ORTHO
RESTORE
FALL 2018
DEPARTMENT OF ORTHOPAEDIC SURGERY

Inside This Edition

CME Credit

Disclosures: *Drs. Fu, Lee, Watters, and Weiss report no relationships with proprietary entities producing health care goods and services. Dr. Anderst reports research/grant support from Smith & Nephew. Dr. Musahl is a consultant for Smith & Nephew.*

Instructions: *To take the CME evaluation and receive credit, please visit* ***UPMCPhysicianResources.com/Ortho****, and click on UPMC Ortho Restore Fall 2018.*

Accreditation Statement: *The University of Pittsburgh School of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The University of Pittsburgh School of Medicine designates this enduring material for a maximum of .5 AMA PRA Category 1 Credits™. Each physician should only claim credit commensurate with the extent of their participation in the activity. Other health care professionals are awarded .05 continuing education units (CEU), which are equivalent to .5 contact hours.*

Individualized Anatomic ACL Reconstruction: The Best Way

Volker Musahl, MD
Associate Professor and Chief, Division of Sports Medicine

Freddie H. Fu, MD, DSc (Hon), DPs (Hon)
Chairman, Department of Orthopaedic Surgery

There are upwards of 200,000 annual anterior cruciate ligament (ACL) reconstructions performed in the United States. Anatomically, the ACL is comprised of two bundles; it represents "a dynamic structure, rich in neurovascular supply and comprised of separate bundles which function together to facilitate normal knee kinematics"[19] (See Figure 1 on Page 2). Reconstruction procedures use a self-tendon (autograft) or donor tendon (allograft) to replace the deficient ligament.

The ACL is a dynamic structure, rich in neurovascular supply and comprised of distinct bundles, which function synergistically to facilitate normal knee kinematics in concert with bony morphology. Characterized by individual uniqueness, the ACL is inherently subject to both anatomic and morphological variations, as well as physiologic aging.

Despite the large number of surgical procedures, and extensive research over the past few decades totaling more than 22,000 research studies, there remains much room for improvement when treating patients with ACL injuries. Those who are treated nonoperatively typically are unable to return to pre-injury levels of activity.[17] As such, there has been an increased focus on treating these injuries surgically, particularly in young individuals who wish to maintain an active lifestyle and compete at high levels. Though outcomes after surgical reconstruction are generally

Continued on Page 2

Individualized Anatomic ACL Reconstruction *Continued from Page 1*

good with 55 percent of athletes being able to return to pre-injury activity levels,[20] failure rates still approach 10 to 15 percent.[16] Moreover, some patients who have had ACL reconstruction were noted to have higher rates of other injuries, such as to their meniscus (25 to 45 percent) and/or cartilage (44 percent).[18] Improving these outcomes has fueled ongoing research efforts on ACL reconstruction at the University of Pittsburgh.

Anatomic repair is the guiding principle in orthopaedic surgery. The late famed anatomist and University of Pittsburgh adjunct faculty, Pau Golanó, put it simply: "Look at nature, don't create nature." While simplified joint reconstruction techniques may be easier or faster, would it not be ideal to reconstruct the ACL so that the joint may function the way nature intended? Indeed, studies have shown that anatomic repair is beneficial in the long term, and not just for the knee. For example, patients who fracture their hip and have an anatomic repair, rather than a non-anatomic repair, typically have higher Harris hip scores, indicated less pain, and had better function and better range of motion.[1] As another example, when anatomic repair of the anterior talofibular ligament (one of the most commonly injured ankle ligaments) is not possible, a hybrid technique using elements of anatomic repair shows better Foot and Ankle Outcome Scores than a non-anatomic repair.[2] A similar pattern is emerging within the ACL literature, which for a long time deviated from the "anatomic" principle.

Anatomic ACL reconstruction is the functional restoration of the ACL to its native dimensions, collagen orientation, and insertion sites according to individual anatomy.

However, new biomechanical studies have demonstrated that an anatomically reconstructed ACL achieves a degree of stability comparable to the native, uninjured ligament — particularly when the knee is bent and turned inwards, which simulates a "cutting maneuver" during sports. On the other hand, a non-anatomically reconstructed ACL experiences more front-to-back and rotational knee motion during this simulated "cutting maneuver," which potentially could result in patients feeling knee instability and/or lacking confidence in their knee during performance.[3]

Comparing the intact ACL to anatomically reconstructed and non-anatomically reconstructed ones, forces are experienced in decreasing magnitude across the native ligament, anatomically reconstructed knee, and non-anatomically reconstructed knee[5]. It is important to remember that the loads and forces the knee experiences do not change, so if the non-anatomic graft experiences less force during knee motion, then it is highly plausible that the surrounding structures (e.g., meniscus and cartilage) are bearing the additional load. Disruptions of the normal knee motion after non-anatomic reconstruction have been shown to increase the long-term risk of knee osteoarthritis.[6]

The definition of an "anatomic" reconstruction can be variable. For example, some believe that to pursue anatomic reconstruction simply means to restore the knee to "as close as possible" original function; this is a subjective and poorly measured definition. Clearly, a less ambiguous definition of "anatomic reconstruction" is needed to reliably measure outcomes. Thus, Carola van Eck, MD, PhD, and Freddie H. Fu, MD, at the University of Pittsburgh Department of Orthopaedic Surgery, published a study that not only set forth a definition, but additionally established guidelines for how to

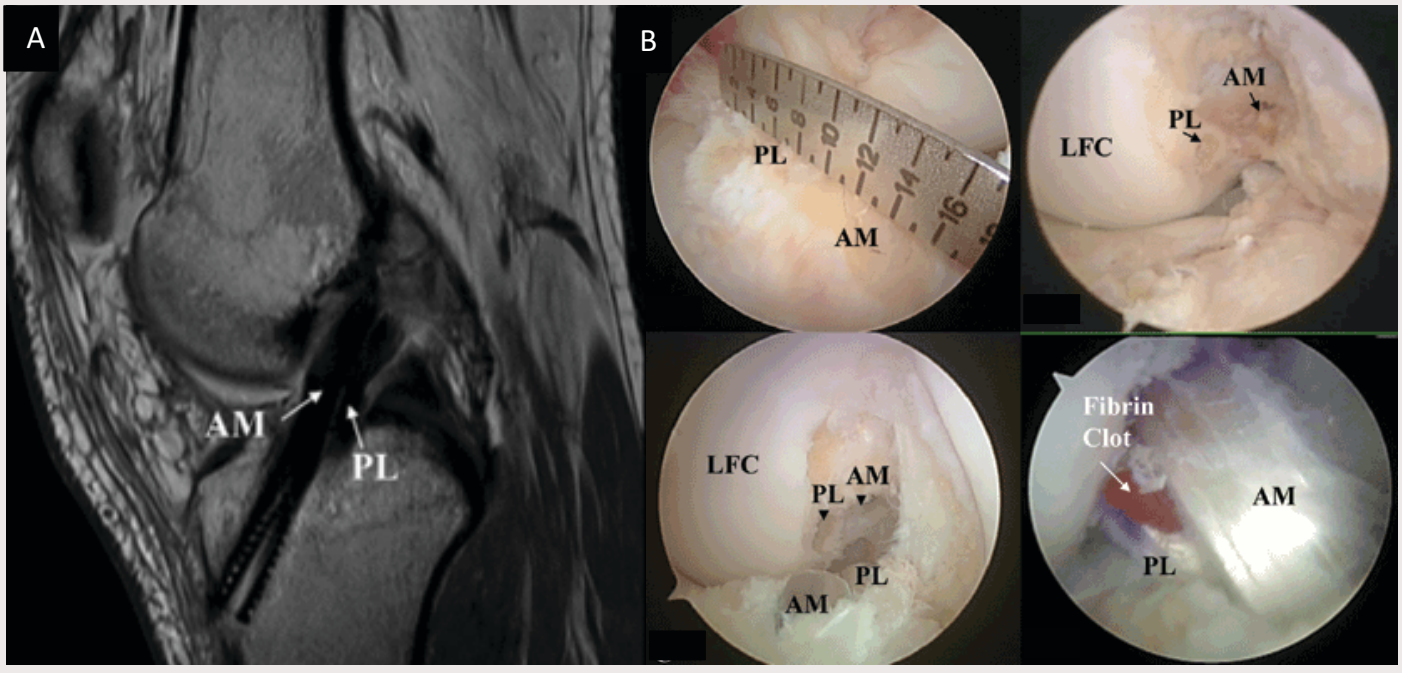


Figure 1. Anatomy of the ACL. (A) MRI demonstrating anatomic positioning of grafts in ACL reconstruction. (B) Arthroscopy images showing the anteromedial bundle (AM) and posterolateral bundle (PL) in relation to the lateral femoral condyle (LFC).

Figure 2. (A) Extensive preoperative planning allows individualized, anatomical ACL reconstruction to be performed for every patient. (B) With a host of graft options, and treating concomitant knee injuries, the ACL graft is sized to match each individual's unique anatomy.

consistently perform ACL reconstruction anatomically. "Anatomic ACL reconstruction is the functional restoration of the ACL to its native dimensions, collagen orientation, and insertion sites according to individual anatomy."[4] The peer-reviewed guidelines, in the form of a checklist, outlined the most important steps when performing anatomic reconstruction surgery. This not only objectifies what it means to perform an anatomic reconstruction, but it gives a score to assess the degree to which the native anatomy was restored.

From an anatomic standpoint, the ACL is not a static soft-tissue bridge between the tibia and femur; real-time imaging has shown that the ACL elongates by up to 20 percent with downhill running, an effect that is replicated in anatomically reconstructed knees.[7] The cross-section of the ACL also varies along its course, depending on the knee flexion angle and loadings experienced by the knee.[8] The ACL is widest at the bottom where it attaches to the tibia and becomes narrowest in the middle before gradually increasing to about 70 percent of its maximum size by the time it inserts into the femur.[9] There are two separate bundles in the ACL that have unique insertion sites and respond separately, but synergistically, to knee motion.[7] Additionally, the unique and dynamic ACL is complemented by unique bone structure. Much like our fingerprints, the bone shape within the knee varies from person to person. An anatomic reconstruction cannot be performed without also considering the anatomy of the surrounding bone, as someone with a narrow area on the femur where the ACL inserts may need an appropriately narrow ACL. Traditionally, this area was enlarged during surgery for better visualization of the femoral origin site, leading to a "one-size-fits-all" surgical approach and a non-anatomic reconstruction that may result in altered knee motion.[10]

Expanding on the concept of "anatomic reconstruction," there is growing evidence that an individualized anatomic approach may be the most appropriate. With a target of covering 50 to 80 percent of the original tibial insertion site area, the choice of graft size can be tailored to each patient so as to not be too small to be functionally incompetent or too large to restrict motion. Using this method, reconstructing just one ACL bundle can provide adequate coverage in patients with smaller anatomy while still providing excellent clinical outcomes.[10,11] While conclusions from some biomechanical, histological, and anatomical studies on cadaveric samples may demonstrate that the aforementioned "one-size-fits-all" surgery is sufficient, the advanced mean ages may not be generalizable to patients who typically undergo reconstruction. In fact, ACL strength may decrease by as much as 80 percent due to aging, with the posterolateral bundle experiencing the most change based on magnetic resonance imaging (MRI) studies.[12]

Rupture of the ACL results in anterolateral instability experienced by the patient subjectively as "giving way." The essential lesion is the ACL and, in some instances, the anterolateral complex (ALC) can be injured. The main structure of the ALC is the iliotibial band (ITB), and less importantly the anterolateral capsule with a variable thickening (30 to 40 percent) called the anterolateral ligament (ALL). A simple repair can be performed in complete ruptures. A lateral extra-articular tenodesis can be performed in especially high-grade instability patterns.

