Published in final edited form as:

Matrix Biol. 2007 May ; 26(4): 324–329.

International Workshop on the Skeletal Growth Plate Stevenson, Washington June 11–15, 2006

William A. Horton, MD

*Director, Research Center Shriners Hospital for Children Professor of Molecular & Medical Genetics
Oregon Health & Science University Portland, Oregon*

Introduction

The International Workshop on the Skeletal Growth Plate was held at Skamania Lodge, Stevenson, WA in June 2006. It was sponsored by the Shriners Hospitals for Children Research Program; Irving A. Lassen Foundation, National Institute of Child Health and Human Development, National Institute of Arthritis, and Musculoskeletal and Skin Diseases, National Institute of Dental and Craniofacial Research, Orthopaedic Research Foundation, Orthopaedic Research and Education Foundation and the Musculoskeletal Transplant Foundation. Over 150 scientists and physicians from 13 countries participated.

The progeny of a successful First International Conference on The Growth Plate held in San Antonio in 2001, the Workshop focused on the molecular and cellular biology of the growth plate and its disorders. The San Antonio meeting brought the growth plate community together from its roots in structural biology, mineralization, molecular endocrinology, signal transduction, energy metabolism, human and mouse genetics and many other disciplines; to a significant extent, the activities the conference brought growth plate biology into its own as a discipline. More specifically, it provided insights into the many molecular players involved in the formation and regulation of the growth plate and the pathways potentially involved in growth plate disease.

The 2006 Workshop was intended to build on this foundation. One goal was to better define how different regulatory circuits, such as the *Ihh*-PTHrP, FGFR3 and TGF- β and BMP circuits, are integrated with one another. Another was to gain further insight into how molecular and cellular events in the growth plate are actually translated into linear bone growth.

While the San Antonio Conference focused on growth plate biology, an aim of the 2006 Workshop was to address the human chondrodysplasias in more depth. These naturally occurring “experiments in nature” offer considerable insights into growth plate formation and function, and the hope was that the recent progress in delineating the genes that harbor chondrodysplasia mutations could be fully integrated into recent advances in the developmental biology of the skeleton. By understanding this process, the goal was to develop novel ideas for molecular treatments of these disorders.

Another aim of the Workshop was to explore the similarities and differences between the events that occur during growth plate development and those that occur during ex vivo cell-based cartilage tissue engineering, particularly involving adult mesenchymal stem cells, i.e., a

email: wah@shcc.org, phone: 503 221-1537, fax: 503 221-3451

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comparison between the biology of cartilage development and regeneration. Another goal was to expose participants to techniques that are new or outside of their own area of expertise that might be potentially useful for growth plate research. The ultimate goal is to enhance research development and collaboration in the skeletal growth plate scientific community.

Summary

The summary below provides a very abbreviated sense of what was covered by the oral presentations. The abstracts of the poster sessions are available at <http://www.growthplate.org>.

The introductory session provided background about growth plate structure and function, growth plate disease and recapitulation of growth plate chondrogenesis during cartilage engineering. **Cornelia Farnum** (*Cornell University, Ithaca*) discussed approaches to investigating growth plate kinetics and differences in structure: function relationships among species. **Stefan Mundlos** (*Max Planck Institute, Berlin*) outlined a developmental approach to understanding growth plate disturbances and **David Rimo** (*UCLA/Cedars Sinai, Los Angeles*) reviewed clinical and pathologic aspects of human chondrodysplasias and the evolution of schemes used for naming and classification. Last, **Rocky Tuan** (*NIAMS, Bethesda*) gave an overview of the use of mesenchymal stem cells in cartilage tissue engineering.

