

Using *Drosophila melanogaster* to study mosquito
infection with Zika virus and RNA localisation in
the peripheral nervous system

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Abstract

Arboviruses such as Zika virus (ZIKV) are an ongoing threat to global health, however transmission dynamics and host- and vector-pathogen interactions are not yet well understood. There is also growing evidence that viral infection can disrupt normal cell functions, including RNA transport and local translation away from the cell body, a process of particular importance in the nervous system due to the asymmetric morphology of neurons and glia. In this thesis, I address both of these themes using *Drosophila melanogaster* as a model organism.

To assess the suitability of *Drosophila* as a model for ZIKV infection, I designed oral infection protocols to challenge both larvae and adult flies. This is in contrast to most infection studies in insects, which systemically infect flies by injection and therefore bypass the natural barrier to the virus: the gut. Importantly, I was able to successfully infect flies orally by using a Sting-deficient genotype, whereas wild-type control flies were largely non-permissive to oral infection. This permissive phenotype supports the use of Sting-deficient *Drosophila* as a model for arbovirus–vector interactions, as *Aedes spp.* mosquitoes, the natural vector of ZIKV, lack a STING homolog. Viral replication and tissue tropism after oral infection were characterised using qPCR and imaging approaches, revealing dissemination to multiple tissues in similar patterns and timings to mosquitoes. These included infection of the adult salivary glands and of ISCs in the gut. I also began to explore some aspects of insect-ZIKV interactions, such as effects on locomotory behaviour, gut plasticity and lifespan. This work explores using STING-deficient *Drosophila melanogaster* as a biologically relevant model for studying arbovirus–vector interactions.

In parallel, I investigated mRNA localisation and local translation of motor components in the peripheral nervous system, focusing on neurons and glial cells at the larval neuromuscular junction (NMJ). I optimised a Hybridisation Chain Reaction (HCR)–based method to visualise single mRNA molecules in the NMJ. Using this method, I confirmed the localisation to the glial and neuronal periphery of a predicted set of motor component mRNAs. Glial-specific knock-down of the candidate genes showed disrupted crawling behaviour, allowing me to select a smaller subset of candidate genes to continue researching the role of local translation of motor proteins.

Declaration

I declare that all the work described in this thesis is my own, and the experiments described were performed by myself unless otherwise specified. The experiments were carried out at the Departament of Biochemistry, University of Oxford. This thesis has not been submitted for any other degree or professional qualifications.

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List of abbreviations

ALS – Amyotrophic lateral sclerosis

AMP – Antimicrobial peptide

ANKLE2 – Ankyrin repeat and LEM domain-containing protein 2

BBB – Blood–brain barrier

CaMKII – Ca^{2+} /calmodulin-dependent protein kinase II

CHIKV – Chikungunya virus

CNS – Central nervous system

DENV – Dengue virus

DMEM – Dulbecco’s modified Eagle medium

dsRNA – Double-stranded RNA

FBS – Foetal bovine serum

FDR – False discovery rate

FISH – Fluorescence in situ hybridisation

GAL4 – Galactose-responsive transcription factor 4

GBS – Guillain–Barré syndrome

GFP – Green fluorescent protein

GO – Gene Ontology

HCR – Hybridisation Chain Reaction

HRP – Horseradish peroxidase

IMD – Immune deficiency (pathway)

ISC – Intestinal stem cell

NMJ – Neuromuscular junction

NF- κ B – Nuclear factor kappa-light-chain-enhancer of activated B cells

PNS – Peripheral nervous system

pfu – Plaque-forming units

RBP – RNA-binding protein

RNAi – RNA interference

ROS – Reactive oxygen species

SEM – Standard error of the mean

SINV – Sindbis virus

smFISH – Single-molecule fluorescence in situ hybridisation

Spz – Spätzle

Sting – Stimulator of interferon genes

UAS – Upstream activating sequence

WNV – West Nile virus

ZIKV – Zika virus

Chapter 1

Introduction

1.1 Studying flavivirus pathogen-vector interactions using *Drosophila melanogaster* as a model

1.1.1 Zika virus (ZIKV)

Zika virus (ZIKV) is a single-strand RNA arthropode-borne virus (arbovirus) from the flaviviridae family (Faye et al. 2014), primarily transmitted by *Aedes spp.* mosquitoes. ZIKV was first isolated in Uganda in 1947 (Dick, Kitchen, and Haddow 1952), but it was declared a significant public health concern in 2016, when an association between ZIKV outbreaks and clusters of microcephaly and Guillain-Barre syndrome (GBS) was discovered (Heymann et al. 2016). Although most people are asymptomatic, there is a causal link between viral infection and the neurological disease clusters mentioned (Rasmussen et al. 2016). The mechanism by which ZIKV is able to produce such detrimental neurological symptoms has been explored in the past ten years (reviewed in Metzler and Tang 2024; Gomes et al. 2023). Cases have fallen since 2017, but the virus is still endemic in four out of the six WHO regions (Pielnaa et al. 2020; Rabe et al. 2025). There are no disease-specific treatments or vaccines currently available.

1.1.1.1 ZIKV genetics and protein structure

ZIKV is a positive single-strand RNA virus. There are three main ZIKV lineages: African, Asian and American strains, but they cluster into one single serotype (Nix et al. 2020). Its 10.7 kbp genome is arranged in a similar manner to other flaviviruses (Dengue, West Nile Virus, Yellow Fever Virus, Ye et al. 2016). It encodes for a single polyprotein (1.1A), which is cleaved into ten proteins by both host and virus proteases (Hou et al. 2017). The three structural proteins, the capsid (C), precursor membrane (prM) and envelope (E) encapsulate the viral genome and aid in entry into the cell by binding host cell receptors (Giraldo et al. 2020; Tan et al. 2020). The seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5) control endoplasmic reticulum (ER) membrane remodelling to assemble replication

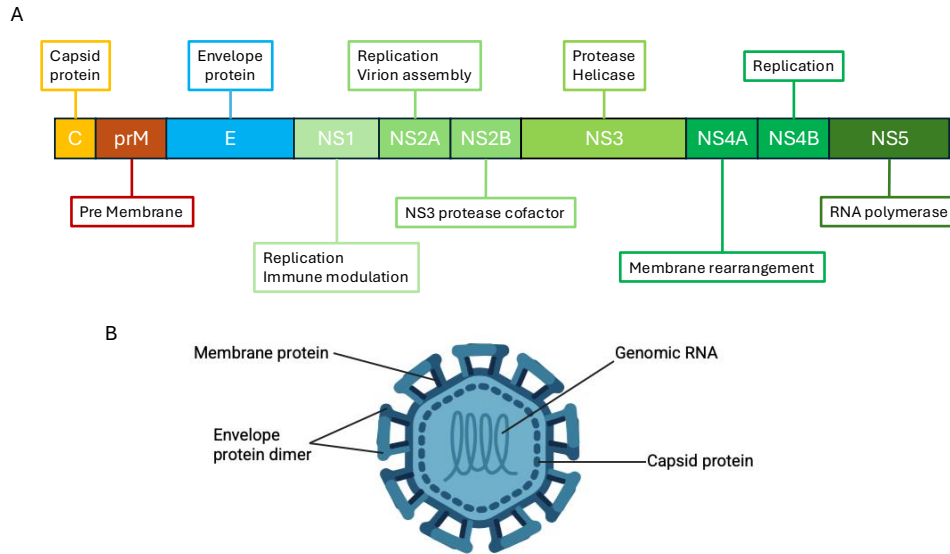


Figure 1.1: A: Schematic representation of the ZIKV genome. Genomic structure of the virus, with the known roles for each of the proteins highlighted. The genome is translated as a single polyprotein that is later cleaved. **B: Schematic representation of the viral particle.** The basic structure of the virus is represented with the location of the structural proteins highlighted. Adapted from Madere et al. 2025, made with biorender.com

factories (Ci et al. 2020; Klaitong and Smith 2021), replication and translation of the viral genome and cleavage of the polyprotein (Zhang et al. 2019; Kumar et al. 2023; Xu et al. 2019; Zhao et al. 2017), as well as evasion and modulation of the host immune system (Zhao et al. 2017; Fanunza et al. 2021; Ci et al. 2020).

