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# REVIEW ARTICLE

## *Developmental Biology: Model Systems - A Series of Reviews*

*This is the fifth and final article focusing on model organisms to study development. In this review Dr. Kamal Bharucha reviews* Drosophila melanogaster *as a model to study metabolism.*

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# The Epicurean Fly: Using *Drosophila Melanogaster* to Study Metabolism

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**ABSTRACT:** In this review, the utility of *Drosophila melanogaster* as a model organism for research in metabolism will be demonstrated. Importantly, many metabolic pathways are conserved in both man and the fly. Recent work has highlighted that these conserved molecular pathways have the potential to give rise to similar phenotypes. For example, it has proven possible to generate obese and diabetic *Drosophila*; conversely, genetic manipulation can also generate lean and hypoglycemic phenotypes. From conserved circulating hormones to key enzymes, the fly is host to a variety of homologous, metabolically active signaling mechanisms. The world of *Drosophila* research has not only a rich history of developing techniques for exquisite genetic manipulation, but also continues to develop genetic methodologies at an exciting rate. Many of these techniques add to the cadre of experimental tools available for the use of the fly as a model organism for studying carbohydrate and lipid homeostasis. This review is written for the pediatric-scientist with little background in *Drosophila*, with the goal of relaying the potential of this model organism for contributing to a better understanding of diseases affecting today's children. **(*Pediatr Res* 65: 132–137, 2009)**

### CHILDHOOD OBESITY AND THE FAT FLY

Over the last few decades, the prevalence of obese children has increased from about 5 to 15% (1). Thus, a staggering number of children in the United States are at risk for obesity-related health problems. The public health consequences of such trends will be enormous in the coming decades, given the serious co-morbidities associated with obesity (2). For example, type 2 diabetes, once a rarity in the pediatric population, has the potential to become an all too common diagnosis, particularly among minority populations. As today's children grow into tomorrow's adults, the trends are at risk for compounding in the near future. Indeed, the National Institutes of Health has issued a "Help Wanted" for the training of more pediatric endocrinologists to help care for the burgeoning population of children requiring care (3).

A multidisciplinary effort is needed to adequately address the enormous health consequences of these trends, ranging from school-based interventions to more basic metabolism research. Laboratory-based investigations will play an indispensable role by providing insight into the fundamental molecular mechanisms that contribute to obesity. Within the context of laboratory-based research, work in model organisms can make a significant contribution to metabolic research, in a cost-effective and expedient manner.

Why study flies? Strikingly, the vast majority of genes causing human disease have a *Drosophila* homolog (4). It is becoming increasingly apparent that the powerful methods of *Drosophila* genetics can be a gateway for a better understanding of human metabolic disorders. Although *Drosophila melanogaster* has been studied for decades, it has only been recently appreciated as a model for human metabolic disease and pathways (5–7). Remarkably, the molecular mechanisms

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**Abbreviations: AKH,** adipokinetic hormone; **dILP,** *Drosophila* insulin-like peptide; **For,** foraging; **NPY,** neuropeptide F; **Ppl,** pumpless

contributing to many metabolic phenotypes observed in *Drosophila* are largely conserved between flies and humans. Recent work has shown that it is possible to generate *Drosophila* with diabetic and obese phenotypes, often with manipulation of pathways that cause parallel clinical manifestations in humans. Therefore, it is reasonable to assume that research in fly metabolism can provide insights with high clinical relevance. Moreover, research in *Drosophila*, with its array of powerful genetic tools, provides an opportunity to delineate conserved signaling pathways and identify novel therapeutic targets.

In this review, recent work in *Drosophila* will be highlighted that has provided insight into lipid and carbohydrate homeostasis relevant to human physiology. It is a growing field of investigation, pioneered by a small but growing cadre of Drosophilists, often working in basic science departments. This nascent *Drosophila* metabolism research community can benefit from interaction with clinicians (and pediatricians in particular) who can often help frame research questions in the context of a clinical milieu. At the outset, apologies are extended to researchers whose work could not be cited given the space constraints of the current review.

