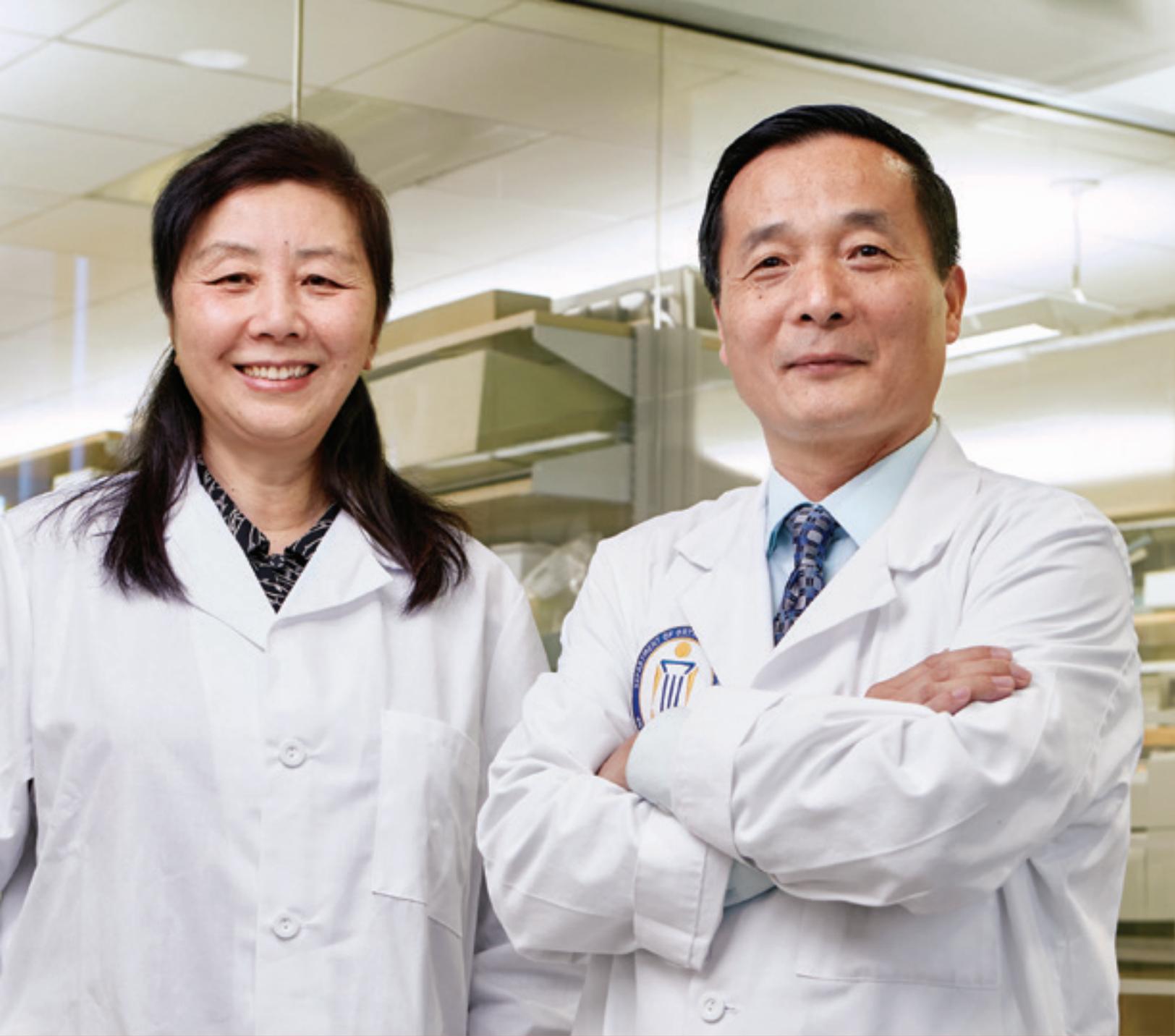
Jiaying Zhang, PhD,
and James H.C. Wang, PhD,
in the MechanoBiology Lab
in the Department
of Orthopaedic Surgery.



The MechanoBiology Lab

James H-C. Wang, PhD, is professor of orthopaedic surgery and director of the MechanoBiology Lab (MBL). Dr. Wang's primary investigative interests are in tendon mechanobiology, particularly in understanding the role of tendon stem/progenitor cells (TSCs) in the development of tendinopathy, and their role in the beneficial effects of exercise on aging tendons. In recent years, working with Freddie Fu, MD, professor and chairman of the department of orthopaedic surgery, Dr. Wang has investigated the action mechanisms of platelet-rich plasma (PRP) on the healing of tendon injuries. Additionally, his research has led to collaborations with MaCalus Hogan, MD, assistant professor of orthopaedic surgery, in testing biologics approaches, including TSCs, PRP, and engineered tendon matrix (ETM) to enhance tendon and tendon-bone interface healing. His research is funded by grants from the National Institutes of Health (NIH), and pilot and developmental funding from the Pittsburgh Claude D. Pepper Older Americans Independence Center.

