

The international exchange of *Drosophila melanogaster* strains

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Summary

Drosophila melanogaster has been a model organism for experimental research for more than a century and the knowledge and associated genetic technologies that have accumulated make it extremely important to contemporary biomedical research. A large international community of highly collaborative scientists investigate a remarkable diversity of biological problems using genetically characterised strains of *Drosophila* and frequently exchange these strains across borders. Despite its importance to the study of fundamental biological processes and human disease-related cellular mechanisms and the fact that it presents minimal health, agricultural or environmental risks, *Drosophila* can be difficult to import. The authors argue that streamlined regulations and practices would benefit biomedical research by lowering costs and increasing efficiencies.

Keywords

Drosophila melanogaster – Insect – Importation – Model organism – Regulation.

Introduction

For over a century, scientists have been using the fly *Drosophila melanogaster* to investigate biological processes. It is probably safe to say that more is known about the genes, genome and genetic regulation of cellular, developmental, physiological and behavioural processes in *Drosophila* than in any other multicellular organism. The genetic

approaches and technologies available for *Drosophila* experimentation are extraordinarily advanced and have led to profound contributions to human health. This role of *Drosophila* as a “research system” makes it different from most other insects described in this volume: it is not a disease vector, a significant agricultural pest or a biocontrol agent...and it is hard to envision *Drosophila* as a significant addition to the diet of anyone. It attracts the attention of scientists solely as a vehicle for discovery.

As directors of a major repository of *Drosophila* strains, the authors will try to give a glimpse into the significance of *Drosophila* research, an idea of the scale of international exchange of *Drosophila* strains, and suggestions for promoting international collaborations by improving import regulations and practices.

The importance of *Drosophila* to biological research

In the wild, *Drosophila melanogaster* is attracted to a wide variety of foods and is among the first animals to find damaged fruit and lay eggs on it. Early development is extremely fast (roughly 5 days) and the young leave the fruit quickly to metamorphose into adults—as one might expect for an insect that relies on fleeting resources. This combination of adaptability and fast development preadapted *Drosophila* to life as a human commensal (or, less flatteringly, a “garbage species”), an organism like the rat that has associated with humans who unwittingly provide it food and habitat. *Drosophila* has spread with human migrations and trade from its origin in southern Africa and it is now found everywhere that people live (1, 2).

In the early 1900s, Thomas Hunt Morgan of Columbia University was the first scientist to take advantage of the flexibility and fast growth of *Drosophila* for extensive genetic experimentation. He needed an easily bred animal to show that inheritance in animals could not possibly be as straightforward as the principles outlined by Gregor Mendel from his work with peas—work that had only recently drawn the attention of scientists after languishing in an obscure journal for decades. To Morgan’s surprise, the experiments in his lab both validated and

extended Mendel's conclusions (3, 4). They led to the explosion of interest in genetics that remains unabated to this day.

Since then, *Drosophila* experiments have been associated with nearly every conceptual advance in genetics. In the first half of the 1900s, *Drosophila* studies were central in establishing broad areas of research including mutagenesis, polygenic inheritance, and the behaviour of genes in populations. The later 1900s saw genetic analysis combined with increasingly sophisticated methods in microscopy, physiology and biochemistry to study ever more detailed *Drosophila* traits. Understanding the genetic control of development became a major interest and with it came intensive efforts to define and dissect signalling pathways controlling cell growth, proliferation and differentiation. In fact, the major intracellular signalling pathways involved in human development, homeostasis and disease were discovered or fleshed out in *Drosophila*.

The advent of molecular biology technologies had a strong impact on *Drosophila* research. The development of cloning vectors in the 1980s for injection into fly eggs allowed DNA sequences to be stably inserted into chromosomes to create transgenes. Indeed, *Drosophila* was the first multicellular organism where it was possible to integrate DNA sequences that had been manipulated in the lab into the genome (5).

Experimental approaches now combine transgenes with the well-established modes of genetic analysis. They provide ways to determine the roles of proteins and RNAs in specific cells at specific times during development, where those proteins and RNAs reside inside cells, how gene expression changes are triggered by different environmental conditions, and much more. Together, they make the experimental genetics of *Drosophila* the most sophisticated among all multicellular organisms. Experiments can be undertaken efficiently and inexpensively that are impossible or extremely expensive in nearly every other animal or plant – especially in the realm of examining gene functions in individual cells or cell types in their normal tissue contexts. These advantages make *Drosophila* indispensable to contemporary biomedical research.

