Oral Bisphosphonates in Children

Nick Bishop, MD, University of Sheffield, Western Bank, Sheffield, United Kingdom

The incorporation of bisphosphonates into multidisciplinary care for individuals with osteogenesis imperfecta (OI) has represented a major change in practice over the last 25 years. Evidence for their efficacy in increasing bone mass is not in doubt. Of the bisphosphonates administered orally to children, first olpadronate and subsequently risedronate have been shown to reduce fracture frequency in more mildly affected individuals, with similar levels of fracture risk reduction. The apparent lack of efficacy in respect of fracture frequency of alendronate used in a multicentre trial of children with OI in North America may reflect trial design, OI severity and treatment dose. Oral bisphosphonates are poorly absorbed but seem in the main to be well tolerated. Irrespective of choice of agent, short term gains do need to be balanced against the need to continue therapy until growth ceases in the majority of treated children. The potential for increasing fracture risk in the vertebrae in the short term, possibly as a result of increased physical activity, also merits consideration.

In adults, alendronate increased bone mass but there was no significant effect on fracture frequency in the largest controlled trial reported; in general, however, bisphosphonates have been disappointing as a therapeutic agent in adults with OI, perhaps reflecting the fact that growth plays an important role in restoring bone architecture during bisphosphonate therapy in childhood. Further larger-scale studies are needed in adults.

The place of oral bisphosphonate therapy in treating children with mild OI and providing "maintenance" therapy in those more severely affected and initially treated with intravenous bisphosphonates merits further discussion.

Professor Nick Bishop, MB ChB MRCP, MD, FRCPCH
Professor of Paediatric Bone Disease, University of Sheffield, UK

Research focus: understanding the causes of bone fragility in children and improving treatment for children with disabling bone diseases.

Nick's main interest is on bone fragility in childhood, from apparently healthy children with one or more fractures, to children with a defined clinical phenotype such as OI, in whom fractures occur frequently.

His work in otherwise healthy children has identified differences in bone architecture among children with one or more fractures, accentuated by obesity, along with differences in genotype that may be protective against fracture.

In children with osteogenesis imperfecta, he focuses on reducing fracture frequency and improving quality of life using oral and intravenous bisphosphonates.

Intravenous Bisphosphonates in Infants with Moderate/Severe Osteogenesis Imperfecta

Francis Glorieux, Michaela Durigova, Frank Rauch, Telma Palomo and Moira Cheung, Shriners Hospitals for Children-Canada and McGill University, Montréal, Québec, Canada

Cyclical pamidronate (PAM) and zoledronic acid (ZOL) iv infusions improve clinical outcome in moderate/severe OI children older than 3 years of age. The treatment improves BMD, vertebral body reshaping, chronic pain, gross motor function, and together with corrective surgery and rehabilitation, improves degree of ambulation. The major drawback is a marked, prolonged decrease in bone turnover. Since the effects of the drug, particularly on cortical thickening, is growth dependent initiating treatment early in life makes sense. We have shown that PAM initiated before 2 years of age improves bone strength and gross motor function, and decreased fracture incidence. In an ongoing study, focus was made on patients under one year of age at entry. In a first set of 10 patients (age: 2-9 months, mean: 5.7) with severe phenotype, ZOL (0.025mg/kg) was infused every 3 months for 2 years. Treatment was well tolerated with only one single brief episode of hypocalcemia and no AEs. Gain in aBMD Z score was evident in 7/10 subjects with a gain in

aBMD in 9/10. Other endpoints (fracture incidence, bone pain, resorption rate, vertebral morphometry) are still being evaluated. The study will eventually include 15 subjects.

Francis Glorieux, OC, MD, PhD, is the Emeritus director of research and the founder of the Genetics Unit at the Shriners Hospitals for Children in Montréal, Canada. He is also an Emeritus professor of surgery, pediatrics and human genetics at McGill University. Dr. Glorieux has studied many facets of bone and mineral metabolism and genetic bone disease, including osteogenesis imperfecta. He helped establish a program of molecular diagnosis of collagen defects, and another program to study bones in growing children, helping to define the characteristics of the various forms of OI and defining new types of OI. Since 1992, Dr. Glorieux has been conducting clinical trials to study the effectiveness of bisphosphonates in children with moderate and severe OI. Results of these studies have been published in several journals including the New England Journal of Medicine. He chaired the organizing committee for the 7th International Research Conference on OI, held in Montréal in 1999. In 2003, he was the recipient of the Elsevier Award of the International Bone and Mineral Society, and the Jonas Salk Award of the Ontario March of Dimes. In 2003, Dr. Glorieux was made an Officer of the Order of Canada, the country's highest honor for lifetime achievement. Dr. Glorieux is the Chair of the I Foundation's Medical Advisory Council, and regular speaker at the biennial National Conferences on OI.

Effect of Long-Term Intravenous Bisphosphonate Treatment in Children with Osteogenesis Imperfecta

Telma Palomo, Francis Glorieux, Frank Rauch, Shriners Hospitals for Children and McGill University, Montréal, Québec, Canada

Cyclical intravenous bisphosphonate therapy is widely used to treat children with osteogenesis imperfecta (OI), but little is known about long-term treatment outcomes. We therefore performed a retrospective chart review on 39 children (22 girls) with OI who started intravenous bisphosphonate therapy before 5 years of age (median, 2.2 years; range, 5 weeks to 4.8 years), and who had a subsequent follow up period of at least 10 years (median, 14.8 years; range 10.7 to 18.2 years) during which they received intravenous bisphosphonate treatment (pamidronate or zoledronate) for at least 6 years. During follow-up, the lumbar spine areal bone mineral density z-score increased from -5.0 (SD: 1.6) to -2.7 (SD:1.3) and weight z-score increased from -3.2 (1.3) to -1.8 (1.8) ($p<0.001$ each). Height z-scores increased ($p=0.04$) from -5.2 (2.9) to -4.0 (2.0) in OI type IV (n=24), but did not change in OI-III (n=14). Patients had a median of 6 femur fractures (range, 0 to 18) and 4 tibia fractures (range, 0 to 17) during the follow-up period, and underwent a median of 9 (range, 0 to 24) intramedullary rodding procedures (upper and lower extremity segments combined). Spinal fusion surgery was performed in 17 patients. The median Cobb angle in the 22 patients who did not undergo spinal fusion was 21 degrees (range, 0 to 56). In conclusion, long-term intravenous bisphosphonate therapy was associated with higher z-scores for lumbar spine areal bone mineral density, weight and, in OI type IV, height, but the disease burden remained very high. More effective treatment approaches are required.

Frank Rauch, MD is Professor of Pediatrics at the Shriners Hospitals for Children and at McGill University in Montréal, Canada. Dr. Rauch is a graduate of the Technical University of Munich, Germany, and did his pediatric training at the Children's Hospital of the University of Cologne, Germany. During the past 13 years, he has performed numerous research projects on osteogenesis imperfecta, in particular investigating the effect of bisphosphonate treatment.

