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Advantage of *Drosophila melanogaster* in Biomedical Research over Mammalian Models

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ABSTRACT

Drosophila melanogaster, the common fruit fly, has emerged as a powerful model organism in biomedical research, offering unique advantages over traditional mammalian models such as mice, rats, and rabbits. While mammalian models have long been preferred due to their genetic and physiological similarities to humans, Drosophila boasts several key benefits, including a fully sequenced and highly manipulable genome, short life cycle, high fecundity, low maintenance costs, and reduced ethical concerns. We provide a detailed comparative analysis of Drosophila and mammalian models, examining their respective strengths in various research areas such as neuroscience, developmental biology, ageing research, and drug discovery. The review also addresses the limitations of Drosophila as a model organism, acknowledging the evolutionary distance from humans and anatomical differences. Case studies highlighting successful applications of Drosophila in studying neurodegenerative diseases, cancer, and circadian rhythms are presented to illustrate its practical utility. Emerging technologies that enhance Drosophila's research potential are discussed, along with future perspectives on its role in biomedical research. This analysis aims to guide researchers in selecting appropriate model organisms and underscores the significant contributions of *Drosophila melanogaster* to advancing our understanding of human health and disease.

Keywords

Drosophila melanogaster, Animal models, Biomedical research, Genetic manipulation, Comparative physiology

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INTRODUCTION

Biomedical research has long relied on animal models to advance our understanding of human biology, disease mechanisms, and potential therapeutic interventions. These model organisms serve as invaluable tools for investigating complex biological processes in a controlled environment, offering insights that can be translated to human health and disease (Bryda, 2013). Traditionally, mammalian models such as mice, rats, and rabbits have been the gold standard in preclinical research due to their genetic and physiological similarities to humans (Vandamme, 2014).

However, in recent years, the fruit fly, *Drosophila melanogaster* has emerged as a powerful alternative model organism, challenging the dominance of mammalian models in various areas of biomedical research (Ugur *et al.*, 2016). This small insect, with its rich history in genetic studies dating back to the early 20th century, has proven to be an exceptionally versatile and efficient model sys-

tem for studying a wide range of biological processes relevant to human health (Yamaguchi and Yoshida, 2018). The genome of *Drosophila melanogaster* was fully sequenced in 2000, revealing a surprising degree of conservation with the human genome. Approximately 75% of human disease-associated genes have functional homologues in the *Drosophila melanogaster*, underscoring its relevance to human health research (Chow and Reiter, 2017). This genetic similarity, combined with the fly's unique advantages, has led to its increased adoption in fields such as neurobiology, developmental biology, and drug discovery (Sonoshita and Cagan, 2017).

One of the most significant advantages of Drosophila as a model organism is its genetic tractability. The availability of sophisticated genetic tools and techniques, such as CRISPR-Cas9 genome editing and the GAL4/UAS system, allows for precise manipulation of gene expression and function (Thurmond *et al.*, 2019). These tools enable researchers to create and study disease models with unprecedented speed and accuracy, facilitating rapid advances in our understanding of complex biological processes (Prüßing *et al.*, 2013). Moreover, the Drosophila's short life cycle, high fecundity, and low maintenance costs make it an attractive option for large-scale genetic screens and high-throughput studies (Markow, 2015). These characteristics allow researchers to conduct experiments that would be prohibitively time-consuming or expensive in mammalian models, accelerating the pace of discovery in biomedical research (Pandey and Nichols, 2011).

In recent years, the application of Drosophila in biomedical research has expanded significantly. From serving as a model for neurodegenerative diseases like Alzheimer's and Parkinson's (Bouleau and Tricoire, 2015) to its use in cancer research (Sonoshita and Cagan, 2017) and drug discovery (Fernández-Hernández *et al.*, 2016), the Drosophila continues to prove its worth in advancing our understanding of human health and disease.

Despite these advantages, it is important to acknowledge that Drosophila, like any model organism, has its limitations. The evolutionary distance between flies and humans, as well as significant differences in anatomy and physiology, can sometimes limit the direct translatability of findings (Gonzalez, 2013). However, many researchers argue that the benefits of using Drosophila often outweigh these limitations, particularly in the early stages of discovery and for studying conserved biological processes (Millburn *et al.*, 2016).

This review aims to provide a comprehensive analysis of the advantages of *Drosophila melanogaster* in biomedical research compared to traditional mammalian models. By examining the unique strengths of the Drosophila model, as well as its limitations, we seek to provide advantageous feedback to researchers considering the most appropriate model system for their studies. Through this analysis, we hope to underscore the significant contributions of Drosophila to biomedical research and its potential to drive future discoveries in the field.

