The translational relevance of *Drosophila* in drug discovery

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After nearly a century of successful research, the value of the fly *Drosophila melanogaster* as a model system for genetic analysis is well established. In the past few years, *Drosophila* has also successfully been used for living-organism-based chemical screenings [1,2]. Because it is still a new tool in this field, the value of flies for drug discovery is still under assessment and one of the recurrent and fair questions that remains open regards whether or not it is likely that compounds identified through screenings in flies are also going to be functional in mammals.

To contribute to an answer, we have inverted the question and searched the literature for compounds that were originally known for their activity in human cells and were later shown to have the same molecular mechanism of action in *Drosophila*. We found that such compounds are not rare. Table EV1 shows a selection of 60 such compounds, including actin and microtubule poisons; inhibitors of DNA topoisomerases, kinases, and phosphatases; alkylating agents; and modulators of membrane channels. Although this observation does not provide a quantitated estimate of future success, it does demonstrate that small compounds identified for their activity in flies may indeed work equally well in mammals, since the reverse is demonstrably true. Indeed, a remarkable corollary from this list is that many known pharmaceuticals, some of which have significant market value, could in fact have been identified in *Drosophila*-based screenings.

Another consideration regarding this question concerns protein homology, because the likelihood of a compound having similar effects in two species strictly

depends on the evolutionary conservation of the binding sequences. *Drosophila* also scores well on this criterion. A remarkable 60% of human disease-related genes have predicted orthologs in the fly and the extent of overall protein conservation is significant [3]. Moreover, and importantly, active compounds are active because they bind to sites that are critical for protein function and are, therefore, more conserved than the average protein sequence. We do not know the actual extent of this type of functional protein conservation, but a good approximation might be the number of human genes that can substitute the corresponding *Drosophila* ortholog.

To estimate the number of such genes, we searched the literature for successful cases of “humanized” *Drosophila* strains engineered to carry a human gene that is capable of rescuing a given mutant phenotype. We found 135 such genes (Table EV2). Of these genes, 127 are listed in FlyBase (www.flybase.org; September 3, 2015) as Hsap genes: constructs containing *Homo sapiens* genes that have been introduced as transgenes in flies. Because we have not systematically reviewed all literature pertaining to the remaining 517 Hsap genes currently listed in FlyBase, it is most likely that the number of published successfully humanized *Drosophila* strains is greater than 135. Moreover, this number will further increase as new Hsap lines are constructed and more human genes are put to the test. We do not know what the final count of functionally equivalent genes will be, but it is reasonable to estimate that it might number in the thousands, considering that in the yeast *Saccharomyces cerevisiae*, which is evolutionarily much more distant to

humans than *Drosophila*, 40% of essential genes can be functionally replaced by their human orthologs [4]. Such a high percentage of functional equivalence suggests a high likelihood that small chemical compounds have similar activities in both species.

Using living *Drosophila* for high-throughput chemical screening is more complex, more cumbersome and therefore slower than traditional screening methods based on biochemical assays or cell cultures. However, taking advantage of the wealth of knowledge and genetic techniques available, living *Drosophila* could afford the implementation of much more sophisticated screening paradigms than those available in simpler setups. Moreover, lead compounds identified by traditional methods often fail to exert the expected effect when administered to living murine models owing to suboptimal pharmacokinetics or pharmacodynamics. Screening in a living animal such as *Drosophila* can filter out at least a fraction of these unwanted leads, hence reducing the duration and cost of the drug discovery process.

The use of *Drosophila*-based models as drug screening platforms is in its infancy, but has already yielded relevant results on models of multiple endocrine neoplasia type 2 (MEN2 [5]), fragile X syndrome [6], epithelial malignant growth [7], intestinal stem cell-derived tumors [8], combinatorial therapy [9], and life span [10]. Moreover, pharmacogenetic studies in *Drosophila* have been successfully applied to optimize molecular entities by reducing side effects without diminishing therapeutic properties [5]. These results strongly substantiate the view of *Drosophila* as a sophisticated and cost-effective model

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organism well suited to contribute to clinically relevant translational research in drug discovery.

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