MECHANISTIC AND THERAPEUTIC ADVANCES IN RARE SKELETAL DISEASES

A meeting in affiliation with the American Society for Bone and Mineral Research (ASBMR)
This meeting is co-organized by the Rare Bone Disease Alliance, The Osteogenesis Imperfecta Foundation, and the NIH Brittle Bones Disorders Consortium

SEPTEMBER 26-27, 2018

Chair: Brendan Lee, MD, PhD, Baylor College of Medicine
Co-Chair: Maurizio Pacifici, PhD, Children’s Hospital of Philadelphia

Program Committee:
- Yang Chai, DDS, PhD, University of Southern California
- Michael Collins, MD, National Institute of Dental and Craniofacial Research
- Matthew Drake, MD, PhD, Mayo Clinic
- Deborah Krakow, MD, UCLA
- Sandesh Nagamani, MD, Baylor College of Medicine

Meeting Agenda

Wednesday, September 26

7:00 am - 7:50 am  
Breakfast

7:50 am - 8:00 am  
Welcome: Brendan Lee, MD, PhD, Baylor College of Medicine

8:00 am - 9:40 am  
Session 1: Diagnostic Approach to Rare Skeletal Diseases
Moderator: Maurizio Pacifici, PhD, Children’s Hospital of Philadelphia

- Next Generation Sequencing and Multi-Omic Approaches for Diagnosing Skeletal Diseases
  Brendan Lee, MD, PhD, Baylor College of Medicine

- Higher Order Chromatin Structure and Distal Genetic Interactions in the Diagnosis of Skeletal Diseases
  Struan Grant, PhD, Children’s Hospital of Philadelphia

- Radiographic and Ultrasound Imaging of Skeletal Diseases
  Deborah Krakow, MD, University of California - Los Angeles

- Past, Current and Future Biomarkers of the Skeleton
  Charlotte Gistelinck, PhD, University of Washington

9:40 am - 9:55 am  
Break
10:00 am - 12:05 pm  **Session 2: Preclinical Models and Pathogenesis (Bones, Cartilage & Craniofacial)**
Moderator: Deborah Krakow, MD, University of California - Los Angeles

*Fibrous Dysplasia*
Michael Collins, MD, National Institute of Dental and Craniofacial Research

*BMP Signaling and Therapeutic Approaches*
Aris Economides, PhD, Regeneron Pharmaceuticals and Dinko Gonzales Trotter, PhD, Regeneron Pharmaceuticals

*Osteogenesis Imperfecta*
Frank Rauch, MD, Shriners Hospital of Montreal

*Progressive Heterotopic Ossification*
Yingzi Yang, PhD, Harvard School of Dental Medicine

*Hereditary Multiple Exostoses*
Maurizio Pacifici, PhD, Children’s Hospital of Philadelphia

12:05 pm - 1:30 pm  **Lunch & Poster Session 1**

1:30 pm - 3:10 pm  **Session 2 Continued**
Moderator: Yang Chai, DDS, PhD, University of Southern California

*Fibrodysplasia Ossificans Progressiva*
Eileen Shore, PhD, University of Pennsylvania

*Craniosynostosis*
Andrew Wilkie, FRS, FMedSci, FRCP, University of Oxford

*Hypo-Oligodontia and Tooth Stem Cells*
Ophir Klein, MD, PhD, University of California - San Francisco

*Osteopetrosis*
Anna Teti, PhD, University of L’Aquila

3:10 pm - 3:25 pm  **Break**

3:30 pm - 5:35 pm  **Session 3: Therapies on the Horizon and New Disease Targets**
Moderator: Michael Collins, MD, National Institute of Dental and Craniofacial Research

*Chemical Biology and Drug Discovery*
Peter J. Brown, PhD, University of Toronto

*Mesenchymal Stem Cells, Craniosynostosis and a Novel Molecular Mechanism in Regulating Cranial Suture Tissue Homeostasis*
Yang Chai, DDS, PhD, University of Southern California
Stem Cells for Treatment of OI and the BOOSTB4 Trial (sponsored by the ICCBH)
Cecelia Gotherstrom, PhD, Karolinska Institutet

Gorham's Disease
Denise Adams, MD, Boston Children's Hospital

Melorheostosis
Timothy Bhattacharyya, MD, National Institute of Arthritis and Musculoskeletal and Skin Diseases

5:35 pm - 7:30 pm  Evening Reception/Poster Session 2

Thursday, September 27

7:00 am - 8:00 am  Breakfast

8:00 am - 9:40 am  Session 4: Targeting Signaling Pathways (Clinical)
Moderator: Matthew Drake, MD, PhD, Mayo Clinic

The Clinical Trial of Anti-TGFb in OI
Sandesh Nagamani, MD, Baylor College of Medicine

The Role of Sclerostin Inhibition in Bone
Andreas Grauer, MD, Amgen

FGF23 and X-Linked Hypophosphatemia
Thomas Carpenter, MD, Yale University

C-Natriuretic Peptide & Achondroplasia
Julie Hoover Fong, MD, PhD, Johns Hopkins University

9:40 am - 9:55 am  Break

10:00 am - 12:05 pm  Session 5: Advances in Endpoints and Assessments (Preclinical & Clinical)
Moderator: Sandesh Nagamani, MD, Baylor College of Medicine

HR-pQCT Evaluation of Bone
Steven Boyd, PhD, University of Calgary

MRI Evaluation of Cartilage
Sharmila Majumdar, PhD, University of California - San Francisco

FDA Approach to Novel Endpoints
Theresa Kehoe, MD and Gemma Kuijpers, PhD, FDA

Novel Growth Plate Markers
William Horton, MD, Oregon Health Sciences University
Hypophosphatasia: What’s Next?
Michael Whyte, MD, Shriners Hospital - St. Louis

12:05 pm - 1:30 pm  Lunch and Poster Session 3

1:30 pm - 2:45 pm  Session 6: Current Industry Clinical Trials and Approach to Clinical Trials Phase 1 through Pivotal Phase 3 and Post-Approval Studies
Moderator: Michael Collins, MD, National Institute of Dental and Craniofacial Research

Burosumab Therapy in Children and Adults with XLH, from Discovery to Approval
Javier San Martin, MD, Ultragenyx

Addressing Scarcity and Heterogeneity in Drug Development for FOP
Scott Mellis, MD, PhD, Regeneron

Fibrodysplasia Ossificans Progressiva: Use of a Natural History Study in the Design and Implementation of a Phase 3 Trial
Donna Grogan, MD, Clementia

Collaborative Use of a Patient Registry in the Design of a Phase 2 Study for a New Indication, Multiple Osteochondroma
Fei Shih, MD, PhD, Clementia

Clinical Development of Asfotase Alfa for the Treatment of Pediatric-Onset Hypophosphatasia
Tom Brown, PhD, Alexion

Development of Setrusumab for Osteogenesis Imperfecta
Anthony Hall, MB, BS, BSc, Mereo Biopharma

2:45 pm - 3:45 pm  Industry and FDA Panel: All speakers above and FDA Representatives
Theresa Kehoe, MD and Gemma Kuijpers, PhD

3:45 pm  Conclusion – Brendan Lee, MD, PhD, Baylor College of Medicine

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Mechanistic and Therapeutic Advances in Rare Skeletal Diseases
A meeting in affiliation with the American Society for Bone and Mineral Research (ASBMR)

SPEAKERS

Brendan Lee, MD, PhD, Baylor College of Medicine

Dr. Lee is the Robert and Janice McNair Endowed Chair, Professor, and Chairman of the Department of Molecular and Human Genetics, Director of the Center for Skeletal Medicine and Biology at Baylor College of Medicine, and co-Director of the Texas Medical Center Bone Disease Program of Texas. As a pediatrician and geneticist, Dr. Lee studies structural birth defects and inborn errors of metabolism. Dr. Lee identified the first genetic causes of human skeletal dysplasias and studies their implications for cancers of the skeleton. In the area of metabolic disease, he has studied nitric oxide dysregulation and developed new treatments for maple syrup urine disease and urea cycle disorders. Dr. Lee has been recognized by election to the National Academy of Medicine, Fellow of the American Association for the Advancement of Science (AAAS), the Association of American Physicians (AAP), the American Society for Clinical Investigation (ASCI), and the Society of Pediatric Research (SPR). He has also been awarded the American Society of Human Genetics Curt Stern Award for Outstanding Scientific Achievement, the Texas Academy of Medicine, Engineering, Science and Technology (TAMEST) Peter and Edith O'Donnell Award in Medicine, the Society for Pediatric Research E. Meade Johnson Award for Pediatrics Research, the Michael E. DeBakey Excellence in Research Award, the American Philosophical Society’s (APS) Judson Darland Prize for Patient-Oriented Clinical Investigation, and Best Doctors in America. Dr. Lee was previously an Investigator of the Howard Hughes Medical Institute prior to his appointment as Chairman of the Department of Molecular and Human Genetics in 2014. The Department is the leading genetics program integrating basic, translational, clinical, and diagnostic laboratory activities. It is composed of over 150 primary faculty members encompassing research, clinical, laboratory diagnostic, and genetic counseling missions. It ranks #1 among genetics departments in total funding and number of grants from the National Institutes of Health.

Struan Grant, PhD, Children’s Hospital of Philadelphia

Dr. Grant has been conducting human genomics research for over 20 years. The highlights of his career are the discovery of the polymorphic Sp1 site in the COL1A1 gene and its association with osteoporosis, the identification of variation in the TCF7L2 gene playing a key role in conferring type 2 diabetes risk and providing leadership in an international genetics effort to characterize genes influencing birth weight and common childhood obesity risk. He has also previously played a role in uncovering genes involved in multiple other traits. As a Director of the Center for Spatial and Functional Genomics at the Children’s Hospital of Philadelphia, Dr. Grant’s current work primarily involves investigating disease genomics with a specific focus on pediatrics. Utilizing high-throughput genotyping and sequencing technologies, combined with statistical and bioinformatic approaches, his goals include unraveling genomic puzzles related to childhood obesity, pediatric bone strength determination, early onset diabetes and cancer.
Dr. Deborah Krakow is Professor and Chair of the Department of Obstetrics and Gynecology at UCLA.

Dr. Krakow is also Professor of Orthopaedic Surgery and Professor of Human Genetics at UCLA.

Dr. Krakow received her bachelor's degree from Arizona State University in Tempe and her medical degree from Chicago Medical School. After an internship and residency in obstetrics and gynecology at Cedars-Sinai Medical Center, she completed fellowships in maternal-fetal medicine at Harbor-UCLA Medical Center and in research and clinical genetics at the UCLA Intercampus Medical Genetics Training Program. Dr. Krakow is Co-Director of the International Skeletal Dysplasia Registry.