BACKGROUND ON MODEL ORGANISMS

Model organisms are non-human species extensively studied to understand specific biological phenomena, with the expectation that discoveries made in these organisms will offer us knowledge about the workings of other organisms, particularly humans (Dietrich *et al.*, 2014). These species are chosen for their amenability to experimental manipulation, genetic similarity to humans, ease of maintenance and breeding in laboratory conditions, and the wealth of biological data already available about them (Leonelli and Ankeny, 2013). The use of model organisms has been pivotal in advancing our understanding of fundamental biological processes, disease mechanisms, and potential therapeutic interventions (Cord *et al.*, 2017).

Mammalian models, particularly mice, rats, and rabbits, have long been the gold standard in biomedical research due to their genetic and physiological similarities to humans (Vandamme, 2014). Mice (*Mus musculus*) have been used in scientific research since the early 20th century and have remained the most widely used mammalian model organism. The mouse genome, sequenced in 2002, revealed that about 99% of mouse genes have human homologues (Perlman, 2016). This genetic similarity, combined with the ease of genetic manipulation in mice, has made them invaluable in studying human diseases and developing new therapies (Kaczmarczyk and Jackson, 2015).

Rats (*Rattus norvegicus*) have played a crucial role in biomedical research, particularly behavioural and neurological studies. Their larger size compared to mice makes them more suitable for certain types of experiments, such as surgical procedures and studies requiring multiple tissue samples (Iannaccone and Jacob, 2009). Rabbits (*Oryctolagus cuniculus*) have been used extensively in research areas such as antibody production, toxicology studies, and cardiovascular research. Soares *et al.* (2022) studied 3,580 human gene sequences and selected sequence alignments with more than 150 base pairs, resulting in 2,793 genes. Rabbits exhibited 2,468 (88%) genes that are homologous to the selected human genes. Recent advances in genetic engineering techniques have also increased the potential of rabbits as models for human diseases (Yang *et al.*, 2014).

In recent decades, *Drosophila melanogaster*, commonly known as the fruit fly, has emerged as a powerful model organism in biomedical research, complementing and sometimes challenging the dominance of mammalian models. The *Drosophila melanogaster*'s genome, fully sequenced in 2000, revealed a surprising degree of conservation with the human genome (Fig. 1). Approximately 75% of known human disease genes have a recognisable match in the genome of *Drosophila melanogaster* (Ugur *et al.*, 2016). Drosophila offers several key advantages as a model organism. Its genetic tractability, facilitated by sophisticated tools such as the GAL4/UAS system and CRISPR-Cas9 genome editing, allows for precise manipulation of gene expression and function (Thurmond *et al.*, 2019). The fly's short life cycle and high fecundity enable rapid genetic studies and large-scale screens (Jenning, 2011). Additionally, *Drosophila mela-*

nogaster are inexpensive to maintain compared to mammalian models, allowing for larger-scale experiments (Markow, 2015). The use of Drosophila in research also generally raises fewer ethical concerns compared to mammalian models, simplifying regulatory requirements (Ankeny and Leonelli, 2011).

These advantages have positioned Drosophila as a valuable complement to mammalian models in biomedical research. Its use has expanded from classical genetics to diverse fields, including neurobiology, developmental biology, ageing research, and drug discovery (Sonoshita and Cagan, 2017). As we examine the subsequent sections, it's important to consider how this small insect has become a powerhouse in biomedical research, offering unique insights alongside traditional mammalian models.

Advantages of *Drosophila melanogaster*

In the landscape of biomedical research, *Drosophila melanogaster* has carved out a unique niche, offering a compelling array of advantages that complement and sometimes surpass those of traditional mammalian models. This diminutive Drosophila, with over a century of use in genetic studies, has evolved into a powerhouse of modern biomedical research. Its rise to prominence is not merely a testament to its historical significance but a reflection of its multifaceted utility in addressing complex biological questions. From its genetic malleability to its practical benefits in the laboratory, Drosophila presents researchers with a versatile toolkit for probing the intricacies of life processes and human diseases (Hales *et al.*, 2015; Ugur *et al.*, 2016). As we discuss the myriad advantages of this model organism, it becomes clear why Drosophila has become an indispensable ally in the effort to uncover biological mysteries and advance human health.

One of the primary advantages of Drosophila is its genetic simplicity and manipulability. The *Drosophila melanogaster* genome, fully sequenced in 2000, consists of only four pairs of chromosomes, compared to 23 pairs in humans (Thurmond *et al.*, 2019). Despite this simplicity, approximately 75% of known human disease genes have functional homologues in Drosophila, highlighting its relevance to human health research (Ugur *et al.*, 2016). This genetic conservation, coupled with the fly's less complex genome, allows researchers to study gene functions and interactions with greater ease and clarity. The genetic tractability of Drosophila is further enhanced by the availability of sophisticated genetic tools and techniques. The GAL4/UAS system, a method for targeting gene expression, has been a cornerstone of Drosophila genetics for decades and continues to be refined and expanded (Choi *et al.*, 2018). Recently, the advent of CRISPR-Cas9 genome editing has revolutionised genetic manipulation in Drosophila by allowing for precise modifications of the genome with unprecedented ease and efficiency (Port *et al.*, 2014). These tools enable researchers to create and study disease models with remarkable speed and accuracy, facilitating rapid advances in our understanding of complex biological processes.

