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Drosophila melanogaster as a Powerful Model for Decoding the Molecular Basis of Animal Disease

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ABSTRACT

Animal models have long served as indispensable systems for exploring how human diseases arise and progress. These organisms span a wide biological range—from Caenorhabditis elegans to non-human primates—and have enabled discoveries that would otherwise remain unattainable. Their usefulness is typically linked to the degree of genetic and physiological similarity they share with humans, making it possible to generalize many research findings. Yet such translational assumptions are not always accurate. Among current model organisms, Drosophila melanogaster has gained significant traction for dissecting the biochemical foundations of numerous human disorders. Its short life cycle, high reproductive rate, simple genome with reduced genetic redundancy compared with vertebrate systems, and the extensive availability of genetic manipulation tools have collectively strengthened its reputation as a powerful disease model. This review outlines the contributions of various animal models to biomedical investigations, with particular emphasis on the fruit fly's role in elucidating biochemical mechanisms underlying persistent human diseases.

Keywords: Biochemical, Homology, Drosophila melanogaster, Disease models, Pathogenesis

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Introduction

A disease may be defined as any state or process that impairs the body, affects normal biological function, and compromises overall health and well-being [1]. It can also be interpreted as a deviation from the expected biomedical condition or from typical human capability [2]. Diseases often arise when the structural or functional integrity of the organism is disturbed, usually because the body's adaptive systems fail to neutralize external stressors or stimuli Ref. [3]. Each disease type exhibits its own set of symptoms, signs, and outcomes. Modern studies investigating disease development have shown that abnormal mechanotransduction and altered mechanical or structural cellular properties contribute significantly to many disorders. Such disturbances interfere with the mechanisms through which cells detect mechanical cues and convert them into biochemical activities, ultimately resulting in compromised physiological function [1].

The use of animals in scientific investigation dates back centuries, with notable early examples including William Harvey's work on blood circulation in the 1600s. Researchers such as Emil von Behring and Louis Pasteur also relied on animal experimentation to support major scientific advances [4]. Although cell culture and tissue-based methodologies provide useful alternatives for examining disease processes and identifying potential treatments, they cannot fully replicate the intricate physiological dynamics and cell-to-cell interactions present in whole organisms [4].

Experimental animal models have substantially advanced our understanding of disease pathways and have been widely used to evaluate new engineered, pharmaceutical, and herbal therapies for disorders ranging from rheumatoid arthritis to multiple sclerosis. Nevertheless, despite encouraging findings in these systems, over 80 % of candidate drugs identified through animal testing do not succeed in human clinical trials [5].

Animal models in biomedical research

Animal models—typically employed in comparative medicine—have been instrumental in clarifying normal biological function as well as pathological processes [6]. They can generally be placed into two broad groups: spontaneous and induced models. Spontaneous models involve animals that naturally display traits mirroring human conditions or atypical individuals with mutation-driven phenotypes. Induced models, in contrast, are created through chemical, surgical, genetic, or related manipulations that modify their native physiology [7].

Mammals such as mice, rats, rabbits, and guinea pigs have traditionally dominated disease modelling due to the substantial genomic overlap between humans and these species [8]. Roughly 95 % of the approximately 30,000 genes found in mice, rats, and humans are homologous [9]. However, increasing attention to animal welfare and the push for reduced reliance on mammalian subjects have accelerated the adoption of alternative model organisms [10]. Consequently, species positioned lower on the evolutionary scale—including C. elegans, D. melanogaster, Danio rerio (zebrafish), and Xenopus laevis—are now widely deployed for studying human disorders. Larger animals such as pigs, dogs, sheep, and non-human primates remain valuable for translational applications, particularly in studies focused on cardiovascular, metabolic, rare genetic, and neurodegenerative diseases (ND) [11].

Choosing an appropriate model is essential for accurately reproducing specific disease features. Disease models help identify genetic causes, clarify phenotype–genotype relationships, and provide platforms for testing prophylactic, therapeutic, and surgical interventions [12, 13]. Each model system offers its own distinct advantages, meaning that selection depends on both the disease characteristics and the primary research question. In many scenarios, employing multiple complementary models yields a more complete understanding of the disorder under investigation [14].

The subsequent section of this review discusses several widely used animal models in biomedical science.

Mouse

The mouse remains the most widely utilized organism for exploring human pathologies. Early on, they were not viewed as ideal representatives because outcomes from mouse-based preclinical studies did not always translate into human therapies [15, 16]. A major reason they later overtook rats in preference was the emergence of powerful genetic-engineering methods specific to mice, particularly following the first published knockout mouse in 1987 [17].

Researchers also favour mice because their small body size, rapid breeding cycle, and straightforward maintenance reduce both cost and logistical burden. In studying human disorders linked to oxidative damage—such as aging, inflammation, or neurodegenerative processes—it is notable that mice generate reactive oxygen species more easily than people [18]. Still, extrapolating mouse data has limitations, stemming from differences in cardiac mechanical and electrical behaviour as well as in the composition of contractile and electrophysiological proteins. Two additional challenges are their very small organs, which complicate surgical work, and their fast heart and metabolic rates [19].

