Abstract 1 - Proteostasis

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The chemical information within the polypeptide chain, co- and post-translational modifications of the amino acids comprising the protein, such as N-linked glycosylation, and the interactions of the polypeptide with proteostasis network components determine whether a given member of the proteome will fold and function, be degraded, remain natively unfolded, or aggregate and create additional proteostatic challenges for the organism. The outset of the seminar will focus on the intrinsic forces that predispose polypeptides to fold, including conformational propensities, hydrogen bonding, the hydrophobic effect and N-linked glycosylation. The second part of the talk will focus on the extrinsic forces that assist and enable proteome maintenance, and the means by which the proteostasis network enhances protein structure, function and clearance to facilitate life and avoid loss- and gain-of-function diseases. The influence of the proteostasis network, comprising transcriptional and translational control of protein synthesis, chaperone- and enzyme-assisted folding, and disaggregation and degradation activities will be covered. Furthermore, the influence of aging-associated signaling pathways on proteome maintenance will be outlined. The lecture will close with a summary of what we have learned about degenerative diseases associated with protein aggregation and loss-of-function diseases associated with excessive mutant protein misfolding and degradation. Specifically, we will focus on how we are ameliorating these diseases with proteostasis regulators, small molecules that readapt the innate biology of proteostasis through signaling pathways that control the proteostasis network.
Abstract 2 - Genome Wide Set of Human Enhancers
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Tissue-specific enhancers are principal regulators of spatiotemporal gene expression and alterations in their activities contribute to many human disorders. Due to their location in non-coding genome regions and limited knowledge about their sequence features, human enhancers have been only minimally annotated. I will describe a large program focused on leveraging extreme evolutionary sequence conservation to identify putative regulatory sequences in the human genome and characterizing their in vivo enhancer activity in a transgenic mouse assay. To date, we have tested more than 500 such elements including all noncoding human-rodent ultraconserved elements in the human genome. More than 200 of them function as tissue-specific enhancers and reproducibly target gene expression to a broad range of anatomical structures. As a community resource, we have established a database to visualize and query the activity of these enhancer sequences at http://enhancer.lbl.gov/ and will be generating additional data for several thousand enhancers over the next several years.
Most “single gene” or monogenic disorders display phenotype variability that is only partially correlated with allelic variation in the disease-causing gene. Cystic Fibrosis, a disorder due to dysfunction of the CF transmembrane conductance regulator (CFTR), is such an example. Lung disease, the major cause of morbidity and mortality in CF, is highly variable even among individuals with identical CFTR mutations. These observations suggest that modifiers play a substantial role in CF lung disease. However, candidate gene methods to identify genetic modifiers have met with limited success with only two genes demonstrating replicated association with the lung severity. Lack of success may be due to poor selection of candidates or predominance of environmental factors rather than genetic modifiers in CF lung disease variability. To determine the relative contribution of genetic and non-genetic factors to variation, twins and siblings with CF have been recruited by the U.S. CF Twin and Sibling Study. Lung function as measured by the forced expiratory volume in 1 second (FEV1) is predictive of disease progression and survival in CF patients. This measure is more highly correlated in monozygous twins than in dizygous twins and siblings. These correlations infer that heritability (degree to which genes contribute to variation in a trait) of CF lung function is approximately .65. This heritability estimate is unchanged in individuals who carry identical CFTR mutations. These results demonstrate that genetic modifiers play an important role in variation in CF lung disease. The remaining 1/3 of the variation in lung disease can be attributed to other factors including those in the environment such as exposure to second-hand cigarette smoke (SHS). We have demonstrated that SHS exposure can modify lung function by 10%. Furthermore, variation in TGFβ1, a genetic modifier identified by Drumm and colleagues, interacts with SHS to double the deleterious effect upon lung function. To identify new genetic modifiers, the Cystic Fibrosis Modifier Gene Consortium was formed among the CF Twin/Sibling Study, the Genetic Modifier Study from University of North Carolina and Case Western, and the Canadian CF Genetic Modifier Study based in Toronto. The Consortium is currently performing genome-wide association and linkage studies to identify novel modifiers for CF lung disease. Twin and sibling analysis of other CF traits demonstrate that intestinal obstruction (termed meconium ileus) and diabetes display high heritability, thereby justifying genome-wide searches for genetic modifiers of these traits. Thus, studies in CF demonstrate that factors beyond variation in the disease-causing gene underlying disease variability can be quantified and used to inform searches for key modifiers.
Abstract 4 - Self-Assembling Bioactive Nanostructures for Regenerative Medicine

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Rapid advances in biology and nanotechnology have led to the possibility of designing bioactive materials for cell signaling in regenerative medicine. The main goal in this new field is to design nanostructures that are molecularly crafted to signal cells both in vitro, or in vivo. The chemistry of such nanostructures should allow them to interact specifically with cell receptors or intracellular organelles, interjecting with signaling pathways. The designs could also offer targeting of nanostructures to specific tissues and organs in order to use systemic delivery of therapies. Ideally, the nanostructures should also disintegrate into nutrients or harmless components within an appropriate time frame after regenerative processes have been triggered by their structure. Our laboratory has developed an extensive family of amphiphilic molecules that self-assemble into nanofiber architectures with capacity to display signals to cells1-7. These systems were designed to be biomimetic of the extracellular matrix and to self-assemble into one-dimensional nanostructures in the presence of electrolytes. They can therefore be delivered clinically as simple injections of aqueous solutions that instantly form networks around cells in vivo. This lecture will illustrate the use of nanoscale molecular features in these systems to regenerate axons in the central nervous system after spinal cord injury and other brain disorders3,8, and will also describe molecular designs targeting bone and cartilage regeneration as well as angiogenesis on demand5. In the case of bone, the systems designed have the capacity to both recognize receptors and also mineralize in physiological environments to generate hydroxyapatite crystals that mimic those found in mammalian bone or enamel1,9. The angiogenic materials to be discussed could be useful in cardiovascular therapies such as peripheral vascular disease, wound healing, and cell transplantation10.

