Drosophila researchers focus on human disease

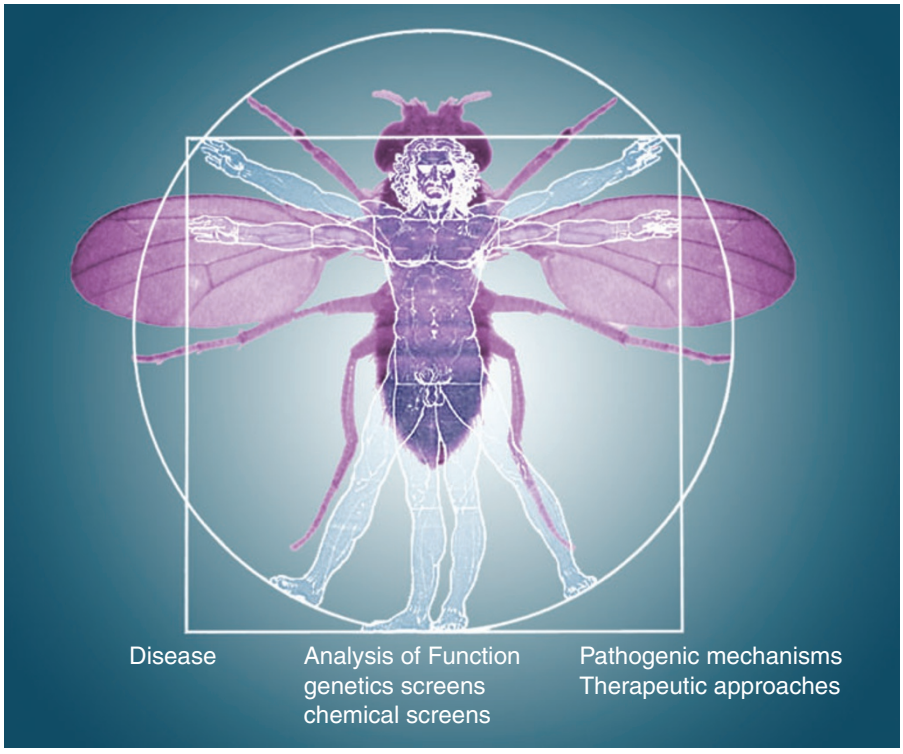
Juan Botas

Barcelona has long been known for its innovation, from the architectural genius of Gaudí to the culinary creations of its world-famous chefs. In recent years, it has reinvigorated Spanish science with the establishment of new, progressive research institutions. From 5 to 7 October 2006, Barcelona was host to a conference focusing on a new approach to human disease.

This was no ordinary meeting—it represented the first time a group of scientists came together to discuss the ways in which the fruit fly *Drosophila melanogaster* could provide innovative contributions to the field of human disease. The conference, entitled '*Drosophila* as a Model for Human Diseases', was organized by Cayetano Gonzalez and Marco Milan and was generously underwritten by the Institució Catalana de Recerca i Estudis Avançats (ICREA) and the Institut de Recerca Biomedica (IRB), which eliminated registration fees for all meeting participants, who numbered over 200.

The conference was timely because it came as a direct response to the recent explosion in *Drosophila* research focusing on human disease. This new research emphasis was boosted by genome projects, which not only facilitated the identification of disease-causing genes but also revealed a surprising level of conservation of these genes in the *Drosophila* genome.

The meeting covered a remarkably diverse array of diseases modeled in *Drosophila*, from cancer, neurological disorders and muscular dystrophies to cardiac failure, diabetes and drug addiction. In addition to presentations on specific disease models, the conference included presentations focusing on specific topics of basic biology that are directly relevant to disease, including signaling pathways, genomic regulatory networks, stem cell division, epithelial polarity, aging, oxidative stress and innate immunity. The mixing of these two types of presentations clearly contributed to the success of the meeting.



Modeling cancer in *Drosophila*

The integration and synergy between basic and disease-targeted research was also evident in many specific presentations, particularly in talks focusing on cancer. This is not surprising, considering the history of *Drosophila* research and the contribution of *Drosophila* genetics to our understanding of signaling pathways involved in oncogenesis, such as Ras/MAPK, Notch, Wnt/wingless, hedgehog and BMP. In this context, Konrad Basler and Mariann Beinz discussed recent work on the molecular mechanisms by which Pygopus, Legless/BCL9 and Hyrax/Parafibromin cooperate with armadillo/β-catenin to transduce the Wnt signal, and Marco Milan discussed two distinct mechanisms by which hedgehog is repressed. Anthony Brumby focused on the Ras pathway to screen for genes that cooperate with activated Ras in promoting tumor formation. Gines Morata illustrated the influence of basic principles of developmental biology on the study of tumor formation, proposing that cell competition is involved in tumor formation by inducing