Rat

During the last three decades of the 20th century, rats were regarded as indispensable experimental models. Their dominance decreased when transgenic and gene-targeting approaches became routine in mice [20]. Like mice, they provide economical disease models due to rapid maturation, short life expectancy, modest housing needs, and small size [9]. Nevertheless, rats remain preferred in certain research areas. For instance, in mammary cancer studies, human and rat breast tumours share developmental patterns and histopathological features; rat mammary neoplasms also show strong hormone dependence for initiation and progression, paralleling human breast malignancies [21].

Rats are roughly ten times larger than mice, which implies greater space and compound requirements. However, this same size advantage improves the feasibility of surgeries such as catheter placements needed in addiction research [22], and they are better suited for serial sampling and longitudinal experiments. Their larger anatomy also allows more precise thoracic interventions—for example, induction of myocardial infarction or assessment of cardiovascular measurements (e.g., blood pressure) via implanted aortic telemetry devices, whose lumen accommodates a sensor while maintaining blood flow [20]. This makes rats superior to mice for various cardiovascular investigations [23, 24].

Recently, rat models have gained renewed relevance in neurodegenerative disease research due to ease of handling and reduced intraspecies aggression [17, 25]. Numerous rat strains now carry or overexpress human genes implicated in disorders such as Alzheimer's (AD), Huntington's (HD), and Parkinson's (PD). Examples include McGill-R-Thy1-APP and TgF344-AD for AD, PINK1 and DJ-1 knockout strains for PD, and tgHD and BACHD for HD [26]. Many behavioural paradigms currently used in rodents were first established in rats, which generally outperform other species in cognitive tasks such as the Morris water maze or decision-making assays due to their faster learning ability [27, 28]. Evidence also suggests that rats exhibit metacognition similar to primates, a feature relevant when modelling impaired self-monitoring in AD and related dementias [29]. Their comparatively larger brains also enhance spatial resolution in neuroanatomical and neurobiological imaging, giving rats an advantage over mice in such studies [23].

Pig

The pig ranks among the most widely raised domestic animals. Compared with other livestock or primates, pigs show rapid growth, short generational turnover, large litters, and compatibility with standard breeding strategies. These traits—combined with close resemblance to humans in genome organization, dietary patterns, anatomical and physiological systems, and overall body proportions—have supported their increasing use as models of human disease [5].

Rodent species, by contrast, differ markedly from humans in cytochrome P450 enzyme families, especially in substrate specificity and the number of P450 subgroups. As a result, they are less suitable for studies involving hepatic first-pass drug metabolism. Pigs, however, show far closer alignment with human P450-mediated drug processing, making them more predictive for pharmacological testing [30].

Pig models have significantly advanced understanding and treatment of multiple human conditions, including metabolic diseases (such as type 2 diabetes, hypertriglyceridemia, and non-alcoholic fatty liver disease), neurological disorders (e.g., AD, PD, and HD), cardiovascular problems (e.g., atherosclerosis and myocardial infarction), and genetic conditions (e.g., cystic fibrosis, breast malignancies, and Duchenne muscular dystrophy) [5]. Numerous medical procedures routinely used in humans—catheterizations, cardiac operations, valve interventions, endoscopies, and broncho-alveolar lavage—can be replicated in pigs when the appropriate breed and age are selected, whereas such interventions are often extremely difficult or unachievable in most other experimental animals [31].

Comparative genomic analyses of humans, pigs, and mice demonstrate that pigs share higher sequence similarity with humans and possess more ultra-conserved regions than mice do [32]. Overall, pigs exhibit greater genetic homology to humans than rodents, supporting their suitability for modelling immune-related diseases, including various forms of cancer [32].

Rabbit

Research on the European rabbit Oryctolagus cuniculus has played a major role in the creation and assessment of humanized polyclonal and monoclonal antibody therapeutics, and has clarified essential aspects of antibody architecture and diversification pathways [33]. Because rabbits are highly susceptible to infection and share pathogenic processes with humans, they have long served as important models for studying human infectious diseases [34]. For instance, intradermal exposure to Treponema pallidum or intrathecal delivery of Mycobacterium tuberculosis (MTB) or Mycobacterium bovis (MBO) in rabbits leads to manifestations resembling syphilis and tuberculosis, respectively [35–37]. Furthermore, rabbit models—both transgenic lines of monogenic cardiac disorders and spontaneous hypercholesterolemia—have contributed to insights into atherogenesis, lipoprotein dynamics, and the development of medications such as statins [38, 39].

Although rabbits were prominent in molecular immunology during the late 1980s, they were progressively replaced by rodents. Lower upkeep expenses, small body size, availability of many inbred strains, straightforward breeding, short gestation periods, large litters, an abundance of commercial immunological reagents, and access to numerous knockout (KO) and transgenic systems are major factors that have favoured mice over rabbits [40, 41]. Still, mouse models are not universally suitable, as their small physique and evolutionary distance from humans can prevent certain mutations from producing comparable disease outcomes [42]. By contrast, the domestic rabbit—due to its mid-sized anatomy and closer evolutionary relationship to primates—has regained scientific attention, especially in cardiovascular studies. Their cardiac electrophysiology, mechanics, and

structural characteristics align more closely with human heart features than those of rodents, making rabbits particularly appropriate for cardiac research [39].

Zebrafish

Approximately 70 % of human genes have orthologues in the zebrafish (Danio rerio), and extensive genome similarity between the two species has been documented [43]. This genetic correspondence, combined with favourable laboratory attributes, has made zebrafish an important tool for analysing human disease genes [13]. They have been employed in investigations of epilepsy, osteoporosis, amyotrophic lateral sclerosis (ALS), inflammatory conditions, atherosclerosis, autism spectrum disorder, heart failure, type 2 diabetes mellitus, sensorineural hearing deficits, disorders of the enteric nervous system, and various cancers [44].

