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Dear Search Committee,

Enclosed you will find my application for a faculty positions in Experimental Systems Biology.

Since I arrived in Virginia in 1996 I have been working with Ray Keller in the Department of Biology, under an NIH postdoctoral fellowship for the first three years and more recently as a Research Scientist.

I am interested in the evolution of morphogenesis. It has become obvious that there are many developmental patterning pathways that are conserved throughout the metazoans. Some of these pathways are involved in directing the morphogenesis of homologous tissues or structures, to produce a more or less conserved phylotypic body plan. The question at this point is what these genes actually do. In the immediate sense, many of them regulate other genes or their protein products. But ultimately, they must direct a change in some cellular process that results in a specific, coordinated, force producing cellular behavior that in turn results in the observed morphogenic movements that give rise to the phylotypic body plan. How this works is one of the remaining fundamental questions of modern biology. Remarkably, while the patterning pathways and body plans are fairly well conserved, my research has shown that the cell behaviors that connect the two are not! Instead, the specific cell behaviors used to drive a morphogenic movement seems to vary much more rapidly than, and mostly independently of, the upstream patterning pathways that direct them. Understanding how the pathways diverge to direct different cell behaviors is important for two reasons. First, this is a mechanism by which morphogenesis can evolve, e.g. to accommodate different reproductive strategies, involving very different eggs. And second, our understanding of human diseases resulting from flaws in morphogenesis (birth defects) or other aspects of cell behavior (e.g. cancer) is based on inferences from a few well developed model systems; my work will help us to better understand the basis of these diseases, by looking at a broader spectrum of possible cell behaviors and the mechanisms for directing them.

I study variations in morphogenic mechanisms used by amphibians during gastrulation and neurulation. The goal of my research is to characterize these mechanisms, their patterning, the underlying cell behaviors and cell biology, and their dependence on biomechanical context in order to address their evolution. By understanding the differences and similarities in how they operate in species of amphibians that utilize different ecological niches and hence have different reproductive strategies and embryonic architectures, I am finding conserved morphogenic design principles, which can be further tested in other chordate species. While species may be evolutionarily “promiscuous” in their use of particular cell behaviors for a given morphogenic movement, there does appear to be a limited “toolbox” of behaviors that species can pick from; I want to understand why a particular cell behavior is used in a particular context.

Working in the Keller lab, I have discovered an ingression mechanism that drives gastrulation in urodeles (tailed amphibians) that has much in common with amniote primitive streak ingression and epithelial mesenchymal transitions, and may prove to be an interesting evolutionary intermediate. The patterning of urodele ingression bears a striking resemblance to that of the much different morphogenic mechanism that the model amphibian, *Xenopus laevis* uses to drive its gastrulation, suggesting that the upstream patterning of these behaviors is conserved. I have also recently uncovered a primary morphogenic mechanism for closing the blastopore in large, slowly developing frog species that may be an ancestral mechanism for amphibian gastrulation, and perhaps chordate gastrulation generally, but which is only cryptically expressed in *Xenopus*. I am currently testing it's operation in a hemichordate and will test the operation of this mechanism in other basal chordates.

My interdisciplinary background in morphogenesis, biomechanics, cell biology, evolution and quantitative genetics, combined with extensive training in advanced imaging techniques and a wide array of amphibian embryological, cellular and molecular techniques, allows me to take a broadly integrated approach to understanding the evolution of morphogenic processes. I am working at the intersection of developmental, cell and evolutionary biology, and so should complement your department well.

Thank you for considering my application; I look forward to hearing from you.