Importance to human medicine

Those who work with insects wax poetic about them, but most people do not share their enthusiasm. It is often hard to convince nonscientists there is any reason to study *Drosophila* other than to find ways to eradicate them. Nevertheless, most tissues and physiological processes in people have counterparts in flies and nearly every activity in human cells occurs in fly cells as well. Overall, *Drosophila* genes are remarkably similar to human genes. It is estimated that an astounding 85% of genes associated with human diseases in the extensive *Online Mendelian Inheritance in Man* database have an equivalent gene in flies (6). This means that characterising gene functions in flies usually has direct benefit in understanding biological processes in people.

In this century, research with *Drosophila* has focused heavily on exploring cellular aspects of human diseases. Significant discoveries related to cancer, neurodegenerative disorders, diabetes and other diseases have been made using the remarkable genetic tools available to *Drosophila* researchers (Table I). This work has focused not solely on the fly versions of human genes. Transgenic technologies have enabled geneticists to substitute human genes for fly genes in the flies themselves, and these ‘humanised’ flies are proving particularly important for dissecting the functions of protein domains and examining the effects of protein–drug interactions.

An extraordinary example of the relevance of flies comes from the Undiagnosed Diseases Network. Many diseases in humans result from mutations, but it is often difficult to determine which particular gene has been disrupted to produce symptoms – even when genome sequence data is available. The *Drosophila* genes corresponding to candidate human genes can be disrupted in an effort to recapitulate cellular or physiological defects, and normal versions of the human genes can be introduced to ameliorate the defects. Experiments in flies by the Undiagnosed Diseases Network have now confirmed more than 25 gene–disease relationships (7).

Scientists often speak of ‘model organisms’ – species that are particularly well suited to dissecting biological phenomena. Often a

model organism proves valuable to understanding one process but offers no advantages in investigating others. Few model organisms have had staying power as versatile research subjects and have large communities of researchers formed around their use. *Drosophila* is among the most popular because it continues to prove its research value.

Drosophila stock resources and international exchange

More than 188,000 scientific papers have been published with ‘*Drosophila*’ in the title – 26,000 in the last decade alone (8). A huge proportion of these studies have involved experiments with fly strains with defined genetic elements such as mutations or transgenes. Morgan and colleagues established an ethos of sharing their fly stocks with other scientists. Stocks built for studying one process often prove valuable in studying seemingly unrelated processes, and the fly research community takes pride in perpetuating the strong tradition of openly exchanging stocks.

The unrestricted exchange of stocks has been formalised through the establishment of repositories where useful stocks are distributed publicly. The center managed by the authors – the Bloomington *Drosophila* Stock Center (BDSC) at Indiana University in lovely Bloomington, Indiana – is the largest. It supports the entire spectrum of research undertaken in over 3,500 *Drosophila* labs in 72 countries and currently maintains over 78,000 genetically defined stocks. Stock centers in Kyoto, Vienna and Zürich also serve the worldwide fly community and smaller centers serve specific research areas or geographical regions.

From 2011 to 2019, the BDSC exported an average each year of 110,555 samples in 5,176 shipments to 809 labs in 460 institutions in 48 countries (Table II; shipments in 2020 were unusually low due to the COVID-19 pandemic). From the shipping statistics of other stock centers and a conservative estimate of shipments among individual researchers, the authors conclude that at least 10,000 boxes cross international borders every year from all sources. It is likely that more

shipments of *Drosophila melanogaster* are made worldwide than of any other live insect.

The BDSC uses both postal and courier services. In 2003–2005, it worked with the United States Postal Service and State Department and international colleagues to push for adoption of an amendment to the Universal Postal Convention formally legalising the use of international mail to move *Drosophila* samples between countries (9).

The international exchange of *Drosophila* stocks should be encouraged by all countries

Progress in exploring biological processes, determining the causes of genetic diseases and devising treatments is obviously beneficial, and *Drosophila* is critical to these efforts. Scientists need to exchange stocks with collaborators across borders and obtain stocks from repositories. Consequently, lowering barriers to importing *Drosophila* should be a priority for regulatory officials in every country.