5. Nano Letters 2006, 6 (9), 2086-2090
6. Biomaterials 2007, 28(31), 4608-4618
7. Science 2008, 319 (5871), 1812-1816
8. J. of Neuroscience 2008, 28 (14), 3814-3823
10. Transplantation, in press
Abstract 5 - FDA Incentives for Development of Therapies for Rare Diseases

Mathew T. Thomas, MD

FDA Office of Orphan Products Development

FDA’s Office of Orphan Products Development (OOPD) was created in 1982 to administer the provisions of the 1983 US Orphan Drug Act (ODA) and assist sponsors (individuals, groups or pharmaceutical companies) in the development of products (drugs, biologics, devices, and medical foods) for the diagnosis, prevention or treatment of rare diseases or conditions in the US population. OOPD offers incentives for product development in rare diseases through four major programs: Orphan Designations, Grants, Humanitarian Use Device (HUD) Designations, and Outreach activities. This presentation will discuss these programs, explain the incentives that were developed and how they contribute to OOPD’s mission, review OOPD’s successes, and provide data to demonstrate the utilization of incentives for the development of products for rare bone-related diseases or conditions.
Classical Osteogenesis Imperfecta (OI) is a dominant negative skeletal dysplasia caused by mutations in COL1A1 or COL1A2 genes, coding for the alpha chains of type I collagen. The main OI clinical outcome is bone fragility and deformity. We generated some years ago a knock-in murine model for OI, BrtIIV carrying a Gly349Cys substitution in the α1 chain of type I collagen. BrtIIV shows a moderate or a lethal OI outcome reproducing the phenotypic variability reported for human patients. Taking advantage of that we investigated the molecular basis of this variability by evaluating bone mRNA expression by microarray and bone protein profile by 2-DE and mass spectrometry in the OI murine model BrtIIV. We generated the first reference 2-DE map for calvarial tissue, identifying 164 spots corresponding to 97 distinct proteins.

In particular we found an increase in lethal BrtIIV of Gadd153 and a lower expression of the αBcrystallin that indicated an effect of the intracellular machinery on the phenotypic outcome. The higher expression in lethal BrtIIV of the extracellular matrix proteins Prelp, Bmp6 and Bmp7 and the reduced expression of Matrilin 4, Microfibril-associated glycoprotein 2 and Thrombospondin 3, revealed that the extracellular matrix composition also modulates OI phenotype.

We then used our murine model to develop a cell therapy treatment which employs in utero transplantation to avoid marrow ablation for this metabolic inborn disorder. The bone marrow cells were isolated from long bones of eGFP-CD1 mice and injected into the liver of E14.5 embryos. Mice were analyzed at 2 m, the age corresponding to the severest BrtIIV bone phenotype, compared to WT. Engraftment with a characteristic patchy distribution was detected in various tissues at sacrifice by inverted microscopy. Confocal microscopy was used to directly quantify the engraftment in long bone diaphysis. The percentage of donor cells was determined by FACS, in both bone marrow and spleen and by Real Time PCR in different tissues. A reduction of the amount of mutated collagen was detected at both trabecular and cortical regions of long bone.

The femur length was increased in transplanted mutant mice (p<0.005). PQCT of the distal femoral metaphysis revealed increased total bone and trabecular density in treated versus untreated mutant mice. Micro CT analysis of BrtI mid-shaft femur detected improvement in Total Mineral Content, Cortical Thickness and Cortical Area. The analysis of the treated mice suggested that in utero cell therapy is a promising treatment for classical OI.
Fibrous dysplasia (FD, OMIM#174800) is a genetic disease caused by postzygotic, activating mutations of the GNAS gene, which impair the GTPase activity of Gs-alpha thus resulting in excess intracellular cAMP. FD is a crippling disease occurring either as an isolated mono or polyostotic disorder, or in association with skin and endocrine lesions in the McCune-Albright syndrome. Although remarkable progress has been made over the last few years in our understanding of the disease, several aspects of FD have not been yet fully defined and no specific therapies are available at this time. Suitable experimental in vivo and in vitro models are necessary to dissect the pathogenetic mechanisms of the disease and to test innovative approaches to correct the genetic defect. Towards these ends, we generated a murine model of FD by using a lentivector based approach. A lentiviral vector containing the rat Gs-alphaR201C cDNA (LV-Gs-alphaR201C) under the control of the constitutive promoter EF-1alpha was injected into the perivitelline space of mouse zygotes. Transgenic animals were generated in which multiple bone lesions were reproduced with typical radiographic and histological features of FD. In some animals, skeletal lesions were also associated with extraskeletal diseases thus reproducing the clinical picture of the McCune-Albright syndrome. Furthermore, interesting and unexpected biological features of the disorder have been observed in transgenic mice, which could change our current interpretation of some aspects of the human disease.
Abstract 8 - Congenital Scoliosis in a Mouse Model of Impaired Matrix-vesicle Calcification

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Matrix vesicle (MV)-mediated mineralization is believed to be the first step during the regulated process of endochondral ossification. After formation of hydroxyapatite (HA) crystals the MV membranes breakdown and release the preformed HA into the extracellular fluid. Tissue non-specific alkaline phosphatase (TNAP) is the major enzyme that regulates extravesicular growth of HA crystals by restricting the size of the calcification inhibitor inorganic pyrophosphate (PPi). In the absence of TNAP, a build up of PPi causes rickets/osteomalacia characteristic of the most severe forms of hypophosphatasia. However, HA crystal formation inside MVs is not affected, suggesting the involvement of other phosphatase(s) during the initial events leading to MV-induced mineralization. In previous studies, expression of a novel orphan phosphatase, PHOSPHO1, was reported in mineralizing regions of skeletal tissues.