Sincerely,



David R. Shook

Research Interests - David R. Shook

The Evolution of Morphogenic Machines

The genetic pathways regulating embryonic patterning are well conserved across the metazoans, as are phylotypic body plans. But surprisingly, the morphogenic mechanisms, directed by the patterning pathways to shape that body plan, are not conserved. For example, Brachyury is expressed around the blastopore in most, if not all, chordates and in many other metazoans, and is thought to be involved in specifying mesoderm and/or morphogenic movements in chordates (Technau and Scholz, 2003). This suggests that the patterning pathway through Brachyury expression is well conserved. But my work shows that the cellular and biomechanical mechanisms of morphogenesis ("morphogenic machines") that are used to shape the body plan are much less well conserved. Although metazoans use a fairly limited set of cellular behaviors to generate the forces, shape changes and tissue level reorganization required for morphogenesis, the specific set of behaviors and their organization into a morphogenic machine is surprisingly variable, from the within-genus level on up (reviewed in Keller, Davidson and Shook, 2003; Keller and Shook, 2004). For example, both the frog *Xenopus laevis* and the salamander *Ambystoma mexicanum* use similar spatio-temporal progressions of cell behaviors by presumptive somitic mesoderm to generate similar forces to drive blastopore closure during gastrulation (Keller and Shook, 2004). Yet the cell behavior used by *Xenopus* is intercalation, expressed by deep mesenchymal cells (Keller *et al.*, 2000; Keller and Shook, 2004), whereas *Ambystoma* uses an epithelial to mesenchymal transition (EMT) of superficial epithelial cells (Shook, *et al.*, 2002). Thus at some point downstream of the expression of Brachyury, or whichever gene is responsible for directing the conserved spatio-temporal progression of cell behaviors, there must be a divergence in the patterning pathway, such that different cell behaviors are specified. How can the patterning upstream of morphogenesis and the resultant phylotypic body plans be so well conserved, when morphogenesis itself is not?

My analysis of variation in morphogenic machines in amphibian gastrulation and neurulation suggests that one correlate may be with the evolution of diverse reproductive strategies to suit a broad range of ecological niches, which in turn is correlated with differences in egg architecture. Molecular patterning pathways appear to be relatively stable in the face of such variation. But the morphogenic machines, which have the biomechanical function of actually reorganizing and reshaping tissues, are faced with dramatic changes in geometric and biomechanical context, including differences in egg size, yolk content and tissue stiffness, as well as a variety of other selective pressures that are the consequence of their reproductive ecology, such as the rate of development, temperature tolerance and physiological exchanges with the external environment. For example, while *Xenopus* uses the intercalation cell behavior mentioned above to converge the dorsal tissues medially and extend them along the anterior posterior axis (convergent extension), beginning during early gastrulation, it appears that in some large-egged, slowly developing anurans, little or no convergent extension occurs dorsally during gastrulation. In the anuran *Gastrotheca riobambae*, all convergent extension is delayed until the neurulation stage, as is all evidence of the Spemann organizer (del Pino, 1996), and a different cell behavior (discussed below) is used to close the blastopore.

Although I have noted that patterning pathways are highly conserved, some downstream elements of these pathways must be divergent, e.g. in timing or position of expression or even identity, to account for the expression of different cell behaviors and the use of different machines. By linking changes in patterning and cell behavior to the use of different machines, and linking these changes to variations in the physical make up of the embryo related to selective ecological pressures, I can gain significant insights into the interaction between different components and different levels of organization. This has significance for 1) understanding how patterning pathways can diverge to direct different cell behaviors, while still directing the formation of very similar phylotypic body plans, 2) understanding the full range of cellular behaviors and their dependence on context, and 3) understanding the evolution of morphogenesis.

By observing the changes in morphogenic machines across amphibian phylogenetic space, and correlating it with changes in the expression of patterning molecules as well as changes in embryonic architecture and reproductive ecology, I can develop hypotheses for the basis of evolutionary change in morphogenesis. Repeated pair-wise changes in these morphogenic characters (from cellular processes

to patterning elements) that are phylogenetically correlated will suggest hypotheses of functional relationships between the correlated characters that can then be tested. Likewise, variations in a morphogenic character that are phylogenetically correlated with variations in embryonic architecture or reproductive ecology, will again suggest functional relationships between the correlated characters. This approach will allow me to both recognize conserved morphogenic machines and to develop a mechanistic understanding of how and why morphogenesis evolves. Understanding the cellular mechanisms of force generation in each case, and how the integration of these mechanisms into a morphogenic machine depends on the broader biomechanical and ecological context, is critical for understanding where the significant regulatory changes have evolved. My approach is thus complementary to a genetic or genomic analysis of development, in that understanding which of the genetic changes are important, and what their significance in the evolution of the process is, will require a mechanistic understanding of their role. My long term goal is to develop a better understanding of general morphogenic design principles that can be broadly applied across the chordates and other metazoans to explain the evolutionary basis for changes in morphogenesis.

