

Drosophila as a Model for Understanding Development and Disease

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The fly sat upon the axle-tree of the chariot-wheel and said, What a dust do I raise!

–Aesop

The fruit fly *Drosophila melanogaster* has proved to be an enduring model for biological research. First established as a genetic model over a hundred years ago by Thomas Hunt Morgan, it remains one of the most popular and powerful model organisms. Thanks to the continued efforts of the *Drosophila* research community, it now serves as a model not only for genetic research, but also for a diverse array of studies, ranging from investigations of basic cellular and molecular mechanisms to modeling human diseases. For this Special Issue, we invited *Drosophila* biologists to submit original research studies and technical advances that would be of interest to the broad readership of *Developmental Dynamics*. In addition, we invited several researchers to submit review articles in their areas of specialization. The collection of reviews and original research papers in this Special Issue highlight some of the continuing and exciting discoveries coming from *Drosophila* research. They emphasize the wide

range of questions being addressed through *Drosophila* studies, and illustrate how the facility of combining diverse techniques, and developing new ones, is deployed in *Drosophila* to elucidate complex biological concepts. While *Drosophila* has long served as a model for basic biological research, more recently its potential as a model for unraveling molecular mechanisms of human diseases is becoming more widely appreciated, and we are fortunate to also have several articles and reviews that highlight this. As studies have revealed that cellular and molecular mechanisms of organogenesis are highly conserved, and *Drosophila* has functional homologs of nearly 75% of the human disease genes, we can anticipate that this aspect of *Drosophila* research will continue to expand.

The accessibility and dispensability (for viability) of the eye, combined with its complex architecture and development, have made it among the most intensively studied organs in the fly. In this issue, Singh et al. (pages 69–84) review one of the earliest patterning steps during eye development, its subdivision into distinct dorsal and ventral compartments, explaining the mechanisms

involved and their role in the growth and differentiation of the eye. The studies described give us an insight into how axial patterning facilitates the transition from a simple larval eye primordium into a complex three-dimensional adult compound eye. Tsachaki and Sprecher (pages 40–56) provide a detailed summary of the molecular processes involved in specifying retinal cell types, beginning with the transcriptional networks involved in eye fate determination, through the patterning and signaling events that specify photoreceptor cells and assign them unique functions. Kumar (pages 136–149) focuses on cellular and genetic mechanisms that are deployed to construct the basic unit of the compound eye, the ommatidium. Terrell et al. (pages 215–228) provide an example of how *Drosophila* can be used as a model to explore the molecular functions of human homologues of *Drosophila* proteins, and to provide molecular insights into human genetic diseases. They use the fly eye as a model to examine the activities of three human genes, OTX1, OTX2, and CRX, along with variants of these genes associated with retinopathies.

Drosophila has also been extensively used to address other aspects of

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neurobiology. Lin and Lee (pages 57–68) provide a detailed review of molecular steps involved in specifying the many distinct neuronal cell types of the *Drosophila* central nervous system, and an appreciation of the complex mechanisms required to achieve neuronal diversity. *Drosophila* has been used for a range of sensory and behavioral studies over the years. Im and Galko (pages 16–26) review one of the newest areas of sensory research in *Drosophila*, that of pain sensation (nociception). They describe how *Drosophila* is becoming established as a model for the study of different processes involved in nociception, including development of neurons responsible for the detection of noxious stimuli, and genetic approaches that are providing new insights into nociception. They also describe some of the outstanding challenges and questions in the field, where we can expect future *Drosophila* studies to contribute.

