Musculoskeletal Research Center

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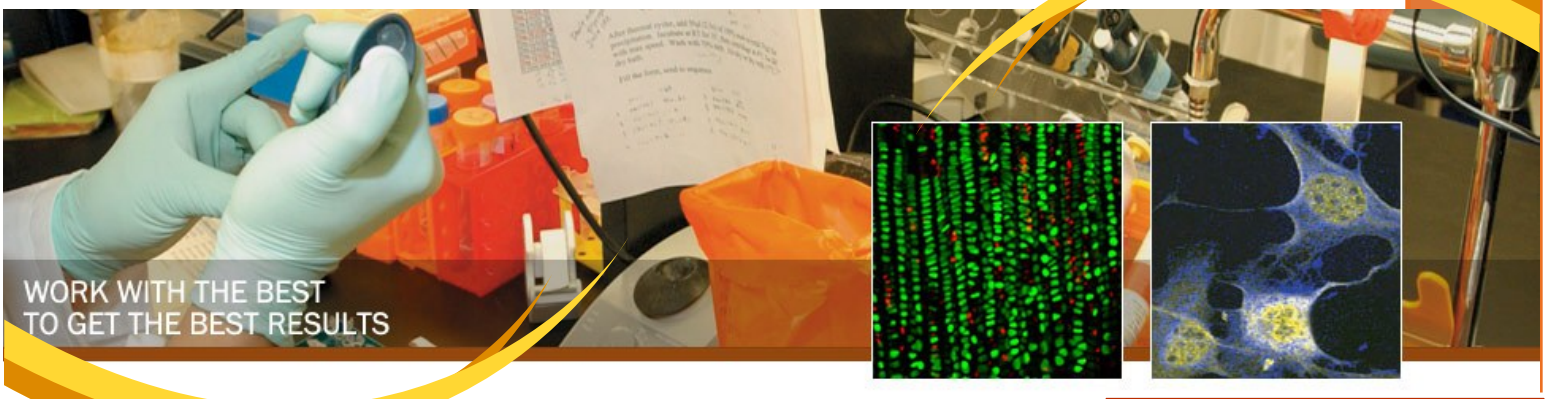
MUSCULOSKELETAL RESEARCH CENTER at Washington University



in this issue

Date Change P&F Grant Submission Date

Due to new NIH approval requirements, we have to change the due date for Pilot and Feasibility Projects. In order to allow the P&F projects to start at the beginning of the funding cycle (April 1st each year), we will need to move up the due date for the P&F proposals. This year, the P&F proposals will be due on November 14, 2014. Please follow the link below for additional information:

http://www.musculoskeletalcore.wustl.edu/content/Pilot-amp-Feasibility-Grants/2990/Call-for-Proposals.aspx

Musculoskeletal Winter Symposium
February 16, 2015

NEW Just In Time program

Just in Time program now available! Applicants may apply for up to $3,000 to support use of the MRC Cores. Please visit our website for more information and to download application form:

http://www.musculoskeletalcore.wustl.edu/content/Core/3035/A-Administrative-Core/Services/Just-In-Time-Funding.aspx

UPDATED! **Core D: Mouse Strain List**

(click to view list)

Avioli Musculoskeletal Seminar Series

Fridays @ 9am | BJCIH Bldg. 11th flr | A/B Conf. Rm.

Date	Speaker
10/03	Michael Whyte, MD *Saint Louis University*
10/10	TBD
10/17	Yihong Wan, PhD *Univ. of Texas, Southwestern Med. Ctr.*
10/24	Regis O'Keefe, MD, PhD– *WU Orthopaedic Surgery Dept.*
10/31	Emel Essen - *Long Lab, WU Orthopaedic Surgery Dept.*
11/07	T. Michael Underhill, PhD - *Univ. of British Columbia*

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.

Molecular Genetics of Rare Heritable Bone Diseases

Steven Mumm, PhD

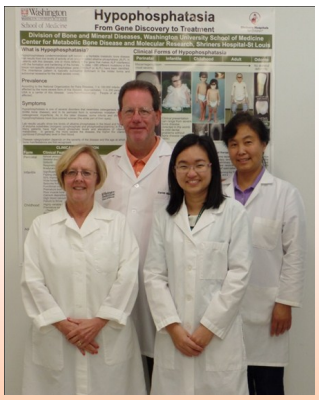


Fig. 1.
Dr. Mumm's current research team: (Left to right). Margaret Huskey, Dr. Mumm, Dr. Voraluck Phatarakijnirund (visiting faculty from Bangkok, Thailand), Shenghui Duan.

