National Bone Health Alliance/Rare Bone Disease Patient Network Workshop:

Mechanistic and Therapeutic Insights into Skeletal Biology Learned from the Study of Rare Bone Diseases

Thursday, September 11, 2014 | George R. Brown Convention Center | Houston, Texas

Workshop Chair:
Matthew Warman, MD, Boston Children’s Hospital

Workshop Organizer
Laura Tosi, MD, Children’s National Health System

Organized by:
September 11, 2014

Dear Colleagues,

It is our pleasure to welcome you to the National Bone Health Alliance/Rare Bone Disease Patient Network Workshop: Mechanistic and Therapeutic Insights into Biology Learned from the Study of Rare Bone Disease.

This workshop is possible because of germinal contributions by the Rare Bone Disease Patient Network, specifically the “First Advances in Rare Bone Diseases Scientific Conference” held at the NIH in 2008 and the Rare Bone Disease Research Summit “Expanding our Knowledge and Developing Strategies to Accelerate Research of Rare Bone Diseases” held in Baltimore, Maryland in 2012.

Your presence here today has helped us to meet our most important workshop goal, which is to engage a multi-disciplinary group of experts including researchers, clinicians, and patients with rare bone diseases to advance our understanding of skeletal biology and encourage the development of novel therapies to improve outcomes for individuals with both common and rare bone diseases. We hope you enjoy the workshop and take advantage of this opportunity to interact with other researchers, clinicians, and representatives from industry and patient-advocacy groups.

We are providing catered breakfast, coffee breaks, and lunch during the conference and there will be plenty of hors d’oeuvres and refreshments at the after-workshop reception. Please take advantage of these breaks to engage attendees and speakers in lively debate and discussion. Our speakers will be at marked tables during the reception, so that you can find them easily.

We would also like to acknowledge the supporting organizations for their outstanding commitment to making this meeting a success. Many thanks to ASBMR for providing the opportunity to bring our message to all of their meeting attendees and for their outstanding logistical support; the National Bone Health Alliance for bringing together a wonderful working group that planned this meeting and the Rare Bone Disease Patient Network for connecting the patient advocacy organizations and the scientific community to develop the outstanding program agenda. This meeting is a true example of partnership at its best.

On behalf of the many volunteers and sponsors who made this event possible, we thank you for joining us at this workshop.

Sincerely,

Matthew Warman, MD
Laura Tosi, MD
# MECHANISTIC AND THERAPEUTIC INSIGHTS INTO SKELETAL BIOLOGY LEARNED FROM THE STUDY OF RARE BONE DISEASES

**Thursday, September 11, 2014 | George R. Brown Convention Center | Houston Texas, USA**

## MORNING SESSION

<table>
<thead>
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<th>Time</th>
<th>Session I, Part I</th>
<th>Moderator: Jacqueline Hecht, PhD, University of Texas, Houston</th>
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<tbody>
<tr>
<td>8:15 AM</td>
<td>Welcome</td>
<td>Drs. Laura Tosi and Matthew Warman</td>
</tr>
<tr>
<td>8:30 - 9:00 AM</td>
<td>The Nosology of Rare Bone Diseases</td>
<td>Dr. Deborah Krakow University of California, Los Angeles</td>
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**WHAT RARE BONE DISEASES HAVE TAUGHT US ABOUT ...**

<table>
<thead>
<tr>
<th>Time</th>
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<tr>
<td>9:00 - 9:30 AM</td>
<td>Osteoblasts and Osteocytes</td>
<td>Dr. Lynda Bonewald University of Missouri, Kansas City</td>
<td>10:30 - 11:00 AM</td>
<td>Chondrocytes</td>
<td>Dr. Maurizio Pacifici Children’s Hospital of Philadelphia</td>
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<tr>
<td>9:30 - 10:00 AM</td>
<td>Osteoclasts</td>
<td>Dr. Stuart Ralston University of Edinburgh, UK</td>
<td>11:30 - 12:00 PM</td>
<td>Vasculature</td>
<td>Dr. Bjorn Olsen Harvard School of Dental Medicine</td>
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<td>12:00 - 12:30 PM</td>
<td>Matrix</td>
<td>Dr. Brendan Lee Baylor College of Medicine, Houston</td>
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*Coffee break*

**Boxed lunches available for pick up in Ballroom Pre Function**

## LUNCHTIME PLENARY LECTURE

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<tr>
<th>Time</th>
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<tbody>
<tr>
<td>12:45 - 1:45 PM</td>
<td>The Transcriptional Landscape in the Skeleton</td>
<td>Dr. Andrew McMahon University of Southern California</td>
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<tr>
<td>Session II, Part I</td>
<td>Moderator: Dr. Christopher Niyibizi, Penn State College of Medicine</td>
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**AFTERNOON SESSION**

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<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker</th>
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<tr>
<td>2:00 - 2:30 PM</td>
<td>Treating Osteoclast Over and Under-Activity</td>
<td>Dr. Graham Russell University of Oxford, UK</td>
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<tr>
<td>2:30 - 3:00 PM</td>
<td>Targeting Enzymes and Other Proteins to Bone</td>
<td>Dr. Michael Whyte Washington University, St. Louis</td>
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<tr>
<td>3:30 - 4:00 PM</td>
<td>Antibody-Based Modulation of Extracellular Signaling</td>
<td>Dr. Matthew Warman Boston Children’s Hospital</td>
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<td></td>
<td><em>Coffee break</em></td>
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**STRATEGIES FOR IMPROVING SKELETAL HEALTH**  
**LESSONS LEARNED FROM RARE BONE DISORDERS...**