Charlotte Gistelinck, PhD, University of Washington

During my graduate studies at Ghent University (Ghent, Belgium), I was trained in biochemistry and biotechnology, giving me a broad scientific training and a solid foundation of both biochemical and molecular (genetic) techniques and knowledge. As a PhD student I worked in the connective tissue lab of Prof. Paul Coucke and Prof. Anne De Paepe (Center for Medical Genetics Ghent, Belgium), where I came in contact with both clinical diagnostic and basic scientific work on a number of human connective tissue disorders. My own research was focused on Osteogenesis Imperfecta (OI), as I worked to establish and validate zebrafish, a small bony fish, as a model organism for OI. My research demonstrated zebrafish to be a use tool in the study of the pathogenetic mechanism of human OI, and delivered multiple zebrafish disease models of OI which will pave the way for further studies. During my PhD research, I spend 6 months at the University of Washington to learn both phenotyping techniques (Prof. Ronald Kwon) and methods to investigate Bone Collagen. During this period, I spent quite some time in the lab of Prof. David Eyre and developed a deep interest in his research on collagen biology and its role in human disease. This is why I was very pleased to receive the opportunity to join the lab of Prof. Eyre as a Senior Fellow, after completing my PhD in July 2017. Currently I am working on investigating the post-translational chemistry of collagen in Osteogenesis Imperfecta, studying both human tissues, as well was murine and zebrafish models. With this combination of approaches, I am trying to establish the role of altered collagen cross-linking and post-translational chemistry in deteriorating the mechanical properties of bone and causing bone fragility in OI patients.
Michael Collins, MD, National Institute of Dental and Craniofacial Research

Dr. Collins is the Chief of the Skeletal Disorders and Mineral Homeostasis Section at the National Institutes of Health in Bethesda, Maryland. He is physician scientist whose research is focused on bone and mineral homeostasis; specifically, the role of PTH, G-proteins, cAMP, and FGF23 in bone cell biology and mineral balance. The primary approach is translational research studies in patients with rare disorders of bone and mineral homeostasis. Current disease under investigation include fibrous dysplasia of bone/McCune-Albright syndrome, hypoparathyroidism, and disorders of FGF23 excess and deficiency such as x-linked hypophosphatemic rickets, tumor-induced osteomalacia, and familial tumoral calcinosis.

Aris Economides, PhD, Regeneron Pharmaceuticals

Dr. Aris N. Economides received his Ph.D. in Biochemistry from Michigan State University in 1992, and promptly joined Regeneron Pharmaceuticals. He currently holds the position of Vice President, leading two groups: Genome Engineering Technologies, and Skeletal Diseases Therapeutic Focus Area. In addition, he is a co-founder of Regeneron Genetics Center (RGC), where he is also Head of Functional Modeling. Dr. Economides co-invented Cytokine Traps, VelociGene®, and VelocImmune®, all part of an integrated methodology for target discovery, validation, and the generation of biologic drugs such as the IL1 and VEGF traps, as well as therapeutic antibodies. More recently, he has been developing a new method for Enzyme Replacement Therapy (ERT), one that addresses two of the main limitations of current ERT, namely immunogenicity and inefficient uptake by the tissues most affected in the corresponding Lysosomal Diseases. As part of his involvement with the RGC, Dr. Economides has been working to elucidate the molecular pathophysiology of genetically-driven disorders. An example is his work in Fibrodysplasia Ossificans Progressiva, where he and his team discovered a novel mechanism that explains important aspects of FOP’s pathophysiology and pinpoints a new potential route to therapy.

Dinko Gonzales Trotter, PhD, Regeneron Pharmaceuticals

Dinko Gonzales Trotter is Senior Director, Early Clinical Development at Regeneron Pharmaceuticals.

Dr. Trotter is a leader in innovation and technologies applied to preclinical and clinical imaging with emphasis in molecular imaging from small molecules and peptides to antibodies. He has expertise in imaging biomarkers applied to drug research and development.

Dr. Trotter previously was Director, Image Analysis and Physiology at Merck.
Frank Rauch, MD, Shriner's Hospital of Montreal

Frank Rauch, MD, is a Professor of Pediatrics and clinician-scientist at the Shriner's Hospital for Children and at McGill University. He obtained his MD degree from the Technical University of Munich, and trained as a pediatrician at the Children's Hospital of Cologne University, Germany. His clinical activities and research program concentrate on improving bone health in children, with a special focus on genetic conditions leading to fractures and on the role of the muscle system in bone diseases. In his recent work, Dr. Rauch has identified new genetic causes of brittle bone disorders and has assessed the long-term effects of bisphosphonate treatment in children with osteogenesis imperfecta. He is also collaborating with Statistics Canada in a study that assesses muscle and bone health in Canadians. Dr. Rauch has authored or coauthored more than 200 original publications.

Yingzi Yang, PhD, Harvard School of Dental Medicine

Dr. Yingzi Yang completed her B.S. degree from the Fudan University in Shanghai, China. She received her research training in the U.S. and studied Wnt and Hedgehog signaling in early limb patterning under the guidance of Dr. Lee Niswander at the Sloan-Kettering Cancer Institute, where she was awarded her Ph.D. in Molecular Biology by the Weill Medical College of Cornell University in New York City.

After completing a postdoctoral fellowship in mammalian developmental biology and genetics in the laboratory of Dr. Andy McMahon at Harvard University, she joined the Genetic Disease Research Branch of the National Human Genome Research Institute (NHGRI) as a tenure-track investigator in 2000 and ventured into the field of skeletal biology and disease. She received tenure at NHGRI in 2006 and was head of the Developmental Genetics Section and a senior investigator of NHGRI. She was recruited by HSDM as Professor of Developmental Biology in 2015.

Dr. Yang has received several honors and awards during her scientific career. Dr. Yang has published extensively in professional journals. She serves or has served on the editorial boards of several major journals including Cell Research, the Journal of Biological Chemistry, the Journal of Bone and Mineral Research and the Journal of Molecular Cell Biology. Dr. Yang enjoys and is committed to training students at all levels and introducing them to the excitement and significance of biomedical research. Dr. Yang also serves on many professional research and education committees.

Dr. Yang has made groundbreaking contributions to understanding the roles of Wnt and Hedgehog signaling in embryonic morphogenesis, skeletal biology and skeletal diseases. Her research has successfully bridged discoveries of fundamental mechanisms with characterization and treatment of diseases including severe birth defects, osteoporosis, osteoarthritis and heterotopic bone formation. Her studies have revealed fundamental mechanisms of Wnt and Hedgehog signal transduction and their critical roles in many aspects of embryonic morphogenesis and adult physiology.
MAURIZIO PACIFICI, PHD 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 two 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 Heterotopic Ossification. 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.

Eileen M. Shore is the Cali/Weldon Professor at the Perelman School of Medicine at the University of Pennsylvania in the Departments of Orthopaedic Surgery and Genetics, and is the co-Director of the Center for Research in FOP and Related Disorders. She received her Ph.D. in Cell and Molecular Biology from the University of Pennsylvania and postdoctoral training at the Fox Chase Cancer Center. Over the past >20 years, she has investigated cell differentiation and development in human genetic disease, with a focus on two rare disorders of de novo formation of extra-skeletal bone, fibrodysplasia ossificans progressiva (FOP) and progressive osseous heteroplasia (POH), to explore the cellular and molecular basis of dysregulated osteogenesis. Her goals are to develop treatments for FOP, POH, and other more common bone disorders, and gain new understanding of the processes that regulate progenitor cell differentiation, and bone and cartilage formation and regeneration.
Andrew Wilkie, FRS, FMedSci, FRCP, University of Oxford

Andrew Wilkie has been an Honorary Consultant in Clinical Genetics at the Oxford University Hospitals NHS Trust since 1993 and Nuffield Professor of Pathology at the University of Oxford since 2003. In collaboration with plastic surgeons at the Oxford Craniofacial Unit, his clinical research aims to identify the molecular genetic basis of craniofacial malformations, particularly craniosynostosis; over the past two decades his team has identified many novel disease genes mutated in these disorders. Work on Apert syndrome has led to fundamental discoveries concerning the mechanisms of mutation associated with paternal age effects. In recognition of these discoveries, Andrew has been elected to Fellowships of the Academy of Medical Sciences and the Royal Society and to membership of EMBO.

Ophir Klein, MD, PhD, University of California - San Francisco

Ophir Klein is Professor of Orofacial Sciences and Pediatrics, the Larry L. Hillblom Distinguished Professor in Craniofacial Anomalies, and the Charles J. Epstein Professor of Human Genetics at the University of California, San Francisco (UCSF). He serves as Chief of the Division of Medical Genetics, Chair of the Division of Craniofacial Anomalies, and Director of the Program in Craniofacial Biology. Dr. Klein was educated at the University of California, Berkeley, where he earned a B.A. in Spanish Literature. He subsequently attended Yale University School of Medicine, where he received a Ph.D. in Genetics and an M.D. He then completed residencies at Yale-New Haven Hospital in Pediatrics and at UCSF in Clinical Genetics. Dr. Klein has received several honors, including a New Innovator Award from the NIH, the E. Mead Johnson Award from the Society for Pediatric Research, and the Craniofacial Biology Distinguished Scientist Award from the International Association for Dental Research. Dr. Klein was elected to the American Society for Clinical Investigation, and he is a Fellow of the American Association for the Advancement of Science. Dr. Klein’s research focuses on understanding how organs form in the embryo and how they regenerate in the adult, with a particular emphasis on the processes underlying craniofacial and dental development and renewal as well as understanding how stem cells in the intestinal epithelium enable renewal and regeneration.

Anna Teti, PhD, University of L’Aquila

Anna Teti, PhD is Professor of Histology and Embryology, Department of Biotechnological and Applied Clinical Sciences at the University of L’Aquila, Italy. Dr. Teti graduated from the University of Bari School of Biological Science in 1977, served as Assistant and Associate Professor of Anatomy there from 1981-1993; became Associate Professor of Histology and Embryology at the University of L’Aquila from 1993-2000 before becoming Full Professor in 2000. Among the honors and prizes Dr. Teti has received are the Chemofux Prize, the Austrian Society for Bone and Mineral Metabolism, the Prix Andre Lichtwitz, INSERM award, the Swiss Bridge Foundation Award, the Mike Horton Basic/Translational Award and the European Calcified Tissue Society Award.

Dr. Teti serves on the editorial boards of several journals and belongs to a number of Professional Societies including the ASBMR. She is currently President of ECTS.
Peter J. Brown, PhD, University of Toronto

Peter J. Brown is Principal Investigator, Epigenetics at the Structural Genomics Consortium, University of Toronto. Dr. Brown’s research interests include using HTS, target-specific arrays, and fragment-based methods to discover chemical probes for epigenetic targets in addition to coordinating collaborations with nine Pharma companies. The Toronto SGC site has developed 26 chemical probes since 2009 and openly shares these with the scientific community. Dr. Brown has coauthored 100 publications and 9 patents.

Dr. Brown received his Ph.D. from the University of Sheffield and performed postdoctoral research at Indiana University with Philip Magnus culminating in the total synthesis of (-)-Pleiomutine, a bis-indole alkaloid. Prior to joining the SGC, Dr. Brown spent nineteen years at GlaxoSmithKline in various roles, most recently Section Head, Medicinal Chemistry, and was focused on the early Hit-ID phase of Drug Discovery and finding tool compounds for the Nuclear Receptor family of proteins.