Michael P. Whyte, MD, is Professor of Medicine, Pediatrics, and Genetics at the Washington University School of Medicine, a staff member of Barnes-Jewish Hospital and St. Louis Children's Hospital, and Medical-Scientific Director at the Center for Metabolic Bone Disease and Molecular Research, Shriners Hospitals for Children in St. Louis, Missouri.

Dr. Whyte earned his M.D. degree at Downstate College of Medicine, State University of New York, Brooklyn, New York and then had internship and residency training in Internal Medicine at Bellevue Hospital in New York City. After two years as Clinical Associate at the National Institutes of Health, Bethesda, Maryland, he did his fellowship in the Division of Bone and Mineral Diseases and joined the medical faculty of the Washington University School of Medicine, St. Louis.

Dr. Whyte's research interests include especially the cause, outcome, and treatment of heritable disorders of bone and mineral metabolism in children and adults. Included are genetic forms of rickets such as hypophosphatasia and X-linked hypophosphatemia, brittle bone diseases like osteogenesis imperfecta, conditions that cause dense bones such as osteopetrosis, and disorders of accelerated skeletal turnover including juvenile Paget's disease. Laboratory

investigations include searches for the underlying mutated genes of new disorders. Phenotype/genotype correlations aim to better understand the pathogenesis of established conditions. Bone-targeted alkaline phosphatase replacement therapy is being evaluated for children and teenagers with hypophosphatasia. The Research Center at Shriners Hospital serves as a national 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 these disorders.

Parathyroid Hormone in Adults

Brendan Lee, MD, PhD, Baylor College of Medicine, Houston, TX

Adults with osteogenesis imperfecta (OI) have a high risk of fracture. Currently, few treatment options are available, and bone anabolic therapies have not been tested in clinical trials for OI treatment. We preformed the largest randomized controlled trial in adult OI. Adults with OI were randomized to receive 20 µg recombinant human parathyroid hormone (teriparatide) or placebo for 18 months in a double-blind, placebo-controlled trial. The primary endpoint was the percent change in areal bone mineral density (aBMD) of the lumbar spine (LS), as determined by dual-energy X-ray absorptiometry. Secondary endpoints included percent change in bone remodeling markers and vertebral volumetric BMD (vBMD) by quantitative computed tomography, estimated vertebral strength by finite element analysis, and self-reported fractures. Compared with the placebo group, the teriparatide group showed increased LS aBMD and total hip aBMD. Vertebral vBMD and strength improved with teriparatide therapy, but declined with placebo. Serum procollagen type 1 N-terminal propeptide (P1NP) and urine collagen N-telopeptide (NTx) levels increased with teriparatide therapy. Teriparatide-induced elevation of P1NP levels was less pronounced in severe forms of OI (type III/IV) compared with the milder form (type I). Type I OI patients exhibited robust BMD increases with teriparatide; however, there was no observed benefit for those with type III/IV OI. Adults with OI, particularly those with less severe disease (type I), displayed a teriparatide-induced anabolic response, as well as increased hip and spine aBMD, vertebral vBMD, and estimated vertebral strength.

Dr. Brendan Lee is the Robert and Janice McNair Endowed Chair in Molecular and Human Genetics, Professor in the Department of Molecular and Human Genetics at Baylor College of Medicine, and an Investigator of the Howard Hughes Medical Institute. Dr. Lee directs the joint MD Anderson Cancer Center and Baylor College of Medicine Rolanette and Berdon Lawrence Bone Disease Program of Texas, and the Baylor College of Medicine Center for Skeletal Medicine and Biology. He is Founder and Director of the Skeletal Dysplasia Clinic at Texas Children's Hospital, and of the Medical Student Research Track at Baylor. 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 that affect the growth and strength of the skeleton. Most recently, he discovered new causes of brittle bone disease in children. In so doing, he is developing new approaches for diagnosing and treating these disorders. In the area of metabolic disease, he is developing new treatments for maple syrup urine disease and urea cycle disorders that are now identified at birth by comprehensive newborn screening. Early diagnosis and treatment will be essential for preventing future complications that may lead to brain injury and death. Dr. Lee has received local and national recognition including induction into the Institute of Medicine (IOM), Texas Academy of Medicine, Engineering, Science, and Technology (TAMEST), Association of American Physicians (AAP), the American Society for Clinical Investigation (ASCI), the TAMEST Peter O'Donnell Award in Medicine, the Society for Pediatrics Research (SPR) 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's research mission is to elucidate developmental and biochemical pathways that regulate organogenesis and postnatal homeostasis, and to translate these discoveries into new diagnostic and therapeutic approaches. By studying Mendelian genetic diseases, he has elucidated physiological mechanisms that can also contribute to common, complex diseases (osteoarthritis, osteoporosis, and hypertension) as well as cancer (osteosarcoma). His program spans from basic mechanistic studies to clinical longitudinal and interventional trials in two areas: Structural birth defects with focus

on the skeletal dysplasias and inborn errors of metabolism (IEM) with focus on the urea cycle disorders (UCD). By identifying targets from these rare diseases, he has developed therapies that may be translated in humans in proof of principle studies and eventually for future commercialization and wider application.

Denosumab Perspectives

Deborah Wenkert, MD, Amgen, Los Angeles, CA

Dr. Deborah Wenkert is a Clinical Research Medical Director in the Bone Therapeutic Area at Amgen. Prior to joining Amgen, she devoted 10 years to the treatment and investigation of pediatric metabolic bone diseases at Center for Metabolic Bone Disease and Molecular Research at Shriner's Hospital, St Louis and cared for pediatric rheumatology patients as an Adjunct Associate Clinical Professor in Rheumatology at St. Louis University.

Dr. Wenkert received her undergraduate (Rice University) and medical education (UTMB) in Texas, pediatric residency (Washington University) in St Louis, pediatric rheumatology fellowship (Tufts) in Boston, and post-doctorate at Harvard University. She has authored or coauthored approximately 25 peer-reviewed manuscripts and book chapters, and is an active member of multiple scientific societies in the areas of pediatrics, rheumatology and bone disease.

