

EDITORIAL

Looking inwards: opening a window onto human development

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The past 30 years or so have witnessed tremendous advances in the field of developmental biology. This has resulted in a growing (although still incomplete) understanding of the molecular basis of embryonic development, including characterization of signals and genes involved in establishing the embryonic axes and controlling organ development. This progress has been made possible largely thanks to a selected set of model organisms, including *C. elegans*, *Drosophila*, zebrafish, *Xenopus*, chicken and mouse, chosen because they are particularly well suited for genetic and/or developmental studies. Large communities of scientists sharing common interests and tools have been built around these model organisms. The genomes of some of these model species were among the first to be sequenced, and huge amounts of data on each of these species have been organized into model organism databases, such as Flybase (www.flybase.org), ZFIN (www.zfin.org) or MGI (Mouse Genome Informatics; www.informatics.jax.org/).

One of the major realizations from the work of the past 30 years is the remarkable conservation of developmental processes between organisms as evolutionarily distant as flies and mice (the ancestors of which diverged over 600 million years ago). We now know that the set of genes found in animals is limited, in the range of 15,000–25,000 (not counting alternative transcripts), and that essentially the same gene families are found across the entire animal kingdom. The same signaling pathways are repeatedly used during development of all species, and key genetic systems involved in patterning the body axis, such as the Hox genes, are also conserved. Moreover, many of the cellular processes that underlie morphogenesis and organogenesis are conserved. Much of this research has been published in the pages of *Development*.

Strikingly, although we understand intimate details of the development of a broad range of vertebrate and invertebrate species, we know almost nothing about the development of the human embryo beyond morphological descriptions. From these descriptions, it is clear that human development broadly resembles that of other mammals. Moreover, given the level of conservation of developmental processes at the genetic level, it seems highly likely that human development will also use the same palette of molecular tools. However – not unexpectedly, given the differences in size and life span – there are a number of important differences in the development of human and mouse embryos (Rossant, 2015). Studies of human development have been very limited, due to the highly restricted accessibility to human embryos. However, we now have the opportunity to study human development using stem cell differentiation as a surrogate. *In vitro* systems, based on the differentiation of pluripotent cells, strikingly recapitulate embryonic morphogenesis in a dish. This work was largely pioneered by Yoshiki Sasai, who showed first in mouse and then in human embryonic stem cell (ESC) cultures that they could self-organize *in vitro* into structures as complex as a developing eye. This groundbreaking work opened the door to a series of studies demonstrating the possibility of differentiating other complex

human neural structures, such as hypothalamus and even cerebral cortex, *in vitro*. Moreover, these self-organizing properties are neither restricted to pluripotent stem cells nor to ectodermal derivatives. As shown in seminal work by Hans Clevers and colleagues, endoderm-derived tissues, such as human intestine and stomach, can now be propagated as organoids and experimentally manipulated. The repertoire of tissues for which we now have three-dimensional (3D) *in vitro* models is growing rapidly, and it is likely that more human embryonic structures will soon become accessible using these approaches. This will undoubtedly constitute a major revolution for our field and open the door to the experimental study of human developmental biology. The deployment of sophisticated molecular and genetic tools already developed in model organisms will now be possible on these human organoids in an ethically acceptable context. Organoid culture might also provide a route to the generation of human tissues or even organs *in vitro* for regenerative medicine, whereas organoids derived from patients via either iPS cells or tissue stem cells will provide outstanding model systems to study the molecular basis of a broad range of pathologies and to identify and test drugs for various diseases.

In recognition of these recent breakthroughs and in line with *Development's* recent expansion into the stem cell field, we organized the meeting 'From Stem Cells to Human Development' in September 2014, as part of The Company of Biologists workshop series. The meeting was a tremendous success, and those of us present had the impression of witnessing at first hand the emergence of this new field of human developmental biology. Many of the speakers were distinguished developmental biologists with a strong record of research using model organisms, but who had recently added human ESCs to their palette of model systems. One of the most striking aspects of the meeting was the recurring theme that, irrespective of the organ system, human ESCs differentiated *in vitro* can be coaxed to self-organize into organoids. These striking structures sufficiently resemble their normal *in vivo* counterparts to provide spectacular experimental systems for studying developing human tissues. We sorely missed Yoshiki Sasai, who had accepted to be the keynote speaker of the meeting but who tragically could not be with us (for a retrospective on his extraordinary career, see (Piccolo, 2014). In a fitting tribute, Austin Smith dedicated the meeting to his memory.

In this issue, you will find a report (Medvinsky and Livesey, 2015) on this meeting from two of the speakers – Alexander Medvinsky and Rick Livesey – as well as several Spotlight articles. Janet Rossant discusses key differences between early mouse and human development, and how these relate to the ability to derive different stem cell lines from these embryos (Rossant, 2015). Looking at much later stages of development, Hans-Willem Snoeck explains, using the lung as an example, why it is essential to understand human development if we are to make progress in treating disease (Snoeck, 2015). Although the potential of human stem cell research is immense, it does raise a number of important ethical issues, and Göran Hermerén and Insoo Hyun,

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who led a discussion session on ethics at the workshop, discuss some of the ethical considerations of working with human stem cells, with a particular focus on the ethics of generating human-animal chimeras (Hermerén, 2015; Hyun, 2015). We hope you enjoy these contributions.

The human development field represents an essential growth area for the developmental biology community, and *Development* is keen to play an active role in supporting and inspiring it. The recent meeting was such a success, and the field is moving so rapidly, that we believe there is a need for further focused meetings in this area. We are therefore delighted to announce that we will be organizing a second meeting on the same topic in early 2016 – look out for further details in the coming months. We are also planning a Special Issue of the journal for Autumn 2015, focusing on human development (for more details, see <http://dev.biologists.org/site/misc/HumanDev.xhtml>). As much as *Development* has promoted

research on model organisms over the past decades, we consider that a major new frontier lies in the emerging field of experimental investigations of human development, and we strongly encourage you to submit your work in this area.

References

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