Here we have assessed the phenotypic changes associated with functional ablation of the Phospho1 gene. We examined survival and growth rate of Phospho1 null mutant mice, skeletal abnormalities by radiography, calcification ability and TNAP activity in MVs, circulating levels of PPi and ALP activity in plasma and osteoblast culture media and osteoblastic gene expression by qRT-PCR. Both male and female Phospho1 null mutant mice display stunted growth with short and distorted long bone and prominent thoracic scoliosis. Increased PPi levels were found in the plasma and calvarial osteoblast culture media. MVs showed a decrease in their calcification ability and reduced TNAP activity. We are currently investigating the metabolic changes that lead to these skeletal deformities. To-date the PHOSPHO1 null mice appear to represent a model of congenital scoliosis.
XLH is a genetic disorder that is inherited as an X-linked dominant trait, and affected individuals share common clinical features with other hypophosphatemic syndromes such as Autosomal Dominant Hypophosphatemic Rickets (ADHR), Tumor Induced Osteomalacia (TIO) and Autosomal Recessive Hypophosphatemic Rickets (ARHR). This syndrome is characterized by hypophosphatemia due to renal phosphate wasting, inappropriately low or normal serum 1,25(OH)2D concentrations and increased circulating serum FGF-23 concentrations. These biochemical abnormalities contribute to the development of skeletal defects including rickets in children and osteomalacia in adults. Severity of the disease varies considerably even among members of the same family. Hypophosphatemia can occur as early as six to nine months of age. However, XLH patients frequently present with short stature, valgum or varus deformities of the lower extremity, bone pain and dental abscesses. Severely affected individuals can have frontal bossing and spinal cord compression. Enthesopathy is common in middle aged patients. Patients with XLH harbor inactivating mutations in the Phex (Phosphate regulating gene with Homologies to Endopeptidases on the X chromosome) gene. The gene encodes for a 749 amino acid protein that closely resembles members of the endopeptidase family. PHEX protein is a type II integral membrane glycoprotein with a short N terminal cytoplasmic domain, a transmembrane domain and a large extracellular domain. Phex mRNA is predominantly expressed in bone and teeth but the exact function of PHEX is unknown. Studies performed in hyp mice, a mouse model of XLH, show increased production of FGF-23 in bone, suggesting that PHEX negatively regulates FGF-23 production. Several animal studies have confirmed that excess circulating FGF-23 is responsible for the biochemical abnormalities seen in these hypophosphatemic disorders including XLH. This hypothesis was confirmed when the hyp phenotype was completely rescued by crossbreeding hyp mice with the FGF-23 knockout mice. However, the exact mechanism by which PHEX interacts with FGF-23 is unknown. Currently there is no curative therapy available to decrease circulating FGF-23 concentrations and thereby improve serum phosphorus and 1,25(OH)2D levels. Therefore, therapy is limited to oral supplementation with phosphate and vitamin D to promote growth in children and prevent skeletal deformation. However, close monitoring is required as this form of supportive therapy can cause hypercalciuria, hypercalcemia, nephrocalcinosis and is a concern for potential long term renal damage. Understanding the relationship between PHEX and FGF-23 and the molecular mechanisms by which FGF-23 regulates phosphate and vitamin D metabolism in the kidney, is crucial to improving clinical outcome and quality of life for patients with XLH.
The Mucopolysaccharidoses (MPS) are inherited, connective tissue disorders that result from deficiencies of specific lysosomal enzymes required for glycosaminoglycan (GAG) degradation. Among the various organ systems involved, the bones and joints are severely affected. MPS animal models have provided important insights into the causes of bone and joint pathology in these disorders. For example, by 6 months of age an abnormal cellular and molecular profile was seen in the bones and joints of rats with MPS type VI (Maroteaux-Lamy disease), with characteristic increases in cytokines, MMPs, and apoptotic cells. We proposed that GAG storage in the MPS disorders leads to inflammation and apoptosis within cartilage, most likely through activation of the toll-like receptor-4 signaling pathway (Simonaro et al., 2001, 2005, 2008). We have also recently performed gene and protein expression analysis on fibroblast-like synoviocytes (FLS) from MPS VI rats, which similarly revealed that numerous inflammatory molecules were elevated, including several molecules important for TLR4 signaling (e.g., lipoprotein binding protein, CD44, and MyD88). TLR4 reporter cells lines have been generated, and will be used to investigate whether GAGs directly activate TLR4 or the lipopolysaccharide signaling pathway in vitro. In addition, MPS VII/TLR4 double mutants are being generated to evaluate the in vivo effects of GAGs on this important signaling pathway. We have also found that treatment of normal FLS and chondrocytes with GAGs leads to proliferation and apoptosis, respectively. This correlated with the production of the “pro-survival” lipid, sphingosine-1-phosphate, in FLS, and the “pro-apoptotic” lipid, ceramide, in chondrocytes. Both lipids have been implicated in signaling. These findings have important implications for the pathogenesis and treatment of MPS, and have defined a novel mechanism of GAG-stimulated disease that may be occurring in other common bone disorders.
Abstract 11 - A Novel Genetic Form of Hypoparathyroidism is Caused by Dominant-Negative Mutations in the Transcription Factor GCMB

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Identification of genetic causes of hypoparathyroidism (HP) is important for enhancing our understanding of parathyroid biology and could help define new drug targets. HP is characterized by hypocalcemia and low/inadequately normal PTH levels. Mutations in several different genes were previously discovered as the cause of autosomal-dominant (AD) or autosomal-recessive (AR) forms of HP, but most sporadic forms remain unresolved at the molecular level.

AD-HP can be caused by heterozygous activating mutations in the calcium-sensing receptor or by heterozygous mutations in the PTH gene that impair intracellular processing of the nascent protein. AR-HP can be caused by homozygous mutations in the genes encoding PTH or glial cells missing B (GCMB), a transcription factor specific for the parathyroid gland. Consistent with these findings, GCMB-null mice lack parathyroid glands, whereas heterozygous carriers of inactivating GCMB mutations appear to be healthy, both in mice and man.

We identified a novel mechanism for AD-HP in two unrelated families. Two different heterozygous, single nucleotide deletions in the last GCMB exon (mutA and mutB) were identified in genomic DNA of the affected members of both families. Both mutations lead to a shift in the open reading frame resulting in the replacement of the second transactivation domain located within the carboxyl-terminal region of GCMB with unrelated amino acid sequence. Consistent with the mode of inheritance, the mutant GCMB proteins exhibited in vitro dominant-negative properties in luciferase-based reporter assays, while two previously reported homozygous GCMB mutations (R47L and G63S) that are the cause of an autosomal recessive form of HP did not affect function of wild-type (WT) GCMB.