The program mainly followed the life cycle of the growth plate chondrocyte beginning with its origin. **Veronique Lefebvre** (*Cleveland Clinic, Cleveland*) discussed how Sox9 acts from a very early stage in chondrogenesis to specify the fate of chondrogenic mesenchymal cells, ensure their survival and activate chondrocyte differentiation markers. She showed that Sox9 induces expression of Sox5 and Sox6, which function redundantly and in cooperation with Sox9 to promote chondrocyte early differentiation and proliferation and delay hypertrophic chondrocyte differentiation. **Michael Underhill** (*University of British Columbia, Vancouver*) discussed his recent findings showing that BMP signals downregulate expression of *Aldh1a2*, which encodes a retinoic acid synthetase, suggesting that BMPs may exert their prochondrogenic action at least in part by down regulating retinoid signaling in chondrogenic mesenchyme.

Karen Lyons (*UCLA, Los Angeles*) reviewed the multiple roles of BMPs in chondrogenesis from commitment to terminal differentiation. Her studies showed that both Smad-dependent and -independent BMP pathways are required for chondrogenesis and that BMPs exert essential roles in the growth plate via regulation of the Indian hedgehog (*Ihh*)/parathyroid hormone-related protein (PTHrP) and fibroblast growth factor (FGF) pathways. She also presented evidence that the BMP receptors BMPRI A and BMPRI B have essential, redundant functions during early chondrogenesis to ensure chondrocyte proliferation, survival and differentiation. They act at least in part through inducing activation of Sox9, Sox5, and Sox6.

Christine Hartmann (*Research Institute of Molecular Pathology, Vienna*) reviewed roles for Wnt canonical signaling in chondrogenesis. This pathway orchestrates skeletogenesis by inhibiting chondrocyte differentiation of skeletogenic mesenchymal cells, promoting osteoblast differentiation, and inducing early steps of joint formation. She also presented data demonstrating that inactivation of Wnt9a, the earliest known marker of presumptive joint regions, is not sufficient to abolish joint formation in the mouse embryo. However, Wnt9a and other Wnt signals significantly contribute to joint proper development. Interestingly, Wnt9a also promotes chondrocyte maturation by transiently upregulating *Ihh* expression at the onset of endochondral ossification in the embryo.

Christa Maes (*Harvard Medical School, Boston*) described the development of two new transgenic mouse lines for tracking the osteoblast lineage in vivo. Both are derived from

osteoblast-specific promoter elements and both are inducible with tamoxifen. The first is osterix-cre-ER^{T2}; the second is collagen I (3.2 kb)-cre-ER^{T2}.

Phyllis LuValle (*University of Florida, Gainesville*) introduced the session on chondrocyte proliferation with a discussion of relevant transcriptional regulation. She presented data suggesting that the c-fos promoter is a target of ATF-2 in chondroblasts and that cyclin D1 is essential for the promoter activity of cyclin A but not E2F in these cells. **Jeffrey Baron** (*NICHD, Bethesda*) examined the stem-cell properties of resting zone chondrocytes. He presented data from surgical transplantation and microdissection experiments showing that resting zone chondrocytes give rise to clones of proliferative chondrocyte and proposed a dual gradient model in which BMPs secreted from hypertrophic cells and BMP signaling inhibitors secreted from resting chondrocytes could regulate maturational events in the growth plate.

Peter Hurlin (*Shriners Research Center, Portland*) presented evidence from the knockout of N-Myc in the developing limb suggesting that although largely dispensable for chondrocyte proliferation, N-Myc is an important determinant of precartilaginous condensation size. N-Myc also seems to be required for programmed cell death of interdigital mesenchyme and presumptive joints. **Razvan Miclea** (*Leiden University, Leiden*) discussed recent findings concerning the role of adenomatous polyposis coli (Apc) – mediated β -catenin degradation, which modulates canonical Wnt signaling, in the growth plate. The severe disruption of growth plate formation that results from ablation of Apc in chondrocytes suggests that properly regulated Wnt signaling is required for the formation and differentiation of cartilage during endochondral ossification. **Elazar Zelzer** (*Weizmann Institute of Science, Rehovot*) presented evidence that VEGF functions as a coordinator of chondrogenesis and angiogenesis during early limb development.