The viral particle is very similar to those of other flaviviruses (1.1B). The virus is comprised of an icosahedral shell made of 180 copies each of the E protein and cleaved prM, both attached to a lipid membrane (Sirohi et al. 2016). The C protein is involved in binding the host lipid system (Martins et al. 2024) and the genomic RNA (Shang et al. 2018), aiding in assembly of the viral particle around the genomic RNA and maturation of the viral particle (Tan et al. 2020).

1.1.1.2 ZIKV life cycle

The life cycle of the virus is also very similar to that of other positive-strand flaviviruses, although it is not yet fully understood 1.2. The virus enters the mammalian host cell via receptor-mediated endocytosis. The receptors involved in this process and their effect is still not well understood (reviewed in Robles-Minutti et al. 2025), with plenty of evidence both for and against the role of phosphatidyl serine receptors, mainly AXL (Li et al. 2017; Strange et al. 2019; Wang et al. 2017; Zwernik et al. 2021; Chen et al. 2018; Jimenez et al. 2021; Pan et al. 2018; Liu et al. 2016; Meertens et al. 2017; Richard et al. 2017). Other receptors believed to be involved in ZIKV entry are TIM/TAM receptors (Meertens et al. 2012; Jemielity et al. 2013; Yu et al. 2025), C-type lectin receptors (Menechino et al. 2023; Wang et al. 2023; Chen et al. 2008), NCAM1 (Srivastava et al. 2020), integrin $\alpha V\beta 5$ (Wang et al. 2020; Zhu et al. 2020), glycosaminoglycans (Kim et al. 2017) and EGFR (Sabino

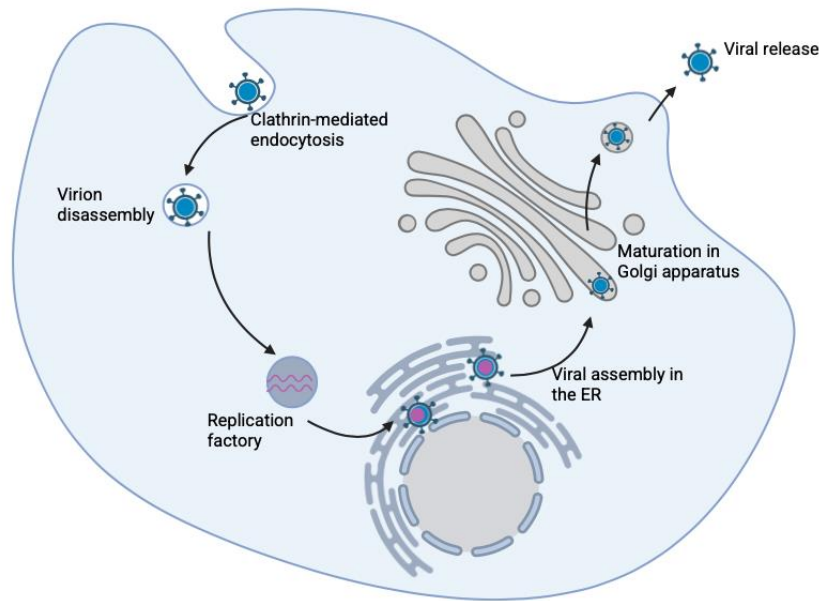


Figure 1.2: Schematic representation of the life cycle of ZIKV inside a cell. The virus is internalised via clathrin-mediated endocytosis, before the acidic pH of the endosome fuses the viral and cell membranes. The endosome fuses with the ER, where the membrane is rearranged to form replication factories. The newly synthesised polyprotein is cleaved and assembled into a virion, which matures in the Golgi apparatus before being released from the cell. Adapted from Hasan et al. 2018, made with biorender.com.

et al. 2021).

The virus is internalised via clathrin-mediated endocytosis (Hackett and Cherry 2018). Due to the acidic pH of the endosome, the viral and endosomal membranes fuse, releasing the viral RNA (Persaud et al. 2018). Cellular structures are heavily rearranged upon infection (Cortese et al. 2017), with the endoplasmic reticulum (ER) forming double-membrane vesicle type viral replication factories (Paul and Bartenschlager 2013; Hamel et al. 2015; Wolff et al. 2020). The vesicles are connected to the cytosol via pore-like structures (Cortese et al. 2017; Wieland et al. 2021), through which the RNA is able to exit to the cytoplasm. The negative strand serves as template for replication inside the vesicle (Yuan et al. 2024). The positive strand is translated into the polyprotein, which spans the ER membrane in several locations and is subsequently cleaved into its ten proteins (Ci et al. 2023). Assembly and maturation of the virus occurs in the Golgi apparatus, where the pr peptide of the prM protein is cleaved, resulting in the mature virus (Prasad et al. 2017; Sirohi et al. 2016). Mature ZIKV is then released from the cell.

1.1.1.3 ZIKV pathogenesis

The main adverse manifestation of ZIKV in humans is the development of microcephaly (an abnormally small head circumference, associated with physical and intellectual disability) in infants born to mothers who contracted the virus during pregnancy, particularly during the first and second trimesters, since this is when the nervous system is developing (Brasil et al. 2016; Araújo et al. 2018). ZIKV is able to cross the placenta, potentially via infected maternal microglia (Muffat et al.

2018). It infects the nervous system of the developing foetus, inducing cell death in this tissue, mainly in neuronal progenitor cells, but also in other cells of the nervous system, including mature neurons and glia (Garcez et al. 2016; Tang et al. 2016; Li et al. 2016; Oh et al. 2017).

The mechanism by which cell death occurs is multifactorial and differs between cell types. The virus has been shown to induce double-stranded breaks in the host genome, ultimately resulting in apoptosis via the DNA damage response pathway (Ledur et al. 2020; Devhare et al. 2017; Rychlowska et al. 2022; Hammack et al. 2019; Oh et al. 2017). It can also cause accumulation of reactive oxygen species and mitochondrial fragmentation, also resulting in apoptosis (Yang et al. 2020; Han et al. 2021; Ledur et al. 2020), and the ER remodelling that occurs to create replication factories activates the unfolded protein response, which when prolonged induces paraptosis (Monel et al. 2017; Gladwyn-Ng et al. 2018). Cell death of neurons and especially of neuronal progenitor cells, which show the highest viral RNA load (Stokes et al. 2025), directly impacts brain size and structure. Other than cell death, ZIKV can also cause issues in division of neuronal stem cells, further depleting the progenitor pool (Gabriel et al. 2017; Link et al. 2019).