## THE METABOLIC FLY

The fly has several discreet organ systems, paralleling those in mammals, that play key roles as metabolic regulators (8). The *Drosophila* fat body (sharing properties of adipose tissue), oenocytes (newly described as hepatocyte-like cells), gastrointestinal tract (functionally segregated, as in mammals), Malphigian tubules (serving as kidneys) and certain areas of the brain are examples of tissues playing a key role in metabolic regulation and energy homeostasis (9–13). Thus, not only are many metabolic pathways conserved, the regulation of energy homeostasis requires interplay between metabolically active tissues, reminiscent of the metabolic regulation in mammals. It is beyond the scope of the current review to discuss each individual tissue, but recent findings on work in the *Drosophila* fat body and oenocytes are highlighted below.

The *Drosophila* fat body is the main depot for the storage of fuel molecules such as glycogen and triglycerides. In the larval stage, it consists of approximately 2000 cells arranged in segmented pattern throughout the body (14). The larval fat body is particularly amenable to visual analysis, as it can be readily assessed through the translucent larval body wall. During metamorphosis and early adulthood, the larval fat body cells undergo autophagy and the adult fat body is formed *de novo* (15). The adult fat body is also characterized by a wide distribution, in intimate contact with a variety of organs throughout the body segments, including the pericerebral region (16).

The fat body is becoming increasingly appreciated to secrete factors that modulate metabolism, reminiscent of mammalian adipokines (17). The fat body has already been known to secrete factors important for the *Drosophila* immune response (18). In a recent study, the fat body was shown to secrete an ortholog of the acid-labile subunit (ALS) that, in humans, forms a ternary complex with IGF binding protein 3 and insulin-like growth factor-1 (IGF-1) (19). *Drosophila* ALS (dALS) binds to *Drosophila* insulin-like peptides (dILPs), and has been proposed to modulate insulin action in the fly. Intriguingly, the *Drosophila* protein Imp-L2 forms a ternary complex with dALS and dILPs, analogous to mammalian IGF-binding proteins (19,20). Thus, the fat body can modulate insulin action *via* secretion of proteins that are homologs of known modulators of the mammalian IGF-1 pathway. Other factors affecting growth and metabolism released by the *Drosophila* fat body await discovery.

A fascinating recent study has demonstrated that *Drosophila* larvae contain hepatocyte-like cells (oenocytes), which accumulate lipids upon starvation (12). Oenocytes express many of the same genes as hepatocytes, such as enzymes required for processing fatty acids, cell surface proteins for the uptake of lipoprotein particles, and orthologs of hepatic transcription factors [such as hepatocyte nuclear factor 4-$\alpha$ and chicken ovalbumin upstream promoter transcription factor]. Thus, oenocytes are currently viewed as involved with the processing of lipids released by the fat body. Unlike the mammalian liver, which exists as a singly assembled organ, *Drosophila* oenocytes are distributed in discreet paired clusters along the larval body wall. The unique anatomical distribution allows oenocytes to be in intimate contact with the hemolymph, which circulates nutrients in *Drosophila*. Thus, both the mammalian liver (as a consequence of its arterial and venous communications) and *Drosophila* oenocytes (as a consequence of their anatomical distribution) are well suited to act as sensors of metabolic status.

Because of its ability to act as a glycogen storage depot, the fat body can also be considered to share some functions performed by the mammalian liver; it uses many of the same enzymes that regulate glycogen synthesis and breakdown. Mechanisms that regulate communication between oenocytes and the fat body are currently unknown, and promise to shed light upon the shuttling of fuel molecules in mammals. Interesting research questions abound; for example, do oenocytes secrete substances that act directly on the fat body to inhibit lipid mobilization, forming a negative feedback loop? The further study of oenocytes can contribute to a better understanding of factors that result in hepatic steatosis (21).

## GENETIC TOOLS TO STUDY METABOLIC DISEASE

The fly offers a myriad of genetic tools to help study metabolism. In addition to the potential to study further mechanisms regulating energy homeostasis that are likely to be conserved, the relative cost-effectiveness and speed are also attractive features. Rather than rest on its laurels, *Drosophila* genetics continues to advance at an exciting pace (22). In the past few years alone, a variety of genetic tools and stock collections have emerged as important components in the *Drosophila* genetics toolbox. In this section, the breadth and utility of these research tools will be illustrated, and how they can be applied to the field of metabolic research.

