Student Bio’s

2016 MBL Embryology Course

Woods Hole, MA
Studying ancient functions across animals: self-repair and sleep in Cnidaria

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Self-repair - We found that young moon jellies can rapidly reorganize their bodies and regain crucial functions after severe injury, a process we call symmetrization. Their normal pulsing behavior generates mechanical forces on their visco-elastic tissues, which enables force balancing and reorganization. This form of self-repair may be present in many radially symmetrical gelatinous organisms, many of which also regenerate, leaving us to question the trade-offs between these two powerful forms of self-repair.

I’ve worked in a close collaboration to study how conserved the sleep behavior is across animals. Flies and worms have sleep-like states, which motivated us to investigate whether jellies, in an earlier branching metazoan lineage, also sleep. We investigated the upside-down jelly, Cassiopea, which naturally pulses with its bell down against the bottom surface of its environment. Monitoring their pulsing activity for consecutive days and nights revealed the presence of three key features of a sleep-state: reversible behavioral quiescence, reversible sensory depression, and homeostatic rebound. Our findings support the hypothesis that sleep evolved early in metazoan evolution.

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Morphogen signaling and cell adhesion: a positive feedback loop to differentiate mesendoderm tissues

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During gastrulation, differentiation of embryonic cells is connected to regulation of their adhesive properties and to segregation into the different germ layers, ectoderm, mesoderm and endoderm. However, how those processes relate to each other remains unclear. We used a combination of in vivo and in vitro assays to clarify the functional interdependency of cell differentiation and cell-cell adhesion during zebrafish gastrulation. Two-photon imaging and transplantation assays allowed us to observe that cell-cell adhesion and expression of mesendodermal marker genes are correlated in the zebrafish embryo. We used in vitro cell culture and molecular biology techniques to clarify the molecular mechanisms responsible for the interaction between cell differentiation and cell-cell adhesion. We found that cell-cell adhesion increases the competence of mesendoderm progenitor cells to respond to nodal signaling, thus influencing their differentiation. At the same time, nodal signaling positively controls cell-cell adhesion of differentiating cells. This results in a positive feedback loop between signaling and cell-cell adhesion, culminating in the segregation of axial mesendoderm cells into mesoderm and endoderm populations.
The role of Wnt signaling on the posterior development and segmentation of the spider *Parasteatoda tepidariorum*

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Oxford Brookes University

United Kingdom

The process of segmentation in arthropods have been so far been understood on the dipteran model fruit-fly *Drosophila melanogaster*, that presents a very singular development among all the other segmented animals. Strikingly, emerging models as the spider *Parasteatoda tepidariorum* possess a very interesting segmentation clock on its embryogenesis, where the first segments appears shortly after the gastrulation occurs and the next to be formed differentiate from a posterior region called segment addition zone. On my Ph. D., I aim to understand how this complex (but still eye-catching) mechanism occurs, first by identifying target genes that could be responsible for it and posteriorly assaying their specific roles on the development of new segments in this spider species. I came from a background that mix classical descriptive embryology with tools of molecular biology, studying crustacean models on my Ms.C. back in Brazil, even though this is a brand new area back in my country. Thus, I started this new project on September 2015 at Oxford, feeling very excited with all the knowledge that I get so far and looking forward to the MBL course in June!
Major transitions in the brain and skull at the origins of modern vertebrate radiations

Bhart-Anjan Bhullar
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I am a paleontologist, an anatomist, and a sometime developmental biologist whose questions arise largely from the great transitions in the history of vertebrates and the origins of the major vertebrate clades. My team and I try to bring to bear a combination of extant comparative anatomy, inference from fossil forms, and molecular developmental biology to uncover the narrative and the mechanisms behind such events as the divergence between amphibians and amniotes and the great enlargement of the brain in the mammal and bird lineages. We have a particular interest in developmental mechanisms that explain multiple seemingly independent morphological transformations. These include phenomena like juvenilization at the origin of birds and numerous aspects of the brain’s influence on the remainder of the skull and head. While we spend most of the year in the lab, in the summers we explore the deserts of the world as fossil hunters to uncover direct evidence of the history of life.
Developmental basis of beak shape variation in Darwin’s finches