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<th>Session II, Part II</th>
<th>Moderator: Dr. Laura Tosi, Children’s National Health System</th>
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<tr>
<td>4:30 - 5:00 PM</td>
<td>Small Molecular Inhibition of Intracellular Signaling</td>
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<tr>
<td>5:00 - 5:30 PM</td>
<td>Synthetic Polypeptides</td>
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<tr>
<td>5:30 - 5:35 PM</td>
<td>Wrap-Up</td>
</tr>
</tbody>
</table>
| 5:35 - 8:00 PM     | **RECEPTION AND POSTER SESSION**  
*(Speakers will be at assigned tables from 6:00 - 7:00 PM)* |
MODERATOR
Jacqueline Hecht, PhD, University of Texas Medical School, Houston, TX

Dr. Hecht is Professor and Division Director of the Pediatric Research Center at the University of Texas Medical School at Houston and Associate Dean for Research at University of Texas School of Dentistry. She is a board certified PhD Medical Geneticist with extensive clinical expertise in common birth defects, skeletal dysplasia (dwarfing conditions) and orthopedic syndromes. Her current research focuses on gene discovery studies in single gene disorders of unknown etiology and complex birth defects including nonsyndromic cleft lip and palate and, understanding the molecular mechanisms that contribute to the pathology that underlies pseudoachondroplasia, a dwarfing condition. Her lab identified that mutations in cartilage oligomeric matrix protein (COMP), a large extracellular matrix protein, are the cause of pseudoachondroplasia. COMP mutations cause a dominant negative effect such that the mutant protein cannot be exported to the extracellular matrix and is retained in the ER of growth plate chondrocytes. Using their transgenic MT-COMP mouse, the Hecht lab defined the molecular mechanisms that contribute to MT-COMP retention and are assessing therapeutic interventions to reduce the intracellular load of MT-COMP. Research in Dr. Hecht’s lab also contributed to a better understanding of the natural history of achondroplasia and hereditary multiple exostosis and to the identification of the EXT2 gene.
Rare bone diseases or osteochondrodysplasias are a heterogeneous group of approximately 450 disorders associated with more than 300 disease-producing genes. Osteochondrodysplasias primarily affect the skeleton, particularly cartilage and bone, though as research advances we have learned that these disorders also affect tendon, ligament, and muscle functions. Dysostoses by definition are disorders that have abnormalities in a single or group of bones, but many of them have also have a generalized effect on the skeleton. Osteochondrodysplasias and dysostoses disorders are inherited in autosomal dominant, autosomal recessive, X-linked, and pseudo-autosomal dominant manners. Copy number variations are particularly common in the dysostoses, particularly those that affect the limb.

As it became evident in the 1970s that these disorders were clinically and radiographically heterogeneous, experts in the areas of clinical genetics, pediatrics, radiology, biochemistry, and molecular biology met to agree on the classification of these increasingly delineated disorders. Early classification schemes were primarily built on shared radiographic and clinical findings, but as technology advanced, newly found histologic and biochemical abnormalities helped group disorders that shared pathology, even prior to gene discovery. Appreciating that the nonlethal diastrophic dysplasia and lethal achondrogenesis IB had common cartilage growth plate abnormalities (“rings or space around the chondrocyte”) linked these two disorders prior to the discovery that SLC26A2 was the responsible gene supporting allelic heterogeneity, now a large theme among these disorders.

With advancements in gene discovery, the molecular basis has been uncovered in the majority of these disorders. This has lead to the further recognition of new disorders and has informed us on the repertoire of genes and pathways that are involved in cartilage and bone patterning, linear growth and homeostatic maintenance. Why classify these disorders in the era of rapid gene discovering? Classifying disorders based on differing criteria, clinical/radiographic, age of onset, biochemical, and molecular basis accomplishes different functions. It allows us to define allelic series of disorders and locus heterogeneity in similar appearing disorders aiding clinicians in directing mutational analysis and natural history. While biochemical and molecular classification that define gene families with similar mechanisms of disease offer insight into functional consequences expanding our knowledge of the genes and pathways that control cartilage and bone homeostasis.


Dr. Krakow is currently a Professor of Orthopaedic Surgery and Human Genetics at the David Geffen School of Medicine at UCLA, Los Angeles, CA. Dr. Krakow received her Bachelor of Science at Arizona State University and her M.D. at the Chicago Medical School. She completed fellowships in Maternal-Fetal Medicine and Medical Genetics. She began her studies in the area of osteogenesis imperfecta under the mentorship of Daniel H. Cohn, PhD. Dr. Krakow is interested in the prenatal findings in osteogenesis imperfecta, as well as the understanding its underlying genetic mechanisms. She is a member of the OI Foundation’s Medical Advisory Council and a speaker at the Foundation’s biennial National Conference on OI.
Osteoblast and Osteocyte Biology

Lynda F. Bonewald, PhD, University of Missouri-Kansas City School of Dentistry, Kansas City, MO