Unbiased forward genetic screens are a staple of *Drosophila* research; they provide the opportunity for the establishment of new and unexpected paradigms that can sometimes elude hypothesis-driven research (23,24). A well-designed screen has phenotypic endpoints that are easily scored on a

large scale, allowing the assessment of hundreds of putative mutants by a relatively small group of researchers. In fact, most genetic screens are initiated by individual academic laboratories rather than by large consortiums of researchers. It is not unusual for a single member of a lab to screen through hundreds (if not thousands) of lines during the early stages of a research project. Indeed, genetic screens in the *Drosophila* have contributed fundamental discoveries in a variety of fields. Screens can be performed on mutant collections on a scale often beyond the feasibility of vertebrate model systems.

Forward genetic screens in *Drosophila* have contributed to our understanding of insulin signaling. As in mammals, the insulin pathway is also an important regulator of growth and metabolism in *Drosophila* (25). Several dILPs bind to a single insulin receptor (dInR) to activate intracellular cascades homologous to those in mammals. As an example of a recent genetic screen, an experimental approach was designed to manipulate the insulin pathway only in the fly eye (without altering with the pathway in the rest of the body) (20). Over-expression of dInR in the photoreceptor neurons (using Gal4/UAS methodology discussed below) results in hyperplasia of the eye, an easily discerned phenotype; the screen was designed to identify suppressors of this dINR-induced phenotype. Indeed, this screen identified Imp-L2, an IGF-binding protein homolog, discussed in the previous section. Such a mosaic experimental platform also allows for the identification of genes involved with insulin signaling that would otherwise be lethal if mutant throughout the entire fly. Of note, several tissues in *Drosophila* are amenable to mosaic analysis, including the fat body (26,27). Artfully designed genetic screens in *Drosophila* have resulted in the identification of novel regulators of the insulin signaling (28,29). There is no doubt that future screens will offer creative and unforeseen insights into the regulation of metabolism that is relevant to humans.

With the availability of robust *Drosophila* cell lines, genetic screens can be performed not only using the intact fly, but also on the cellular level (30). *Drosophila* cell lines have proven their efficacy in RNAi-mediated gene silencing, with *Drosophila* cells having distinct advantages over mammalian cells lines. With the establishment of genome-wide RNAi screening methodologies, powerful genetic screens can be designed on the cellular level. RNAi screens asking metabolic questions have been recently published, and will no doubt continue to be a source of critical leads and hypotheses. Recent examples of screens in the field of metabolism include those probing for genes affecting mitochondrial function and lipid droplet morphology (31,32). The potential wealth of information gleaned from cellular screens can often be readily translated into *in vivo* testing of candidate genes in live flies.

Another strength of *Drosophila* genetics is the exquisite control of gene expression. A commonly used tool is the binary Gal4/UAS system for the spatial and temporal regulation of gene expression (33). Transgenic flies are generated that express the yeast transcriptional activator Gal4 in a tissue specific manner; when such tissue specific-Gal4 lines are crossed to transgenic flies containing UAS sites (the Gal4 binding site), sequence downstream of the UAS sites are expressed. Of note, tissue-specific Gal4 drivers are available for many tissues including those involved with metabolism. In fact, public stock centers house large collections of Gal4- and UAS-containing transgenic lines (34). It is possible to over-express or mis-express virtually any gene, and assess any resulting metabolic phenotypes. An exciting development over the last few years is the establishing of stock centers that house collections of transgenic UAS-RNAi flies that allow for the controlled knockdown of genes *in vivo* (35). Thus, it is also now possible to knockdown virtually any gene in a tissue-specific manner.

## CONSERVED MECHANISMS OF CARBOHYDRATE HOMEOSTASIS

Inactivation of *Drosophila* insulin-producing cells (IPCs) in larvae yields phenotypes that recapitulate many of the presenting features of type I diabetes, such as high circulating carbohydrate levels and poor growth (36). As discussed previously, many of the downstream components of the insulin pathway are conserved in *Drosophila*, and their mutation also results in growth phenotypes. For example, mutation of *chico*, the *Drosophila* homolog of insulin receptor substrate proteins, results in dwarf flies (37). The homology of the insulin pathway extends from the cell surface dInR to downstream nuclear effectors such as the *Drosophila* forkhead transcription factor dFOXO (38). Thus, both the structure and metabolic function of many of the components of the insulin pathway are conserved between the flies and humans.