Thus, drawing definitive conclusions requires observing many patients for many years after all types of ACL surgery; but these studies also have their limitations. For example, studies have used the Multicenter Orthopaedic Outcomes Network (MOON) patient group to analyze non-anatomic vs. anatomic ACL reconstructions. These studies use a few outcome instruments, most notably the Knee Injury and Osteo-arthritis Outcome Score (KOOS) to support their conclusion that there is no difference in clinical outcomes between anatomic and non-anatomic reconstruction.[13] However, the KOOS was developed to measure out-comes for a wide range of knee pathologies, which is reflected by a broad questionnaire. While patient-reported outcomes may be a subjective analysis of how good an ACL reconstruction was, complication rates are far more objective. Data from the same MOON patient group also show that a non-anatomic ACL femoral tunnel position increased the odds of repeat surgery on the same knee when compared to a more anatomic femoral tunnel position.[14]

Continued on Page 13

Dynamic Imaging: Allowing UPMC Physicians to Analyze Spinal Stability More Closely

A Common Problem

As we age, the discs between the vertebral bones that comprise our spinal column lose water. This results in less flexible cushions between our bones that consequently cannot resist vertebral motion to the extent that they previously could. It is believed that this change in biomechanics is the primary event in a degenerative cascade that results in degeneration of the facet joints of the vertebral bodies and eventual macroinstablity.[1] This macroinstability can cause a condition known as degenerative spondylolisthesis, where the vertebral bodies slip forward potentially causing stenosis of the spinal canal or the vertebral foramen.

Degenerative spondylolisthesis is quite common, affecting an estimated six percent of the population.[2] Affected patients will usually notice mechanical back pain that is usually relieved with rest and sitting. Others may notice leg pain and discomfort while walking.[3] Regardless, these symptoms are uncomfortable and can have huge detrimental effects on a patient's quality of life. When a patient's symptoms fail to resolve with nonoperative management, including activity restriction, nonsteroidal anti-inflammatory medications, and physical therapy, it is appropriate to consider surgery.[4] However, which surgical technique should be employed is a topic that UPMC physicians and scientists have sought to address.[5]

A Gap in the Knowledge

Degenerative spondylolisthesis in the setting of symptomatic lumbar spinal stenosis is commonly treated with spinal fusion in addition to decompression with laminectomy and is accepted by many as the surgical standard of care.[6-9] Historically, it has been argued that decompression and laminectomy without fusion will destabilize the degenerated segment, resulting in progressive listhesis with eventual restenosis.[9-10] This perspective has become more controversial, however, as some studies have shown acceptable results with decompression alone,[10-12] while others demonstrate fusion confers superior clinical outcomes.[6-8,13]

Lumbar stability is a key component in the progression and contemporary management of degenerative spondylolisthesis. However, the use of a simple binary classification of "stable" or "unstable" is inadequate to fully characterize degenerative spondylolisthesis and may be insufficient to guide clinical decision making. Specifically, degenerative spondylolisthesis can be further defined by the presence or absence of dynamic instability. Dynamic instability may be defined as segmental anterior–posterior translation that occurs actively with flexion or extension of the lumbar spine. The presence of a dynamic phenotype has been shown to be an important risk factor for failure of decompression and laminectomy without fusion.[14]

Clinically, instability currently is identified by measuring anterior–posterior translation on static end-range flexion and extension lateral radiographs[15-16] with a change of greater than 3 mm considered by many to indicate dynamic instability.[17-23] However, ascertaining anterior–posterior translation on static clinical radiographs is problematic because not only is this technique prone to high measurement error and relatively poor reliability,[24] but it also precludes analysis of potentially important midrange kinematics. Mid-range kinematics could evince occult dynamic instability. UPMC spine surgeon **Joon Y. Lee, MD**, and Biodynamics Laboratory director **William J. Anderst, PhD**, realized that it is essential to characterize the translational behavior of lumbar degenerative spondylolisthesis in its entirety to deepen our understanding of this common clinical entity and to predict which patients are at higher risk of post-laminectomy destabilization necessitating fusion.

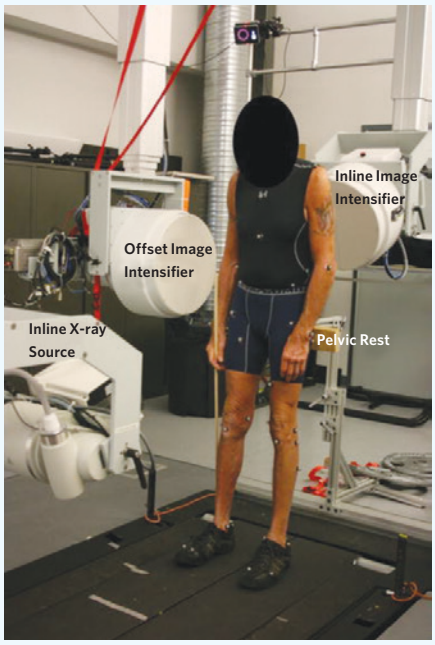


Figure 1. Positioning of the participant within the biplane dynamic stereo x-ray.

A High Tech Investigation

In order to tackle this conundrum, the Biodynamics Laboratory utilized a custom-built biplanar imaging system to perform motion analysis of patients with degenerative spondylolisthesis and control subjects. Participants performed continuous flexion and extension of their trunk from an upright position to as far as comfortably possible without knee bending (Figure 1).

A volumetric model-based tracking process was used to determine the position and orientation of each vertebra in the radiographic images (Figure 2).

Dynamic In Vivo Kinematic Analysis

Researchers at the Biodynamics Laboratory performed kinematic analysis on the diseased motion segments by utilizing vertebral anatomical coordinate systems. These coordinate systems were defined by three mutually orthogonal axes defined by placing virtual markers on the 3D bone models of each participant. Rotation and translation of the superior vertebra relative to the inferior vertebra were determined presurgery by relating frame-by-frame position of the superior vertebral anatomical coordinate systems relative to the inferior vertebral anatomical coordinate systems. Antero-posterior translation was measured as the antero-posterior distance from the manually identified point of the most inferior-posterior aspect of the superior vertebral body and the most superior-posterior aspect of the inferior vertebral body (Figure 3).

Static Clinical Radiographic Analysis

Researchers at the Biodynamics Laboratory also measured intervertebral flexion and extension and antero-posterior translation on presurgical upright and full flexion static radiographs via the standard measuring approach.[18,25] Statistical analysis was used to identify differences between static clinical imaging and dynamic imaging in terms of static listhesis in the neutral upright position, maximum AP translation (i.e., slip), and sagittal range of motion.

A Shift in Paradigm

This study found that static clinical flexion–extension radiographs appear to underestimate the true degree of antero-posterior translation that occurs during trunk flexion when compared with dynamic in vivo continuous kinematic analysis in patients with degenerative spondylolisthesis. Additionally, degenerative spondylolisthesis appears to exhibit distinct kinematic heterogeneity when compared with asymptomatic

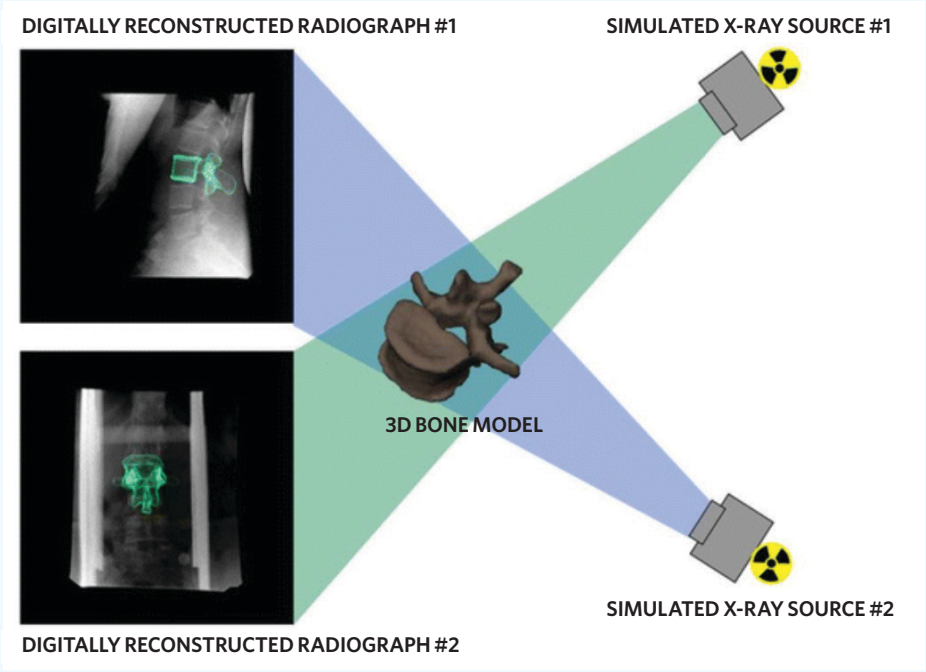


Figure 2. Two radiographic source and detector pairs. The volumetric model-based tracking technique. Each subject-specific 3D bone model created from CT is placed in a computer-generated reproduction of the biplane system (middle). Simulated X-rays are passed through the 3D bone model to generate digitally reconstructed radiographs (DRRs). Bone position and orientation are determined by an optimization process that matches the DRRs to the edge-enhanced radiographs. This process is completed for each vertebra.

age-matched controls. This has previously not been described in the literature, particularly during mid-range of motion. This study confirms that there may be more to the story that is not readily obtainable on current functional clinical imaging.

