

EDITORIAL

A renaissance for developmental biology driven by new *in vitro* platforms

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Over the past 30 years, I have routinely told my students that this is the most exciting time in history to be a developmental biologist. This has been especially true over the last decade, with the emergence of new technologies and *in vitro* platforms to investigate foundational concepts in developmental biology. This Special Issue of Development features articles that span multiple organ systems, developmental mechanisms and disease pathologies. What links these papers is that they all use new *in vitro* systems that provide unfettered access to mammalian cells and tissues. These platforms allow for manipulation of signaling gradients, biomechanical forces, genes, pathogens and toxins, and then use live imaging, morphometry, biochemistry and various omics technologies to study cell and tissue behaviors. Many of these new approaches enable studies of human development and disease that were previously unimaginable. When you add these new platforms to our existing toolbox of model systems, we have unprecedented opportunities to explore new concepts in developmental biology and disease mechanisms.

There are many areas of developmental biology that are challenging to study but have benefitted from new *in vitro* platforms. The challenges of studying early implantation- and gastrulation-stage embryos are linked to their small size and inaccessibility *in vivo*, which limits the experimental manipulations possible and the types of readouts one can use. On top of these technical limitations, experiments using peri-implantation human embryos need to be carefully considered based on ethical guidelines. These challenges are being met with new *in vitro* systems in which one can scale up, manipulate multiple signaling gradients, environmental factors (e.g. metabolites, toxins, oxygen levels), mechanical forces and gene-gene interactions, and use multiple dynamic readouts to study cell fate decisions and morphogenesis. Several articles in this issue highlight systems that can be used to study early embryonic development, including a review of synthetic embryo-like structures (Terhune et al., 2022) and a poster discussing human assembloids (Kanton and Pașca, 2022). Research articles cover topics such as the mechanisms of pluripotency (Yoney et al., 2022), embryonic-extraembryonic interactions (Vrij et al., 2022), the role of hypoxia in gastrulation (López-Anguita et al., 2022), mouse endoderm formation (Medina-Cano et al., 2022) and placode development (Conti and Harschmidt, 2022). Pluripotent stem cell (PSC)-based organoid technologies have been transformative for studies of organogenesis, and this issue also highlights how such approaches have been applied to the development of lung progenitors (Hein et al., 2022), hippocampal

progenitors (Dunville et al., 2022) and pancreatic organoids (Grapin-Botton and Kim, 2022).

Arguably, some of the most exciting uses of these systems involve mechanistically studying and even treating human diseases. There are now many published examples of human PSC-derived systems to model congenital diseases, and one example in this issue involves using cerebral organoids to study Leigh syndrome (Romero-Morales et al., 2022). In addition, these systems are being used to study the many parallels between development and cancer (Morales and Andrews, 2022; Bain et al., 2022). One exciting new use of human organoids, described in this issue (Niethammer et al., 2022), is to identify how environmental toxins impact human development. Moreover, new approaches in generating therapeutics using tissue engineering and transdifferentiation are discussed (Huch and Gouti, 2022; Tanabe et al., 2022). Although the potential of new *in vitro* systems has generated tremendous enthusiasm, there are justifiable questions as to how accurately they represent their human counterparts. This highlights the crucial importance of benchmarking to human samples. For example, there are now many studies comparing human organoids to organs functionally, histologically and by single cell RNA-sequencing. In the case of diseases, phenotypes identified *in vitro* should be validated with samples from patients. These concepts are discussed in a Spotlight article (Childs et al., 2022), as well as in a Techniques and Resources article comparing human esophageal organoids to human esophagus (Ferrer-Torres et al., 2022).

The experimental tractability of these new *in vitro* platforms has been warmly embraced by the biomedical engineering and quantitative cell biology communities. Using engineering-inspired approaches, scientists have used these platforms to study the role of mechanical forces like flow, stiffness, stretch and bending on cell and tissue behaviors, as highlighted in Tlili et al. (2022) and Munger et al. (2022). The ability to quantitatively map and measure cell behaviors by live imaging has facilitated the construction of three-dimensional maps of developing human brain organoids (Rodríguez-Gatica et al., 2022) and computational reconstruction of neuronal networks (Räsänen et al., 2022). This issue also highlights new cell biological mechanisms at play during development, including molecular mechanisms of luminogenesis (Lobert et al., 2022) and an unappreciated role for the endoplasmic reticulum in neural progenitor cell division (bin Imtiaz et al., 2022).

As a final note, I would like to point out that I have used flies, frogs, chickens, mice and human cells to study basic principles of developmental biology. All of these model systems have unique strengths and weaknesses. The expanding arsenal of *in vitro* platforms does not diminish the strengths of *in vivo* model systems, but importantly overcomes some of their weaknesses and gives us a more diverse set of systems to work with. Development aims to embrace this diversity so, whatever your model, I hope you will consider submitting your very best work to the journal. It is really the most exciting time in history to be a developmental biologist.

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