We generated three antibodies in rabbits against peptides corresponding to GCMB residues 111-130 (N1), 225-245 (C1) and 481-500 (C2). WT-GCMB was well expressed in fibroblast DF-1 cells as assessed by Western blot analysis of cell lysates using antibodies N1, C1, or C2. As expected, when using antibody N1, Western analysis of lysates from cells transfected with mutA and mutB revealed a slightly larger protein band than lysates from cells expressing WT-GCMB; no mutant protein was detected when using antibody C2 that is directed against the portion of the protein that is replaced in GCMBmutA and GCMBmutB. GFP-tagged mutant GCMB demonstrated normal nuclear localization.

In summary, two novel, heterozygous mutations in the parathyroid-specific transcription factor GCMB were identified in the affected members of two families with autosomal-dominant hypoparathyroidism. In vitro analyses revealed a dominant-negative effect of the mutant GCMB proteins, thus providing evidence for a novel disease mechanism.
Abstract 12 - Melorheostosis  
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Melorheostosis (OMIM #155950) is a rare (0.9 per million) sclerosing bone disease reported ~300 times in the literature. It features monostotic or polyostotic, asymmetric irregular dense linear bony thickening of the cortex of one or more long bones. This radiographic finding, named for its flowing candle wax appearance, begins with an endosteal hyperostosis. The disorder, typically unilateral, most often involves the extremities, scapula, and pelvis in an apparently sclerotomal distribution. Although it can be a radiographic finding without clinical consequences, melorheostosis can be associated with pain, asymmetrical growth, soft tissue fibrosis, vascular anomalies, and contractures.

On occasion, melorheostosis can be found in association with other sclerosing bone disorders when it is called “mixed sclerosing bone dystrophy” or with the LEMD3 associated disorders, osteopoikilosis or Buschke-Ollendorff Syndrome. The cause and pathogenic basis of isolated sporadic melorheostosis, however, is not known. Current theories include postzygotic mutation with mosaicism, reaction to trauma, infection or sensory neuropathy, and autoimmune disease.

There have been 10 new papers regarding melorheostosis so far in medline in 2008 including reviews and case reports. Two papers revealed possible clues to pathogenesis (elevated FGF-23 levels in one patient, coexistence of tricho-dento-osseous syndrome and melorheostosis in another). The Melorheostosis Association website, on which >130 people with melorheostosis have posted medical histories, may give additional clues. Although review of these histories contains questions of accuracy and ascertainment bias, a review of histories posted before 8/27/2008 yielded 121 nonfamilial, nonaxial cases: Only 6 patients clearly indicated bilaterality of x-ray findings; 98 had unilateral involvement. Twice as many had lower as had upper extremity involvement (77 vs 37) and only 6 indicated both upper and lower extremity involvement. Only 16 patients indicated they experienced no pain; 93 complained of pain. Other complications included limb shortening (17), decreased range of motion (37), swelling (14), and only 1 patient mentioned Raynaud’s phenomena.

Thus, the patients who posted their histories of sporadic melorheostosis on the melorheostosis website had more complaints of pain but otherwise mimic the clinical characteristics of the disease as reported in the literature. Interestingly, the distribution of patients across the United States is similar to census data which may argue against an infectious or local toxic etiology for the disease.

References:

Abstract 13 - Molecular Mechanisms of Skeletal Development

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During vertebrate development, mesenchymal cells from cranial neural crest, paraxial mesoderm and lateral plate mesoderm migrate into regions of future bones, condense into elements that outline the skeletal pattern and differentiate into chondrocytes or osteoblasts. Chondrocytic differentiation, controlled by SOX transcription factors, results in the formation of cartilage “bone” models in the limb and axial skeleton. Osteoblastic differentiation, requiring WNT signaling and controlled by the transcription factors RUNX2 and OSTERIX, results in the formation of membranous bones in the cranial vault and the facial skeleton.

Membranous bone formation takes place in a capillary-rich environment and is stimulated by vascular endothelial growth factor (VEGF). In contrast, cartilage formation requires the absence of blood vessels. As the cartilage models grow, hypertrophic chondrocytes express high levels of VEGF. This triggers the process of endochondral ossification, during which cartilage models are replaced by bone and bone marrow.

Insights into mechanisms that regulate skeletal development have come from different types of studies. In many cases, genetic studies of human single gene disorders have led to discoveries that paved the way for more detailed and mechanistic work in animals or cell culture. Experimental studies in mice have been extremely important as well. However, it is clear that elucidation of signaling pathways and transcription factors is not sufficient for understanding how the architecture of each and every bone in the skeleton is specified and how osteoblasts build bone along trajectories of mechanical stress. Such understanding requires investigations of morphogenetic mechanisms associated with “architectural” properties of cells and tissues; namely, studies of cytoskeletal functions, mechanisms of cellular polarity, and mechanical stress responses of cells and pericellular matrices. With the discovery that hedgehog signaling is coupled to processes regulating protein trafficking into and out of primary cilia, a major signaling pathway associated with skeletal development has been coupled to cellular polarity mechanisms. Also, recent studies indicate that the primary cilia-associated cation channel polycystin 1/2 is important for the proliferative response of osteochondroprogenitor cells to postnatal mechanical stress in craniofacial sutures and synchondroses at the skull base. This work, together with investigations of cellular behavior on engineered matrices, represents the beginning of what may lead to deeper understanding of skeletal morphogenesis and help stimulate development of effective tissue engineered products for bone and cartilage repair.
Abstract 14 - Central Control of Bone Mass  
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Based on clinical observations we hypothesized that these must be a common control of bone and energy metabolism. This hypothesis that is still being explored in our laboratory led us to show that the adipocyte-derived hormone leptin regulates bone mass through a central relay. Physiological, molecular and genetic evidence identified the ventromedial hypothalamic nuclei as being critical for this function of leptin. Downstream of these neurons the sympathetic tone mediates leptin regulation of bone formation by acting on osteoblasts. We will also review the evidence indicating that CART is a leptin-dependent regulator of osteoclast differentiation.
Abstract 15 - Osteocytes