Yang Chai, DDS, PhD, University of Southern California

Dr. Yang Chai is a Professor and the George and MaryLou Boone Chair in Craniofacial Biology at the University of Southern California (USC). He serves as Director of the Center for Craniofacial Molecular Biology and Associate Dean of Research at the Herman Ostrow School of Dentistry of USC. He is most noted for his research on molecular regulation of cranial neural crest cells during craniofacial development and malformations. His laboratory has developed multiple animal models to investigate how craniofacial organs are formed. Most importantly, his research interest has always been focused on linking animal models with human diseases. His research has led to the successful rescue of craniofacial malformations by manipulating signaling pathways during embryogenesis. More recently, Dr. Chai’s research has uncovered important mechanisms on the regulation of mesenchymal stem cells and their potential in craniofacial tissue regeneration.

Dr. Chai authored more than 140 scientific papers and numerous book chapters, and recently edited a book on craniofacial development. His work has earned him multiple awards, including the 2011 IADR Distinguished Scientist Award. He is an elected member of the American Academy of Arts and Sciences. He has also served on the Board of Scientific Counselors at the National Institute of Dental and Craniofacial Research (NIDCR), National Institute of Health (NIH) and is currently serving on the National Advisory Dental and Craniofacial Research Council for the NIDCR, NIH. Dr. Chai earned a DMD degree from Peking University School of Stomatology and a DDS and PhD in Craniofacial Biology from USC.
Cecelia Götherström, PhD, Karolinska Institutet

Cecelia Götherström is Associate Professor in Stem Cell Research at Karolinska Institutet in Sweden and her research is in the field of perinatal regenerative medicine. She was one of the first in the world to isolate and characterize human fetal mesenchymal stem cells. Dr Götherström has developed fetal mesenchymal stem cells for prenatal and postnatal transplantation purposes and since then the cells has indeed been used clinically to treat children suffering from severe osteogenesis imperfecta with promising results. Dr Götherström is leading an international multicentre trial, Boost Brittle Bones Before Birth (BOOSTB4), to evaluate the clinical effect of mesenchymal stem cell transplantation for the treatment of severe osteogenesis imperfecta.

Denise Adams, MD, Boston Children’s Hospital

Denise M. Adams, MD, has been an academic Pediatric Hematologist-Oncologist for just over twenty years. She received her Bachelor’s and Medical degrees from Georgetown University in Washington D.C. After completing her Pediatric Residency Training at the University of Vermont, she was a Pediatric Hematology-Oncology Fellow at Duke University. She was a faculty member at Duke University and the University of Vermont prior to moving to Cincinnati Children’s Hospital Medical Center for 13 years where she became the Medical Director of the Hemangioma and Vascular Malformation Center and was the Director of the Pediatric Hematology/Oncology Fellowship Program. She moved to Boston Children’s Hospital in February of 2016 to be one of the Co-Directors of the Vascular Anomalies Center (VAC). She is actively involved in clinical and translational research in the field of vascular anomalies. She is on the scientific committee of the International Society for the Study of Vascular Anomalies (ISSVA) and is a member of several patient and family advisory boards related to vascular anomalies and well as a member of the National Cancer Institute - PDQ. She has obtained funding through the FDA for the study of sirolimus for the treatment of vascular anomalies and is pursuing other medical therapies for these rare disorders. She is actively involved in teaching medical students, residents and fellow trainees and it committed to mentorship. She has been honored to receive several awards for her teaching and mentorship. In addition, she reviews manuscripts for several journals related to hematology/oncology, vascular anomalies and vascular biology. She has authored numerous publications, and has been an invited speaker both nationally and internationally on the subject of vascular anomalies. She has served on several committees both locally, nationally and internationally. Her main emphasis has been in serving the American Society of Pediatric Hematology-Oncology (ASPHO). She is an active member of several ASPHO committees and is presently the Chair of the Program Committee and the Chair of the Research Committee of the ASPHO Vascular Anomaly Special Interest Group.
Timothy Bhattacharyya, MD, National Institutes of Arthritis and Musculoskeletal and Skin Diseases

I am an academic orthopaedic surgeon in Bethesda, MD.

I am interested in improving the outcomes of patients with orthopaedic conditions, especially fractures and other injuries. I spend the bulk of my time in active clinical orthopaedic surgery practice, performing over 350 cases per year. I primarily perform fracture fixation of the upper and lower extremity as well as total joint replacement. My best research ideas spring from seeing patients in the hospital and working in the operating room. Clinical care has inspired me to perform a number of outcome studies in orthopaedic surgery, always with an eye towards providing information of use to orthopaedic surgeons.

Recently, I have been organizing a multidisciplinary team which discovered a genetic cause for the rare bone disease meleorheostosis. By performing surgical biopsies on these patients with this “candle wax bone,” we have uncovered an interesting facet of bone biology.

Matthew Drake, MD, PhD, Mayo Clinic

Matthew T. Drake, M.D., Ph.D., studies bone loss across both normal and disease states. Specifically, Dr. Drake is interested in the mechanisms underlying age-related bone loss and the skeletal microarchitectural changes that accompany this condition. Additionally, he is working toward a better understanding of the effect of cancer on the skeleton, and particularly of the mechanisms at the root of skeletal metastasis and malignancy-associated bone loss.

Dr. Drake is the program director and principal investigator (PI) on a study focused on the origins and development of monoclonal gammapathy bone disease, with funding from the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Dr. Drake led an investigation, funded by the Multiple Myeloma Research Foundation, aimed at better understanding how the disease causes bone destruction. He was also the PI on Mayo Clinic studies looking specifically at the molecular basis for bone destruction in multiple myeloma as well as bone microarchitecture in multiple myeloma, smoldering multiple myeloma, and monoclonal gammapathy of undetermined significance (MGUS).

The long-term aim of Dr. Drake’s research is to improve understanding of how both normal aging and the presence of malignancies can lead to the softening or destruction of bone mass, with the ultimate goal of contributing to new or improved methods for the prevention and treatment of bone loss.
Sandesh Nagamani, MD, Baylor College of Medicine

Dr. Sandesh CS Nagamani is an Associate Professor in the Departments of Molecular and Human Genetics and Internal Medicine at Baylor College of Medicine. He is focused on translational research that involves evaluating new and potential therapies for various genetic disorders. Dr. Nagamani is a clinical geneticist and provides clinical care for adult patients with a wide variety of heritable conditions including OI, heritable disorders of bone, and other common forms of metabolic bone diseases. He is an Investigator of the Brittle Bone Disorders Consortium.

Andreas Grauer, MD, Amgen

Dr. Grauer is Vice President of Global Development, Therapeutic Area Head for Bone and Nephrology and Inflammation at Amgen in Thousand Oaks, CA. He is an Internist and Endocrinologist by training with a long-standing scientific interest in metabolic bone diseases. Before joining Amgen in December 2008, he was the Executive Medical Director for New Technology Development and the Global Medical Director for Bone at Procter & Gamble Pharmaceuticals.

Dr. Grauer received his medical education at the University of Heidelberg in Germany and at the Royal Postgraduate Medical School at the Hammersmith Hospital in London, UK and his subsequent clinical training at the University of Heidelberg. He performed part of his postdoctoral research during a fellowship in Molecular and Cellular Endocrinology at the Baylor College of Medicine in Houston, TX, USA. Dr. Grauer is an active member of numerous scientific societies around the world, has authored more than 100 manuscripts and book chapters in the field of endocrinology and metabolic bone diseases and has received multiple national and international research awards for his work. Since 1997 he holds a faculty appointment as an Associate Professor of Medicine at the University of Heidelberg, Germany.
Thomas O. Carpenter, MD, is Professor of Pediatrics and Professor of Orthopaedics and Rehabilitation at the Yale School of Medicine. After undergraduate studies at the University of Virginia (B.A., 1973), he received his medical degree (1977) and general pediatrics training at the University of Alabama. His fellowship training in endocrinology at Boston Children’s Hospital, under the tutelage of Drs. Constantine Anast and John Crigler, began his career-long involvement in clinical research focused on metabolic bone diseases in children. He has been at Yale for over 30 years, where his major interest relates to metabolic bone diseases in children. He serves as director of Yale’s Pediatric Metabolic Bone Disease clinic, and is Director of the Yale Center for X-Linked Hypophosphatemia (XLH), which is focused on translational science as relates to XLH and related disorders of phosphorus metabolism. The program serves as a nucleus for clinical research, education, and the care of families with XLH in the Northeastern region and throughout the country. He is frequently contacted by colleagues throughout the US and internationally regarding advice on patient management for children with XLH and other disorders of bone and mineral metabolism. His recent activities have played a major role in the clinical development of burosumab, a novel anti-FGF23 inhibitory antibody for patients with XLH. Dr. Carpenter also serves as Medical Director of the Yale Center for Clinical Investigation’s Hospital Research Unit, an NIH-supported facility for patient-centered clinical and translational research. He served on the Endocrine and Metabolic Drugs Advisory Committee for the FDA, and has been active on various editorial boards of Pediatric, Endocrinology, and Bone journals, currently serving as an Associate Editor of the Journal of Bone and Mineral Research. He has authored over 150 articles, reviews, and book chapters related to metabolic bone disease in children.

Julie Hoover Fong, MD, PhD, Johns Hopkins University

Julie Hoover-Fong, MD, PhD is an Associate Professor in the Department of Pediatrics and Director of the Greenberg Center for Skeletal Dysplasias in the McKusick-Nathans Institute of Genetic Medicine at Johns Hopkins University. As a board certified clinical geneticist, she practices and oversees the clinical operations and research ventures for the patients with genetic skeletal conditions who are served by the Greenberg Center. Her clinical team develops and improves diagnostic and treatment guidelines for comprehensive care of patients with all types of bone conditions including dwarfism, orofacial clefting, craniosynostosis and others. Dr. Hoover-Fong also mentors and teaches medical students, residents and genetic medicine trainees. As an active clinical researcher, she is the Principal Investigator of multiple multi-center clinical trials and investigator-initiated clinical studies for patients with a variety of genetic conditions including achondroplasia, cleft lip and palate, and hypophosphatasia. She is also a co-investigator on the ELSI and Phenotype Review Committees for an NIH-sponsored grant to identify the genetic cause of Mendelian conditions via whole genome sequencing. From a clinical service perspective, she is an active member of the Medical Advisory Board of the Little People of America, the Miller-Coulson Academy of Clinical Excellence, and a charter member of the International Skeletal Dysplasia Management Consortium.
Steven Boyd, PhD, is a Professor in the Cumming School of Medicine (Department of Radiology) at the University of Calgary, and is jointly appointed at the Schulich School of Engineering (Mechanical Engineering) and Faculty of Kinesiology. He received his undergraduate degree in Mechanical Engineering in 1994 from the University of Victoria, and his MSc and PhD degrees in Mechanical Engineering at the University of Calgary, with specialization in Biomedical Engineering, in 1995 and 2001, respectively. Following a postdoctoral fellowship at the Swiss Federal Institute of Technology in Zürich, Switzerland, he started his faculty position at the University of Calgary in 2002. Currently, he serves as the Director of the McCaig Institute for Bone and Joint Health, and holds the Bob and Nola Rintoul Chair in Bone and Joint Research and the McCaig Chair in Bone and Joint Health. His research program is based at the Bone Imaging Laboratory, which he established in 2004, and is focused on bone and joint health research. He and his team have published over 130 papers in peer-reviewed journals, with a focus on bone mechanics related to osteoporosis and osteoarthritis. His work includes the development of image-based computational methods to assess bone quality, and is often applied to large cohort or clinical trials aimed at detection, monitoring and treatment of osteoporosis and osteoarthritis. His research program is supported by the Canadian Institutes for Health Research, the Natural Sciences and Engineering Research Council (NSERC) of Canada, Canadian Space Agency, Canada Foundation for Innovation and Alberta Innovates – Health Solutions. He currently serves as an Associate Editor of the journal Bone, and was recently appointed a Fellow of the American Society of Bone and Mineral Research.