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I am a new postdoc in the lab of Arkhat Abzhanov. We study the genetic programs active during craniofacial development in Darwin’s finches. This closely related (monophyletic) group of birds is endemic for the Galapagos archipelago and Cocos island, and is a classical example of adaptive radiation under natural selection as all 14 (15) species evolved from a single ancestor that landed on the islands about 2 million years ago. Darwin’s finches diversity is reflected by the great variation in their beak size and shape, and hence in their diet. On mainland, such variation is seen in representatives of different bird families. Abzhanov’s team has shown that the three dimensions of the beak are independent developmental modules that evolve separately, and that beak diversity among all Darwin’s finches can be reduced to three “group shapes”. They revealed developmental mechanisms causing variation within one of the groups. I am currently using RNAseq screens of embryonic beaks from most species of Darwin’s finches, to identify candidate molecular mechanisms controlling variations among group shapes. I will validate the best candidates via in situ gene expression visualization and gain- and loss-of-function tests using retroviral vectors on chicken embryos, followed by µCT scanning-based morphometrics. I am also planning to continue the study on closely related to Darwin’s finches Caribbean species, and to extend it to other groups that are examples of adaptive radiation with even greater beak diversity, e.g. Hawaiian honeycreepers and Madagascan vangas.
Mechanisms of primordial germ cell motility and migration in the purple sea urchin

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University of California, San Diego

My research with the Hamdoun Lab focuses on the mechanisms of primordial germ cell (PGC) migration in the sea urchin model system. I use high-resolution confocal microscopy to describe the morphology of PGCs in vivo. From these data I have described the motility of PGCs throughout their migration. In the future I will investigate the role of sphingosine-1-phosphate (S1P) signaling, a conserved mechanism of PGC migration, and its effects on sea urchin PGC motility and morphology. In addition, I am investigating active transport by ATP binding cassette (ABC) transporters in the PGCs of sea urchins and vertebrate models. Previously, our lab showed that sea urchin PGCs downregulate the ABC transporter ABCB1a, possibly as a prerequisite to their migration. Initial results suggest that this phenomenon is conserved in both zebrafish and mouse PGCs.
Functional relationship between Snail1 and Prrx1 EMT transcription factors in embryonic development

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In the lab we study the epithelial-mesenchymal transition (EMT) during embryonic development and its reactivation during some pathologies, such as fibrosis and cancer. The EMT endows cells with migratory and invasive properties and it is crucial for the formation of many tissues and organs during embryonic development. We use the mouse, the chick, and the zebrafish, as animal models.

The EMT program is triggered after the activation of transcription factors, referred to as EMT-TFs. Prrx1 was recently identified as a novel EMT-TF in our lab (Ocaña et al., Cancer Cell, 2012). Prrx1 presents several isoforms as a result of alternative splicing, and only one of them induces EMT. Experiments in cultured cells suggest that the function of the short isoforms can be the attenuation of the EMT induced by long isoform (unpublished). In order to test this, we are generating mouse models in the lab that lack the isoforms that cannot induce EMT. Characterizing the phenotype of these mice during development will tell us more about their function. In addition, we have observed a complementarity between the expression patterns of Prrx1 and the classical EMT-TF Snail1 during embryonic development. The described phenotype of single mutants indicates that although they differ, they affect similar cell populations, including mesoderm and neural crest derivatives. In my project, I am generating mouse models in which the expression of both transcription factors is compromised with the aim of better understanding putative genetic interactions and/or cooperation during embryonic development, which can also shed new light into the interpretation of the phenotypes observed in pathological contexts.
Cell invasion and cancer metastasis