These principles will also have direct relevance for our understanding of human developmental pathologies that is based on research in model organisms. Our understanding of morphogenic mechanisms and morphogenic diseases depends on inferences from model systems; thus learning how and where homologous patterning pathways can diverge to direct different morphogenic machines will provide greater insight for those inferences and improve their accuracy. Studying the cell biological basis for variation in diverse morphogenic machines also has general biomedical relevance, in terms of understanding the full palette of behaviors of which cells are capable; this has relevance for understanding the basis of developmental morphogenic diseases or defects (i.e. birth defects) as well as pathological cell behaviors such as metastasis. Further, finding treatments for most diseases, which have complex causes involving the interaction of components over many levels of organization, will require a better understanding of such interactions, and the possible outcomes of variations in them.

Amphibians are ideal for study of variation in morphogenic mechanisms because they have greater diversity of reproductive strategy than any other chordate group. Moreover, the early developmental processes of gastrulation and neurulation are the most sensitive to evolution of reproductive strategy since these movements involve reshaping the embryonic tissues in the context of the early, yolk laden egg. Finally, they are experimentally accessible for studies of this type, and well-developed model systems are available as a baseline for studies of less commonly used species that reflect the spectrum of egg architecture and are phylogenetically well distributed. The large size of amphibian cells allows me to easily visualize both the behaviors and movements of individual cells as well as the localization of components within cells. Visualization of cell movements and morphogenic machines is further facilitated because amphibian embryos are uniquely amenable to microsurgery and explants survive well in culture. This allows me to image otherwise hidden regions of the embryo (see my movies 13_1 to 13_14 at <http://www.gastrulation.org>). These explants are also amenable to biomechanical analysis. I can study the operation of these machines in isolation, by explanting tissues, or in novel contexts, by transplanting them. Although amphibians do not have well developed genetics, it is entirely practical to test the effects of many types of genetic disruptions via the injection of artificial genetic reagents that over-express the wild type protein, express an antimorphic version, or act as a type of interfering or anti-sense RNA. Gene expression is also easily visualized in amphibian embryos.

Current Work & Planned Research: Different amphibians use different morphogenic machines to drive germ layer reorganization during gastrulation. In order to understand the evolutionary basis for this divergence, we need to understand how these machines function, and how they are regulated, and how that regulation changes in diverse species. My current work includes two examples, in the first case, of different species using different morphogenic machines to drive the same morphogenic process, and in the second case, of different species using the same two morphogenic machines, but with different emphasis and at different times.

Epithelial-mesenchymal transition (EMT) occurs to some extent during gastrulation and neurulation in all amphibians studied. In at least some urodeles (*Ambystoma mexicanum*, *A. maculatum*, and *Taricha granulosa*), a broad expanse of superficial presumptive somitic and lateroventral mesoderm undergoes an EMT (Shook *et al.*, 2002), apically constricting and then ingressing through an amniote-

like, but bilateral primitive streak, separated medially by the yolky vegetal endoderm (Shook and Keller, 2003). Cell behavior(s) involved in the EMT generate micronewton level forces of convergence that function to close the blastopore during gastrulation (Shook *et al.*, *in progress B*). In contrast, only a few superficial mesodermal cells undergo EMT in the anuran, *Xenopus*, and this occurs only later, during neurulation (Shook *et al.*, 2004). Also in contrast to the urodeles, *Xenopus* generates the micronewton level forces for convergence and blastopore closure by intercalation of presumptive deep somitic mesoderm cells, rather than by EMT of superficial somitic mesoderm. Using a force measuring “tractor pull” apparatus I have designed in collaboration with Lance Davidson, I have been able to measure the convergence forces produced during gastrulation by *Ambystoma* and *Xenopus*, and to identify the time course of force production, which is strongly correlated with the observed EMT and intercalation behaviors, respectively (Shook *et al.*, *in progress A, B*). Convergence forces in the notochord appear to be generated by intercalation of deep cells in both the urodeles and in *Xenopus* (Shook, preliminary results). In both *Xenopus* and the urodeles, the cell behaviors generating the observed forces occur in very similar spatio-temporal progressions, implicating a common upstream patterning mechanism (Shook *et al.*, 2002; Keller *et al.*, 2000). Thus, the urodeles and the anuran *Xenopus* share strategy to generate similar convergence forces, with a similar pattern of expression, to close the blastopore, but using different morphogenic machines to generate these forces.