Compared with mice, zebrafish are less costly and allow rapid generation of transgenic lines. Their popularity stems from their low maintenance needs, high reproductive output, short life cycle, external embryonic development, transparent early stages, and ease of genetic modification. These features provide a vertebrate system well-suited for live imaging of biological processes, as well as for genetic screening and pharmacological assessment [44].

Use of fluorescent proteins in transparent zebrafish offers real-time visualization of specific cells. With these technologies, scientists can monitor cell behaviour and obtain detailed spatiotemporal patterns of gene expression. Consequently, zebrafish are highly suitable for observing transgenic tumours from initiation through metastasis and transplantation [45]. Despite their advantages, differences in brain organization, cardiac complexity, and respiratory and reproductive biology create challenges for modelling human diseases directly. Therefore, caution is required when drawing disease parallels between zebrafish and humans [46–48].

Round worm

Caenorhabditis elegans (round worm) is a nematode valued as a model organism because it grows with minimal nutrient requirements, produces many offspring rapidly through self-fertilization (since individuals are primarily hermaphroditic), and is easy to maintain. C. elegans became a landmark species in biology as the first multicellular organism to have its genome completely sequenced [49]. Mapping its entire cell lineage—work that revealed how apoptotic regulation is influenced by stochastic factors—provided insights later confirmed in mammalian systems [50]. Lineage studies continue to illuminate physiology, pathology, and mechanisms underlying cell-fate decisions [51].

Its importance is highlighted by several Nobel Prizes awarded for research conducted using C. elegans [52]. Even though roughly 65 % of human disease-associated genes have worm homologs, their transparency throughout life allows direct observation of numerous biological processes [52, 53]. The clarity of the organism also enables the use of green fluorescent protein (GFP) markers for imaging defined cells, neurons, and synapses in vivo [54]. The worm's compact nervous system—around 302 neurons with fully mapped connectivity [53]—supports rapid identification of genetic modifiers and therapeutic agents that counteract neurodegeneration, some of which have shown effectiveness in mammalian models [55, 56]. Introducing human gene variants into C. elegans permits detailed analysis of their cellular roles and potential functions in human biology [57]. A key example is the worm expression of presenilin-1, associated with early-onset Alzheimer's disease, which aided in clarifying cellular mechanisms linked to Notch signalling [58].

It is likely that the identification of a "longevity gene" in C. elegans, revealing that aging can have a genetic basis, significantly elevated its status as a premier aging research model. The recognition that the daf-23, daf-2, and daf-16 genes influence lifespan in C. elegans, along with the fact that their mammalian counterparts participate in the insulin/insulin-like growth factor signalling pathway, further strengthened the worm's importance in aging biology [59, 60].

Despite its advantages, C. elegans lacks several physiologically relevant systems found in humans, including an adaptive immune system, a circulatory system, a blood–brain barrier, and DNA methylation machinery. Additionally, telomere length in worms does not correlate with aging as it does in humans. These features represent some of the constraints associated with using C. elegans to model human disease processes [61–63].

Fruit fly

Drosophila melanogaster (fruit fly) is an arthropod belonging to the Drosophilidae family within the order of two-winged insects. It is among the most extensively studied eukaryotic organisms and has driven major advances in

numerous areas of biological science. Drosophila has become increasingly valuable as a model for human disorders [64], including neurodegenerative, cardiovascular, inflammatory, infectious, and metabolic diseases [65]. Comparative genomic studies indicate that approximately 75 % of human disease-associated genes have functional counterparts in Drosophila [12], enabling significant progress in understanding diverse aspects of human pathology [66]. Although commonly observed around orchards and vineyards, the fly feeds primarily on yeast that grows on fruit surfaces rather than on the fruit itself [67].

The fruit fly has served as a biological model for over a century, contributing extensively to genetics and related disciplines [65]. Over this period, Drosophila research has generated landmark findings that shaped modern biomedical science. A pivotal discovery by Thomas Hunt Morgan demonstrated that genes reside on chromosomes, forming the basis of contemporary genetics [66]. He greatly expanded on Mendel's early inheritance concepts, well before DNA was recognized as the genetic material, and received the 1933 Nobel Prize in Physiology or Medicine for elucidating the role of chromosomes in heredity. His student Hermann Muller later earned the 1946 Nobel Prize for demonstrating—via Drosophila studies in the 1920s—that X-rays can break chromosomes and markedly increase mutation rates [68]. It was subsequently determined that the D. melanogaster genome contains roughly 14,000 genes across four chromosomes, making it less complex than that of humans and many other model organisms [10]. Overall, eight Nobel Prizes have been awarded for research involving Drosophila [69].

Fruit flies exhibit extremely high reproductive capacity; females can deposit up to 100 eggs daily for as long as 20 days. Their life cycle is also short: development from egg to adult requires about 10 days at 25 °C [70]. The four-stage life cycle begins with the egg, which remains viable for roughly a day. A larva then emerges and feeds continuously for approximately five days. Pupation follows for about four days, culminating in the emergence of an adult fly [71]. During pupal development, most tissues characteristic of the embryo and larva are removed [72]. Adult structures—such as wings, legs, and eyes—derive from imaginal discs established during early embryogenesis. Similar to humans, most adult tissues in Drosophila have minimal regenerative capacity [68, 73]. Adult fruit flies contain complex organ systems, including homologues of mammalian lungs, heart, gut, kidneys, and reproductive structures [65].