Sharmila Majumdar, PhD, is currently Professor and Vice Chair for Research in the Departments of Radiology and Biomedical Imaging, with joint appointment in the Departments of Bioengineering and Therapeutic Sciences and Orthopedic Surgery at UCSF. She obtained her Ph.D. degree from Yale University in Engineering and Applied Sciences. After a short stay at Yale as a post-doctoral researcher and Assistant Professor, she joined UCSF as an Assistant Professor in 1989. Her research work on imaging, particularly magnetic resonance and development of image processing and analysis tools, has been focused in the areas of osteoporosis, osteoarthritis, and lower back pain. Her more recent focus has been on artificial intelligence applied to biomedical imaging. Her research is supported by grants from the NIH, corporate entities and is diverse ranging from technical development to clinical trials. She was selected as a fellow of the American Institute of Medical and Biological Engineers in 2004 and a fellow of the International Society of Magnetic Resonance in Medicine (ISMRM) in 2008. In 2007, the UCSF Haile T. Debas Academy of Medical Educators at UCSF awarded her the “Excellence in Direct Teaching and/or Excellence in Mentoring and Advising Award”. She was awarded the ISMRM Gold medal in 2016. She has published extensively in highly regarded journals including Magnetic Resonance in Medicine, etc. and serves as a reviewer and on the Editorial Board of scientific journals.
Theresa Kehoe, MD, FDA

Theresa Kehoe is a lead medical officer for bone drugs in the Division of Reproductive and Urologic Products, Center for Drug Evaluation and Research at the Food and Drug Administration. Her team is responsible for the review of drug therapies targeting bone diseases including rare metabolic bone diseases. Prior to joining the FDA, she was an assistant professor of Medicine and Endocrinology at Georgetown University Medical Center. Dr. Kehoe received her medical degree from the University of Maryland medical school. She completed her internal medicine internship and residency at Dartmouth Hitchcock Medical Center and her fellowship in endocrinology at Duke University Medical Center.

Gemma Kuijpers, PhD, FDA

Gemma Kuijpers, PhD, is a pharmacologist/toxicologist at FDA and has been working on the regulatory review of drugs for bone and calcium metabolism disorders since 1995. She has expertise in the field of animal models for bone disease, and is particularly interested in the quantitative analysis of bone characteristics.

William Horton, MD, Oregon Health Sciences University

Dr. Horton is a medical geneticist, whose research on human skeletal dysplasias has spanned four decades. His work has focused on both clinical and basic science aspects of these conditions ranging from generating growth curves to developing methods to study growth plate biology to defining mechanisms by which mutations disturb FGFR3 functions. He is currently Emeritus Director, Research Center, Shriners Hospital for Children and Professor of Molecular & Medical Genetics, Oregon Health & Science University, Portland, OR 97239
MICHAEL P. WHYTE, MD 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, 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. 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.
Brendan Lee, MD, PhD, Baylor College of Medicine

Next generation sequencing and multi-omic approaches for diagnosing skeletal diseases

The rapid advances in next generation sequencing technologies have empowered a rapid increase in genotype-phenotype correlations in rare skeletal diseases. There are currently close to 4000 known disease genes but over 6000 unique genotype-phenotype associations underscoring increasing discovery of novel phenotypic manifestations caused by mutations in the same gene (Online Mendelian Inheritance in Man, OMIM). Two thousand six hundred (2600) of these clinical phenotypes involve skeletal manifestations. Hence, there is an enormous opportunity for discoveries in skeletal development and homeostasis. Beyond the importance of the diagnostic impact on patients, these correlations point to altered protein function beyond traditional loss of function and highlight the contribution tissue-dependent, structure-function correlations to diverse skeletal phenotypes. Past approaches to diagnoses was based on targeted gene Sanger sequencing. Currently, multi-gene panels using next generation sequencing allow for high coverage analysis enabling detection of single nucleotide variation, insertions-deletions, and copy number variations. Capture-based whole exome sequencing has the potential of high throughput analysis of known and potential new gene associations as well as identification of blended phenotypes due to oligogenic inheritance. As part of the NIH Undiagnosed Diseases Network (UDN), the Baylor College of Medicine UDN Clinical site has implemented a multi-omic approach to diagnosis including whole genome sequencing and RNAsequencing of blood and fibroblasts. Whole genome sequencing has further identified regulatory mutations that have the potential to alter allele specific expression, splicing, and isoform utilization. Combined RNAsequence analysis of blood and fibroblast RNA could identify 80% of known OMIM skeletal dysplasia genes and correlated with potential pathogenicity of variants identified by NGS. Hence, a multi-omic approach combining whole exome/genome sequencing and RNAsequencing can increase the yield of diagnostic findings in rare skeletal diseases as well as point to novel genotype-phenotype correlations that will inform new structure function discoveries.

Struan Grant, PhD, Children’s Hospital of Philadelphia

Higher order chromatin structure and distal genetic interactions in the diagnosis of skeletal diseases

Struan F. A. Grant1,2,3

Professor of Pediatrics, Perelman School of Medicine, University of Pennsylvania
Co-Director, Center for Spatial and Functional Genomics
Daniel B. Burke Chair for Diabetes Research
Divisions of Human Genetics and Endocrinology
Children’s Hospital of Philadelphia

1Divisions of Human Genetics and Endocrinology, The Children’s Hospital of Philadelphia; 2Department of Pediatrics and
3Department of Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Genome wide association studies (GWAS) have revealed many loci for complex skeletal traits. However, GWAS just reports genomic signals and not necessarily the precise localization of effector genes, with eQTLs making strong inferences to only a subset of such loci. Chromatin conformation capture-based techniques that detect contacts between distant regions of the genome offer an opportunity to understand GWAS signals that principally reside in non-coding regions, thus likely influencing regulatory elements. To move beyond analyzing one locus at a time and to improve on the low resolution of available Hi-C data, we have developed a massively parallel, high resolution Capture-C based method to simultaneously characterize the physical genome-wide interactions of all human promoters in any cell type. In parallel, we are generating ATAC-seq open chromatin maps to filter for informative proxy single nucleotide polymorphisms (SNPs) for each of the common independent sentinel SNPs reported to date. By querying our promoter ‘interactome’ data in a skeletal setting, we are well positioned to determine contacts to “open” promoters relevant to such bone-related loci. Only by establishing which genes such loci regulate in the correct cellular context can one truly translate genetic association findings.
Recent advancements in genomic technologies have dramatically changed our understanding of the molecular and biochemical basis of diseases. The ability to determine disease causality with less detailed phenotypic information, particularly radiographic imaging, is becoming increasingly common. This is particularly applicable to the prenatal period. Noninvasive prenatal testing in the first trimester of pregnancy via fetal DNA in the maternal circulation has allowed for diagnosis of some aneuploidies, as well as de novo dominant inherited disorders, for example, achondroplasia. Yet there remains a role for radiographic and ultrasound imaging in skeletal diseases, particularly in defining novel disorders, expanding on allelic series of diseases, and following progression of disease and/or treatment. Ultrasound imaging has also provided information on normal human skeletal development in the fetal period. Evaluation of key radiographic features can help illuminate underlying biology by correlating the findings with the skeletal role of the gene(s), particularly in genes or pathways that have previously unknown skeletal roles. Radiographic and ultrasound imaging remain a valuable tool in a deeper of skeletogenesis and skeletal diseases.

Charlotte Gistelinck, PhD, University of Washington
Past, Present, and Future biomarkers of bone and cartilage metabolism

Body fluid markers of bone and cartilage metabolism are potentially useful in the diagnosis and monitoring of various subtypes of skeletal disease including rare heritable diseases. Potential uses of current biochemical assays and new approaches to target disease-associated metabolic products of the skeleton non-invasively will be discussed. The focus will be on collagen metabolic products and subtypes of osteogenesis imperfecta, in most of which collagen post-translational chemistry is disturbed. Specifically, evidence that urine can provide a non-invasive window on the quality of bone (and cartilage) if collagen fragments produces by osteoclastic bone resorption are profiled will be presented. Using peptide mass spectrometry, the ratios of pyrrole to pyridinoline cross-links and hydroxylysyl pyridinoline/lysyl pyridinoline (HP/LP), can reveal the underlying effect of OI on bone type I collagen quality. These ratios are characteristic of certain genetic subtypes of OI. Potentially this information could be useful in monitoring response to therapy longitudinally for example in clinical trials. Related degradation products from collagen types II and III that are profiled in the same mass spectral peptide screen provide useful quantitative reference points in evaluating subtypes of OI and potentially in other skeletal disorders.

The background, molecular basis and recent progress will be summarized.

Michael Collins, MD, National Institute of Dental and Craniofacial Research
Fibrous Dysplasia: Observations, Questions, Models, and Answers

Fibrous dysplasia (FD) is a mosaic skeletal disease caused by one of three somatic, gain-of-function mutations in the Gαs transcript of GNAS (gsp oncogene). Mutations impair GTPase activity, and are associated with increased cAMP. Normally, GDP-bound Gαs is inactive, but recent evidence suggests that GDP-bound gsp interacts with adenylyl cyclase to generate cAMP. FD is mosaic even at the tissue level with evidence that gsp-bearing cells co-opt WT cells, possibly through Wnt/β-catenin signaling, and are induced to behave like mutant cells. Lesions are an admixture of giant cell-rich fibrous tissue and discontinuous trabeculae of poorly-mineralized woven bone, devoid of adipocytes and hematopoiesis. FD can affect craniofacial, axial, or appendicular skeleton with region-specific manifestations and complications that include deformation, fractures, and pain. Most FD lesions appear in childhood; activity wanes with age, is accompanied by a decrease in mutation-bearing cells, a decrease in bone turnover markers, and a change in the radiographic appearance. Pain increases with age, and is not correlated with skeletal burden or activity. Extraskeletal gsp mutation involvement (McCune-Albright syndrome) is associated with hormone-over production and greater skeletal morbidity.