The study by the Biodynamics Laboratory offers insight as to a potential patient-specific factor that may predispose patients to unsuccessful outcomes with decompression only surgery. The study suggests a subset of patients with "occult" dynamic instability and may be a source of failure of decompression alone surgery. The Biodynamics Laboratory has found that the concept of clinical dynamic instability needs to be revised to include midrange motions and further studied for appropriate surgical considerations to be made.

Continued on Page 6

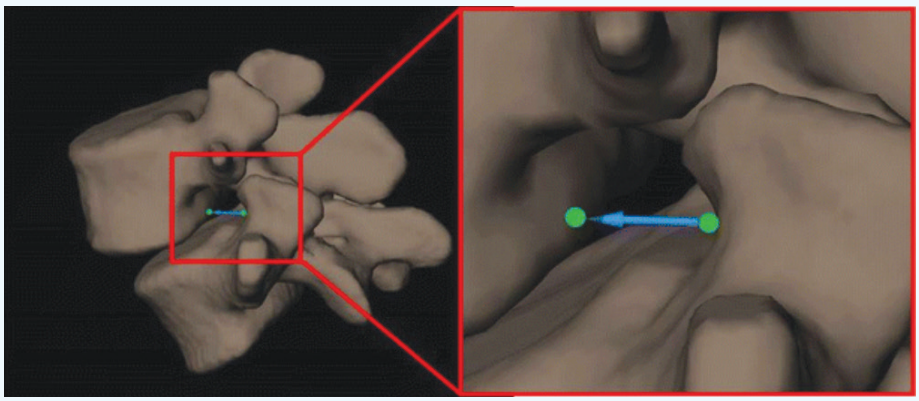


Figure 3. Kinematic analysis of in vivo kinematics. AP translation (slip) measured from in vivo kinematics. Landmarks placed on the inferior-posterior endplate of the superior vertebra and the superior-posterior endplate of the inferior vertebra were used to calculate dynamic slip during flexion.

Dynamic Imaging *Continued from Page 5*

Researchers at the Biodynamics Laboratory concluded that degenerative spondylolisthesis in fact represents a spectrum of aberrant motion with significantly greater kinematic heterogeneity than previously realized. Furthermore, they propose some patients exhibit so-called occult dynamic instability, namely antero-posterior translation not apparent using standard static clinical imaging, which may have important clinical implications for surgical management. Improving the detection of dynamic instability as well as furthering the understanding of different kinematic subgroups in degenerative spondylolisthesis will make possible more patient-specific rather than disease-specific surgical interventions. For their hard and innovative work, the Biodynamics Laboratory was awarded the prestigious best bioengineering study by the International Society for Study of the Lumbar Spine.

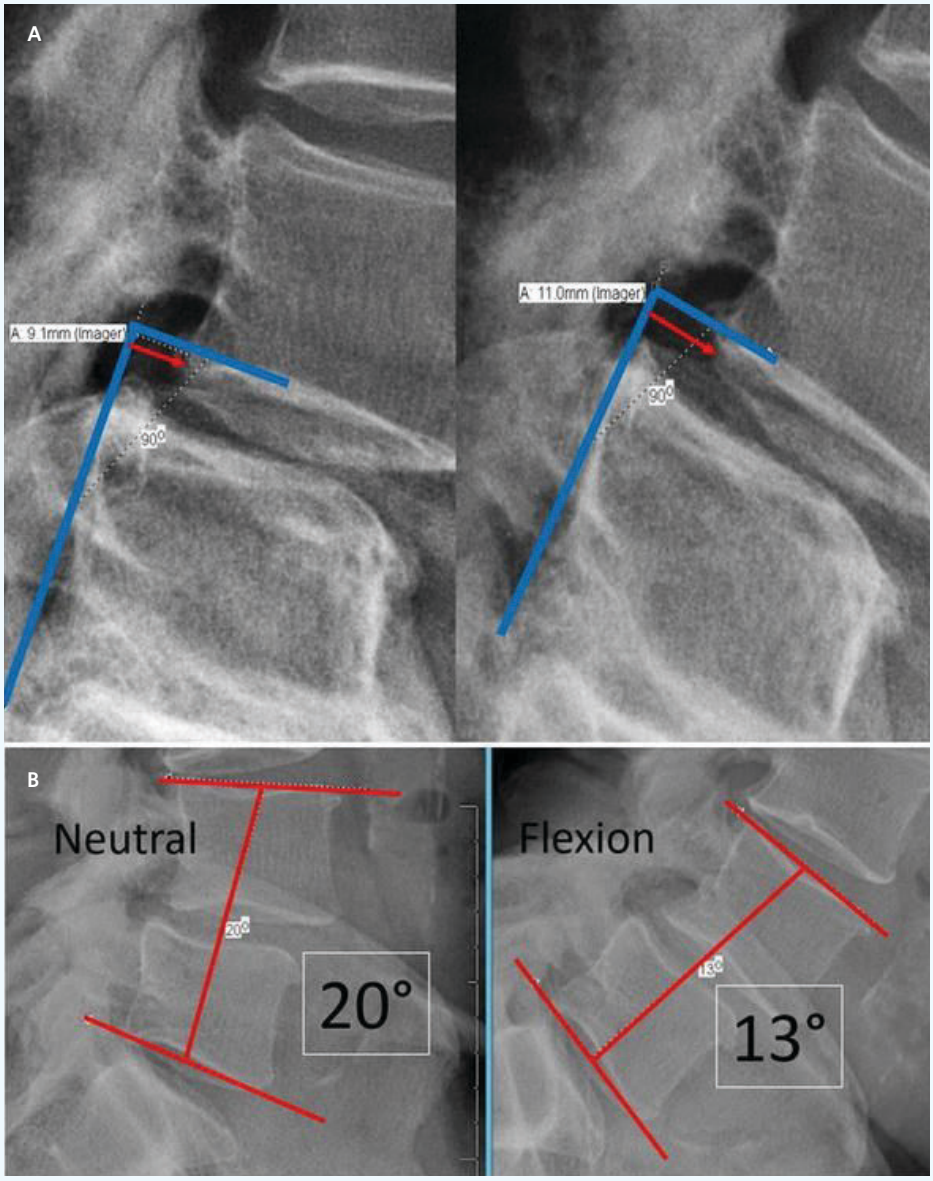


Figure 4. Clinical measurement of AP translation and intervertebral flexion on static radiographs. A) AP Translation. B) Intervertebral flexion.

References

1 Modic MT, Ross JS. Lumbar Degenerative Disk Disease." *Radiology.* 2007; 245.1: 43-61.

2 Kalichman L, et al. Spondylolysis and Spondylolisthesis: Prevalence and Association With Low Back Pain in the Adult Community-based Population. *Spine.* 2009; 34.2: 199.

3 Frymoyer, JW. Degenerative Spondylolisthesis: Diagnosis and Treatment." *JAAOS.* 1994; 2(1): 9-15.

4 Katz JN, Mitchel HB. Lumbar Spinal Stenosis. *NEJM.* 2008; 358(8): 818-825.

5 Dombrowski, ME, et al. ISSLS PRIZE IN BIOENGINEERING SCIENCE 2018: Dynamic Imaging of Degenerative Spondylolisthesis Reveals Mid-Range Dynamic Lumbar Instability Not Evident On Static Clinical Radiographs. *Euro Spine J.* 2018; 27(4): 752-762.

6 Resnick DK, Watters WC 3rd, Sharan A, Mummaneni PV, Dailey AT, Wang JC, Choudhri TF, Eck J, Ghogawala Z, Groff MW, Dhall SS, Kaiser MG. Guideline Update for the Performance of Fusion Procedures for Degenerative Disease of the Lumbar Spine. Part 9: Lumbar Fusion for Stenosis With Spondylolisthesis. *J Neurosurg Spine.* 2014; 21(1): 54–61.

7 Weinstein JN, Lurie JD, Tosteson TD, Zhao W, Blood EA, Tosteson AN, Birkmeyer N, Herkowitz H, Longley M, Lenke L, Emery S, Hu SS. Surgical Compared With Nonoperative Treatment For Lumbar Degenerative Spondylolisthesis. Four-Year Results in the Spine Patient Outcomes Research Trial (SPORT) *Randomized* and Observational Cohorts. *J Bone Joint Surg Am.* 2008; 91(6): 1295–1304.

8 Ghogawala Z, Dziura J, Butler WE, Dai F, Terrin N, Magge SN, Coumans JV, Harrington JF, Amin-Hanjani S, Schwartz JS, Sonntag VK, Barker FG 2nd, Benzel EC. Laminectomy Plus Fusion Versus Laminectomy Alone for Lumbar Spondylolisthesis. *New Engl J Med.* 2016; 374(15): 1424–1434.

9 Herkowitz HN, Kurz LT. Degenerative Lumbar Spondylolisthesis With Spinal Stenosis. A Prospective Study Comparing Decompression With Decompression and Intertransverse Process Arthrodesis. *J Bone Joint Surg Am.* 1991; 73(6): 802–808

10 Austevoll IM, Gjestad R, Brox JI, Solberg TK, Storheim K, Rekeland F, Hermansen E, Indrekvam K, Hellum C. The Effectiveness of Decompression Alone Compared With Additional Fusion for Lumbar Spinal Stenosis With Degenerative Spondylolisthesis: A Pragmatic Comparative Non-Inferiority Observational Study From the Norwegian Registry For Spine Surgery. *Eur Spine J.* 2017; 26(2): 404–413.

11 Forsth P, Olafsson G, Carlsson T, Frost A, Borgstrom F, Fritzell P, Ohagen P, Michaelsson K, Sanden B. A Randomized, Controlled Trial Of Fusion Surgery For Lumbar Spinal Stenosis. *N Engl J Med.* 2006; 374(15): 1413–1423.

12 Sigmundsson FG, Jonsson B, Stromqvist B. Outcome of Decompression With and Without Fusion In Spinal Stenosis With Degenerative Spondylolisthesis In Relation To Preoperative Pain Pattern: A Register Study Of 1624 Patients. *Spine J.* 2015; 15(4): 638–646.

13 Weinstein JN, Lurie JD, Tosteson TD, Hanscom B, Tosteson AN, Blood EA, Birkmeyer NJ, Hilibrand AS, Herkowitz H, Cammisa FP, Albert TJ, Emery SE, Lenke LG, Abdu WA, Longley M, Errico TJ, Hu SS. Surgical Versus Nonsurgical Treatment For Lumbar Degenerative Spondylolisthesis. *N Engl J Med.* 2007; 356(22): 2257–2270.

14 Blumenthal C, Curran J, Benzel EC, Potter R, Magge SN, Harrington JF Jr, Coumans JV, Ghogawala Z. Radiographic Predictors Of Delayed Instability Following Decompression Without Fusion For Degenerative Grade I Lumbar Spondylolisthesis. *J Neurosurg Spine.* 2013; 18(4): 340–346.