Drosophila has been used as a model for several fundamental processes required for organogenesis. One area that owes an extensive debt to *Drosophila* studies is that of tubulogenesis. Tubular organs like vasculature, kidneys, salivary glands, and lungs, are required for efficient secretion, and for transport of resources and waste products. Maruyama and Andrew (pages 119–135) review decades of work that have led to the present day understanding of the mechanisms involved in the elongation and formation of epithelial tubes, highlighting contributions from *Drosophila*. Homeostasis of organs in the adult often requires stem cells, and *Drosophila* has also been an important model for stem cell biology. Micchelli (pages 85–91) reviews studies of the origin of the stem cells for the *Drosophila* intestine, describing the elucidation of their origin from adult midgut precursors, as well as outstanding questions. An original research article from Amodio et al. (pages 190–199) describes how organogenesis in *Drosophila* can be used to provide insight into human disease genes. They show how several transcription factors involved in human

cardiogenesis can also function in the *Drosophila* heart, providing a basis for evaluating mutant isoforms associated with congenital heart defects.

The identification and characterization of intercellular signaling pathways is another area where *Drosophila* studies have made major contributions. One of the most recently discovered signaling pathways, the Hippo Pathway, was first identified several years ago in *Drosophila*, and Staley and Irvine (pages 3–15) review recent progress in our understanding of this pathway that has come from continued *Drosophila* studies. This pathway is highly conserved, and now recognized a major growth regulatory pathway from flies to mammals, with roles not only during development but also in regeneration. Another fast moving area of signal transduction is that of planar cell polarity signaling, which polarizes cells within the plane of a tissue. Although what is widely referred to as the core PCP pathway is better known, a second PCP pathway, the Fat/Dachsous pathway, always controls PCP. Thomas and Strutt (pages 27–39) provide a comprehensive review of Fat/Dachsous PCP signaling, its relationship to core PCP signaling, and some of the outstanding questions and controversies in the field. Efficient signaling is dependent upon cellular architecture and dynamics. This is highlighted by the essential roles of lipids and glycans in multiple signaling pathways. Pontier and Schweisguth (pages 92–106) review some of the diverse roles of glycosphingolipids, describing how information from biophysical and biochemical studies can be integrated with genetic studies in model organisms like *Drosophila*, and how such studies have emphasized the importance of glycosphingolipids to different steps of signal transduction. A research article by Le and Wharton (pages 200–214) describes characterization in *Drosophila* of BMP receptor mutations associated with a human genetic disease, Fibrodysplasia Ossificans Progressiva (FOP). Beyond its importance for understanding FOP, this extends our appreciation of signal transduction research in *Drosophila* by reminding us that in addition to

identifying and characterizing signaling pathway components, *Drosophila* can also be used to model the effects of disease variants.

Drosophila was one of the first metazoans to have its genome sequenced, and it continues to be an outstanding model for genomic studies. A techniques article from Brody et al. (pages 169–189) describes their creation of a bioinformatics resource to identify conserved *cis*-regulatory elements, and its application to identifying *cis* elements that control gene expression in neuroblasts. While a wealth of gene expression data is available in *Drosophila*, it remains challenging to systematically abstract high-resolution spatial information. Konikoff et al. (pages 150–160) have addressed this through creation of a resource for comparing expression patterns, which they call FlyExpress. Flies have also been an important model for characterization of microRNA genes, and the article by Kennell et al. (pages 161–168), describing the identification of a novel role for mir-8, provides an example of this.

Drosophila has long been appreciated as a model for basic cancer research through the identification of genes that control growth, such as components of the Hippo pathway. However, what is less widely appreciated is that *Drosophila* can also be used to model for other aspects of cancer biology. These are highlighted in the review by Rudrapatna et al. (pages 107–118), which describes how *Drosophila* can be used to study not only growth but also metastasis of tumors, and how *Drosophila* can be used to model specific genetic lesions first identified in human cancers. They also provide a description of progress and future perspectives for using *Drosophila* as a model for drug discovery relevant to cancer and other diseases.

Altogether, this collection of reviews, research and techniques papers helps us to celebrate a century of *Drosophila* research, and provides an appreciation of where *Drosophila* researchers equipped with current technologies and knowledge can take us. We hope you enjoy reading them as much as we did.