Annual *Drosophila* Research Conference, 2006

Amit Singh†* and Madhuri Kango-Smith‡**

Accepted 31 May 2006

INTRODUCTION

The *Drosophila* Research Conference is a yearly meeting organized by the Genetics Society of America (GSA) for the researchers who use the fruit fly model organism to study different facets of biomedical science. This meeting serves as a platform to present the cutting edge research in the fly model and provides an opportunity for interaction and exchange of ideas. The 47th Annual *Drosophila* Research Conference took place in Houston, Texas, USA, and was organized by Hugo J. Bellen, Ronald L. Davis, Graeme Mardon (Baylor College of Medicine), and Georg Halder (M.D. Anderson Cancer Center). Nearly 1,500 *Drosophila* researchers from different parts of the world attended this meeting and were treated to presentations on a broad spectrum of biomedical problems.

The meeting opened with a keynote address by Prof. Thomas Kaufman from Indiana University, Bloomington. Kaufman has a long legacy of excellent research contributions to *Drosophila* science and community. His talk on “A century of *Drosophila*: 100 years of counting” presented major milestones of *Drosophila* research along the time axis in a very exciting and informative fashion. These findings have contributed significantly to our understanding of *Drosophila* genetics and development. The “lowly” fruit fly, as Kaufman jokingly refers to the insect, has been a favorite of geneticists for nearly 100 years, longer than any other model organism in the history of genetics. He presented hallmarks of his research about the homeotic gene complex, primarily based on his studies on the Antennapedia (Antp) gene complex and their interacting genes in flies. Another interesting aspect was his study on how morphological changes among different arthropods take place during evolution as a result of changes in their Hox genes, in particular the Antennapedia Complex genes. His presentation had clips from one of the famous science fiction TV shows where a fly mutant (Antp) was used as a central plot. It was followed by presentation of the Larry Sandler Memorial Lecture award to Daniel Ortiz-Barrientos (Indiana University, Bloomington) for his PhD dissertation work on the molecular genetics of speciation.

The meeting had 18 platform sessions encompassing 136 talks and 13 workshops and around 1,000 posters. The extent of participation of the fly community in the meeting validates the claim that it is one of the biggest annual fly meetings in the world. Since the topics presented in the meeting cover a broad spectrum of fly research, it is impossible to cover all topics in this commentary. Therefore, we will focus on some of the common themes and topics.

PATTERN FORMATION

Pattern formation is essential in the development of higher eukaryotes. The versatility of the *Drosophila* model system has been exploited to study basic phenomenon like pattern- ing and growth. In recent years, the potential of model-organism-based studies has grown substantially. During the first plenary session, Richard Mann (Columbia University, New York) gave a talk on the transcriptional logic of appendage development. He talked about regulation of Distal-less (Dll) expression during proximo-distal (PD) axis generation in limbs. The highly conserved transcription factor Dll is important for specifying distal fates in the appendages. They identified a two-component regulatory system that controls Dll expression. One component is responsive to wingless (wg) and decapentaplegic (dpp) and the second component behaves as an autoregulatory element. Another interesting story was the ability of selector genes to modulate morphogen signaling as a means of generating diverse tissue sizes. Richard Mann addressed the question of why the haltere has five times fewer cells than the wing even though both

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*Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, Texas
†Department of Biochemistry and Molecular Biology, MD Anderson Cancer Center, Houston, Texas
*Grant sponsor: Retina Research Foundation; Grant sponsor: Fight for Sight, Inc.; Grant sponsor: Knight’s Templar Ophthalmology Research Foundation
**Correspondence to: Amit Singh, Department of Molecular and Cellular Biology, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030. E-mail: asingh@bcm.edu or Madhuri Kango-Smith, Department of Biochemistry and Molecular Biology, MD Anderson Cancer Center, Houston, TX 77030. E-mail: mksingh@mdanderson.org

DOI 10.1002/dvdy.20893
Published online 26 July 2006 in Wiley InterScience (www.interscience.wiley.com).
wing and halters are dorsal thoracic appendages. It was found that there is no intrinsic proliferation difference inherent to the cells of the two developing fields. However, it is the intervention of the Hox gene Ultrabithorax (Ubx) that manifests changes in Dpp ligand distribution by altering the way Dpp signaling controls the transcription of thickveins (thv) and daily—genes that shape the dpp morphogen gradient.