Platelet-Rich Plasma and the Effects of Exercise on Tendon Injury



James H-C. Wang and colleagues at the MechanoBiology Lab in the Department of Orthopaedic Surgery are investigating the efficacy of platelet-rich plasma (PRP) for the treatment of tendon injuries, and the beneficial effects of exercise on aging tendons and tendon stem cells.



What Is Platelet-Rich Plasma?

In recent years, the use of platelet-rich plasma (PRP) to treat acute and chronic tendon injuries by speeding the recovery process has undergone significant growth in clinical practice. It also has garnered the attention of researchers to study more deeply the underlying mechanisms of its potential healing properties.

PRP is a highly concentrated, autologous preparation of a patient's own platelets. "It is well known that PRP is rich in platelets, which are natural reservoirs of growth factors that are able to stimulate the healing of injured tissues by inducing proper proliferation and differentiation of tissue-specific stem cells," says Dr. Wang.

As Dr. Wang notes, PRP formulations contain numerous growth factors including PDGF, EGF, HGF, TGF, and many others. Along with certain adhesive proteins and clotting factors, there are perhaps more than 1,000 different factors at play in PRP injections. These growth factors have been shown, in a number of studies, to play an important role in enhancing the healing of injured tissues such as tendons. Dr. Wang indicates that in addition to the multiple growth factors contained in PRP formulations, PRP also "forms a fibrin gel after platelet activation by thrombin, Ca²⁺ or collagen. The fibrin gel itself is believed to contribute to tendon healing by providing a conductive scaffold for cell migration and new matrix formation."

Is Platelet-Rich Plasma Safe and Effective in Treating Tendon Injuries?

Acute tendon injury and chronic tendinopathies affect millions of people every year, and provide a strong rationale for the increased attention surrounding PRP as a promising treatment option. It is currently used to treat acute tendon injury and chronic tendinopathy in orthopaedic and sports medicine patients. "It's a very popular method and physicians are increasingly using it. If you review the literature on PRP, there are studies showing the effectiveness of this treatment. However, in clinical trials with human patients, studies are showing inconsistent and contradictory results," says Dr. Wang. There are numerous complex factors that may contribute to these inconsistent findings in clinical trials, factors such as the age, gender, injury, specific tendon, past treatment of the patient, and the formulations of the PRP injections themselves.

Contradictory findings in past studies and trials, along with the apparent promise of PRP as an effective treatment agent for soft tissue injuries, has led Dr. Wang and his laboratory, including his collaborator on the studies, Jianying Zhang, PhD, to investigate both the efficacy and safety of PRP to treat injured tendons. For the last five years, their investigations have looked at several aspects of PRP using *in vitro* and *in vivo testing*, and their basic science research findings do point to PRP as a treatment modality with promise to treat acutely or chronically injured tendons — in certain circumstances.

His study, *Platelet-Rich Plasma Release Promotes Differentiation of Tendon Stem Cells Into Active Tenocytes*, and its findings were published in the *American Journal of Sport Medicine*. [*Am J Sports Med*, 38: 2477-2486, 2010].

Dr. Wang's *in vitro* experiments used patellar tendons from adult rabbits to derive the necessary cells for the study. A key finding of the study points to the relative safety of PRP as a treatment for injured tendons; PRP treatment: "Did not induce non-tenocyte differentiation of TSCs into chondrocytes, adipocytes, or osteocytes". This suggests that PRP treatment does not increase the risk of non-tendinous tissue formation in treated tendons. If this process were to occur it would most likely lead to structural and functional deficits in the treated tendons.

Dr. Wang states, "This is an important finding from the study. It means that PRP treatment of tendon injuries is likely safe because it does not cause the formation of non-tendinous tissues inside the treated tendons. So far, there are no adverse effects on PRP-treated tendons reported in clinics. Clinicians are more comfortable than before with the use of PRP to treat injured tendons, either by injection of PRP or implantation of PRP gels."

PRP Releasate and TSC Differentiation

One of Dr. Wang's basic science studies sought to understand and demonstrate that PRP treatment, and specifically a form called PRP-clot releasate (PPCR), could stimulate tendon stem cell (TSC) differentiation into active tenocytes, thereby increasing collagen production and providing a pathway for healing.



PRP and Its Anti-inflammatory Properties

As with any tendon injury — acute or chronic degenerative conditions — inflammation and its associated pain are the main symptoms for which patients seek treatment. “The effectiveness of PRP treatment reported in clinics means that PRP must somehow have the ability to suppress tendon inflammation, thereby reducing pain. We wanted to further investigate the biochemical mechanisms of PRP’s anti-inflammatory properties, and pinpoint the source or sources,” says Dr. Wang.