Another significant advantage of Drosophila is its short life cycle and high fecundity. The entire life cycle of Drosophila, from egg to adult, takes only about 10-12 days under optimal conditions (Hales *et al.*, 2015). Female flies can lay up to 100 eggs per day and about 2000 in a lifetime (Castelfolk *et al.*, 2017). This rapid generation time and high reproductive rate allow for large-scale genetic screens and the quick establishment of genetically modified lines, accelerating the pace of research significantly compared to mammalian models. The practicality of using Drosophila extends to its maintenance and care. Drosophilas are small, requiring minimal space, and are inexpensive to maintain compared to mammalian models (Markow, 2015). Their diet is simple and cost-effective, typically a variable mixture of cornmeal media, banana media, white cream media and so on. These factors make it feasible to maintain large populations and perform large-scale experiments that would be prohibitively expensive or logistically challenging with mammalian models.

Ethics considerations also favour the use of Drosophila in research. The use of insects in scientific studies generally raises fewer ethical concerns and faces less stringent regulatory requirements compared to vertebrate animals (Ankeny and Leonelli, 2011). This simplifies the process of obtaining approval for experiments and can accelerate the research timeline. The optical transparency of Drosophila during its embryonic and larval stages presents another unique advantage. This characteristic allows for real-time imaging of developmental processes and the visualisation of fluorescently tagged proteins in living organisms (Lye and Sanson, 2011). Recent advances in microscopy techniques have further enhanced this capability, enabling researchers to observe cellular and subcellular processes with unprecedented detail in vivo (Lemon *et al.*, 2015).

Drosophila also offers advantages in the field of neurobiology. Despite its small size, the Drosophila's brain contains approximately 100,000 neurones and exhibits complex behavi ours (Chung *et al.*, 2011). The relative simplicity of the Drosophila nervous system, compared to

Fig. 1: Illustration of the arrangement of fly and some common traditional mammalian models in order of increasing genome conservation with humans. (a) *Drosohila melanogaster* (b) Rabbit (c) Rat (d) Mice (e) Human

vertebrates, makes it an excellent model for studying neural circuits, behaviours, and neurological disorders. Advanced techniques such as optogenetics and thermogenetics have been successfully applied in Drosophila, allowing for precise manipulation of neural activity (Riemensperger *et al.*, 2016).

In the realm of drug discovery, Drosophila has proven to be a valuable tool for initial screening and testing of potential therapeutic compounds. The fly's rapid life cycle and the availability of disease models make it possible to quickly assess the effects of drugs on various biological processes and disease states (Sonoshita and Cagan, 2017). Moreover, the conservation of many drug targets between flies and humans means that findings in Drosophila often translate well to mammalian systems (Pandey and Nichols, 2011).

Furthermore, the Drosophila research community has developed extensive resources and databases that further enhance the utility of this model organism. Platforms such as FlyBase provide comprehensive genetic and genomic information, while stock centres maintain and distribute a vast array o f Drosophila strains and genetic tools (Thurmond *et al.*, 2019). These communal resources facilitate collaboration and accelerate research progress across the field.

Lastly, the combination of genetic tractability, rapid life cycle, cost-effectiveness, ethical considerations, and the wealth of available tools and resources make *Drosophila melanogaster* an exceptionally powerful model organism in biomedical research. While it cannot completely replace mammalian models, particularly for studies of complex physiological systems unique to vertebrates, Drosophila offers unique advantages that complement and enhance traditional approaches to biomedical research.

COMPARATIVE ANALYSIS: DROSOPHILA VS MAMMALIAN MODELS

The choice of model organism in biomedical research is crucial, as it directly impacts the relevance, efficiency, and translatability of findings to human health. While mammalian models have long been the gold standard, *Drosophila melanogaster* has emerged as a powerful alternative, offering unique advantages in many research areas. This comparative analysis examines the strengths and limitations of Drosophila and mammalian models across various aspects of biomedical research.

Genetic Manipulation

Genetic manipulation is a cornerstone of modern biomedical research, and both Drosophila and mammalian models offer sophisticated tools for genetic studies. However, Drosophila frequently surpasses mammalian models in terms of the ease and speed of genetic manipulation. The GAL4/UAS system in Drosophila allows for precise spatial and temporal control of gene expression, a technique that has been continually refined over the years (Choi *et al.*, 2018). The advent of CRISPR-Cas9 genome editing has revolutionised genetic manipulation in both systems, but the simplicity of the Drosophila genome often allows for more rapid and efficient editing (Port *et al.*, 2020). In contrast, while mammalian models, particularly mice, offer a closer genetic match to humans, the complexity of their genomes can make genetic manipulation more challenging and time-consuming (Gurumurthy and Lloyd, 2019).