Reinhard Fässler (*Max Planck Institute, Martinsreid*) introduced a session on post-mitotic events in the “proliferative” zone with a review of how adhesion complexes are formed. He discussed how integrin binding to extracellular matrix elements can trigger assembly of filamentous (F) actin into signaling hubs that may contribute to changes in chondrocyte behavior following proliferation. **Bjorn Olsen** (*Harvard Medical School, Boston*) talked about the actions of polycystin-1 (PC1), which along with PC2 forms a calcium channel at the base of primary cilia, which are present on growth plate chondrocytes. He showed that shear stress causes calcium influx in a way that is influenced by PC1 in osteoblasts. Using appropriate promoters to drive cre, he also demonstrated that PC1 is essential for formation of normal synchondroses in the base of the skull.

Silvio Garofalo (*University of Moilise, Naples*) used the type II collagen promoter to express hedgehog protein throughout the growth plate in transgenic mice. The mutant mice exhibited severe skeletal abnormalities with loss of the usual longitudinal orientation of terminal chondrocyte differentiation. Disturbed expression of several markers of terminal differentiation suggested that localized expression of these proteins is required to establish growth plate orientation. Also studying hedgehogs, **Benoit St-Jacque** (*Shriners Research Center, Montreal*) presented evidence that the Ihh promoter contains several Smad as well as Runx2 binding sites. **Maurizio Pacifici** (*Jefferson Medical College, Philadelphia*) presented evidence from several mouse models supporting SHH and IHH co-regulation of the development of the occipital and cranial base regions of the skull. Moreover, he hypothesized that primary cilia are the transducers of these signals during craniofacial development.

Several presentations focused on chondrocyte terminal (hypertrophic) differentiation and its regulation in the growth plate. **Henry Kronenberg** (*Harvard Medical School, Boston*) reviewed the evidence that PTHrP and Ihh regulate each other to determine the pace of chondrocyte differentiation and, indirectly, the site of bone collar formation during fetal bone

development. He discussed new data showing that *Ihh* hastens the conversion of round proliferating chondrocytes to flattened columnar chondrocytes. He then summarized the intracellular actions of PTHrP. Activation of the PTH/PTHrP receptor leads to activation of $G_s \alpha$ and subsequent activation of adenylate cyclase and protein kinase A. These actions, in turn, lead to suppression of p57, the cdk inhibitor, suppression of Runx2 expression in chondrocytes and phosphorylation of SOX9. These actions favor chondrocyte proliferation and delay terminal differentiation.

Brendan Lee (*Baylor College of Medicine, Houston*) presented data showing that two transcription factors, Sox9 and Trps1 (a zinc finger protein), can decrease transcriptional activity of Runx2. He showed that Sox9 and Runx2 are expressed together in early mesenchymal condensations and suggested that Sox9 suppression of Runx2 transcriptional activity may be crucial for the development of chondrocytes within the condensations. **Klaus von der Mark** (*University of Erlangen, Erlangen*) described the generation and use of BAC transgenic reporter mouse lines with efficient and specific LacZ expression in hypertrophic chondrocytes under the control of the complete collagen X promoter.

Sherrill Adams (*University of Pennsylvania, Philadelphia*) explored the interactions of retinoic acid and thyroid hormone in controlling transcription of the collagen X gene. She discussed a retinoic acid response element consisting of three half-sites capable of binding retinoic acid receptors in the collagen X gene promoter. In transcription assays, binding to these sites can stimulate reporter gene expression promptly. Thyroid hormone can also increase transcription, but more slowly. At least part of this action of thyroid hormone can be explained by the action of thyroid hormone to increase the expression of the retinoic acid receptor gamma gene.