The osteoblast is descended from mesenchymal stem cells to become a miniature factory for the production of bone matrix proteins, primarily collagen type 1. These cells line up to form a phalanx that simultaneously produces, in unison, osteoid that will become mineralized bone matrix. The osteoblast appears to have three fates. While producing osteoid, it can differentiate into an osteocyte, becoming embedded in its matrix. Or once sufficient osteoid has been produced, the osteoblast may quiesce and flatten to become a lining cell covering the new bone surface, or it may undergo a programmed, orderly cell death when no longer needed. Osteocytes are matrix embedded bone cells, once thought to be relatively inactive, now known to function as endocrine secretory cells and to function in mechanosensation and regulation of bone remodeling. Specific proteins are expressed in a stage specific manner during differentiation of the pre-osteoblast to the osteoblast, early osteocyte and finally to the mature osteocyte. Mutations in many of the genes coding for these proteins are responsible for causing a number of rare bone diseases. Examples of these include mutations in osteoblast genes such as collagen type 1 and tissue non-specific alkaline phosphatase resulting in osteogenesis imperfecta and hypophosphatasia, respectively. Examples of mutations in osteocyte genes such as SOST and FGF23 result in sclerosteosis/Van Buchems’ disease and autosomal dominant hypophosphatemic rickets, respectively. The study of rare bone diseases has significantly contributed to our understanding and insight into the normal physiology and function of osteoblasts and osteocytes. Understanding the function of these cells has led to a number of potential therapeutics not only for rare but also common bone disease.

Dr. Bonewald is the Vice Chancellor for Translational and Clinical Research, Curators’ Professor, Lee M. and William Lefkowitz Professor, Director, UMKC-CEMT, and Director, Bone Biology Research Program in the UMKC School of Dentistry, Department of Oral Biology. She performs research in the area of bone and directs the Mineralized Tissue Biology. She is a member of the American Society for Bone and Mineral Research, the Association of Biomolecular Resource Facilities, and the International Bone and Mineral Society. Dr. Bonewald is also a member of the American Association for Dental Research, and the International Association for Dental Research.
**Osteoclast Biology: Insights from Rare Bone Diseases**
Professor Stuart H. Ralston, MD, FRCP, FMedSci, FRSE, Western General Hospital, Edinburgh, UK

Major strides have been made in understanding the causes of genetic diseases associated with osteoclast dysfunction and this has advanced understanding of osteoclast biology. Osteopetrosis is a disease where osteoclast differentiation and function are defective. Deficiency of carbonic anhydrase II was the first identified cause in 1983; followed 13 years later by the identification of CATK mutations in patients with pycnody sostosis. Now the causal genes have been identified in the majority of patients with osteopetrosis giving important insights into the molecular machinery used by osteoclasts to resorb bone. The other side of the coin is Paget’s disease of bone (PDB) in which osteoclast activity is increased. Like osteopetrosis, PDB and related syndromes have a strong genetic component. In 2001, activating mutations in TNFRSF11A (which encodes RANK) were found to cause familial expansile osteolysis and subsequently loss-of-function mutations in TNFRSF11B (which encodes OPG) were found to cause juvenile PDB. More recently, genome wide association and linkage studies have identified numerous genes for PDB including SQSTM1, OPTN, CSF1, RIN3, and TM7SF4 all of which play roles in osteoclast function. The advances in understanding of these rare diseases have not only yielded novel insights into osteoclast biology but also have provided novel targets for drug design. For example, odanacatib, which targets Cathepsin K, the defective gene in pycnody sostosis, shows great promise as a new treatment for osteoporosis. Continued research in this area is likely to provide further insights into osteoclast biology and hopefully new treatments for both rare and common bone diseases.

**Dr. Ralston** graduated in Medicine from Glasgow University in 1978 and underwent higher medical training in General Internal Medicine and Rheumatology. He previously held the chair of Medicine and Bone Metabolism at the University of Aberdeen and moved to Edinburgh University in 2005 when he now holds the Arthritis Research UK Chair of Rheumatology. He is academic director of Edinburgh Clinical Trials Unit and director of Edinburgh University’s online distance learning MSc in clinical trials. Professor Ralston holds an honorary consultant rheumatologist position with NHS Lothian where he is clinical lead for the osteoporosis service and clinical director of the rheumatology service. Professor Ralston has researched widely on the molecular and genetic basis of osteoporosis and other bone and joint diseases. He has a special interest in the pathogenesis and management of Paget’s disease of bone. He is joint editor-in-chief of the scientific journal Calcified Tissue International and an editor of Davidson's Textbook of Medicine. Professor Ralston currently chairs the Commission for Human Medicines for the Medicines and Healthcare Regulatory Authority of the UK.
**Chondrocyte Biology**

Maurizio Pacifici, PhD, Division of Orthopaedic Surgery, The Children’s Hospital of Philadelphia, Philadelphia, PA

Chondrocytes -the main cell type present in fetal and postnatal cartilage- are complex in their biology and the varied, multiple and essential roles they play. During embryogenesis, chondrocytes differentiate from mesenchymal condensations and assemble the cartilaginous template of much of the craniofacial, axial and appendicular skeleton. The cells go on to produce: (i) permanent structures including articular cartilage and tracheal rings that persist through life; and (ii) growth plate cartilage in which the cells undergo maturation, propel skeletal growth and ossification and eventually disappear by the end of puberty. The biological complexity of chondrocytes has attracted research interest for years, and work by numerous research groups including ours has provided critical insights into the regulation of their development, phenotype, function and fate. I will highlight some of these key findings. In addition, important insights have come from studies on the pathogenesis of rare congenital skeletal disorders. I will describe our own work on Hereditary Multiple Exostoses that is caused by mutations in the glycosyl syntheses EXT1 and EXT2 and is characterized by cartilaginous tumors forming next to, but not within, the growth plates. The work is shedding light on diverse aspects of growth plate biology, including the regulation of growth plate-perichondrium interactions and tissue-tissue boundary. I will also highlight a recent study by Seemann and coworkers on a new GDF5 point mutation (W414R) associated with both brachydactyly and multiple synostoses syndrome 2 that has provided new information on limb skeletal morphogenesis and synovial joint formation.