Their low cost, high offspring production, short generation times, and ease of genetic manipulation make Drosophila exceptionally useful in research environments [74]. The species has been central to elucidating mechanisms underlying numerous human conditions—ranging from rare Mendelian disorders to neurodegeneration and cancer—and to discoveries related to fundamental biological functions such as development, neural formation and activity, and behaviour [12, 75]. The fly has also permitted high-resolution investigation of gene regulation at speeds not achievable in most other animal systems [66].

D. melanogaster is currently employed in toxicology for mechanistic studies of key environmental pollutants and toxic substances, as its use meets existing regulatory requirements [76]. Because of its rapid life cycle, the species is suitable for toxicological experiments spanning development through maturity [12]. Ultimately, the model's versatility and well-characterized genome have supported large-scale pharmacological research aimed at identifying new therapeutic agents and clarifying the interactions between chemicals and genetic pathways [77].

Drosophila melanogaster as an excellent disease model

The genetic parallels between Drosophila melanogaster and humans highlight its value as a system for exploring disease mechanisms and fundamental biology. Approximately 60 % of homologous nucleotide or protein sequences are shared between fruit flies and mammals [78], and the similarity within conserved functional domains can reach 80–90 % [78]. Supporting its versatility, the fly can effectively serve as several model organisms in one, with each developmental stage offering specific advantages. The embryo is widely applied to foundational developmental studies involving patterning, lineage specification, and neuronal formation. The larval phase—particularly the third-instar period—is commonly employed to investigate physiological and developmental mechanisms [79].

The fly's high degree of genetic manipulability further strengthens its reputation as a model for analyzing gene roles in pathways tied to both biomedical and economic relevance. A central strategy enabling targeted genetic alterations is the GAL4/UAS expression system. GAL4, an 881-amino-acid transcription factor from Saccharomyces cerevisiae that regulates galactose-responsive genes [80], acts through an upstream activating sequence (UAS) located in the promoters of responsive genes. Although GAL4 has no known natural targets within flies, it robustly drives transcription of Drosophila transgenes containing UAS sites. These transgenes are

introduced through genetic crosses between UAS-responsive lines and Enhancer-GAL4 drivers, producing offspring in which specific genes are activated [81]. This approach has been broadly adopted for dissecting gene functions and creating tailored disease models [82].

Drosophila disease models

D. melanogaster has been employed in many experimental contexts beyond classical genetics. Its disease models include the following categories.

Immune system–related diseases

As with other insects, D. melanogaster relies solely on innate immunity, avoiding the variability associated with adaptive immune processes [83]. In this species, three principal pathways govern humoral immune-gene activation following infection: the Toll, immune deficiency (imd), and JAK/STAT pathways. The Toll and imd routes regulate most immune-associated genes, whereas JAK/STAT controls transcription of thioester-containing protein genes and Turandot genes—both contributing to antimicrobial defense [83, 84].

Insights from Drosophila research also facilitated the discovery of mammalian toll-like receptor signaling, a contribution recognized with the 2011 Nobel Prize in Physiology or Medicine, awarded to Jules Hoffmann [85, 86]. A hallmark of fly humoral immunity is the production of antimicrobial peptides (AMPs) by the fat body, which are secreted into the hemolymph [87]. The cellular arm of innate immunity is carried out by circulating hemocytes, which differentiate into plasmatocytes, crystal cells, and lamellocytes depending on their structural characteristics and immune roles [88].

The fruit fly has supported numerous influential studies on host–pathogen interactions involving a wide range of agents, including HIV, Zika virus, SARS-CoV, Epstein–Barr virus, Vibrio cholerae, Pseudomonas aeruginosa, and Salmonella enterica [89]. It has also been central to research exploring the possibility of innate immune memory, owing to its conserved disease-related gene homologs and shared regulatory mechanisms, including transcription factors, signaling networks, and immune cascades found in vertebrates [90, 91].

Earlier work showed that pre-exposing flies to Streptococcus pneumoniae with a non-lethal dose—or with heat-inactivated bacteria—enhanced survival during later lethal challenges. This Toll-dependent, phagocyte-mediated protection persisted throughout the fly's lifespan, suggesting that innate immunity, like adaptive immunity, can exhibit memory [92]. However, other investigations returned conflicting evidence: heat-killed Salmonella typhimurium, Mycobacterium marinum, or Listeria monocytogenes failed to confer protection against subsequent infections, whether against the same species or S. pneumoniae [92].

Work in Drosophila first demonstrated that lethal factor (LF) and edema factor (EF)—the two major virulence proteins of Bacillus anthracis—act cooperatively, such that removing either component markedly diminishes pathogenicity [89, 93]. Additional foundational fly-based investigations showed that LF and EF trigger their harmful effects through both the Notch and MAPK signaling systems [94, 95].