In vitro models utilizing patient-derived bone marrow stromal cells, and gsp-transfected cell lines, including skeletal cells, have provided key insights. These include evidence for tissue level mosaicism, and the role of IL-6, RANK/RANKL, and Wnt/β-catenin signaling in the pathophysiology of FD. Ectopic ossicle xenographs in immunocompromise mice have confirmed tissue mosaicism. Yeast lines expressing mammalian GPCR pathway proteins (gsp and WT Gαs, adenylyl cyclases and phosphodiesterases) are being utilized to probe gsp signaling, and screen molecular libraries to identify and test potential therapeutics. There are five published mouse lines that model FD, all differently engineered, and complementary in the information they provide. They model various important features of the biology and pathophysiology of FD, including confirmation of the necessity and sufficiency of the gsp mutation in skeletal lineage cells to cause FD.

Key questions these models can address are: 1) the molecular basis of pathway activation (GTP- vs GDP-bound gsp), 2) the mechanisms of gsp-mediated skeletal stem cell transduction, including how mutant cells co-opt WT cells, 3) the mechanism of
the establishment and evolution of FD lesions across the lifecycle, including mutant cell dropout; 4) the biological nature of pain in FD, including variability in prevalence, onset, and response to certain therapies; 5) which models demonstrate utility, fidelity, and complementarity in preclinical testing of therapeutics.

Aris Economides, PhD and Dinko Gonzales Trotter, PhD, Regeneron Pharmaceuticals
A receptor serine/threonine kinase gone wild: insights into the mechanism of signaling by ACVR1 in Fibrodysplasia Ossificans Progressiva

The type I Bone Morphogenetic Protein (BMP) receptor ACVR1 is a serine/threonine kinase that transduces signal after forming a heterotetrameric complex with its cognate type II receptors – ACVR2A, ACVR2B, or BMPR2 – comprised of two molecules of ACVR1 and two molecules of any of these type II receptors. The signaling complex is formed following binding of ligands belonging to the BMP/TGFbeta family. Mutations in this receptor system result in several genetic disorders. Perhaps the most profound is Fibrodysplasia Ossificans Progressiva (FOP), an ultra-rare disorder characterized by episodic but cumulative formation of heterotopic bone in select skeletal muscles, tendons, ligaments, and fascia. FOP is caused by mutations in the intracellular domain of ACVR2, with ~97% of patients carrying the variant ACVR1R206H. A significant breakthrough in understanding the molecular mechanisms that drive heterotopic ossification (HO) in FOP was the discovery that Activin A, a BMP/TGFbeta family member, is a required factor for the initiation, growth, and continued expansion of the heterotopic bone by acting as an agonistic ligand on ACVR1R206H (Hatsell, Idone et al, 2015; and, Upadhyay, Xie et al, 2017). In contrast, Activin A normally acts as a competitive inhibitor of BMP signaling mediated via wild type ACVR1. Hence, in FOP, a ligand that normally acts as an antagonist of BMP signaling via ACVR1 is utilized as an agonist by the mutant receptor. In addition to ACVR1, Activin A also utilizes ACVR1B (ALK4) and ACVR1C (ALK7) as type I receptors, but in contrast to ACVR1, Activin A acts solely as an agonist on these two receptors. These data raise the question of how the FOP-causing mutations of ACVR1 that are intracellular and hence do not alter the binding of Activin A to ACVR1, change the response of this receptor to Activin A. Our latest results of experiments exploring this question will be presented and placed in context with recent findings in mouse FOP.

Frank Rauch, MD, Shriner’s Hospital of Montreal
Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is a heritable bone fragility disorder of variable severity; other connective tissue defects are frequently associated. Pathogenic variants in more than 20 genes, mostly related to collagen type I production, have been associated with an OI phenotype. About 98% of individuals with a typical clinical appearance of OI have a disease-causing mutation that is detectable by sequence analysis of these genes. Even though most individuals with OI have low bone mineral density as measured by dual-energy x-ray absorptiometry, material bone density is increased in most forms of OI, regardless of which gene harbors the pathogenic defect. This may contribute to the brittleness of the bone tissue in OI. On the cellular level, children with OI have increased bone formation and bone resorption rates, which makes anti-resorptive treatments with drugs such as bisphosphonates a logical therapeutic option, even though the primary pathogenic defect is expressed in osteoblasts rather than osteoclasts. Beyond the bone fragility, OI is also associated with reduced muscle mass and function. The close correlation between muscle and bone mass that is present in healthy individuals is also found in OI, indicating that in OI higher muscle mass is associated with higher bone mass, as it is in healthy individuals. Muscle may therefore become an additional target for therapeutic intervention in OI.

Yingzi Yang, PhD, Harvard School of Dental Medicine
Loss of Gαs signaling induces osteoblast differentiation in soft tissues of POH patients and during normal cranial bone development by activating Hedgehog signal

Yingzi Yang1,2, Ruoshi Xu1,3; Xuedong Zhou3
1Harvard School of Dental Medicine; 2Harvard Stem Cell Institute; 3West China Hospital of Stomatology

How osteoblast cells are induced during bone development is a central question for understanding the organizational principles underpinning a functional skeletal system. Abnormal osteoblast differentiation leads to a broad range of devastating diseases such as craniosynostosis (premature suture fusion), heterotopic ossification (HO) and osteoporosis. Molecular analyses of skeletal genetic diseases with abnormal osteoblast differentiation have provided important insights in the regulation of osteoblast induction. Progressive osseous heteroplasia (POH) (OMIM#166350) and Albright’s hereditary osteodystrophy (AHO, OMIM 103580) are caused by loss function mutations in the GNAS gene, which encodes the stimulatory alpha subunit, Gαs, of heterotrimeric G protein that transduces signals from G protein coupled receptors (GPCRs). POH and AHO are characterized by
progressive extra-skeletal bone formation through an intramembranous process. We have demonstrated that G\(\alpha\)s restricts bone formation to the skeleton by inhibiting Hedgehog (Hh) signaling in mesenchymal progenitor cells. More recently, we have investigated intramembranous ossification during cranial bone development in mouse models of POH. We find here while Hh ligand-dependent Hh signaling is essential for endochondral ossification, it is dispensable for intramembranous ossification, where G\(\alpha\)s regulates Hh signaling in a ligand-independent manner. We further show that G\(\alpha\)s controls intramembranous ossification during cranial bone development by regulating both Hh and Wnt signaling. In addition, sustained G\(\alpha\)s activation in the developing cranial bone leads to reduced ossification, but increased cartilage presence due to reduced cartilage dissolution, not cell fate switch. Small molecule inhibitors of Hh signaling can effectively ameliorate cranial bone phenotypes in mice caused by loss of G\(\alpha\)s function mutations. Our work shows that studies of genetic diseases provide invaluable insights in normal bone development and understanding both leads to better diagnosis and therapeutic treatment of bone diseases.

Yingzi Yang: This author has nothing to disclose
Ruoshi Xu: This author has nothing to disclose
Xuedong Zhou: This author has nothing to disclose

Maurizio Pacifici, PhD, Children’s Hospital of Philadelphia
Hereditary Multiple Exostoses: New Insights into Pathogenesis and Potential Treatments

Hereditary Multiple Exostoses (as known as Multiple Osteochondromas) is a pediatric musculoskeletal disorder characterized by cartilage-bony tumors termed osteochondromas that form next to the growth plate of long bones, ribs, vertebrae and other skeletal elements. The osteochondromas cause a number of health problems including skeletal deformities, growth retardation and chronic pain, and current surgical treatments to resect most symptomatic osteochondromas are quite helpful but not fully remedial. Most HME cases are linked to heterozygous mutations in EXT1 or EXT2 that encode Golgi glycosyltransferases responsible for the synthesis of heparan sulfate. HS is an essential component of mechanisms regulating many physiologic processes and most importantly, the distribution and activity of signaling proteins. HME patients have a systemic HS deficiency of about 50% that can in itself cause certain health problems including liver malfunctions, but osteochondroma formation requires a “second hit” such as loss-of-heterozygosity, leading to steeper local loss of HS. Over the last few years, we have carried out a number of studies using HME mouse models to elucidate the pathogenesis of osteochondroma formation and identify plausible therapeutic strategies. It has become clear that osteochondromas originate from progenitor stem cells residing within perichondrium flanking the growth plates. The cells normally maintain their mesenchymal-fibroblastic phenotype via action of multiple anti-chondrogenic mechanisms including FGF-ERK signaling and Noggin expression. We found that in Ext1-deficient mutant perichondrium, those traits are rapidly down-regulated, while there is a reciprocal ectopic up-regulation of pro-chondrogenic pathways including canonical BMP signaling. Counterintuitively, the steep loss of Ext1 expression and HS production in mutants was accompanied by excessive expression of heparanase, likely contributing to further decrease the local HS levels and boosting the pathogenic phenotype. Based on these and other data and insights, we tested a potent BMP signaling antagonist (LDN-193189) and a potent anti-chondrogenic drug (Palovarotene). Both treatments were quite effective and substantially reduced the formation and growth of osteochondromas in HME mutant mice. In sum, HME has turned out to have a complex pathogenesis, a reflection of the multiple, intricate and multi-facet roles that HS normally plays in human physiology. Despite such complexity, it appears that targeting certain pathways and cellular mechanisms provides an effective pharmacologic means to inhibit ectopic chondrogenesis and in turn, osteochondroma formation.

Eileen Shore, PhD, University of Pennsylvania
Fibrodysplasia Ossificans Progressiva (FOP)

Fibrodysplasia ossificans progressiva (FOP) is a rare human genetic disease in which extensive and progressive heterotopic (extra-skeletal) ossification occurs in soft connective tissues such as skeletal muscle. At birth, there is usually little indication of the disease, except for a characteristic malformation of the great toes. Heterotopic bone formation, typically associated with swelling and inflammation, begins during early childhood and is episodic and progressive through the patient's lifespan. In all patients examined to date who have a classic clinical presentation of the disease, FOP is caused by a recurrent heterozygous single nucleotide substitution (c.617G>A; R206H) in the BMP type I receptor ACVR1 (Activin A receptor, type 1; ALK2) that causes enhanced signaling pathway activation.

Heterotopic ossification in FOP frequently forms in response to tissue injury, although also develops in the absence of overt tissue trauma. Rare patient biopsies revealed that within affected tissues, heterotopic bone formation in FOP progresses through
initial catabolic events that are followed by aberrant cell differentiation and the formation of endochondral bone tissue. In vivo mouse models have been instrumental in providing a more detailed understanding of the tissue, cellular, and molecular impact of the ACVR1 R206H mutation both in skeletal bone as well as in the soft connective tissues that are transitioning to heterotopic cartilage and bone. In response to soft tissue injury, initial steps of wound healing in mutant tissue appear to be normal, including an early immune response that leads to tissue degradation and removal of damaged tissue. However, this tissue repair trajectory rapidly diverges and, instead of repairing and regenerating the injured muscle tissue, ectopic cartilage and bone are formed. Understanding these events are providing more detailed insight into the consequences of the ACVR1 R206H mutation and the cellular mechanisms that regulate tissue maintenance, repair, regeneration, and heterotopic bone formation.