Drosophila serves as an excellent model for genome-wide screens. In the pattern formation session, a gain-of-function screen to search for the genetic circuitry required for selection of dorsal versus ventral imaginal disc fate was reported. Interestingly, very little is known about how the imaginal discs for dorsal- (like wing) or ventral- (like leg) appendages are selected. Using a gain-of-function approach, a factor required for generation of notum, a part of the wing imaginal disc, was identified (N. Grieder, W. Gehring, Biozentrum, Basel, Switzerland).

During patterning, once the cell fate is determined, it is mostly irreversible. However, rarely, there is a switch in cell determination, and the phenomenon is referred to as transdetermination. For example, misexpression of Wg induces leg-to-wing switch. In a DNA microarray screen to profile the expression patterns within developing imaginal discs and have made a temporal and spatial map of each gene's ability to induce ectopic eye formation, they have expressed the members of the RD pathway in over 200 unique expression patterns within developing imaginal discs and have made a temporal and spatial map of each gene's ability to induce ectopic eye development in non-retinal tissues. This map will be used in future efforts to identify genes that both promote and suppress eye development. They also conducted structure-function studies of several eye specification genes to study the evolutionary differences between sets of duplicated genes (sine oculis/optix and eyegone/twin of eyegone).

The Drosophila model has also been exploited for high-throughput screens. Retinal cell fate determination is the early phase during fly eye development, and only a handful of RD genes are known to control this process. To better understand the genetic network controlling this early process, a combinatorial approach of genetics, comparative genomics, and computational biology was used to further identify potential direct downstream targets of the RD gene, eyeless (ey) (Y. Li, G. Mardon, R. Chen, Baylor College of Medicine, Houston, TX). These studies identified nearly 20 new putative direct targets of Ey and such targets are currently being validated and characterized in vivo. Initial analysis revealed three genes eyes absent, shifted, Optix as novel targets of Ey.

In the receptor tyrosine kinase pathway, the mechanism of activation of the Raf kinase by GTP-bound Ras needs further understanding. A novel gene Aveugle was reported to be required for RAF activation in the Drosophila EGF receptor signaling pathway (J. Rogniant, J. Treisman, Skirball Institute, New York University School of Medicine). Aveugle encodes an SAM domain protein that can physically interact with the scaffold protein Connector enhancer of Ksr (Cnk) to promote Raf activation, perhaps by recruiting an activating kinase. Recently, a paper published from Marc Therrien’s group suggests that the gene Hyphen recruits Ksr to Cnk, and that Ksr promotes an allosteric transition in Raf that allows it to autophosphorylate.

The Dpp signaling pathway has various functions like growth, proliferation, and differentiation in all developing organs. In pupal retina, the Dpp pathway plays multiple roles that are essential for the regulation of cell shape and patterning of the pupal retina. Dpp has two roles: First, Dpp is required for stable positioning of cells within the epithelium. Second, retinal cells require Dpp signaling to achieve their correct shape and position within the ommatidial hexagon (J.B. Cordero and R.L. Cagan, Washington University, St. Louis, MO).

NEUROGENETICS AND NEURAL DEVELOPMENT

Axonal growth and targeting is a very important and interesting problem in biology. Mike O’Connor’s group (University of Minnesota, Minneapolis) presented the role of TGF β signaling in axonal targeting from the photoreceptors in the eye to the brain. They demonstrated that non-canonical signaling of BMP ligands through an Activin-like Type 1 receptor, Baboon (Babo), couple proliferation and differentiation in the optic lobe during development and allow targeting of photoreceptor axons in the brain.