**Dr. Pacifici** is Director of Research and the B. S. Lee Professor of Pediatric Orthopaedics in the Division of Orthopaedic Surgery at the Children’s Hospital of Philadelphia. Dr. Pacifici received his doctorate degree from the University of Rome and postdoctoral training under the auspices of a European Molecular Biology Fellowship. He joined the faculty at the University of Pennsylvania where he rose to the rank of Professor. He subsequently moved to Jefferson University Medical School where is served as Director of Research in Orthopaedics. About three years ago, he and his team were recruited by the Children’s Hospital of Philadelphia. Dr. Pacifici’s biomedical research work focuses on mechanisms controlling skeletal development and growth in fetal and postnatal life. Emphasis is on the identification of molecular regulators acting at the nuclear levels that direct commitment, determination and differentiation of progenitor skeletal cells. Overall goal is to target those regulators using gene-, cell- and drug-based therapies to treat skeletal pathologies including congenital skeletal malformations or growth defects and acquired conditions such as Fibrodyplasia Ossificans Progressiva. Emphasis is also on signaling diffusible factors that normally act within developing skeletal elements to coordinate growth and morphogenesis. When these factors act abnormally and affect adjacent non-skeletal tissues due to failure of signaling or restraining mechanisms, they can trigger pathologies, including benign tumors such as those seen Hereditary Multiple Exostoses. Experimental therapies are being tested to restore normal signaling mechanisms and block or reverse these and related pathologies. Dr. Pacifici’s biomedical research work has been continuously funded by the NIH for over 25 years.
**Vascular Biology**

Bjorn R. Olsen, PhD, Department of Cell Biology, Harvard Medical School, Boston, MA

Angiogenesis is essential for development and maintenance of the skeleton. Osteoblastic differentiation in membranous bones takes place within a capillary-rich environment. During endochondral ossification, sprouting blood vessels, preosteoblasts, hematopoietic progenitors and osteoclasts penetrate into cartilage templates of future bones in response to VEGF produced by hypertrophic chondrocytes. Mutations affecting vascular development and maintenance can therefore have substantial indirect skeletal effects. In Klippel-Trenaunay syndrome venous and lymphatic malformations are associated with soft tissue and/or skeletal hypertrophy. Intraosseous venous malformations may result in skeletal deformities. Overgrowth of craniofacial bones and other skeletal abnormalities can occur in syndromes of combined vascular anomalies, such as Sturge-Weber, Bannayan-Riley-Ruvalcaba and Schimmelpenning-Feuerstein-Mims syndromes. In Gorham-Stout disease overgrowth of lymphatic vessels is associated with massive bone loss. In addition, mechanisms required for differentiation of vascular cells, such as VEGF and BMP/TGF-β signaling, are also critical for differentiation and maintenance of skeletal cells. Mutations in genes involved in these pathways can therefore result in both skeletal and vascular defects. Examples are Proteus and Cloves syndromes, caused by mosaic mutations in the VEGF signaling pathway genes AKT1 and PIK3CA, and Marfan, Loeys-Dietz and Myhre syndromes, consequences of mutations in genes that affect BMP/TGF-β signaling. Finally, the discovery that a functional interaction between intracellular VEGF and the major nuclear envelope protein lamin A controls postnatal osteoblastic and adipogenic differentiation by mesenchymal stem cells, provides insights into potential mechanisms of age-dependent cardiovascular and skeletal abnormalities in patients with Hutchinson-Gilford Progeria and Mandibuloacral Dysplasia, caused by mutations in LMNA.

Dr. Olsen, Hersey Professor of Cell Biology at Harvard Medical School and Dean for Research and Professor of Developmental Biology at the Harvard School of Dental Medicine, has made fundamental contributions to extracellular matrix biology, skeletal and vascular biology. He received his medical and doctoral degrees from the University of Oslo, Norway, where he became a faculty member at the Anatomical Institute and conducted molecular studies on the structure of collagen. In 1971, he came to the United States to work with Dr. Darwin Prockop and joined the faculty of the Department of Biochemistry at Rutgers Medical School, now Robert Wood Johnson Medical School, where he was Professor of Biochemistry from 1976 until he moved to Harvard in 1985. Based on a combination of mouse and human genetic, biochemical and cell biological approaches, research in his laboratory has uncovered disease mechanisms in genetic disorders ranging from dwarfism to congenital vascular anomalies, osteoporosis and other types of bone loss, early-onset osteoarthritis, excess and ectopic bone formation, corneal dystrophy and retinal degeneration. The studies have uncovered fundamental roles of collagens, transcription factors and receptors that affect not only skeletal development, but also angiogenesis and blood vessel morphogenesis. Currently, studies in his laboratory are leading to new insights into the role of vascular endothelial growth factor in mesenchymal stem cell differentiation to osteoblasts and adipocytes, pathogenetic mechanisms of infantile hemangioma and genetic syndromes with severe craniofacial, skeletal, and connective tissue anomalies.
Matrix Proteins and their Processing in Rare Bone Diseases

Brendan Lee, MD, PhD, Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX

Over the past three decades the study of Mendelian forms of brittle bone disease best represented by Osteogenesis Imperfecta has led to the identification of disease mechanisms that affect both the quality and quantity of bone. This has been revolutionized by next generation sequencing and whole exome analysis. They have led to the discovery of enormous genetic heterogeneity that is becoming the rule for genetic phenotypes. In the case of OI, structural mutations in the most abundant components of matrix type I collagen, protein complexes that modify and chaperone collagen, and most recently components of signaling pathways have all been implicated. Together they underscore the factors that regulate mineralization of extracellular matrix and the differentiation and function of osteoblasts, osteoclasts, and osteocytes. In so doing they have also pointed to novel therapeutic strategies that may also need to be customized based on nature and consequence of mutation. Finally, the most recent data on the mutations that affect matrix-cell signaling and cell-cell signaling point to overlap with early onset osteoporosis phenotypes.

