Studies in tetrapod and teleost fish model systems have yielded detailed insight into the molecular basis of limb/finn bud outgrowth and polarity, but we have relatively little understanding of how skeletal patterning and regeneration are directly controlled. I approach this problem by exploiting the natural diversity of vertebrate fin and limb morphologies and regenerative strategies. Through comparative analyses of non-model organisms drawn from all major vertebrate groups cartilaginous fishes, ray-finned fishes, and tetrapods I have identified two mechanisms of appendage morphogenesis primitive to vertebrates: the conserved role of Sonic hedgehog (Shh) in anteroposterior patterning, and the ability to regenerate the adult endoskeleton. However, taxon-specific differences were observed in both the regulation of Shh signaling and the mechanism of appendage regeneration. These differences may have important implications for understanding how evolution generates lineage-specific variation, such as the loss of humans’ ability to regenerate limbs.

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Program/Abstract # 230
Non-autonomous control of the orientation of actin-based protrusions
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The ability of epidermal cells to form elaborately shaped actin-based protrusions is vital to many cellular functions such as hearing and mechanosensation, but it is unknown how protrusions are shaped. Certain Drosophila embryonic epidermal cells construct actin-based protrusions, called denticles, which exhibit stereotyped, row-specific differences in size, density, and hook orientation. This precise dentine pattern is conserved throughout all drosophilids yet studied, and screening for mutations that affect this pattern has been used as a powerful approach to identify genes involved in developmental decisions and signaling pathways. However, how row-specific differences are specified and the mechanism(s) involved have remained elusive. Here, we link developmental patterning signals to the morphogenetic event of dentine shaping via the transcription factor stripe and the spectraplakin shortstop (shot). First, we demonstrate that stripe is required, non-autonomously, for the unique anterior hook orientation observed in the row one and four denticles. Secondly, we show that stripe specifies anterior dentine hooking via upregulation of shot. Spectraplakins are extremely large cytoskeletal proteins, generally thought to function by linking cytoskeletal elements to one another or the membrane. Consistent with this, the interaction of shot with microtubules is required for proper dentine hooking, revealing novel roles for spectraplakins and the microtubule cytoskeleton in the shaping of actin-based protrusions.

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Program/Abstract # 231
Using gene ontology to study branching morphogenesis in mice
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Branching is a key morphological feature in the development of many anatomical structures in mammalian embryos. Genes that control the normal branching morphogenesis of these structures also have been implicated in neoplastic disease. Branching during development occurs in structures such as the lung, kidney, prostate gland, mammary gland, submandibular glands, placenta and blood vessels. We are interested in understanding the similarities and differences in the genetic programs involved in normal branching morphogenesis. We are actively extending the Gene Ontology (GO) resource to include processes of branching morphogenesis in mammals. We are linking genes with these processes by capturing information from the primary scientific literature. We present an analysis of the similarities and differences of the genetic programs that influence different types of branching morphogenesis processes in the mouse. This analysis is the first step in understanding the evolution of branching morphogenesis within an organism and between organisms, and how this morphogenetic process may undergo perturbation that results in malignancy.

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Program/Abstract # 232
Regulation of Bcl2 family members by retinoic acid and Fgf8 during interdigital regression
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Retinoic acid (RA), a derivative of vitamin A, signals through the binding to RAR and RXR receptors. During mouse limb development RA functions as a proximalizing factor in the limb bud and, at later stages, as a cell death inducer in the interdigital regions. We have determined that RA is the persistent cell death-inducing signal acting on distal mesenchymal cells of the developing limb. This death-inducing activity of RA is counteracted by the survival activity of Fgf8 during limb/digit growth. Crosstalk between RA and Fgf8 involves the transcriptional regulation of genes involved in signaling. In order to find an interaction between these two molecules at the level of the cell death machinery, we studied the regulation of Bcl2 family members. Using a bioinformatics approach, we found that the promoter of the proapoptotic Bax gene contains several putative binding sites for RAR nuclear receptors. In agreement with a transcriptional regulation, RA up-regulated the Bax expression in the whole distal region of mouse limbs. Pharmacological inhibition of RARα, RARβ and RARγ suggests that RARγ is the main receptor responsible of the RA-inducing death activity. The role of Fgf8 and antiapoptotic Bcl2 family members in counteracting the Bax activity in growing limb regions will be presented.

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Program/Abstract # 233
A flip trap screen reveals a novel transcript in the HoxB genomic region
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Branching is a key morphological feature in the development of many anatomical structures in mammalian embryos. Genes that control the normal branching morphogenesis of these structures also have been implicated in neoplastic disease. Branching during development occurs in structures such as the lung, kidney, prostate gland, mammary gland, submandibular glands, placenta and blood vessels. We are interested in understanding the similarities and differences in the genetic programs involved in normal branching morphogenesis. We are actively extending the Gene Ontology (GO) resource to include processes of branching morphogenesis in mammals. We are linking genes with these processes by capturing information from the primary scientific literature. We present an analysis of the similarities and differences of the genetic programs that influence different types of branching morphogenesis processes in the mouse. This analysis is the first step in understanding the evolution of branching morphogenesis within an organism and between organisms, and how this morphogenetic process may undergo perturbation that results in malignancy.

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