Regis O'Keefe (*University of Rochester, Rochester*) explored the mechanisms explaining the growth plate phenotypes of Smad 3 knockout mice. Smad 3^{-/-} chondrocytes exhibit accelerated maturation. BMP expression is increased and noggin can block the acceleration of chondrocyte hypertrophy suggesting that the increase in BMP expression contributes to the Smad 3^{-/-} phenotype. He suggested that multiple pathways downstream of TGF- β receptors, besides the Smad pathway contribute to TGF- β action on chondrocytes and discussed interactions of the Smad, p38, and Jnk pathways. **Pia Hermanns** (*University of Freiburg, Freiburg*) discussed the unusual RNA, the untranslated product of the *RMRP* gene, that is mutated in cartilage hair hypoplasia. This non-coding RNA regulates mitochondrial RNA processing and nuclear 5S RNA processing. Mutations lead to low levels of the RNA transcript, which may explain the dysfunctional properties of the mutant RNA.

Several presentations dealt with growth plate mineralization and related events. **Francis Glorieux** (*Shriners Research Center, Montreal*) reviewed mutations of vitamin D (3) hydroxylase in humans and discussed mouse models of these conditions. **Barbara Boyan** (*Georgia Tech, Atlanta*) presented data suggesting sex hormones differentially influence terminal chondrocyte differentiation. **Clarke Anderson** (*University of Kansas, Kansas City*) showed that products of Saos-2 cells can induce formation of complete bone marrow when implanted into nude mice, which he suggested may be mediated by BMPs.

René St-Arnaud (*Shriners Research Center, Montreal*) reviewed the metabolism of vitamin D and the relevance of its metabolites to mineralization in the lower growth plate. He discussed a mouse model of pseudovitamin D-deficiency rickets due to genetic ablation of 1 α -hydroxylase (CYP27B1). **Thorsten Kirsch** (*University of Maryland, Baltimore*) addressed the role of annexin V in the apoptosis of growth plate chondrocytes. He presented findings suggesting that this process involves binding of annexin V to active PKC α and to $\beta 5$ integrin.

Zena Werb (*UCSF, San Francisco*) introduced the session on growth plate remodeling, vascular invasion and marrow establishment with a review of her findings regarding skeletogenesis in MMP-9 and MMP-13 deficient mice emphasizing that the two work synergistically and their actions are rate-limiting to bone growth. She also discussed her findings suggesting that galectin-3 could be an endogenous substrate for MMP-9 and that MMP-9-cleaved galectin-3 may directly influence certain events associated with vascular invasion. **Ernestina Schipani** (*Harvard Medical School, Boston*) discussed mouse experiments showing that hypoxia in the central part of the zone of proliferating chondrocytes and the upper hypertrophic chondrocytes induces expression of the transcription factor HIF-1 α and reduces its turnover through a mechanism that in the absence of hypoxia involves proteosomal targeting by the von Hippel-Lindau tumor suppressor protein (VHL).

Olena Jacenko (*University of Pennsylvania, Philadelphia*) presented evidence linking chondrocyte hypertrophy and endochondral ossification to the establishment of a hematopoietic marrow environment. She focused primarily on mice with disrupted collagen X function, demonstrating that in addition to growth plate changes, all mice had altered hematopoietic profiles and impaired immune function. She proposed that in hypertrophic cartilage, collagen X forms a network stabilized by PGs and GAGs that sequesters hematopoietic cytokines, and that disruption of this network leads to a cytokine imbalance that may cause altered hematopoiesis in the marrow.

Scott Saunders (*Washington University, St Louis*) described a delay in endochondral ossification in the glypican-3 deficient mouse. It involved abnormal persistence of hypertrophic chondrocytes and a reduction of trabeculae in subchondral bone accompanied by abnormal differentiation of bone-marrow cells of the hematopoietic lineage suggesting a common requirement for this heparan sulfate proteoglycan.

Danny Chan (*Hong Kong University, Hong Kong*) presented a collagen X knock-in mouse model lacking an MMP cleavage site needed for its degradation. Persistence of a degradation-resistant collagen X in the ECM resulted in delayed marrow formation, subtle changes in trabecular bone density, and a delay in mineralization. Although hematopoietic profiles were not significantly altered in the marrow, lymphatic organs were affected, including reduced spleen size and enlarged thymuses. These data are consistent with a role for collagen X and the chondro-osseous junction in contributing to a proper marrow environment for blood cell differentiation.