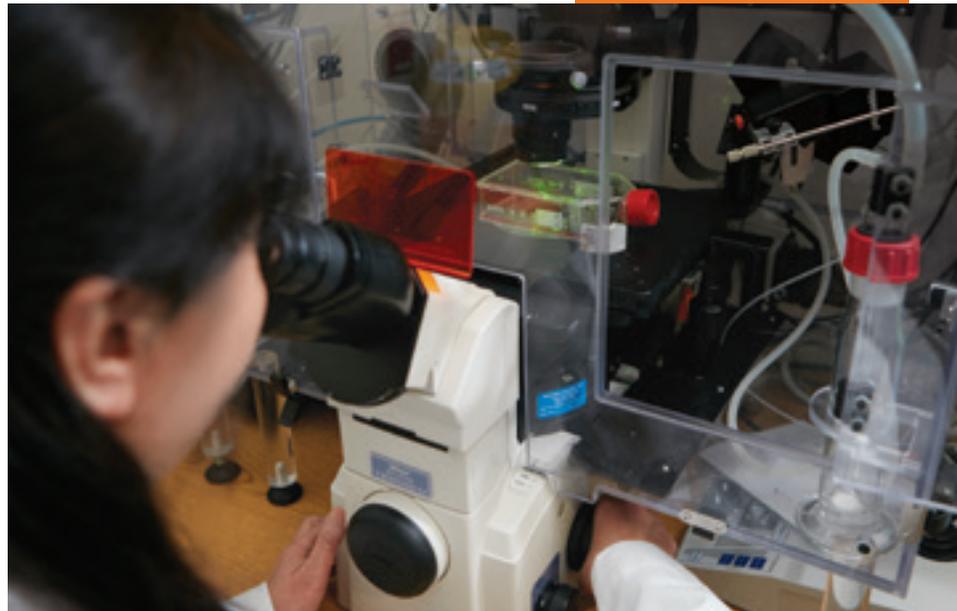
Dr. Wang’s anti-inflammatory studies on PRP proceeded with both cell culture and *in vivo* animal models to attempt to demonstrate that PRP has certain anti-inflammatory properties. Their study *HGF Mediates the Anti-inflammatory Effects of PRP on Injured Tendons* [*PLoS ONE*, 8(6): e67303, 2013] focused on understanding whether or not hepatocyte growth factor (HGF) contained in PRP could be the likely candidate given its known anti-inflammatory properties. The findings of Dr. Wang’s studies in both the cell culture experiments using rabbit tendon cells and the *in vivo* studies of injured Achilles tendons in mice showed correlating results.

Dr. Wang indicates, “We were able to show that HGF acts by suppressing levels of the prostaglandin biosynthetic components (COX-1, COX-2, and mPGES-1), and PGE₂ production. Our animal model studies corroborated the cell culture models by showing that PRP injections reduced COX-1 and COX-2 protein expression and lowered PGE₂ levels in the injured Achilles tendons of the mice.”

PRP Formulation Matters; So Too Does Tendon Location

Current PRP treatments administered to patients with either an acute injury or a chronic tendon inflammation tend to be prepared in the same way and use the same dose regardless of the injured tissues. Research by Dr. Wang and his team has shown that this approach is not optimal, and may, in certain circumstances prove detrimental to the injured tendons.

“For example, we have found that P-PRP (pure platelet-rich plasma) is not a good choice, particularly when platelet concentration is high, for the treatment of acutely injured tendons in young, adult rabbits because it promotes fibrosis. Our research also suggests that L-PRP (leukocyte-containing platelet-rich plasma) may not be a good choice for chronic tendinopathy, as excessive leukocytes in the PRP preparation may prolong tendon inflammation and lead to pain. It also may inhibit tendon healing due to the strong catabolic effects of L-PRP, as shown in our study,” says Dr. Wang.



Dr. Wang goes on to say, “Perhaps more importantly, our research has shown that, L-PRP induces inflammatory and catabolic responses in differentiated tenocytes while P-PRP mostly augments anabolic responses.” Dr. Wang and his collaborators theorize that the preparations used to treat injured tendons must take into account the specific tendon. He points out that in their studies, “Tendon location matters because cell types and matrix composition can differ depending on the tissue. We do not think that all tendons respond similarly to PRP treatment. One reason for this is that even in the same animal (rabbit), we found that different types of tendons (patellar vs. Achilles) contain varying amounts of TCSs, and their activities in terms of proliferation and differentiation potential also differ greatly.”

Jiaying Zhang, PhD,
research assistant
professor at the
MechanoBiology Lab
examining tendon
stem cells.



“ Our hypothesis is that tendon location matters because cell types and matrix composition can differ depending on the tissue. We do not think that all tendons respond similarly to PRP treatment. ”

James H-C. Wang, PhD

Exercise and Its Effects on Tendons

For a number of years Dr. Wang's laboratory has sought to understand the biological and mechanical roles that exercise plays on tendons, the ability of tendons to heal following an injury, and the degenerative effects caused by the aging process on tendon stem cells. His investigations have shed light on these processes, and may one day be able to directly influence the clinical approaches that treat and rehabilitate injured and aging tendons. Dr. Wang and his colleagues in the MechanoBiology Lab performed studies to understand the ability of exercise to mitigate these factors and revealed interesting findings.