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Osteocytes make up over 90-95% of all bone cells and the surface area of their lacunae and canaliculi are several of orders of magnitude greater than the bone surface in the adult skeleton. These cells are functional from the moment they become embedded in osteoid as well as when they are deeply embedded cells in a mineralized matrix. The cell on the bone surface destined to become an osteocyte must make connections with existing embedded cells to insure communication and no disruption to the flow of bone fluid. Once embedded, the cell is in contact with the vascular system, with other osteocytes and with cells on the bone surface. While their morphology is dramatically changing from a cuboidal cell on the bone surface to a dendritic cell, they are also regulating the mineralization process enclosing them. Molecules thought to play a role in dendrite formation such as E11/gp38 and RhoA are called into action, along with Phex and Dentin Matrix Protein 1 to regulate mineralization. Once surrounded by mineral, the mature osteocyte can control bone formation through the production of factors such as sclerostin and Dkk1, both inhibitors of the Wnt/β-catenin pathway. Osteocytes, whether viable or apoptotic can signal bone resorption.

Osteocytes appear to be exquisitely sensitive to mechanical loading and are postulated to sense strain on the skeleton and translate that strain into either signals of resorption or formation. This cell can extend and retract its dendritic processes, thereby acting as a switchboard to (re)direct signals. Multiple mechanisms may exist whereby these cells sense load such as deformation of the cell body or its numerous dendritic process by fluid flow shear stress, by cilia, or by a combination. Important early, essential signals include calcium, ATP, nitric oxide, and prostaglandin, whereas downstream molecules include components of the wnt/β-catenin pathway.

Osteocytes are regulated by a number of factors, such as glucocorticoid and parathyroid hormone. Whereas glucocorticoid and elevated PTH as in hyperparathyroidism can induce loss of osteocyte perilacunar matrix, PTH may increase bone mass through down regulation of factors such as sclerostin. Estrogen is essential for normal osteocyte health and viability. The osteocyte network appears to function as an endocrine organ that regulates phosphate metabolism through the production of factors such as FGF23, while the osteocyte perilacunar matrix may function as a source of calcium under conditions such as pregnancy/lactation. Therefore functional osteocytes are essential for bone health.
Abstract 16 - Academic and Industry Partnerships for Orphan Diseases
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It has been over 25 years since the passage of the Orphan Drug Act and great progress has been made in the development of novel products which can be used to treat patients rare and debilitating disorders. Orphan drug legislature has developed in numerous regions of the world including the European Union, Japan, Australia, Taiwan and many other countries. While there are economic and exclusivity incentives offered by countries to encourage drug development in rare diseases, the clinical development hurdles are just as difficult as they are for common diseases such diabetes and hypertension. The example of a complicated development pathway is the treatment for Pompe disease. The clinical development process began for Genzyme in 1998, involved the development of three different drug products and processes, initial registration in the US and Europe in occurred in 2006 but regulatory work continues to this day with the example of an FDA Advisory Panel in October 2008. The importance of academic partners for industry in these rare disease treatments cannot be overstated and can be beneficial to everyone involved but especially the patients. An example of a private, public and industry collaboration for the gene therapy treatment of GM2 gangliosidosis is likely to be a model for further collaboration in ‘ultra-orphan indications’. The future for treatments for orphan diseases remains bright but the regulatory and financial obstacles must be overcome in order to assure the continued development of treatments for rare diseases.
Osteogenesis Imperfecta is a well-known condition characterized by fragile bones, and a variety of associated secondary features such as short stature, hearing loss, blue sclerae. Classical OI is an autosomal dominant condition described clinically by the Sillence Classification and caused by defects in either of the two genes encoding type I collagen, COL1A1 or COL1A2. Mild type I OI is caused by defects in COL1A1 with quantitative consequences for collagen, while the lethal, progressive deforming and moderate types II, III and IV OI, respectively, are caused by defects in the structure of either type I collagen alpha chain. These structural defects (80% glycine substitutions and 20% splice site defects) and their genotype-phenotype correlations have been described in a report of the OI Mutation Consortium (Hum Mutat 28:209-212, 2007). Lethal mutations in COL1A1 are associated with the Major Ligand Binding Regions, while the clustering of lethal mutations in COL1A2 in regularly spaced regions along the chain coincides with PG binding sites (Regional Model). In addition, there is new insight into the effects of mutations that interfere with the processing of type I collagen, such as those located in the amino terminal anchor domain of type I collagen which cause OI/EDS, and some substitutions of Y position residues in the Gly-X-Y triplets (especially Arg to Cys substitutions) which affect processing by register shift of the chains.

