DEPARTMENT OF ORTHOPAEDIC SURGERY

HIGHLIGHTS 2013

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UPMC LIFE CHANGING MEDICINE

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DEPARTMENT OF ORTHOPAEDIC SURGERY: HIGHLIGHTING TRANSLATIONAL RESEARCH

Over the past year, the Department of Orthopaedic Surgery has made significant progress in the understanding of bone diseases and ligament injuries, from both causative factors and improving treatment approaches, and that progress means improved patient care.

Studies conducted by our team included stem cell regeneration of ligaments and bone, and the effects of stem cell tissue regeneration on the aging process. We developed better diagnostic techniques for sports injuries — including the latest technologies to assess ACL tears, as well as vestibular ocular sideline tests to identify concussions and their trajectory quickly. With better diagnostic ability came enhanced treatment options, some surgical, others therapeutic.

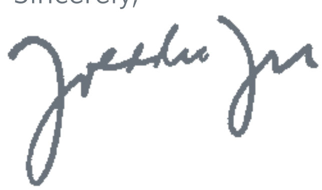
Departmental research ranges from basic science to clinical trials and practice outcomes, and I would describe our operational philosophy as translational. We're not just doing the abstract research that won't yield applicable results for 200 years. We want to take basic science and translate what we learn into clinical practice as soon as that's feasible. We want our patients to benefit from the knowledge we gain as soon as possible. Alternatively, if we find something that works in clinical practice, we will do the studies to support what we've learned.

We also want to share our learned information with others. We put a lot of effort into education so all patients can benefit from what we learn. In the past year, we published more than 274 studies in peer reviewed journals, and we made approximately 270 podium presentations at orthopaedic conferences in the United States and around the world, along with more than 278 instructional courses and 330 poster presentations. We also provide education for future orthopaedic surgeons and investigators nationally and internationally through residencies, fellowships, and instructional programs.

The 19 fellows and 40 residents we have this year join the 600 fellows we've trained from around the world in the past 25 years. Recently, I was in Germany, where UPMC was recognized for the 51 fellows we trained from that country in the past two decades. We want to do the best training we can, and we're able to do this through support from UPMC and the University of Pittsburgh.

We are trained, and we train with very high integrity and credibility — the two words we practice by.

Sincerely,



Freddie H. Fu, MD, DSc (Hon.), DPs (Hon.)
Distinguished Service Professor
David Silver Professor and Chairman
Department of Orthopaedic Surgery

MULTIDISCIPLINARY CARE FOR ORTHOPAEDIC TRAUMAS

Brian S. Zuckerbraun, MD, associate professor, general surgery;
Ivan S. Tarkin, MD, chief, Division of Orthopaedic Traumatology;
and **Peter A. Siska, MD,** director, Post Traumatic Reconstructive Center,
in an operating room at UPMC Presbyterian.

Bring together the brightest people in their field and let them do what they do.

That's the philosophy that drives research in the Division of Orthopaedic Traumatology, says Ivan S. Tarkin, MD, division chief.

"When you collaborate in a think tank using a multidisciplinary team, you always come up with progress. I look at how general surgeons or urologists would attack an abdominal trauma, and ask, why can't we bring that to orthopaedics?"

The results, he says, are groundbreaking techniques that should change the field of orthopaedic traumatology.

CLINICAL TRIALS

Minimally Invasive Pelvic Surgery

The most recent evidence that the approach works began when Peter A. Siska, MD, and Dr. Tarkin, whose area of specialty is pelvic traumatic injury, witnessed general surgeon Brian S. Zuckerbraun, MD, performing a laparoscopic hernia repair. They realized, "This is our anatomy. This is the part of the body we repair. We can do pelvic surgery this way."

The outcome of pelvic trauma surgical repair can determine long-term use and patient satisfaction. Working as a team, Drs. Tarkin, Siska, and Zuckerbraun collaborated to determine how to adapt minimally invasive techniques to a fractured pelvis and avoid potential complications, such as infection and blood loss, which can occur from large incision repair.

Trying to determine the best method, they decided a hands-on approach was essential. In a recent report, the trauma team outlined how they designed laparoscopic-assisted techniques for reduction of anterior pelvic ring dislocation. The team also developed methods to insert and adjust an anterior pelvic-locking plate and screws through much smaller incisions than conventional surgery.

"Initially, we did it with cadavers to see if we could figure it out. Since the general surgeons never deal with plates and screws, that was sort of exciting for them. We asked one of our general surgeons who is excellent at laparoscopic procedures to help with this endeavor. It turned out that it was actually quite easy to work out on a cadaver. That led to clinical cases."

The laparoscopic views needed for the pelvic anatomy were already available for laparoscopic hernia repair. The issue became finding a way to reduce the incision and still be able to get a plate in, and then apply the screws safely.

MULTIDISCIPLINARY CARE FOR ORTHOPAEDIC TRAUMAS

The team decided to make a tiny portal, an incision that would accommodate the thickness of the plate. They slid the plate in an atypical way, so that it was in the pelvic cavity. Subsequently, they used laparoscopic tools to manipulate the plate on the anterior portion of the pelvis, then used the previous portals again to insert a drill bit and screws.