What Mice Running on Treadmills Can Reveal

In a first-of-its-kind study, Dr. Wang and colleagues have shown the beneficial effects of moderate exercise on aging tendon stem cells (TSCs), using both *in vitro* and *in vivo* experiments. The study, *Moderate Exercise Mitigates the Detrimental Effects of Aging on Tendon Stem Cells* [PloS ONE, 10(6):e0130454, 2015] revealed a number of important results.

For the *in vivo* studies, 9-month-old mice were trained to run on treadmills, and then to complete moderate running consisting of running at 13 meters/min speed, 50 min/day, for five days, over three consecutive weeks. Dr. Wang's control population of mice was simply allowed to move about their cages without restricting their normal motion. Upon completion of the exercise regimen, Dr. Wang and his team harvested the patellar tendons from both groups and analyzed the effect that the exercise had on the TSCs of the running mice relative to the control group. Their findings showed, "TSCs isolated from the control group without treadmill running were sparse in culture and were round in shape. In contrast, TSCs subjected to moderate treadmill running (MTR) exhibited a cobblestone-shaped structure that is typical for active TSCs."

Further, "TSCs from mice in the MTR group proliferated significantly quicker in cultures when compared to those from the control group. After five days in culture, the number of TSCs in the MTR group was 1.3-fold more than the TSC numbers in the control group."

In two additional studies on tendons and tendon stem cells, Dr. Wang and his research colleagues again used similar mouse models to look at the effects of exercise on the presence of myofibroblasts, and how exercise modulates tendon stem cell proliferation and production of collagen.



Mouse treadmill running experiment

In his study *Treadmill Running Exercise Results in the Presence of Numerous Myofibroblasts in Mouse Patellar Tendons*, Dr. Wang's group used a similar cohort of mice subjects, trained for one week on the treadmill then completing an exercise regimen consisting of 50 minutes per day, five days per week, for three weeks, running at a pace of 13 meters per minute. These mechanical loads on the mice, particularly their patellar tendons, had several outcomes including, "cells from the exercised mice grew faster, generated larger traction forces, and produced more collagen than cells from control mice. As myofibroblasts are known to repair and remodel injured tissues, their presence in tendons after treadmill running suggests that the tendon is in a 'healing state,' possibly due to repetitive loading induced tendon micro-injuries," indicates Dr. Wang in his findings.

From a general perspective, Dr. Wang summarizes the results of this recent research by indicating, "The findings from our animal treadmill running studies suggest that moderate treadmill running is beneficial at the cellular and molecular levels. It enhances the quality of tendon stem cells (TSCs) and encourages TSCs to differentiate into active tenocytes, which are required to maintain the tendon and repair it when injured. The exercise also suppresses the expression of those molecules involved in cellular senescence."

While these studies have primarily used patellar and Achilles tendons from mouse models to understand the effects of moderate exercise, Dr. Wang suggests, "The beneficial effects seen in the aging patellar tendons in our animal study would be 'universal,' meaning that moderate exercise would enhance the quality of other aging tendons and ligaments — the Achilles, the medial collateral ligament in the knee, and so forth." Future research will be needed to conclusively prove the universal effects on any similar structure, but the preliminary findings show promise in this regard.

Furthering the Knowledge Base

While these recent studies have shown interesting findings in Dr. Wang's mouse models, he points out that there is additional research needed to further identify and understand the underlying mechanical and biological mechanisms at play in the ability of moderate exercise to induce healing in injured tendons. Dr. Wang indicates that one such study will focus on "moderate exercise regimens prescribed to aging patients with tendinopathy problems prior to surgery to examine how such pre-surgical exercise may enhance tendon surgery outcomes, in terms of healing and the speed of recovery of tendon function." In addition, his basic science studies of tendon stem cells will be augmented with an investigation of "which molecules play a key role in enhancing the quality of tendon stem cells in aging animal models." ■



Concussion:

Building a Consensus Framework for Treatment and Research



A Leading Authority

The UPMC Sports Medicine Concussion Program is a leading authority in the comprehensive evaluation, testing, treatment, and research of concussions. Clinicians in the program see more than 17,000 patients every year. This volume of patients allows the program to conduct extensive research to validate and inform treatment protocols, and advance the overall understanding of what a concussion is, what clinical profiles are presently understood to exist, and how best to treat the physical, emotional, and cognitive effects patients may experience post-concussion. A truly multidisciplinary effort in terms of clinical care, the UPMC Sports Medicine Concussion Program encompasses providers from neuropsychology, physical medicine and rehabilitation, sports medicine, primary care, exertion training, neuroradiology, and neurovestibular rehabilitation.

The program's clinical and executive director, Michael "Micky" Collins, PhD, is an internationally respected expert in sports-related concussion, and a leader in education on baseline and post-injury neurocognitive testing. Dr. Collins was an instrumental source in developing concussion-management policy in youth sports, return-to-play laws, and the Centers for Disease Control's concussion toolkit. He is a co-founder of ImpACT® (Immediate Post-Concussion Assessment and Cognitive Testing), the most widely used computerized sports-concussion evaluation system that has become a standard of care in nearly all organized sports at all levels.