Eric Hastie

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My graduate work combined the study of virology and cancer biology. I used vesicular stomatitis virus (VSV) as an oncolytic virus against pancreatic cancer. I generated multiple novel viruses to examine mechanisms involved in resistance to virus therapy, specifically: p53 signaling and interferon-mediated resistance to infection. In my postdoctoral position I am studying cell invasion in a C. elegans model. While I have just begun this work, I am interested in molecular mechanisms of cell invasion as they relate to metastatic cancer. I look forward to immersing myself in cell and developmental biology and using model systems to examine signaling pathways and cytoskeletal architecture/modification that may be involved in cell migration. When I am not in the lab you can find me teaching at the local community college or in my home lab (kitchen) testing recipes or outside practicing other hobbies like birding, photography, or glass working. If I am not at home, I am probably out to sea on my sailboat, Pier Reviewed.
Investigating *Hox* genes and their function during development and regeneration of the starlet sea anemone, *Nematostella vectensis*

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*Hox* genes are generally conserved through evolution. This statement holds true for all Bilaterians, yet lacks support outside this clade. Based on a series of phylogenetic studies, “true” *Hox* genes are only identified in Cnidaria and Bilateria, indicating an ancestral innovation of *Hox* genes before the divergence of these two clades. However, the biological function and regulation of Cnidarian *Hox* genes are still poorly understood. In order to address this question, I used the starlet sea anemone, *Nematostella vectensis*, as a model organism and started mutagenesis of different *Hox* genes using CRISPR/Cas9 technology. Besides constitutional knockout mutants, I am also making conditional allele for several *Hox* genes, which will allow me to bypass embryonic lethal caused by *Hox* mutation and carefully interrogate different functions of the same gene at different developmental time points. Meanwhile, I am generating transgenic reporter lines for different *Hox* genes. This provides the basis for further studies, such as investigating the upstream signal that regulates *Hox* expression in Cnidarians. By applying careful genetics analysis in a Cnidaria model, I’m looking forward to providing a new perspective on the origin and evolution of *Hox* genes.
Growing apart: characterizing the development of charismatic throat morphology in lizards

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Gainesville

The boring version: Species vary widely in their pattern and magnitude of sexual dimorphism, yet the proximate mechanisms that regulate these differences remain poorly understood. Sexually dimorphic characters present a novel perspective to our understanding of anatomical evolution because the sexes share the majority of their genomes yet diverge in size and shape during development. Closely related species can have dramatically different degrees of sexual dimorphism and I am interested in how this diversity is generated during development. For my graduate work, I am collecting data across biological levels or organization to understand sexually dimorphic developmental processes, primarily using lizards in the genus Anolis. This genus has been well studied from both ecological and evolutionary perspectives, making it an excellent system to answer integrative, developmental questions.

The exciting version: I study how/why dewlaps (colorful throat fans - photo below) grow to different sizes in male and female Anolis lizards!!
The *Dicyema japonicum* genome provides insights into the phylogenetic position, regressive evolution, and adaptive adaptation of dicyemid mesozoans

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Japan

Dicyemid mesozoans are microscopic endosymbionts inhabiting in the renal sacs of octopuses or cuttlefishes. Due to their simple body organization, approximately forty cells per individual without differentiated tissues, dicyemid mesozoans were once thought as an intermediate between Protozoa and Metazoa. However, referring to the spiral cleavage during their early developmental stages and a spiralian peptide encoded by dicyemid DoxC gene, recent studies suggested that the Dicyemida should be considered as a member of Spiralia. The phylogenetic position of dicyemids has been debated for a long time. Currently, I am using phylogenomic approaches to clarify the phylogenetic position of dicyemids. Besides, I also plan to obtain evidences from comparative developmental studies to support the phylogenomic results, and further comprehend the evolution of spiralian. The simple morphology of dicyemids could be regarded as the secondary simplification associated with their symbiotic life style. No nervous system has been reported in dicyemids, but they may possess the crucial regulatory networks for sensory functions which are important to sense the uncertain cues triggering the transformation from asexual to sexual reproduction. Hence, I want to investigate the crucial cell differentiation mechanisms and regulatory gene networks which dicyemids conserved for the essential sensory functions during the process of regressive evolution. In addition, dicyemids also represent an example of adaptive radiation. In some cases, three to five close dicyemid species with variant collate morphologies occupying different niches of renal sac were described within one octopus host species. I will perform the analyses on accelerated gene family evolution, gene duplication, transposable element insertion, and SNPs of regulatory elements using genomic data. I hope to discover possible molecular mechanisms to interpret the adaptive radiation in dicyemids.
Understanding the role of Sonic Hedgehog signaling on neural stem cell proliferation in the zebrafish hypothalamus