We focus on the molecular genetics of heritable metabolic bone diseases and skeletal dysplasias. The wide variety of the bone diseases studied includes hypophosphatasia (caused by mutations in the TNSALP gene), juvenile Paget's disease (osteoprotegerin gene), familial Paget's disease (SQSTM1), familial expansile osteolysis (RANK gene), Camurati-Engelmann disease (TGFB1), high bone mass disease (LRP5 and SOST), hypophosphatemic rickets (PHEX, DMP1, FGF23), and many others. We are also studying several families with unique bone diseases where the genetic defect is still unknown, using genetic approaches to identify the defective genes. My colleague, Michael Whyte, MD performs clinical, biochemical, etc. investigation of these patients and families at Shriners Hospital for Children and at Barnes-Jewish Hospital. Here, I highlight a few of our recent findings by focusing on two of these disorders.

As we reported in the New England Journal of Medicine in 2002, juvenile Paget's disease (JPD) features accelerated bone turnover caused by deactivating mutations in the osteoprotegerin (OPG) gene (Fig. 2). OPG is a decoy receptor that prevents RANK ligand from binding to its receptor, RANK, a major regulator of osteoclast development and activation. Since our initial discovery that OPG mutations cause JPD, we have reported several additional patients. We have in press, a manuscript describing a Bolivian girl who is clinically diagnosed with JPD, but instead has a unique 15 base pair duplication in the signal peptide of RANK.[1] We now call this new clinical variation, JPD2.

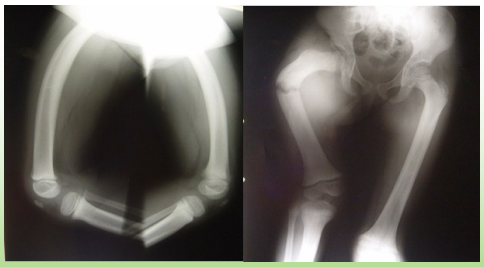


Fig. 2. Radiographs from JPD2 patient showing widened femurs with bowing, thickened cortices, coarse trabeculation, and subsequent fracture.

X-linked hypophosphatemic rickets (XLH) is a dominant disease caused by mutations in the PHEX gene, and results in short stature, bowed legs, and fractures (Fig. 3). Typically, genetic defects causing XLH disrupt the PHEX protein coding region, including single amino acid changes (missense), termination of protein translation (nonsense), or disruption of mRNA splicing. However, we have in press, a report of an unusual genetic defect near the polyadenylation signal for PHEX.[2] In our study of 52 sporadic XLH patients, we documented a gender bias where boys are more often, and more severely, affected than girls. Further, we find that this unique mutation is relatively common in the U.S. and results in a milder phenotype than other PHEX mutations that disrupt protein translation.

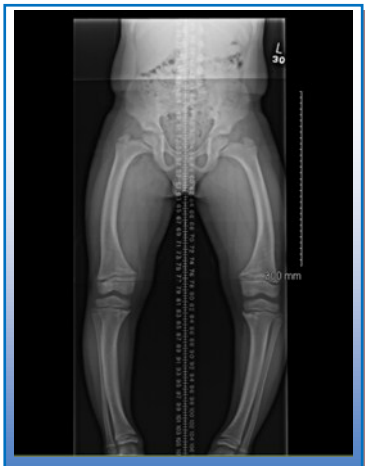


Fig. 3. Radiograph of typical XLH patient showing bowed lower extremities.

Our genetic studies of these rare heritable bone diseases generates new information that helps us understand and treat these disorders, but also provides new insight into the mechanisms of bone remodeling and mineralization.

Whyte MP, Tau C, McAlister WH, Zhang X, Novack DV, Preliasco V, Santini-Araujo E, Mumm S. (2014) Juvenile Paget's Disease With Heterozygous Duplication In TNFRSF11A Encoding RANK. Bone (in press). Read more...

Mumm S, Huskey M, Cajic A, Wollberg V, Madson KL, Wenkert D, Gottesman GS, McAlister WH, Whyte MP. (2014) PHEX 3'-UTR c.*231A>G Near the Polyadenylation Signal Is A Relatively Common, Mild, American Mutation That Masquerades As Sporadic Or X-Linked Recessive Hypophosphatemic Rickets. Journal of Bone and Mineral Research (in press). Read more...

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