Beyond being ‘the right thing to do’, easing *Drosophila* importation usually aligns with national research priorities. For example, United States funding agencies have invested heavily in *Drosophila* research and resources. The RePORTER database (10) shows that the National Institutes of Health are funding more than US\$ 520 million in *Drosophila* research grants this year (2021). The National Science Foundation also invests strongly in fly research and other agencies such as the Department of Agriculture fund projects. National agencies in many other countries provide substantial support. Nongovernmental organisations such as the Howard Hughes Medical Institute, the Muscular Dystrophy Association and the Wellcome Trust also support *Drosophila* research generously.

Most countries do not support domestic *Drosophila* repositories, so their scientists rely heavily on external stock centers. In turn, the stock centers depend on scientists outside their own countries to donate important stocks and to cover costs through purchases (nearly 40% of routine BDSC operating expenses are paid from non-US revenue). This mutually beneficial relationship depends on efficient import practices.

When a country establishes procedures that discourage scientists from importing model organisms, it not only undermines the well-being of stock centers, it places its domestic research programmes at a disadvantage.

***Drosophila melanogaster* strains are safe**

Drosophila melanogaster poses essentially no risks. It is not a major agricultural pest because it cannot harm growing fruit like the Mediterranean Fruit Fly. (The fact that Drosophilids are often called ‘Fruit Flies’ makes some people think they are similar to Medflies and other Tephritids, but they are very different and even untrained people can distinguish them readily.) Its only interaction with the agricultural supply chain is relatively minor: it can be a nuisance for fruit processors—hence its other common names Pomace (mashed fruit) Fly and Vinegar Fly. Likewise, it poses no problems as an invasive species; it had spread to most of the world before geneticists got interested in it. Endangered species regulations are irrelevant.

Drosophila poses no health risks. It does not bite or sting. It is not the intermediate host for any parasite, nor is it naturally infected by any pathogen of human or agricultural concern. Likewise, it is nearly impossible for lab cultures to be contaminated with a microbe of concern. Nearly all experiments are conducted with stocks whose origins can be traced to flies brought into lab in the early to mid-1900s. Most fly geneticists will spend their entire careers never having worked with wild-caught flies. The cultures are maintained on artificial media with nothing living from the outdoors introduced intentionally. Additionally, most experiments involve strains that must be used in closed facilities approved for transgenic animals, where exposure of flies to pathogenic microbes is also minimal. When flies are shipped between labs, the goal is to transfer them from one closed facility to another with no release into nature.

Can transgenes make *Drosophila* strains dangerous? The authors are confident that none of the nearly 47,000 transgenes in BDSC stocks or any transgenes in other repositories increase risks and that almost all of the more than 145,000 transgenes currently listed in *FlyBase* (11) from

the fly literature are harmless. To their knowledge, the only unintentional environmental release of transgenic flies that would pose higher-than-usual risks to the genetic structures of natural populations would be from “gene drive” experiments where the spread of transgenes through lab-created populations is accelerated artificially—usually to model the transgenic control of disease vectors such as mosquitoes (12). The few researchers investigating gene drive in flies use strict containment measures. The authors are aware of only one line of investigation where fly transgenes have presented disease risks to other organisms; namely, examining the cellular effects of expressing transgene-encoded prion proteins (13). That research has also been limited to a small number of labs and done under strict conditions. In both of these rare situations, the relevant experimental conditions have been created by combining transgenes in progeny via the mating of parental strains. The parental strains, by themselves, pose no increased risks and could, in principle, be moved between labs without undue concern—even though their distribution has been tightly controlled.

These facts lead to the conclusion that *Drosophila melanogaster* is an innocuous organism reared under clean conditions that carries transgenes that do not increase risks in the strains that would be moved. It should, consequently, be one of the easiest research animals to exchange between countries and, in the opinion of the authors, every country should encourage its importation to further scientific progress. Box 1 discusses other *Drosophila* species.