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Work from Altman and Das in 1960s, showing the birth of new neurons from neural progenitor cells, reversed the traditionally held view that neurogenesis occurs only during embryonic development. Understanding the cellular and molecular processes that regulate adult neurogenesis has been a major challenge in the field. In the rodent brain, cell-cell signaling in stem cell niches, including Shh-mediated signaling, regulates neural precursor proliferation. Much less is known about the regulation of neurogenesis in the ventral hypothalamus, despite the fact that proliferation in this region has been clearly documented and is tied to its function. Sonic Hedgehog (Shh) is among several cell-cell signaling proteins that are well established as regulators of ventral forebrain development in the embryo. My Ph.D. project is focused on understanding how Sonic Hedgehog signaling (Shh) regulates neural stem cell proliferation in the larval and adult zebrafish hypothalamus. I am using a suite of zebrafish transgenic tools to manipulate Hh signaling levels and assaying cell proliferation and cell differentiation in the hypothalamus and pituitary gland.
Role of tissue mechanics in the morphogenesis of zebrafish semicircular canals

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Tissue morphogenesis drives several developmental processes and is required for the basic organization of embryos and organs. The semicircular canals (SC) in the vertebrate inner ear present a fascinating example, whereby the motion-sensing function relies on their complex shape and orientation. Failure of normal development of SC results in vestibular dysfunction. The SC formation requires budding and extension of epithelial projections from an ovoid embryonic structure called the otic vesicle. These projections fuse to form pillars, and the space around them becomes the SC. The patterning and tissue mechanics underlying the SC formation is largely unknown. My research involves studying the cellular and tissue dynamics involved in projection of budding during SC morphogenesis in zebrafish using in toto imaging, molecular-mechanical perturbations, quantitative analysis and theoretical modeling. I am testing the role of tissue-scale forces that may result in tissue buckling to initiate bud projection. I will also study the role of intrinsic forces generated by the actomyosin networks in cells undergoing shape changes during bud projection as well extrinsic forces from the extracellular matrix. The fundamental, multi-scale principles revealed from this study will be widely applicable to other morphogenetic events involving budding and curvature formation.
Relationship between the primordial germ cells and remodeling of blood vessels in avian embryos

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Kyoto University
Japan

During early development, primordial germ cells (PGCs) translocate over long distances until they find the final destination, the gonad. PGCs in avian, which circulate in blood vessels, achieve site-specific capture and transmigrate out from the vessels. I would like to understand how PGCs influence the remodeling of vascular formations. I examined the distribution patterns of translocating PGCs in blood vessels in quail with immunohistochemistry. I would like to observe the alteration of vessels when I remove PGCs or the gonad.
Establishment of planar cell polarity of sensory hair cells in the zebrafish lateral line