Infection of other cell types can also indirectly affect the developing brain. ZIKV has also been shown to disrupt neurovascular development (Shao et al. 2016) and induce cell death of neuroendocrine cells (Liu et al. 2018a). ZIKV infection of glia (reviewed in Quincozes-Santos et al. 2023) also affects brain development and function negatively, as glial cell function is tightly interconnected with that of neurons. Astrocytes are of particular interest, since ZIKV not only can infect this cell type (Rubio-Hernández et al. 2023; Bell, Field, and Narang 1971), but it shows preferential tropism toward astrocytes compared to neurons (Retallack et al. 2016; Stokes et al. 2025), even if at a lower grade than neuronal stem cells (Retallack et al. 2016; Stokes et al. 2025). Astrocytes can undergo cell death due to mitochondrial damage upon infection (Ledur et al. 2020), but most cells remain productively infected for more than a month, potentially functioning as a viral reservoir around which neuronal apoptosis is more frequent (Limonta et al. 2018; Veilleux and Eugenin 2023). Infected astrocytes also display structural changes upon ZIKV infection (Stefanik et al. 2018; Jorgačevski et al. 2019), as well as differences in the way they respond to cytokines (Das et al. 2022). It is therefore very likely that infection of astrocytes is enhancing neuronal cell death indirectly, as well as playing a role in other aspects of ZIKV pathogenicity, such as changes in brain structure and functional connectivity (Bido-Medina et al. 2018; Raper et al. 2020; Pomar et al. 2019), working alongside the more direct effects of the virus on the neurons and neuronal progenitor cells.

Lastly, the immune response, particularly neuroinflammation, can also contribute to the pathogenesis of ZIKV-associated microcephaly. Activation of innate immune genes such as toll-like receptor (TLR)-3 triggered by ZIKV infection have been shown to disrupt neurodevelopment, resulting in organoid shrinkage (Dang et al. 2016; Ojha et al. 2019), and the expression of inflammatory cytokines and chemokines elicited by the virus (Azevedo et al. 2018; Clé et al. 2020; Hamel et al. 2015) have been associated with neurotoxicity (Takeuchi et al. 2006; Brown 2010; Jhan et al. 2021) and damage to blood brain barrier (BBB) and neurovasculature integrity (Shao et al. 2016; Puhlmann et al. 2005; Garcez et al. 2018), which might help the virus

invade the nervous system. The extracellular matrix of the brain is also affected by ZIKV-induced neuroinflammation, further contributing to the structural changes in the brain (Aguiar et al. 2020).

In addition to microcephaly in infants, ZIKV infection can lead to development of GBS in adults (Santos et al. 2016; Cao-Lormeau et al. 2016). GBS is an autoimmune neuropathy, usually preceded by an infection, characterised by rapidly progressing muscle weakness and paralysis due to motor neuron damage. The later this is diagnosed, the poorer the recovery prognosis is, with about 15% of cases resulting in respiratory muscle weakness and therefore requiring mechanical ventilation, and about 7.5% in death (Willison, Jacobs, and Doorn 2016).

The mechanism by which GBS develops is not yet understood. Even though ZIKV can directly induce cell death of both peripheral nervous system (PNS) neurons and Schwann cells (Dhiman, Abraham, and Griffin 2019; Oh et al. 2017), these are less susceptible to direct ZIKV infection than central nervous system (CNS) cells (Cumberworth et al. 2017). However, the inflammation associated with CNS infection can also affect myelination of the PNS cells (Cumberworth et al. 2017). One of the possible causes for ZIKV-related GBS is molecular mimicry, where high amounts of ZIKV antibodies can cross-react with neuronal membrane proteins (Lucchese and Kanduc 2016), particularly against gangliosides (Anaya et al. 2017). There is also evidence supporting antibody-dependent enhancement of ZIKV: previously existing antibodies can bind to a virus but are incapable of effectively neutralising it, instead diminishing the immune response and allowing for increased viral production and mediating viral entry into the cell resulting in more infected cells (Flipse, Wilschut, and Smit 2013). There is a higher incidence of GBS in patients with pre-existing ZIKV and Dengue virus (DENV) infections (Anaya et al. 2017), as well as with *Mycoplasma pneumoniae* (Meyer Sauter et al. 2016).

1.1.1.4 Immune reaction against ZIKV infection

ZIKV infection triggers an innate immune response, mainly through TLR3, TLR7, TLR8, retinoic-acid inducible gene 1 (RIG-1), melanoma differentiation-associated gene 5 (MDA-5) and stimulator of interferon genes (STING) (Dang et al. 2016; Santos et al. 2023; Garcia et al. 2023), all of which are activated upon detection of viral genetic material. Downstream effects through phosphorylation and subsequent migration to the nucleus of NF- κ B, interferon regulatory factor (IRF) 3 or IRF7 include activation of the interferon response (Shao et al. 2016) and production of pro-inflammatory cytokines (Silva et al. 2019).

ZIKV has evolved to evade the immune response. ZIKV NS3, NS2a and NS4a proteins inhibit the RIG-1 and MDA5 downstream signalling pathways (Ngan et al. 2019; Riedl et al. 2019), and NS1 is able to downregulate the NF- κ B-dependent interferon- α response (Bos et al. 2020). The virus is also able to reduce expression of immune components RIG-1, TLR8, myeloid differentiation primary response gene 88 (Myd88) and tumour necrosis factor TNF- α (Silva et al. 2019), as well as directly impairing translation of type I INF (Bowen et al. 2017), further inhibiting the immune response.

1.1.1.5 ZIKV transmission and current challenges

ZIKV is mainly transmitted by *Aedes spp.* mosquitoes, especially *Aedes aegypti* and *Aedes albopictus*. Some studies have also tested the vector competence of *Culex spp* mosquitoes, but although viral RNA can be detected early post-infection in a very small number of them, they are unable to transmit the disease. (Boccolini et al. 2016; Hall-Mendelin et al. 2016; Liu et al. 2017).

Besides mosquito vector and mother-to-child transmission, there is also evidence for sexual transmission of the virus, although this is not very frequent (Counotte et al. 2018; Duggal et al. 2017). There is also the possibility of infection via blood transfusions (Magnus et al. 2018). Mosquitoes get infected most frequently via ingestion of a viraemic blood meal, but they can also acquire the virus from urine-contaminated water (Du et al. 2019; Grassly, Shaw, and Owusu 2025).

Even though ZIKV cases have declined since 2017, ZIKV, along with other closely related mosquito-borne viruses, such as DENV, West Nile fever (WNV), Chikungunya (CHIKV) are still endemic in some regions of the world, affecting thousands of people globally every year (Rabe et al. 2025). Importantly, due to climate change, the mosquito habitats are expanding (Tjaden et al. 2013; Brady et al. 2013; Franklino et al. 2019), leading to autochthonous cases of infections in regions previously not at risk, including Europe and the USA (Calle-Prieto et al. 2024; Logiudice et al. 2025).

Climate change also increases the frequency of extreme weather events, which affect water sanitation and hygiene practises, thus resulting in potential increased infection of mosquitoes via contaminated wastewater (Grassly, Shaw, and Owusu 2025). Changes in precipitation frequency can also improve larval survival and provide more mosquito breeding sites (Franklino et al. 2019; Chowell et al. 2019), although heavier rainfall can also dilute nutrients in stagnant water, thus affecting larval growth (Chevalier, Tran, and Durand 2013).

Deforestation and intensive farming can enhance contact between human hosts and animal reservoirs (Carlson et al. 2022), thus further increasing transmission of disease and spillover events from new zoonotic infectious diseases and animal reservoirs of known pathogens (Milbank and Vira 2022). Overall, due to the combination of factors described, the regions at risk of arbovirus disease, including ZIKV, are expanding (1.3).

In addition, there are currently no approved disease-specific treatments or vaccines available (reviewed in Malik et al. 2024, and transmission is mainly controlled by limiting contact with the vector (Siew et al. 2025; Onen et al. 2024). Rising numbers of insecticide resistance, particularly organophosphates and pyrethroids in recent years (Kauffman and Kramer 2017) also contribute to the problem, making researching these diseases and their transmission of vital importance looking into the future (Lackritz et al. 2025).