In the last several years, rapid developments in several labs have shifted the paradigm for OI with the discovery that the long-sought cause of recessive OI is deficiency of either of two protein components of the prolyl 3-hydroxylation complex in the ER, CRTAP and P3H1. An exciting conjunction of information from different fields, including the delineation of the components of the 3-hydroxylation complex, the recessive chondro-osseous dysplasia resulting from knock-out of CRTAP in a mouse model and the prior delineation of human type VII OI as a recessive rhizomelic condition, made the components of this complex prime candidates for severe/lethal recessive OI. We identified the first clinical causes with defects in CRTAP and P3H1, and have designated these conditions as type VII and VIII OI respectively. Null mutations in these genes have both intracellular and matrix consequences, and include delaying the folding of type I collagen, while increasing the total collagen secreted per cell. Further investigations will lead to new insights on the regulatory and chaperone roles of this complex and its components.
Osteogenesis Imperfecta (OI) is a rare heritable condition characterized by bone fragility and reduced bone mass. Traditionally OI was classified into OI types I to IV and linked to mutations in the genes encoding Type I collagen. However through the discovery of the new types of OI–V to VII, breakthroughs have been made in understanding the patho-physiology of autosomal recessive OI through the characterization of mutations in such genes as CRTAP and P3H1 (to be discussed by Dr Marini). OI can present at any age and be difficult to diagnose because of its wide phenotypic variation. In the current absence of a cure for OI, efforts have focused on medical and surgical means to improve clinical picture and quality of life. Based on the observed increase in bone turnover rate, we evaluated the use of bisphosphonates to reduce turnover and thus favor the formation phase. The observed benefits are an increase in bone mass (mostly by cortical bone thickening) and in the degree of ambulation, and a decrease in bone pain and incidence of fractures. Cyclical intravenous pamidronate is now the standard of care for moderately to severely affected children with OI, given in combination with good orthopedic, physiotherapy and rehabilitation programs. The benefits and short term safety of cyclic bisphosphonates have been amply reported in the literature; however their long-term effects are still under investigation. Although treatment should be maintained during the whole growing period, continuation after fusion of the epiphyses should be individually assessed in each patient. Newer more potent forms of bisphosphonates such as zoledronic acid are still being subject to international multicentric drug trials. At present it is recommended not to treat mild forms of OI as sufficient benefits have not been demonstrated.
Fibrous dysplasia of bone (FD) usually presents with pain, limp, pathologic fracture, or deformity. The somatic nature leads to variable involvement of skeletal tissues in a varied spectrum; from a single site, to the entire skeleton. In the NIH cohort, the skeletal sites most commonly affected are the proximal femur and skull base (86%), upper extremities, ribs and spine (72%). The “map” of involved tissues is established early in life, with 90% of the lesions in the craniofacial region established by 4 years of age, extremities by 13y, and axial skeleton by 15y. Other tissues that may be involved include the skin (café-au-lait spots), and the endocrine glands; ovaries/testes (precocious puberty), thyroid (hyperthyroidism), pituitary (growth hormone excess), and adrenal (Cushing’s syndrome). In a subset of patients, FD can be accompanied by renal phosphate wasting. When FD is found in association with extraskeletal manifestations, it is known as the McCune-Albright syndrome (MAS). FD/MAS is caused by somatic, activating mutations of the signaling protein, Gs\textalpha. The vast majority (>90%) of the mutations occur at residue R201. Pathophysiology is tissue specific and related to the role of the Gs\textalpha/cAMP in the given affected tissue. In bone, the primary target appears to be the bone marrow stromal cell (BMSC). In BMSCs, the mutation leads to proliferation of immature osteogenic cells and abnormal BMSC differentiation, with replacement of the bone marrow by fibrous tissue. It is overproduction of the phosphate regulating hormone, FGF23, by this fibrous tissue that is the cause of renal phosphate wasting. It has recently been shown that there is an age-dependent loss of mutation-bearing BMSCs from FD lesions that, at least at the microscopic level, can lead to “normalization” of the bone lesion. While there has been significant progress in our understanding of the pathophysiology of the disease, much remains to be done in the area of treatment. Clinically, consensus criteria are lacking for the care and treatment of both craniofacial and orthopedic disease. There is a wide variation in the criteria for surgery, and the specific surgical technique and hardware to be used. Recent insight into the molecular and cell biology of FD suggests new avenues of translational research. The adaptation of matrices being developed for tissue engineering, combined with insights into BMSC biology the possibility of replacing regions of pathologic bone. Research is currently underway using high throughput screening techniques and molecular libraries to identify mutant Gs\textalpha-specific molecules to silence the mutation in affected cells.
Abstract 20 - Melorheostosis: The Mystery Not Yet Solved
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Melorheostosis is a rare skeletal dysplasia characterized by a hyperostosis of cortical bone. The hyperostotic bone lesions have a linear pattern and are mainly located along the diaphyses of tubular bones. They can extend internally into the medullary canal or externally with periosteal involvement resulting in the characteristic wavy outline of the affected bone. Melorheostosis lesions are most frequently found in the appendicular skeleton. They usually show an asymmetric distribution with involvement of one or more bones located in an area innervated by the same spinal sensory nerve. Melorheostosis can also affect the surrounding soft tissues including the subcutis, muscles and blood vessels. The disorder can be asymptomatic but usually cause chronic pain and functional limitations because of joint contractures, bone deformities and limb length discrepancy.

Melorheostosis is predominantly a sporadic disorder. However, individuals with melorheostosis have been observed in a few families with autosomal dominant osteopoikilosis or the Buschke-Ollendorff syndrome. By combining linkage analysis with microdeletion mapping in these families, we could map the disease gene to chromosome locus 12q14. Inactivating germline mutations in the LEMD3 gene were subsequently identified in the affected individuals. The LEMD3 gene codes for an integral protein of the inner nuclear membrane. LEMD3 interacts with the MH2 domain of both BMP-specific and TGFβ-specific receptor activated SMAD proteins (R-SMADs). Through its interaction with the R-SMADs, LEMD3 acts as a specific repressor of TGFβ and BMP signaling. Loss-of-function mutations in the LEMD3 gene result in an increase in transcriptional activation of TGFβ, activin or BMP responsive promoters. These pathways have been shown to be very important in the regulation of bone mineral density and control of fibroblast activity.

In the great majority of sporadic patients with isolated melorheostosis, no germline LEMD3 mutations are found. The sporadic occurrence and localized distribution of melorheostosis lesions in these patients suggest the possibility of somatic mosaicism as underlying genetic defect. However, no somatic LEMD3 mutations have been documented so far. With the advent of high-performance technologies such as high density micro-arrays and next-generation sequencers, we are currently planning to analyse the whole exome in affected tissue samples in order to unravel the genetic defect causing this debilitating disorder.
Osteopetrosis results from a reduction in bone resorption relative to bone formation. Defects in bone resorption and increased bone formation result in inadequate osteoclastic resorption and a simultaneous stimulation of osteoblastic formation (Karsdal et al., 2007). Data suggest that coupling factors also increase osteoblastic bone formation leading to further thickening of bone. A decrease in medullary space results in sclerosis of the skull, long bones, and vertebrae. Excessive accumulation of bone reduces marrow space resulting in inadequate hematopoiesis and marrow failure. Extramedullary hematopoiesis cannot adequately compensate for the lost hematopoiesis. Cranial nerves and vascular canals are compromised, resulting in poorly vascularized bones, fractures, necrosis, and infection. The risk of morbidity and mortality increases dramatically during anesthesia. The increased risk of death in children with osteopetrosis is due to airway incompetency and severe inflammatory reactions. (Burt et al., 1999). An understanding of osteopetrosis in humans has been intertwined with the discovery of a variety of animal mutations. Mutants have led to new understanding of osteopetrosis and treatment strategies.
Abstract 22 - Is X-Linked Hypophosphatemia a Disorder of Phosphate Homeostasis or a Skeletal Dysplasia, or Both?