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My main interest is trying to understand how, when and where cells in the lateral line of zebrafish get polarized. In particular, I am studying planar cell polarity (PCP) of the mechanosensory hair cells present in the volcano-shaped organs called neuromasts, which form the lateral line system. I am characterizing two mutants that affect hair cell orientation: wnt11r (wnt11-related, a non-canonical wnt ligand) and knypek (gpc4, a heparan sulfate proteoglycan). While an already characterized mutant called trilobite (vangl2, a core PCP protein) displays orientation defects in all neuromasts, mutations in wnt11r and gpc4 genes only affect hair cell orientation in a subset neuromasts. gpc4 is expressed in the lateral line; and wnt11r is expressed in the CNS, the Schwann cells that surround the axon that innervates the hair cells, the underlying muscle and in an unidentified group of cells on top of the lateral line placode. Removing the wnt11r-expressing glia does not affect hair cell polarity, and wild type muscle does not rescue hair cell orientation. Therefore, I am proposing that PCP is already established at the level of the placode, even before the primordium starts migrating. Furthermore, I discovered that trilobite mutants, and wnt11r and knypek mutants have different kind of polarity defects. Therefore, I will analyze the PCP pathway in wnt11r and knypek mutants. Using long-term time lapse analysis of several transgenic lines that I crossed with the mutants, I will also be able to determine if the hair cell polarity defects arise as a consequence of PCP defects in the cell, kinocilium positioning defects or defective cell rearrangements.
Genetic regulation of tooth replacement in the axolotl

Jason Pardo

University of Calgary
Canada

Although mammals only replace their teeth once, most vertebrates replace their dentition throughout their lives. I am studying the regulation of continuous tooth replacement in a model organism, the axolotl, in order to better understand generalized vertebrate tooth replacement. In the axolotl, replacement teeth form along an infolded lamina of epithelium, the successional lamina, through interactions between this lamina and the underlying mesenchyme. I am using histology and immunohistochemistry to describe cell dynamics and gene regulation of this process, and experimental manipulations to explore how this process may have been lost in some evolutionary lineages.
Genomics of embryonic development of *Rhodnius prolixus*

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Currently I am a PhD student in the Rivera-Pomar lab, and performing an extensive screening for genes and networks of gene regulation during the early development of *Rhodnius prolixus*. For this aim, first, we have already annotated most of the developmental biology genes of the recently sequenced genome and initiated the study of gene expression by transcriptome analysis. Currently, I am analyzing in detail the expression of developmental genes by means of transcriptomics during embryonic development of *R. prolixus*, with a focus on early genes, maternal genes and oogenesis; I am also using different molecular techniques such as parental RNA interference and in situ hybridization to determine gene function.
Advancing CRISPR-Cas technologies for effective gene perturbations in the ascidian Ciona intestinalis

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CRISPR-Cas functions with fidelity and efficiency in our lab’s model organism, the marine invertebrate chordate Ciona intestinalis. I have modified the system into a practical transcriptional repressor by fusing a co-repressor-recruiting domain to the C-terminal end of a nuclease-dead version of Cas9. This repressor can then be targeted to any gene of interest by using the appropriate guide-RNAs. I have also expanded the use of CRISPR-Cas in Ciona and found that gene knock-ins can be efficiently generated, allowing real-time spatial and temporal visualization of endogenous proteins. In addition, I have found that using a polII-class promoter to express gRNAs flanked by ribozymes further increases the knock-in rate. I am generally interested in gene regulation during animal embryonic development. Specifically my research focus aims to characterize the regulatory relationships of Pou4, a gene involved in neural development and in our model organism is required for peripheral nervous system differentiation of ciliated epidermal sensory neurons. In vertebrates, this gene plays a critical role in an analogous cell type, developing inner ear hair cells. Using the CRISPR-Cas tools I have developed, I seek to investigate the inputs to this gene, its degree of self-regulation, and, Pou4 downstream targets.
Muscle fate specification in *Xenopus laevis*

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Berkeley

I study the intriguing ability of neural tissue to induce muscle fate during *Xenopus laevis* development. In amphibians, Spemann’s Organizer (functionally analogous to the embryonic shield of the zebrafish and Hensen’s node of amniotes) has traditionally been considered the major signaling center responsible for the formation of somites, blocks of paraxial mesoderm cells that give rise to muscle and other tissue types. However, my data suggests that the neural plate may also play a role in specifying somitic (specifically muscle) tissue. Expanding or restricting neural tissue has a corresponding, non-cell autonomous effect on the underlying somitic tissue. Using RNA-sequencing and classical embryological techniques, I plan to identify the neural plate signal(s) that specify the muscle fate and influence somite morphogenesis. These experiments will revise long-held assumptions about the role of signaling centers such as the Organizer on morphogenesis and differentiation.
The road to uniform gene expression – How zebrafish embryos overcome a game of chance