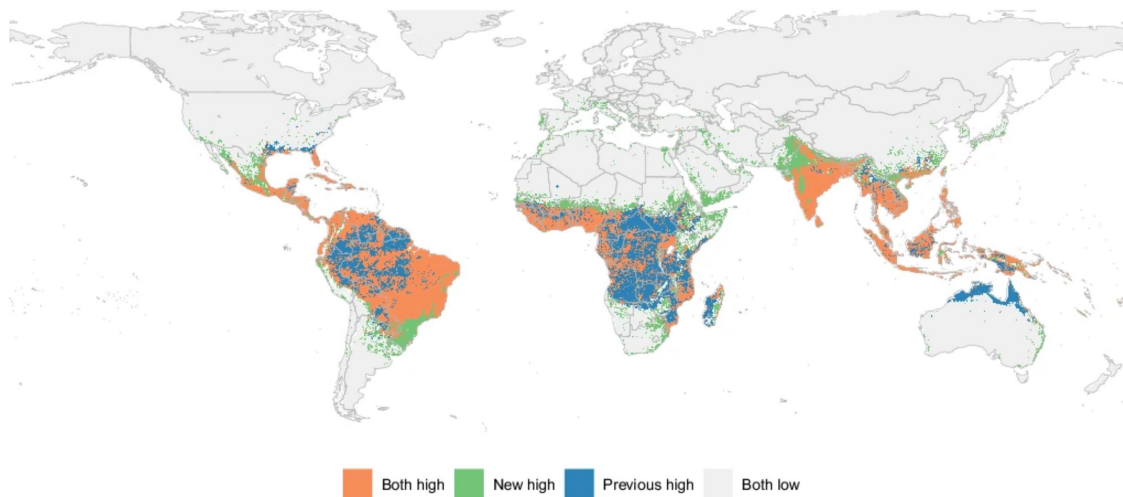


Figure 1.3: Map comparing previous and current global environment suitability for ZIKV transmission. In blue, regions with environmental conditions suitable for ZIKV in 2016 (blue, Messina et al. 2016), 2024 (Lim et al. 2025, green) and both (orange). Image from Lim et al. 2025.

1.1.2 *Drosophila melanogaster* as a model organism

The fruit fly *Drosophila melanogaster* was first described and classified by entomologist J.W. Meigen in 1833. Barely seventy years later, in 1901, C.W. Woodworth recommended its use as a model organism to W.E. Castle, who published the first paper on this organism in 1906 (Castle 1906). It was through him and F.E. Lutz that Thomas Hunt Morgan was introduced to *Drosophila*, which he used as an inexpensive model to study genetics and heredity. His discoveries of genetic linkage (Morgan 1910), chromosomal biology (Morgan 1911) and heredity (Morgan 1915) earned him a Nobel prize in 1933.

Since then, the fly has been one of the most frequently used model organisms, with six Nobel prizes being awarded to work done using it. The advantages that first led Thomas Hunt Morgan to use it (short generation time, large amounts of progeny, cheap and easy to maintain in a lab in large quantities) still stand, plus more than a century of advances have left us with a very good understanding of its genetics, development and physiology, in addition to the wide availability of tools, stock centres and *Drosophila*-specific resources that are publicly accessible.

Most importantly, *Drosophila* is also highly genetically tractable, allowing us to easily generate stable stock lines with complex genetic alterations and thus making experiments that require manipulation of several genes at the same time a lot easier than when working with mammalian models. Thanks to balancer chromosomes, multiply inverted and rearranged chromosomes that are lethal if homozygous (Stone and Thomas 1935), we are able to maintain recessive mutations in stable laboratory stocks. This, added to male flies not show meiotic recombination (Morgan 1914), and

easily identifiable genetic markers, allows for a relatively fast and easy generation of a stable laboratory stock of flies with multiple genetic manipulations. Importantly, with the GAL4-UAS system (Brand and Perrimon 1993), we are able to express a specific gene (or genes) in a time- and tissue-dependent manner. The GAL4-UAS system is described in detail in the Materials and Methods section. Briefly, flies containing the gene we desire to express controlled by the yeast promoter UAS are crossed with flies expressing the GAL4 transcription factor under a promoter with a known tissue or cell-specific expression. The progeny of this cross will express our gene of interest only in the expression pattern of interest.

1.1.2.1 Modelling infection using *Drosophila melanogaster*

Although in their very long time as a model organism fruit flies have been used to study mainly genetics and development, in recent years it has emerged as a very useful model for human infection and innate immunity (reviewed in Harnish, Link, and Yamamoto 2021; Tafesh-Edwards and Eleftherianos 2020). In addition to the advantages previously mentioned, about 75% of human disease-associated genes are significantly conserved in *Drosophila*, making it a useful model for studying human diseases. Importantly, while invertebrates lack adaptive immunity, innate immunity pathways are largely conserved from *Drosophila* to mammals (Rock et al. 1998; Medzhitov, Preston-Hurlburt, and Janeway 1997; Ip et al. 1993; Steward 1987). *Drosophila* has proved a very powerful tool to increase our understanding of this system, since it is possible to dissect their innate immune response without its effects being masked by adaptive immunity (Yu et al. 2022). In fact, the immune function of the two main innate immunity pathways, Toll and Immune deficiency (Imd), were discovered and largely studied in the fly (Rosetto et al. 1995; Lemaitre et al. 1996; Reichhart et al. 1993; Rutschmann et al. 2000; Lemaitre et al. 1995b, reviewed in Valanne, Wang, and Rämet 2011 and Myllymäki, Valanne, and Rämet 2014).

In addition to studying innate immunity by directly infecting flies with pathogens, either via injection or orally (Neyen et al. 2014), the potent advantages of the GAL4-UAS system have allowed us to study virulence factor action by dissecting detailed host-pathogen interactions by ectopically expressing pathogen proteins (Shah et al. 2018) or disrupting part of an immune pathway (Chauhan et al. 2024) in a tissue-specific manner. There are also commercially available stocks, deficient for different components of the immune pathways, which can be used to study the interactions between them and pathogens (Xu et al. 2023). *Drosophila* has also been used for drug screening (Jefferson et al. 2006) and finding potential drug targets (Wongsaroj et al. 2018). Overall, *Drosophila* has proved to be a very powerful model organism in the context of infection.

1.1.2.2 Modelling ZIKV infection using *Drosophila*

Despite the many advantages of the fly as a model for human infection, modelling human neurological infections in this organism has some disadvantages, namely the lack of adaptive immune system and the differences in the morphology and physiology of the nervous system. However, *Drosophila* still remains a useful model for preliminary studies, as well as for detailed dissections of molecular mechanisms

of pathogenesis and innate immunity (reviewed in Benoit et al. 2022). Even then, several successful studies on ZIKV biology and pathogenesis have been performed in this model.

In 2018, Shah et al. used the GAL4-UAS system to express ZIKV NS4 in the brain, discovering it interacted with ANKLE2, a microcephaly-related gene, to provoke microcephaly via disruption of asymmetric cell division in neuroblasts (Shah et al. 2018; Link et al. 2019). Overexpression of ZIKV viral proteins using this system also helped find other potential effects of the virus, such as perturbation of the JAK/STAT and Notch pathways, which resulted in reduced eye growth independently of apoptosis (Harsh et al. 2020). Further research on *Drosophila* has also been used to elucidate innate immunity responses to ZIKV, infecting whole flies deficient for certain pathway components via **injection** (Harsh et al. 2018b; Liu et al. 2018b). The metabolic response to infection, including its effect on immunity, has been studied in *Drosophila* for both ZIKV and other arboviral infections (Trammell and Goodman 2019; Tafesh-Edwards, Kalukin, and Eleftherianos 2022). Importantly, use of *Drosophila* lines deficient for STING helped elucidate an important role for this highly conserved protein, present in humans, in the immune response against ZIKV in the brain (Liu et al. 2018b; Liu et al. 2022; Martin et al. 2018).