Research — developing an evidence base for understanding the different types of concussions, how to assess them, and ultimately treat them — is a core component of the program. Director of Research, Anthony Kontos, PhD, leads the collective study efforts of the concussion program. Since 2000, the efforts of the UPMC Sports Medicine Concussion Program have revolutionized the understanding, care, and research of these brain injuries, furthering the field by developing the Targeted Evaluation and Active Management (TEAM) approach to concussion, and developing a consistent understanding of the different clinical trajectories of concussion. "Ours is the largest clinic in the country, treating more than 17,000 patients every year. The expertise of our staff, along with the volume of patients allows us to study concussion injury, develop the clinical trajectories, and match these to specific treatments, which we were the first to do," says Dr. Collins.

For two days in October 2015, UPMC hosted a first-of-its-kind meeting of concussion experts from across the country and across disciplines to develop a consensus statement on the understanding and treatment of concussions, and to establish a roadmap for future research and validation of treatment protocols.



Michael "Micky" Collins, PhD, and **Anthony Kontos, PhD,** discuss concussion treatment research at the UPMC Sports Medicine Concussion Program facilities.



“ The expertise of our staff, along with the volume of patients, has allowed us to study concussion injury, develop the clinical trajectories, and match these to specific treatments, which we were the first to do. ”

Michael “Micky” Collins, PhD

Genesis of the Meeting

The depth and strength of the UPMC Sports Medicine Concussion Program, along with its long-standing collaboration and care of the Pittsburgh Steelers, led National Football League Commissioner Roger Goodell to visit UPMC in the summer of 2013 to learn more about the clinical care tenets developed by the program, and the current research activities in concussion study.

“Commissioner Goodell spent the entire day in our clinic, observing our program, treatment programs, and rehabilitation therapies, and came away very impressed,” says Dr. Collins. After this meeting interest began to develop about replicating the UPMC program model across the country in a collaborative effort with other institutions. And while this effort was not completed, it did lead to the idea of UPMC hosting a first-ever meeting of the leading clinicians, researchers, and key stakeholders from government, military, and sports entities from across the country.

“The goal was to have a first-ever meeting on the treatment of concussion, which had never occurred before. The consensus statements that existed before the meeting really only dealt with nomenclature and diagnosis, and lacked a real discussion about treatment,” indicates Dr. Collins.

Finding Consensus: Two Days in October

October 15 and 16, 2015 saw 37 of the leading experts from across the country convene in Pittsburgh at the Targeted Evaluation and Active Management (TEAM) Approaches to Treating Concussion meeting. The primary authors of the statement — Michael W. Collins, PhD, Anthony P. Kontos, PhD, and David O. Okonkwo, MD, PhD, — facilitated the collaborative meeting with the myriad contributors in attendance. The singular purpose of the meeting was to unify under a consensus framework on concussion and publish the statement for the clinical community at large (the paper is currently under peer review in the journal *Neurosurgery*). As the executive summary of the white paper states, there were several overarching purposes of the meeting and statement:

- Challenge common misconceptions about treating concussion
- Review the current state of evidence-based best clinical practices to assist clinicians with the treatment of concussion
- Describe and discuss a heterogeneous approach to conceptualizing and classifying concussion profiles
- Describe and discuss interdisciplinary, targeted evaluation and active management (TEAM) approaches for treating concussion
- Establish the level of evidence and empirical gaps in the research related to the treatment and rehabilitation of concussion
- Identify areas requiring further research

“The spirit of this white paper meeting was a multidisciplinary, multi-institutional collaboration. A special part of the meeting was seeing the interactions between clinicians. It was powerful to see how collaborative the meeting was. There are not many fields like this one where you literally have seven or eight different disciplines coming together — neuro, rehab, training, primary care, sports medicine — to solve a problem,” says Dr. Collins.

At the core of the the paper are 17 individual statements of agreement on areas that include current approaches to treating concussions; the heterogeneity and evolving understanding of concussion clinical profiles and their symptoms and functional impairments; and the Targeted Evaluation and Active Management approach

to concussion which has as its foundational tenet: concussion is treatable and best achieved through a multidisciplinary approach.