Dr. Lee is the Robert and Janice McNair Endowed Chair in Molecular and Human Genetics, Professor and interim Chairman of the Department of Molecular and Human Genetics at Baylor College of Medicine. Dr. Lee co-directs the joint MD Anderson Cancer Center and Baylor College of Medicine Rolanette and Berdon Lawrence Bone Disease Program of Texas, and the Baylor College of Medicine Center for Skeletal Medicine and Biology. He is Founder and Director of the Skeletal Dysplasia Clinic at Texas Children’s Hospital, and of the Medical Student Research Track at Baylor.
**Sox9 Regulation of Chondrocyte Programs**

Andrew P. McMahon, PhD, Eli and Edythe Broad-CIRM Center for Regenerative Medicine and Stem Cell Research, W.M. Keck School of Medicine of the University of Southern California, Los Angeles, CA

Sox9, an HMG-box containing transcriptional regulator, is essential for chondrocyte specification and differentiation. To determine Sox9’s direct regulatory actions in mammalian skeletogenesis, we analyzed Sox9-association at chondrocyte targets with a broad catalogue of regulatory indicators of chromatin organization and transcriptional activity. To address the specificity of Sox9 action in chondrocytes arising from different lineages, we compared Sox9’s regulatory interactions in rib (paraxial mesoderm-derived) and nasal (neural crest-derived) cartilage. Genome-scale analysis provides novel insights into Sox9 regulatory programs of chondrogenesis and novel predictions of regulatory action by unrelated transcription factors.

**Professor McMahon, FRS** joined the University of Southern California in July 2012 after 19 years at Harvard College where he was a Chairman of the Department of Molecular and Cellular Biology and faculty member in the Department of Stem Cell and Regenerative Biology, a founding member of the Harvard Stem Cell Institute and the Frank B. Baird Jr., Professor of Science. Professor McMahon is now the Keck Provost Professor at the University of Southern California, and Chair of the Department of Stem Cell Biology and Regenerative Medicine and Director of the Eli and Edythe Broad-CIRM Center for Regenerative Medicine and Stem Cell Biology within the Keck School of Medicine of USC. Professor McMahon is an elected Fellow of Royal Society, the American Association for the Advancement of Science, the American Academy of Arts and Sciences, and an elected Associate Member of the European Molecular Biology Organization. The McMahon group’s research focuses on the regulatory processes that construct, maintain and repair mammalian organ systems with a principal focus on the central nervous system, skeleton and kidney.
MODERATOR
Christopher Niyibizi, PhD, Department of Orthopaedics and Rehabilitation, Penn State College of Medicine, Hershey, PA

Dr. Niyibizi is an Associate Professor of Orthopaedics and Rehabilitation and Biochemistry and Molecular Biology at Penn State College of Medicine, Hershey PA. Dr. Niyibizi received his MSc. Degree in Biochemistry from Rutgers University and PhD in Biochemistry in division of Experimental Medicine at McGill University in Montreal Canada. While at Rutgers University, Dr. Niyibizi began his studies on collagen Biochemistry under the direction of Dr. Peter Fietzek of the department of Biochemistry then headed by Dr. Darwin Prockop. After completing his Ph.D. studies, Dr. Niyibizi pursued postdoctoral fellowships at Harvard Medical School and University of Washington in Seattle where he continued his studies in Collagen Biochemistry and the pathologies that result from them. Dr. Niyibizi moved to the University of Pittsburgh and continued his studies on connective tissue biochemistry with a major interest on the application of stem cells and gene therapies for Osteogenesis Imperfecta. Dr. Niyibizi research continues to focus on stem cells and bone biology at his present institution.
Treating Osteoclast Over-Activity with Bisphosphonates and Other Agents

Graham Russell MD, PhD, FRS, The Mellanby Centre, Sheffield University and the Botnar Research Centre, Oxford University, UK

The use of drugs that inhibit bone resorption ("anti-resorptives") continues to dominate the therapy of bone diseases, many of which are characterized by enhanced bone destruction.

The commonest of these is osteoporosis, and treatments have historically included hormones such as estrogens and SERMs (Selective Estrogen Receptor Modulators), as well as calcitonins. Currently the mainstay of treatment is with bisphosphonates, and more recently with denosumab.

It is fascinating to note how the study of rare diseases have led us to several of drugs now being developed or used for treating skeletal diseases. Among potential anti-resorptives derived from studies of various osteopetrotic disorders are src inhibitors, chloride channel blockers, ATP proton pump inhibitors, but to date only denosumab, as an anti-RANK-ligand antibody, has been registered for clinical use. Another example is how cathepsin K deficiency in pycnodysostosis led to the development of cathepsin K inhibitors such as odanacatib. Treatment of osteopetroses themselves remains challenging, but marrow transplantation, or interferons, can be helpful in selected cases.

Even the bisphosphonates, as stable chemical analogues of pyrophosphate can be traced back to studies on hypophosphatasia, in which increased pyrophosphate, the body’s natural water softener, contributes to the defective skeletal mineralization. Altered pyrophosphate metabolism occurs in other calcification disorders, eg chondrocalcinosis and infantile vascular calcification.