Cathepsin K Inhibitor Odanacatib Reduces Bone Resorption While Maintaining Bone Formation

Le T. Duong, Merck Research Laboratories, West Point, PA

An emerging target for the treatment of osteoporosis is cathepsin K (CatK), an osteoclast cysteine protease. This enzyme is primarily responsible for the degradation of demineralized collagen type I. Genetic and pharmacologic evidence has consistently demonstrated that inhibition of CatK reduces bone resorption (BR) while allowing bone formation (BF) to continue. CatK knock-out mice develop high bone mass, associated with 3-fold increase in BF rate relative to wild type. Odanacatib (ODN) is a selective and reversible CatK inhibitor currently in phase III clinical trials for the treatment of postmenopausal osteoporosis. *In vitro* ODN reduces BR without impairing osteoclast formation or survival. In ovariectomized (OVX)-rabbits, while alendronate (ALN) generally reduced remodeling, ODN inhibited BR without reducing BF. In osteopenic monkeys, ODN reduced remodeling-based BF in lumbar vertebrae and hip, while dose-dependently enhancing modeling-based BF, particularly at the periosteal cortical surface of the hip. In another monkey study, treatments with ODN or ALN for 20-mo. were effective in increasing BMD of the spine, total hip and femoral neck. High resolution imaging of cortical sites revealed that ODN increased cortical thickness, translating to improved bone strength. From Phase II clinical studies, treatment with ODN 50-mg once-weekly showed significantly less reduction in BF than bisphosphonates. As the results, the patients who continued to be on 50-mg of ODN for 5 years, showed almost linear rate of accrual BMD gains at the spine and total hip compared to baseline. Taken together, our findings demonstrate that the CatK inhibitor ODN protects bone mass at all sites and builds cortical bone in the hip via a molecular mechanism distinct from the bisphosphonates.

Dr. Le Duong, a graduate from Wellesley College and Georgetown University, is currently the Bone Biology Disease Area Lead at Merck and also lead the Odanacatib preclinical efforts. From her 20-plus year career as a Basic Research scientist at Merck, Le has developed a broad scientific background and gained experiences in managing both early discovery and late-stage development programs. She made contributions to a number of drug discovery programs, including the development of 6 preclinical candidates, several of which advanced to Phase II and III clinical development. Her team has developed proof-of-concept of the □v□3 integrin antagonists for the treatment of osteoporosis. More recently, Le manages multidisciplinary drug discovery teams and integrates end-to-end cross functional efforts to support the development of the cathepsin K inhibitor odanacatib for the treatment of osteoporosis and other bone related indications. During her career, she also directly trained many post-doctoral fellows and research associates. Le's list of professional publications include more than 80 original papers, chapters, and 8 patents. Her research focus have been on the fundamental mechanisms of protein secretion, pathways regulated osteoclast differentiation and bone resorption, as well as developing animal models of diseases associated with bone loss.

An Fkbp10 Mouse Model Recapitulates Joint Contractures Found in Bruck Syndrome
Lietman, C., Machol, K., Munivez, E., Dawson, B., Bertin, T., Chen, Y., Krakow, D., Lee, B.

Mutations in FK506 Binding Protein 10 (*FKBP10*) that encode the FKBP65 protein result in recessive OI as well as Bruck Syndrome, characterized with congenital joint contractures in addition to the low bone mass phenotype. We generated a mouse model using the EUCOMM allele to further elucidate the function of *Fkbp10* in connective tissues. We have utilized the LacZ knockin allele to assess expression during development as well as the knockout allele to discern the phenotypic outcomes of FKBP65 loss in the mouse. Furthermore, mouse embryonic fibroblasts (MEFs) have been used for comparison to human cells and for collagen studies and analysis. We found that *Fkbp10* is expressed at low levels at E13.5 particularly in skeletal tissues and increasing through E17.5 with expression in not only skeletal tissues, but also other mesothelial lined tissues, and vessels. Postnatally, expression is limited to developing bone, tendons and ligaments, suggesting a more restricted role at this time point. Null mice display neonatal lethality with viable embryos isolated up to E18.5 but not after birth, growth delay and generalized tissue fragility. *Fkbp10*$^{-/-}$ mouse embryonic fibroblasts show retention of procollagen in the cell layer, similar to what is seen in patient fibroblasts. Furthermore, we generated conditional knockout mice with scleraxis Cre in order to further investigate the tendon/ligament requirement for *Fkbp10*. We show that these mice recapitulate human features of Bruck syndrome and characterize this phenotype. Together, we suggest that this is a model mimicking joint contractures in humans due to alterations in tendons and ligaments.

Caressa Lietman graduated from Rochester Institute of Technology in 2009 with a B.S. in biotechnology. Ms. Lietman began graduate studies the same year at Baylor College of Medicine in Molecular and Human Genetics. She then joined Brendan Lee's lab in 2010 for graduate thesis work.
She has received the following awards:

- NIH Ruth L. Kirschstein Individual Predoctoral National Research Service Award (NRSA), 2011-2014
- Graduate Education Committee Student Representative 2012-2013
- NIH Training Grant, Baylor College of Medicine 2009-2010
- Several poster awards at Gordon Conference, ASBMR and Rolanette and Berdon Lawrence Bone Disease Program Retreat.

Caressa currently works on mouse models of Osteogenesis Imperfecta and specifically focuses on FKBP10 and OI Type V.

Sclerostin Antibody
Matt Warman, MD, Boston Children's Hospital, Boston, MA

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

TGF-beta in OI Mouse Models

Ingo Grafe, Tao Yang, Stefanie Alexander, Erica Homan, Caressa Lietman, Ming-Ming Jiang, Terry Bertin, Elda Munivez, Yuqing Chen, Brian Dawson, Yoshihiro Ishikawa, Mary Ann Weis, Kuber Sampath, Catherine Ambrose, David Eyre, Hans Peter Bächinger, Brendan Lee

Mutations in *CRTAP*, which is involved in post-translational collagen modification, can cause recessive OI. Interestingly, the phenotype of *Crtap*$^{-/-}$ mice overlaps with phenotypes resulting from upregulated TGFβ signaling, including low bone mass and increased alveolar airway space in lungs. We hypothesized that alterations of collagen in OI result in dysregulation of matrix-cell signaling which contributes to phenotype manifestation.

In mouse models of both recessive (*Crtap*$^{-/-}$) and dominant OI (*Col1a2*$^{+/G610C}$) we found dysregulated TGFβ activity in bone, as evidenced by a higher ratio of pSmad2/Smad2 protein and expression of TGFβ target genes. Furthermore, increased immunostaining for pSmad2 in lungs of *Crtap*$^{-/-}$ mice demonstrated similarly dysregulated TGFβ activity in extraskeletal tissues. To block the excessive TGFβ activity, we treated 8 week old *Crtap*$^{-/-}$ and *Col1a2*$^{+/G610C}$ mice for 8 weeks with the pan-TGFβ neutralizing antibody 1D11 (Genzyme), control antibody treated mutant and WT mice served as controls. MicroCT analysis of vertebrae showed that compared with control mutant mice, 1D11 treatment significantly improved the trabecular bone parameters including BV/TV, BS, Tb.N and Tb.Th. In addition, 1D11 ameliorated the lung phenotype in *Crtap*$^{-/-}$ mice, as demonstrated by a significant reduction of the alveolar airway space.