15 Takayanagi K, Takahashi K, Yamagata M, Moriya H, Kitahara H, Tamaki T. Using Cineradiography For Continuous Dynamic-Motion Analysis Of The Lumbar Spine. *Spine.* 2001; 26(17): 1858–1865

16 Anderson DG, Limthongkul W, Sayadipour A, Kepler CK, Harrop JS, Maltenfort M, Vaccaro AR, Hilibrand A, Rihn JA, Albert TJ. A Radiographic Analysis Of Degenerative Spondylolisthesis At The L4-5 Level. *J Neurosurg Spine.* 2012; 16(2): 130–134.

17 Quinnell RC, Stockdale HR. Flexion And Extension Radiography Of The Lumbar Spine: A Comparison With Lumbar Discography. *Clin Radiol.* 1983; 34(4): 405–411.

18 Boden SD, Wiesel SW. Lumbosacral Segmental Motion In Normal Individuals. Have We Been Measuring Instability Properly? *Spine.* 1990; 15(6): 571–576.

19 Hammouri QM, Haims AH, Simpson AK, Alqaqa A, Grauer JN. The Utility Of Dynamic Flexion-Extension Radiographs In The Initial Evaluation Of The Degenerative Lumbar Spine. *Spine.* 2007; 32(21): 2361–2364.

20 Majid K, Fischgrund JS. Degenerative Lumbar Spondylolisthesis: Trends In Management. *J Am Acad Orthop Surg.* 2008; 16(4): 208–215.

21 Bendo JA, Ong B. Importance Of Correlating Static And Dynamic Imaging Studies In Diagnosing Degenerative Lumbar Spondylolisthesis. *Am J Orthop (Belle Mead, NJ).* 2001; 30(3): 247–250.

22 Wood KB, Popp CA, Transfeldt EE, Geissele AE. Radiographic Evaluation Of Instability In Spondylolisthesis. *Spine.* 1994; 19(15): 1697–1703.

23 Phan KH, Daubs MD, Kupperman AI, Scott TP, Wang JC. Kinematic Analysis Of Diseased And Adjacent Segments In Degenerative Lumbar Spondylolisthesis. *Spine J.* 2015; 15(2): 230–237.

24 Danielson B, Frennered K, Irstam L. Roentgenologic Assessment Of Spondylolisthesis. I. A Study Of Measurement Variations. *Acta Radiol (Stockholm, Sweden: 1987).* 1988; 29(3): 345–351.

25 Even JL, Chen AF, Lee JY. Imaging Characteristics Of "Dynamic" Versus "Static" Spondylolisthesis: Analysis Using Magnetic Resonance Imaging And Flexion/Extension Films. *Spine J.* 2014; 14(9): 1965–1969.

26 Matz PG, Meagher RJ, Lamer T, Tontz WL Jr, Annaswamy TM, Cassidy RC, Cho CH, Dougherty P, Easa JE, Enix DE, Gunnoe BA, Jallo J, Julien TD, Maserati MB, Nucci RC, O'Toole JE, Rosolowski K, Sembrano JN, Villavicencio AT, Witt JP. Guideline Summary Review: An Evidence-Based Clinical Guideline For The Diagnosis And Treatment Of Degenerative Lumbar Spondylolisthesis. *Spine J.* 2016; 16(3): 439–448.

27 Penning L, Wilmink JT, van Woerden HH. Inability To Prove Instability. A Critical Appraisal Of Clinical-Radiological Flexion-Extension Studies In Lumbar Disc Degeneration. *Diagn Imaging Clin Med.* 1984; 53(4): 186–192.

28 Schroeder GD, Kepler CK, Kurd MF, Vaccaro AR, Hsu WK, Patel AA, Savage JW. Rationale For The Surgical Treatment Of Lumbar Degenerative Spondylolisthesis. *Spine.* 2015; 40(21): E1161–E1166.

Joon Y. Lee, MD
Professor and Clinical Director, Ferguson Laboratory for Orthopaedic and Spine Research, Department of Orthopaedic Surgery

William J. Anderst, PhD
Director, Biodynamics Laboratory, Department of Orthopaedic Surgery

Osteosarcoma Research at the Musculoskeletal Oncology Laboratory

The University of Pittsburgh Department of Orthopaedic Surgery Musculoskeletal Oncology Laboratory (MOL) began operation in 2010. The mission of the MOL is to understand the biology of primary and metastatic musculoskeletal malignancies. The MOL's team of clinicians, scientists, and students work toward the goal of translating these discoveries into effective treatments for our musculoskeletal oncology patients. The MOL is directed by **Kurt R. Weiss, MD**, and **Rebecca J. Watters, PhD**.

Osteosarcoma

A major area of focus of the MOL is osteosarcoma (OS), the most common primary malignancy of bone that mainly afflicts children and teens. As with other sarcomas, virtually all metastatic spread is to the lungs, which ultimately causes patient mortality. Before the chemotherapeutic era, overall survival with surgery alone was only 10 to 20 percent, with the majority of patients succumbing to overwhelming pulmonary metastases. Modern treatment paradigms employ neoadjuvant (preoperative) chemotherapy, surgery, and adjuvant (postoperative) chemotherapy. The combination of cytotoxic chemotherapy and surgical ablation has improved survival to approximately 65 percent in most large series.[1-12]

Although the addition of chemotherapy for the treatment OS has dramatically improved outcomes, enthusiasm is limited by several realities. Most importantly, the prognoses of children with OS have not improved in over three decades despite multiple clinical trials.[13-17] Children who present with pulmonary metastases at the time of diagnosis, or develop them during the course of their treatment, have especially poor prognoses of 15 to 30 percent survival.[6] Additionally, children who survive OS do so at great cost. OS chemotherapy is extraordinarily toxic, causing dose-dependent multi-organ toxicity.[18,19] **The two greatest obstacles to improvement of the prognoses of OS patients are:**

1. The absence of treatments that specifically target OS metastatic biology
2. The deleterious long-term consequences of chemotherapy for OS survivors

The efficacy of cytotoxic chemotherapy regimens in OS has likely reached its zenith, necessitating the discovery and application of more biologically intelligent approaches. The MOL is working to understand the biology of OS through genomic approaches and drug discovery.

OS Genomic Approaches

As metastatic biology is tied closely to the prognosis of OS, it would seem logical to compare OS primary and metastatic tumors from the same patient to observe whether and how the disease evolves from the primary to the metastatic setting. It would also be advantageous to observe whether there are differences in the primary tumors of patients who experienced the clinical event of metastasis versus those who did not. Indeed, large-scale molecular characterizations of patient-matched samples of primary tumors and matched metastases have demonstrated that metastatic lesions acquire genetic features distinct from primary tumors that are either clinically actionable or that confer therapeutic resistance.[20-22]

Paired primary OSs and lung metastases have proven difficult to both obtain and study, mainly due to their rarity. After resection or biopsy, patient tissues are formalin-fixed and paraffin-embedded (FFPE) for pathologic analysis. It is well-documented that formalin results in denaturation of nucleic acids, specifically in AT-rich regions, while it also causes severe degradation and hydrolysis of RNA, thus resulting in poor yields of nucleic acids.[23] Bone tissues undergo even further processing via decalcification, which is essential for embedding and sectioning of bone-containing specimens. OS primary

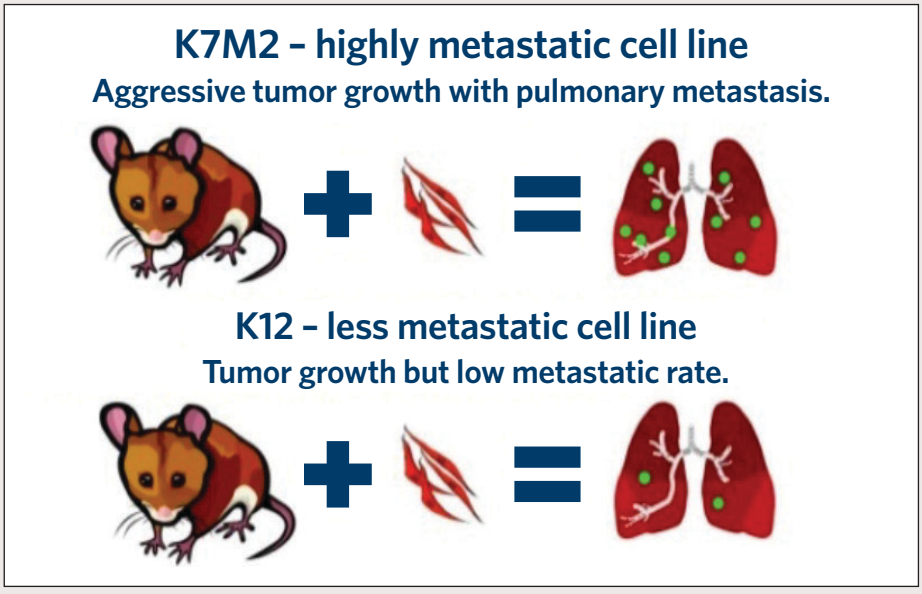


Figure 1. The Murine K series: 2 related cell populations with differing metastatic potentials.

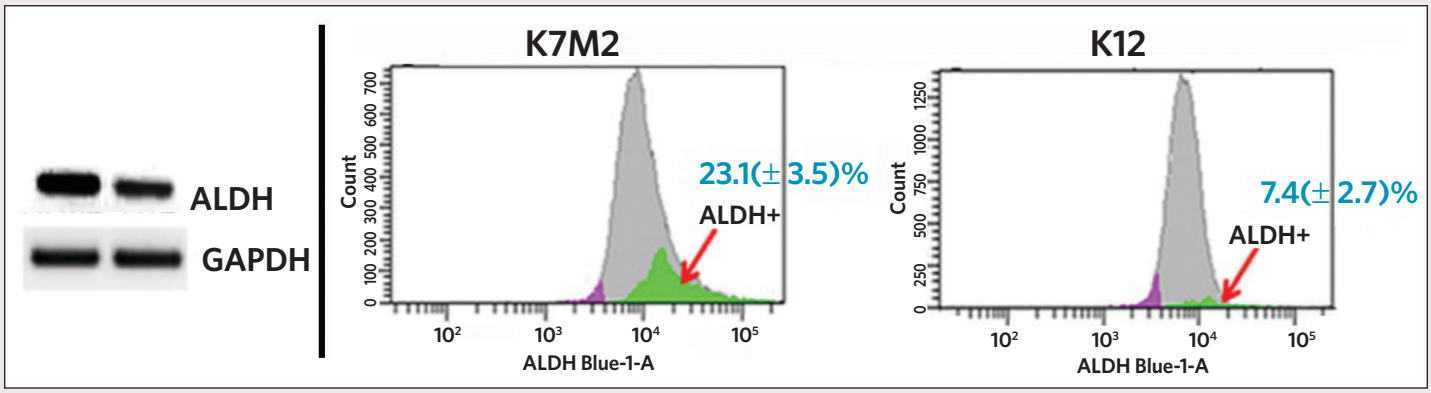


Figure 2. ALDH expression (left) and activity (right) as measured by PCR and the aldefluor FACS-based assay, respectively.

tumors and corresponding metastases preserved in FFPE blocks thus represent an untapped and vast resource for the molecular profiling of clinical OS samples. To access the genetic information and identify novel targets from this vital resource, we have previously developed a pipeline to extract and sequence the RNA from decalcified and FFPE bone metastases of breast cancer.[24]

For this ongoing OS study, we utilize matched trios (biopsy, primary OS, and lung metastasis) as well as pairs (biopsy and primary OS) from patients who did not develop metastases. These tissues reside in FFPE blocks that are obtained from the University of Pittsburgh Biospecimen Core, a certified honest broker facility at UPMC that maintains an IRB approval for collecting tissue and biological materials. De-identified clinical and biological patient data are collected under the approval of the University of Pittsburgh IRB (protocol# PRO17060270). This powerful study will be the first of its kind in OS and will hopefully yield insights into the factors and processes that drive OS metastases.