CRISPR/Cas9 is a revolutionary genome editing tool that allows for precise modifications to the DNA of organisms. In Drosophila, CRISPR/Cas9 is used to create specific gene knockouts, insertions, deletions, and even precise nucleotide changes (Fig. 2). The process involves designing a guide RNA (gRNA) to target a specific DNA sequence, introducing the Cas9 enzyme to create a double-strand break at the target site, and then allowing the cell's natural repair mechanisms to correct the break either by non-homologous end joining (NHEJ) or homology-directed repair (HDR), leading to gene knockouts or insertions, respectively. Compared to rodents, generating CRISPR/Cas9 mutants in Drosophila is significantly faster, with mutants obtainable in a few weeks versus several months in mice. Additionally, the costs associated with CRISPR/Cas9 in Drosophila are much lower due to simpler housing and feeding requirements. The delivery of CRISPR components in Drosophila is straightforward, often involving simple microinjections into embryos, whereas in rodents, it requires more complex procedures (Housden and Perrimon, 2016).

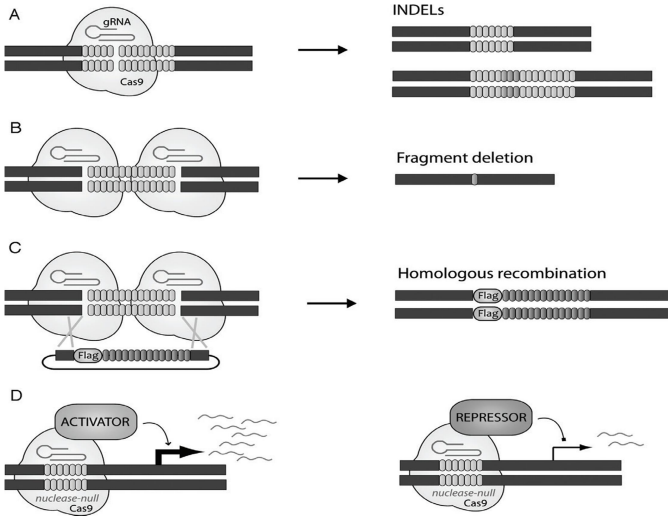

Fig. 2: CRISPR/Cas9 applications for Drosophila gene editing. The figure shows Cas9-DNA interactions that result in changes in gene expression (D) or in the genomic sequence (A–C). Thick lines indicate the genomic DNA, a grey shape represents Cas9, grey lines indicate guide RNA (gRNA), and nucleotides targeted as grey ovals by gRNA. (A) DNA double-strand breaks caused by single gRNA are rectified by non-homologous end joining, which results in INDELs. (B) Double gRNAs cause close double-strand breaks (left), which, when fixed, cause the DNA between the breaks to be deleted (right). (C) When two gRNAs are used in the presence of homology-containing sequences (left) that match the target DNA, the target DNA is replaced (knock-out) by the chosen sequence (knock-in), in this case a tagged version of a coding region (Flag). (D) Targeting inactive Cas9 variants Neural expression variations from adjacent promoters correlate to the fused (nuclease-null Cas9) activating (left) or repressor (right) domains.

RNA interference (RNAi) is a technique used to silence gene expression by degrading mRNA molecules. In Drosophila, RNAi is a powerful tool for knocking down gene expression in a tissue-specific and temporal manner. The process involves introducing double-stranded RNA (dsRNA) corresponding to the target gene, which is then processed into small interfering RNAs (siRNAs) that guide the degradation of the target mRNA, effectively silencing the gene (Mohr and Perrimon, 2012). RNAi lines in Drosophila can be generated quickly, allowing for rapid functional analysis. The specificity of tissue-specific and inducible RNAi can be achieved using the GAL4/UAS system, providing precise control over gene knockdown. High-throughput RNAi screens are feasible in Drosophila due to the large number of offspring and ease of genetic crosses. For instance, RNAi has been used to knock down genes involved in Alzheimer's disease pathways, such as genes associated with amyloid-beta production and tau protein, to study their effects on neuronal health and lifespan (Mohr and Perrimon, 2012).

SOME NEURODEGENERATIVE DISEASES GENETIC HOMOLOGUES BETWEEN HUMAN AND *DROSOPHILA MELANOGASTER*

Alzheimer's Disease

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder, mainly affecting the elderly. More than 95% of AD cases are sporadic, while less than 5% are familial. Familial cases have identified genes like APP, presenilins 1 and 2 (PSN-1/2), and tau, which are involved in AD when mutated (Table 1). The Apolipoprotein E epsilon4 isoform is also a risk factor (Hardy, 2006). AD is marked by progressive memory loss and extensive brain degeneration. Pathologically, it features neuritic plaques made of Abeta peptides and neurofibrillary tangles composed of abnormal tau protein. Abeta peptides arise from the proteolytic cleavage of the APP receptor (Bu, 2009). Mutations in APP lead to increased production of the amyloidogenic Abeta42 peptide, which is more prevalent in plaques than Abeta40 (Braak and Del Tredici, 2008). The enzymes BACE, PS1, and PS2 are involved in this cleavage process (Nelson *et al.*, 2009).