In summary, we found that dysregulated TGFβ signaling is a common molecular mechanism contributing to the bone defects in recessive and dominant forms of OI. In addition, increased TGFβ signaling contributes to the lung abnormalities in *Crtap*$^{-/-}$ mice. These findings could potentially be translated into signaling based therapies to alleviate skeletal and extraskeletal manifestations in patients with OI.

Ingo Grafe, MD is a postdoc in the laboratory of Brendan Lee, MD, PhD in the Department of Molecular and Human Genetics at the Baylor College of Medicine, Houston, Texas, USA. During his clinical training in the Department of Medicine I and Clinical Chemistry of the University Clinic Heidelberg, Germany, he focused on the treatment of patients with disorders of the endocrine system and with various bone disorders including Osteogenesis Imperfecta. As a member of the Division of Osteology he helped conducting clinical trials for the treatment of patients with bone disease and studied basic mechanisms of bone biology. Dr. Grafe's current research on mechanisms of OI is supported by a Michael Geisman fellowship from the Osteogenesis Imperfecta Foundation (OIF).

TGF-β Neutralizing Antibody: A Potential Therapy for High Bone Turnover Diseases

Shiguang Liu, PhD, Genzyme Inc., Framingham, MA

TGF-β is an important regulator of almost all major cell functions and activities including proliferation, adhesion, motility, apoptosis, and differentiation. It influences many biologic processes including embryonic development, wound repair, immune function, malignant transformation, aging, and bone remodeling. More importantly TGF-β has been implicated in playing important roles in pathological fibrosis, tumor growth and metaphases, and bone disorders. TGF-β neutralizing antibody is a potential therapy for the above diseases. Chronic toxicity studies of TGF-β neutralizing antibodies, Fresolimumab (GC-1008, human antibody) and 1D11 (murine monoclonal antibody), have demonstrated that despite aggressive dosing regimens, neither 1D11 nor GC1008 seriously disrupt key homeostatic roles of TGF-β in rodents, non-human primates, or humans. We explored the effect of 1D11 on bone in high turnover bone disorders using *Jck* mouse, a genetic model of polycystic kidney disease with high-turnover renal osteodystrophy (ROD). TGF-β1 mRNA and downstream signaling is increased in bones from *jck* mice. 1D11 administration to *jck* mice significantly suppresses the elevated bone-turnover evidenced by attenuation of the increased serum OCN and CTX and reductions in osteoblast and osteoclast surface areas measured by bone histomorphometric analysis. 1D11 treatment improves bone quality by increasing trabecular bone volume and cortical thickness. The bone effects of 1D11 are mediated by

inhibiting SMAD2/3 pathway in osteoblasts. In conclusion, TGF- β neutralizing antibody is safe and effective in both animal models and human, and could be a potential therapy for high bone turnover diseases including ROD.

Shiguang Liu, MD, PhD, is a Principal Scientist of the Tissue Protection and Repair Unit at Genzyme R&D, Sanofi. He is a leader of a research team at Genzyme focusing on identification and validation of new therapeutic targets for genetic bone diseases and genetic kidney diseases. He is currently a leader of a project on developing anti-miR-21 therapy for Alport Syndrome. Dr. Liu has studied bone and mineral metabolism and genetic bone diseases for more than 15 years. He has published more than 30 papers in this research area. More recently, his research on the effect of anti-TGF-β antibody on high bone turnover renal osteodystrophy was published in JBMR, and provided strong evidence to support that anti-TGF-β antibody could be a therapy for high-turnover bone disease, including Osteogenesis Imperfecta (OI). Dr. Liu received his M.D. and Ph.D. in Cell Biology in China, and his postdoctoral training at Duke University Medical Center. He was a faculty member of the Kidney Institute at the University of Kansas Medical Center before joining Genzyme.

Lower Extremity Rodding

François Fassier, MD, Shriners Hospitals for Children, Montréal, Québec, Canada

1-Long term follow-up of patients with FD rods
2-OI and DDH: a new mutation?
3-Spine MRI and FD rods: Is there a risk of rod migration?

1 - Long term follow-up of patients with FD rods
This is a preliminary report on 76 patients with 139 FD rods who were followed more than 5 years (5 to 13 years). There was no infection or growth arrest. Sixty three (63) rods had to be replaced (reoperation rate of 45%).
The reasons for rod replacement were: Fracture (30), bending without fracture (4), broken rod without fracture (3), migration of the rod without fracture (6), non-expanding without fracture (7) no details (13).
As fractures represent 47% of the indications for reoperation, we are now looking at this subgroup to be able to precise if the fractures were caused by significant traumas (because OI children have raised their level of activity?), if it is related to a particular type of OI, or the result of a mechanical complication (rod placement).

2 - OI and DDH: a new mutation?
Among 688 patients with OI, 6 patients (9 hips) with DDH were identified (Incidence of 0,8% which is much higher than in the general population). Four (4) out of 5 children who did a genetic testing were found to have a C-propeptide mutation in the proalpha chain of collagen type I.

3 - Spine MRI and FD rods: Is there a risk of rod migration?
Ten (10) patients with 19 FD rods underwent spine MRI's (basilar invagination, basilar impression, platybasia and complex scoliosis) using a 1,5 Tesla magnet. None of the implants have shown any migration, heating effect and artifact.

Dr. François Fassier was born and raised in France. He completed his medical school in Lyon and his orthopaedic residency in Grenoble and Paris. After a year of fellowship in pediatric orthopedic surgery at Ste Justine Hospital (University of Montréal), Dr. Fassier went back to Grenoble as a young staff (Chef de clinique) for one year. In 1982 he emigrated to Canada and became a member of the Ste Justine Hospital staff until 1993. He was then appointed at McGill University and became Chief of Orthopedics at the Montréal Children's Hospital. He played a role in the development of complementarity between the MCH and the Shriners Hospital – Canada. Director of Pediatric Orthopaedic Surgery at McGill University, he became Chief of Staff of the Shriners Hospital – Canada in 2001. Dr. Fassier has many points of interest in pediatric orthopaedics: He introduced the Ilizarov method for bone lengthening in Canada and developed a telescopic implant for children with bone fragility (The Fassier-Duval rod for Osteogenesis

Imperfecta). Besides metabolic and rare genetic disorders, Dr. Fassier has developed a special interest for sports medicine and arthroscopic surgery (hip, knee and ankle). His leadership in the field of surgery in children with fragile bones allows him to travel a lot as a guest speaker in medical meetings or parents' association meetings. He has operated on children in many countries and trained many foreign surgeons in Montréal.

Treatment of the Upper Extremity in Individuals Living with Osteogenesis Imperfecta

Paul Esposito, MD, Children's Hospital, Omaha, NE

Recurrent fractures as well as progressive deformities or joint instability in the upper extremities can be extremely disabling. Individuals living with OI can be dependent on their upper extremities for weight bearing and sitting, and anything that causes pain or instability in the arms can negatively alter quality of life.