A novel secreted glial factor Tangled was identified from a genome wide screen, which interacts with the Robo receptor to position longitudinal axon tracts in the embryonic nervous system (T. Das, U. Gaul, The Rockefeller University, New York). Interestingly,
the tumor suppressor gene Adenomatous Polyposis Coli 1 and 2 (APC) was shown to play an important role in cell adhesion and axonal outgrowth in the developing larval brain (M. Hayden, M. Peifer, University of North Carolina, Chapel Hill).

The establishment of cellular polarity is a crucial step in the development of epithelial tissues. The Drosophila eye contains a highly organized neurocrystalline lattice consisting of ommatidia. Planar Cell Polarity (PCP) is manifested in the arrangement of the photoreceptor cells in the ommatidial clusters. PCP is generated during the third larval instar. In an interesting talk, Numb, a cell membrane–associated protein, previously studied in the context of asymmetric cell division, was shown to be required for PCP establishment in the eye (P. Domingos, H. Steller, B. Mollereau, Rockefeller University, New York).

Olfactory systems confer the recognition and discrimination of a large number of structurally distinct odor molecules. The Drosophila model has provided major insights into the sense of smell or odor perception. The focus of the field is how the olfactory world is represented in the brain and how genes shape our perception of the sensory environment. In the first plenary session, Lesslie Voshall (The Rockefeller University, New York) showed that odor coding in Drosophila depends on precise regulation of 60 odor receptor (or) genes. Their studies on or genes and circuits has led to a model of odor coding in which a population of olfactory sensory neurons (OSNs) expressing a single OR converges upon a unique olfactory glomerulus. Drosophila is a powerful system to test this model because the entire repertoire of 60 ORs can be manipulated genetically. Voshall presented a nearly complete map of OR projections from OSNs to the antennal lobe (AL) in the fly brain. This olfactory sensory map provides an experimental framework for relating ORs to glomeruli and ultimately behavior. Another study from John Carlson’s group identified a novel POU domain gene that regulates some of the or genes (Yale University, New Haven, CT).

**NEURAL PHYSIOLOGY AND BEHAVIOR**

To understand Drosophila memory formation, there is a need to develop a high-resolution map of the brain. Ronald Davis’s group reported a digital map of the brain using two-photon confocal microscopy. They introduced transgenes into the fly that report changes in GFP fluorescence, changes in intracellular calcium concentration, as well as changes in synaptic transmission. They have used these to monitor calcium influx during neuronal depolarization and to visualize synaptic activity as the animals are exposed to odorants. This approach resulted in visualization of an olfactory memory trace for the first time (D. Yu, R. L. Davis, Baylor College of Medicine, Houston, TX).

The molecular mechanisms underlying acute and chronic ethanol tolerance in the nervous system and short- and long-term memory formation, is poorly understood. It was reported that homer, a gene encoding a scaffolding protein located at the postsynaptic density in mammals, is required for sensitivity and fast tolerance to the sedative effects of ethanol (N. Urizar, R. L. Davis, Baylor College of Medicine, Houston, TX).

In the second plenary session, Barry Dickson (Research Institute of Molecular Pathology, Vienna, Austria) gave an interesting talk entitled “Love and War in Drosophila.” Male and female flies generally have dramatically distinct and innate sexual behaviors. Dickson’s team demonstrated that the mating ritual of Drosophila is orchestrated by the activity of a single “master-gene” fruitless (fru). An obvious but nonetheless remarkable aspect of this behavior is that mature males court only females, never other males, whereas females do not court at all. Male courtship involves multiple sensory inputs and complex motor outputs, and requires products of the fru gene, which is differently spliced in males and females. The Dickson team was able to demonstrate that male splicing is essential for male courtship behavior and sexual orientation. The concept that a switch gene can specify an entire innate behavior in no way denies the critical role of complex gene networks it regulates. Another challenging and exciting story Dickson shared was their attempt to find the downstream effectors of the fru gene. They designed an interesting screen in which they used their fru-GAL4 line and genome-wide set of transgenic RNAi lines to look for genes that act in fru-expressing neurons to regulate courtship behaviour. They have cleverly used the white (w) gene reporter to screen which gene mutation prevents the mating behavior of the males. The screen has resulted in a collection of genetic mutations that affect male mating behavior. These studies will generate fuller insights into the innate behavior of courtship.