Using the fly model, Hleihel and coworkers identified a previously unknown post-translational regulation capable of reshaping the activity of Tax1, the Human T Cell Lymphotropic Virus type 1 (HTLV-1) transactivator. HTLV-1 is an oncogenic infectious agent associated with adult T cell lymphoma (ATL), a disease with limited survival prospects. Their research established that elevated expression and covalent attachment of Urm1 (ubiquitin-related modifier 1) to Tax1 relocates the protein from the nucleus to the cytoplasm, where Tax1 stimulates the imd pathway downstream of NF-κB by engaging cytoplasmic pathway components [96].

The ability of Drosophila to uncover new pathogenic genes and mechanisms was emphasized by Chan *et al*. (2007). They showed that overexpressing the SARS-CoV-1 M protein in the fly eye induced a rough eye phenotype, linked to heightened apoptosis in the peripheral region of the developing eye disc. This cellular damage was reversed when Pdk1 (Phosphoinositide-dependent kinase 1) was overexpressed. Later experiments revealed that M promotes apoptosis by altering phosphorylation levels of Akt1, a central kinase in the PKB/AKT pathway and a known Pdk1 substrate. Their findings indicated that M enhances cell death by modulating the Pdk1–Akt1 node of the pathway. Notably, phosphorylation of Akt1 had already been recognized as a critical signaling step in the Toll pathway of Drosophila innate immunity, where it drives caspase-mediated apoptosis [97, 98].

Cardiovascular diseases

Cardiovascular disorders (CVDs) remain the foremost cause of mortality worldwide, affecting the structure or performance of the heart and vasculature. Many cardiac conditions manifest as channelopathies or

cardiomyopathies [99]. The fruit fly serves as a major system for studying human cardiac defects, age-related decline, and heart physiology because it expresses conserved master regulators of heart development and can be manipulated genetically with ease [100, 101]. Remarkably, it is one of the few invertebrates that possesses a functioning organ closely analogous to the vertebrate heart [102].

The transcription factor tinman (Tin)—an NK2 homeobox protein first characterized in flies—plays a central role in specifying cardiac cell lineages and responds to signals promoting cardiogenesis. The discovery of tinman paved the way for identifying its homolog, Nkx2-5, in urochordates, chordates, and humans, where it retains the same essential function [103, 104]. Given its short life cycle and well-studied aging profile, Drosophila has become especially useful for examining chronic, age-associated heart dysfunction [105].

Congenital heart defects (CHD) comprise a wide set of abnormalities in the heart or major vessels, occurring in roughly 0.8 % of newborns. Despite significant efforts, approximately 75 % of CHD-linked genes remain unidentified [106, 107]. Multiple tools have been developed to assess the fly heart, revealing strong parallels in cardiac morphology and function between flies and humans, and enabling rapid disease-gene testing at low cost [108, 109]. In one investigation, an RNAi-based screen covering 134 CHD-related genes found that more than 70 were essential for heart formation in the fly. A notable gene was WDR5: suppressing its Drosophila counterpart Wds caused complete developmental lethality, structural heart abnormalities in late larvae, reduced myofiber organization, and excessive pericardin buildup. Conversely, expressing wild-type human WDR5 rescued these defects [110]. Prior fly studies had also linked genes involved in H3K4 and H3K27 histone methylation to CHD [110].

The fly model has additionally clarified cardiac dysfunction that accompanies progressive degeneration in muscular dystrophy. Both Duchenne and Becker dystrophies are associated with cardiomyopathy, impairing effective pumping of blood [111]. Two isoforms of the Drosophila dystrophin gene—the gene responsible for the structural protein mutated in these disorders—are present in the adult myocardium, suggesting a conserved role in cardiac performance [102]. Proper calcium regulation is essential for contraction and relaxation, and levels of intra- and extracellular calcium are controlled by several genes, including RyR (ryanodine receptor) and SERCA (sarcoplasmic reticulum calcium ATPase) [112, 113]. Work in flies previously showed that reduced RyR expression leads to defective calcium dynamics, a result later confirmed in vertebrate systems [114]. Additionally, mutations in sarcolamban, a SERCA-associated protein in flies, caused abnormal rhythmic contractions owing to disrupted calcium handling. These studies support that multiple genes governing calcium cycling in cardiomyocytes are functionally conserved between flies and mammals [115].

Cancer

Extensive biochemical and genetic work on Drosophila melanogaster has greatly contributed to understanding human tumor biology [116]. Cancer-associated hyperproliferation can arise when the fly cell cycle bypasses its usual regulatory checkpoints. By generating fly models that mimic human tumors, researchers have identified numerous tumor-suppressor genes involved in controlling proliferation and differentiation [117]. Tumors formed in Drosophila display traits comparable to human cancers, including altered cellular architecture, avoidance of programmed cell death, autonomous growth signaling, invasive expansion, and metastatic behavior [117]. Many human disease-causing genes have functional equivalents in the fly—covering pathways tied to cell division, fate specification, migration, polarity, cell adhesion, and apoptosis—all of which are central to cancer progression [118, 119].

Because Drosophila contains less genetic redundancy than mammals, mutations in key pathways appear at lower frequencies, meaning fewer genetic alterations are required to generate a sensitized state suitable for drug testing. This, along with the availability of powerful genetic tools, enables the creation of complex fly tumor genotypes and phenotypes [120]. Consequently, Drosophila preserves the interaction between the host and the tumor in ways that conventional in vitro systems cannot replicate and often models the disease environment more realistically [116].