There is evidence that medical management improves upper extremity function and comfort. There is limited information with regard to effective treatment of upper extremity fractures and prevention of progressive deformity.

Conservative management with external devices such as casts and braces cannot predictably prevent deformity, and may actually cause loss of strength, decrease bone density and at least transiently decrease independence and function.

Surgical management to stabilize fractures and prevent deformity and non-union may allow maintenance of alignment and stability to enhance more complex fine motor functions. However, there is limited information in the surgical literature to define exactly how these patients are best treated.

Surgical treatment options, predominantly utilizing percutaneous techniques with intramedullary implants work well in many instances. However, there are significant limitations to the devices and techniques available related to patient size, implant materials and design, as well as growth issues and the complex stresses placed on the upper extremities. Further collaborative research to improve the surgical treatment options as well as defining surgical indications and patient selection criteria is critical.

Paul Esposito, MD is the Pediatric Orthopaedic Surgeon of the Osteogenesis Imperfecta Clinic of the Children's Hospital and Medical Center, Omaha, Nebraska, as well as the Clinical Service Chief of Pediatric Orthopaedics. He is Professor of Orthopaedics and Pediatrics at the University of Nebraska Medical Center, Omaha, Nebraska. Dr. Esposito has presented clinical research on OI at the Pediatric Orthopaedic Society of North America and the American Academy of Pediatrics as well as publishing review articles and a surgical technique chapter to extend the reach of the work of the surgical approach to OI developed by Dr. François Fassier and his team in Montreal. Dr. Esposito's ongoing interests are to assist the OI foundation in its efforts to improve access to scientific, multidisciplinary care and research to ensure that children with OI obtain maximum function and comfort with the least intrusive treatment.

Orthopedic Treatment Needs in Adults

Laura Tosi, MD, Children's National Health System, Washington, DC

The Osteogenesis Imperfecta Foundation established the Adult Natural History Initiative (ANHI) in 2010 to give voice to the health concerns of the adult OI community and begin to address existing knowledge gaps for this condition. In the ANHI survey, musculoskeletal concerns were primarily explored using standard review of system queries, as the focus of the survey was to primarily identify previously unrecognized non-musculoskeletal issues. However, the respondents were also given the opportunity to write open-ended responses. Review of those responses has revealed a broad range of musculoskeletal/orthopaedic issues which, although perhaps not common, speak to the complexity of aging with OI and the need for an expanded and on-going natural history effort in order to arm adults with OI with the tools to recognize and articulate their healthcare needs.

Laura L. Tosi, MD is a pediatric orthopaedic surgeon at Children's National Health System in Washington, DC, where she has been on staff for over 25 years. Her clinical practice focuses on the orthopedic care of children with physical disabilities, bone health, and the medical and orthopaedic challenges faced by adults with childhood onset conditions. Dr. Tosi is the founder and director of the Children's National Pediatric Bone Health Program. She has served on the Board of Directors of the American Academy of Orthopaedic Surgeons (AAOS), the Pediatric Orthopaedic Society of North America, the Orthopaedic Research and Education Foundation, the Academic Orthopaedic Society, the Society for Women's Health Research, and the US Bone and Joint Initiative. Dr. Tosi is a past President of the Ruth Jackson Orthopaedic Society, the professional association for women in orthopaedics. Dr. Tosi currently serves on the Medical Advisory Council of the Osteogenesis Imperfecta Foundation and is the Chair of the OI Adult Natural History Initiative. She will be a speaker at the biennial National Conference on OI.

Antiresorptive Medication and Fracture Healing

Nancy Pleshko, PhD, Temple University College of Engineering, Philadelphia, PA

Antiresorptives are standard treatments for osteoporosis and osteogenesis imperfecta, but recent studies have presented conflicting data on the association of these drugs with delayed fracture healing. Questions have been raised concerning the need for intermittent discontinuation of the treatment, e.g., a "drug holiday", particularly in children with OI who have been undergoing long-term treatment. Several studies have found an association with non-healing atypical femoral fractures and prolonged bisphosphonate use in osteoporosis patients, and at least one earlier study found negative impacts on osteotomy healing in OI patients who received pamidronate treatment. Conversely, other studies have concluded that differences in healing time between patients that takes bisphosphonates and those that don't are not significant, and don't outweigh the benefits of antiresorptive therapy. To date, there has been no evidence presented that use of the RANKL inhibitor denosumab in osteoporosis patients negatively impacts fracture healing. Pre-clinical studies may yield additional insight into potential adverse affects, particularly in OI models. Although studies have shown antiresorptives are linked with reduced callus remodeling in OI mouse models, negative effects on the mechanical properties of the healing bone have not been observed, either with RANKL inhibitors or bisphosphonates. It is likely that longer term use of antiresorptives in OI will provide additional evidence-based information to aid in weighing the risks and benefits of antiresorptive use.

Nancy Pleshko, PhD, is a Professor in the Department of Bioengineering at Temple University, with a secondary appointment in the Department of Anatomy and Cell Biology at Temple University School of Medicine. Dr. Pleshko's research program focuses on assessment of tissues at the molecular, cellular, and structural level through application of optical spectroscopy, including mid- and near-infrared spectroscopy and spectroscopic imaging, in concert with complementary techniques. She has a long-standing interest in translational research in connective tissue pathophysiology and orthopedics, including osteogenesis imperfecta, osteoporosis, osteoarthritis and cartilage repair. Dr. Pleshko's research in OI emphasizes evaluation of therapeutics in pre-clinical studies by assessment of bone quality and mechanics, and the effects of therapeutics on fracture healing. She has received funding for her research in OI from the Children's Brittle Bone Foundation, the OI Foundation, and NIH, and has participated in several OI Foundation Scientific Meetings.

Scoliosis - Risk Factors and Prevention

Peter A. Smith, MD, Ali Anissipour, MD, Joe Krzak, PhD, Angel Caudill, MPT, Sahar Hassani, MS, Kim Hammerberg, MD, Shriners Hospitals for Children, Chicago Hospital, Rush University Medical Center, Chicago, IL

Purpose: The purpose of the study was to examine the behavior of scoliosis during growth in individuals with Osteogenesis Imperfecta (OI) and establish its relationship to disease severity, mobility status and bisphosphonate treatment.

Methods: The medical records and radiographs of 316 children and young adults with OI were retrospectively reviewed. Patients were classified according to the modified Sillence classification and by the Functional Mobility Score (FMS). For each participant with scoliosis, serial curve measurements were recorded throughout follow up.

Results: A total of 157 patients with scoliosis associated with OI were identified, a prevalence of 50%. The incidence of scoliosis of the modified Sillence type I, III, and IV OI groups was 39, 68, and 54 percent respectively. The most severely affected group of OI patients, modified Sillence type III, had both the highest prevalence of scoliosis and rate of progression (6 degrees per year). The FMS 50 meter score was also predictive, with those using a wheelchair (FMS=1) showing increased curve prevalence and progression than the independent ambulators without an assistive device (FMS= 5 or 6). Early treatment, before age 6, with bisphosphonate therapy in type III OI decreased the progression rate by 3.8 degrees per year, which was statistically significant.