Table 1: Alzheimer's Disease-Associated Genes

Gene/Protein	Inheritance	Fly Homologue	Protein Function
APP	AR	Appl/CG7727	Pre-synaptic protein
PSN-1/2	AR	dPs/CG18803	Gamma-secretase activity
Tau	unclear	tau/CG31057	Microtubule stabilization
APOe4	unclear	None	Lipid/cholesterol metabolism

APP = amyloid precursor protein; Appl = amyloid precursor protein-like; PSN-1/2 = presenilin-1/2; dPS = Drosophila presenilin; APOe4 = apolipoprotein e4; AR = autosomal recessive

This understanding supports the amyloid cascade hypothesis as a central factor in AD. Drosophila, with its homologous AD-related genes, serves as a model system for AD research.

Parkinson's Disease

Parkinson's disease (PD) is the most common neurodegenerative movement disorder, characterised by tremors, imbalance, slowness, and rigidity. It involves the progressive loss of dopamine neurons in the substantia nigra, affecting motor control through the nigrostriatal pathway (Thomas and Beal, 2007). Lewy bodies, composed of alpha-synuclein, are also present. PD prevalence increases with age, with most cases sporadic and a small percentage familial. Males are more likely to develop PD. The disease is progressive, with treatments focusing on symptom management, primarily using dopamine replacement therapy (Hardy *et al.*, 2009). Genetic factors, including mutations in alpha-synuclein, parkin, and LRRK2, contribute to PD pathogenesis through protein aggregation, oxidative damage, and mitochondrial dysfunction (Shulman and de Jager, 2009). Drosophila models have offered clues about PD pathogenesis, except for alpha-synuclein homologues (Table 2).

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Trinucleotide Repeat Expansion Diseases

Trinucleotide repeat expansion diseases (TREDs) account for more than 16 neurological disorders that are caused by aberrant expansion of triplet reiterations in either coding or non-coding regions of disease-specific genetic loci that result in dysfunction of the respective protein, eventually leading to neurodegeneration and, ultimately, patient death (Orr and Zoghbi, 2007). The genetic loci affected by the expansion of unstable trinucleotide repeats have been identified, and with the exception of the androgen receptor, there is a fly homologue known for each of them (Table 3), which in turn led to the establishment of Drosophila models of PolyQ diseases, FRX and FRDA (Hands *et al.,* 2008; Yamada *et al.,* 2008).

Motor Neuron Diseases

Motor neuron diseases (MND) encompass various diseases that affect upper motor neurons in the primary motor cortex and/or lower motor neurons in the spinal cord and brainstem. MNDs include amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), hereditary spastic paraplegia (HSP), and some forms of frontotemporal dementia and frontotemporal lobar degeneration. These diseases cause neuronal dysfunction and muscle wasting, leading to locomotor disabilities and potentially death when breathing muscles are involved. Prevalence rates vary, with SMA at 1/6,000-10,000, HSP at 3-10/100,000, and ALS at 4-6/100,000. Most cases are sporadic with unknown causes, though genetic factors have been identified (Table 4). No effective therapy or cure exists, but Drosophila models have been used to study these diseases through gene analysis (Burghes and Beattie, 2009).

Table 2: Parkinson's disease-associated genes

Gene/Protein	Inheritance	Fly Homologue	Protein Function
Alpha-synuclein	AD	None	Pre-synaptic protein
Parkin	AR	parkin/ CG10523	E3 ubiquitin ligase
UCH-L1	unclear	Uch/CG4265	E3 ubiquitin hydrolase/ligase
PINK1	AR	Pink1/CG4523	Mitochondrial kinase
DJ-1	AR	DJ-1a/CG6646 DJ-1b/CG1349	Redox sensor/Chaperone
LRRK2	AD	lrrk2/CG5483	Kinase/GTPase
HtrA2	AD	HtrA2/CG8486	Mitochondrial pro-apoptotic protease
GBA	unclear	CG33090	Lysosomal enzyme
POLG	unclear	tamas/CG8987	Mitochondrial DNA polymerase
Tau	unclear	tau/CG31057	Microtubule stabilisation

UCH-L1 = ubiquitin carboxyl-terminal esterase L1; PINK1 = PTEN induced putative kinase 1; LRRK2 = leucine-rich repeat kinase 2; HtrA2 = high temperature requirement protein A2; glucocerebrosidase = GBA; POLG = polymerase gamma; AD = autosomal dominant; AR = autosomal recessive.