These results raise several important questions. First, how do patterning pathways differ such that some amphibians have large amounts of surface mesoderm and others very little? Second, how are the mechanisms regulating tissue type (i.e. somitic mesoderm) uncoupled from the mechanisms regulating behavior of that tissue type, to be cell intercalation on the one hand, and EMT on the other? Likewise, assuming there is a common mechanism patterning the similar spatio-temporal progressions of the two behaviors, how does it diverge to direct EMT or intercalation, and is this related to the divergence of the somitic mesoderm specification pathway to produce the two behaviors? Third, which specific cellular mechanisms are actually responsible for generating the observed forces, and how are they incorporated in cell behaviors and integrated into a tissue-level? What is the underlying cell biology of these behaviors, and how is it regulated? Fourth, are there geometric and physical properties of the larger urodele eggs that favor the use of EMT rather than cell intercalation as a mechanism of blastopore closure? What is the function of the decreased and delayed but retained EMT in anurans, in absence of any function during gastrulation?

I am currently focused on understanding the cellular mechanisms of force production by these cell behaviors. Using my tractor pull apparatus, I am measuring the physical and biomechanical properties (tension, stiffness, visco-elasticity) of these species, with respect to the hypothesized location, timing and direction of force generation, to determine which variations in biomechanical context correlate with force production. I have shown that force production in both species is dependent on a myosin II based contraction mechanism (Shook, *et al.*, *in progress B, C*). In *Xenopus*, we have found that the force generated by convergence is dependent on different isoforms of myosin II at different stages of morphogenesis. In *Ambystoma*, I have found that actin is preferentially localized to the apical cortex of cells as they approach the region where subduction behaviors, in particular apical constriction, begin.

Future Goals for EMT: In order to address questions about the specification of presumptive mesoderm in different locations and the specification of these different cell behaviors, I will begin by looking at the expression of a variety of candidate patterning molecules. I will look more carefully at the expression of early markers of mesoderm, such as Brachyury, as well as more tissue specific markers, such as MyoD, Xnot, Xnr-3 and their homologs, to determine how well correlated they are with the expression of different cell behaviors. I will look at the expression of more downstream molecules, thought to be more directly related to the expression of cell intercalation or EMT, such as Wnt-11 and Snail, respectively. Temporal and/or spatial correlations between variations in the expression of these candidates and cell behaviors will suggest functional relationships, which I will further test with artificial genetic techniques. I will continue to study the cellular basis of these behaviors by looking at the dynamic localization of various other cellular components, such as small Rho GTPases, cadherins and microtubules, and using force measurements as an assay for the effects of disrupting them. I am currently testing probes for activated myosin II, to determine whether it shows an increased localization to the apical cortex of cells approaching the region where they will undergo

apical constriction as part of subduction behavior in *Ambystoma*. Understanding the dynamic localization of activated myosin II with respect to apical actin localization in these same cells will help me to understand the regulation of the apical constriction behavior.

Convergent thickening is a process in which cells within the marginal zone converge circumblastoporally, but rather than this convergence producing extension along the anterior-posterior axis, the convergence is channeled into thickening in the radial direction. Convergent thickening occurs around the ventral blastopore lip of *Xenopus* (Keller and Danilchik, 1988) and generates a component of the convergence forces there that acts together with the convergence force associated with axial extension dorsally to close the blastopore. I am currently investigating the cellular and the molecular basis of convergent thickening, which was previously completely uncharacterized. I have demonstrated that ventralized *Xenopus* embryos, which express convergent thickening around the entire marginal zone, can close their blastopores and produce convergence force similar to that in untreated embryos. In collaboration with Eugenia del Pino and Rick Elinson, I have shown that in some large egged, slowly developing anurans, little or no convergent extension occurs dorsally and convergent thickening occurs throughout the marginal zone. In the anuran *Gastrotheca riobambae* for example, all dorsal convergent extension is delayed until the neurulation stage, as is all evidence of the Spemann organizer. Thus convergent thickening generates only part of the force to close of the blastopore in *Xenopus* but all of the force in the large egged *Gastrotheca*.