Conclusion: These findings showed a high rate of significant spinal deformity in children and young adults with severe OI, as defined by Sillence type and the functional mobility score. Our data indicate significant benefits of treating children with severe OI with bisphosphonates at an early stage.

Kim Hammerberg, MD is the Chief Spine Surgeon at Shriners Hospitals for Children. He is an Assistant Professor in the Department of Orthopaedic Surgery at Rush Medical College in Chicago. Dr. Hammerberg is involved in numerous spine deformity studies with many publications. His participation in the multicenter VEPTR study allowed this technique to be approved for further use in the United States and worldwide.

Functional Outcomes & Pulmonary Function Following Spinal Fusion Surgery in Children with Osteogenesis Imperfecta

Jean Ouellet, MD, FRCS (C), Montréal General Hospital, Montréal, Québec, Canada

Patient with Osteogenesis Imperfecta have multiple spinal abnormalities, such as Scoliosis, kyphosis, Basilar invagination and spondylolysis / lesthesis. The surgical management of such spinal deformities is challenging. However, level IV evidence demonstrates that patients with Osteogenesis Imperfecta can successfully undergo spinal surgery to halt the progression of such spinal pathologies. Our results have shown that we are able to obtain and maintain spinal correction in both the coronal and sagittal plane. Patients do go onto fusions even when on pamidronate treatment. Of note, complication rates can be as high as 50% but tend to be transient. Functional status is maintained in children with OI undergoing spinal arthrodesis with actual minor trend towards improvement. Pulmonary function test are stabilized post-operatively and do not worsen over time.

Dr. Jean A. Ouellet is the Director of the McGill Scoliosis & Spinal Group, recipient of the MUHC Scoliosis and Spinal Research Chair and Director of the AOSPINE North America spinal fellowship. He is also the Deputy Chief of the Montréal Shriners Hospitals for Children.

Dr. Ouellet is an Associate Professor of Surgery at McGill University and his training includes spine/scoliosis and Pediatric Orthopaedic Surgery. He has a great passion for improving the care of the patients and he oversees the Neuromuscular Spinal Clinic at the Montréal Children Hospital, the Spina Bifida and Spine Clinics at the Shriners Hospitals for Children.

He received a "*Chercheur Boursier – Fond de Recherche en Santé du Québec (F.R.S.Q.)*" 2010-2012) award.

He supervised many undergraduate, postgraduate, Master Degree, Post-Doctoral Fellows and Ph.D. students. He was also selected as teacher of the year at McGill's Division of Orthopaedic Surgery in 2009.

Orthodontic Treatment

Jean Marc Retrouvey, DMD, MSc, FRCD (C), McGill University, Montréal, Québec, Canada

This presentation will focus on some of the craniofacial manifestations of Osteogenesis Imperfecta, particularly type III and IV, the clinical challenges presented by the disease and the potential effects of bisphosphonates on the outcome of treatment.

Possible genetic correlations will be presented, as well as the results of research efforts jointly conducted by McGill University and the Montréal Shriners Hospital. This OI mouse model based research focuses on the craniofacial effects of OI and the affected bone response to orthodontic treatment.

Jean-Marc Retrouvey, DMD, MSc, FRCD (C), is the director of the division of Orthodontics at McGill University in Montréal, Canada. He is also staff at the Montréal General Hospital and practices orthodontics part time in Pointe Claire Québec. He is an examiner at the Royal College of Dentists and a contributor to the National Dental Examination Board. Between 2008 and 2012, Dr. Retrouvey has been involved with the cranio facial research center at the Montréal Children Hospital whose goal is to study the cranio facial characteristics of several syndromes. Since 2012, he is involved with the McGill research group. Several research projects on OI are in progress in collaboration with Dr. Rauch from the Montréal Shriners Hospital. Dr. Retrouvey, has collaborated to a chapter on dental and craniofacial manifestations of OI in "*Osteogenesis Imperfecta: A Translational Approach to Brittle Bone Disease."*

New Technologies in Rehabilitation

Gerald Harris, PhD, PE, Marquette University, Medical College of Wisconsin, Milwaukee, WI

This overview will investigate current and emerging technologies for assessment and assistive therapy. Technologies will be presented which assess joint range of motion (ROM), muscle strength, gait and mobility, and postural stability. Phone apps, wearable sensors and markerless systems will be presented as well as technologies suitable for 2D and 3D motion assessment. Hand-held as well as automated instrumentation for muscle strength assessment will be covered as well as novel dynamometry for assistive device applications. Recent assistive therapy technologies will be highlighted for portable myoelectric devices, interactive gaming and functional electrical stimulation. Approaches for providing gait and wheeled mobility assistance will be presented with a focus on exoskeletal support, rehabilitation robotics, push activated and power assisted wheeled systems. Technologies for creating more immersive environments through interactive gaming and virtual reality technologies will also be reviewed. Approaches utilizing recent technologies for the design and construction of customized models of triaxial lower extremity (LE) motion will be presented to illustrate development flexibility and clinical application. An approach will also be presented for assessment of bony foot motion through the use of fluoroscopic imaging. Similar approaches for upper extremity (UE) model development will be summarized with examples of customized models for assistive device and wheelchair propulsion assessment. Robotic technology that provides active (motivating) therapy will be described with applications at the ankle, knee, elbow and wrist. Finally, a scenario for case- specific assessment of children with OI will be presented that utilizes a family of advanced technologies including synchrotron micro-CT, finite element analysis, 3D gait, and musculoskeletal simulation.

Gerald F. Harris, PhD, PE, is a professor of Biomedical Engineering at Marquette University and serves as the Director of the Orthopaedic & Rehabilitation Engineering Center (OREC) at Marquette University and the Medical College of Wisconsin. He received the B.S.M.E degree from the U.S. Naval Academy in and the Ph.D. degree in Biomedical Engineering / Biomechanics from Marquette University. From 1981 to 1987, he was Director of the Biomedical and Biomechanics Research Laboratories at Shriners Hospital, Chicago, IL. In 1987, he joined the Biomedical Engineering faculty at Marquette University, and in 1989 was appointed Director of Research in the Department of Orthopaedic Surgery at the Medical College of Wisconsin. His research interests include orthopaedic biomechanics (pediatric and adult), rehabilitation engineering and human motion analysis. Dr. Harris has utilized nanoindentation to better

characterize the structural properties of OI bone in children and young adults. He has also been active in the construction and validation of finite element models of the long bones of children and adolescents with OI for fracture prediction. Recent modeling results include 3-D quantitative gait kinetics (loading constraints and boundary conditions) combined with material property data from nanoindentation studies. He is currently evaluating alterations in model boundary conditions to explore the influence of factors such as bone size, geometry (bowing), structure and functional loading in the development of fractures. Comparisons of modeled parameters to clinical assessment results are ongoing in order to gain insight with regard to fracture development, therapeutic intervention and longer-term outcomes.