**DROSOPHILA MODEL OF HUMAN DISEASES**

The genomics revolution has revealed the underlying commonality between the cells and tissues of eukaryotic organisms from yeasts to humans. The common evolutionary heritage makes it possible to use genetically tractable organisms to model important aspects of human medical disorders such as cancer, birth defects, and neurological dysfunction, wound healing, malnutrition and aging. The use of these models will allow identification of the genetic circuitry that underlies human medical conditions. Further, disease models have the potential to address a growing gap between our ability to collect human genetic data and to productively interpret and apply it.

Great progress has been made in modeling neurodegenerative diseases in the fruit fly. Misexpression of proteins containing engineered triplet repeats encoding amino acids such as glutamine cause neural defects reminiscent of human triplet repeat diseases. Spinocerebellar ataxia type 3 (SCA3) also known as Machado Joseph disease (MJD) is one of at least nine human neurodegenerative diseases caused by the expansion of an unstable CAG repeat within an open reading frame of the gene. In the Drosophila model of SCA3 that recapitulates key features of human trinucleotide repeat instability, Bonini’s research group found that both males (lacking meiotic recombination) and females display similar repeat instability. Transcription dramatically en-
hances repeat instability and is modulated by mutations in nuclear excision repair pathways. (J. Jung, N. Bonini, University of Pennsylvania, Philadelphia).

Recently, Drosophila genes that parallel genes for human neurological disease including Spinocerebellar ataxia (SCA1) and Huntington's disease (HD) have been uncovered. Both of these diseases are polyglutamine disorders and evidence suggests a common mechanism of their pathogenesis. Using Drosophila eye as an assay system, Juan Botas's group utilized a collection of known SCA1 genetic modifiers to define common and specific mechanisms for SCA1 and Huntington pathology (J. Branco, J. Botas, Baylor College of Medicine, Houston, TX).

Stress in the endoplasmic reticulum (ER-stress) and the ensuing cellular response, collectively known as the Unfolded Protein Response (UPR), is implicated in a wide variety of diseases. To assay for the UPR in Drosophila tissues, Ryoo et al. (H.D. Ryoo, New York School of Medicine, H. Steller, The Rockefeller University, New York) analyzed an unconventional mRNA splicing of xbp1 that occurs during ER-stress, which was used to develop the xbp1-EGFP marker showing green fluorescence specifically in response to ER-stress. This marker revealed that the UPR is activated in Rh-1 G69D mutant animals that serve as a model for the human retinal degenerative disease, retinitis pigmentosa. Further, xbp1 mutants dominantly accelerate retinal degeneration caused by Rh-1 mutants, indicating that the xbp1 branch of the UPR serves as a protective mechanism against the disease.

Wallerian degeneration occurs in distal axons and synaptic terminals due to nerve injury without local inflammation. In slow wallerian degeneration (Wlds) mutant mice, which have chimeric genes for Ube4h/Nnmnt (nicotinamide mononucleotide adenyltransferase), this degeneration process is delayed by 2–3 weeks. However, the mechanism of delayed degeneration is not fully understood. Hugo Bellen's group reported the fly model for Nnmnt. They showed that mutation in Nnmnt results in degeneration in photoreceptors, rhabdome, cell bodies, and photoreceptor terminals in eye. Furthermore, they demonstrated that Nnmnt over-expression can protect Ataxin-1-induced neurodegeneration and may serve as a potent neuroprotective agent (R. Zhai, H. J. Bellen, Baylor College of Medicine, Houston, TX).