Carine Stapel

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I'm a PhD student in the lab of Dr. Nadine Vastenhouw at the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden, Germany. In the lab we study how the embryonic genome is activated during the maternal-to-zygotic transition. During this transition, the embryo ceases to depend on maternally provided transcripts and proteins and starts to transcribe its own genes for the very first time. We study this process in zebrafish, where the genome is activated about three hours post fertilization. At this time the embryo already consists of a thousand cells and is still pluripotent. In my project, I study how gene expression patterns are being set up during zygotic genome activation using single molecule RNA imaging.

Many developmental processes depend on precise expression of patterning genes. However, transcription activation consists of a complex series of events, which lowers the chance that it occurs in all cells at the same time and with the same frequency. Because of this, transcription activation is an inherently stochastic process. This raises the question whether and how embryos manage to set up uniform expression profiles. This question is especially relevant in zebrafish, where gastrulation and cell fate specification already start within two hours after the first onset of transcription.

To find out how embryos deal with the stochastic process of transcription, I adapted single molecule fluorescent in situ hybridization for zebrafish. With this technique I can image and count single RNA molecules at subcellular resolution in the embryo. I acquired a fine-grained time series of embryonic stages, spanning from zygotic genome activation to lineage specification, which I am analyzing right now. These data help us understand how gene expression patterns are being set up in embryos to support robust embryonic development.
Identifying novel targets of Sox9 in mammalian sex Determination

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Disorders of sexual development (DSD) are genetic conditions which can cause genital abnormalities and sex reversal. The gene pathways involved are complex and our comprehension of the molecular mechanisms leading to DSD is currently limited. In 1990, it was discovered that SRY is the sex determining gene on the Y chromosome which triggers testicular development. The key target gene of SRY to be characterised in the gonad is another transcription factor, SOX9. SOX9 is both necessary and sufficient for the formation of the testis and is a DSD gene. Soon after its expression, SOX9 upregulates down-stream target genes such as FGF9, AMH and PGD2. These genes are involved in either the repression of female specific genes, or induction of male specific gonad development. As 70% of 46, XY DSD cases remain unexplained, it is likely that there are more targets of SOX9 to be discovered. Therefore, my research aims to characterise target genes of SOX9 in the embryonic testis and their function in the male gonad, in order to clarify their roles in DSD to gain further understanding of mammalian sex determination pathways.
For my Ph.D. I am investigating the role of vertebrate development in the evolution of dental morphological diversity. Dental diversity is profound yet current understanding of dental development is limited to a select group of models exhibiting relatively simplistic dentitions. Consisting of approximately 25,000 species and being exceptionally diverse, fish serve as ideal models to study the modification of developmental regulation in the evolution of morphological dental diversity. Few morphological adaptations can rival the unique pufferfish ‘beak’. Pufferfish dental morphology transitions from a simplistic uniform first-generation dentition, to a replacement dentition composed of composed of multiple stacked generations of elongated dentine bands. To date, my Ph.D. has focused on elucidating the developmental mechanisms that underlie the evolution of the beaked pufferfish dentition (Tetraodontidae). I have utilised in situ hybridisation and immunohistochemistry to identify spatio-temporal expression patterns of key developmental genes during pufferfish odontogenesis, and carried out small molecule treatments to highlight the roles of Wnt, Shh and Notch signalling during pufferfish odontogenesis. Cell-labelling experiments have localised a putative epithelial stem cell niche that enables lifelong dental replacement in pufferfish. Having carried out a successful preliminary CRISPR-cas9 experiment resulting in the ablation of pufferfish ventral spines, I will utilise this technique to functionally test the role of various developmental genes during the initiation of dental replacement from these epithelial dental progenitors. Throughout this project, I hope to greater understand the developmental mechanisms by which extreme teleost dental morphology has evolved.
Glandular morphogenesis of the mouse uterus