Several presentations focused on regulation of the growth plate. **David Ornitz** (*Washington University, St Louis*) presented data showing that FGF9 and FGF18 cooperate in signaling to growth plate cells. They regulate not only chondrogenesis and osteogenesis, but also vascular invasion through a mechanism that is mediated by VEGF both in mature hypertrophic chondrocytes and in perichondrial cells. **Andrea Vortkamp** (*University of Essen, Essen*) addressed the question of whether Ihh signals directly or indirectly regulate Pthrp expression in distal chondrocytes. Her findings suggested a direct effect, through suppression of gli3 expression, without the need for other morphogens such as BMPs or TGF- β s. She also discussed potential interactions between Ext1, which is mutated in hereditary multiple exostosis, and the Ihh-Pthrp regulatory circuit. **Malgorzata Wiweger** (*University of Sheffield, Sheffield*) discussed abnormal stacking of chondrocytes observed in human exostoses and presented evidence that mutations of Ext-like genes in zebrafish produce similar stacking abnormalities.

John Hassell (*University of South Florida, Tampa*) discussed the perlecan knockout mouse whose growth plate exhibits decreased aggrecan and *Col10a1* expression and decreased cell proliferation. In slices of cultured bovine cartilage, perlecan is secreted into the media.

Interestingly, the ratio of chondroitin to heparan sulfate differs between the proliferative and hypertrophic chondrocyte zones suggesting different functions with respect to growth factor binding. **Kathryn Rodgers** (*University of Pennsylvania, Philadelphia*) discussed the generation of perlecan knock-in mice to model Schwartz-Jampel syndrome, a progressive skeletal dysplasia that results from decreased perlecan. Her data indicate altered transcription leading to impaired perlecan secretion. Mice are dwarfed and exhibit a transient expansion of hypertrophic cartilage in growth plates, aberrant trabecular bone orientation, marrow hypocellularity, misshapen skeletal elements, and osteonecrosis.

Lynn Sakai (*Shriners Research Center, Portland*) presented data suggesting that fibrillins regulate growth plate chondrogenesis and that one mechanism may be to influence local TGF- β activity. She showed that fibrillins have a binding domain for the precursor form of TGF- β and that BMPs 4,5,7,10 and GDF 5 and 8 bind to fibrillin. Interestingly, BMP signaling is increased in fibrillin-1 knockout mice. **Linda Sandell** (*Washington University, St Louis*) also discussed BMPs and chondrogenesis. She showed that mature chondrocytes respond to the inflammatory cytokine TNF-alpha by increasing the expression of BMP2. In the 3' UTR of *BMP2* there is a sequence (AUUUA motif) that mediates increased mRNA stability in response to cytokines. She showed that TNF-alpha modulates mRNA stability via the p38 signal transduction pathway and by increasing mRNA expression through NF-kappaB.

Benjamin Alman (*University of Toronto, Toronto*) discussed a transgenic mouse model of human enchondroma generated by introducing a mutation into the Pthrp receptor gene that activates the receptor, activates Ihh signaling in the growth plate and leads to cartilage nodules in subchondral trabecular bone. He also presented data on a comparison of growth plates from *Gli2*^{-/-} and *Gli3*^{-/-} mice, which displayed increased and decreased hypertrophic zone thicknesses, respectively.

Rebecca Williams (*Cornell Univ., Ithaca*) described the use of multiphoton microscopy to visualize transport of fluorescent tracers from the vasculature into the growth plate. Her data revealed a highly diffusible cartilage channel at the proliferative and early hypertrophic regions of the growth plate, where communication occurs between chondrocytes and the perichondrium. She suggested that bone-derived molecules would be distributed throughout the growth plate, whereas perichondrial- or cartilage-derived would be concentrated in the proliferative and early hypertrophic zones.