Clinical trials are now underway, and while it's still early, the results so far are impressive, says Dr. Tarkin.

"It was absolutely night and day. These are horrendous injuries. When you superimpose all the surgical trauma of parting the abdominal muscles, these recoveries are usually painful and protracted.

"The laparoscopic patients came back in two weeks with hardly any symptoms whatsoever. Their pelvis was bolted together so they were rid of their pelvic pain, and they had no iatrogenic surgical pain. Recovery time in terms of healing and walking is more or less the same, but the human suffering is reduced substantially. All of that is avoided with tiny little poke holes in the skin."

An additional benefit, at least theoretically, is that because the musculature brings the blood supply, and the laparoscopic approach doesn't disrupt the blood supply, healing will be improved."

The multidisciplinary trauma team is convinced that the laparoscopic approach will be widely accepted as best medical practice in the near future.

Triceps-Sparing Humerus Repair

For years, UPMC has been a leader in helping to determine best practices. While always exploring for new methods to improve patient care, the Division of Orthopaedic Traumatology is committed to continually assessing the tools currently available to determine which offer the best outcomes for patients. In a recent retrospective study, Drs. Tarkin and Siska compared the outcomes of triceps-sparing and triceps-splitting approaches to fixating extra-articular distal humerus fractures.

While the triceps-sparing approach is technically more challenging, it does appear to provide better range of motion for the elbow, as well as more strength. Researchers, however, found little difference in the functional outcome for both procedures.

By taking the time and making the effort to assess treatment approaches and to make that data accessible to physicians across the country and around the world, UPMC wants to ensure patients receive the best care possible. ■

"When you collaborate in a think tank using a multidisciplinary team, you always come up with progress." **Ivan S. Tarkin,** MD

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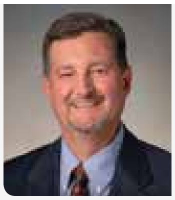
CHANGING THE PARADIGM OF RETURN-TO-PLAY GUIDELINES

James J. Irrgang, PhD, PT, ATC, FAPTA



At any given time, there are more than 200 clinical studies underway within the Department of Orthopaedic Surgery. They range from retrospective studies of medical records to clinical outcome studies to clinical trials. Coordinating this work comes under the purview of James J. Irrgang, PhD, director of clinical research.

Dr. Irrgang says not only is care taken to ensure that the research is not duplicative but that it also builds on existing knowledge and provides significant contributions to the field.

Among these studies is the Department's look into how successful current approaches to ACL reconstruction are in helping athletes return to their sports.

"I think the public's perception is that 100% of athletes return to play within six months. You look at [Robert Griffin III]. Six months after surgery and he's back, and everybody thinks that's the norm. Look at Adrian Peterson. Everybody thinks that's normal, but Adrian Peterson is on a different level."

During a recent conference hosted by UPMC, a panel discussion of orthopaedic surgeons revealed that after ACL reconstruction the return-to-play rate might be lower, and the time it takes to return to play might be longer than commonly perceived. Dr. Irrgang says one issue causing the ambiguity in determining the rate of return to pre-injury level in sports has been that there is no strict definition of return-to-play.

RETURN-TO-PLAY PERCEPTIONS

Dr. Irrgang's team sent surveys to UPMC patients who had ACL reconstruction performed within the last five years. About 250 surveys were returned by patients who were asked to assess their return to pre-injury level of sports and answer general questions about their current ability. The study indicated a lower rate of return when judged by defined guidelines versus the patients' subjective opinions.

Dr. Irrgang says the survey indicated that the younger the patients undergoing reconstruction were, the more likely they were to go back to full participation in their sports. About 70% of 14 to 18 year-old patients were able to go back to full activity. That rate dropped to about 50% for 19 to 23 year-olds, and only 20% for patients over the age of 25. Overall, about 44% of ACL reconstruction patients returned to their sports at the same level that they had participated before the injury.

Return rates aren't the only factor being studied. Researchers wanted to determine the reasons why athletes had not returned — the most cited being ongoing pain or swelling, fear of re-injury, and a lack of confidence in the previously injured knee. Of those returning, 25% did suffer re-injury. Dr. Irrgang describes those issues as troubling and says they have led to an examination of post-operative rehabilitation and counseling, as well as various reconstruction techniques.

"We recently started a study to compare performing reconstruction with a single bundle of the ligament to using two grafts in a double bundle to more anatomically reconstruct the knee."

That study, which has been funded by the National Institutes of Health, is being done under the direction of Dr. Irrgang, department chair Freddie H. Fu, MD, and Scott Tashman, PhD, director of the Orthopaedic BioDynamics Laboratory.

INNOVATION IN PIVOT SHIFT TESTING

Another groundbreaking study that is supported by Dr. Irrgang is led by Volker Musahl, MD, and uses some of the newest technology to more accurately quantify the pivot shift test rather than subjective grading of the test. An engineering fellow, under the oversight of Dr. Musahl at the University of Pittsburgh, developed an iPad® application that can show surgeons how much shift occurs in the lower leg following ACL injuries and repair.