1.1.2.3 Modelling mosquito vectors using *Drosophila*

In addition to using the fly to model infection pathogenesis and molecular interactions in human disease, there is also a large potential in its usage to model mosquito vectors, taking advantage of the very established model organism to elucidate viral interactions with the vector.

Drosophila melanogaster is closely related to mosquitoes, both groups diverging 250 million years ago (Yeates and Wiegmann 1999), and several studies on the homology between the fruit fly and different species of mosquitoes have been published. A study comparing 121 *Aedes aegypti* genes with the *Drosophila melanogaster* genome found 72% of *Aedes* genes were conserved, even if there was evidence of large chromosomal rearrangements through evolution (Severson et al. 2004). My own analysis (Chapter 4) found 68% of *Drosophila melanogaster* genes to have an ortholog in *Aedes aegypti*. Immune related genes in particular are remarkably conserved across both organisms (Waterhouse et al. 2007). In addition, there is further evidence that the two species have retained similarities outside of the protein-coding sequences in terms of gene regulation (Skavdis et al. 1996; Schember et al. 2024; Engström et al. 2007; Nene et al. 2007).

In fact, *Drosophila melanogaster* has already been used as a model for mosquito vector infection before: in 2008, S. Brandt et al were able to identify genes that regulate *Plasmodium* growth using *Drosophila melanogaster*. Flies were able to sustain an active infection after injection with the parasite, even if it is not one of its natural hosts in the wild (Brandt et al. 2008). *Drosophila melanogaster* has also been used to study flavivirus infection, including with ZIKV, of the salivary glands (Palmer et al. 2020). Nevertheless, limitations remain and these will be discussed in the relevant chapters.

Overall, due to the aforementioned effects of climate change and other human-related disruptions to the environment, the overall consensus amongst scientists is that vector-borne diseases will continue to expand, both geographically with mosquito habitats expanding, and in time, as mosquito breeding seasons are extending into earlier in spring and later in autumn (Caminade, McIntyre, and Jones 2018). Improving our understanding of the basic biology in pathogen-vector interactions might help us implement new vector control measures, a crucial step in controlling their spread (Thomson and Stanberry 2022). While *Drosophila melanogaster* has been used to model human infection and pathogenesis, including with ZIKV, only a few studies have used it to model the closely related mosquito in the context of infection.

1.1.3 Objectives

The growing importance of studying pathogen-vector interactions led me to study the suitability of using *Drosophila melanogaster* as a model for flavivirus infection of their mosquito vectors, particularly with ZIKV. In Chapter 3, I studied oral infection of *Drosophila melanogaster* larvae. In Chapter 4, I explored oral ZIKV infection in adults, with a focus on the dissemination of the virus through the organism.

1.2 Local translation of RNA in the peripheral nervous system (PNS)

ZIKV has been shown to affect expression levels of motor proteins when infecting mammalian tissue culture (Giovannoni et al. 2020). In turn, this can affect RNA localisation, which can disrupt cellular asymmetry. Cellular asymmetry is essential to life, as it allows for functional specialisation of different regions of the cell. This is especially true for the nervous system, as both neurons and glial cells are very large cells with long cytoplasmic processes, which make highly specialised contacts with many other cells. This local specialisation is achieved by the different protein composition of the cell regions, which in turn is the result of a combination of protein transport and locally translated RNA (Steward and Schuman 2003).

1.2.1 Cell asymmetry and local translation in neurons

Santiago Ramon y Cajal defined the neuron as the primary structural and functional unit of the nervous system in the late 1800s. He used Golgi's silver staining method to study their morphology, producing hundreds of beautiful drawings of this cell's highly ramified morphology (Ramón y Cajal 1909). Although the specific morphology varies between neuronal subtypes, the basic structure includes the cell body or soma, shorter dendritic protrusions and a longer axonal protrusion. The axon and dendrites constitute more than 75% of the neuronal volume (Beining et al. 2017), and they can make connections with up to ten thousand other cells (Pakkenberg et al. 2003). As such, it is very important that the cell is able to simultaneously and dynamically respond to stimuli in individual synapses. This is a remarkably

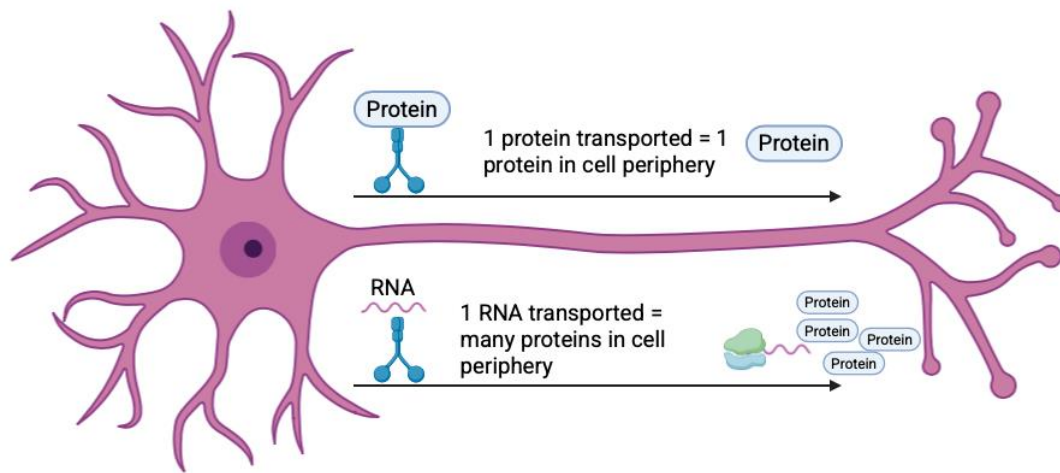


Figure 1.4: Diagram highlighting the benefits of local translation at the cell periphery.

A neuronal axon is used as an example, where transporting a single copy of a protein results in one copy of the protein in the synapse, compared to transport of RNA and local translation in the distal region of the axon, which can result in many copies of the protein with lower load on the transport system. Created with biorender.com.

complex challenge, since there are between one to three thousand different proteins in each pre- and post-synapse (Pielot et al. 2012), each present in 150-20000 copy numbers (Richter et al. 2018), and they must be tightly controlled in quantity, space and time. Given that some motor neuron axons can be metres long, local translation of proteins at the synapse can facilitate the process (Biever, Donlin-Asp, and Schuman 2019; Glock, Heumüller, and Schuman 2017), by allowing for dendrite-specific protein expression (Govindarajan et al. 2011; Andersen et al. 1977) that is faster than transporting synthesised protein from the cell body and more energy efficient, as several proteins can be produced from a singular mRNA molecule (Fonkeu et al. 2019; Williams et al. 2016; Rangaraju, Dieck, and Schuman 2017, 1.4) .

Ribosomes were first found in dendrites forty years ago (Steward and Levy 1982). The prevailing view has been that local translation was only important in the context of axonal development or repair after injury (Giuditta, Cupellot, and Lazzarini 1980; Bartlett and Banker 1984; Terenzio et al. 2018) or synaptic plasticity in a post-synaptic environment (Martin et al. 1997; Kang and Schuman 1996; Aakalu et al. 2001; Steward et al. 1998; Ouyang et al. 1999), but in recent years, there has been a raise in research of local protein synthesis in the presynapse (Hafner et al. 2019; Mathur et al. 2018; Briese et al. 2016; Biever et al. 2020; Younts et al. 2016; Scarnati et al. 2018). This advance has been aided by the development of new methods such as primary cultures in microfluidics chambers (Saal et al. 2014) and highly multiplex single-molecule RNA hybridisation methods such as seq-FISH (Shah et al. 2016), FISSEQ (Lee et al. 2015) and MERFISH (Moffitt et al. 2016), which have helped bypass the difficulty of isolating local transcriptomes in synapses, where the tight interactions between neurons and glia and small size of the axon make applying traditional RNA-seq methods extremely challenging.