One session specifically addressed disturbances of chondrogenesis. **Matthew Warman** (*Case Western Reserve, Cleveland*) discussed mutations of the C-type natriuretic peptide (CNP) receptor that occur in acromesomelic dysplasia. Both CNP and its receptor are expressed in the growth plate. Given that acromesomelic dysplasia is inherited as an autosomal recessive condition, he raised the possibility that some patients with idiopathic mild short stature could be carriers for CNP receptor mutations. **William Wilcox** (*UCLA/Cedars Sinai Medical Center, Los Angeles*) presented in vitro studies showing that CNP downstream signals inhibit FGFR3 signals transmitted through MAP kinase pathway. His findings suggested the inhibition was at the level of Raf-1.

William Horton (*Shriners Research Center, Portland*) discussed disturbances of ubiquitin-mediated lysosomal targeting of activated FGFR3 in achondroplasia. He provided evidence that Sprouty 2, usually considered an inhibitor of FGF signaling, may modulate FGFR3 signals upward contributing to gain of receptor function. **Avner Yayon** (*ProChon Biotech, Rehovot*) discussed therapeutic strategies for countering the excess of FGFR3 signals in achondroplastic growth plate. He talked about the use of tyrosine kinase inhibitors selective for FGFR3 and blocking antibodies for FGFR3 in mouse models of the disorder. He also discussed the potential

use of CNP analogs for this purpose, but acknowledged that their very short half-life in the circulation represents a challenge.

Hans Peter Bächinger (*Shriners Research Center, Portland*) addressed disturbances of matrix protein biosynthesis and secretion with special attention to the role of prolyl 3-hydroxylase in the posttranslational modification of a unique 3-hydroxyproline residue in collagen types I, II, and III, which are the primary structural proteins of bone, cartilage and other connective tissues. His data implied that matrix-cell signaling may be specified by posttranslational modifications of structural proteins such as the fibrillar collagens.

Kathryn Cheah (*Hong Kong University, Hong Kong*) discussed ER stress as a pathogenetic mechanism in disorders due to mutations of matrix protein genes. She provided evidence for the unfolded protein response for a frame-shift mutation in the carboxyl-terminal domain of collagen X associated with Schmid metaphyseal chondrodysplasia. Transgene expression in mice prevented association of the mutant chains with full-length collagen X polypeptides; this led to intracellular retention of the mutant chains, a reprogramming of the terminal differentiation events of the hypertrophic chondrocytes, and a subsequent down-regulation of transgene expression. **Paul Holden** (*Shriners Research Center, Portland*) examined disturbed secretion of cartilage oligomeric matrix protein (COMP) in pseudoachondroplasia. He compared secretion of COMP harboring several different mutations and showed they all were associated similar induction of ER chaperones, but differed in their ability to be retro-translocated to the cytoplasm and degraded.

The cartilage engineering session began with a review of the development and use of bone marrow-derived mesenchymal stem cells for cartilage engineering by **Brian Johnstone** (*Oregon Health & Science University, Portland*). He presented current methods used to analyze mesenchymal stem cell differentiation and discussed the challenges and hurdles related to the cell biology of this technology. **Rocky Tuan** (*NIAMS, Bethesda*) extended this discussion to the application of biomaterial scaffolds for cartilage tissue engineering. Specifically, he presented data indicating the efficacy of nanofibrous scaffolds in supporting lineage-specific differentiation of mesenchymal stem cells, and the development of three dimensional cartilage constructs in vitro and in vivo. Robert Guldberg (*Georgia Tech, Atlanta*) provided a review on imaging technologies for skeletal tissues, with particular attention on high resolution micro-coherent tomography (micro-CT).

Hari Reddi (*University of California, Davis*) reviewed the roles of BMPs in skeletal development and articular cartilage homeostasis. He discussed the important balance between anabolic morphogens, such as BMPs, and catabolic cytokines, such as interleukins and tumor necrosis factor alpha. Shifts in this balance in favor of catabolic cytokines may contribute to the poor ability of articular cartilage to repair itself. Treatments aimed at correcting this imbalance may be useful therapies for articular cartilage damage. **Juan Taboas** (*NIAMS, Bethesda*) described a dual culture system in which chondrocytes and vascular cells were cultured in or on alginate or fibrin gels respectively. Both cell types were shown to influence the behavior of the other in co-culture and conditioned media switching experiments suggesting cross-talk between the two cell types.

