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# Something old, something new

Before it was rebranded as 'developmental biology,' the study of embryonic development was usually called 'embryology and experimental morphology,' reflecting a century-long tradition of meticulous tissue-grafting experiments. This tradition is far from dead, as any number of investigators are still profitably carrying out the kinds of delicate experiments that would not have been out of place in the pioneering laboratories of Driesch and Spemann. That said, the use of high-throughput methods to dissect developmental processes is on the rise, as illustrated by presentations at the 14th International Congress of Developmental Biology*. If the fast-paced ethos of genomics is not entirely new to developmental biology, the sheer variety of molecular approaches and model organisms on display suggests that it now informs every area of the field.

**From screens to genes.** Developmental biologists continue to appropriate any method that promises to elucidate gene expression, protein function and morphogenesis. Standard genetic screens—whether in brute force applications or in clever, modified form—still deliver the goods. In the latter category, Dunja Knapp (Univ. Cambridge) presented preliminary work on a screen to identify cell surface molecules involved in cell migration during gastrulation in *Xenopus*. Recognizing that gastrulation is probably initiated in part by post-transcriptional mechanisms, and thus will not be cracked by a subtractive cDNA screen, Knapp outlined an antibody phage display approach. The screen employs a phagemid library encoding $10^9$ random immunoglobulins attached to a phage surface protein. The library is first enriched for clones that recognize proteins of interest by several rounds of selection on activin-treated animal cap cells, and then is depleted of irrelevant clones by selection on untreated animal cap cells. The activin-treated cells, which give rise to mesoderm, essentially serve as an *in vitro* stand-in for migrating cells during formation of the three germ layers of the embryo. With luck, this approach may identify signaling and adhesion molecules that are required for the still poorly understood events of gastrulation.

A similarly thoughtful approach was outlined by Claudio Stern (Univ. College, London) who provided an update on two screens in the chick embryo—one meant to identify secreted factors that promote neural induction, and the second designed to isolate those genes that constitute the early response to the inducers[1]. A subtractive screen between cDNAs from naive epiblast tissue and cDNAs from epiblast exposed to a grafted Hensen's node (a neural inducer) identified 15 genes that are expressed in the prospective neural plate and may mediate neurogenesis.

*14th International Congress of Developmental Biology, Kyoto, Japan, 8–12 July, 2001.

In light of these and other successful screens, Hitoshi Okamoto (RIKEN Brain Sciences Institute) noted that the identification of interesting genes expressed during embryogenesis is outstripping our ability to assign a function to each. As a contribution to functional analysis, he described a new method for precise, photo-mediated, conditional gene expression in the zebrafish embryo using a novel caging agent[2]. Combined with maturing *in utero* gene electroporation methods (Tetsuichiro Saito, Kyoto Univ.), the use of ultrasound technology to deliver viruses or cells to embryos in a precise manner (Stuart Foster, Univ. Toronto), and now-standard methods for gene targeting, there is hope that real biological insight will not lag too far behind gene discovery.

**Upstream, downstream.** By far the most ambitious effort to map the gene regulatory elements involved in any aspect of embryogenesis is that of Eric Davidson (Caltech) and his colleagues. Their work to assemble a complete, annotated network of transcription factors and the *cis*-acting elements to which they bind during endomesoderm specification in the sea urchin embryo is, one suspects, the leading edge of a long-term effort to understand not just the broad outlines of development (and evolution), but every last detail as well. The complexity of the wall chart of endomesoderm specification (see http://www.its.caltech.edu/~mirsky/endomeso.htm) is already approaching that of intermediary metabolism, and one is tempted to ask whether development isn't simply, in the immortal words of Henry Ford, "one damn thing after another". From this mass of data, Davidson has already extracted the idea that the "bio-logic" of development, as he puts it, is hard-wired in the genome[3,4]. As for other principles of development, their emergence from this exhaustive approach will no doubt require both time and some very good databases. The completion of *in silico* molecular maps of embryonic tissues in time and space[5] will no doubt represent a significant achievement; whether it will be possible to make sense of all of this complexity, however, remains a pressing question.

**Microarrays and morphogenesis: a marriage.** Developmental biologists have discovered the joys of chips. A significant number of planned and ongoing microarray-based studies of development were presented. These include not just genome-wide views of 'model' embryos, but, to a surprising degree, systematic analyses of organisms with smaller constituencies, such as the slime mold *Dictyostelium discoideum* (Hideko Urushihara, Univ. Tsukuba) and the flatworm *Schmidtea mediterranea* (Alejandro Alvarado Sanchez, Carnegie Institution of Washington). Some of the other projects mentioned include global views of gene expression in: *Drosophila* embryos lacking one or more growth cone chemoattractants (Corey Goodman, Univ. California, Berkeley), *Xenopus* embryo animal caps treated with activin (Ken Cho, Univ. California, Irvine), *Drosophila* leg imaginal discs engineered to express *eyeless*, the master control gene of eye development (Lydia Michaut, Biozentrum, Basel), and *Drosophila* genital discs from both sexes (Bruce Baker, Stanford Univ.).

The appealing thing about each of these proposed studies, made clear by speaker after speaker, is that they can be followed up immediately by high-throughput whole-mount *in situ* hybridization and functional analysis *in vitro* or *in vivo*. Indeed, unlike microarray data generated in other areas of biology, catalogs of embryonic gene expression that are generated in highly focused experiments can be assessed in the context of classical embryology, which immediately suggests new experiments in which to test gene function. Whether in gastrulation, neurulation, sex determination or eye development, the potential of microarrays to advance the study of embryogenesis—in fact, the promise of almost all high-throughput genomic approaches—would seem to be in direct proportion to the degree to which they readdress old, well-defined problems[6]. Fortunately, developmental biologists are a historically-minded lot, and the sort of marriage between the old and the new that seems to be in the offing is well worth keeping tabs on, in these pages and elsewhere.


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