OS Drug Discovery

A spontaneously occurring OS from a BALB/c laboratory mouse was successfully cultured and single cell clones were grown by limiting dilution.[25] One of these clones, designated K12, displayed weak metastatic potential in vivo. Another clone, designated K7, had greater metastatic potential than K12. K7 was subsequently serially passaged through the lungs of experimental mice to yield a vigorously metastatic variant known as K7M2. As these cell lines are related but differ in their metastatic rates, K7M2 and K12 are powerful tools through which the factors that confer OS metastatic potential may be elucidated (Figure 1).[26-34]

One of the metastasis-associated factors that we have investigated is aldehyde dehydrogenase (ALDH).[30-32,35,36] ALDH is a tetrameric enzyme that oxidizes aldehydes to carboxylic acids and enables cells to resist oxidative stress. ALDH has been implicated as a cancer stem cell marker. Cells with high ALDH levels have demonstrated enhanced tumorigenicity in multiple cancer cell types.[37-47] We observed that highly metastatic K7M2 cells displayed greater resistance to oxidative stress than less metastatic K12 cells when challenged with H_2O_2. We hypothesized that diminished ALDH activity in K12 cells might explain this difference. Indeed, we demonstrated and published that ALDH expression and activity are significantly greater in K7M2 cells than in K12 cells (Figure 2).[30,31] After fluorescence-activated cell sorting (FACS) based on ALDH activity, ALDH-high K7M2 cells were more invasive than ALDH-low K7M2 cells through a semisolid matrigel matrix (Figure 3). These findings led us to treat the K series cells with the irreversible ALDH inhibitor, disulfiram (Dis). Dis, also known as Antabuse, is FDA-approved and has been used since the 1940s as a treatment for alcohol abuse. Only recently have its anti-neoplastic effects been recognized.[48-52] We were the first to suggest that Dis could play a role in the treatment of OS.[30]

Continued on Page 10

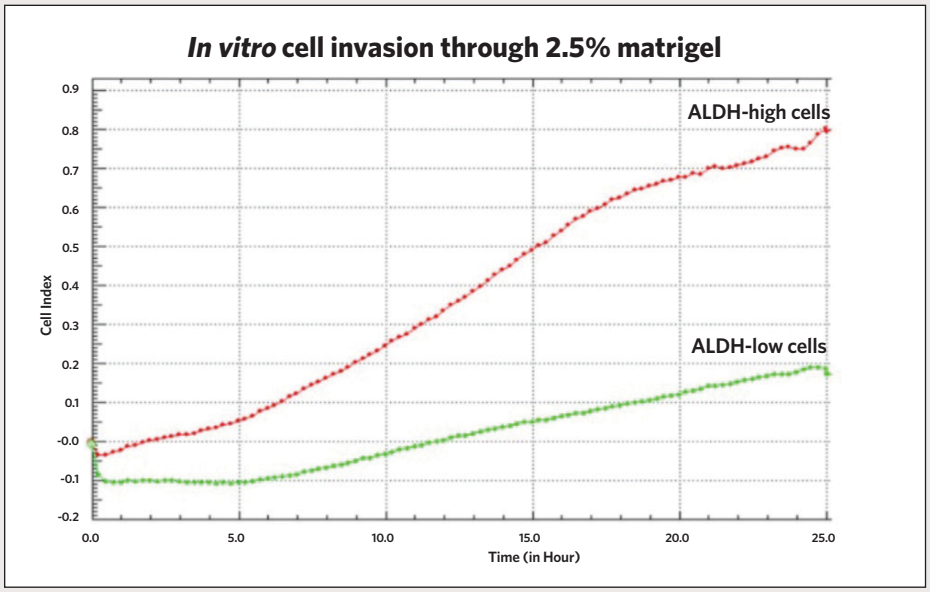


Figure 3. K7M2 cells with greater ALDH activity are more invasive through a semisolid Matrigel matrix than K7M2 cells with less ALDH activity.

Osteosarcoma Research *Continued from Page 9*

We observed and published that Dis alters K7M2 cell morphology, resulting in fewer invadopodia and greater uniformity of shape. Encouraged by these in vitro data, we sought to ascertain whether a correlation existed between the ALDH activity of human bone sarcoma patients' cultured cells and the clinical event of metastasis. Using our IRB-approved Musculoskeletal Oncology Tumor Registry and Tissue Bank, we evaluated the ALDH activity of the cells of 10 consecutive bone sarcoma patients from our UPMC musculoskeletal oncology clinic, and compared these with their metastatic histories. Using a cutoff of 3.1 percent ALDH-high cells, we observed 100 percent correlation of ALDH activity with the clinical event of metastasis in these patients. Furthermore, we noted a dose-dependent decrease in sarcoma cell viability with in vitro Dis treatment.[36] These data suggested that Dis should be further explored as a biologically intelligent treatment for anti-metastatic OS therapy.

We recently reported our findings from a preclinical study investigating the ability of disulfiram to affect OS metastasis in our validated orthotopic model.[27] We used this model to compare conventional doxorubicin (Dox) chemotherapy and Dis monotherapy. Briefly, 20 mice per group were treated with saline (20 ×μL daily subcutaneously), Dox (2 mg/kg/week via retro-orbital injection), and Dis (80 mg/kg/day subcutaneously). Interestingly, the only mortalities were in the Dox group (n=4), but this did not reach statistical significance. At the end of 10 weeks, two of 16 (12.5 percent) of Dox-treated animals had ICG evidence of metastases. Nine of 20 (45 percent) of Dis-treated animals had evidence of metastases, and there was not statistical significance between these groups. Both experimental groups were statistically superior to saline controls that had metastases in 19 of 20 (95 percent) animals. These data suggest that Dox and Dis monotherapy were therapeutically equivalent.

We also evaluated the primary tumors of amputated limbs via qPCR. Dis-treated animals had much lower Akt and higher Bad levels within their tumors than Dox-treated animals, demonstrating in vivo that Dis and Dox treatment elicit different responses within the tumor cells (Figure 4).

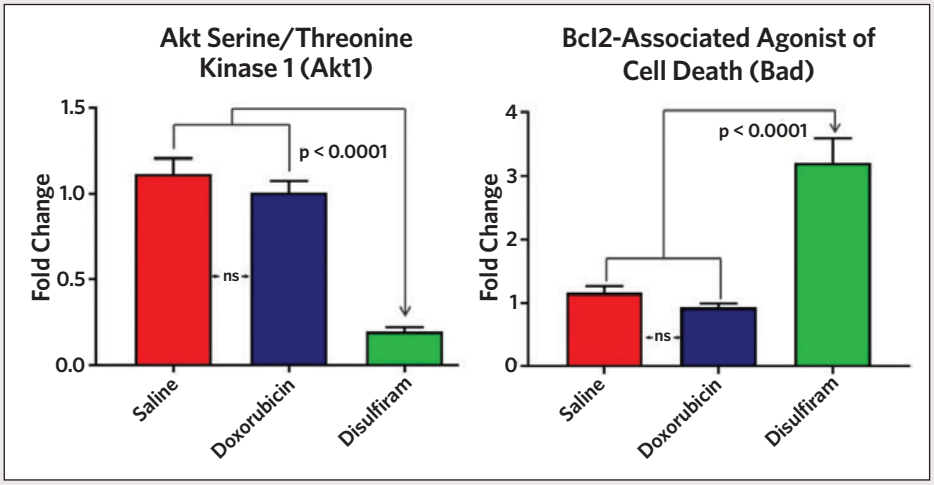


Figure 4. qPCR of mouse tumors of Dox- and Dis-treated mice.

Future Directions

As these recent studies indicate, the MOL is at the cutting edge of OS translational research. We anticipate that the results of our genomic experiments will yield new insights into OS metastatic biology. We will continue our Dis experiments with the hope of bringing novel anti-metastatic treatments to patients with OS and their families.

References

1 Luetke A, Meyers PA, Lewis I, Juergens H. Osteosarcoma treatment — where do we stand? A state of the art review. *Cancer Treat Rev.* 2014 May; 40(4): 523–532.

2 Bishop MW, Janeway KA, Gorlick R. Future directions in the treatment of osteosarcoma. *Curr Opin Pediatr.* 2016 Feb; 28(1): 26–33.

3 Whelan JS, Bielack SS, Marina N, Smeland S, Jovic G, Hook JM, et al. EURAMOS-1, an international randomised study for osteo-sarcoma: results from pre-randomisation treatment. *Ann Oncol.* 2015 Feb; 26(2): 407–414.

4 Bielack SS, Hecker-Nolting S, Blattmann C, Kager L. Advances in the management of osteosarcoma. [version 1; referees: 2 approved]. F1000Res. 2016 Nov 25; 5: 2767.

5 Bielack SS, Kempf-Bielack B, Delling G, Exner GU, Flege S, Helmke K, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. *J Clin Oncol.* 2002 Feb 1; 20(3): 776–790.

6 Bacci G, Briccoli A, Mercuri M, Ferrari S, Bertoni F, Gasbarrini A, et al. Osteosarcoma of the extremities with synchronous lung metastases: long-term results in 44 patients treated with neoadjuvant chemotherapy. *J Chemother.* 1998 Feb; 10(1): 69–76.