Thanks to these advances, we have been able to gather information on the transcriptome in axonal and dendritic projections (Briese et al. 2016; Perez et al. 2021; Middleton, Eberwine, and Kim 2019; Cajigas et al. 2012). Interestingly, even though there is no ER and Golgi apparatus in neuronal protrusions (Krijnse-Locker et al. 2017), RNA encoding transmembrane proteins has been identified in these transcriptomes (Briese et al. 2016), some of which have been shown to be actively translated: injecting ion channel RNA to isolated squid giant axon changes the electrical current transmitted by the axon (Mathur et al. 2018), thus demonstrating that there is active local translation in the axon. Although the exact translation mechanism is not known yet, the abundant components of the signal recognition pathway (SRP), which transiently binds ribosomes to an ER membrane, present in the axon (Merianda and Twiss 2013; Chuang et al. 2018; Maciel et al. 2018) might explain the difficulty of identifying rough ER in axons, suggesting a transient binding of ribosomes instead (Mathur et al. 2018; Biever, Donlin-Asp, and Schuman 2019). Several research groups have used puromycin or other methods of labelling nascent peptides to detect protein synthesis in neuronal protrusions (Erdmann et al. 2015; Yuet et al. 2015; Sambandan et al. 2017), and Ribosomal cross-linking and RNA sequencing has been used to detect which genes are being actively translated in developing and mature axons of the visual system (Shigeoka et al. 2016). Fluorescent tagging of specific genes of interest with the MS2 system has allowed *in vivo* visualisation of translation dynamics in neurons (Wu et al. 2016).

Asymmetric protein composition and local translation are particularly important for synaptic plasticity, given the need for rapid and specific production of the proteins needed for the strengthening of the connection that takes place after long term potentiation of the synapse (Chen et al. 2022; Williams et al. 2016; Fonkeu et al. 2019). Synaptic plasticity has been associated with processes such as memory formation, emotional processing and learning (Abbott and Nelson 2000), thus making it very important for adult brain function. In the post-synaptic compartment, there are abundant signalling and scaffolding protein mRNAs (Cajigas et al. 2012), and local translation of several of them is required for neuroplasticity (Nayak et al. 1998; Miller et al. 2002; Huber, Kayser, and Bear 2000). Activity-dependent local translation of CaMKII in particular has been studied in depth and shown to be essential for synaptic plasticity (Bagni et al. 2000; Aakalu et al. 2001; Kuklin et al. 2017), thus demonstrating the importance of local translation in the post-synaptic compartment for neuroplasticity. Neurotransmitter receptors are also locally translated at the dendrites (Nayak et al. 1998; Muddashetty et al. 2007; Sutton et al. 2006; Smith et al. 2005; Ju et al. 2004), and their localisation is essential for plasticity (Swanger and Bassell 2013; Udagawa et al. 2012; Mameli et al. 2007; Malinow and Malenka 2002; Schiweck and Kiebler 2019). There is also evidence for the importance of local translation in the presynaptic compartment in establishing and maintaining synaptic plasticity (Zhang and Poo 2002; Beaumont et al. 2001; Scarnati et al. 2018; Younts et al. 2016; Martin et al. 1997; Shigeoka et al. 2016). Synaptic plasticity is therefore tightly controlled by local translation of mRNA in both the pre- and post-synaptic compartments.

1.2.2 Cell asymmetry and local translation in glial cells

When glial cells were discovered, at the same time as neurons, they were believed to act only as structural support for neurons (hence their name, which derives from the Greek word for glue, "glia"). Although research into this cell type is years behind that of neurons, it has become clear over the past half century that glia are much more than simply neuron glue.

These cells are very abundant, constituting one to two thirds of the brain mass in mammals (Azevedo et al. 2009). There are four main types of glia in the human central nervous system (CNS): astrocytes, oligodendrocytes, microglia and glial progenitor cells. Less common glial cells in the brain are tanycytes and pituicytes. In the PNS, Schwann cells replace oligodendrocytes and myelinate the neuronal axons. There are also non-myelinating Schwann cells, which engage with the motor neuron at the neuromuscular junction (NMJ), as well as enteric glia in the digestive system and satellite glia engaging with sensory neurons.

Oligodendrocytes and astrocytes are also highly ramified cells, with protrusions that extend up to several hundred micrometers from the cell body and which can make contact with thousands of cells, in the case of astrocytes going as far as to respond to respond to calcium signalling and inhibiting neuronal activity (Ma et al. 2016). As such, there is a similar need to that of neurons of tightly controlling the protein composition in the different regions of the cell. Localised translation in glial cells was first reported back in 1982, in oligodendrocytes (Colman et al. 1982).

1.2.2.1 Oligodendrocytes

Oligodendrocytes are highly asymmetric, branched cells (Pfeiffer, Warrington, and Bansal 1993). Myelin transcript in PNS oligodendrocytes was the first RNA detected in the cellular periphery (Colman et al. 1982), but many other transcripts (Garcia-Ladona et al. 1997; Thakurela et al. 2016; Holz et al. 1996; Lopresti et al. 1995; Ghandour and Skoff 1991) have also been found to be localised to the cellular protrusions. Given the importance of myelination in health and disease, especially in motor neuron disease, the transport of myelin basic protein mRNA granules along microtubules via binding of RNA-binding proteins (RBP) has been of interest to several research groups (Herbert et al. 2017; White et al. 2008; Torvund-Jensen et al. 2014; Laursen, Chan, and FrenchConstant 2011), and is the most well-studied system of mRNA localisation in elongated cells. Thanks to local translation, one oligodendrocyte is able to produce 10^5 myelin molecules per minute (Yeung et al. 2014), and aggregation of the RBP TDP-43 in the cell type results in 97% of cases of ALS (Lorente Pons et al. 2020), thus showcasing the importance of RNA transport and local translation in this cell type.

The role of oligodendrocytes in neuroplasticity is not yet well understood, especially beyond the effect of myelination (Pan et al. 2020; Fields 2008; Faria et al. 2021; Bacmeister et al. 2020). However, they have been shown to regulate neurotransmission: oligodendrocyte progenitor cells express voltage-activated ion channels that can react to nervous impulses (Káradóttir et al. 2008; Kirischuk et al. 1995), and oligodendrocytes increase speed of action potentials along the axon (Yamazaki et al.

2007). They also express proteins with the ability to regulate transmission directly at the pre- and post-synaptic components (Raiker et al. 2010; Jang et al. 2019; Hughes and Appel 2019). Overall, research points towards a more complex role for oligodendrocytes in synaptic plasticity.

1.2.2.2 Astrocytes

Astrocytes are another highly branched glial cell subtype. They are the most abundant glial type in the human brain, where they support neurons metabolically and structurally (Magistretti and Allaman 2018; Nortley and Attwell 2017), contribute to synapse formation (Minocha et al. 2015; Kucukdereli et al. 2011; Vainchtein et al. 2018), function (Araque et al. 2014; Kofuji and Araque 2021; Breton-Provencher et al. 2022) and plasticity (Ota, Zanetti, and Hallock 2013; De Pittà, Brunel, and Volterra 2016; Sanz-Gálvez et al. 2024) and conform the blood-brain barrier (BBB) (Daneman and Prat 2015). Astrocytes are also able to respond to calcium signalling and influence neuronal activity (Ma et al. 2016; Khakh and McCarthy 2015; Araque, Carmignoto, and Haydon 2001; Adamsky et al. 2018; Araque et al. 2014). In all of these functions, their asymmetric morphology and composition plays an important role (Sapkota et al. 2022; Oudart et al. 2020; Mazaré et al. 2020; Boulay et al. 2017), although the mRNA localisation and translation, as well as its role, are less well-understood than that of oligodendrocytes.