Despite anatomical differences between flies and humans, certain cancers can be modeled more effectively in Drosophila than in cell culture, even though mammalian in vivo systems remain indispensable for particular aspects of research [120]. High-throughput drug testing in genetically engineered fly cancer models—whether tailored to specific tumor mutations or to an individual patient's genotype—can screen FDA-approved anticancer and non-cancer drugs that meet defined genetic criteria [121].

Cell competition is a fundamental quality-control process in multicellular organisms in which fitter "winner" cells eliminate neighboring "losers." This mechanism supports tissue integrity by promoting the expansion of healthy cells and removing compromised ones. Importantly, the concept of cell competition was originally discovered in Drosophila, highlighting its influence on cancer biology [122]. Tissues naturally suppress the expansion of oncogenic cells—such as those lacking the polarity gene scribble (scrib)—through a process referred to as epithelial defense against cancer (EDAC) in mammals and tumor-suppressive cell competition in flies. When this protective system is disrupted, for example, through mutations in tumor suppressors or oncogenes combined with microenvironmental factors like inflammation, emerging tumors can overtake adjacent wild-type cells. This has led to the suggestion that manipulating cell competition could provide new avenues for cancer therapy [122, 123].
A recent investigation using Drosophila eye epithelium identified inositol-requiring enzyme-1 (Ire1), one of three ER stress/UPR sensors, as a crucial determinant in competitive interactions. The study found that either loss-of-function or hyperactive forms of Ire1 enhanced the removal of scrib clones by stimulating apoptosis and autophagy. Conversely, disturbance of Ire1 activity in neighboring wild-type cells helped scrib clones persist. These data suggest that with further in vivo mechanistic work, Ire1 may represent a promising therapeutic target [124].
Among all cancers, colorectal cancer (CRC) has the second-highest global mortality, with approximately 935,000 deaths in 2020. CRC arises from a sequence of events including oncogene activation, loss of tumor suppressors, and defects in DNA repair [125]. Flies possess a midgut and hindgut that functionally parallel the mammalian intestine and colon, allowing CRC-associated changes to be effectively modeled in Drosophila [126–128].
In work by Bangi *et al*. (2016), the potential of Drosophila for individualized cancer therapy was emphasized. Using the GAL4/UAS system to engineer flies with alterations in genes such as ras, p53, pten, and apc, the authors identified combination treatments for CRC involving BEZ235 (the first PI3K/mTOR inhibitor to reach clinical trials) with SC79 (an FDA-approved AKT activator), as well as bortezomib paired with BEZ235. Importantly, they observed that BEZ235 must be administered second for the combinations to be effective, demonstrating that administration sequence strongly influences therapeutic outcome [129]. These synergistic effects and underlying mechanisms were reproduced in Drosophila, mammalian systems, and engineered mouse CRC models [129].
Recent global estimates indicate that lung cancer caused roughly 1.8 million deaths in 2020, making it the most lethal cancer type [130]. Roughly 85 % of lung cancer cases fall under non-small cell lung carcinoma (NSCLC) [131]. Strong developmental parallels exist between the epithelial cells of the fly tracheal network and vertebrate lungs [132], and the branching morphology of the tracheal system resembles that of the mammalian respiratory tree [133]. Overactivation of epidermal growth factor receptor (EGFR) accounts for nearly 80 % of NSCLC cases [134], and the receptor's intracellular tyrosine kinase domain is structurally similar in flies and humans [90]. Fly models using ectopic EGFR expression led to the identification of tyrosine kinase inhibitors (TKIs) such as afatinib, ibrutinib, and gefitinib [135], which were effective at preventing lethality in whole-organism assays. Furthermore, screening of an FDA-approved compound library revealed that bazedoxifene combined with afatinib produced synergistic suppression of hypoxia-induced JAK/STAT activation, thereby reducing EGFR-mediated lethality [120].
Ewing sarcoma (EwS) is a malignancy of bone and soft tissue, typically driven by the Ewing's sarcoma breakpoint region 1–Friend leukemia virus integration 1 (EWS-FLI) fusion oncogene. Because the native EWS-FLI product is highly cytotoxic, generating an in vivo genetic model had long been challenging. This obstacle was overcome when a frame-shift version of the fusion, which preserves oncogenic activity while eliminating toxicity, was engineered in Drosophila. In addition, full-length unaltered EWS-FLI has been ectopically produced in flies, resulting in distinct phenotypes that vary according to the protein's expression level. These findings open new possibilities for dissecting transcriptional abnormalities driven by EWS-FLI [136].

Diabetes

Diabetes is a long-term metabolic disorder characterized chiefly by elevated circulating glucose due to impaired β-cell performance, defective insulin signaling, or both [137, 138]. In 2019, it ranked eighth among conditions contributing to combined mortality and disability. Despite initiatives aimed at reducing global diabetes prevalence by 2025, an analysis by the NCD Risk Factor Collaboration (NCD-RisC) in 2016 predicted less than 1 % probability of achieving this goal for women, with an even smaller likelihood for men [139, 140]. Diabetes also serves as a major precursor to ischemic heart disease and stroke, the first and second leading causes of global disease burden, respectively [140].

Advances in the understanding of Drosophila endocrinology, sugar regulation, and general metabolism have established the fly as a suitable organism for investigating human metabolic dysfunction and diabetes, particularly for therapeutic discovery [65]. The fly genome encodes seven insulin-like peptides (ILP1–7), all homologous to vertebrate insulin and synthesized by insulin-producing cells in the brain. Among these, ILP2 most closely resembles vertebrate insulin. Multiple fly models have been used to explore mechanisms underlying type 1 and type 2 diabetes, supported by the evolutionary conservation of insulin signaling [141].