7 Bacci G, Ferrari S, Mercuri M, Bertoni F, Picci P, Manfrini M, et al. Predictive factors for local recurrence in osteosarcoma: 540 patients with extremity tumors followed for minimum 2.5 years after neoadjuvant chemotherapy. *Acta Orthop Scand.* 1998 Jun; 69(3): 230–236.

8 Bacci G, Picci P, Ferrari S, Casadei R, Brach Del Prever A, Tienghi A, et al. Influence of adriamycin dose in the outcome of patients with osteosarcoma treated with multidrug neoadjuvant chemotherapy: results of two sequential studies. *J Chemother.* 1993 Aug; 5(4): 237–246.

9 Meyers PA, Gorlick R. Osteosarcoma. *Pediatr Clin North Am.* 1997 Aug; 44(4): 973–989.

10 Mazanet R, Antman KH. Adjuvant therapy for sarcomas. *Semin Oncol.* 1991 Dec; 18(6): 603–612.

11 Williams RF, Fernandez-Pineda I, Gosain A. Pediatric Sarcomas. *Surg Clin North Am.* 2016 Oct; 96(5): 1107–1125.

12 Antman KH. Chemotherapy of advanced sarcomas of bone and soft tissue. *Semin Oncol.* 1992 Dec; 19(6 Suppl 12): 13–20.

13 Picci P. Osteosarcoma (osteogenic sarcoma). *Orphanet J Rare Dis.* 2007 Jan 23; 2: 6.

14 Carrle D, Bielack SS. Current strategies of chemotherapy in osteosarcoma. *Int Orthop.* 2006 Dec; 30(6): 445–451.

15 Reed D, Altiok S. Metastatic soft tissue sarcoma chemotherapy: an opportunity for personalized medicine. *Cancer Control.* 2011 Jul ;18(3): 188–195.

16 Blay JY. Updating progress in sarcoma therapy with mTOR inhibitors. *Ann Oncol.* 2011 Feb; 22(2): 280–287.

17 Penel N, Van Glabbeke M, Marreaud S, Ouali M, Blay JY, Hohenberger P. Testing new regimens in patients with advanced soft tissue sarcoma: analysis of publications from the last 10 years. *Ann Oncol.* 2011 Jun; 22(6): 1266–1272.

18 Moussa E, Zamzam M, Kamel A, Salah Z, Attia I, Gaber L, et al. Risk stratification and pattern of cardiotoxicity in pediatric Ewing sarcoma. *J Egypt Natl Canc Inst.* 2017 Mar 20; 29(1): 53–56.

19 Hamilton SN, Carlson R, Hasan H, Rassekh SR, Goddard K. Long-term Outcomes and Complications in Pediatric Ewing Sarcoma. *Am J Clin Oncol.* 2015 Jan 16;

20 Hugo W, Shi H, Sun L, Piva M, Song C, Kong X, et al. Non-genomic and immune evolution of melanoma acquiring MAPKi resistance. *Cell.* 2015 Sep 10; 162(6): 1271–1285.

21 Brastianos PK, Carter SL, Santagata S, Cahill DP, Taylor-Weiner A, Jones RT, et al. Genomic characterization of brain metastases reveals branched evolution and potential therapeutic targets. *Cancer Discov.* 2015 Nov; 5(11): 1164–1177.

22 Priedigkeit N, Hartmaier RJ, Chen Y, Vareslija D, Basudan A, Watters RJ, et al. Intrinsic subtype switching and acquired ERBB2/HER2 amplifications and mutations in breast cancer brain metastases. *JAMA Oncol.* 2017 May 1; 3(5): 666–671.

23 Srinivasan M, Sedmak D, Jewell S. Effect of fixatives and tissue processing on the content and integrity of nucleic acids. *Am J Pathol.* 2002 Dec; 161(6): 1961–1971.

24 Priedigkeit N, Watters RJ, Lucas PC, Basudan A, Bhargava R, Horne W, et al. Exome-capture RNA sequencing of decade-old breast cancers and matched decalcified bone metastases. *JCI Insight.* 2017 Sep 7; 2(17).

25 Schmidt J, Strauß GP, Schön A, Luz A, Murray AB, Melchiori A, et al. Establishment and characterization of osteogenic cell lines from a spontaneous murine osteosarcoma. *Differentiation.* 1988 Dec; 39(3): 151–160.

26 Fourman MS, Mahjoub A, Mandell JB, Yu S, Tebbets JC, Crasto JA, et al. Quantitative primary tumor indocyanine green measurements predict osteosarcoma metastatic lung burden in a mouse model. *Clin Orthop Relat Res.* 2018 Mar; 476(3): 479–487.

27 Mu X, Sultankulov B, Agarwal R, Mahjoub A, Schott T, Greco N, et al. Chick embryo extract demethylates tumor suppressor genes in osteosarcoma cells. *Clin Orthop Relat Res.* 2014 Mar; 472(3): 865–873.

28 Weiss KR, Cooper GM, Jadlowiec JA, McGough RL, Huard J. VEGF and BMP expression in mouse osteosarcoma cells. *Clin Orthop Relat Res.* 2006 Sep; 450: 111–117.

29 McManus MM, Weiss KR, Hughes DPM. Understanding the role of Notch in osteosarcoma. *Adv Exp Med Biol.* 2014; 804: 67–92.

30 Mu X, Isaac C, Schott T, Huard J, Weiss K. Rapamycin inhibits ALDH activity, resistance to oxidative stress, and metastatic potential in murine osteosarcoma cells. *Sarcoma.* 2013 Feb 14; 2013: 480713.

31 Mu X, Isaac C, Greco N, Huard J, Weiss K. Notch Signaling is Associated with ALDH Activity and an Aggressive Metastatic Phenotype in Murine Osteosarcoma Cells. *Front Oncol.* 2013 Jun 11; 3: 143.

32 Mu X, Patel S, Mektepbayeva D, Mahjoub A, Huard J, Weiss K. Retinal targets ALDH positive cancer stem cell and alters the phenotype of highly metastatic osteosarcoma cells. *Sarcoma.* 2015 Dec 24; 2015: 784954.

33 Yu S, Fourman MS, Mahjoub A, Mandell JB, Crasto JA, Greco NG, et al. Lung cells support osteosarcoma cell migration and survival. *BMC Cancer.* 2017 Jan 25; 17(1): 78.

34 Mu X, Brynien D, Weiss KR. The HDAC inhibitor Vorinostat diminishes the in vitro metastatic behavior of osteosarcoma cells. *Biomed Res Int.* 2015 Feb 17; 2015: 290368.

35 Weiss KR, Mu X, Agarwal R. Notch signaling and inflammation in a murine model of sarcoma-associated cachexia. *Cancer Res.* 2015; 75(15 Supplement): 3435.

36 Greco N, Schott T, Mu X, Rothenberg A, Voigt C, McGough RL, et al. ALDH activity correlates with metastatic potential in primary sarcomas of bone. *J Cancer Ther.* 2014 Mar 31; 5(4): 331–338.

37 Bortolomai I, Canevari S, Facetti I, De Cecco L, Castellano G, Zacchetti A, et al. Tumor initiating cells: development and critical characterization of a model derived from the A431 carcinoma cell line forming spheres in suspension. *Cell Cycle.* 2010 Mar 15; 9(6): 1194–1206.

38 Burger PE, Gupta R, Xiong X, Ontiveros CS, Salm SN, Moscatelli D, et al. High aldehyde dehydrogenase activity: a novel functional marker of murine prostate stem/progenitor cells. *Stem Cells.* 2009 Sep; 27(9): 2220–2228.

39 Charafe-Jauffret E, Ginestier C, Iovino F, Tarpin C, Diebel M, Esterni B, et al. Aldehyde dehydrogenase 1-positive cancer stem cells mediate metastasis and poor clinical outcome in inflammatory breast cancer. *Clin Cancer Res.* 2010 Jan 1; 16(1): 45–55.

40 Charafe-Jauffret E, Ginestier C, Iovino F, Tarpin C, Diebel M, Esterni B, et al. Aldehyde dehydrogenase 1–Positive cancer stem cells mediate metastasis and poor clinical outcome in inflammatory breast cancer. *Clin Cancer Res.* 2010; 16(1): 45–55.

41 Clay MR, Tabor M, Owen JH, Carey TE, Bradford CR, Wolf GT, et al. Single-marker identification of head and neck squamous cell carcinoma cancer stem cells with aldehyde dehydrogenase. *Head Neck.* 2010 Sep; 32(9): 1195–1201.

42 Croker AK, Goodale D, Chu J, Postenka C, Hedley BD, Hess DA, et al. High aldehyde dehydrogenase and expression of cancer stem cell markers selects for breast cancer cells with enhanced malignant and metastatic ability. *J Cell Mol Med.* 2009 Aug; 13(8B): 2236–2252.

43 Croker AK, Allan AL. Inhibition of aldehyde dehydrogenase (ALDH) activity reduces chemotherapy and radiation resistance of stem-like ALDHhiCD44+ human breast cancer cells. *Breast Cancer Res Treat.* 2012 May; 133(1): 75–87.

44 Deng S, Yang X, Lassus H, Liang S, Kaur S, Ye Q, et al. Distinct expression levels and patterns of stem cell marker, aldehyde dehydrogenase isoform 1 (ALDH1), in human epithelial cancers. *PLoS One.* 2010 Apr 21; 5(4): e10277.

45 Ginestier C, Wicinski J, Cervera N, Monville F, Finetti P, Bertucci F, et al. Retinoid signaling regulates breast cancer stem cell differentiation. *Cell Cycle.* 2009 Oct 15; 8(20): 3297–3302.

46 Ginestier C, Hur MH, Charafe-Jauffret E, Monville F, Dutcher J, Brown M, et al. ALDH1 is a marker of normal and malignant human mammary stem cells and a predictor of poor clinical outcome. *Cell Stem Cell.* 2007 Nov; 1(5): 555–567.

47 Honoki K, Fujii H, Kubo A, Kido A, Mori T, Tanaka Y, et al. Possible involvement of stem-like populations with elevated ALDH1 in sarcomas for chemotherapeutic drug resistance. *Oncol Rep.* 2010 Aug; 24(2): 501–505.

Continued on Page 12

Osteosarcoma Research *Continued from Page 11*

[48] Lun X, Wells JC, Grinshtein N, King JC, Hao X, Dang N-H, et al. Disulfiram when combined with copper enhances the therapeutic effects of temozolomide for the treatment of glioblastoma. *Clin Cancer Res.* 2016 Aug 1; 22(15): 3860–3875.

