Musculoskeletal Research Center

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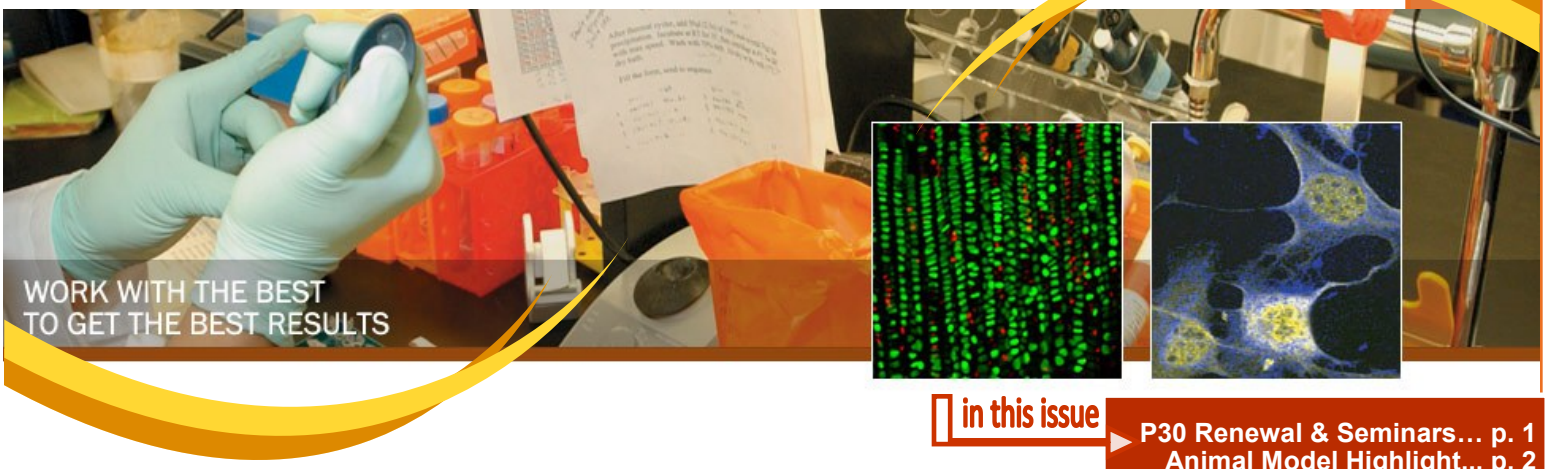
MUSCULOSKELETAL RESEARCH CENTER at Washington University



in this issue

P30 Renewal Submitted

On July 1, 2013, we submitted our competitive renewal for the P30 Core Center for Musculoskeletal Biology and Medicine Grant (award period: 2014-2018) to the National Institutes of Arthritis and Musculoskeletal and Skin Diseases). Thank you to everyone that participated!

Skeletal Biology & Pathophysiology Mini-Course

Date	Speaker	Topic
Aug 23th	Deborah Novack, MD., PhD Division of Bone and Mineral Diseases	Bone Pathology
Aug 30th	Linda Sandell, PhD Dept. of Orthopaedic Surgery	Osteoarthritis: New Approaches
Sept 6th	Chris Weihl, MD., PhD Dept. of Neurology	Muscle Disease
Sept 13th	Kathy Weilbaecher, MD Division of Oncology, Molecular Oncology Section	Bone Metastasis
Sept 20th	Roberta Faccio, PhD Dept. of Orthopaedic Surgery	Rheumatoid Arthritis and Inflammatory Bone
Sept 27th	Roberto Civitelli, MD Division of Bone and Mineral Diseases	Osteoporosis

4th Annual

Winter Symposium

February 12, 2014

***Guest Speaker*:**

Farshid Guilak, PhD

(Duke University Medical Center)

"Engineering New Therapies for Osteoarthritis"

For more information about the MRC and the Cores, please click here:
http://muscoloskeletalcore.wustl.edu

Please remember to include reference to support from the Musculoskeletal Research Center in your abstracts and publications.
Cite Grant # P30AR057235
from the National Institute Of Arthritis And Musculoskeletal And Skin Diseases.