Another interesting talk came from Rolf Bodmer's group. They have been using the Drosophila model to study heart development. They have developed several assays for studying the heart, one of which is the image-based cardiacography of human hearts as to M-mode records created from echo video images and to automatically monitor pixel intensity changes in the movie. If the heart tube edges are electronically "removed" and aligned with slices taken from successive frames of the movie. If the heart tube edges are clear enough, one obtains a trace that turns out to be similar in appearance to M-mode records created from echocardiograms of human hearts as shown in Figure 1. They have developed a computer program in collaboration with Martin Fink at UCSD to monitor pixel intensity changes in the video images and to automatically track a number of parameters such as systolic and diastolic intervals, diameters, and contraction velocity, among others. These procedures work best with dissected, semi-intact fly heart preparations but they can also apply them to intact flies as the anterior end of the heart can be visualized through the cuticle under the right conditions (K. Ocorr, Li Qian, R. Bodmer, The Burnham Institute for Medical Research, La Jolla, CA).

CANCER AND GROWTH CONTROL

A handful of highly conserved signaling pathways are critical regulators of cell proliferation, differentiation, developmental patterning and morphogenesis, and disease pathogenesis. In fact, some 67% of known human cancer genes have parallel genes in the fly. Several groups presented their findings on the regulation of tissue growth and epithelial integrity. Regulation of tissue growth is dependent on both extrinsic and intrinsic signals. Translationally Controlled Tumor Protein (TCTP) was characterized in Drosophila, and genetic and biochemical studies showed that TCTP suppresses organ growth in flies and acts as a GEF for Rheb - a GTPase in the TSC pathway (Y. C. Hsu, K. Choi, Baylor College of Medicine, Houston, TX).

The Drosophila NF2 homolog-Merlin and a related FERM domain protein Expanded were shown to act as tumor suppressors through the recently identified Hippo signaling pathway. Genetic epistasis experiments and biochemical assays placed Mer and Ex upstream of hippo. In addition, their expression was tightly regulated by the Hippo signaling pathway in a negative feedback loop (F. Hamaratoglu, G. Halder, M. D. Anderson Cancer Center, Houston, TX). Another study presented the mechanisms of regulation of Merlin and a third FERM domain protein, Moesin. Moesin acts in organizing the apical cytoskeleton and thus has distinct cellular functions from Merlin. The sterile 20-like kinase, Slik, was shown to act as an upstream regulator that controls the localization and phosphorylation of Merlin. Merlin and Moesin functionally compete for Slik kinase activity, thus acting coordinately to regulate cell proliferation and epithelial integrity (S. C. Hughes, R. Fehon, University of Chicago, IL).

Seth Blair (University of Wisconsin) presented evidence to separate the growth and adhesive function of fat (ft) and dachshous (ds) using structure function analysis. He suggested that Ft has a receptor-like function in...
growth, proximo-distal patterning, and planar cell polarity (PCP), whereas Ds has a ligand-like function. They show, for example, that the extracellular domain of Ft is not needed for its functions in growth, PCP establishment, and PD patterning, but the extracellular domain of Ds is necessary and sufficient for its effects on PCP.

Several groups presented genes affecting epithelial integrity and/or invasion. The tumor suppressor genes warts and mats were identified as enhancers of the invasion phenotypes in the follicular epithelium of Drosophila disc large (dlg) and fust2 mutant ovaries (S. Goode, Baylor College of Medicine, Houston, TX). Dynemin heavy chain and dynactin were identified in a genetic screen for genes required for the apico-basal architecture of follicular epithelial cells (Horne-Badovinac and Bilder, University of California, Berkley). Daftary et al. (Yale University, New Haven, CT) presented their findings from genetic screens aimed at identifying mutations that cause RASV12-induced benign tumors to become metastatic. The role of Jun N terminal kinase (JNK) in tumor formation and malignancy was investigated by Uhlirova and Bohmann (University of Rochester, NY). They showed that expression of activated Raf induces growth-promoting survival signals that can antagonize JNK-induced apoptosis, and instead induce JNK-mediated non-cell autonomous proliferation. They propose that the output of the JNK signal may vary depending on the genetic background of the tumor.