Traditionally, the test is done with a physical examination, and the shift is subjectively assessed by the examiner with no objective measurement. Although some image testing has been developed, the equipment is not always readily available, and the procedure can be expensive and sometimes invasive.

With the new iPad application, the measurement is made by placing three markers on the thigh and shin. The application records a video tracking the markers throughout the test. Even a slight shift can be objectively quantified and accurately compared months after surgery to determine if the graft is functioning as it should over time.

Currently, an international multicenter trial is being conducted to evaluate the iPad application and clinical grading.

STEM CELL-BASED CARTILAGE REGENERATION

Rocky S. Tuan, PhD, director, Center for Cellular and Molecular Engineering (CCME), sits at a microscope in the CCME Lab at the University of Pittsburgh.

The potential that stem cells offer to medical care keeps expanding as researchers continue to identify new possibilities.

The McGowan Institute for Regenerative Medicine, a program of the University of Pittsburgh and UPMC, is hovering on the brink of the future, using the advances already made in stem cell research to catalyze the next generation of innovations.

One of the most exciting aspects of the work is its potential to help repair and replace cartilage for many people with damaged joints, whether the cause is sports-related injury, accidental trauma, or disease. Osteoarthritis is the number one cause of physical disability, particularly in older adults. With an aging population, between 20 and 25 million Americans are affected.

Rocky S. Tuan, PhD, associate director of the Institute, director of the Center for Military Medicine Research, and executive vice chairman of the Department of Orthopaedic Surgery, says the challenge is to figure out a way to restore mobility.

"While joint replacements are a life-changing answer for many with injured or deteriorating joints, they don't last forever. If patients are 60 or 65 and have a knee replaced, they're generally in good shape for the rest of their life. If, however, patients need knee replacements at the age of 40, most likely they will need a revision, which is another major surgery, and that means digging a bigger hole into the bone."

EXTENDING THE LIFE SPAN OF KNEE REPLACEMENTS

A major focus of Dr. Tuan's research is looking for a way to make knee replacements last longer.

"Replacing a knee is major surgery and destructive surgery. Everything is replaced with metal or plastic, so you don't have any joint left. That part of you is robotic. It's not a therapy; it's a replacement. It would be much nicer to simply repair or resurface the joint because the rest of the bone is okay. It's the lining of the bone that is falling apart, causing pain, discomfort, and loss of mobility. If the joint could be resurfaced — that's sort of the Holy Grail to those of us who work in this area."

Dr. Tuan says he and his researchers are moving in that direction. They are working on an artificial matrix that can fool stem cells into reacting as if they were in cartilage and start producing new cartilage that will protect the joint.

Nanofibers are being combined with a hydrogel to create a viscoelastic material similar to the viscous, elastic nature of cartilage. A recently published study details how they developed a method of light-mediated, cross-linking

STEM CELL-BASED CARTILAGE REGENERATION

polymerization of the gel to give it viscous properties. It's important because it uses visible light rather than the commonly used, harmful UV light.

The goal is to use the process to create a material similar enough to cartilage that it will trick cells in the joint into manufacturing more cartilage.

"The key feature is that everything we use is biodegradable. So after a number of months, everything we put in at the beginning will be gone and replaced by actual cartilage produced by the stem cells."

CLINICAL TRIAL

Dr. Tuan says the process has worked in the knees of large animals. Now, a grant from the National Institutes of Health will support the laboratory's large-scale testing using micro (4 mm diameter) osteochondral junction-like tissue analogs. The study will determine how and why the disease process begins in the tissue, and which therapeutic drugs are effective in preventing osteoarthritis.

"We will have a large statistical powerbase, with built-in variability, at a much lower cost than the more commonly used animal studies."

Beyond finding ways to treat osteoarthritis, Dr. Tuan explains that it's important to determine how to best protect new stem cell-generated cartilage from falling prey to the same degenerative factors that initially cause the disease.

This work could help to delay the need for joint replacements, so that only one will be needed during a patient's lifetime.

Injured Joint Regeneration

Growing cartilage material also will enable injured joints to heal more quickly.

Dr. Tuan says every study from the laboratory generates new avenues of research to explore.

"A new report we published shows that if we can remove cells from tendon, the residual tendon matrix itself can stimulate stem cells to make them turn quickly into tenocytes, cells that make up tendon. That's very exciting."

As co-director of the country's largest consortium of military regenerative medicine, the Armed Forces Institute of Regenerative Medicine (AFIRM), Dr. Tuan says that his stem cell research is also helping to determine ways to block the formation of heterotopic ossification at amputation sites in combat veterans.

Using mouse models, his laboratory has identified cells in blast-traumatized muscle that stimulate cells to form bone in muscle, involving the action of bone morphogenetic proteins (BMP), particularly near amputation sites. Preliminary data shows that by injecting a BMP inhibitor, the development of bone was blocked in the mice. Researchers are now looking at how that process can be adapted for human amputees who suffer from heterotopic ossification. ■

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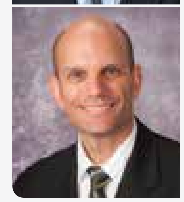
NEW FRONTIERS IN CONCUSSION

Michael W. Collins, PhD

Anthony P. Kontos, PhD



Focus on sports-related concussions continues to grow among sports medicine professionals, but the emphasis on concussion is nothing new for the UPMC Sports Medicine Concussion Program, where researchers are continuously looking for ways to better understand, diagnose, and manage concussions.