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X-linked hypophosphatemia (XLH), once classified as vitamin D-resistant rickets, is characterized by low serum phosphate levels due to renal phosphate wasting, and limited production of the vitamin D metabolite, 1,25 dihydroxyvitamin D. Skeletal findings are predominantly manifest as rickets and osteomalacia, but other deformities including craniosynostosis, dental abscesses, and calcified entheses often occur. Recent advances have identified that XLH involves several gene products that are associated with osteocytes, the bone cells thought to sense demands for skeletal mineralization. Two products of the osteocyte are now known to be central to the pathogenesis of XLH: 1) PHEX, a member of a small family of metalloendopeptidases, and 2) FGF23, a unique member of the fibroblast growth factor family. The predominant genetic basis for XLH is dominant loss of function mutations of PHEX, and the disorder is mediated by increased circulating levels of FGF23. Moreover, loss of function in another osteocyte product, DMP1, can lead to elevated FGF23 levels and a similar phosphate-wasting disorder. Conventional therapy for XLH has consisted of calcitriol and phosphate salts. This therapy has been applied to most children, with a less uniform approach in adulthood. Outcomes of conventional therapy are generally favorable, but do not completely cure the disorder. Interestingly, patients with XLH are occasionally misdiagnosed with metaphyseal dysplasia, implicating that XLH has features that are clinically analogous to skeletal dysplasias, some of which are characterized by mutations of FGF receptors. Conceptually, XLH represents pathology evident due to both its mineral deficiency state, as in acquired rickets, but potentially also influenced by alterations in FGFR signaling, as with some of the skeletal dysplasia syndromes. It is hopeful that as more detailed information regarding the complex system involved in the pathogenesis of XLH is discovered, newer therapeutic strategies will be developed that have the potential to improve treatment outcomes in affected individuals.
Metamorphosis, the transformation of one normal tissue or organ system into another, is a biological process rarely seen in higher vertebrates or mammals, but exemplified pathologically by the disabling autosomal dominant disorder, fibrodysplasia ossificans progressiva (FOP). Individuals with FOP experience episodes of spontaneous or trauma-induced metamorphosis that convert normal functioning connective tissue into a highly ramified and disabling second skeleton of heterotopic bone. A recurrent single nucleotide missense mutation in the gene encoding activin receptor IA/Activin like kinase II (ACVR1/ALK2), a bone morphogenetic protein (BMP) type I receptor, causes FOP in all classically affected individuals worldwide. This mutation is one of the most specific disease-causing mutations in the human genome, and the first identified human metamorphogene. FOP provides deep insight into a signaling pathway that regulates tissue and organ stability following morphogenesis, and that when dysregulated in a specific manner, orchestrates the metamorphosis of one normal tissue or organ system into another. The discovery of the FOP gene establishes a critical milestone in understanding FOP, reveals a highly conserved target in the BMP signaling pathway for drug development, and stimulates therapeutic approaches for the development of inhibitors for ACVR1/ALK2 signaling. Effective therapies for FOP, and possibly for more common conditions of heterotopic ossification, will be based on interventions that selectively block promiscuous ACVR1/ALK2 signaling, and/or the molecular triggers, responding cells, and tissue microenvironments that facilitate aberrant skeletal metamorphosis. Such therapies may be applicable to a broad range of human afflictions.
Hypophosphatasia (HPP) is a rare, heritable form of rickets or osteomalacia characterized biochemically by subnormal activity of the tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP). Although TNSALP is normally present in all tissues, HPP disturbs primarily the skeleton and teeth. Approximately 350 case reports reveal a remarkable range of disease severity with four overlapping clinical forms described according to patient age when skeletal disease is discovered: perinatal, infantile, childhood, and adult. Odonto-HPP features dental manifestations only.

Perinatal HPP manifests in utero. At birth, extreme skeletal hypomineralization causes a soft skull and short, deformed limbs. Most patients succumb from increasing respiratory compromise. Prolonged survival is rare. The radiographic features are pathognomonic; sometimes the skeleton is so poorly calcified that only the skull base is seen.

Infantile HPP presents before age 6 months. Development appears normal until poor feeding, inadequate weight gain, hypotonia, and wide fontanels are noted. Rachitic deformities are then recognized. Vitamin B6-dependent seizures indicate a lethal outcome. Hypercalcemia and hypercalciuria can cause recurrent vomiting, nephrocalcinosis, and renal compromise. Functional craniosynostosis may occur. A flail chest predisposes to pneumonia. There can be spontaneous improvement or progressive skeletal deterioration with approximately 50% of patients dying in infancy. Radiographic changes are characteristic, but less striking than in perinatal HPP. Progressive skeletal demineralization leading to fractures and thoracic deformity heralds a fatal outcome.

Childhood HPP causes premature loss of deciduous teeth (< age 5 years), without root resorption, from hypoplasia of dental cementum. Delayed walking with a waddling gait, short stature, and dolichocephaly are common. Static myopathy is a poorly understood complication. After puberty, patients improve, but skeletal symptoms will likely recur in middle-age. Radiographs show characteristic “tongues” of lucency projecting from growth plates into metaphyses. Premature fusion of cranial sutures with craniosynostosis can cause a “beaten-copper” appearance of the skull.

Adult HPP usually presents during middle age, often with poorly-healing, recurrent, metatarsal stress fractures. Pain in the thighs or hips can reflect femoral pseudofractures. Chondrocalcinosis from calcium pyrophosphate dihydrate crystal deposition may occur.

HPP rickets/osteomalacia is remarkable because serum calcium and inorganic phosphate (Pi) are not reduced and ALP is low, not high. In fact, hypercalcemia occurs frequently in perinatal and infantile HPP, apparently from dyssynergy between gut absorption of calcium and the defective skeletal growth and mineralization. In childhood and adult HPP, ~50% of patients are hyperphosphatemic due to increased TmP/GFR. Serum PTH and 1,25(OH)2D concentrations are suppressed if there is
hypercalcemia. Nondecalcified sections of HPP bone reveal rickets or osteomalacia without secondary hyperparathyroidism.