Bisphosphonates have been used since the 1970s across the whole spectrum of bone resorption disorders, including Paget’s disease and cancer related bone destruction. Their exact molecular mechanisms of action are now better understood, especially as inhibitors of farnesyl pyrophosphate synthase (FPPS), a key enzyme in the mevalonate pathway of cholesterol biosynthesis, which generates isoprenoid lipids. Prenylation leads to the post-translational modification of many proteins that are essential for the function of osteoclasts and other cell types. These properties have opened up a wide range of new potential medical uses of these compounds, including effects on T cells, tissue repair, and enhanced life span in animal progeria models.

Dr. Russell graduated in Biochemistry from Cambridge University and spent his formative years in Leeds, Davos, Bern, Oxford and Boston before becoming Professor and Head of the Department of Human Metabolism at Sheffield University in 1977. In 2001 he moved back to Oxford University as the Norman Collisson Professor of Musculoskeletal Sciences, and became the first Director of the Botnar Research Centre. His research interests are in skeletal biology and disease, and he is author of over 500 publications. In particular, his early work with Herbert Fleisch in Switzerland led to the discovery of the biological effects of bisphosphonates, and to their eventual successful clinical use in the treatment of bone disorders, including Paget’s disease, cancer metastases in bone, and osteoporosis. Later his group elucidated how bisphosphonates act within cells, especially as inhibitors of the mevalonate pathway of cholesterol biosynthesis, resulting in inhibition of protein prenylation. These properties have opened up a wide range of new potential medical uses of these compounds.
Graham Russell has held many national and international appointments in scientific and charitable activities, including being President of the International Bone and Mineral Society (IBMS) from 1998-2001. Among awards, he was recipient of the John B. Johnson award of the Paget’s Foundation (USA) in 1997, the Pieter Gaillard Founders award of the IBMS in 2007, and the Charles Dent award of the Bone Research Society UK in 2013. He is a Fellow of the Royal Society of London (FRS). From the ASBMR he was recipient of the W F Neuman award in 2000, and this year (2014) of the Gideon A. Rodan Excellence in Mentorship award.

After ‘retirement’ he has continued his research as Professor of Musculoskeletal Pharmacology in Oxford and also in the Mellanby Centre for Bone Research at Sheffield University.

http://www.ndorms.ox.ac.uk/profiles.php?profile=grussell
http://www.mellanbycentre.org/members/russell.htm
Treating Hypophosphatasia By Targeting Enzyme Replacement Therapy To Bone

Michael Whyte, MD, Center for Metabolic Bone Disease and Molecular Research at Shriners Hospitals for Children in St. Louis, MO

Hypophosphatasia (HPP) reflects deactivating mutation(s) within the gene for “tissue-nonspecific” alkaline phosphatase (TNSALP). Its biochemical hallmark, hypophosphatasemia, parallels an extraordinary range of HPP disease severity largely explained by autosomal recessive versus dominant transmission from among several hundred, primarily missense, TNSALP mutations. In HPP, disruptions of vitamin B6 metabolism revealed that TNSALP functions as a cell-surface enzyme. The biochemical villain is inorganic pyrophosphate (PPI), a TNSALP substrate and inhibitor of mineralization. In HPP, matrix vesicles (MVs) contain hydroxyapatite (HA), but excess extracellular PPI inhibits HA crystal growth after MVs rupture, causing tooth loss and rickets or osteomalacia. Perinatal HPP is nearly always lethal from profound skeletal hypomineralization. Infantile HPP presents before age six months with rickets and sometimes failure-to-thrive, hypercalcemia, or vitamin B6-dependent seizures. Progressive chest deformity heralds respiratory failure and death. Childhood HPP features tooth loss, rickets, and a static myopathy. Adult HPP causes osteomalacia and sometimes PPI arthropathies. Odonto HPP is tooth loss without skeletal disease.

There is no established medical treatment for HPP. Failure of intravenous infusions of ALP-rich Paget plasma or purified placental ALP for infantile HPP indicated that ALP levels must be corrected within the HPP skeleton. Healthy marrow and bone cell transplantation or “off-label” use of teriparatide (to engraft TNSALP replete osteoblasts, or to drive osteoblast ALP biosynthesis) seemed to have some success for infantile and adult HPP, respectively. Now, TNSALP replacement using a recombinant protein containing a terminal deca-aspartate motif for bone targeting (asfotase alfa) is undergoing evaluation for HPP. Rapid improvements for life-threatening HPP in infants and young children and for severely affected older children with HPP have been described. Sustained improvements after 3-years of asfotase alfa treatment, supported by information emerging from HPP historical control studies, will be presented throughout the 2014 ASBMR meeting.

Dr. Whyte is Professor of Medicine, Pediatrics, and Genetics at the Washington University School of Medicine and is the Medical-Scientific Director of the Center for Metabolic Bone Disease and Molecular Research at Shriners Hospital for Children in St. Louis, Missouri, USA. Dr. Whyte earned his M.D. degree at Downstate College of Medicine, Brooklyn, New York and then trained in Internal Medicine at Bellevue Hospital in New York City before Clinical Associateship at the National Institutes of Health in Bethesda, Maryland. After fellowship in the Division of Bone and Mineral Diseases, he joined the faculty of Washington University School of Medicine in St. Louis. Dr. Whyte’s research interests include the cause, pathogenesis, and treatment of metabolic bone diseases in children and adults; especially genetic forms of rickets such as hypophosphatasia and X-linked hypophosphatemia (XLH), brittle bone diseases like osteogenesis imperfecta, and conditions that cause dense bones such as osteopetrosis. Laboratory investigations include chromosomal mapping and then searches for mutated genes to relate to clinical observations for phenotype/genotype correlations. Bone-targeted enzyme-replacement therapy is being evaluated for hypophosphatasia, and it is hoped that a monoclonal antibody against FGF23 can be evaluated for XLH. The Research Center at Shriners Hospital serves as a national and international resource for the diagnosis, treatment, and investigation of disorders of bone and mineral metabolism and skeletal dysplasias in children. Dr. Whyte has authored or coauthored more than 300 scientific papers or book chapters concerning pediatric and adult metabolic bone diseases.
Antibody-Based Modulation of Extracellular Signaling
Matthew Warman, MD, Orthopedic Research Center, Boston Children’s Hospital, Boston, MA