Michael "Micky" Collins, PhD, clinical and executive director of the program, is clear about its mission.

"UPMC is redefining the word, and the condition, concussion. We're finding out that what we've always known is not necessarily true. That redefinition has led to new and more effective therapies for treating and resolving concussions. I think you're really going to see the field change as a result of this work."

CLINICAL TRIALS

Concussions in Sports

Dr. Collins says concussions have long been considered a homogenous event, but UPMC research shows there are different sub-types of concussions — each one a little different, requiring varying therapeutic approaches. One identifying factor that Dr. Collins says has been underutilized is vestibular ocular screening. Current sideline screenings don't evaluate the vestibular ocular aspects of a concussion, and he says new studies indicate that it should be done quickly.

"We've just validated a three-minute exam that looks at the vestibular and ocular aspects that we've found are among the most common and most predictive of the outcome following concussion."

This vestibular ocular exam, which can be done on the sidelines immediately following an injury, is extremely sensitive in picking up symptoms of a concussion and indicating where the injury is coming from. It folds in effectively with the ImPACT® (Immediate Post-Concussion Assessment and Cognitive Testing) evaluation. Once the trajectory of the injury is identified, treatment can be determined.

Dr. Collins says six trajectories have been defined to help understand the heterogeneity aspect of concussion, and different therapies are more effective with each one. With that knowledge, Dr. Collins says doctors will be able to give concussion patients a more complete idea of the time needed for rehabilitation.

"We're not finding that concussions leave lifelong effects. They are treatable, and it means a lot to patients, when we can say: this is what you have, this is the treatment, and you're going to be fine."

It's the uncertainty surrounding concussions that Dr. Collins says creates many problems for patients.

"It creates a lot of anxiety and fear. We're seeing a lot of comorbid psychiatric issues because athletes are so anxious. Mental health is one of the trajectories of concussion, and it's made worse by the uncertainty of the outcome."

Concussions in Combat

It's not just athletes who are the focus of research being conducted at the UPMC Sports Medicine Concussion Program. Researchers are also working with the military to improve the treatment of concussions suffered by personnel in combat.

Anthony P. Kontos, PhD, assistant director of research, says a study of military concussions has replicated what they've seen in sports: a history of concussion can set a person up for complications if future concussions are suffered.

"We saw that U.S. Army Special Operations personnel who had a documented, medically diagnosed history of mild traumatic brain injury or concussion had much more significant drops in neurocognitive performance, using the military version of the ImPACT test. When you look at their scores, they are significantly lower than the group without a history of concussion."

Also analogous to high-level athletes, Special Forces personnel want to return to active duty immediately.

Within the group of personnel suffering from mild traumatic brain injury, there is a subgroup of soldiers who are exposed to regular blast forces. Some have experienced hundreds of explosions, causing a different type of mild traumatic brain injury (mTBI).

Dr. Kontos says Special Forces take a progressive approach to concussion treatment. The UPMC study shows that when soldiers with a previous mTBI experienced a large drop in neurocognitive performance, they could return to the field in a couple weeks, with proper management.

UPMC received a grant from the Department of Defense to develop a clinical practice guideline manual for Special Forces to update current practices to include knowledge gained from the most recent study of the military, as well as what has been learned at the UPMC Sports Medicine Concussion Program.

REDEFINING THE APPROACH TO ACL RECONSTRUCTION

Freddie H. Fu, MD, chairman, Department of Orthopaedic Surgery, at the UPMC Center for Sports Medicine.

Hundreds of thousands of ACL injuries occur every year, many in athletes. Finding better options for treating those injuries is a major focus of research in the Department of Orthopaedic Surgery.

Physician-scientists and researchers at UPMC have found that the common wisdom surrounding this condition may not provide the wisest treatment.

Not only is the Department's Orthopaedic BioDynamics Laboratory using new methods to determine whether the best treatment approach is therapy or surgery, Freddie H. Fu, MD, chairman of the Department, says studies are showing that when surgery is the best practice for treating the injury, better surgical approaches are available that may improve on common techniques.

ACL MOUNTING

"Recently there have been a lot of arguments about the mounting of the ACL, with some people saying the ACL is like a ribbon, and some thinking it's really small in the middle. Sometimes when surgeons are operating on the ACL, they just dissect it with their bare eyes, so they may be too aggressive."

In one of Dr. Fu's research group studies, cadaver knees were mounted on a robotic arm, and each knee was dissected so that only attachments to the femur and tibia remained. The knee was remounted on the robot so that the ACL would be returned to the exact position, with the distance remaining exactly the same.

STRENGTH AND HEALING TIME

Restoring the ACL as close as possible to its original position is the goal of reconstruction.

"We do a laser scan to look at the shape and size; it's a more objective and accurate assessment of the placement. Our goal here at UPMC is to repair the ACL to 100% of its original strength, not just 50%. We want it to be identical to its original position and condition."