Three phosphocompounds accumulate endogenously in HPP: phosphoethanolamine (PEA), inorganic pyrophosphate (PPi), and pyridoxal 5'-phosphate (PLP). If vitamin B<sub>6</sub> is not being supplemented, elevated plasma PLP is an especially good marker for HPP. The worse the hypophosphatasemia and the more severe the clinical manifestations, the greater the plasma PLP.

Perinatal and infantile HPP are autosomal recessive traits. Milder forms of HPP (odonto-HPP, childhood HPP, and adult HPP) represent either autosomal dominant or autosomal recessive inheritance. Pyridoxine given orally causes exaggerated increments in plasma PLP levels in all patients and in some carriers.

HPP is diagnosed from a consistent clinical history and physical findings, radiographic or histopathological evidence of rickets or osteomalacia, and hypophosphatasemia together with TNSALP substrate accumulation. Mutation analysis of TNSALP is available commercially. Approximately 190 mutations (~79% missense) have been identified.

Disturbances in vitamin B<sub>6</sub> metabolism in HPP indicated that TNSALP functions as an ectoenzyme. Extracellular accumulation of PPi, an inhibitor of hydroxyapatite crystal growth and dissolution, impairs skeletal mineralization.<sup>(2,3,15)</sup> TNSALP knockout mice manifest infantile HPP.<sup>(16)</sup>

Sonography has detected perinatal HPP in the second trimester. First trimester diagnosis requires TNSALP mutation identification. Importantly, some fetuses with HPP manifest worrisome bowing in utero that then corrects postnatally and resembles childhood HPP.

There is no established medical treatment for HPP. Unless deficiencies are documented, avoiding traditional treatments for rickets or osteomalacia seems best because circulating levels of calcium, Pi, and 25(OH)D are usually not reduced. Hypercalcemia in perinatal or infantile HPP responds to restriction of dietary calcium, and perhaps to salmon calcitonin and/or glucocorticoid therapy. Fractures can mend, but healing may be delayed, including after osteotomy. Load-sharing intramedullary rods, rather than load-sparing plates, seem best for fractures and pseudofractures in adults. Expert dental care is important. Soft foods and even dentures may be necessary for some pediatric patients.

Marrow cell transplantation seemed to rescue and improve two severely affected infants. Teriparatide stimulated TNSALP biosynthesis by osteoblasts and apparently healed ununited fractures in a woman with HPP. Enzyme replacement therapy using a bone-targeted, recombinant form of human TNSALP prevented or improved infantile HPP in TNSALP knockout mice and has entered clinical trials for patients. In childhood HPP, dietary restriction and binders to correct hyperphosphatemia (to thereby reduce inhibition of TNSALP by Pi) requires study.
Abstract 25 - Gorham's Disease and Related Vascular and Lymphatic Disorders of Bone and Soft Tissue

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Lymphangiomatosis and angiomatosis involving bone and soft tissue, with or without concomitant visceral disease, are rare conditions. Gorham's disease, classified as an aggressive form of skeletal angiomatosis associated with progressive skeletal resorption, is extremely rare. Since the definitive descriptions of this entity by Gorham and Stout in the 1950's, fewer than 200 cases have been reported in the literature, the vast majority as individual case reports. Gorham's disease can affect patients of all ages, and can arise in virtually any bone. Affected patients often present with pain, sometimes following a traumatic event. The diagnosis of Gorham's disease is usually straightforward for radiologists and pathologists familiar with the entity. Radiographically, affected bones show marked resorption, often resulting in a "licked stick of candy" appearance. The diagnosis is confirmed by correlating the radiographic appearance with the histologic finding of a benign vascular or lymphatic proliferation replacing the bone. Medical treatment for Gorham's disease has included radiotherapy, interferon, and bisphosphonates. However, surgical intervention is often necessary for stabilization of large bone defects. With early treatment, the risk of morbidity and mortality is usually low; however, patients can die from involvement of viscera, spinal cord, or thoracic duct.

The etiology and pathogenesis of Gorham's disease is poorly understood, and the role of osteoclasts in this disorder is unclear. Common to all cases is the prominent angiolymphatic proliferation, but it is not clear whether this is the primary inciting factor or a secondary phenomenon. In some cases, a marked increase in osteoclastic activity is evident at the interface between the angiolymphatic proliferation and cortical or cancellous bone. Even though increased osteoclastic activity is not always identified histologically, bisphosphonates appear to be effective in limiting the massive resorption in patients with Gorham's disease. Studies on the cellular and humoral mechanisms leading to bone resorption in Gorham's disease suggest that IL-6 and VEGF play a central role in pathogenesis.

The purpose of this presentation is to introduce the clinical, radiographic, and pathologic features of Gorham's disease and related disorders of bone and soft tissue, as well as current treatment recommendations. Current theories on pathogenesis will also be discussed.
Research for rare diseases and conditions leading to the development of orphan products for the prevention, diagnosis and treatment is evolving. Successful research and development programs require significant contributions from many organizations, including the patient advocacy groups. In recent years the role of the patient advocacy group has changed dramatically from one of providing support services and information to patients and families to an active participant in many phases of basic and clinical research and product development. An organization is now required to have significant interactions with government organizations such as the NIH and the FDA, the academic research community, the pharmaceutical, biotechnology, and medical devices industries, medical specialists and other healthcare providers, and organizations responsible for reimbursement and providing healthcare services. Research of rare diseases and the development of orphan products have also evolved to become a global effort with multi-national research activities for these interventions now required due to the distribution of patients throughout the world. These changes are reflected in increased levels of research and development activities in Europe, Latin America and Asia and are frequently led by the patient advocacy group as the coordinator of these organizations and their numerous activities.

Many services and programs with support are now available to assist the patient advocacy groups to reach their goal of developing interventions for their disease(s). Gaining access to these programs can provide vital resources and services to patient advocacy groups. An overview of the activities of the Office of Rare Diseases at the NIH and the need for a global approach to the development of products from basic research discoveries will be presented.