Andrew Wilkie, FRS, FMedSci, FRCP, University of Oxford
Craniosynostosis: from mutations to pathways and mechanisms

Eduardo Calpena,¹ Nils Koelling,¹ Kerry A Miller,¹ Yan Zhou,¹ David Johnson,² Steven A Wall,² Stephen R F Twigg,¹ Andrew O M Wilkie¹²
¹MRC Weatherall Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Headington, Oxford OX3 9DS, UK
²Craniofacial Unit, Oxford University Hospitals NHS Trust, John Radcliffe Hospital, Headington, Oxford OX3 9DU, UK

andreewilkie@imm.ox.ac.uk

Craniosynostosis describes the process whereby one or more of the cranial sutures, narrow strips of fibrous mesenchyme that separate the skull bones, fuse prematurely during development. To accommodate continued growth of the brain, other sutures compensate by increased growth and osteogenesis, leading to distortion of skull shape. The overall prevalence of craniosynostosis is ~1 in 2000, but behind this figure lies substantial causal heterogeneity, in terms of sutures affected, predisposing genetic or environmental factors, and syndromic associations.

A 13-year birth cohort (1998-2010) of 668 patients attending Oxford, UK has been extensively investigated genetically, providing the most complete picture available of the genetic contribution to craniosynostosis. Pathogenic mutations or chromosomal abnormalities were identified in 175 (26%) of affected individuals. Emphasising the causal heterogeneity, marked variation is observed in the proportion of affected subjects who have an identified cause, depending on the pattern of suture fusion: from 10% for sagittal synostosis to 91% for bicoronal synostosis. Potentially correlating with this observation is the surprising fact that sutures differ in the relative developmental contributions made by neural crest and cephalic mesoderm to the origins of the mid-suture undifferentiated cells and flanking osteogenic compartments. From a clinical standpoint, we have recently made substantial progress in identifying potentially causative mutations in clinically non-syndromic patients in this cohort (from 22 to 35 subjects, a 59% increase). I will present unpublished data on three contributing genes, SMAD6, SIX1 and PRRX1. For each of these genes, two complicating factors in clinical interpretation are first, that substantial non-penetrance of craniosynostosis
occurs in association with the observed mutations and second, that different, apparently unrelated phenotypes also arise from mutations in the same gene.

By collating information on all genes mutated in human craniosynostosis with developmental studies of mouse models, a pathophysiological framework can be constructed. Observed mutations usually display dominant genetics and the underlying disease mechanisms are correspondingly diverse (haploinsufficiency, gain-of-function, dominant-negative action). The emerging picture is that many different classical signalling pathways have been co-opted as part of an evolutionarily late vertebrate elaboration to make the sutures, but feedback homeostatic regulation in the presence of genetic insult seems frequently to be less tightly controlled in the sutures than in other developmental contexts. Analysis of mouse models highlights the role of abnormalities in both developmental patterning and in proliferation-differentiation balance in craniosynostosis. Future integrated analyses, including single cell transcriptomics, will be needed to delineate these mechanisms with greater precision.

**Ophir Klein, MD, PhD, University of California - San Francisco**  
Genetics of tooth development as a window into rare dental disorders

Ophir Klein¹ ²

¹Departments of Orofacial Sciences and Pediatrics and ²Program in Craniofacial Biology, University of California, San Francisco

Teeth are unique to vertebrates and have played a central role in their evolution, and the tooth is an important model system for many areas of research. Clinically, dental anomalies are common congenital malformations that can occur either as isolated findings or as part of a syndrome. I will use discussion of the molecular pathways and morphogenetic processes involved in tooth development as a point of entry to analysis of abnormal tooth development in patients. Developmental biologists have exploited the clear distinction between the epithelium and the underlying mesenchyme during tooth development to elucidate reciprocal epithelial/mesenchymal interactions during organogenesis. The preservation of teeth in the fossil record makes these organs invaluable for the work of paleontologists, anthropologists, and evolutionary biologists. In addition, with the recent identification and characterization of dental stem cells, teeth have become of interest to the field of regenerative medicine. All of these advances provide opportunities for development of novel therapeutic approaches to dental anomalies.

**Anna Teti, PhD, University of L’Aquila**  
Autosomal Dominant Osteopetrosis Type 2: not only a bone disease

Autosomal Dominant Osteopetrosis type 2 (ADO2) is a brittle bone disease induced by mutations of the CLCN7 gene encoding the CIC7 chloride/proton antiporter. ADO2 is characterized by a variety of skeletal symptoms, including bone pain, multiple fractures, osteomyelitis and dental problems, and by skeletal-related events, including nerve compression syndrome, with reduced vision and hearing, and hematological failure, with anaemia and low blood cell counts. However, fragmented clinical information in our small cohort of ADO2 patients showed that they may present with extra-skeletal alterations as well, consistent with a systemic disease. This is in line with the observation that the CLCN7 gene is expressed in many organs. Using our heterozygous Clcn7G213R knock-in mice, carrying the mouse homolog of the most frequent CLCN7 ADO2 mutation (CLCN7G215R), we confirmed that ADO2 is not a mere skeletal disease. In fact, several other organs, including lungs, kidney, muscle and brain, are altered in ADO2, with a consistent perivascular fibrosis apparently associated with high numbers of macrophages and lymphoid infiltrates. This alteration is observed also in muscle, which does not express the CLCN7 gene endogenously, but recruits CIC7-positive macrophages especially in the perivascular areas. Interestingly, RNA-dSeq data sets confirm enriched macrophage and fibrotic signatures in ADO2 extra-skeletal organs and suggest the involvement of the profibrotic TGFβ pathway, confirmed by conventional RT-PCR and immunofluorescence. ADO2 mice also show behavioral signs of anxiety and depression while cognitive functions are unremarkable. Furthermore, their brains present with perivascular fibrosis as well, and with β-amyloid accumulation and astrogliosis. In vitro and in vivo, ADO2 cells from various organs exhibit accumulation of CIC7 in the Golgi stacks, suggesting an impairment of the Golgi CIC7 exit pathway. Consequently, localization of CIC7 in downstream organelles, including late endosomes and lysosomes, is impaired, leading to a high vesicular pH. Furthermore, ADO2 cells show an accumulation of the autophagosome marker, LC3b, and an increase of its partner protein, p62. Finally, an experimental siRNA therapy, previously used by our group to rescue the ADO2 bone phenotype, also improves the extra-skeletal alterations. Therefore, we believe that our results could clinically impinge ADO2 and might help improve future diagnosis, follow up and therapeutic options, which could also include our patent-protected siRNA approach.
Chemical biology involves the application of chemical techniques, analysis, and small molecules produced through synthetic chemistry, to the study and manipulation of biological systems.

In the beginning of the process of drug discovery, small molecules are used to validate a target for a particular disease indication which complements gene-based techniques of target validation, such as gene knockout or RNAi methods. Throughout the drug discovery process small molecules are optimized for their potency, selectivity, and drug-like properties using structure-based and computational chemistry techniques.

In order to test the selectivity of various ligands in a cellular setting (as opposed to in vitro), compounds can be immobilized via a biotin tag which enables the identification of all proteins binding to that ligand. This tagging system can also be used to identify proteins which act in a complex and thus do not directly bind to the ligand in question.

Chemical biology techniques are also used to help study complex biological systems. As an example, several techniques have been established to produce nucleosomes containing specific post-translational modifications. One method involves the introduction of modified side-chains using a cysteine alkylation procedure, another involves native chemical ligation of a synthetic peptide with another peptide which can be produced recombinantly, while a third method introduces modified amino acids using a technique called Amber suppression.

A relatively new technique using PROTAC reagents promotes the degradation of target proteins via ubiquitinylation and directs mobilization of the targeted protein to the proteasome.

In reality, the term “Chemical Biology” can be widely interpreted, but involves the use of techniques at the interface of Chemistry and Biology.

Yang Chai, DDS, PhD, University of Southern California

Mesenchymal stem cells, craniosynostosis and a novel molecular mechanism in regulating cranial suture tissue homeostasis

Yuxing Guo, Yuan and Yang Chai*
Center for Craniofacial Molecular Biology, University of Southern California, Los Angeles, CA 90033

Cranial sutures are joints composed of fibrous tissue and skeletal progenitors. The cranial sutures separate the bones of the skull vault, allowing compression of the skull during childbirth and continued skull growth until adulthood. Craniosynostosis is a common birth defect in which bones of the skull vault fuse prematurely at the sutures. If not corrected, craniosynostosis results in improper growth of the skull, altered brain development and compromised brain function. The only treatment option for patients with craniosynostosis is surgery, which is typically done in infancy. A major complication for children with craniosynostosis is the recurrence of skull bone fusion after corrective surgery, which may necessitate reoperation. The invasive and risky nature of such surgeries is associated with high morbidity and mortality. An unresolved question is whether the genetic defects that lead to synostosis in the first place also contribute to the recurrence of synostosis after surgery. Recently, we identified a Gli1+ stem cell population in the sutures that both self-renews to maintain sutural mesenchyme and gives rise to new osteoblasts for growth and repair of the skull bones (Zhao et al., 2015). Specifically, the suture provides a niche that includes mesenchymal stem cells (MSCs), osteoblasts and osteoclasts, which help maintain calvarial bone homeostasis. However, the cross-talk mechanism among these cells in regulating calvarial bone homeostasis and injury repair remains unknown. In this study, we show that postnatal suture MSCs depend on BMP-mediated IHH signaling to balance osteogenesis and osteoclastogenesis activity. IHH signaling and RANKL function synergistically to promote the differentiation and resorption activity of osteoclasts. Compromised BMP signaling in MSCs leads to diminished cranial sutures. Activation of hedgehog signaling restores osteoclast resorption activity and rescues suture patency in Bmpr1a mutant mice. In addition, MSC-mediated IHH signaling also plays a crucial role during the healing of calvarial defects after injury. Our study reveals the molecular and cellular mechanisms governing cell-cell interactions that regulate calvarial bone homeostasis and repair. Collectively, we demonstrate the important function of Gli1+ MSCs in regulating suture tissue homeostasis. Our study also provides an opportunity for possible future intervention for prevention of suture re-fusion for patients with craniosynostosis.

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ABSTRACT
Severe Osteogenesis Imperfecta (OI), or brittle bone disease, is present already in utero. Persons with severe OI are affected throughout their lifetime with repeated, multiple fractures, short stature, considerable pain and handicap. There is no sufficiently effective treatment for OI. Preliminary clinical experience indicates that transplantation of mesenchymal stem cells (MSC) before and/or after birth may ameliorate symptoms.

The Boost Brittle Bones Before Birth (BOOSTB4) project is focused on translating MSC transplantation into the clinic as a therapy for OI. The main objective of the BOOSTB4 phase I/II multicentre trial is to evaluate the safety and efficacy of postnatal infusions or prenatal and postnatal infusion of MSC for treatment of severe forms of OI (type III and severe type IV). The study will include three groups:

1) Four postnatal infusions (n=15)
2) One prenatal and three postnatal infusions (n=15)
3) Historical and prospective controls (n=30-150)

Over twelve months, the subjects will receive four infusions of same-donor MSC at 4-month intervals.