In another study, Dr. Fu explains that what might seem like a faster, stronger way to repair the ACL may actually leave it weaker and more prone to re-injury.

"Traditionally, we've been trying to reduce the amount of time it takes to recover from an ACL injury, but that resulted in the ACL being placed in the wrong spot during reconstruction."

Dr. Fu is the 2014 recipient of the Kappa Delta Elizabeth Winston Lanier Award for his research on Anatomic Anterior Cruciate Ligament Reconstruction.

REDEFINING THE APPROACH TO ACL RECONSTRUCTION

"Interestingly, this study showed that when the ACL is placed in the correct location, if return-to-play is rushed, the ACL does re-tear more easily. Six months after surgery, it would look great on an MRI, the patient would return to play, it would pop, and we didn't understand why."

Dr. Fu explains, "The whole rehab has to be different. If the ACL is put in the wrong place, versus the right place, the in situ force changes. If the ACL is replaced incorrectly, the force on the ligament may be reduced and it may appear to heal more quickly. Placed in the right location, there is more force on the knee, and it won't be 100% healed in six months, but it is better for the long-term health of the knee."

"Some people are more concerned with getting back into competition faster. They don't understand that the ACL can just end up tearing again. It can take nine months to a year for the ACL to heal properly and reduce the risk of re-injury."

Using robotic procedures allows the surgeon to replace the reconstructed ACL accurately back in its native position, exposing the graft to higher forces, while nonanatomic reconstruction increases the risk of failure.

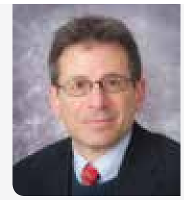
FUTURE TRIALS

Quadriceps Tendon Autograft ACL Reconstruction: Single-Bundle vs. Double-Bundle

The Department of Orthopaedic Surgery and the Anatomic ACL Reconstruction Research Group are currently conducting an NIH-funded randomized clinical trial to compare single-bundle versus double-bundle ACL reconstruction using quadriceps tendon autograft. Patients will be evaluated through patient-reported outcomes, clinical measurements, and dynamic stereo imaging. The goal is to reach a consensus in the controversy over which technique provides the best practice for ACL reconstruction. ■

"Some people are more concerned with getting back into competition faster. They don't understand that the ACL can just end up tearing again. It can take nine months to a year for the ACL to heal properly and reduce the risk of re-injury." **Freddie H. Fu,** MD

BIODYNAMIC MOTION IMAGING


Scott Tashman, PhD

How does muscle function influence joint behavior? How does dynamic joint function change in the presence of an injury? Those are just two of the questions Scott Tashman, PhD, director of the Orthopaedic BioDynamics Laboratory, believes can be answered with the lab's unique dynamic stereo x-ray system.

Motion analysis has become a standard approach to assessing how ligaments, tendons, and other body parts work. There are now hundreds of motion analysis laboratories around the country, but the Orthopaedic BioDynamics Lab has designed a system that goes beyond the conventional technology of video-motion analysis and can assess how bones and the adjacent tissues move in relation to each other when they are engaged in natural motion.

While traditional motion analysis provides excellent information on injured joints, Dr. Tashman says more information will help in developing treatments for joints plagued by injury or disease, such as osteoarthritis.

UNCONVENTIONAL 3D SCANS

Dr. Tashman explains that, in addition to the conventional, video-based motion analysis technology, the dynamic stereo x-ray system adds high-speed x-rays to the measurements accumulated by the computers.

"They're not conventional x-rays; these would be more like x-ray strobe lights. They send pulses of x-rays that are only a millisecond long, up to 180 times per second, capturing blur-free images even for fast-moving limbs. Traditional fluoroscopy is unsuitable for dynamic studies because it runs at much lower frame rates and requires at least eight times longer to capture an image."

The set-up allows doctors to collect information on virtually every joint during every motion the body can perform within the field of view of the imaging system.

Dr. Tashman knows some people suggest that MRIs or CT scans can provide 3D images, and question why this biodynamic system is needed.

"I ask them when was the last time they ever did anything physical while lying on the gantry of an MRI magnet. How do they get joints to work the way they do in the real world when they're lying on their back in a tube?"

The challenge now facing Dr. Tashman and his team is how to put all of the radiographic images together to get a 3D reconstruction that will show exactly how the body moves. The semi-automated process for matching the x-ray images to 3D bone models requires between 10 and 60 hours per test of intensive effort, requiring a small army of lab staff and undergraduate or graduate students to keep up with the many ongoing studies. That's not exactly cost effective for widespread clinical use, but the information provided by the process is invaluable for a wide range of research applications. Based on his experience with these imaging methods, Dr. Tashman is currently working with a computer firm on an NIH-funded project to develop software that will reduce the processing time by a factor of 10 or more, opening the door to future clinical use.

IMPLICATIONS OF IMAGING

According to Dr. Tashman, knowing how the bones and tissues move can help doctors to determine whether injured or diseased joints can be treated with therapy rather than surgery, and if surgery is required, which procedure would be most beneficial for the patient.