Table 3: Trinucleotide repeat expansion disease-associated genes

TRED	Gene/Protein	Inheritance	Fly Homologue	Protein Function
HD	HTT	AD	htt/CG9995	Microtubule binding, transport
SCA	ATXN1/2/3/7	AD	Atx-1/CG4547 Atx2/CG5166	unknown
SCA17	TBP	AD	Tbp/CG9874	Transcriptional regulation
SBMA	AR	AD	None	Nuclear receptor
DRPLA	ATN1	AD	Gug/CG6964	Transcriptional regulation
FRX	FMR1/2	X and AD	dFMR1/ CG6203	RNA regulation
FRDA	FXN	AR	fh/CG8971	Mitochondrial protein

TRED = Trinucleotide repeat expansion disease; HD = Huntington's disease; SBMA = spinal bulbar muscular atrophy; SCA = spinocerebellar ataxias; DRPLA = dentatorubropallidoluysian atrophy; FRX = fragile X syndrome; FRDA = Friedreich's ataxia; HTT = Huntingtin; ATXN-1/2/3/7 = ataxin-1/2/3/7; AR = androgen receptor; TBP = TATA box binding protein; CACNA1A = calcium channel, voltage-dependent, P/Q type, alpha 1A subunit; ATN1 = atrophin-1; Gug = Grunge; FMR1/2 = fragile X mental retardation 1; FXN = frataxin; fh = frataxin homologue; AD = autosomal dominant; X = X-linked chromosomal segregation; AR = autosomal recessive.

AGEING (LIFE CYCLE), COST, AND ETHICAL CONSIDERATIONS

In terms of life cycle and fecundity, Drosophila has a notable advantage. The Drosophila's rapid life cycle (approximately 10-12 days from egg to adult) and high reproductive rate allow for the quick establishment of genetically modified lines and large-scale genetic screens (Castelfolk *et al.,* 2017). This rapid generation time is particularly advantageous in ageing research, where multiple generations can be studied in a relatively short period (He and Jasper, 2014). Mammalian models, while offering closer physiological similarities to humans, have much longer generation times. Mice, for instance, reach sexual maturity at about 6-8 weeks, with a typical lifespan of 2-3 years, making longitudinal studies more time-consuming and resource-intensive (Kõks *et al.,* 2016).

Cost and maintenance considerations often favour Drosophila in research settings. The cost of maintaining and breeding Drosophila is significantly lower than that of rodents. Drosophilas require minimal space, have simple dietary needs, and are inexpensive to maintain compared to mammalian models (Markow, 2015). This cost-effectiveness allows for larger sample sizes and more extensive experimental designs, which can be crucial for statistical power in genetic studies (Ugur *et al.,* 2016). Mammalian models, particularly mice and rats, require more sophisticated housing facilities, specialised diets, and greater care, leading to higher costs and potentially limiting experimental scale (Vandamme, 2014).

Ethical considerations and regulatory requirements present another area where Drosophila often has an advantage. The use of insects in research generally raises fewer ethical concerns and faces less stringent regulatory oversight compared to vertebrate animals (Reiter *et al.,* 2022). Such advantages can significantly streamline the research process, allowing for more rapid progression from concept to experimentation. Mammalian models, while invaluable for certain types of studies, often require more extensive ethical review processes and stricter adherence to animal welfare guidelines, which can extend project timelines and increase administrative burden (Sneddon *et al.,* 2017).

Neurobiology Research, Behavioural Assays and Cognitive Studies

In neurobiology research, both Drosophila and mammalian models offer unique insights. The Drosophila brain, despite its relatively small size (approximately 100,000 neurons), exhibits complex behaviours and has been instrumental in studying fundamental neurobiological processes (Chung *et al.,* 2011). Advanced techniques such as optogenetics have been successfully applied in Drosophila, allowing for precise manipulation of neural circuits (Riemensperger *et al.,* 2016). Mammalian models, particularly mice and rats, offer brains that are anatomically closer to humans, making them indispensable for studying higher cognitive functions and complex neurological disorders (Homberg *et al.,* 2021). However, this complexity can also make it more challenging to isolate and study specific neural circuits.

Drosophila melanogaster is equipped with sophisticated behavioural assays that can be used to study learning, memory, and sensory processing. Behavioural paradigms such as conditioned courtship, negative geotaxis, phototaxis, and olfactory learning provide insights into cognitive functions and how they are affected by genetic or environmental factors (Tully and Quinn, 1985; Krashes *et al.,* 2009). These assays are generally more accessible and less resource-intensive compared to behavioural tests in rodents.