Important questions emerge from these studies. First, how does convergent thickening differ from convergent extension in terms of force production, cellular behavior, adhesion, and motility? What is the relative contribution of the two behaviors to the convergence force produced in *Xenopus*? In other species? Second, how are the two regulated differently? As convergent extension is a dorsally focused behavior, are there dorsal organizer molecules that specifically direct convergent extension, rather than convergent thickening? Third, is the convergent thickening observed in *Xenopus* ventral marginal zones in fact the same behavior that occurs throughout the marginal zone of *Gastrotheca* and other frogs? Is convergent thickening and delay of convergent extension an obligatory mechanism of blastopore closure in large egged amphibians? Fourth, how are the timing of convergent thickening and convergent extension regulated?

My work with other species, in collaboration with Eugenia del Pino and Rick Elinson, suggests that there are species that are intermediate between *Xenopus* and *Gastrotheca* in the amount of convergent extension expressed during gastrulation, especially among the Bufonoidae. I am currently trying to develop one or more of these species as model systems for studying convergent thickening as a primary mechanism for blastopore closure. In the meantime, I am using ventralized *Xenopus* embryos, which express convergent thickening around the entire blastopore and successfully close their blastopore in the complete absence of dorsal axial extension, as a model for convergent thickening. Because these embryos lack dorsal tissues, neurulation fails; but during gastrulation I find that they exert forces similar to that produced by untreated embryos.

Future Goals for Convergent Thickening: To understand the cellular basis of convergent thickening, I will compare the cellular behaviors in explants of ventralized *Xenopus* embryos to the well characterized behaviors driving convergent extension. Using force production as an assay, I will test the role of various cellular components, as above for EMT. In particular, I will study the effects of disrupting myosin II isoforms in ventralized *Xenopus*. As we are pursuing the hypothesis that the different isoforms have different roles in different cell behaviors, this may help us understand the relationship of convergent thickening to convergent extension. I plan to disrupt the non-canonical Wnt pathway, thought to be involved in directing mediolateral intercalation in convergent extension in several different vertebrates, in ventralized *Xenopus* to ask whether this pathway also affects convergent thickening. As I develop other model species that use less or no convergent extension during gastrulation, I will apply these approaches to these species. Once convergent thickening is better understood, I will begin looking at candidate dorsal organizer molecules that can induce convergent extension behavior, to determine whether there are any that do so, independently of specifying dorsal fate. Candidate screening will benefit by comparing their expression in *Xenopus* vs. species that do not show early convergence and extension.

Long terms goals: I will expand to other morphogenic machines and amphibian species as the size of my lab expands. My general goals are to 1) determine the cellular mechanisms underlying the cell behaviors driving morphogenic machines and the biomechanical forces they produce; 2) understand the specification and patterning of these cell behaviors; 3) explore phylogenetically distributed variations in the morphogenic machines used to drive morphogenic movements; and 4) mapping variations in characters pertaining to morphogenesis and reproductive ecology onto amphibian phylogeny to map evolutionary changes in development.

This last point will take some time to yield broadly applicable results (although the data may suggest more limited sets of characters that can be focused on initially) and will require substantial collaboration, but should be very powerful in terms of developing an understanding of a set of general "rules of morphogenesis" and of the evolution of morphogenesis. I will gather data on characters for as broad a phylogenetic distribution of amphibians as possible. The distribution of these characters will then be tested for correlations, to determine whether specific changes occur together reproducibly in different lineages, suggesting potential causal relationships, which can then be tested.