"There are a lot of orthopaedic procedures for which the criteria for whether you do the procedure, a different procedure, or no procedure, is very subjective. A classic example is an ACL injury. The reality is that some people can adjust their muscular coordination to protect their knee after an ACL injury, and they may do well without ACL reconstruction. Some people can keep their knee stable during activity, and some can't.

"This is the first technology that can actually measure whether the knee is stable when a person is doing sporting event-type movements. This data can help to guide the best choice of treatment (surgical or nonsurgical) for patients, based on their individual knee function and the kinds of activities they would like to return to after their injury."

Along with restoring stability, an additional rationale for ACL reconstruction was that injured joints have an increased risk of arthritis, and reconstruction was thought to reduce that risk. Dr. Tashman says studies in the last 10 years have shown the risk of arthritis is not reduced following conventional ACL reconstruction.

"Using anatomical studies, we've identified that the way people were doing reconstructions was not restoring native anatomy. The geometry was wrong, and motion of the knee was still abnormal."

Dr. Tashman is currently collaborating with his colleagues (Freddie Fu, MD, and James Irrgang, PhD,) at the University of Pittsburgh to evaluate newer, more anatomically based ACL reconstruction techniques that might better restore knee function and preserve joint health.

Beyond ACL injuries, the technology is being used to better understand how the spine works, whether approaches other than surgery might be better for the patient, and how implant designs might be improved. Rotator cuff injury improvement can also be compared pre- and post-therapy or surgery.

There are several labs throughout UPMC and the University of Pittsburgh working with tissue engineering and cartilage, and Dr. Tashman says the Orthopaedic BioDynamics Lab provides the best facility to test how well the tissues they design are functioning. It can offer information on the mechanical environment the tissues will be living in and how much they will be loaded or stretched. Tissue engineering researchers can then make sure their designs are able to meet those requirements.

STEM CELL RESEARCH FOR ORTHOPAEDIC RESTORATION

Johnny Huard, PhD, director, Stem Cell Research Center, in his office at the Stem Cell Research Center.

Ideally, research not only leads to answers, but it also produces questions.

Research at the Department of Orthopaedic Surgery could be described as spiraling (or circular) in nature: basic science investigation leads to ideas that can be tested in clinical studies, which can then result in the development of best medical practices. Conversely, the practice of good medicine by experienced physicians who know a treatment works often stimulates clinical research to explain how it works, then basic science answers why it works.

Researchers at the McGowan Institute for Regenerative Medicine, a program of the University of Pittsburgh and UPMC, have successfully used adult muscle stem cells to repair cardiac and bladder tissue in clinical trials. More than 15 patients with myocardial infarction have been treated effectively with stem cells, while 100 patients have been treated for stress urinary incontinence during trials that began in 2005.

The results attained by those treatments encouraged the Stem Cell Research Center to widen its investigations into what stem cells are capable of doing and becoming. Orthopaedic researchers are looking to expand the use of stem cells to include the regeneration of tendons, muscles, bones, and articular cartilage.

Johnny Huard, PhD, director of the Stem Cell Research Center, says the potential of stem cells to speed up the repair of injured skeletal muscle, bones, and articular cartilage has shown promise in animal models and, consequently, can potentially improve musculoskeletal repair in humans. There is one added level of complexity that increases the difficulty of utilizing stem cells for bone, tendon, and cartilage — the stem cells must be modified to express a given growth factor in order to work on those tissues — and because the modification factor is viral in nature, its use must be approved by the FDA.

Some viruses have now been FDA approved, so UPMC researchers are busy testing virus-modified stem cells in mice, with more animal studies on the horizon.

Dr. Huard says these stem cells should make the healing of skeletal muscle and bones significantly faster and stronger.

"Once a bone is broken, that point on the bone is generally weakened and more prone to re-injury. The modified stem cells should be able to make that point stronger and protect it from re-injury."

Stem cells could also have a beneficial effect on diseased bones, such as those exhibiting signs of osteoporosis.

STEM CELL RESEARCH FOR ORTHOPAEDIC RESTORATION

Studying Progeria mice, the Center found that the quickly aging mice develop very tired stem cells, which lead the mice to develop numerous health issues, including numerous musculoskeletal tissue defects. Researchers harvested stem cells from newborn mice and injected them into Progeria mice when they were 17 days old. The typical Progeria mice died after 21 days, but the mice that received the young stem cells lived for up to 75 days, remaining healthier much longer. Those findings opened a number of new doors of research.

Could stem cells lead to possible treatments for numerous aging-related disorders in humans? Dr. Huard says that eventually the idea may lead to harvesting stem cells when children are born and storing them for later on in life.

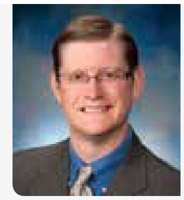
But Dr. Huard says the question of how the stem cells work is still unanswered.

"When we look for the stem cells we've injected, we cannot find them. They appear to be releasing anti-aging signals that are paracrine in nature, but a lot of work is needed to determine what those cells are secreting and whether it can be used for tissue repair without the need for stem cells."