Additional features that make Drosophila advantageous for dissecting the insulin pathway include reduced genomic redundancy relative to vertebrates and access to highly refined genetic-modification tools unavailable in many other model systems [142]. Suppressing or removing ILP expression produces phenotypes analogous to type 1 diabetes, whereas type 2 diabetes-like states can be induced through diet-based protocols or via genetic lesions affecting downstream insulin-signaling components [143–145].

Lagunas-Rangel and co-workers demonstrated the utility of flies for early-stage drug screening by assessing Diprotin A, a dipeptidyl peptidase-4 (DPP4) inhibitor that is not an approved medication. DPP4 inhibitors act indirectly—they prevent degradation of several substrates, including incretins, glucose-dependent insulinotropic polypeptide (GIP), neuropeptides, and pituitary adenylate cyclase–activating polypeptide (PACAP) [146]. When Diprotin A was tested in Drosophila, it lowered hemolymph glucose levels without altering total protein or triglyceride content. This result underscores the fly's potential for identifying compounds with DPP4-blocking activity and, more broadly, for preliminary screening of agents with therapeutic promise [147].

In another application, Drosophila facilitated the identification of type 2 diabetes risk genes involved specifically in insulin secretion. Screening fourteen candidates revealed three—BCL11A, SIX3, and PRC1—as regulators of β-cell function in humans. Subsequent work showed that reducing BCL11A expression in primary human islets enhances insulin release, and transcriptomic analyses indicated that BCL11A influences multiple genes tied to insulin secretion [148].

Capa peptides and their receptor, CapaR, which are mainly active in adult flies, participate in signaling within renal tubules, cardiac tissue, and hyperneural muscles, and contribute to both diuretic and myotropic functions. The Drosophila Capa locus encodes a preprohormone processed into four peptides. These peptides share functional and evolutionary parallels with vertebrate Neuromedin U (NmU) signaling [149, 150]. In mammals, NmU affects insulin output, feeding behavior, metabolic balance, and gastric acid production. Studies using the fly Capa/CapaR system showed that well-fed CapaR-null animals developed strong hyperglycemia accompanied by elevated AKH (the glucagon equivalent), implying that Capa peptides influence metabolic balance via AKH modulation. Considering the conserved relationship between fly Capa and vertebrate NmU—and the emerging view of NmU as an endocrine regulator of energy homeostasis—these findings may help clarify mechanisms underlying human metabolic conditions, including diabetes and obesity [151].

Neurodegenerative diseases

Neurodegenerative conditions represent the leading cause of global cognitive and motor impairment, affecting roughly 15 % of the population [152]. Their prevalence has risen sharply over the last thirty years, and projections indicate that the number of individuals living with long-term neurodegenerative disorders will at least double within the coming two decades [153].

Drosophila exhibits several core physiological, biochemical, biological, and neural traits that parallel those of mammals, making it a practical model for biomedical investigations into neurodegenerative disorders (NDs) such as Alzheimer's disease (AD) and Parkinson's disease, both of which are increasingly prevalent in aging populations [65]. Its compact brain contains neurons and glial cells that fulfill roles comparable to those in vertebrates, supporting its extensive use in ND-related studies [154].

A number of theories have been proposed to explain the origin of AD. A leading concept involves aggregation of amyloid-beta 42 (Aβ42), produced when amyloid precursor protein (APP or APP-like in Drosophila) is sequentially processed by β-site APP cleaving enzyme-1 (BACE1) and γ-secretase rather than α-secretase [141]. Another central idea focuses on intracellular buildup of hyperphosphorylated Tau, likely driven by amyloid-related changes. Additional interconnected mechanisms include vascular impairment, glial inflammation, metal imbalance, oxidative injury, disruptions in cholinergic and mitochondrial function, and altered calcium regulation [155].

Models of AD in Drosophila can be developed through various approaches, including modification of orthologous human disease genes, introduction of human pathogenic alleles via transgenic constructs, or environmental factors influencing Aβ toxicity [156, 157].

AD-like traits in flies can be produced by inducing amyloid plaque formation and expressing Drosophila amyloid β1-42 using genetic tools such as the GAL4/UAS system [158]. Even though flies lack endogenous Aβ-equivalent peptides, expression of human Aβ results in plaque accumulation, shortened lifespan, learning impairment, and neuronal degeneration—hallmarks consistent with human AD [154]. Neurofibrillary tangle-like features can likewise be generated using the GAL4/UAS method to introduce the R406W mutation in human tau, a tauopathy-associated variant, into flies [65, 159].

Fly AD models have provided insights into the influence of metals on Aβ-related degeneration. Diets enriched with copper or zinc reduced survival and exacerbated motor defects in Aβ42-expressing flies, while metal-chelating diets mitigated these effects [160]. Further genetic manipulation of metal regulation networks reinforced the critical role of zinc and copper in Aβ42-driven toxicity [161, 162].

Multiple experimental studies indicate that excessive activation of poly(ADP-ribose) polymerase-1 (PARP-1) contributes to AD pathology [163, 164]. Maggiore *et al*. (2022) employed Drosophila to clarify the molecular involvement of PARP-1, showing that AD transgenic flies displayed improved climbing performance and increased survival when PARP-1 activity was reduced either pharmacologically or through genetic suppression. Their findings also showed that PARP-1 inhibition decreased Aβ oligomer accumulation and altered chromatin structure and activity, preventing transposable element activation associated with AD [165].