The primary outcome is safety and tolerability for the infant, pregnant woman and fetus. Secondary outcomes relate to efficacy (fracture frequency, time to fracture, number of fractures at birth, growth, bone mineral density, biochemical bone turnover and clinical OI status). Experience, impact and perception of the therapy will be evaluated in both treatment groups. Non-invasive prenatal diagnosis of OI using rapid exome sequencing of a panel targeted for skeletal disorders for molecular diagnosis of OI will be developed on cell-free DNA.

We have established a European network centred in Stockholm, Cologne, London and Utrecht/Leiden. Ethical and regulatory applications are underway. The BOOSTB4 consortium welcomes clinical cases for non-invasive prenatal diagnosis of OI and for inclusion in the clinical trial. Contact Cecilia Götherström for more information: Cecilia.Gotherstrom@ki.se and WWW.BOOSTB4.EU

Successful clinical demonstration of MSC therapy in OI will pave the way for the treatment of many disorders diagnosed before or after birth. Curing or decreasing the severity of these congenital diseases will result in life-long benefits for the affected individuals and their families from birth onwards.

Denise Adams, MD, Boston Children’s Hospital

Lymphatic anomalies encompass a spectrum of diseases with marked heterogeneity. In 2014, The International Society for the Study of Vascular Anomalies (ISSVA) reclassified complex lymphatic anomalies into Generalized Lymphatic Anomaly (GLA), Gorham-Stout Disease (GSD), Kaposiform Hemangioendothelioma (KLA) and Chanel Type Lymphatic Malformation (CTLM). These disorders can aggressively destroy bone, with significant impact on morbidity, mortality and overall quality of life. The pathophysiology of bony involvement and destruction is still poorly understood. The mTOR inhibitor, sirolimus was used in a prospective trial for complicated vascular anomalies and although numbers were small, sirolimus appeared effective at stabilizing or reducing signs/symptoms of disease including bony manifestations. Based on the addition of mTOR inhibition to bisphosphonate therapy in metastatic cancer therapy, modified regimens have been used for refractory or high risk GLA, KLA, CTLM and GSD but limited information is published on the effectiveness and safety of these regimens. Furthermore, a clearer definition of response and an improved radiologic classification to describe the intricate manifestations of these disorders is essential as many patients are misdiagnosed leading to confusion in treatment options and long term outcomes. Current studies are assessing the intricate radiologic manifestations of these disorders in order to improve classification. Using
this information new response criteria will be defined for assessment of efficacy and outcome measures. This investigation is important as recent discovery in somatic mutations have already lead to other treatment options. A discussion of the ISSVA classification for these disorders, treatment options to date, efficacy and safety results for present limited therapy, new genomic information and future therapy options will be the outline for this presentation.

**Timothy Bhattacharyya, MD, National Institutes of Arthritis and Musculoskeletal and Skin Diseases**

MAP2K1 Mutations and Melorheostosis

Melorheostosis is a rare dysostosis resulting in increased bone formation along a peculiar anatomic distribution. Whyte et al. first demonstrated that somatic mutations cause melorheostosis in adults. We prospectively biopsied melorheostostotic bone in 15 patients and found somatic activating mutations in MAP2K1 in 8 patients. The mutations lead to increased MEK1 signaling and increased osteoblast proliferation, yet decreased in vivo mineralization. Patients with MAP2K1 mutations are a genetically and clinically distinct from other forms of melorheostosis. The ability to obtain pathologic tissue for research can enable marked progress in the study of rare diseases.

**Sandesh Nagamani, MD, Baylor College of Medicine**

Safety and Efficacy of Fresolimumab Therapy in Adults with Osteogenesis Imperfecta — a study by the Brittle Bone Disorders Consortium

Sandesh Nagamani\(^1,\^2\), Dianne Dang\(^1\), Ingo Grafe\(^1\), Eric Orwoll\(^3\), Catherine Pedersen\(^1\), Reid Sutton\(^1,\^2\), and Brendan Lee\(^1,\^2\)

\(^1\) Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA

\(^2\) Texas Children’s Hospital, Houston, TX, USA

\(^3\) Division of Endocrinology, School of Medicine, Oregon Health & Science University, Portland, OR, USA

Osteogenesis imperfecta (OI) refers to a phenotypically and genetically heterogeneous group of Mendelian disorders that manifest with increased bone fragility, recurrent fractures, and bone deformities. OI is caused by pathogenic variants in genes that encode: 1) proα1(I) and proα2(I) chains of type I collagen, 2) proteins required for the posttranslational modification and processing of type I collagen, 3) components required for normal mineralization of bone, and 4) transcription and signaling proteins required for the maturation and function of osteoblasts, and 5) genes whose functions are yet to be understood. The current medical therapy for OI is limited to medications that are FDA-approved for treatment of osteoporosis. Bisphosphonates (BPNs) are generally considered as standard of care in OI. BPN increase bone mineral density (BMD) in children and adults with OI; however, evidence for reduction of fractures is hard to prove. Teriparatide, an anabolic agent, increases BMD in the milder form of type I collagen-related OI but not in the more severe forms of the disorder. Repurposing therapy with use of denosumab and antisclerostin antibody are currently being investigated. None of these therapeutic approaches address the basic pathogenetic mechanism in OI. In two murine models of OI (Crtap -/- and Col1a2tm1.1Mcbr), we have discovered that increased TGFβ activity in the bone matrix is a primary mechanism that contributes to the decreased bone mass, impaired biomechanical properties, and susceptibility to fracture. Increased TGFβ is also a key mechanism responsible for the pulmonary pathology observed in the Crtap -/- model. Importantly, we have shown that inhibition of TGFβ in these two preclinical models leads to increase in bone mass and strength and reversal of the pulmonary pathology in the Crtap -/- mouse model. We are now translating this basic discovery by conducting a clinical trial exploring the safety and efficacy of fresolimumab, a pan-TGFβ blocking antibody, in adults with moderate-to-severe OI (NCT: NCT03064074). This is the first disease-specific therapy trial in OI and is being conducted by the NIH Rare Disease Clinical Research Network’s Brittle Bone Disorders Consortium. The study is continuing to enroll participants and we present the initial safety and biomarker data from clinical trial.

**Andreas Grauer, MD, Amgen**

The Potential Role of Sclerostin Inhibition in Osteogenesis Imperfecta

Andreas Grauer\(^1\), Catrinel Galateanu\(^2\), Rachel B. Wagman\(^1\)

\(^1\) Global Development, Amgen, Inc, Thousand Oaks, CA, USA and UCB Pharma, Brussels, Belgium

\(^2\) Division of Endocrinology, School of Medicine, Oregon Health & Science University, Portland, OR, USA

The effects of the pharmacological inhibition of sclerostin on bone have been well characterized in patients with postmenopausal and male osteoporosis. Sclerostin inhibition has a dual effect with an increase in bone formation and a decrease in bone resorption which has been shown to increase BMD at the spine and the hip in postmenopausal women and in men with osteoporosis. Twelve months of treatment with romosozumab, an investigational anti-sclerostin antibody, followed...
by alendronate, has been shown to reduce the risk of vertebral, clinical, non-vertebral, and hip fractures compared to alendronate alone in postmenopausal women with osteoporosis at high fracture risk. An imbalance in serious cardiovascular adverse events was noted in that study.

Although the pathophysiology of osteogenesis imperfecta (OI) is based on the reduced production of normal collagen or formation of abnormal collagen, abnormal bone turnover and decreased bone formation are both features of the disorder. Pharmacological inhibition of sclerostin in preclinical models of OI have shown increases in cortical and cancellous bone formation, bone mass and strength and (in severe models) a reduction in fracture incidence, while not affecting brittleness. The scientific community has explored a variety of pharmacologic strategies to manage ongoing fracture risk in patients with OI, which can be significant and debilitating, depending on the subtype. Based on our understanding of the mechanism of action and available nonclinical and clinical data, patients with OI may benefit from treatment with romosozumab.

The translation of these effects into benefits for patients, in particular children, with OI is not without challenges, which will be further discussed.

Disclosures: The authors are full time employees of Amgen (AG, RBW) and UCB (CG) and own stock and stock options

Thomas Carpenter, MD, Yale University

FGF23 and X-Linked Hypophosphatemia

X-linked hypophosphatemia (XLH), caused by loss-of-function mutations in PHEX, is the most commonly encountered form of inherited rickets. Leg deformity and short stature are typical features in children. Adults suffer from multiple morbidities (including enthesopathy, myopathy, and osteoarthritis) related to cumulative effects of persistent disease, and underscoring the limitations of currently available therapy. The pathophysiologic hallmark of XLH is impaired renal tubular phosphate reabsorption, with consequent hypophosphatemia that results in impaired skeletal mineralization. Altered vitamin D metabolism also occurs in XLH, manifest by inadequate circulating levels of 1,25 dihydroxyvitamin D (1,25D). Thus, conventional therapy for XLH consists of frequent administration of oral phosphate together with 1,25D as a replacement strategy. Although this approach has been used for decades, the therapy is cumbersome and often leaves patients with incomplete correction of deformity. More recently, an endocrine mediator, FGF23, has been identified as the proximal cause of the combined disturbances in renal tubular phosphate transport and vitamin D metabolism, providing an important target for novel therapeutic approaches to the disorder.

A humanized monoclonal antibody (burosumab) designed to inhibit FGF23 activity was developed as a novel treatment for XLH. We present here a summary of the extended clinical trial experience with burosumab in children and adults: In an initial pediatric trial, 5-12 year-old children with XLH received burosumab every 2 or every 4 weeks with both groups showing improvements in biochemical, radiographic, and patient-reported outcomes, despite prior conventional therapy. Next, 1-5 year-old children with XLH were treated with burosumab every 2 weeks, and improvements in biochemical and radiographic outcomes were evident by week 24 of therapy. A study of burosumab in adults with XLH has shown improved biochemical, radiographic, and patient-related outcomes compared to a placebo-treated group, with increased healing of fractures and pseudofractures identified at baseline.

Many children and adults affected with XLH would benefit from more effective and better-tolerated therapy than the currently available replacement strategy with oral phosphate salts and 1,25D. Administration of burosumab every 2-4 weeks improved clinically important outcomes in growing children, and treatment of affected adults every 4 weeks improved biochemical, radiographic, and patient-reported outcomes. The medication was well-tolerated in both age groups. Inhibition of FGF23 activity using an anti-FGF23 inhibitory antibody appears to be a safe and effective strategy for children and adults with XLH. Long-term follow up studies should inform the development of the cumulative morbidities that occur in adulthood.