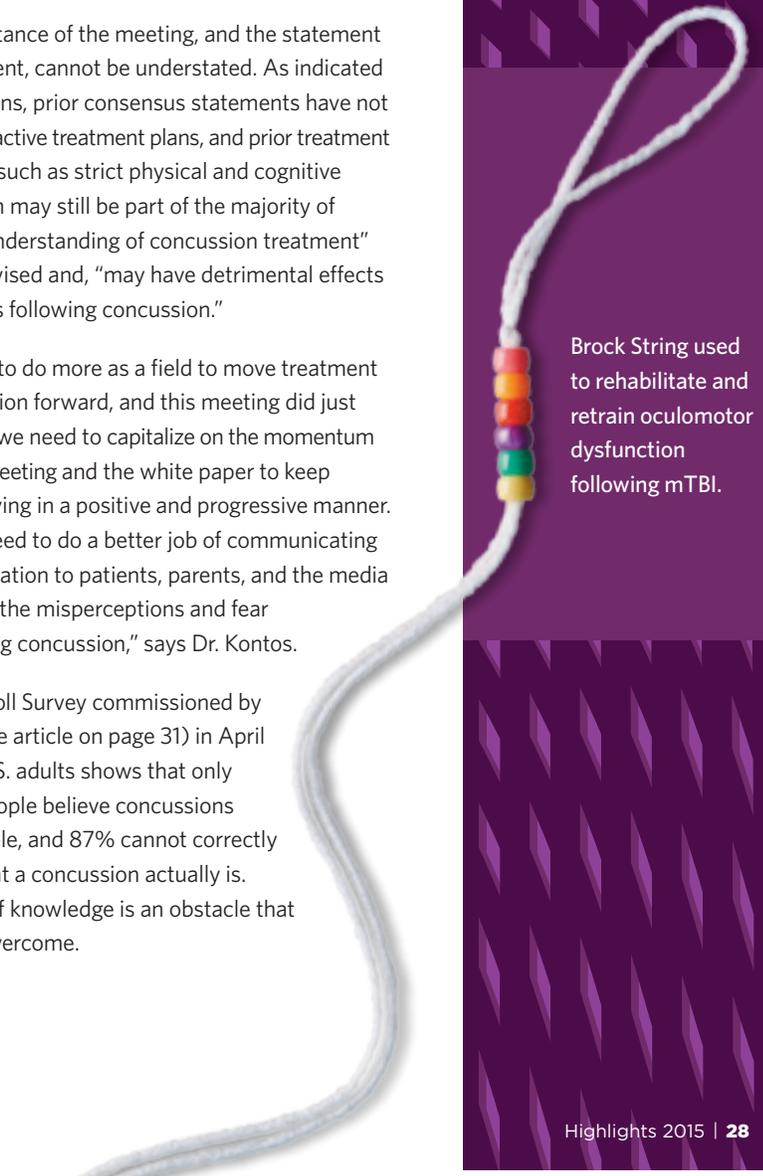
With a conclave of so many individual perspectives and disciplines at the table for this kind of discussion, it would be natural to assume that arriving at unanimous agreement would be a great challenge, but not so indicates Dr. Kontos.

“Interestingly, the biggest challenge we faced was right out of the gate. Following our first session on the current state of treatments, the first bullet that we proposed, which was focused on “a one size fits all” approach,” met with the most resistance. In fact, we ended up completely changing that statement and developed much better statements as a result of the initial discussion. Having a little friction initially helped to clear the air and get things moving in a positive direction.”

The importance of the meeting, and the statement of agreement, cannot be understated. As indicated by Dr. Collins, prior consensus statements have not dealt with active treatment plans, and prior treatment protocols, such as strict physical and cognitive rest “which may still be part of the majority of people’s understanding of concussion treatment” are not advised and, “may have detrimental effects on patients following concussion.”

“We need to do more as a field to move treatment of concussion forward, and this meeting did just that. Now we need to capitalize on the momentum from the meeting and the white paper to keep things moving in a positive and progressive manner. We also need to do a better job of communicating this information to patients, parents, and the media to combat the misperceptions and fear surrounding concussion,” says Dr. Kontos.

A Harris Poll Survey commissioned by UPMC (see article on page 31) in April 2015 of U.S. adults shows that only 29% of people believe concussions are treatable, and 87% cannot correctly define what a concussion actually is. This lack of knowledge is an obstacle that must be overcome.



Brock String used to rehabilitate and retrain oculomotor dysfunction following mTBI.

All Concussions Are Not the Same, But All Are Treatable

Of all the major points of agreement to come out of the meeting, the one that is of highest importance — for clinicians, the media, and the public at large — is that concussion is treatable. “The fact that we had unanimous agreement that concussion is treatable, that’s a pretty big deal. There are so many misconceptions or misperceptions about concussion — this meeting will bring awareness that there are different types of concussions and that they are treatable,” says Dr. Collins.

And in terms of treatment, an interdisciplinary team is critical to both the comprehensive assessment and targeted treatment of concussion. Having experts in neuropsychology, vestibular and physical therapy, neuro-optometry, orthopaedic and sports medicine, and physical medicine and rehabilitation affords patients a comprehensive clinical care team. Patients who present with different clinical profiles can be helped, and this is where the TEAM approach is most valuable.

From Dr. Kontos’ perspective, “It doesn’t sound like a lot, but it has tremendous potential to change the perception that all you can do with this injury is rest and be passive in nature. This statement opens the door to agreements about more active and targeted approaches to treatment. I also think the simplicity of the statement lends itself well to getting the word out to the general public.”