DILPs and adipokinetic hormone (AKH) are two counter-regulatory systems that regulate circulating carbohydrate levels in *Drosophila* (39). As mentioned above, genetic ablation of dILP-producing cells yields larvae with high circulating carbohydrate levels, reminiscent of diabetic phenotypes. Conversely, impairing AKH secretion, a functional analog of mammalian glucagon, results in larvae with low circulating carbohydrate levels (for example, see 40). Remarkably, the distinct groups of cells that secrete dILPs and AKH each have extensive branching around the dorsal vessel. Such extensive juxtaposition of these cells with the vasculature is reminiscent of the intimate contact of pancreatic islets with circulating blood. Thus, both the human and the fly have evolved their anatomy to allow for two counter-regulatory groups of hormone secreting cells to regulate circulating extra-cellular sugar levels.

Strikingly, the molecular mechanisms by which *Drosophila* larvae sense circulating glucose levels are the very same that are used by pancreatic islets (41). The AKH-producing cells also express the *Drosophila* homolog of the sulfonylurea receptor (SUR). In mammals, insulin-secreting pancreatic cells use SUR to trigger hormone release (42). In contrast, it is the glucagon-like AKH peptide secreting cells that use *Drosophila* sulfonylurea receptor to trigger AKH release in response to low sugar levels. Sulfonylurea drugs, used in the treatment of diabetes in humans, also affect sugar levels in *Drosophila*, providing a dramatic example of how both humans and flies use the same mechanisms to regulate sugar homeostasis. However, in contrast to humans, sugar levels are *increased* in *Drosophila* upon administration of sulfonylureas,

reflecting the expression of SUR on only the glucagon-like AKH-producing cells.

## CONSERVED MECHANISMS REGULATING LIPID HOMEOSTASIS

There is such a thing as a fat fly. Indeed, recent work has generated both lean and obese mutant flies in the laboratory. Furthermore, mechanistic studies of naturally occurring obese mutant flies has revealed mechanisms regulating adiposity across species. One of the first characterized mutant flies with increased triglyceride content was mapped to the *Drosophila adipose* (*adp*) gene (43). Recently, it was demonstrated that the mammalian homologs of *adp* are also regulators of lipid content in mammals (44). Obese flies have also been generated upon mutation of critical regulators of lipolysis in *Drosophila* (see below); these studies highlight the importance of pathways involved with triglyceride mobilization as critical determinants of adiposity.

*Drosophila* fat body cells share many characteristics of mammalian adipocytes. Both cells contain numerous lipid droplets, which are now appreciated to be dynamic organelles regulating lipid mobilization and storage (45). The protein composition of *Drosophila* lipid droplets shares significant homology with mammalian lipid droplet proteins (46). For example, PAT families of proteins are major components of membranes of both mammalian and *Drosophila* lipid droplets. *Drosophila* LSD2 is a homolog of mammalian perilipin, both of which are major components of lipid droplet membranes, and are thought to be key regulators of lipolysis. Flies mutant for the *lsd2* gene are lean, recapitulating the phenotypes observed in perilipin knockout mice (47–49). Interestingly, over-expression of *lsd2* in a fat body-specific manner results in obese phenotypes. Undoubtedly, other conserved lipid droplet proteins will be shown to assume similar roles across species. In some cases, the role in *Drosophila* will be implicated before a clear physiologic role has been assigned in mammals, perhaps acting as a stimulus for further investigation.

In *Drosophila*, the AKH hormone pathway and the lipid droplet-bound *brummer* (*bmm*) lipase are the two major lipolytic mechanisms. The role of the AKH pathway in carbohydrate homeostasis has already been discussed. The AKH receptor (AKHR) is expressed in the *Drosophila* fat body, consistent in its role in mediating energy homeostasis (50,51). Double mutants of the AKHR and *bmm* are markedly obese, yet lack the ability to mobilize their lipid stores upon starvation. Whereas starvation resistance in *Drosophila* is correlated with lipid content, mutation in both genes effectively renders these flies starvation sensitive. The existence of two lipolytic pathways in *Drosophila* parallels the existence of both hormone-sensitive and adipose triglyceride lipase pathways in mammals. The investigation of lipolytic mechanisms in *Drosophila* is ripe for investigation. Ironically, the intracellular signaling cascade mediating mobilization of triglycerides from lipid droplets has not been as fully elucidated in insects as it has in mammals (52). As more information is gleaned in the fly, clear links to mammalian physiology will undoubtedly be uncovered.