Dr. Huard says it is the way studies work together that is so exciting about the inquiries underway at the Stem Cell Research Center. He suggests that this work, and the investigations that will follow, could change the way people look at aging. In the future, he says, it may become common practice to harvest umbilical stem cells at birth and freeze them. They could then be used later in life to help repair broken bones or injured ligaments, or to offset the effects of aging. ■

"Once a bone is broken, that point on the bone is generally weakened and more prone to re-injury. The modified stem cells should be able to make that point stronger and protect it from re-injury." **Johnny Huard,** PhD

UNDERSTANDING THE BIOLOGY OF OSTEOSARCOMA


Kurt R. Weiss, MD

Improving the survival rate for osteosarcoma and identifying new treatment options for patients are ongoing challenges for musculoskeletal oncologists.

Osteosarcoma claimed the lives of approximately 90% of its victims until the 1980s because surgery and amputation were the only treatment options. There was renewed hope for patients when chemotherapy for the bone cancer was developed, and the survival rate improved to 60-70%. Unfortunately, progress came to a screeching halt around 1990. Although researchers continued to explore chemotherapy combinations, nothing made any real impact on survival. The survival rate today is virtually the same as it was 20 years ago.

To Kurt R. Weiss, MD, a musculoskeletal oncologist and researcher in the Department of Orthopaedics, that means chemotherapy has gone about as far as it can go on its own, and it's time to take the fight against osteosarcoma to the next level.

CELLULAR UNDERSTANDING

One of just a few physician-scientists searching for a cure for the disease, Dr. Weiss says, "I think we need to fight the disease from a biologic standpoint: figure out how cells are metastasizing, what molecular machinery they're using, and deprive them of that. While I don't have a defeatist point of view about trying different chemotherapy combinations, we've been doing the same thing for 25 years and nothing's happened. So perhaps we need to fight the disease in a more biologically intelligent way.

"No one dies of a tumor on the arm or leg. I can take care of that in the operating room. The problem isn't what can be seen, it's what can't be seen: the individual cells floating around the body looking for a home. Targeted therapy has been successful recently in oncology. We need to understand the biology of how a sarcoma cell gets from the femur into the lung and how to interrupt that process because chemotherapy is not going to do it, and surgery is not going to do it."

That is now the focus of Dr. Weiss's work — trying to understand the characteristics of an osteosarcoma cell and the processes that occur in order for the cancer to metastasize from the limb to the lung.

"My brain works in a very translational way. My patients are dying and I want to ask, 'what do we have now?' What small molecule inhibitors might we research quickly and get quickly into clinic as adjuvants for osteosarcoma? I'm more a translational scientist than a basic scientist.

"Mechanisms concern me, but show me a drug that makes osteosarcoma cells stand still and decreases their ability to withstand oxidative stress, and I'm less concerned about the mechanism of how that happens. I want to get something that works in my patients now."

CLINICAL TRIALS

Epigenetic Repression

Dr. Weiss was not interested in epigenetic regulation because he was looking for that usable treatment, but his post-doc suggested looking into changing the epigenetic fingerprint of the osteosarcoma cells.

While DNA methylation will generally block genes from being translated, with cancer cells that process appears to work in reverse. Dr. Weiss' team wondered if it was possible to reprogram cancer cells so that they might fix themselves and release the epigenetic silencing of tumor suppressor genes.

The team developed a study treating cancer cells with a chicken embryo extract (CEE) that has been found to have an effect on DNA demethylation. Administering CEE in a dose-dependent fashion made the K7M2 cells express tumor suppressors. The study showed that the CEE helped to transform cancer cells to more normal-type cells and could have the potential to repress the metastasis of osteosarcoma in people.

"How we get to the point where we can use this therapy in children and teenagers, I'm not sure, but it's fascinating to think about and should be explored as a therapeutic option to treat osteosarcoma."

Retinol Treatment

Another study Dr. Weiss oversaw was the treatment of osteosarcoma cells with retinol. The effects of retinol on the cancer cells relates to aldehyde dehydrogenase (ALDH), which allows cells to withstand oxidative stress. Retinol appears to target ALDH in metastatic osteosarcoma cells by promoting apoptosis and differentiation.

"We put all trans-retinoic acid on the osteosarcoma cells, and we decreased the proliferation of cancer cells and caused them to die because it decreased ALDH expression and activity. It decreased their invasiveness and their ability to survive oxidative stress."

Dr. Weiss is excited about looking for ways to apply this research to actual treatments. He expects that it would be used in conjunction with chemotherapy, since that is the accepted treatment now. He knows it won't happen overnight but thinks these two approaches offer the promise of new and effective treatments for osteosarcoma in the future.

"The biologic method is the way of the future, but it doesn't stop people from wanting to do what they know, which is experiment with different chemotherapy combinations. I don't think that's without merit, but neither do I think it's mutually exclusive to look for other approaches."

Dr. Weiss is getting help with his efforts to disrupt the metastasis of sarcoma to the lungs. The NIH just awarded him an $827,280 grant for laboratory research into sarcoma. His goal is to identify more methods of blocking the movement of cancer through the body and translate them into clinical treatments for patients with osteosarcoma.