Conclusions

The Workshop was considered a significant success. Many new ideas and concepts were presented. For example, two cellular structures were described that appear to influence growth plate chondrocyte behavior. The first are actin-based signaling hubs that are activated by integrins; the second are calcium channels formed from polycystin-1 and polycystin-2 at the base of cilia. The output from these functional structures may influence cell orientation in the

postmitotic phase of chondrocyte maturation. Renewed interest in vascular access to the growth plate including a rediscovered perichondrial capillary bed that surrounds the growth plate provides a fresh view of how circulating and perichondrial growth factors physically reach growth plate cells. This finding has important implications for growth plate therapeutics in the future.

Several new insights were gained into the potential interplay between growth plate regulatory circuits. For example, genetic interactions between Sox9, Sox5 and Sox 6 and between Sox9 and Runx2, were better defined, allowing one to envision how chondrocyte proliferation and terminal differentiation are coordinated and fine-tuned. Continuing on the theme of pathway integration, evidence was presented that both Smad-dependent and Smad-independent BMP pathways are involved in regulating the Ihh/PTHrP circuitry, that BMPs exert their effects on chondrogenesis through retinoic acid intermediates and also through activation of Sox9, Sox 5 and Sox6, and that canonical Wnt signaling acts through altering Ihh expression to influence chondrocyte maturation.

New approaches for keeping track of the human chondrodysplasias that integrate developmental, clinical, genetic and pathological observations were presented. Disturbances responsible for these disorders are now beginning to be understood at the molecular level. For instance, failure to hydroxylate proline residues at the 3 position of type I collagen leads to recessive osteogenesis imperfecta, and induction of the unfolded protein response to mutant type X collagen and COMP contributes to the pathogenesis of Schmid metaphyseal dysplasia, pseudoachondroplasia and multiple epiphyseal dysplasia. Similarly, delineating the intersection of two signaling pathways, the pathway downstream of the CNP receptor, which is mutated in acromesomelic dysplasia, and the pathway downstream from FGFR3, which is mutated in achondroplasia, provides a conceptual basis for treatment of achondroplasia. Mutations are being found in more and more of the genes that play important roles in growth plate development and function. Similarly, a growing number of human chondrodysplasias are being modeled through genetic engineering in mice.

Several new research tools were presented including genetically engineered mice that allow specific events important to growth plate formation and function to be dissected. Of particular note were new mouse strains harboring osterix-cre-ER^{T2}, collagen I (3/2kb)-cre and Col10-LacZ transgenic reporter mice. A number of new analytical techniques were discussed, including real-time multiphoton imaging of growth plate and articular cartilage of live mice, microsurgical techniques to dissect and transplant rodent growth plate zones, three-dimensional culture systems to study interactions between cartilage and vascular cells, and improved high-resolution imaging technologies to assess bone structure and mineralization in mice.

In short, the Workshop substantially advanced the understanding of how the growth plate develops, works and is disturbed by disease, and also how it can be modeled and its components experimentally dissected in vitro, in vivo and even in silico. There was a consensus of the significant consolidation of the field, which is now poised for substantial progress building on a strong scientific foundation that it now enjoys. We hope that the ideas, interactions and collaborations stimulated by the 2006 Workshop will contribute to the continued advancement of this field and serve as the basis for future workshops on the growth plate.

Finally, we thank the session chairs for their help in preparing this summary including Veronique Lefebvre, Phyllis LuValle, Reinhard Fässler, Henry Kronenberg, Francis Glorieux, Zena Werb and David Ornitz. We also thank the Advisory Committee for assistance in planning the Workshop: Clarke Anderson, Barbara Boyan, Benoit de Crombrughe, Reinhard Fässler,

Francis Glorieux, Henry Kronenberg, Bjorn Olsen, David Ornitz, Hari Reddi, Linda Sandell, Irving Shapiro and Zena Werb.