Julie Hoover Fong, MD, PhD, Johns Hopkins University

Clinical Experience in Targeting CNP in Achondroplasia

Background: Per the last published nosology, there are 436 distinct genetic skeletal disorders. Of these, over 250 diagnoses are considered a skeletal dysplasia and achondroplasia is the most common with an estimated incidence of 1 in 20,000 (therefore ~370,000 affected individuals worldwide). Achondroplasia is marked by prenatal onset of short limbs relative to the trunk, macrocephaly, midface hypoplasia, lordosis, genu varus and final adult height in the 4’ to 4’4” range. Complications associated with this short stature dysplasia are related to central and obstructive sleep apnea, spinal stenosis, a constricted
foramen magnum, and a variety of otolaryngology problems. Treatment of patients with achondroplasia is largely symptomatic (e.g. tonsillectomy, adenoidec tomy and/or CPAP for obstructive sleep apnea, spinal laminectomy to relieve spinal stenosis) or directed at increasing height via surgical limb lengthening or growth hormone injections.

About 80% of affected individuals have a spontaneous mutation in the fibroblast growth factor receptor gene (FGFR3). A single nucleotide gain-of-function mutation in FGFR3 causes abnormal endochondral bone formation by altering intracellular STAT and MAPK pathways. Continuous infusion of CNP and overexpression of CNP in cartilage of an achondroplasia mouse model successfully normalized linear growth and body proportions. Application to humans was not feasible though due to the short half-life of CNP and this unfavorable mode of administration. More recently, however, CNP modifications to prolong its half-life and other molecular mechanisms have been studied to attempt to alter FGFR3 activity in achondroplasia. These advances in academia have partnered well with new interest in the pharmaceutical industry to study rare genetic conditions, together creating a fruitful moment for treatment options for these patients.

Methods: We will outline pathways involved in chondrocyte biology in achondroplasia in the context of what is known publicly about new investigational pharmaceuticals that have been developed to modify these pathways.

Discussion: In our discussion of the new investigational pharmaceuticals that have been developed for patients with achondroplasia, we will also address unique clinical trial considerations for the participant, the investigator clinician and the pharmaceutical company. This will include the rationale for clinical trial endpoints, short and long-term safety considerations, and differences in risk-benefit considerations in different parts of the world, all as related to achondroplasia.


Steven Boyd, PhD, University of Calgary

High-resolution peripheral quantitative computed tomography (HR-pQCT) provides in vivo assessment of human bone microarchitecture at the upper and lower extremities. Originating from micro-computed tomography (µCT) technology, it became commercially available for human applications in 2005. The newest system has a nominal isotropic resolution of 61 µm, which provides sufficient detail to quantify 3D bone microarchitecture and bone mineral density (BMD) in separate cortical and trabecular compartments.

In contrast to traditional 2D dual-energy x-ray absorptiometry (DXA) that uses BMD as a surrogate for bone strength, HR-pQCT is a 3D measure that can be combined with the finite element (FE) method to provide a patient-specific estimate of bone strength from an individuals' underlying microarchitecture. The promise of HR-pQCT and FE analysis as a new tool for osteoporotic-related fragility fracture prediction has been explored in several cross-sectional studies based on prevalent fractures, and more recently on incident fractures in longitudinal studies. These studies suggest that HR-pQCT provides information about fracture risk that is independent from DXA-BMD, but the establishment of the technology as a clinical tool for monitoring of osteoporosis has remained challenging, in part because of the lack of clinical relevance to the data that is generated.

The development of normative data has been an important step toward providing contextual information in the form of percentiles, Z-scores or T-scores. However, whereas with DXA-BMD, these measures are associated with categories of normal, low bone mass and osteoporotic bone, along with estimates of fracture risk, the same type of relationships are not yet established for HR-pQCT. It would be prohibitively expensive to establish risk stratum de novo using a large prospective cohort to capture major osteoporotic fractures, an alternative approach that is more practical and affordable may be to tie HR-pQCT outcome measures with the primary DXA measures correlated in the same patients. The challenge then becomes to identify a microarchitectural feature that best captures the concept of ‘bone quality’ from HR-pQCT. The number of parameters measured by HR-pQCT is large, which makes it difficult to decide how best to interpret these complex data. A proposed approach to intrinsically include the complex microarchitectural information into a single outcome measure is to use the FE method to estimate bone strength. It is intuitive that bone strength would be an important factor in terms of fracture risk, and it intrinsically captures the complex milieu of microarchitectural features derived from HR-pQCT.

Overall, while there remains significant obstacles to HR-pQCT being adopted as a clinical tool, largely due to the need to tie HR-pQCT outcomes directly to fragility fracture risk, this technology provides a promising alternative for monitoring bone
strength and as an alternative endpoint for bone-related diseases.

**Sharmila Majumdar, PhD, University of California - San Francisco**

In an effort to develop quantitative biomarkers for degenerative joint disease and fill the void that exists for diagnosing, monitoring and assessing the extent of whole joint degeneration, the past decade has been marked by a greatly increased role of noninvasive imaging. This coupled with recent advancement in image processing and deep learning opens new possibilities for promising quantitative techniques for which clinical translation was previously hampered by tedious non-scalable and subjective image analysis.

Magnetic resonance (MR) imaging of articular cartilage and the joint as whole has recently been recognized as a tool for the characterization of morphology, biochemistry and function in osteoarthritis (OA). In this talk MR imaging methods related to imaging cartilage, meniscus, muscle, bone and relating the quantitative tissue imaging to function, pain and movement changes in osteoarthritis will be discussed. The joints that are typically affected by OA leading to joint replacement are the hip and knee, and in this talk we will focus on methods to quantitatively characterize these two joints.

The hyaline articular cartilage is composed of a few chondrocytes surrounded by a large extracellular matrix (ECM). The ECM is composed primarily by water and two groups of macromolecules: proteoglycan (PG) and collagen fibers. These macromolecules in the ECM restrict the motion of water protons. Changes to the ECM, are said to precede morphological changes in articular cartilage and may prove to be early biomarkers of osteo-arthritis. ECM changes such as PG loss, therefore, may be reflected in measurements of T$_{1\rho}$ of water protons, while collagen content and orientation changes can be probed using T$_2$ relaxation time measures. In vitro studies have evaluated the relationship between T$_{1\rho}$ relaxation time and the biochemical composition of cartilage. In vivo studies showed increased cartilage T$_{1\rho}$ values in OA subjects compared to controls. In addition to evaluating cartilage in patients with OA, T$_{1\rho}$ quantification techniques have been applied to cartilage in patients with acutely injured knees, who have a high risk of developing OA. In vitro imaging studies have evaluated the relationship between biochemistry of cartilage and T$_2$, and significant correlations to Young's Modulus. Studies have shown an inverse relationship between cartilage T$_2$ and cartilage thickness and that higher medial cartilage T$_2$ results in greater loss of medial cartilage volume at twelve months. The inter-relationship between different joint tissues to gait, motion and joint loading has also been explored. The inter-relationship between different joint tissues to gait, motion and joint loading will be explored.

Newly emerging artificial intelligence methods applied to quantitative OA imaging holds tremendous promise. Osteoarthritis diagnosis using x-rays can today be automated by using deep learning models and pilot studies showed feasibility of using similar techniques to reliable segment multiple musculoskeletal tissues and to detect and stage severity morphological abnormalities in MR imaging. Analyses based on voxel based relaxometry have shown local patterns in relaxation time elevations and local correlations with outcome variables. Bone cartilage interactions are also widely studied with the analysis of bone morphology and the assessment of metabolic activity with simultaneous PET/MR systems.

Issues related to implementing the quantitative tools across multiple sites demands significant rigor and issues related to disseminating these tools, and barriers to translation will be addressed. In addition, to MR the use of multi-modality PET-MR will be introduced.
Scientific advances are rapidly occurring in the field of rare skeletal diseases and this is leading to an increased interest in therapeutics. Consistent with treatments for other diseases, evidence of safety and effectiveness is required for the regulatory approval of drugs for rare bone diseases. Important issues in drug development include the natural history and pathophysiology of the disease, the mechanism of action of the candidate drug in the affected population, the design of nonclinical and clinical studies, the selection of efficacy endpoints and the adequacy of safety assessments. Regulatory considerations of the FDA related to the development of products for rare bone diseases will be discussed in this program.

William Horton, MD, Oregon Health Sciences University
Endochondral ossification by-product is real-time biomarker for bone growth velocity

Despite its importance as a key parameter of child health and skeletal development, growth velocity is difficult to measure in real time because skeletal growth is so slow and reliable clinical tools to accurately detect very small increments of growth do not exist. Current practice is to calculate average growth velocity from measurements taken typically at 6-12 month intervals, a significant hinderance for clinical trials of new agents developed to normalize bone growth. Within this context, we have identified a novel biomarker for skeletal growth velocity in infants and children. It is the intact trimeric noncollagenous 1 (NC1) domain of type X collagen, a degradation by-product of endochondral ossification that is released into the circulation in proportion to overall growth plate activity. We designated it CXM for Collagen X bioMarker. Levels of CXM correspond to the rate of linear bone growth at time of measurement. Serum concentrations of CXM plotted against a child’s age shows a pattern similar to well-established height growth velocity curves and correlate well with height growth velocity calculated from incremental height measurements in this study. The CXM biomarker is stable once collected and can be accurately assayed in serum, plasma, and dried blood spots. CXM testing should be useful for monitoring growth in the pediatric population, especially growth responses of infants and children with genetic and acquired growth disorders to interventions that target the underlying growth disturbances. As a quantitative readout of endochondral ossification, its utility may extend to managing other conditions such as fracture healing and hyperostosis syndromes.
Hypophosphatasia (HPP) is the inborn-error-of-metabolism caused by loss-of-function mutation(s) of the ALPL gene that encodes the tissue-nonspecific (bone/liver) isoenzyme of alkaline phosphatase (TNSALP). TNSALP is a cell-surface phosphohydrolase that promotes skeletal development by hydrolyzing extracellular inorganic pyrophosphate (ePPi), a potent inhibitor of biomineralization. Consequently, there is in untreated HPP tooth loss and often rickets during growth or osteomalacia in adult life. In 2015, asfotase alfa (StrensiqTM), a hydroxyapatite-targeted TNSALP replacement therapy, was approved multinationally typically for pediatric-onset HPP. To date, one publication summarizes the one-year experience using asfotase alfa for the most severely affected patients; i.e., those infants and young children with life-threatening perinatal and infantile HPP (Whyte et al, NEJM 366: 904-13, 2012), and one summarizes the 5-year experience with survivors of infantile HPP and what can be called the severe childhood form of HPP (Whyte et al, JCI Insight 1: 1-10, 2016). Where we go next is to document the complete experience from these now completed clinical trials that have 7-year experience with the perinatal, infantile, and severe childhood forms of HPP, and the unpublished 5-year experience with adolescents and adults with HPP. The observations and conclusions from each of these studies are now submitted for publication, and the principal findings will be reviewed at the meeting to help guide evaluation and management of HPP patients of all ages as we await new therapeutic approaches for this metabolic bone disease that has the most broad-ranging expressivity of all skeletal disorders.
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Meeting Organizer
Charlene Waldman
waldmancharlene234@gmail.com