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Editorial

A new century of amphibian developmental biology

Amphibian embryology has a long, rich history tracing back more than century in the recorded literature. Newt, salamander and frog embryos collected in the wild and subject to the keen minds and crafty hands of early embryologists yielded some of the most important first principals of developmental biology, including those of fate maps, egg polarity, embryo polarity, the concept of specification and determination, and first evidence that vertebrates develop by induction. Progress in the early days was hampered, however, by the seasonality of egg availability. The introduction into labs of the highly fecund and lab-friendly African Clawed Frog *Xenopus laevis* changed all that, and changed the field of vertebrate embryology in the 1960s by allowing researchers anywhere around the world to obtain "eggs on demand." While this may have removed the fun of field trips to collect amphibian eggs, adopting *X. laevis* as a model paved the way for a long series of breakthroughs that have revealed the molecular nature of developmental phenomena initially described in the preceding century using various amphibia. This continues right up to present day.

In this issue of *Seminars* we explore some of the ongoing and forward reaching topics in *Xenopus* embryology. In fact, from the reviews that follow it is apparent that future work is likely to transcend *X. laevis* to include its genetically amenable cousin *Xenopus tropicalis*, as well as other amphibians. In our lead review, Elizabeth Callery provides an elegant historical and evolutionary perspective on amphibian development, pointing out functional as well as comparative embryological opportunities with new amphibian species that harken back to the "good old days". The growing incorporation of other amphibians into traditionally *Xenopus* research programs promises to yield new insights into embryonic mechanisms (and possibly prompt some field work).

When a newcomer to the field first encounters an amphibian egg one of the most obvious features is the distinct light and dark coloration of its animal and vegetal halves. This pigment polarity reflects molecular asymmetries within the egg that drive the early developmental program by functioning as building components, cell fate determinants, and molecules that provide inducing activities. Janet Heasman takes us on a tour of these maternal substances and how they contribute to early development. This is an area that is a continuing source of surprise and phenotypic novelty, illustrated most recently by the demonstration by Heasman and colleagues that Vg1, a TGFβ family member and one of the first vegetally localized mRNAs discovered in *Xenopus*, provides endogenous mesoderm inducing activity in the embryo (a finding so fresh that it did not make it into her review). For those of us who have struggled directly with Vg1, or even watched with some bewilderment from a distance, this is a very satisfying revelation, and one that probably would not have occurred had genomic and EST sequencing efforts not been vigorously supported by the *Xenopus* community.

Closely linked to the function of maternal determinants and inductive signals is the genetic circuitry that specifies cell fate in the *Xenopus* embryo. Fiona Wardle and Jim Smith provide us with an overview of an emerging network of gene interactions that integrate maternal transcription factors with inductive signals, and subsequently activate downstream genetic programs. One of the most important take-home messages to emerge from their review is how much more remains to be learned about this important aspect of early development. Puzzling out the "wiring diagram" of temporal and spatial *Xenopus* gene regulation will likely comprise one of the most fertile areas of future endeavor and doubtless inform us of regulatory networks that are evolutionarily conserved among vertebrates.

The maternal and early zygotic phases of amphibian development generate one of the most notable tissues in embryology, the Spemann Organizer, described first by Hans Spemann and Hilde Mangold and sometimes contemporarily referred to as the Spemann–Mangold Organizer (SMO). This bit of tissue directly contributes to dorsal-anterior mesendodermal structures and induces nearby mesendodermal tissues to develop dorsal-anterior fates, induces the nervous system in the ectoderm. These fascinating properties have made the Organizer one of the most intensely studied tissues in embryology, but only within the past decade and a half has it yielded many of its molecular secrets. Surprisingly, many of these secrets correspond to growth factor inhibitors that prevent nearby TGFβ and wnt signals from exerting ventral-posteriorizing affects on the SMO and adjacent tissues, thereby allowing latent dorsal-anterior fates to emerge in the adjacent tissues. The SMO has been subject of many reviews, and in this issue Mike Jones presents his perspective. Although highly studied, the SMO continues to yield surprises and many of its mysteries are still not fully explained, such as the precise function of "positive acting" signals, as opposed to inhibitors,

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produced by the SMO (e.g., nodals, anti-dorsalizing morphogenetic proteins, insulin-like growth factors). No doubt the SMO will continue to surprise in the future.