Research Will Validate and Guide Clinical Care

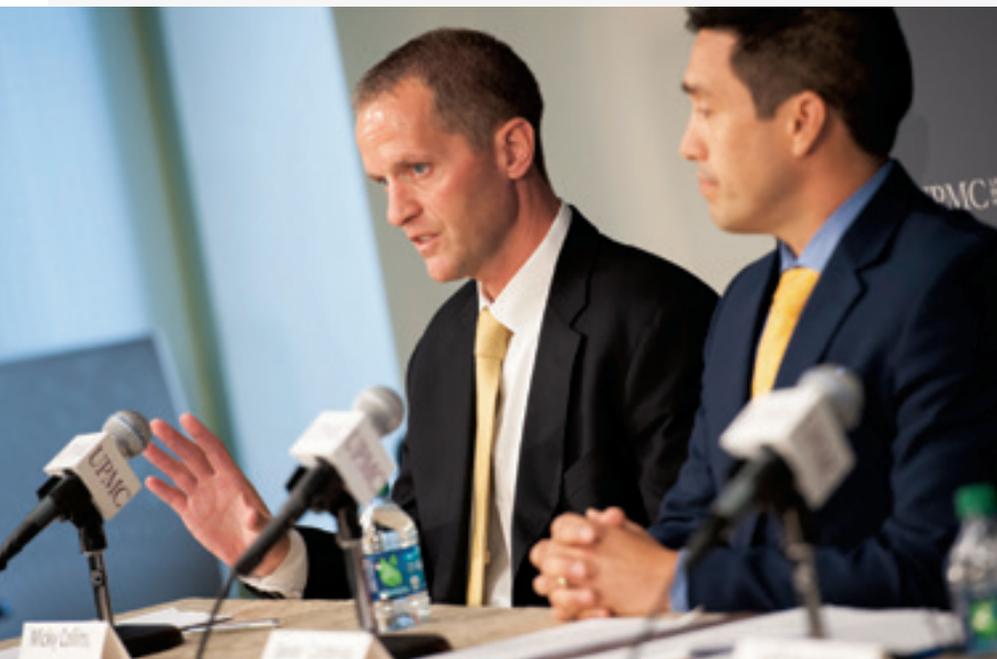
While there has been much research into concussion diagnosis and treatment, there exist gaps in the knowledge base that only randomized controlled trials (RCT) will be able to answer. One of the key principles of the consensus statement seeks to spur this avenue of investigation, in particular to validate the identified clinical profiles and effectiveness of the treatment guidelines that are a part of the TEAM approach.

Research published in 2014 by Drs. Collins, Kontos, and colleagues shows the profiles of concussion to include: vestibular, ocular-motor, cognitive/fatigue, post-traumatic migraine, cervical, and anxiety/mood. Understanding, and agreement, that the “flavors” of concussion are varied will carry forward and improve assessment and ultimately clinical care with targeted approaches. “We have come up with six

clinical profiles for concussions, and feel confident of the different trajectories but we need to empirically validate them over time. There really hasn’t been a successful RCT in that way, but we’re positioned now to do this,” says Dr. Collins.

Echoing Dr. Collins, and the sentiments of the consensus statement, Dr. Kontos indicates that the next steps in research “need to do two things: better characterize the clinical profiles of concussion with empirical data — the symptoms, impairments, overlap and other factors — and use this information to design and conduct RCT studies to determine the effectiveness of targeted treatments. We have to start now by conducting prospective trials to determine the effectiveness of current approaches that can help inform subsequent RCTs.”

Other areas of future research identified as priorities by the group include: the clinical benefits of prescribed active interventions, the role of modifying factors on the effectiveness of treatments, and complementary and integrative therapies for concussion treatment.



Dr. Collins discusses aspects of the October concussion meeting at a press conference.



“ Concussions are not simple injuries with singular recovery trajectories but instead reflect an amalgamation of symptoms and dysfunctions that recover differentially, not unitarily. ”

Anthony P. Kontos, PhD

A Robust Research Program

Since the UPMC Sports Medicine Concussion Program began in 2000, clinicians and researchers have published well over 150 papers on the various aspects of concussion, each informing and adding to the evidence base of the program's clinical care and assessment strategies, and advancing the entire field of concussion care nationally and internationally. “To think that we have many different knee or ankle injuries, but only one type of concussion is counterintuitive. After all, we are talking about an injury to the brain — the most complicated and least understood part of our body. With that in mind, the concept of concussion clinical profiles is logical. Our clinicians see these profiles every day in the clinic, and the data are starting to support the different clinical profiles. Our research has provided good initial evidence for the vestibular (*Mucha et al., 2014*), oculomotor

(*Pearce et al., 2015*), and post-traumatic migraine (*Kontos et al., 2013*) clinical profiles,” says Dr. Kontos.

In 2015, Drs. Kontos, Collins, and colleagues in the UPMC Center for Sports Medicine published several new papers that informed aspects of the October concussion meeting and the statements of agreement in the white paper, and, more broadly, add to the growing evidence base in the field. A first-of-its-kind cohort study on *The Effect of Preinjury Sleep Difficulties on Neurocognitive Impairment and Symptoms After Sport-Related Concussion* in *The American Journal of Sports Medicine* showed that difficulties with sleep — quality, duration — in patients prior to concussion may increase post-concussion symptoms and neurocognitive impairment.