However, astrocytes have been a lot more studied than oligodendrocytes in the context of synaptic plasticity, due to their close physical and physiological interactions with neurons. Astrocytes have a known function regulating plasticity, able to both regulate long-term potentiation (LTP) or strengthening of the synapse (Tazerart et al. 2020; Ceglia et al. 2023; Bonansco et al. 2011; Valtcheva and Venance 2016; Martinez-Gallego et al. 2022; Falcón-Moya et al. 2020) and long-term depression (LTD) or weakening of the synapse (Cuaya, Martínez-Gallego, and Rodríguez-Moreno 2024; Pérez-Rodríguez et al. 2019; Cui et al. 2016; Min and Nevian 2012). The ability of astrocytes to regulate extracellular Ca^{2+} is also important for neuroplasticity, as post-synaptic Ca^{2+} must be elevated for plasticity to take place. Disruption of some Ca^{2+} -binding proteins such as $\text{A100}\beta$ or L-type voltage- Ca^{2+} channels (VGCCs) leads to abnormal regulation of LTP and LTD (Inglebert et al. 2020; Brockett et al. 2018; Kim et al. 2015). Gliotransmitters secreted by astrocytes have also been shown to mediate synaptic plasticity (Bannon et al. 2017; Shen et al. 2008; Andrade-Talavera et al. 2016; Rebola et al. 2011; Henneberger et al. 2010; Fossat et al. 2012). Lastly, there is evidence for cooperation between astrocytes and oligodendrocytes for regulation of neuronal excitability and axonal conduction via K^+ buffering (Kamasawa et al. 2005; Micu et al. 2016; Looser et al. 2024; Bettefeld, Klooster, and Kole 2016). Although this phenomenon has predominantly been studied along axons, the tight interactions between neurons and glia that occur at the synapse point toward a model where all cell types regulate synaptic plasticity jointly.

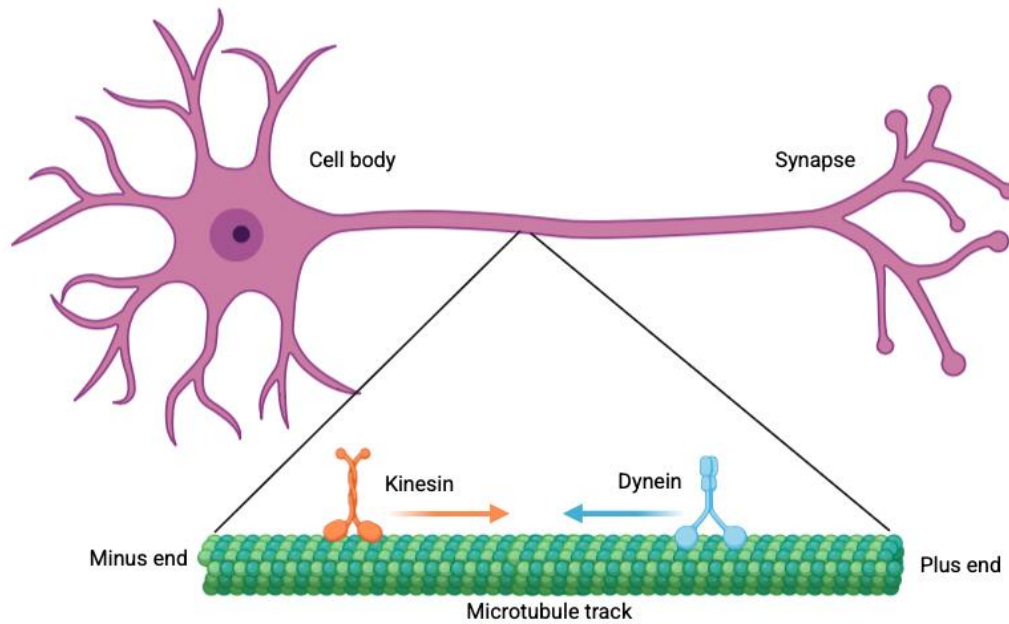


Figure 1.5: Representation of molecular transport polarity in neurons. The axon contains microtubules (green), arranged so that their plus end is at the synapse and the minus end towards the cell body. Molecular motors are only able to move in one direction, indicated with an arrow: kinesin (orange) can only move towards the plus end and dynein (blue) can only move towards the cell periphery. Made with biorender.com.

1.2.3 Mechanism of RNA transport and local translation in elongated cells

The importance of RNA transport and local translation in brain health and disease (Lin, Tartwijk, and Holt 2021) has led to research into the RNA transport and local translation process. Work done mostly in oligodendrocytes has allowed us to develop a basic understanding of the process, although research is still ongoing on the details of the process and how it extrapolates to other cell types. The process begins with RBPs binding mRNA in a transcriptionally repressed state. Together, the RNA and the binding proteins form membrane-less RNA granules, which are bound to motor proteins and transported along the cytoskeleton toward their destination (Blanco-Urrejola et al. 2021). Although in most cases the RNA remains in a translationally repressed state (Buxbaum, Wu, and Singer 2014), there are cases where the protein is synthesised along the axon (Cioni et al. 2019) or dendrites (Wang et al. 2016). It is yet unclear how RNAs are targeted to their final translation locations, as well as how they are made accessible for ribosomes (Das, Singer, and Yoon 2019).

Transport of RNA granules occurs mainly along the microtubule cytoskeleton (Kanai, Dohmae, and Hirokawa 2004), via binding to kinesins and dyneins. Microtubules are polar structures, and transport by one motor protein is unidirectional: kinesins can move toward the plus end of the microtubule, and dyneins, toward the minus end (Hirokawa 2006). That means the directionality of movement of the RNA granule is determined by its affinity toward one or other type of motors (1.5).

The microtubule cytoskeleton is not arranged at random within the cell: in axons, microtubules extend so that their minus end is in the cell soma and the plus end

grows toward the synapse, while dendrites have a mix of orientations (Baas et al. 1988). Oligodendrocytes have their microtubules arranged in the same way axons do (Weigel, Wang, and Fu 2021; Lunn, Baas, and Duncan 1997; Fu et al. 2019). The microtubule structure of astrocytes is not known yet, but the microtubule cytoskeleton in their cytoplasmic protrusions is very stable compared to that of their cell body (Eom et al. 2011).

1.2.4 Objectives

In a now published paper, previous work in the Davis lab had predicted transcripts of motor proteins to be localised at glial protrusions (Lee et al. 2024). I became interested in the role of distally translated motors in the nervous system, as their disruption has been associated with neurodegenerative diseases (Millecamps and Julien 2013). In Chapter 5, I described how I used the *Drosophila melanogaster* larval neuromuscular junction (NMJ), a well-established model of neuroplasticity, to perform my experiments. I optimised a protocol for single-molecule imaging of RNA molecules (Olivares-Abril et al. 2024), which I used to validate the predicted localised transcripts. I then used behavioural analysis of glial knock-down of the candidate genes to screen for phenotypic effects.

One of the candidate genes, kinesin heavy chain (khc) was also predicted to be disrupted by ZIKV infection from a mammalian tissue culture RNA-seq screen (Giovannoni et al. 2020).