As inductive interactions by the Organizer proceed into gastrulation, one of the most important events is the emergence of the nervous system. Alin Vonica and Ali Hemmati–Brivanlou take us on a tour of this process, which has been a mystery and field of intense effort ever since Hans Spemann and Hilde Mangold revealed the neural inducing properties of the amphibian Organizer. What has been so surprising about neural induction, and the general inductive action of the Spemann–Mangold Organizer, is that inhibitors of growth factors dominate these processes, particularly the BMP inhibitors. Of course, "positive" influences must underlie neural cell fate specification at some level, and Vonica and Brivanlou take on the challenge of integrating the role of BMP inhibitors with the emerging recognition that MAP Kinase signals and maternal/early transcription factors must also contribute to the functioning of the "default model."

A key feature of amphibian and vertebrate Organizers in general is that their cells lead the way during gastrulation movements. Understanding these and other movement and shape-generating mechanisms in vertebrate embryos is one of the most exciting and accelerating areas of investigation in vertebrate embryology, and arguably *Xenopus* and other amphibian embryos lead the way. In large part this is because amphibian embryo tissues, in whole embryos or easily cultured explants, can be microscopically scrutinized and physically and molecularly perturbed. A future issue of Seminars in Cell and Developmental Biology addresses mechanisms governing *Xenopus* morphogenesis.

Downstream of early patterning and morphogenesis, organogenesis is assured to be a hot topic in *Xenopus* development in forthcoming years. *Xenopus* embryos provide easy access to developing organs of all stages, which will facilitate experimental probing by gene knockdown, transgenic and emerging genetic methods. *Xenopus* is poised to make a big splash in this area, and in fact the first waves have already hit. Ira Blitz, Gregor Andelfinger and Marko Horb provide an overview of where *Xenopus* embryos have been, and where they will lead us in puzzling out the cell fate and morphogenetic processes of organ formation. An exciting aspect of studying organogenesis in *Xenopus* is the rapid rate at which "classical" experiments can be done, and *X. tropicalis* genetic screens promise to augment such approaches to uncover the rules for making an organ. Studies of organogenesis in *Xenopus* are also likely to inform the human condition in ways not usually encountered in our basic science driven field.

The words "*Xenopus*" and "genetics" are rarely juxtaposed, much less uttered in the same sentence (unless in some derogatory fashion). However, that is about to change as *X. tropicalis*, with its small, fully sequenced genome and relatively short life cycle is propelling amphibians directly into the vertebrate genetic games. This arena, historically dominated by mouse and zebrafish, will perhaps make the widest impact on our field through the synergy of two worlds—the classical methods of a century of amphibian biology and the power of genetic screening. Samantha Carruthers and Derek Stemple provide a unique perspective on the future of this field since their own research uses both organisms. Lessons learned from zebrafish genetics certainly will inform *Xenopus* efforts as we move into this new frontier, and properties unique to *Xenopus*, such as its maternal and localized supply of information and the classical methods of *Xenopus* egg and embryo manipulation (e.g., gynogenetics, nuclear and cell transplantation, in vitro assays and lineage-specific mRNA/DNA delivery/rescue), should result in a novel marriage of methods. Carruthers and Stemple illustrate how a harmonious fusion between these apparently rival model organisms can be achieved. The perceived battle of fish fin and frog claw may be an illusion after all.

Amphibians have been a mainstay of experimental embryology extending back to the 1800s, and with the 21st century in full swing the future of amphibian research remains bright and moving forward. Yet, even as this happens we find ourselves beginning to reach back to our historical roots to incorporate other amphibian species in the search for answers to fundamental questions about animal development.

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