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apoptosis in non–tumor cells. Also demonstrating this field's deep roots in basic cell biology, Cayetano Gonzalez investigated the distribution of centrosomes during asymmetrical stem cell division and discussed the implications of spindle dynamics in tumor formation. Loss of both cell proliferation control and epithelial polarity is a feature of certain mammalian and *Drosophila* tumors and was discussed by David Bilder in the context of tumor suppressors involving the endocytic pathway. Ross Cagan demonstrated the power and versatility of *Drosophila* to model cancer; he used an activated form of the receptor tyrosine kinase Ret to generate a model of multiple endocrine neoplasia type 2 (MEN2, a type of cancer for which there are no available mouse models). Cagan described genetic screens that lead to the identification of Ret modifier genes, including C-terminal Src kinase (Csk), a gene that is also a tumor suppressor and a regulator of the Src oncogene. In addition, Cagan described chemical screens that have identified a suppressor of the activated Ret phenotypes in flies that is currently being evaluated in phase III clinical trials as a treatment for MEN2.

Kevin White described a large-scale model of genome- and proteome-wide molecular interactions in *Drosophila*. This model is based on a combination of gene expression, protein-DNA interaction mapping, automated literature mining and protein interaction data. The application of this systems biology approach to disease and other complex biological processes was discussed in a variety of contexts to uncover previously unknown regulatory interactions. One prediction of the model is that the *SPOP* gene is involved in tumor necrosis factor (TNF) signaling. Experimental evidence for this prediction was obtained using both *Drosophila* and mammalian systems, and these findings led to the identification of *SPOP* as a biological marker for clear cell renal carcinoma. Other presentations related to cancer included the use of *Drosophila* as a tool for screening for radiation sensitizers (Tin Tin Su), the function of retinoblastoma proteins (Dessislava Dimova) and transcriptional profiling of *Drosophila* tumors (Pradip Sinha).

Understanding neurological disease

Together with cancer, neurological diseases were the most common topic of discussion during the meeting presentations. In recent years, a remarkable variety of *Drosophila* models of specific neurological conditions have been reported in the literature. Those triggered by gain-of-function mechanisms (for example, polyglutamine diseases) were generated using transgenes expressing the human protein, and those triggered by loss of function (for example, spinal muscular atrophy) were generated by knocking out the conserved fly orthologs. As I pointed out, *Drosophila* models recapitulate key neuropathological features observed in affected individuals. For example, fly models of spinocerebellar ataxia type 1 (SCA1), Huntington disease and Alzheimer disease show late-onset, progressive neuronal degeneration and formation of protein aggregates that accumulate chaperones and components of the protein degradation machinery. I presented genetic and biochemical interaction data between the gene products of two distinct spinocerebellar ataxias that suggest common mechanisms of pathogenesis among these polyglutamine diseases. I also presented data illustrating the potential of flies to combine genetic and chemical screens to define therapeutic targets. Alex Whitworth reported that mutational analysis of parkin and pink1 (two genes that can cause Parkinson disease) uncovered similar phenotypes in flies that suggest mitochondrial dysfunction. Moreover, overexpression of parkin suppresses the pink1 mutant phenotype, but not vice versa, suggesting that parkin is downstream and in the same pathway as pink1. Spinal muscular atrophy (SMA) was the topic of the presentation by Spyros Artavanis-Tsakonas, who described SMA models generated in both *Drosophila* and *C. elegans* by loss of function of the respective orthologous survival motor neuron (smn) genes. Artavanis-Tsakonas reported ongoing parallel genetic screens aimed to identify modifiers of the smn loss-of-function phenotype in both species. Mark Tanouye discussed epilepsy in the context of *Drosophila* mutations leading to seizures. Tanouye used these mutants as a starting point to isolate seizure suppressor mutants like *shakB*, a mutant in a gap junction protein that impairs electrical connections between neurons. Ulrike Heberlein discussed drug addictions, revealing remarkable similarities between the behaviors of *Drosophila* and mammals after acute and chronic drug administration. Heberlein's work using fruit flies identified the *dLmo* gene as a gene controlling sensitivity to cocaine: increased *dLmo* levels reduce responsiveness to cocaine, whereas reduced *dLmo* function has the opposite effect. The significance of these finding was established later, as the mammalian ortholog *Lmo4* is highly expressed in brain regions implicated in drug addiction, and its downregulation also leads to enhanced sensitivity to cocaine. Other topics discussed in the field of neurological diseases included pantothenate kinase–associated neurodegeneration (PKAN) and the CoA biosynthetic pathway (Ody Sibon), retinal degeneration and cell polarity (Elisabeth Knust) and functional analysis of genes causing hereditary spastic paraplegia (Cahir O'Kane).