Jenner (1789) reported that inoculating persons with Cow-pox prevented severe disease from occurring when these same individuals were subsequently inoculated with Small-pox. Thus, Jenner demonstrated that the immune system could intentionally be harnessed to impact disease, ushering in the practice of vaccination. Behring and Kitasato (1891) demonstrated that serum from an animal that had been immunized with diphtheria toxin would lessen disease severity when given to another animal exposed to this same toxin. Thus began the practice of using “anti-serum” and gamma-globulin to treat diseases as diverse as tetanus, snake-bite, and Rh incompatibility. Kohler and Millstein’s (1975) method for producing monoclonal antibodies and work by many scientists to “humanize” antibodies created in other species and to modify an antibody to improve its bioavailability and pharmacokinetics, has led to the rapid increase in antibody-based biopharmaceuticals currently in clinical use and in clinical development.

Research involving patients with rare Mendelian Genetic diseases has identified targets for antibody-mediated therapies for common conditions. This is particularly powerful when the consequence of disease is tissue-specific or organ-specific, the mechanism of mutational effect is a loss-of-function, and the mutated gene encodes a protein that is secreted or localized to the outer cell membrane. I will describe how patients with the recessive loss-of-function diseases Sclerosteosis, van Buchem disease, and Osteoporosis-Pseudoglioma syndrome informed us about the potential use of antibodies that modulate Wnt signaling to increase bone strength. I will present proof-of-principle experiments in mice that suggest Sclerostin-neutralizing antibodies will benefit patients with Osteogenesis Imperfecta and the Osteoporosis-Pseudoglioma syndrome, in addition to patients with common skeletal fragility conditions such as osteoporosis.

Dr. Warman went to college at Brown University and to medical school at Cornell University. After medical school he trained in Pediatrics at the Children's Hospital in Washington, D.C., in Genetics at the Children's Hospital in Boston, and he performed post-doctoral research with Professor Bjorn R. Olsen at Harvard Medical School. Dr. Warman's clinical and scientific interests focus on genetic diseases, particularly those that affect the skeletal system. In 1994 Dr. Warman established an independent laboratory and clinical program in the Department of Genetics and Center for Human Genetics at Case Western Reserve University and University Hospitals of Cleveland. He and the members of his laboratory are committed to identifying genetic causes of skeletal disease, to understanding how these genes participate in the biology of the skeletal system, and to using this knowledge to improve the skeletal health of the human population. In 2006, Dr. Warman returned to Boston, where he is continuing his research as the Director of the Orthopaedic Research Laboratories at Boston Children's Hospital, Professor of Genetics and Orthopaedic Surgery at Harvard Medical School, and Investigator with the Howard Hughes Medical Institute. Dr. Warman is a member of the OI Foundation’s Medical Advisory Council.
MODERATOR
Laura Tosi, MD, Department of Orthopaedic Surgery, Children’s National Health System, Washington, DC

Dr. Tosi, is a pediatric orthopaedic surgeon at Children's National Health System in Washington, D.C., where she has been on staff for over 30 years. Her clinical practice focuses on the orthopedic care of children with physical disabilities, bone health, and the medical and orthopaedic challenges faced by adults with childhood onset conditions. Dr. Tosi is the founder and director of the Children's National Pediatric Bone Health Program. She has served on the Board of Directors of the American Academy of Orthopaedic Surgeons (AAOS), the Pediatric Orthopaedic Society of North America, the Orthopaedic Research and Education Foundation, the Academic Orthopaedic Society and the Society for Women's Health Research. Dr. Tosi is a past President of the Ruth Jackson Orthopaedic Society, the professional association for women in orthopaedics. She received their Presidential Special Merit Award in Year 2000 for her outreach on topics on women's musculoskeletal health. She received the AAOS Diversity Award in 2005. Dr. Tosi currently serves on the Medical Advisory Council and Board of Directors of the Osteogenesis Imperfecta Foundation and is the Chair of the OI Adult Natural History Initiative.
Small Molecule Inhibitor of the mTOR Signaling Pathway

Denise M Adams, MD, Cincinnati Children’s Hospital Medical Center, Cancer and Blood Diseases Institute, University of Cincinnati, Cincinnati, OH

P13k/mTOR pathway is a complex interplay of intracellular signaling networks that are involved in critical cellular functions including protein synthesis, cell cycle progression, apoptosis and drug resistance. To the clinician, the pathway is a central control of cell growth, proliferative metabolism and survival. The pathway is disregulated in cancers and in vascular anomalies.