Funding: I will soon submit a revision of my initial RO1 NIH grant application. The grant is focused on the cell biological and patterning aspects of the EMT cell behavior in *Ambystoma*. I expect that the NIH will be interested in funding my characterization any further morphogenic machines I discover. The ACS may also be interested in funding my work on EMT. Once I have secured NIH funding, I will acquire NSF funding for my more explicitly comparative evolutionary research. My first attempt at grant writing, for postdoctoral funding (NRSA) for my work on superficial presumptive mesoderm, was funded by the NIH with a high score. Reviewers for my RO1 indicated that my approach, described above, was highly significant and innovative, and had strong relevance from the biomedical and human health perspective. The importance of my work with Dr. del Pino was recognized by the editors of *Development*, who awarded me a travelling fellowship to set up my initial collaboration with her in Ecuador. I have participated in writing several RO1s in the Keller lab, all of which have been funded. I am confident that I will be able to obtain further funding for my unique, innovative and highly integrated line of research, addressing as it does fundamental questions about morphogenesis, including questions of basic biomedical interest, such the mechanisms of cell motility, and EMT.

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Teaching Interests — David R. Shook

My goal for my students is to provide an understanding of the subject I am teaching, integrated across several levels of analysis. Since it is always more enjoyable to teach interested students, it is my hope that I can inspire in my students an appreciation for the breadth and depth and the important questions of the subject I'm teaching. More specifically, I would like to develop an interactive teaching style that encourages students to ask questions, as well as responding to mine. As part of this effort, and to encourage critical thinking, I will have students take part in group discussions or presentations to the class. I am familiar and comfortable with web-based teaching tools, and will be quite happy to incorporate any such available tools into my teaching. I am committed to quality teaching and will strive to improve my skills in these areas throughout my career.

I feel that the benefits of teaching for me are as a valuable exercise in clearly understanding the broader scope and the important questions of the subject being taught, and the integration of its different facets, and as an additional mechanism for staying abreast of the field. I would therefore welcome the opportunity to teach subjects that reflect my interests and expertise in developmental, evolutionary and cellular biology, and their intersection. As a postdoc at the University of Virginia, I have taught an upper division undergraduate developmental biology lecture class and an independent developmental biology lab class that was designed to teach upper division undergraduates how to do research, using *Xenopus* embryos as the model system. I am familiar and comfortable with web-based teaching tools, and will be quite happy to incorporate any such available tools into my teaching.

I could currently participate in teaching an undergraduate or graduate evolution class. I am of course most familiar with developmental aspects of evolution and, recalling my graduate work, the evolution and quantitative genetics of life history traits. To a lesser extent, I am also familiar with cladistics and phylogenetic analysis. With some opportunity to review, I would be happy to teach an entire undergraduate evolution course.

I would also be interested in teaching evolutionary aspects of developmental biology to undergraduates and graduates, either alone, or as part of a team-taught course. I have found in teaching undergraduates, that in addition to the usual survey of developmental patterning and differentiation mechanisms, emphasis on the concept of homology as a tool for understanding the relationships between developmental mechanisms allows the students to form a more coherent "big picture" of development. I think that it is also important that students have a basic understanding of the phylogenetic distribution of body plans, and their hypothesized evolutionary relationship to one another. Incorporating discussion of the morphogenic basis for development into my curriculum is also valuable in teaching the relationship between patterning and the formation of the body plan. Understanding how morphogenesis leads to new juxtapositions of tissues and the potential for further inductive interactions, as in the mesodermal induction of the neural tissues and the multiple tissue interactions that give rise to the induction of eye, helps to clarify the hierarchical patterning of the body plan. It also allows students to better understand the role of morphogenesis in the evolution of homologous structures.

I would of course be particularly interested in teaching a graduate level "evolution of development" class. I feel that while the use by different species of homologous patterning molecules has been our most profound recent insight into the evolution of development, too much emphasis is generally placed on this as the sole mechanism, and that a more complete understanding of the evolution of development requires a more comprehensive approach. In addition to more thoroughly exploring the basic evolutionary concepts that I would introduce into a standard developmental biology class, I would also juxtapose the evolution of patterning mechanisms with the evolution of cell biology and its role in allowing new morphogenic mechanisms and finer organization of body plans to evolve.