A study published in the journal *Neurosurgery* — *Examining The Recovery Trajectories After Sport-Related Concussion With a Multimodal Clinical Assessment Approach* looked at recovery times in patients with a sport-related concussion (SRC). As the paper reports, previous research estimated a 7 to 10-day recovery period for most SRCs. The findings of this paper point to a longer recovery period of 21-28 days and different recovery patterns for symptoms, neurocognition, and equilibrium providing “more evidence that concussions are not simple injuries with singular recovery trajectories but instead reflect an amalgamation of symptoms and dysfunctions that recover differentially, not unitarily.” This study, along with numerous ones of the past, support and echo a major point of agreement in the white paper; that no two concussions are alike and management and rehabilitation are best applied in a targeted approach. ■

Does America Understand Concussions?

In short, no.

Misconceptions about concussion abound at every level. In April 2015, UPMC commissioned a consumer research survey from Harris Poll to assess the current level of knowledge about concussions with U.S. adults. The poll set out to understand perceptions around adults':

- Interest, involvement, and attitude toward contact sports
- Perceived and actual knowledge about concussion
- General attitudes about concussion and the information available to them
- Personal experiences with concussions
- Treatments for concussions

The results of the poll point clearly to a general misunderstanding about what a concussion is, how they are caused, and how they can be treated.

Michael "Micky" Collins, PhD, clinical and executive director of the UPMC Sports Medicine Concussion Program, indicates that the facts need to be better communicated, not only to the public but to the clinical community treating these patients. "There's just a tremendous misunderstanding of this injury. The fact that, according to the survey, 25% of U.S. parents do not allow their children to play contact sports for fear of concussions, and only 29% of adults understand that concussion is a treatable injury, this is a big problem not only for our program but the entire clinical community," he says.

While the incidence of concussion each year approaches 3.8 million in the United States, and media attention and discussion have been on the increase with high profile discussions occurring around professional and amateur sports, misconceptions and old thinking are still quite prevalent.

The online survey, conducted in April 2015, polled 2,012 U.S. adults over the age of 18 with 948 respondents who were parents. From a general perspective, the survey revealed the following:

- Approximately 9 in 10 adults (89%) believe concussions are a moderate or serious health concern, while only 2% say it is not a concern at all
- 41% feel that getting a concussion is living a nightmare
- If they personally sustained a concussion, 24% would be scared it would change their life forever and 22% would be anxious that they wouldn't be able to live their life the way they want to

For Dr. Collins, the heart of the matter lies in fostering an understanding that concussion is a treatable injury. To further this understanding, and work to develop consensus agreements on the many aspects of concussion, the UPMC Sports Medicine Concussion Program organized and led a symposium of the nation's leading experts in the field in October 2015 (See page 26) "The meeting we organized in Pittsburgh in October with the country's leading clinical experts, there was unanimous agreement that concussion is treatable. If you understand what we know, and what we continue to learn about concussion, and juxtapose that against what the public understands about the injury, it's very



- Only 18% feel that concussions aren't as bad as people think they are
- 83% feel that people generally do not take concussions seriously enough
- 32% of parents live in fear that their child will get a concussion
- 25% of parents do not let their kids play some contact sports because of fear of concussions

The survey also revealed a number of critical deficiencies in public knowledge. Almost 9 in 10 (87%) U.S. adults do not know how a concussion is defined, while 79% wrongly believe there is no real way to recover from a concussion; the symptoms can only be lessened.

clear that we as clinicians and scientists really need to start disseminating the right information about this injury to the public as well as our fellow clinicians. There are tremendous advances we've made in assessing, managing, and yes, treating this injury. It's a highly manageable injury. Clinicians need to arm themselves with the right knowledge, training, and understanding of how to approach concussions, so that every patient has the best chance of a full recovery. It's clear that we have a lot of work to do in this respect."

To read the full report of the survey with accompanying data tables, visit RethinkConcussions.com.

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MaCalus Hogan, MD | *Assistant Residency Director*

W. Timothy Ward, MD | *Vice Chairman for Pediatric Surgery*

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James J. Irrgang, PhD | *Vice Chairman for Clinical Outcomes Research*



A world-renowned health care provider and insurer, Pittsburgh-based UPMC is inventing new models of accountable, cost-effective, patient-centered care. It provides more than \$888 million a year in benefits to its communities, including more care to the region's most vulnerable citizens than any other health care institution. The largest nongovernmental employer in Pennsylvania, UPMC integrates 60,000 employees, more than 20 hospitals, more than 500 doctors' offices and outpatient sites, a 2.8-million-member health insurance division, and international and commercial operations. Affiliated with the University of Pittsburgh Schools of the Health Sciences, UPMC ranks No. 13 in the prestigious *U.S. News & World Report* annual Honor Roll of America's Best Hospitals. For more information, go to UPMC.com.