Recently, several groups have reported identification of a number of tumor-suppressor genes that act non-cell autonomously to control cell proliferation (Vps25, Tsg101). Many genes that act similarly were identified by Vaccari and Bilder, for example, Vps20, Vps28, and Vps32 (University of California, Berkeley). Analysis of these genes will help elucidate how defects in endosomal sorting and degradation of receptors may alter signaling outputs and cause aberrant growth.

In support of stem cell–like characteristics of tumors, Hirth et al. (University of Basel, Switzerland) showed that loss of the tumor suppressor gene brain tumor (brat), results in loss of expression of the cell fate determinant Prospero. Thus, the ganglion mother cells transform to stem cell–like cells and continue to proliferate by self-renewal.

**STEM CELLS**

Stem cells are critically important for homeostasis and acute repair of human blood, immune system, epithelia, gut, brain, breast, cornea, lung, and probably many other tissues. In addition, embryonic cells converted to the stem cell state in culture are promising sources of replacement cells for a wide variety of human disorders. Studies of stem cells in Drosophila, mouse, and other model systems, have greatly advanced our understanding of their regulation within stem cell niches. The Drosophila model has been instrumental in understanding the signaling pathways involved in stem cell formation. In this meeting, Sumana Datta (Emory University of Medicine, Atlanta, GA) and Haifin Lin (Duke University, Durham, NC) organized a stem cell workshop. It’s a strong belief that the fly community can rapidly and rigorously provide novel insights into many aspects of stem cell biology that will be conserved in mammalian systems.

Some beautiful studies on the maintenance of stem cell identity/self-renewal, the role of microRNAs on cell fate decisions and cell cycle progression, and the development of new stem cell systems were presented in this workshop. Datta’s group presented their work on elucidating the signals required to initiate cell division in mitotically arrested stem cells in the brain and the role of the extracellular matrix, or niche, in modulating those signals in Drosophila. Their results suggest that developmentally distinct populations of neural stem cells use the same mechanisms signaling by Hedgehog (Hh) and Branchless (Bnl) through the proteoglycan Trol, at different times in development to activate the cell proliferation program.

The concept that stem cells are controlled by particular microenvironments known as “niches” has been widely invoked. But niches have remained largely a theoretical construct because of the difficulty of identifying and manipulating individual stem cells and their surroundings. Mechanisms regulating the interactions between stem cells and their niche can be elucidated in great detail using genetics in model organisms and can inform the study of stem cell–niche interactions in humans as well. The presentation from Ruohola-Baker’s group demonstrated that activation of Notch signaling can induce niches for the Drosophila germline stem cells (University of Washington, Seattle).

It is clear that the conference was a great success in providing an overview of broad spectrum of research in the fly model system. The credit for the success of the conference goes to the local organizers, the fly community, and the Genetics Society of America. An important point that emerges from this meeting is that model organism genetics continues to hold great promise for advancing biology, medicine, and human genetics. Much more work is needed to identify similarities across the biological species and to develop valid models of normal physiology and disease pathology. We must look for ways to bring clinician scientists and human geneticists into the fly model and bring their knowledge and perspectives to further strengthen the model.

**ACKNOWLEDGMENTS**

We extend our apology to those whose work we could not cite due to space constraints. We thank members of the fly community for their inputs. A.S. is supported by Retina Research Foundation, Fight for Sight Inc., and Knight’s Templar Ophthalmology Research Foundation.