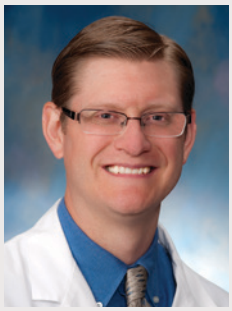
[49] Denoyer D, Pearson HB, Clatworthy SAS, Smith ZM, Francis PS, Llanos RM, et al. Copper as a target for prostate cancer therapeutics: copper-ionophore pharmacology and altering systemic copper distribution. *Oncotarget.* 2016 Jun 14; 7(24): 37064–37080.

[50] Kim JY, Cho Y, Oh E, Lee N, An H, Sung D, et al. Disulfiram targets cancer stem-like properties and the HER2/Akt signaling pathway in HER2-positive breast cancer. *Cancer Lett.* 2016 Aug 28; 379(1): 39–48.

[51] Skrott Z, Mistrik M, Andersen KK, Friis S, Majera D, Gursky J, et al. Alcohol-abuse drug disulfiram targets cancer via p97 segregase adaptor NPL4. *Nature.* 2017 Dec 14; 552(7684): 194–199.

[52] Papaioannou M, Mylonas I, Kast RE, Brüning A. Disulfiram/copper causes redox-related proteotoxicity and concomitant heat shock response in ovarian cancer cells that is augmented by auranofin-mediated thioredoxin inhibition. *Oncoscience.* 2014; 1(1): 21–29.

[53] Crasto JA, Fourman MS, Morales-Restrepo A, Mahjoub A, Mandell JB, Ramnath K, et al. Disulfiram reduces metastatic osteosarcoma tumor burden in an immunocompetent Balb/c or-thotopic mouse model. *Oncotarget.* 2018 Jul 10; 9(53): 30163–30172.



Kurt R. Weiss, MD
Associate Professor and Director,
Musculoskeletal Oncology Laboratory

Rebecca J. Watters, PhD
Research Assistant Professor, Co-Director,
Musculoskeletal Oncology Laboratory

UPMC PhysicianResources.com

Visit **UPMCPhysicianResources.com/Ortho** for the latest news, events, CME courses, and videos from the Department of Orthopaedic Surgery.

CME Courses

Orthopaedic Surgery Grand Rounds — Winter Sports Injuries
Presented by Jared A. Crasto, MD, and Carola F. van Eck, MD, PhD

Cervical Spondylotic Myelopathy
Presented by Joon Y. Lee, MD; Chris A. Cornett, MD; Jason O. Toy, MD

Active Management of Ocular Problems Following Concussion
Presented by Anne Mucha, DPT

Advances in the Clinical Management and Treatment of Concussion
Presented by Michael Collins, PhD

UPMC Concussion Program Exertion Therapy
Presented by Victoria Kochick, PT, DPT

Video Rounds

Approaches to Foot and Ankle Injuries
Presented by MaCalus V. Hogan, MD Chief, Division of Foot and Ankle Surgery

Trends in Hip Arthroscopy for Sports Injuries
Presented by Dharmesh Vyas, MD

Considerations on Repairing the Anterolateral Capsule
Presented by Volker Musahl, MD Medical Director, UPMC Center for Sports Medicine

Orthopaedic Surgical Treatments for Upper Extremity Injuries
Presented by Bryson Lesniak, MD

PRP and Tendon Injury
Presented by Kentaro Onishi, DO

Early Detection and Treatment of Osteosarcoma
Presented by Kurt R. Weiss, MD

Individualized Anatomic ACL Reconstruction *Continued from Page 3*

The most dreaded complication after ACL reconstruction is graft failure. The Multicenter ACL Revision Study (MARS) looked specifically at patients undergoing non-anatomic ACL reconstruction to identify risk factors or potential causes of repair failure. The study highlighted that prior lateral or medial meniscus removal was the most consistent predictors of revision, not technical factors.[15] However, the MARS group analyzed their own data, and biases may have affected these results. An independent third-party group analyzed the MARS database and found that of the 460 ACL reconstruction revision cases, 60 percent cited a specific "technical cause of failure,"[16] with improper position of the femoral tunnel being the most common. This may represent a downstream effect of a "one-size-fits-all" approach in the setting of diverse and unique bone morphology. Using the checklist set forth by *van Eck and Fu et al* can ensure that the reconstruction is performed in a reliably anatomic position and orientation, and that it also is best suited to the unique bony anatomy of the patient.[19] Existing and ongoing studies continue to show that individualized anatomic reconstruction of the ACL is not just another technique, but that it is the gold standard second only to an uninjured knee.[19]

References

1 Mears DC, et al. Displaced Acetabular Fractures Managed Operatively: Indicators of Outcome. *Clin Ortho Res.* 2003; 407: 173–186.

2 Kennedy JG, et al. Anatomic Lateral Ligament Reconstruction in the Ankle. *Am J Sports Med.* 2012; 40(10): 2309–2317.

3 Lim H-C, et al. Anatomical versus Non-Anatomical Single Bundle Anterior Cruciate Ligament Reconstruction: A Cadaveric Study of Comparison of Knee Stability. *Clin Ortho Surg.* 2012; 4(4): 249.

4 Eck CF Van, et al. Evidence to Support the Interpretation and Use of the Anatomic Anterior Cruciate Ligament Reconstruction Checklist. *J Bone Joint Surg.* 2013; 95(20).

5 Yagi M, et al. Biomechanical Analysis of an Anatomic Anterior Cruciate Ligament Reconstruction. *Am J Sports Med.* 2002; 30(5): 660–666.

6 Tashman S, Collon D, Anderson K, Kolowich P, Anderst W. Abnormal Rotational Knee Motion During Running After Anterior Cruciate Ligament Reconstruction. *Am J Sports Med.* 2004; 32: 975-83.

7 Tang J, et al. In Vivo Posterior Cruciate Ligament Elongation in Running Activity After Anatomic and Non-Anatomic Anterior Cruciate Ligament Reconstruction. *Knee Surg Sports Traumatol Arthrosoc.* 2017: 1177–1183. PMC. Web. 10 July 2018.

8 Fujimaki Y, et al. Quantitative In Situ Analysis of the Anterior Cruciate Ligament. *Am J Sports Med.* 2015; 44(1): 118–125.

9 Fujimaki Y, et al. Quantitative In Situ Analysis of the Anterior Cruciate Ligament: Length, Midsubstance Cross-Sectional Area, and Insertion Site Areas. *Am J Sports Med.* 2016; 118–125.

10 Hofbauer M, et al. The Concept of Individualized Anatomic Anterior Cruciate Ligament (ACL) Reconstruction. *Knee Surg Sports Traumatol Arthro.* 2014; 22(3): 979–986.

11 Hussein M, et al. Individualized Anterior Cruciate Ligament Surgery: a Prospective Study Comparing Anatomic Single- and Double-Bundle Reconstruction. *Am J Sports Med.* 2012; 40(8): 1781–1788.

12 Woo, S L-Y, et al. Tensile Properties of the Human Femur-Anterior Cruciate Ligament-Tibia Complex. *Am J Sports Med.* 1991; 19(3): 217–225.

13 Spindler KP, et al. Prognosis and Predictors of ACL Reconstructions Using the MOON Cohort: A Model for Comparative Effectiveness Studies. *J Ortho Res.* 2012; 31(1): 2–9.

14 Duffee A, et al. Transtibial ACL Femoral Tunnel Preparation Increases Odds of Repeat Ipsilateral Knee Surgery. *J Bone Joint Surg.* 2013; 95(22): 2035–2042.

15 Wright RW, et al. Descriptive Epidemiology of the Multicenter ACL Revision Study (MARS) Cohort. *Am J Sports Med.* 2010; 38(10): 1979–1986.

16 Morgan J, et al. Femoral Tunnel Malposition in ACL Revision Reconstruction. *J Knee Surg.* 2012; 25(05): 361–368.

17 Frobell RB, et al. A Randomized Trial of Treatment for Acute Anterior Cruciate Ligament Tears. *NEJM.* 2010; 363(4): 331–342.

18 Luc B, et al. Osteoarthritis Prevalence Following Anterior Cruciate Ligament Reconstruction: A Systematic Review and Numbers-Needed-to-Treat Analysis. *J Athletic Train.* 2014; 49(6): 806–819.

19 Burnham JM, Fu FH. The Importance of Individualized, Anatomic Anterior Cruciate Ligament (ACL) Reconstruction — for Annals of Joint Special ACL Edition. *Ann Joint.* 2017; 2: 36–46.

20 Davies GJ, et al. ACL Return to Sport Guidelines and Criteria. *Curr Rev Musculoskel Med.* 2017; 10(3): 307–314.

21 Ranuccio F, et al. Effects of Notchplasty on Anterior Cruciate Ligament Reconstruction: A Systematic Review. *Joints.* 2017; 5(3): 173–179.

Zlatan Ibrahimović is one of only three active soccer players in the world that have scored more than 500 goals. In April 2017, he had ACL reconstruction surgery at UPMC. Since his surgery, he has returned to peak form and has scored more than 20 goals for his current club, the LA Galaxy.

DEPARTMENT BRIEFS

Planning for the **2019 Panther Global Summit: Anatomic ACL Reconstruction Symposium** is underway and scheduled for June 5 – June 7, 2019, at the University Club in Pittsburgh, Pennsylvania. Co-directed by **Freddie Fu, MD, Volker Musahl, MD, James Irrgang, PhD, PT, Bryson Lesniak, MD,** and **Andrew Lynch, PhD, PT**, this three-day conference will feature inspiring and engaging presentations and live surgeries with 45 nationally and internationally recognized colleagues and leading sports medicine experts. Please save the date and plan to attend.

In November 2017, global leaders in the field of orthopaedic foot and ankle surgery recently gathered in Pittsburgh at UPMC for the International Consensus Meeting on Cartilage Repair of the Ankle. The first-of-its-kind meeting was the result of a year-long collaboration among national and international experts to develop a consensus on key focus areas like the diagnosis, treatment, and rehabilitation for common, yet complex, injury to the ankle. Local co-hosts for the meeting included **MaCalus V. Hogan, MD**, vice chairman of education and division chief of the Division of Foot and Ankle Surgery in the Department of Orthopaedic Surgery at UPMC; and Christopher D. Murawski from the University of Pittsburgh School of Medicine. The meeting included over 100 orthopaedic surgeons, physical therapists, radiologists, and scientists from 26 countries.

Following an eight-month search and selection process of international candidates by the search committee, **Rocky Tuan, PhD**, was unanimously recommended to serve as Vice-Chancellor and President of The Chinese University of Hong Kong (CUHK). His installation as the Eighth Vice-Chancellor and President of The Chinese University of Hong Kong (CUHK) was held in April 2018. Dr. Tuan will continue to oversee research in the Center for Cellular and Molecular Engineering in the Department of Orthopaedic Surgery and will maintain ongoing collaborations with his research colleagues at the University of Pittsburgh.