Exchanging *Drosophila* strains between countries is more difficult than it should be

To ship *Drosophila*, the BDSC puts adults in plastic vials with solidified food where they lay eggs. As long as the vials do not get too cold or hot, or take too long *en route*, stocks can be propagated from these starter cultures. Of the approximately 5,000 shipments the BDSC exports every year, roughly 15% of the shipments arrive with dead cultures. It provides free replacements if customers pay shipping costs. Losses from weather and transportation conditions are inevitable and the BDSC largely accepts them as ‘part of doing business’, but most

losses come from delivery delays associated with import regulations and practices. The BDSC takes regulatory compliance seriously, but satisfying import officials in every country often seems like an unattainable goal. Here the authors will make a few points about importation that will, admittedly, reflect their frustration.

Import practices should reflect the identity of the animal and how it was raised

A major improvement would be for practices to make sense for the animals being imported. Import rules seem to be predicated on all animals being treated the same and therefore requiring similar paperwork and inspections. Consequently, the BDSC often completes paperwork for *Drosophila* that makes no sense.

One illogical ‘one-size-fits-all’ imperative is the insistence by some countries on receiving export health certificates signed by a government-approved veterinarian – an expensive requirement that makes sense for pets and farm animals, but makes little sense for model organisms raised in isolation. It is particularly difficult to justify for *Drosophila* because veterinarians generally have little knowledge of insects or insect diseases, and there are no formal guidelines for ‘giving a fly a checkup’. Veterinarians rely on what they know about *Drosophila* in general and on the fact that flies are reared in a lab to certify the absence of diseases of public health concern – two things that obviously do not require culture-by-culture inspections.

Nearly all biomedical research with animals is conducted with less than two dozen species, which are reared and used in closed facilities. Given the simplicity of this situation, the authors contend that model organisms should be given special consideration and expedited processing. The European Union has recently taken steps in this direction by exempting research organisms from domestic veterinary inspections upon arrival (14). Likewise, US Department of Agriculture regulations were recently changed to exempt many *Drosophila melanogaster* strains from import permit requirements and to allow the substitution of simplified import documents (15, 16). Nevertheless, agency decisions in some countries have made model organism

importation unreasonably difficult. For example, most model organisms cannot be imported into the United Kingdom via courier services because inspectors at major courier hubs are authorised to clear shipments of only large farm animals. The OIE and other organisations with influence over import regulations and practices should strongly support the streamlined importation of research organisms.

Permits should be long lasting

In many countries, a specific import permit is required for each shipment. This is a burden when many projects require multiple shipments and the strains are uniform with respect to regulations. Permits for multiple shipments would save everyone time and effort.

Fees should be appropriate

Application and inspection fees can be expensive. Until the EU changed its regulations, scientists were often paying hundreds of euros in veterinary fees per box of flies (for which repositories could be charging as little as €3). Fees should cover actual costs for justifiable expenses.

Import rules should be articulated clearly

The BDSC has seen from its interactions with import officials that there can be considerable uncertainty about applying regulations to *Drosophila*. Import officials often find it difficult to advise scientists on importing flies instead of mammals, and shipments are treated inconsistently in many, if not most countries. The authors hope the articles in this volume will spur regulatory agencies to clarify internal practices regarding insect importation.

In general, repositories do not have the personnel resources to keep up with the import practices of all the countries they serve and to supply scientists with up-to-date information. Users are often surprised when they learn repositories cannot provide all the paperwork necessary for importation and they must acquire permits themselves. Ideally, scientists would figure out what kinds of preapproval and documentation they need for their countries and pass along that information to repositories and their colleagues, but requirements are

usually complicated and often require lengthy registration and application processes, and it is rare to find a scientist who has mastered the intricacies well enough to provide definitive explanations. There is an immense need for instructions on *exactly* how to import insects into most countries. This lack of explicit guidance has led to an enormous amount of misinformation among scientists, and it is often hard to convince them that their workarounds do not comply with regulations of their own countries.

The BDSC has a standing offer to work with scientists and import officials to assemble instructions for importing *Drosophila* into other countries and to post them on its website in the same way it has provided guidance on U.S. importation (15). It is, nevertheless, difficult to interest busy scientists in the task and nearly impossible for the BDSC to interact with government officials in other countries without a domestic intermediary. It would be much better for regulatory agencies themselves to provide clear guidance for importing insects specifically.