Another major ND in which Drosophila has been instrumental is Parkinson's disease (PD). PD is a highly variable disorder attributed to multiple genetic and molecular pathways leading to neuronal loss. It is defined by degeneration of dopaminergic (DA) neurons in the substantia nigra pars compacta and by intraneuronal inclusions known as Lewy bodies, which contain α-synuclein (α-Syn) among other components. Because Drosophila does not possess an endogenous α-synuclein gene—one linked to familial PD [166]—human α-synuclein has been introduced via the GAL4/UAS system, resulting in neurodegeneration, protein inclusions, and movement deficits typical of α-synuclein toxicity [167]. Tyrosine hydroxylase staining was used to visualize DA neuron loss in brain tissue, and climbing assays were employed to assess motor performance. Reported outcomes included male sterility, reduced viability, and defects in both flight and climbing behavior [65, 159].

Evidence shows that the ubiquitin/proteasome system (UPS) is impaired in NDs, leading to the buildup of ubiquitinated substrates [168]. The SCF (Skp1/Cullin1/F-box) E3 ligase complex confers substrate selectivity within the UPS. Previous observations indicate that S-phase kinase-associated protein 1 (Skp1) is under-expressed in sporadic PD. Reducing SkpA—the fly homolog of Skp1—in adult neuronal tissue increased protein aggregation and loss of dopaminergic cells, while SkpA overexpression reduced aggregates in α-synuclein-induced PD models and improved survival in wild-type flies. SkpA was also shown to interact with the F-box protein nutcracker (Nut) and other unidentified F-box proteins. These results highlight a protective function for SkpA and suggest its potential value in ND diagnostics and therapy [169].

Spinocerebellar ataxia type 3 (SCA3), or Machado-Joseph disease, is an autosomal dominant disorder caused by expanded CAG trinucleotide repeats that lengthen the polyglutamine (polyQ) tract of ataxin-3. The same pathogenic mechanism underlies several polyQ diseases, including Huntington's disease (HD), spinal and bulbar muscular atrophy (SBMA), dentatorubral-pallidoluysian atrophy (DRPLA), and other spinocerebellar ataxias. In HD, the severity of neurodegeneration correlates with polyQ repeat length [170]. Drosophila models for these disorders date back to 1998, when the first transgenic SCA3 fly was generated, reproducing key features of the condition and establishing the fly as a valuable model for studying mechanisms of neuronal dysfunction and death in SCA3 [159].

In HD, the Huntingtin (Htt) protein contains a polyglutamine region expanded to 36 or more residues due to a trinucleotide repeat mutation [157]. This neurodegenerative disorder follows an autosomal dominant inheritance pattern and manifests clinically with progressively worsening choreiform movements, cognitive decline, and psychiatric disturbances. Studies in Drosophila have shown that the normal huntingtin protein is largely localized in the cytoplasm, whereas the mutant form accumulates in the nucleus. Neurons implicated in disease mechanisms also develop inclusions—large aggregates consisting of the mutant protein together with transcriptional co-activators. Apart from clarifying the origin and mechanisms of Huntington's disease, Drosophila melanogaster has also been utilized to explore potential therapeutic strategies [157, 159].

PolyQ-related pathology has been linked to the suppression of acetyltransferase activity. Expression of polyQ sequences in flies is commonly used to generate an HD-like model that reproduces key characteristics observed in humans. A pivotal breakthrough in the study of HD-associated proteinopathies using Drosophila was reported by Steffan and colleagues. Employing a fly HD system, they showed that histone deacetylase (HDAC) activity can exacerbate polyQ-driven neuronal damage—an effect later confirmed in human studies. They further demonstrated that HDAC inhibitors can counteract this neurodegeneration in flies and may hold value in slowing or preventing the progressive neural decline observed in HD and other polyQ-related conditions [171].

Drawbacks of using Drosophila as a disease model

Although Drosophila offers extensive advantages for modeling human disorders, several limitations should be taken into account. A notable constraint is that some crucial pathogenic mechanisms may be unique to vertebrates and therefore absent in invertebrate organisms. Disorders involving complex immune responses, such as multiple sclerosis, cannot be faithfully reproduced in Drosophila melanogaster. In addition, stroke-related conditions—including infarctions and hemorrhagic events—cannot be studied in flies because they lack a vascular system, and their blood cells consist mainly of primitive hemocytes [172]. Another drawback is the challenge of long-term storage; unlike many vertebrate models, Drosophila strains cannot be cryopreserved easily and must be maintained as continuously living stocks [162].

Conclusion

The wide array of animal models used in biomedical science has significantly enriched our understanding of human biology and disease. Despite over a century of scientific use, Drosophila continues to serve as a powerful tool for investigating both established and emerging medical conditions. It is anticipated that, notwithstanding its limitations, research will keep drawing on the current and future possibilities offered by Drosophila melanogaster. Moreover, fly models may be incorporated alongside other animal systems when a multi-model approach is required for deeper insight. This is particularly relevant for drug development, as the US Food and Drug Administration recommends—though does not strictly require—demonstrating a drug's effectiveness in more than one animal species to better predict human responses [173].

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