Dr. Regis O’Keefe Visits Washington University Medical School

Dr. Regis O’Keefe is a national leader in the field of orthopaedics and musculoskeletal research. He is the Chair of the Department of Orthopaedics and Rehabilitation, and the Director of the Center for Musculoskeletal Research at the University of Rochester School of Medicine and Dentistry in Rochester, New York. Dr. O’Keefe is an orthopaedic oncologist, caring for patients with fragility fractures from osteoporosis, osteopenia, osteogenesis imperfect, and low vitamin D.

While visiting Washington University, Dr. O’Keefe gave a lecture entitled “Improving Orthopaedic Care Through Translational and Clinical Research: Opportunities and Challenges” the Arthur H. Stein, Jr. Lecture in the Department of Orthopaedic Surgery. He also gave the Louis V. Avioli Memorial Lecture entitled “Stem Cell Population and Their Regulation in Bone Repair.”

Dr. O’Keefe is a member of the External Advisory Committee for the Center for Musculoskeletal Research here at Washington University Medical Center.

For more information on the Cores, please click on the links below:
Core A—Administrative Core
Core B—Structure and Strength Core
Core C—In Situ Molecular Analysis Core
Core D—Mouse Genetics Models Core
Osteoporosis is endemic in western society and is always caused by a relative increase in the activity of osteoclasts, the unique resorptive cells of bone. Our laboratory focuses on the molecular and cellular mechanisms by which osteoclasts form and degrade the skeleton with the goals of understanding the pathogenesis of osteoporosis and identifying potential therapeutic targets. With the help of Core C, we have determined the significance of the \( \alpha v \beta 3 \) integrin and its outside-in activation induced signaling pathway including c-Src, Syk, ITAM proteins, the adapter SLP-76, the guanine nucleotide exchange factor, Vav3 and the Rho GTPases, Rac and cdc42.

Inside-out activation is an indirect process in which signals derived from an occupied receptor, typically that of a cytokine or growth factor, targets the intracellular domain of an integrin resulting in the conformation change of its external domain. The conformational change causes the integrin to bind its ligand with high affinity and transmit matrix-derived (outside-in) signals including those that organize the cytoskeleton.

The interaction of talin1 with \( \beta \)-subunit cytoplasmic domains is an essential step in integrin activation. Therefore, we are using mice in which talin has been specifically removed in mature osteoclasts.

This project required preparation of numerous high quality, TRAP stained histological sections of bone as well as whole calvariae which was expertly performed by Core C. The core also generated non-decalcified sections for dynamic analysis of bone formation. We quantified these sections histomorphometrically using Core C microscope and image analysis system.

**Figure 1:** TRAP-stained histological sections of proximal tibia of 8 wk old control (\(-\)) and CtsK-\( \times TLN1 \) (\( +\)) mice. (top panel 25X; middle panel 200X; lower panel 400X). It shows enhanced trabecular bone volume in the mutant mice, despite normal numbers of osteoclasts.