Rehabilitation in OI: Looking Back, Going Forward

Kathleen Montpetit, OT, MSc, Shriners Hospitals for Children, Montréal, Québec, Canada

The role of rehabilitation in individuals with OI has evolved considerably in the past 20 years given the advent of bisphosphonate treatment, less invasive orthopedic surgery and the explosion of information and resources via the internet. Therapists work closely with the medical team and family to promote motor development, strength, range of motion, endurance and autonomy in self-care. The broad variability in impairment and function across OI type makes goal setting a challenge. However the ICF model is an important tool for planning clinical interventions and research objectives. This paper will report on the functional outcomes of ambulation, mobility, and self-care in 41 young adults with OI type III and IV after 15 years of bisphosphonate treatment. At last follow up with a mean age of 18.3 all individuals with type IV OI were fully independent for self-care and 87 % were independent community ambulators. In comparison the 17 young adults with type III OI were mainly nonambulators; 65% and only 35% were independent for the essential skills of transfers, grooming, dressing, toileting. Analysis of the barriers to independence and participation in autonomous living for this group revealed weight, upper extremity deformity and motivation to be key factors. Possible facilitators were the ability to stand and step and early acquisition of gross motor abilities.

Kathleen Montpetit, OT, MSc has worked at the Shriners Hospital - Canada since 1979 and is currently the Head of Rehabilitation Services and Clinical Outcomes Coordinator. Kathleen is a graduate of McGill University, with a BSc in Occupational Therapy and a Master's in Rehabilitation. Kathleen has been working with families of children with OI for over 20 years in the multidisciplinary OI program at SHC-Canada. Her focus has been seating and mobility interventions and strategies to be independent in daily life. Another interest is measuring outcomes of treatments and patterns in function across types, ages. She has presented at several international conferences on OI and is author or co-author of several journal articles related to OI.

Mechanical Stimulation of OI Bone

Sandra Shefelbine, PhD, Northeastern University, Boston, MA

Bone is mechano-adaptive, adapting to the mechanical environment by forming bone under high mechanical stimulus or resorbing bone when the mechanical stimulus is low. Bone is responsive to both high magnitude and low frequency loads (impact) as well as high frequency, low magnitude loads (vibrations). Because of the fragility of OI bone, high magnitude loading is not a viable mechanical treatment. However, whole body vibration may provide a viable non-pharmaceutical treatment for increasing bone mass in OI. Previous studies have demonstrated that whole body vibration is particularly effective in young, growing bone and in bone with low bone density. We examined the effects of vibration treatment on young *oim* and wild type (WT) mice. Mice were vibrated in a custom vibration platform from 3 to 8 weeks of age, 5 days per week for 15 minutes per day, at 45 Hz and 0.3g acceleration. We also explored the effects of higher frequency (90 Hz) and longer vibration treatment (9 weeks). We found a significant increase in tibia and femur cross sectional parameters (cross sectional area, cortical thickness, moment of area) in *oim* and WT vibrated mice compared to shams. Trabecular bone volume fraction increased in the proximal tibia in *oim* vibrated mice compare to shame, but not in WT mice. Mechanical strength (yield load) was higher in vibrated WT femurs compared to shams, but not in *oim* femurs due to high standard deviations. Interestingly histomorphological measures of bone formation were not different between vibrated and sham animals, indicating that vibration may reduce resorption rather than promote

formation. Though improvements in bone strength were moderate this study demonstrates that vibration therapy may be a potential non-invasive, non-pharmaceutical treatment for increasing bone mass in young OI bone.

Dr. Sandra J. Shefelbine is an Associate Professor at Northeastern University in the Department of Mechanical and Industrial Engineering. She was previously on the faculty in the Department of Bioengineering at Imperial College London. Her integrative multi-scale approach and the combination of animal experiments, computational models, and clinical studies provides a unique backdrop for determining the relationship between mechanical stimuli and the biological response and how we may use this adaptive response in treating skeletal pathologies.

Muscle Function in Mouse Models of Osteogenesis Imperfecta

Charlotte Phillips, PhD, University of Missouri, Columbia, MO

In addition to bone fragility osteogenesis imperfecta (OI) patients report muscle weakness, though it is unclear if this is due to sedentary lifestyles or pathology. We examined skeletal muscle function and physical activity levels in the *oim* and the Amish (*G610C*) mouse models to determine if they exhibit muscle weakness or altered physical activity levels. We found homozygous *oim* (*oim/oim)* hindlimb skeletal muscles have decreased contractile generating force and an inability to sustain a maximal contraction, with heterozygous +/*oim* mice less affected. Whereas, *+/G610C* hindlimb skeletal muscles showed no differences in muscle mass/body mass ratios, fiber cross-sectional areas or contractile generating capacity relative to Wt (wildtype). We examined activity levels of *oim* and +/*G610C* mice using activity chambers and found one month old *oim/oim* were less active than Wt and *+/oim* littermates, but from 2-4 months there were no differences. +/*G610C* mice did not exhibit different activity levels from Wt littermates. Since activity chambers also reflect behavioral responses to new environments we examined *oim* and +/*G610C* mouse willingness to use running wheels. From 6 weeks-4 months of age *oim* and +/*G610C* mice were individually housed with custom running wheels attached to bicycle computers to monitor speed and distance. All mice exhibited willingness to use the running wheel and the relative use reflected the findings of the activity chambers, except the *oim/oim* mice ran less than +/*oim* and Wt littermates. Our findings suggest OI muscle function and physical activity are mutation specific and should be considered when designing physical therapeutic strategies.

Charlotte L. Phillips, PhD, Associate Professor of Biochemistry and Child Health, University of Missouri School of Medicine, Clinical Molecular Geneticist (American Board of Medical Genetics), Columbia, MO. Dr. Phillips' received her PhD in Biochemistry from North Carolina State University, Raleigh, NC. During her post-doctoral training with Dr. Richard Wenstrup and Dr. Sheldon Pinnell at Duke University Medical Center, Dr. Phillips was also a Michael Geisman Research Fellow. Dr. Phillips' research focus is to investigate the molecular/biochemical pathogenesis of osteogenesis imperfecta (OI), and to develop alternative therapeutic strategies to enhance bone quality and biomechanical integrity. Dr. Phillips has a broad background in biochemistry, molecular biology, medical genetics, biomechanical testing of mineralized and non-mineralized tissues, and more recently skeletal muscle biology and contractile function, and exercise modalities in mouse models of OI (*oim* and *G610C*).