Sirolimus, the initial mTOR inhibitor, also known as rapamycin, was recently found to be efficacious in the treatment of several complicated vascular anomalies some of which had PTEN and TIE-2 mutations. This initial clinical discovery came prior to the recent report of PIC3CA somatic mutations in patients with CLOVE syndrome and other lymphatic anomalies. Interestingly, some of these disorders can cause massive osteolysis and or multiple bone lesions that improve symptomatically and radiographically on sirolimus.

mTOR inhibition has recently been effective in combination treatment regimens for estrogen-receptor positive breast cancer. A recent study revealed the mTOR inhibitor everolimus having beneficial effects on bone metabolism, potentially reducing bone resorption and contributing to a bone-protective effect.

Currently, six classes of PI3K/mTOR pathway inhibitors have been developed: pan-class I PI3K inhibitors, isoform selective PI3K inhibitors, Akt inhibitors, MTIs/rapalogs, dual PI3K/mTOR inhibitors and TORC1/TORC2 inhibitors. All of these agents remain under active pre-clinical study. mTOR inhibitors are well tolerated as single-agents but can potentiate the toxicities of cytotoxic chemotherapies. Clinical evaluation of next-generation PI3/mTOR pathway inhibitors remain in early stages but toxicities appear to be related to immunosuppression and associated infections, effects upon cellular metabolism and, GU symptoms and skin rash.

The ability of targeted therapies, especially kinase inhibitors, to alter osteoclast survival and function is the subject of substantial clinical research that will substantially improve the outcome for many disease entities.

Dr. Adams is fellowship director of the Hematology / Oncology Fellowship Program and medical director of the Hemangioma and Vascular Malformations Center at Cincinnati Children’s. One of the vascular team’s main priorities has been establishing standards of care for patients with these diagnoses so they can follow outcome measures. Of key interest to Dr. Adams, as an oncologist, is the improvement in care of patients with kaposiform hemangioendotheliomas (KHE). The team of experts has established a clinical registry for these patients to gain insight into the clinical characteristics of KHE patients and the long term outcomes of these patients. They also have a phase II FDA funded trial for complicated vascular anomalies and KHE patients are included in this trial. These tumors are rare but have a very high mortality and morbidity rate. It is important that the group learn more about the clinical characteristics, phenotype, biomarkers which can lead to further investigations and clinical trials.
Promotion of Skeletal Growth Using Peptides
Laurence Legeai-Mallet, PhD, INSERM U1163-Imagine Institute-Paris Descartes University, Paris, France

Skeleton is formed via two distinct processes during embryogenesis. Intramembranous bone formation produces many of the craniofacial bones by mesenchymal condensation. In contrast, endochondral bones are formed via a cartilage intermediate and generate most of the long bones of the skeleton. Genetic disorders of the skeletal system affect both bone and cartilage formation from early embryo-fetal development up to post-natal growth. Over the last three decades, the molecular bases of many genetic disorders of the skeleton have been elucidated with the identification of key genes regulating skeletal formation. The understanding of disease mechanisms lead to targeted treatment. To date, the development of innovative therapies to treat skeletal genetic disorders are expanding; they include replacement of defective/missing proteins or genes, or normalization of aberrant signaling pathways. Growth hormone and Insulin-like growth factor I are major examples of the use of peptides for the treatment of short stature. Recently, BMN 111, a CNP peptide (C-type natriuretic peptide) analog, has been investigated in achondroplasia, the most common form of dwarfism. CNP acts as a key regulator of longitudinal bone growth by down-regulating the MAPK pathway. This peptide, promotes skeletal growth in a mouse model of the disease supporting the use of this molecule in the treatment of achondroplastic children.

Dr. Legeai-Mallet is currently Director of Research at Imagine Institute-INSERM U1163-Paris Descartes University. Since 1993, Dr. Legeai-Mallet’s research focuses on skeletal diseases. Her activities range from the identification of disease genes involved in cartilage and bone pathologies, to the understanding of the molecular and cellular mechanism of normal and pathologic bone development up to the clinical development of therapeutic approaches. Among other activities, she currently leads an effort with academic and industrial partners to develop therapeutic approaches for various osteochondrodysplasias. Recently, she reported the therapeutic potential of a novel natriuretic peptide C analogue (BMN 111) as the first investigational therapy for the most frequent dwarfism, achondroplasia. She is a member of International skeletal dysplasia Society, European Skeletal Dysplasia Network and the French reference center of bone dysplasias. She received her Ph.D. in Genetics from University of Paris-V.
The workshop “Mechanistic and Therapeutic Insights into Skeletal Biology Learned from the Study of Rare Bone Diseases” was developed by a Scientific Program Committee consisting of the following:

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Boston Children’s Hospital

**Workshop Organizer:**
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Children’s National Health System

Michael Econs, MD
Indiana University

Tracy Hart
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Osteogenesis Imperfecta Foundation

Craig Langman, MD
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Brendan Lee, MD, PhD
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Charlene Waldman
Consultant, Rare Bone Organizations

Taylor Wallace, PhD
National Bone Health Alliance
The meeting organizers would like to thank the following for their participation in developing the workshop:

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<th>The members of the National Bone Health Alliance Working Group on Rare Bone Diseases:</th>
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<td>Laura L. Tosi, MD, Chair</td>
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The National Bone Health Alliance (NBHA) is a public-private partnership launched in 2010 that brings together the expertise and resources of its member organizations to collectively: promote bone health and prevent disease; improve diagnosis and treatment of bone disease; and enhance bone research, surveillance and evaluation.

The members of the Rare Bone Disease Patient Network:

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<td>Soft Bones, Inc.</td>
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The Rare Bone Disease Patient Network is a coalition of rare bone disease organizations, established to share information, expertise and resources, in a collaborative effort to increase awareness, understanding, and research of rare bone disorders.
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