Conclusions

Import officials probably wonder why scientists do not do a better job complying with regulations and are undoubtedly unhappy that they need to use their discretion so often to release shipments for delivery when documents are missing or incorrect. Scientists need to learn the rules and understand the practices of their own countries better and engage with import officials for advice. Nevertheless, the complexity of requirements and the unavailability of specific guidance make importation genuinely confusing and difficult. The authors know improvements are possible because compliance within the United States has improved as the BDSC and the Department of Agriculture have worked together to provide clearer import instructions for *Drosophila* and as the agency has simplified regulations and processes.

The authors hope this volume of articles on the international shipment of insects will help bridge the knowledge and cultural divides between scientists and regulators. The world benefits tremendously from the work of the *Drosophila* research community, and regulations and practices that make collaborations among fly labs easier help everyone.

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Table I

A sampling of the many human diseases where *Drosophila* research has provided valuable insights

Disease	Reference
Addiction	(17)
Age-related disorders	(18)
Alcoholism	(19)
Alzheimer's disease	(20; 21)
Amyotrophic lateral sclerosis	(22; 23)
Angelman syndrome	(24)
Autism spectrum disorder	(25)
Cancer	(26)
Cardiomyopathies and other heart diseases	(27; 28)
Cystic fibrosis	(29)
Diabetes	(30)
Epilepsy and other seizure disorders	(31; 32)
Fragile X syndrome	(33)
Galactosemia	(34)
Huntington's disease	(35)
Inflammatory bowel disease	(36)
Intellectual disability	(37)
Kidney diseases	(38)
Lysosomal storage diseases	(39)
Metabolic disorders and syndromes	(40)
Microcephaly	(41)
Mitochondrial-related disorders	(42)
Muscular dystrophies	(43)
Myotonic dystrophy	(44)
Neurofibromatosis	(45)
Obesity	(40)
Parkinson's disease	(46)
Creutzfeld–Jakob disease	(13)
Retinitis pigmentosa	(47)
Sleep disorders	(48)
Spinal muscular atrophy	(49)
Spinocerebellar ataxia	(50; 51)

Table II**Drosophila shipments from the Bloomington Drosophila Stock Center**

Year	Total samples shipped	Total shipments	Total labs shipped to	Total institutions shipped to	Samples exported	Shipments exported	Labs exported to	Institutions exported to	Countries exported to
2011	214,718	14,540	1,736	829	104,533	5,830	755	428	44
2012	222,981	12,822	1,788	871	116,973	5,149	782	455	44
2013	228,432	13,726	1,875	909	112,508	5,581	825	475	47
2014	236,340	13,739	1,864	903	116,724	5,496	796	456	45
2015	243,148	14,180	1,947	930	114,983	5,465	833	462	46
2016	217,072	13,521	1,988	956	106,326	5,175	854	480	53
2017	218,429	13,672	1,978	977	111,007	5,124	828	474	50
2018	222,975	13,173	1,976	972	110,560	4,488	820	467	52
2019	204,672	12,736	1,950	973	101,383	4,277	790	447	51
2020	160,105	9,044	1,736	767	83,587	2,996	719	422	41

Box 1

Other *Drosophila* species

In popular culture, most scientific literature and this article, “*Drosophila*” is used as the common name of *Drosophila melanogaster*. Nevertheless, many other species in the genus *Drosophila* are routinely reared in labs. Indeed, there are non-*melanogaster* strains that have been maintained for nearly as long as the oldest *D. melanogaster* strains. Some species are well suited for studying specific biological phenomena, but many experimental uses of non-*melanogaster* species arise from them being evolutionarily related to *D. melanogaster*. Large strain collections are maintained by government-sponsored repositories at Cornell University, the Kyoto Institute of Technology and Kyorin University. Non-*melanogaster* strains are exchanged internationally, albeit not as frequently as *melanogaster* strains. *D. suzukii* is the only species in the genus that poses a significant agricultural risk and it is studied primarily in the context of pest control. Its movement should be carefully controlled, but other *Drosophila* species are like *D. melanogaster* in presenting minimal risk. Because of their research importance, the authors feel they should receive special consideration when being imported for use at closed facilities.