Table 4: Motor neuron disease-associated genes

MND	Gene/Protein	Inheritance	Fly Homologue	Protein Function
ALS	SOD1	AD/ (AR)	Sod/ CG11793	Superoxide dismutase
ALS	Alsin	AR	CG7158	unknown
ALS	SETX	AD	None	DNA/ RNA helicase
ALS	FUS/TLS	AD/ (AR)	caz/CG3606	Transcription/ RNA processing
ALS	VAPB	AD	Vap-33-1/CG5014	Cargo transport
ALS	TDP-43	AD	TBPH/ CG10327 CG7804	Transcription/ RNA processing
ALS	CHMP2B	unclear	CG4618	Endosomal sorting/ transport
SMA	SMN-1/2	AR	Smn/ CG16725	Transcription/RNA processing
HSP	SPAST	AD	dSpast/CG5977	Microtubule organisation
HSP	NIPA1	AD	spict/CG12292	Synaptic growth/BMP signalling
HSP	ATL-1	AD	atl/CG6668	Membrane fusion/ER

MND = motor neuron disease; ALS = amyotrophic lateral sclerosis; SMA = spinal muscular atrophy; HSP = hereditary spastic paraplegia; SOD1 = Cu/Zn superoxide dismutase 1; SETX = senataxin; FUS/TLS = fused in sarcoma/translocated in liposarcoma; caz = cabeza; VAPB = vesicle-associated membrane protein B; Vap-33-1 = vesicle-associated membrane protein 33-1; TDP-43 = transactive response DNA-binding protein 43; TBPH = transactive response DNA-binding protein homologue; CHMP2B = charged multivesicular body protein 2B; SMN-1/2 = survival of motor neuron protein 1/2; SPAST = spastin; NIPA1 = non-imprinted in Prader-Willi/Angelman syndrome 1; spict = spichthyin; ATL-1 = atlastin-1; ER = endoplasmic reticulum; AD = autosomal dominant; AR = autosomal recessive.

Drug Discovery and Toxicology

In the realm of drug discovery and toxicology studies, both models play crucial roles. Drosophila's rapid life cycle and the availability of disease models make it an excellent system for initial drug screening and toxicity assessment (Sonoshita and Cagan, 2017). Housing requirements for Drosophilas are minimal, and their short lifespan allows for rapid assessment of drug effects across multiple generations. This economic advantage makes large-scale drug screening studies more feasible and less resource-intensive (Hofmann *et al.,* 2013).

The conservation of many drug targets between flies and humans means that findings in flies often translate well to mammalian systems (Pandey and Nichols, 2011). Mammalian models, however, are often considered essential for later stages of drug development due to their closer physiological similarity to humans, particularly in terms of metabolism and systemic responses (Garner *et al.,* 2017).

One area where mammalian models maintain a clear advantage is in the study of complex physiological systems unique to vertebrates, such as the adaptive immune system, complex organ systems like the heart and lungs, and certain aspects of embryonic development. For these studies, the evolutionary distance between Drosophila and humans becomes a significant limitation (Gonzalez, 2013). However, it's worth noting that Drosophila has contributed valuable insights even in these areas by elucidating fundamental cellular and molecular mechanisms that are often conserved across species (Bangi, 2013).

IIn conclusion, *Drosophila melanogaster* offers a powerful complementary system with unique advantages in genetic manipulation, cost-effectiveness, and experimental efficiency, while mammalian models remain indispensable for certain aspects of biomedical research. The choice between these models often depends on the specific research question, with many studies benefiting from a combined approach that leverages the strengths of both systems. As technologies continue to advance, the synergy between Drosophila and mammalian models is likely to drive significant progress in biomedical research, offering new insights into human health and disease.

FUTURE PERSPECTIVES

As biomedical research continues to evolve, the role of *Drosophila melanogaster* as a model organism is poised to expand and adapt, driven by emerging technologies and the growing recognition of its complementary strengths to mammalian models. This section explores the future perspectives of Drosophila in biomedical research, focusing on emerging technologies, potential for complementary use with mammalian models, and areas for further development and research.

Emerging technologies are significantly enhancing Drosophila's utility in biomedical research. One of the most promising advancements is the development of more sophisticated genome editing techniques. While CRISPR-Cas9 has already revolutionised genetic manipulation in Drosophila, newer variants such as base editors and prime editors are offering even more precise and versatile genome modification capabilities (Bosch *et al.,* 2021). These tools allow researchers to make subtle changes to the fly genome, mimicking human genetic variations with unprecedented accuracy. Additionally, the development of tissue-specific CRISPR systems in Dro-

sophila is enabling more nuanced studies of gene function in specific cell types or developmental stages (Port *et al.,* 2020).

Advances in imaging technologies are also expanding the research potential of Drosophila. Light-sheet microscopy, for instance, has enabled real-time, high-resolution imaging of entire Drosophila embryos and larvae, which offers fresh perspectives on developmental processes and neural activity (Chhetri *et al.,* 2015). Furthermore, the application of expansion microscopy to Drosophila tissues is allowing for super-resolution imaging of cellular structures, bridging the gap between light microscopy and electron microscopy (Jiang *et al.,* 2018).