A range of models

In addition to cancer and neurological disorders, the conference included presentations focusing on other disease conditions. Rolf Bodmer discussed arrhythmias and cardiac failure, describing conserved genes required for normal cardiac function both in humans and fruit flies. These include *NKX2-5*, *GATA4* and *TBX*, genes implicated in congenital heart disease whose partial loss of function leads to increased heart failure in *Drosophila*. Furthermore, mutations in the genes encoding KCNQ1 potassium channels lead to arrhythmias both in humans and fruit flies, and electrophysiological data suggest that arrhythmias are generated similarly in *Drosophila* and humans. Muscle disease was discussed in the context of models of oculopharyngeal muscular dystrophy (Martine Simonelig) and myotonic dystrophy type 1 (my own work). Additionally, it was reported that *Drosophila* was successfully used to model diabetes and explore potential therapeutic avenues (Ross Cagan) and to investigate host genes required for bacterial toxin activity (Ethan Bier).

Among topics in basic biology of particular relevance to disease were presentations describing the use of fruit flies to dissect the molecular mechanisms during aging (Marc Tatar) and the mechanisms and genes involved in oxidative stress (William Orr). Jules Hoffmann summarized striking work establishing the antimicrobial defense of *Drosophila* as a model for innate immunity. Hoffmann also described the roles of the Toll pathway regulating antibacterial peptides in response to fungal infections and the activation of the Imd pathway in response to gram-negative bacteria.

How valuable are fruit fly studies to mouse geneticists and human geneticists studying disease? Obviously, a longer perspective is needed to adequately assess the impact of *Drosophila* as a model system for human disease. However, it is evident from this meeting that *Drosophila* is well beyond the stage of validating itself as a suitable system for many disease conditions, including cancer, drug addiction and muscle and neurological disorders. This was best demonstrated in a number of presentations in which discoveries in *Drosophila* were later validated in mammalian systems or in humans.

From screen to screen

A common theme among many presentations was the forward genetic screens designed to identify genetic modifiers of disease. In many cases, modifiers identified in *Drosophila* have further validated disease models, as the modifiers were previously known to be involved in pathogenesis in humans. Other *Drosophila* modifiers point to genes not previously known to be involved in disease and identify new mechanisms of pathogenesis, thus providing an abundant source of pathways for validation in mammalian models. Among the genetic modifiers, suppressors are generally considered the sexiest because they are also potential therapeutic targets. Nonetheless, modifiers identified as enhancers deserve their share of attention, particularly from human geneticists, as they may identify human susceptibility genes. Compared with experiments in vertebrates, large screens are facilitated in *Drosophila* by the low cost, the short generation time, the capacity for experiments with large numbers of animals and the availability of large collections of loss-of-function and overexpression mutant strains. Genetic screens were discussed in the context of pathways cooperating with Ras to promote tumors (Anthony Brumby), novel genes causing neoplastic tumors (David Bilder), susceptibility genes in Ret-mediated tumorigenesis (Ross Cagan), functional analysis of parkin and pink1 (Alex Whitworth), genetic modifiers of HD and SCA1 (Juan Botas), genetic modifiers of SMA (Spyros Artavanis-Tsakonas), genes capable of suppressing or enhancing seizures (Mark Tanouye), PKAN neurodegeneration (Ody Sybon), genetic modifiers of OPMD (Martine Simonelig) and sensitivity to cocaine (Ulrike Heberlein).

In addition to genetic screens, other common approaches included proteomics, transcriptional profiling and chemical screens. It is noteworthy that several presentations included data from screens of small molecules in *Drosophila*, as it is likely that combining genetic and chemical screens in *Drosophila* to identify 'druggable' targets will become common in the near future. Chemical screens were presented for molecules conferring radiation sensitivity (Tin Tin Su), molecules ameliorating pathogenesis in the SCA1 fruit fly model (Juan Botas) and molecules with the potential to treat individuals with MEN2 (Ross Cagan). Quite significantly, the potential of *Drosophila* as a whole-animal chemical screening tool has caught the attention of the biotech industry. Two companies, VASTox (Oxford) and EnVivo Pharmaceuticals (Boston), presented details of their screening assays and automated screening platforms. As new developments surface, one can anticipate increased interest from this sector in the future.

The tiny fruit fly has been a workhorse for genetic studies for many years and has had a major role in unraveling the mechanisms of normal development. Basic research discoveries in *Drosophila* have laid the foundation for placing many disease-causing genes in the context of known gene networks. What is apparent from this groundbreaking conference is that *Drosophila* is now becoming an important model for human disease. Consequently, the promise of this innovative approach is that it will also make important contributions to our understanding of disease mechanisms and to the design of therapeutic strategies. In the coming years, mouse and human geneticists are likely to be great beneficiaries of the fast pace of *Drosophila* research, as it will provide them with an abundant source of new data and hypotheses to be validated and further investigated in mammalian systems.

COMPETING INTERESTS STATEMENT

The author declares no competing financial interests.