Twenty physicians from the **Department of Orthopaedic Surgery** were selected by *Pittsburgh Magazine* as 2018 **"Best Doctors."**

Promotions

MaCalus V. Hogan, MD, was promoted to associate professor of Orthopaedic Surgery in August 2018. Dr. Hogan is chief of the Division of Foot and Ankle Surgery, residency program director, and vice-chairman of education.

Albert Lin, MD, was promoted to associate professor of Orthopaedic Surgery in July 2018. Dr. Lin is a physician in the Division of Sports Medicine.

Peter Siska, MD, was promoted to associate professor of Orthopaedic Surgery in May 2018. Dr. Siska is a physician with the Division of Traumatology and General Orthopaedic Surgery.

Alicia Sufrinko, PhD, was promoted to assistant professor of Orthopaedic Surgery in January 2018. Dr. Sufrinko is a provider with the Division of Sports Medicine and the UPMC Sports Medicine Concussion Program.

James Wang, PhD, was appointed to the Albert B. Ferguson Jr, MD Endowed Chair in Orthopaedic Surgery. Dr. Wang is professor of Orthopaedic Surgery, vice-chairman for Orthopaedic Research, and serves as director of the MechanoBiology Laboratory.

Kurt R. Weiss, MD, was promoted to associate professor in Orthopaedic Surgery in February 2018. Dr. Weiss is a physician with the Division of Musculoskeletal Oncology and serves as director of the Musculoskeletal Oncology Laboratory.

New Faculty

Joel D. Himes, DO, joined the Division of Primary Care Sports Medicine in August 2018 as an assistant professor. Dr. Himes received his DO degree at Lake Erie College of Osteopathic Medicine in 2012. He completed a residency in emergency medicine at Saint Vincent Mercy Medical Center in June 2015, followed by the completion of a primary care sports medicine fellowship at UPMC in June 2018.

Stella Lee, MD, joined the Division of Musculoskeletal Oncology in September 2018 as an assistant professor. Dr. Lee received her medical degree at Saint Louis University in 2012. She completed orthopaedic surgery residency training at Indiana University in 2017, and completed fellowship training in orthopaedic oncology at Massachusetts General Hospital in July 2018.

Feng Li, MD, PhD, was appointed research assistant professor in December 2017, joining the research team in the MechanoBiology Laboratory.

Michael P. McClincy, MD, joined the Division of Sports Medicine in September 2018 as an assistant professor. Dr. McClincy graduated from the University of Pittsburgh School of Medicine in 2010. He remained at Pitt to complete his orthopaedic surgery residency training in 2015. He completed fellowship training at Boston Children's Hospital in Pediatric Sports Medicine in July 2016, and completed further fellowship training in pediatric and adolescent hip preservation in July 2018.

Jeremy Shaw, MD, joined the Division of Spine Surgery in September 2018 as an assistant professor. Dr. Shaw received his medical degree at Case Western Reserve University School of Medicine in 2012. He completed his orthopaedic surgery residency training at the University of California, San Francisco, and was a scholar in the UCLS Global Health Clinical Scholars Program. He completed fellowship training in adult and pediatric spine surgery at the University of Utah in July 2018.

Natalie Sandel Sherry, PsyD, joined the Division of Sports Medicine/Concussion in July 2018 as an instructor. Dr. Sandel received her master's and PsyD from Widener University Institute for Graduate Clinical Psychology in 2014 and 2016, respectively. She also earned her MBA from the Widener University School of Business Administration in 2016. She completed internships in the Department of Physical Medicine and Rehabilitation at Temple University in 2015, and the Department of Neurology at the Hospitals of the University of Pennsylvania in 2016. She has been a neuropsychology postdoctoral fellow under the direction of Dr. Micky Collins at the UPMC Sports Medicine Concussion Program.

Christine McDonough, PT, PhD, joined the Department of Physical Therapy, School of Health and Rehabilitation Sciences, and the Orthopaedic Surgery, School of Medicine as an assistant professor in January 2018. Dr. McDonough will collaborate with orthopaedic surgery faculty, doctoral and postdoctoral trainees, residents, and fellows to conduct clinical and health services research to inform best practices in orthopaedic surgery and rehabilitation. Her current research projects focus on the development and testing of patient-centered outcome measures using item response theory and computer adaptive testing methods; clinical and health services research in fall and fracture prevention and management for older adults; the measurement of function for work disability determination and rehabilitation; and cost-effectiveness of alternative management approaches for musculoskeletal disorders.

Faculty Notes

Freddie H. Fu, MD, chairman of the Department of Orthopaedic Surgery, gave numerous presentations and keynote lectures during 2018. Dr. Fu's speaking engagements included:

- The Raine Visiting Professor Lecture Series at the University of Western Australia, Perth, Australia, in February 2018. Dr. Fu's presentation was "Innovation in Sports Medicine: Is the Latest Always the Greatest?"
- Keynote Speaker at the International Cartilage Regeneration & Joint Preservation Society Meeting, Hong Kong, in April 2018. Dr. Fu's presentation was "The History of Cartilage Research."
- Philip A. Deffer, Sr., MD Endowed Lectureship at the UT Health San Antonio, San Antonio Texas, in April 2018. Dr. Fu's presentation was "Innovation in Sports Medicine: Is the Latest Always the Greatest?"
- Plenary Speaker at the AOA Continuing Orthopaedic Education and APKASS Congress, Sydney, Australia, in May 2018.

Dr. Fu received Elite Reviewer recognition by the *Journal of Bone and Joint Surgery* (JBJS). Reviewers on this list have completed four or more reviews in a one-year period, have maintained an exceptional review turnaround time, and consistently achieve review ratings in the top 1 and 2 percentile. Only two percent of JBJS reviewers have achieved this elite status. Elite Reviewers are recognized on the JBJS Elite Reviewers Program webpage and are acknowledged alongside the Editorial Board members in print and online.

UPMC has partnered in Ireland with Affidea, Bon Secours Health System Ltd., and ImPACT Applications Inc. to establish the first countrywide network for the diagnosis and treatment of concussion in people of all ages. **Micky Collins, PhD**, executive and clinical director of the UPMC Sports Medicine Concussion Program, will oversee The UPMC Concussion Network.

Effective July 2017, **MaCalus V. Hogan, MD**, was appointed program director, and **Joon Lee, MD**, was appointed associate director of the orthopaedic surgery residency program.

Thomas Lozito, PhD, was appointed to the Graduate Faculty in the Cellular and Molecular Pathology Program at the University of Pittsburgh School of Medicine.

Awards

The Alumni Council of the Geisel School of Medicine at Dartmouth selected **Freddie H. Fu, MD**, for the 2018 Distinguished Career Achievement Award. This award celebrates a Dartmouth alumnus who has made an impact on the medical or scientific field over the course of their career. Recipients were honored at the 2018 Alumni Awards Celebration in May 2018. Dr. Fu credits Dartmouth Medical School Dean James Strickler (a Pittsburgh native) for his advice and for encouraging him to work with the legendary Albert Ferguson, MD, a Dartmouth alum (DC '41, M '42), and chair of Orthopaedic Surgery at the University of Pittsburgh School of Medicine from 1953 to 1986.

Micky Collins, PhD, and **Anthony Kontos, PhD**, were one of five research teams selected to receive an Inaugural Research Grants from the Chuck Noll Foundation for Brain Injury Research for their project "Randomized Controlled Trial of a Precision Vestibular Treatment in Adolescents." The Chuck Noll Foundation for Brain Injury Research has awarded five grants to Pittsburgh research teams at the University of Pittsburgh, Carnegie Mellon University, and UPMC. The Foundation's Board of Directors approved grants totaling over $600,000.

Aaron Mares, MD, was recognized as an awardee in the 19th Annual 40 Under 40 Awards, sponsored by *Pittsburgh Magazine* and PUMP. The program recognizes 40 individuals under the age of 40 whose creativity, vision, and passion enrich the Pittsburgh region.

Richard Debski, PhD, Sene Polamalu, and **Volker Musahl, MD**, received the first-place award in the ORS Scientific Photo Competition for their photo "Bony Morphology of the Distal Femur."

The University of Pittsburgh received a $7.5M Department of Defense grant to support rehabilitation services for military personnel. Of this grant award, James Irrgang, PhD, chair of the University of Pittsburgh School of Health and Rehabilitation Sciences Department of Physical Therapy, and **Volker Musahl, MD**, chief of Sports Medicine in the Department of Orthopaedic Surgery, received $4.5 million for a large-scale trial to determine the optimal timing of surgery and rehabilitation for knee injuries.

UPMC
LIFE CHANGING MEDICINE
200 Lothrop St.
Pittsburgh, PA 15213-2582

DEPARTMENT OF ORTHOPAEDIC SURGERY

Centers of Excellence

- Adult Reconstructive Surgery and Musculoskeletal Oncology
- Concussion
- Foot and Ankle Surgery
- Hand, Upper Extremity, and Microvascular Surgery
- Orthopaedic Trauma
- Pediatric Orthopaedics
- Research
  - Biomedical
  - Clinical Outcomes
  - Computer-assisted Surgery
  - Kinematics
  - Regenerative Medicine
  - Stem Cell
- Spinal Surgery
- Sports Medicine and Shoulder Surgery

A Resource for You: UPMC Physician Resources brings world-class physicians and free educational opportunities to your computer. Learn new information while watching CME-accredited videos in the convenience of your home or office. Find out more at **UPMCPhysicianResources.com/Ortho**.

To learn more about the UPMC Department of Orthopaedic Surgery, please visit **UPMCPhysicianResources.com/Ortho**.

UPMC PHYSICIAN RESOURCES

University of Pittsburgh
School of Medicine
Department of Orthopaedic Surgery
Pittsburgh, Pennsylvania

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

ADDRESS CORRESPONDENCE TO:
Department of Orthopaedic Surgery
Kaufmann Medical Building
3471 Fifth Ave., Suite 1010
Pittsburgh, PA 15213
412-687-3900

A $19 billion world-renowned health care provider and insurer, Pittsburgh-based UPMC is inventing new models of patient-centered, cost-effective, accountable care. UPMC provides more than $900 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 85,000 employees, 40 hospitals, 600 doctors' offices and outpatient sites, and a 3.4 million-member Insurance Services Division, the largest medical insurer in western Pennsylvania. As UPMC works in close collaboration with the University of Pittsburgh Schools of the Health Sciences, *U.S. News & World Report* consistently ranks UPMC Presbyterian Shadyside on its annual Honor Roll of America's Best Hospitals. UPMC Enterprises functions as the innovation and commercialization arm of UPMC, and UPMC International provides hands-on health care and management services with partners around the world. For more information, go to UPMC.com.

USNW509015 AS/MP 9/18