In the field of neuroscience, optogenetic and thermogenetic tools are becoming increasingly sophisticated in Drosophila. These techniques allow for precise temporal and spatial control of neural activity, enabling detailed studies of neural circuits and behaviour (Simpson and Looger, 2018). The development of new fluorescent sensors for neurotransmitters and intracellular signalling molecules is further enhancing our ability to monitor neural activity in the fly brain (Lerman *et al.,* 2017).

The potential for the complementary use of Drosophila with mammalian models is a key area of future development. As research becomes increasingly interdisciplinary, there is growing recognition that combining insights from multiple model systems can provide a more comprehensive understanding of biological processes. For instance, initial high-throughput screens in Drosophila can identify potential therapeutic targets or compounds, which can then be validated and further studied in mammalian models (Sonoshita and Cagan, 2017). This approach can significantly accelerate the drug discovery process while reducing costs and the use of mammalian subjects in early-stage research.

In the field of personalised medicine, Drosophila is emerging as a valuable tool for creating "personalised" disease models. By introducing human disease-associated mutations into fly genes, researchers can rapidly generate models that reflect individual patients' genetic profiles. These models can then be used to test potential treatments, paving the way for more personalised therapeutic approaches (Vos *et al.,* 2020). This approach is particularly promising for rare genetic disorders, where traditional drug development approaches may not be economically viable.

The integration of Drosophila research with big data and artificial intelligence is another area with significant potential. Machine learning algorithms can analyse vast amounts of genetic and phenotypic data from Drosophila studies, identifying patterns and generating hypotheses that can guide further research in both fly and mammalian models (Kopp *et al.,* 2021). This data-driven approach could significantly enhance our ability to translate findings from Drosophila to human health applications.

Despite these advancements, there are several areas where further development and research are needed to fully realise the potential of Drosophila in biomedical research. One key area is the development of more sophisticated "humanised" fly models. While many human genes have functional homologues in Drosophila, some human proteins may not function identically in the fly system. Creating fly lines that express human versions of these proteins could provide more accurate models for studying human diseases (Rincon-Limas *et al.,* 2012).

Another area for development is the creation of more complex, multicellular Drosophila models that better recapitulate human tissue environments. For instance, recent advances in Drosophila intestinal stem cell research have led to the development of 3D culture systems that mimic aspects of the human intestine (Bonfini *et al.,* 2016). Expanding these techniques to model other organ systems could provide valuable tools for studying tissue-specific diseases and regenerative processes.

Improving our understanding of the evolutionary conservation of molecular pathways between flies and humans is also crucial. While many pathways are known to be conserved, there are likely many more similarities yet to be discovered. Systematic comparative studies of fly and human biology could reveal new areas where Drosophila research can inform human health (Ugur *et al.,* 2016).

Finally, there is a need for continued development of standardised protocols and resources for Drosophila research. While the fly community has a strong tradition of resource sharing, further standardisation of experimental procedures and data reporting could enhance reproducibility and facilitate meta-analyses across studies (Roote and Prokop, 2017).

Ultimately, the future of Drosophila in biomedical research is bright, with emerging technologies and innovative approaches expanding its utility. As our understanding of the connections between fly and human biology deepens, and as new tools and techniques are developed, Drosophila is likely to play an increasingly important role in advancing our understanding of human health and disease. The key to maximising its potential lies in fostering interdisciplinary collaborations, continuing to develop innovative technologies, and maintaining a focus on translating findings from the fly to human health applications.

Conclusion

Drosophila melanogaster has emerged as a powerful model organism in biomedical research, offering unique advantages that complement traditional mammalian models. Its genetic tractability, rapid life cycle, cost-effectiveness, and ethical advantages make it an invaluable tool for studying a wide range of biological processes relevant to human health. While the evolutionary distance between flies and humans presents some limitations, the high degree of genetic conservation and the sophistication of available research tools have enabled significant discoveries across various fields, including neurobiology, developmental biology, and disease modelling. As emerging technologies continue to enhance Drosophila's utility and new approaches for integrating insights from multiple model systems are developed, the *Drosophila melanogaster* is poised to play an increasingly important role in advancing our understanding of human health and disease. The future of biomedical research lies in leveraging the complementary strengths of both Drosophila and mammalian models, promising more

efficient, comprehensive, and translatable research outcomes.

DECLARATION

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Authors Contributions
OOA conceptualised and designed the topic and wrote the introduction and conclusion; EOS and YOS wrote the model background and the advantages of the model of mammals; OFO, ROK, and NOA wrote the comparative analysis; YAS, OLW, and ROA wrote the neurodegenerative diseases aspect; IVA wrote the future perspective of the manuscript.

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