NEMO SUMOylation Regulates Osteoclastogenesis and Bone Reporption.

Kyuhwan Shim, Yousef Abu-Amer

IKKγ/NEMO is the regulatory subunit of IκB kinase complex and regulates NF-kB activation. The *Nemo* gene is X-linked, and certain mutations in this gene result in Incontinentia Pigmenti and skeletal defects in human hemizygous females suggesting that NEMO regulates bone metabolism. To elucidate the role of NEMO in the skeleton, we used myeloid conditional deletions of *nemo* floxed mice. Phenotypic and molecular analyses showed that NEMO-deficiency in the myeloid compartment caused osteopetrosis owing to defective osteoclastogenesis. The function of NEMO is governed by post-translational modifications, primarily poly-ubiquitinations and sumoylations at multiple lysine residues which appear to be cell and signal specific. To this end, several viral constructs representing strategic point mutations at key residues in coiled-coil-2 and leucine zipper domains were utilized to examine their osteoclastogenic potential in NEMO deficient OCPs. Of these mutants, K270A -NEMO (K270 sumoylation-deficient) elicited higher osteoclastogenesis in NEMO-null compared to wild type cells. In contrast, expression of the mutant K319A NEMO into NEMO-null cells was lower and failed to restore osteoclastogenesis, indicating that K319-modification is essential for NEMO stability and function. To further investigate the physiological significance of K270-mediated osteoclastogenesis, we utilized the SUMO inhibitor Ginkgolic Acid (GA). sumoylation of NEMO has been known as important for localization of NEMO in the nucleus, and SUMO-free NEMO is directed to the cytosol where it stages IKKβ activation. GA showed enhanced osteoclastogenesis *in vitro* compared to DMSO (carrier)-treated control. We also tested the in vivo effects of GA on mouse bone remodeling and osteolysis. TRAP-stained histological sections of tibia indicated that the GA-treated mice showed significant increase in osteoclast number along the growth plates and decrease in trabecular bone mass. Thus, NEMO SUMOylation is crucial for regulation of osteoclasts and bone loss.

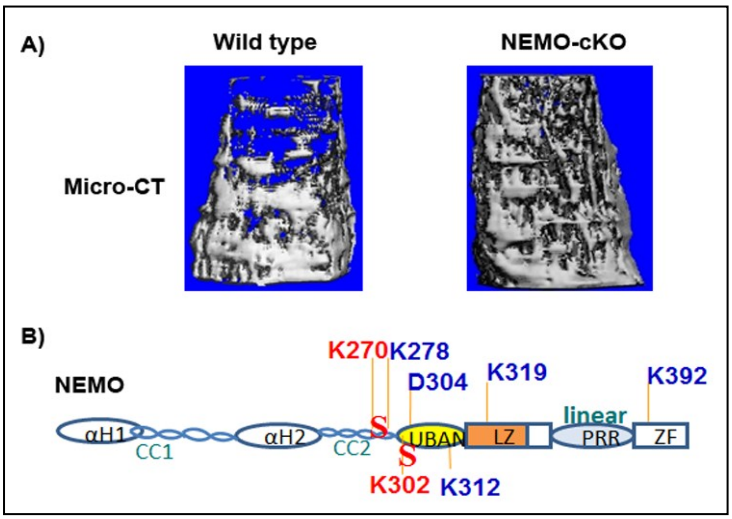


Fig 1: Upper panels represent micro-CT analysis of epiphyseal tibia from wild type and NEMO conditional myeloid knockout mice depicting denser bones (ostepetrosis) in the latter mice. Lower panel illustrates stick figure highlighting the different NEMO domains and the var-

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