THE FIGHT AGAINST DISC DEGENERATION

Gwendolyn A. Sowa, MD, PhD, co-director, Ferguson Laboratory for Orthopaedic and Spine Research;
James D. Kang, MD, co-director, Ferguson Laboratory for Orthopaedic and Spine Research;
and **Nam V. Vo, PhD,** assistant professor, Department of Orthopaedic Surgery, in the Ferguson Laboratory.

Research into ways to battle signs of aging — both cosmetically and scientifically — are common, but in the Department of Orthopaedic Surgery's Ferguson Laboratory for Orthopaedic and Spine Research, basic science investigation is underway to discover what actually causes aging of the disc on a molecular basis.

Lower lumbar pain is a common complaint of aging. Many factors are known to cause or contribute to back pain — such as disc degeneration from aging, obesity, diabetes, or smoking. But the molecular mechanisms that cause the degeneration are not understood. James D. Kang, MD, vice chairman in the Department of Orthopaedic Surgery and co-director of the Ferguson Laboratory, says their goal is to shrink the gap between what is known and what is not.

"Lower lumbar pain costs society 50 to 70 billion dollars annually. Although we can't stop aging, if we can try to slow down the process, it would potentially have a huge clinical impact. We used to think aging was a natural consequence and there was nothing we could do about it. Now we're unlocking some of the mechanisms of the aging process. That's exciting."

BASIC SCIENCE STUDIES

DNA Damage and Mechanisms of Aging

Dr. Kang says that one of the underlying cause of aging is that the body is bombarded constantly with agents that can cause DNA damage (UV radiation, chemicals in foods, oxidants, etc.), but the mechanism of how DNA damage causes aging is not clear. Dr. Kang has been working with basic science researchers Nam V. Vo, PhD, and Laura J. Niedernhofer, MD, PhD, to unravel some of the mechanisms behind the aging process in the disc. Through their research, they have shown that chronic activation of a transcription factor called NF-kß plays a major role in mediating the aging process in the disc when DNA damage occurs.

"NF-kß is activated in response to DNA damage, inflammation, or excessive mechanical loading, which triggers a cascade of molecular events leading to slow and progressive tissue damage and the ravages of aging. Therefore, if we block NF-kß, it may eventually help slow down the aging process of the disc."

Using a mouse model of human Progeria (a disease which causes rapid premature aging in patients), Dr. Kang and his research team have been able to determine some of the basic mechanisms of the aging process in the disc. They have been able to inhibit ▸

THE FIGHT AGAINST DISC DEGENERATION

NF-kß with a peptide called 8K-NBD. When the aging Progeric mice were treated with this peptide, degeneration of the disc was substantially slowed, and the mice actually lived longer.

Dr. Kang says that the aging process does not always lead to back pain, and conversely not all back pain comes from aging.

"We want to determine if factors such as obesity, smoking, aging, and diabetes share a common pathway — a common molecular mechanism — that causes the disc to start breaking down. If NF-kß is the predominant driver, we can focus on inhibiting it, if that can be done safely."

The result could be better medical treatment and less surgery to treat back pain.

Glucosamine Therapy and Disc Cartilage

In line with the studies of disc degeneration and treatment, another study conducted in the Ferguson Lab could discredit some commonly accepted wisdom in the field of holistic medicine, Dr. Kang says. Responding to a NIH call to determine whether there is any validity to the claims made for various therapies, Gwen Sowa, MD, PhD, who works with Dr. Kang as co-director of the Ferguson Laboratory, looked into glucosamine — a supplement used by millions of Americans for arthritic conditions, costing billions of dollars. The molecular make-up of glucosamine is reputed to be good for cartilage in the disc.

Dr. Kang says glucosamine users swear by its anti-inflammatory properties, which relieve the pain of arthritis. The problem is that, despite its immediate benefits, evidence indicates long term damage could potentially result.

"What we're seeing in our petri dishes and our animal models is that glucosamine decreases the production of chemical mediators that cause inflammation, but it also can make disc cells produce less proteoglycans, which is the major "backbone" of disc extracellular matrix. So while glucosamine blunts the inflammation response and makes the patient feel better, paradoxically, it inhibits the production of matrix proteins that maintain its structural integrity. That means cells will make less matrix, and potentially make their underlying condition worse in the long run. If cells aren't making the protein, then the disc's structural matrix will wear out faster."

That raises additional questions: everyone suffers some disc degeneration (due to aging itself as previously described), but how much of the degeneration is natural versus the amount of degeneration that is potentially self-inflicted with the glucosamine? Secondly, what is the molecular mechanism that causes glucosamine to interfere with the production of the proteoglycans?

Answering those questions, Dr. Kang says, would have a huge impact on public safety, as well as a financial impact because of the billions of dollars people spend on these products.

Dr. Kang says, as a surgeon, he generally approaches orthopaedic problems surgically, but the research being done by his team could result in nonsurgical solutions to patient problems.

"I could deprive myself of a lot of work, but it will always benefit patients more if we can avoid surgery altogether, or at least help define when surgery is the appropriate solution. We're getting there and it's exciting; it's good." ■

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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