## THE HUNGRY FLY

*Drosophila* research has made important early contributions in connecting genes with behavior, and flies have a variety of feeding behaviors that have been described (53,54). Studies in each stage of the *Drosophila* life cycle can increase our understanding of molecular mechanisms that can affect food intake, food preferences, and satiety. Larvae feed continually to acquire enough energy stores for undergoing pupation and metamorphosis. In contrast, adult flies feed intermittently to maintain energy homeostasis. Thus, each stage of the life cycle offers a unique milieu in which to conduct metabolic studies. The ability to define and analyze feeding in *Drosophila* allows researchers to design forward genetic screens with discreet behavioral endpoints.

Studies in the larval stage have shed light on the genetics of food-intake and signals that mediate the cessation of feeding. *Drosophila* larvae can be characterized as "sitters," localizing closer to a food source, or "rovers," meandering further from a food source. The dichotomy in behavior can be attributed to the variation of the single gene *foraging* (*for*), which encodes a cGMP-dependent protein kinase. Higher levels of kinase activity lead to a rover phenotype; in fact, sitters can be converted to rovers by transgenic expression of *for*. Variations in *for* also account for differences in feeding behaviors in the adult stage, indicating that the effect of certain genes can persist throughout the entire life cycle. Of note, the human homolog of *for*, c-GMP-dependent protein kinase 1 (*cGK1*), has been may play a role in energy homeostasis, with altered expression patterns have been associated with obesity and diabetes (55).

As mentioned earlier, the transparent larval body wall allows for the design of facile screens for genes that regulate food intake. An elegant example can be found in a screen employing dye-labeled yeast paste to monitor ingestion dynamics of whole intact larvae (56). The screen uncovered mutants that had decreased feeding with impaired passage of food from the hindgut to midgut despite having normal anatomy. The screen identified the fat body-specific gene *pumpless* (*ppl*), which encodes a protein homologous to those found in vertebrate glycine cleavage systems. *Ppl* mutants accumulate food in the pharynx, with decreased overall growth. Indeed, feeding larvae large amounts of amino acids also suppressed growth and, under certain conditions, can recapitulate *ppl* mutant phenotypes. Any potential interaction of *ppl* with the insulin-signaling pathway remains to be determined. Thus, work in *Drosophila* can provide a rich template for the study of general mechanisms that link nutrient-dependent signaling with feeding behavior.

## ENERGY HOMEOSTASIS AND THE FLY BRAIN

The brain profoundly affects feeding behavior and satiety in humans; similarly, recent work points toward a rich regulation of energy homeostasis in the fly by neuronal feeding circuits (11). Although containing only approximately 100,000 neurons, the investigation of the fly brain has provided a myriad of insights into neurobiology; for example, studies in the *Drosophila* brain have provided a wealth of information for understanding neuronal development and connectivity. It is now apparent that the *Drosophila* brain contains regions that are highly specialized for

specific functions, such as for processing chemosensory information (57). The study of the neuronal circuitry of feeding behavior is a nascent field that has the potential to uncover remarkable parallels between the human and fly.

Circulating neuropeptides can have a profound effect on energy homeostasis in mammals, and the same holds true for flies. Remarkably, many of the same families of peptides are used in both to affect energy homeostasis and feeding behavior. For example, homologues of neuropeptide Y (NPY) and neuromedin U modulate feeding behavior in the fly, reminiscent of their roles in mammals. Of note, not all peptides are conserved across species. For example, leptin, a major determinant of energy homeostasis in humans, has no clear homolog in the fly. Nonetheless, a better understanding of *Drosophila* neuropeptides that regulate energy homeostasis has the potential to uncover conserved mechanisms of intracellular neuronal signaling, neuronal-neuronal communication, and neuronal-peripheral tissue communication that are critical for maintaining and distributing energy stores.