Zer Vue

Baylor College of Medicine

Houston, Texas

Uterine glands are interesting because they have an important role in fertility and disease. Without the presence of these glands, mammals are able to get pregnant, but the embryo is unable to implant because glands are needed to provide nutrients for its maintenance. Strikingly, 75% of adenocarcinomas are thought to originate directly from the glands themselves. By studying how these glands develop will give us important insights into how things may go awry. I have three main directions in the lab (1) to characterize the 3D structures of uterine glands during adenogenesis and in adults undergoing the estrous cycle; (2) to understand the behavior of specific cell types during gland formation; and (3) to identify the factors involved in adenogenesis through an unbiased approach (RNA-seq).

Currently, I have been able to reconstruct uterine glands in 3D using multiple imaging techniques (optical projection tomography, confocal and lightsheet microscopy) and using different mouse reporter lines. To explore the cell behaviors and morphologies, I have used different reporter mouse lines and used the incorporation of EdU to detect DNA synthesis in proliferating cells. I am currently in the process of making my RNA-seq libraries. We FACS-sorted the epithelial and mesenchymal cells to look for intrinsic and extrinsic factors that may be playing a role in the formation of glands.
Elucidating mechanisms of mechanosensation during secondary chondrogenesis

Katherine Woronowicz
University of California
San Francisco

I am working to understand how form and function are integrated during embryonic development. Particularly, I am interested in how mechanical forces applied by muscle contractions influence the form of the developing skeleton. Without proper mechanical stimulation, secondary cartilage, which forms on the surface of bone in select articulations and muscle insertions, fails to form. To gain insight into the biomechanical and signaling mechanisms which elicit secondary cartilage, I am using an avian model system. These embryos are large and develop externally, which makes them easy to observe, easy to treat with chemicals, and easy to surgically manipulate.
Effect of hedgehog pathway suppressors on follicle stem cell function and fertility in drosophila

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Fox Chase Cancer Center
Philadelphia, Pennsylvania

Follicle Stem Cells (FSCs) in the Drosophila ovary are a dynamic population of stem cells that divide frequently to self-renew and generate the differentiated daughter cells that comprise the follicular epithelium. Complex and poorly understood interactions between multiple cell types within the FSC niche contribute to the differentiation process, with direct contact between germ cells and follicle cell precursors promoting polarization and loss of stem cell function. In a recent study, we found that FSCs produce large cytoplasmic projections that assemble into a collective network that spans the FSC niche. Based on our initial observations, we propose a 3-step mechanism for building a pre-follicle cell communication network designed to receive differentiation signals from germ cells during cyst encapsulation. First, coordinated FSC proliferation and projection dynamics populate the FSC niche with pre-follicle cell daughters that remain interconnected via projections. Next, pre-follicle cells around the circumference of the niche generate a projection network that establishes a physical barrier at the Region 2A/2B border. Finally, germ cell contact with the projection network initiates signaling events that are transmitted via projections to induce a mesenchymal to epithelial transition in pre-follicle cells, enabling wrapping of germline cysts.

Projections are dynamic structures that undergo dramatic morphological changes upon stimulation of FSC proliferation, a process that depends on signaling via the Hedgehog pathway. We conducted a forward genetic screen to uncover suppressors of constitutive Hedgehog signaling, based on the premise that downstream effectors of the Hedgehog pathway likely control projection dynamics. We previously showed that constitutive Hedgehog mutants arrest egg production at 4 weeks after eclosion, in contrast to wild type females, which lay eggs for approximately 6 weeks. We reasoned that loss of genes in FSCs that promote transmission of the Hh signal would suppress the early sterility caused by constitutive Hh signaling. Conversely, loss of negative regulators of the Hh pathway in FSCs would further reduce reproductive lifespan. We validated the premise of the screen by demonstrating that reduction of
Smoothened, an essential effector in the Hedgehog pathway, suppressed the observed fertility defects. The goal of this project is to characterize how a group of mutations isolated in the screen affect projection dynamics to affect FSC function and overall female fertility.