conditions. Case reports and small series suggest that radiation and medical therapies (predominantly interferon and/or bisphosphonates) can stabilize progressive disease. These studies are limited by inconsistent phenotyping, variation in length of therapy and follow-up, and publication bias. We performed a retrospective study of 102 patients who have been referred to our center (24 with G-SD and 78 with GLA). Our data suggest medical therapies may allow remineralization; however, we do not know whether all patients benefit or whether those that do have sustained improvement. Important next steps include a thorough study of natural history and responses to therapy in large patient cohorts, prospective interventional trials with clearly defined outcome measures, and discovery of the genetic cause(s). Recent technologic and analytic advances in DNA and RNA sequencing, improvements in recreating human disease-causing mutations in model organisms, and in high-throughput screening for new therapeutic agents create optimism that the scientific and medical community will soon achieve a detailed understanding of the causes of G-SD and GLA and devise improved therapies for patients.

Melorheostosis ... *By Michael Whyte, MD; Shriners Hospital, Washington University School of Medicine, St. Louis, MO*

Melorheostosis (MEL) refers to "flowing hyperostosis" (dense bone), typically in the limbs, appearing radiographically like wax dripping down a candle. Reports of ~200 cases show sporadic occurrence (not inherited), although MEL can appear in the genetic "spotted bone" disorders, osteopoikilosis (OPK) and Buschke-Ollendorff syndrome (BOS). MEL typically presents during childhood in one limb, and otherwise is asymmetrical. Skin changes may overlie dense bone and can include scar-like tissue, excessive hair, and small blood vessels. The collagen appears normal, i.e., linear melorheostotic scleroderma. Pain and stiffness are major symptoms. Affected joints can contract and deform. Leg-length inequality sometimes occurs from soft-tissue contractures or premature fusion of growth plates. The skeletal lesions seem to progress most during childhood. In adults, MEL may gradually extend, but pain is especially frequent. Thickening of the inner cortical bone occurs during childhood, and then at the surface during adulthood. Irregular, eccentric, osteosclerosis is the radiographic consequence. Any bone may be affected, but most commonly within lower limbs. Ectopic bone can develop, particularly near joints. MEL bone is hyperemic and causes a "hot" bone scan. Routine biochemical studies are unremarkable. Its anatomic distribution in sclerotomes, myotomes, and dermatomes suggests a segmentary defect during embryogenesis. Linear scleroderma may reflect the primary abnormality that descends into bone. Affected skin has an altered expression of several adhesion proteins. Germline mutation of *LEMD3* causes OPK and BOS, but not classic MEL. Contractures or neurovascular compression can require surgery, but it is challenging and recurrent deformity is common. Distraction techniques have been promising.

Studies of Osteoclast Pathogenesis of Craniometaphyseal Dysplasia (CMD) in a Mouse Model and in Patient-specific IPS Cells ... *By I.-Ping Chen, DDS, PhD, Liping Wang, MD, Keiichi Fukuda, MD, PhD, Noemi Fusaki, PhD, Akihiro Iida, PhD, Alexander Lichtler, PhD, and Ernst J. Reichenberger, PhD; University of Connecticut, Farmington, CT*

Rare genetic bone disorders are of significant clinical relevance because of their number and their life-time debilitating impact on patients. Treatment options are often limited due to insufficient knowledge of their pathogenesis. Studies have been plagued by the unavailability of primary cells/tissues and suitable animal models. Patient-specific induced pluripotent stem (iPS) cells offer new avenues for studying bone cells from patients with rare diseases. We study craniometaphyseal dysplasia (CMD) utilizing a knock-in mouse model and patient-specific iPS cells. CMD is characterized by hyperostosis of craniofacial bones concurrent with widened metaphyses in long bones. Mutations for autosomal dominant CMD have been identified in the *ANK* gene (*ANKH*). A knock-in (KI) mouse model expressing a human *Ank* mutation (Phe377del) replicates many features of CMD. We observed defects in *Ank*KI/KI osteoclast (OC) cultures including (1) decreased OC formation; (2) reduced mineral resorption; (3) reduced OC migration shown by live-cell time-lapse imaging; and (4) altered podosome organization. The bone mass phenotype of *Ank*KI/KI mice is partially rescued by wild-type bone marrow transplants. We hypothesize that CMD-causing *ANKH* mutations decrease the osteoclast activity by negatively affecting the actin cytoskeleton. Our ultimate goal is to test this hypothesis in the human system using patient-specific inducible pluripotent stem cells (iPSCs). We derived iPSCs from peripheral blood mononuclear cells of CMD patients and healthy controls with four separate Sendai-virus vectors encoding OCT3/4, SOX2, KLF4, and c-MYC. The Sendai virus, a cytoplasmic RNA vector, can produce iPSCs free of vector integration into chromosomes. The pluripotency of these iPSCs is tested by (1) expression of hES cell markers; (2) embryoid body