Muscle Weakness in OI Type I

Angela Caudill, MPT; Ann Flanagan, PT, PCS; Sahar Hassani, MS; Adam Graf, MS; Gerald Harris, PhD; Peter Smith, MD, Shriners Hospitals for Children, Chicago, Illinois; Orthopedic and Rehabilitation Engineering Center, Marquette University

Purpose: To determine whether children with osteogenesis imperfecta (OI) type I demonstrate muscle weakness, specifically at the ankle plantarflexors, and does ankle plantarflexor strength correlate with physical function.

Methods: 20 children and adolescents with OI type I and 20 control subjects, age 6-18 years old, were age and gender matched. They participated in a single evaluation session that consisted of strength assessment, Pediatric Outcome

Data Collection Instrument (PODCI), Gillette Functional Assessment Questionnaire, and the Faces Pain Scale – Revised.

Results: When compared to the control group, the OI group demonstrated ankle plantarflexor weakness. Isometric ankle plantarflexor strength correlated with the heel-rise strength value. Outcome assessment using the PODCI identified limitations in the subscales sports and physical function and pain/comfort in the OI group.

Conclusions: Weakness of the ankle plantarflexors is present in children and adolescents with OI type I and this weakness correlates with physical function. Tools that are valuable to physical therapists when assessing strength in children and adolescents with OI type I include: PODCI, Gillette Functional Assessment Questionnaire, the heel-rise test as well as isometric biodex strength assessment.

Angela Caudill, MPT is a Pediatric Physical Therapist currently working in the Motion Analysis Laboratory and in Research Study Coordinator for the Longitudinal Study of Osteogenesis Imperfecta.

Muscle Anatomy, Muscle Function and the Muscle-Bone Unit in Osteogenesis Imperfecta Type I

Louis-Nicolas Veilleux, PhD, Shriners Hospitals for Children and McGill University, Montréal, Québec, Canada

Osteogenesis imperfecta (OI) type I is a heritable bone fragility disorder that is caused by mutations affecting collagen type I. OI type I may be associated with muscle weakness which may contribute to low bone mass and thus bone fragility. We therefore investigated muscle anatomy, muscle function and the functional muscle-bone unit of the lower leg in 54 patients with OI type I (age range, 6.4 to 21.3 years; mean [SD] age, 12.6 [4.2] years; 34 females) and 54 healthy age- and gender-matched controls. The muscle-bone unit was assessed in a subgroup of 30 patients who had not received bisphosphonate treatment (age range: 6.5 to 21.0 years; mean age [SD] 11.2 [4.0]; 20 females) and their age and gender-matched controls. Calf muscle cross-sectional area, muscle density as well as tibia bone mineral content (BMC; mg/mm) were measured by peripheral quantitative computed tomography. Lower extremity muscle function (peak force per body weight and peak power per body mass) was measured by mechanography through 5 tests: multiple two-legged hopping, multiple one-legged hopping, single two-legged jump, chair-rise test, and heel-rise test. Compared with age- and sex-matched controls, patients with OI type I had smaller muscle size (P=0.04) but normal muscle density (P=0.21). They also had 10% lower average peak force and 16% lower specific force (peak force/muscle cross-sectional area; all P<0.008). Average peak power was lower in patients with OI type I but not significantly so (P = 0.054). Compared to age- and gender-matched controls, patients with OI type I had 16% lower BMC ($p < 0.001$). Regression analyses showed that muscle force was a significant predictor of bone mineral content or in other words a predictor of bone strength ($r^2 = 0.81$, $p < 0.001$) and that the disease status did not influence this relationship. In conclusion, children and adolescents with OI type I have, on average, a significant force deficit in the lower limb as measured by dynamic force tests. Nonetheless, the data also show that OI type I is compatible with normal muscle performance in some individuals. The results also suggest that the muscle-bone relationship in OI type I is similar to that observed in a healthy population. Thus, lower muscle force may contribute to decreased bone strength in OI type I.

Louis-Nicolas Veilleux has a PhD degree in kinesiology from the University of Montréal, specialized in movement control and learning. For the past three years he has been working with Dr. Frank Rauch as a postdoctoral fellow at the Shriners Hospitals for Children and the Marie Enfant Rehabilitation Center in Montréal. His main research interest is focussed on the investigation of the musculoskeletal system and the role of physical activity as an adjunct therapy in pediatric bone and neuromuscular disorders.

New Pharmacological Approaches to Treat Muscle Deficits

Matthew Meriggioli, MD, New Pharmacological Approaches to Treat Muscle Deficits, Novartis Institutes for BioMedical Research, Cambridge, MA

The molecular mechanisms underlying the maintenance of skeletal muscle mass and function comprise a complex interplay involving multiple signaling pathways. Loss of skeletal muscle mass or atrophy may be seen in a variety of clinical conditions, in which the balance between protein synthesis and proteolysis in muscle is perturbed. Excessive loss of muscle mass is associated with poor prognosis in several diseases, including primary myopathies and muscular dystrophies, as well as in systemic disorders such as cancer, chronic obstructive pulmonary disease, sepsis and heart failure. Muscle loss also occurs during aging.

Exercise intolerance, muscle fatigue, and weakness are symptoms reported by patients with Osteogenesis Imperfecta (OI), but the precise patho-molecular mechanisms underlying these complaints are unclear. Recent studies have defined the pathways leading to muscle atrophy and dysfunction, and have identified molecular targets for intervention. As a result, a new generation of drugs is emerging, primarily aimed at inducing muscle hypertrophy, but also targeting muscle contraction and energy utilization. Relevant therapeutic approaches include the use of anabolic agents (testosterone, GH, IGF-1), the inhibition of the myostatin signaling pathway, and maintaining or enhancing mitochondrial function.

Dr. Matthew N. Meriggioli is a clinical neurologist and translational researcher. Currently, he is senior translational medicine expert in musculoskeletal diseases at the Novartis Institutes for Biomedical Research in Cambridge, MA, a position he has held since November 2012. Previously, he was associate professor and director of the Neuromuscular Disorders Division, Department of Neurology and Rehabilitation Medicine, University of Illinois Hospital and Health Sciences Center in Chicago, IL.

Dr. Meriggioli is board certified in Neurology with added qualifications in Clinical Neurophysiology and Neuromuscular Medicine. He completed his neurology residency at Loyola University Medical Center in Chicago, and completed a two-year neuromuscular fellowship at Duke University in Durham, North Carolina.

His publications include more than 75 scientific papers, abstracts and reviews covering a various areas of neuromuscular medicine, but focusing on disorders of the neuromuscular junction, particularly myasthenia gravis. Dr. Meriggioli serves on the editorial board for Muscle and Nerve and European Neurology and is an ad hoc reviewer for another 15 scientific journals. In his current position Dr. Meriggioli is involved in preclinical and early clinical drug development in the musculoskeletal disease area.