The *Drosophila* NPY homologue short neuropeptide F has recently been shown to play a role in modulating the secretion of dILPs (58,59). Insulin-producing pancreatic islets are also response to NPY in mammals. In contrast to the localization of human insulin-secreting cells in peripheral pancreatic tissue, dILPs are secreted by small-paired clusters of neurons in the *Drosophila* brain. Interestingly, the development of dILP-secreting neurons has been shown to involve pathways homologous to those involved in the formation of the mammalian hypothalamic axis (60). Taken together, recent studies in *Drosophila* suggest the intriguing possibility that insulin-producing pancreatic islets may have a hypothalamic origin. The neuropeptide F and dILP systems have also been shown to play a role in feeding behavior in *Drosophila* larvae, consistent with their role in appetitive behavior and metabolic regulation in humans. The *Drosophila* neuropeptide hugin is thought to be a homolog of human neuromedin U, and it also has been implicated in regulation of feeding behavior (61). Hugin-expressing neurons are situated to integrate gustatory information to higher brain centers and may serve as critical interneurons in the *Drosophila* feeding circuit.

## A MODEL FOR INBORN ERRORS OF METABOLISM

In addition to the power of forward genetic screens, which hold the potential for unexpected, paradigm-shifting findings, the study of *Drosophila* homologs of genes that cause human disease is an important, complementary approach. If there is a human disease caused by a specific genetic defect, what are the chances that a homolog exists in *Drosophila*? The answer to this question is approximately 70%; that is to say, the vast majority of disease-causing genes in humans have a *Drosophila* version (4). Do mutations in human and *Drosophila* genes cause similar phenotypes? In other words, do parallels exist beyond molecular mechanisms of action to conserved sequelae at the level of the whole organism? As many *Drosophila* homologs of disease-causing genes have not been extensively studied, particularly with respect to metabolic disease, the area remains ground for fertile investigation (62).

The study of *Drosophila* homologs of enzymes that cause human metabolic disease is an avenue of research that can yield insight into disorders of both lipid and carbohydrate homeostasis. There is no guarantee that the phenotypes in *Drosophila* will resemble human phenotypes; nonetheless, there is a high probability that the molecular mechanisms are conserved, yielding insights into protein-protein interactions and intracellular signaling. A variety of enzymes are conserved between flies and humans that are important for both lipid and carbohydrate homeostasis. As an example, flies mutant for *bgm*, the *Drosophila* homolog of the very long fatty acid CoA synthetase that causes adrenoleukodystophy, have phenotypes that include neurodegeneration and abnormal fatty acid metabolism (63). Remarkably, administration of Lorenzo's Oil, used to treat human adrenoleukodystophy, also ameliorates the phenotypes observed in the fly.

Glycogen storage diseases are caused by a variety of mutations in enzymes important for the synthesis and breakdown of glycogen. Although the main circulating carbohydrate in *Drosophila* is trehalose (a dimer of sucrose), many of the same enzymes regulate the conversion of trehelose to *Drosophila* glycogen (64,65). Thus, studies in *Drosophila* can form a rich template for a better understanding of mechanisms of glycogen storage and breakdown. In summary, *Drosophila* offers the potential for mechanistic investigation of a variety of genes causing metabolic disease, including key enzymatic regulators of carbohydrate and lipid metabolism.

## THE PEDIATRICIAN AND THE DROSOPHILIST

As pediatricians, we are often the first to diagnose and manage patients with genetic mutations. As highlighted above, the vast majority of genes that cause human disease have a *Drosophila* homolog. Thus, it is particularly imperative for the pediatric researcher to appreciate that there is a likely *Drosophila* version of any gene that may be under investigation. Befriending a colleague with a fly laboratory may be the first step in establishing a productive collaboration. The fly worker is often a bench scientist, with limited exposure to the clinical arena. Thus, a mutually beneficial, complementary relationship can often be established. Interestingly, there is a growing (but still small) contingent of pediatricians doing fly research, who are in a position to synthesize both clinical and basic sciences into their research programs.

## KEY POINTS

In summary, the three most important reasons that make the fly important to metabolic research are 1) the conservation of many major metabolic pathways and potential for conserved phenotypes that result upon their manipulation; 2) the unprecedented ability to perform forward genetic screens with metabolic and behavioral endpoints; and 3) the short life cycle offers both relative speed and cost-effectiveness in obtaining data with cross-species significance.

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