Chapter 2

Materials and Methods

2.1 *Drosophila melanogaster* stock lines

Fly stocks were kept at 25°C or 18°C with 12h light-dark cycles. They were fed on cornmeal food. Larvae were collected at wandering L3 stage. Adults were collected at the time points specified for each experiment. For infection experiments, unless otherwise specified, only mated females were collected.

The stocks used were:

Line	Genotype	Description	Source
OrR	;;;	Wild type background	Davis lab stocks
W ¹¹¹⁸	W ¹¹¹⁸	Wild type background	Davis lab stocks
Repo>GFP	UAS-mcd8-GFP/" ; Repo-Gal4/TM6,tb	Expresses membrane-targeted GFP driven by repo in a pan-glial manner	Davis lab stocks
Mdr65>GFP	UAS-mcd8-GFP/" ; Mdr65-Gal4/TM6,tb	Expresses membrane-targeted GFP driven by Mdr65 in subperineurial glia	Stock created by Dr D. Gala
mCh RNAi	;;UAS-mCherry-RNAi/"	Expresses dsRNA for RNAi of mCherry under UAS control	BDSC (35785)
Sting RNAi	;;Sting RNAi/"	Expresses dsRNA for RNAi of Sting under UAS control	BDSC (31565)
Sting ^{EY06491}	;;Sting ^{EY06491} /"	Transgenic insertion stock with decreased expression of Sting (Liu et al. 2018b)	BDSC(16729)
Didum RNAi	;;UAS-Didum RNAi;	Expresses dsRNA for RNAi of Didum	BDSC (55740)
DCTN1-p150 RNAi	;;UAS-DCTN1-p150 RNAi;	Expresses dsRNA for RNAi of DNCT1-p150 under UAS control	BDSC (24760)
Dlic	;;UAS-Dlic RNAi;	Expresses dsRNA for RNAi of Dlic	BDSC (66981)
Khc RNAi	;;UAS-khc RNAi;	Expresses dsRNA for RNAi of khc under UAS control	VDRC(44337)
Klc RNAi	;;UAS-klc RNAi	Expresses dsRNA for RNAi of klc under UAS control	BDSC (33934, stock no longer available)
Klp10A RNAi	;;UAS-Klp10A	Expresses dsRNA for RNAi of Klp10A under UAS control	BDSC (33963)
Lis-1 RNAi	;;UAS-Lis-1 RNAi	Expresses dsRNA for RNAi of Lis-1 under UAS control	BDSC (28663)
Mhcl	;;UAS-Mhcl RNAi;	Expresses dsRNA for RNAi of Mhcl RNAi	BDSC (51456)
sw RNAi	;;UAS-sw RNAi	Expresses dsRNA for RNAi of sw RNAi	BDSC (30505)
unc-104 RNAi	;;UAS-unc-104 RNAi;	Expresses dsRNA for RNAi of unc-104 RNAi	BDSC (53296)

Table 2.1: List of *Drosophila melanogaster* stocks used in this thesis.

2.2 Spatio-temporal control of RNAi and marker expression

For experiments that required tissue- or time point-specific gene knock-down or expression of fluorescent markers, a GAL4-UAS system was used (Brand and Perrimon 1993). This method relies on the yeast transcriptional activator Galactose 4 (GAL4) and Upstream Activator Sequence (UAS). A transgenic line that expresses the GAL4 activator in a known pattern is crossed to a second transgenic line, which

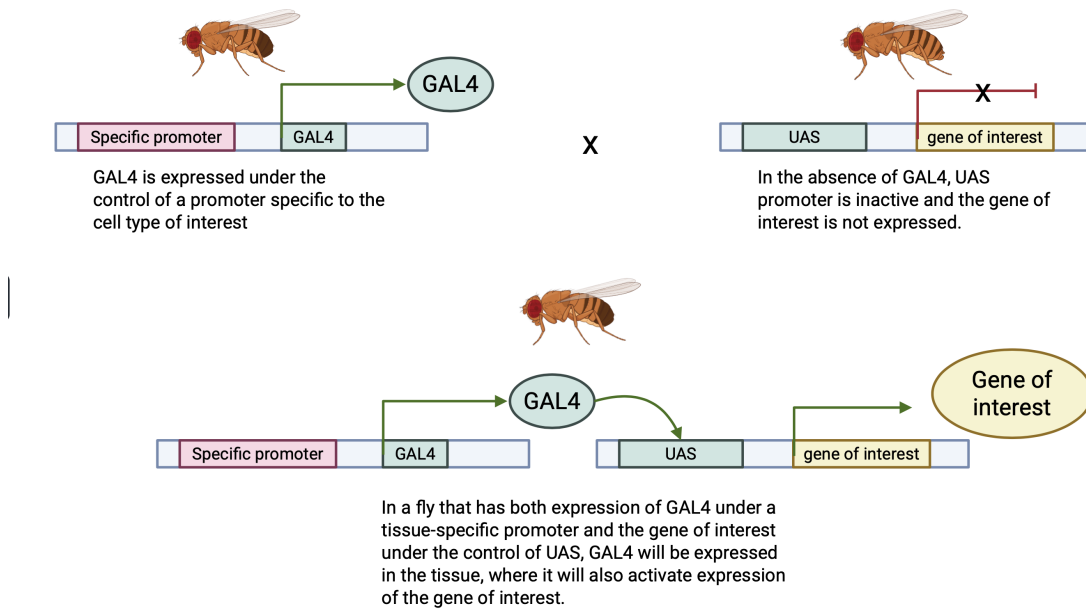


Figure 2.1: Schematic representation of the use of GAL4-UAS in *Drosophila melanogaster* for spatial control of expression of a gene of interest. In one transgenic fly stock (left), transcriptional activator GAL4 is expressed under the control of a specific promoter, known to activate expression in a cell type or tissue of interest. therefore, GAL4 will only be expressed in this cell type or tissue. A separate fly stock (right) contains our gene of interest (RNAi, fluorophore, gene for overexpression, etc.), which is expressed under the control of the GAL4-dependent UAS promoter. In the absence of GAL4, the gene is not expressed. The progeny of these two lines (bottom) will inherit both the GAL4 gene, to be expressed in the tissue-specific pattern, and the UAS-dependent gene of interest. As a result, GAL4 expression will activate expression of the gene of interest in a tissue-specific manner. Diagram made with Biorender

contains a gene of interest preceded by the UAS sequence. Therefore, transcription of the gene of interest will only be active in those cells where GAL4 is expressed. To silence expression of a gene, a transgenic line containing the UAS promoter preceded by inverted repeat sequences complementary to the gene of interest (RNAi). When in a cell that expresses GAL4, the RNAi will be transcribed and, thanks to the silencing RNA machinery, will result in degradation of the RNA, therefore effectively knocking down the gene specifically in the tissue (Figure 2.1).

Fly cross details can be found in the specific chapters the lines are used.

2.3 ZIKV strains, production and titration

2.3.1 Cell culture

CCL81 Vero monkey kidney cells were maintained at 37°C in Dulbecco's modified Eagle Medium (DMEM) supplemented with 10% foetal bovine serum (FBS) and 1% penicillin-streptomycin, at 5% CO₂, or without CO₂ equilibration in Leibovitz L-15 media supplemented with 10% FBS and 1% penicillin-streptomycin. C6/36 cells were maintained at 28°C in Leibovitz L-15 media supplemented with 10% FBS and 1% penicillin-streptomycin, without CO₂ equilibration. For C6/36, 25%

of the primed media was maintained when passaging the cells.

2.3.2 Virus production

Viral strains were kindly gifted by Prof. Alfredo Castello and Prof. Sumana Sanyal. The virus was initially propagated in CCL81 cells by infecting approximately 3×10^7 cells with around 2×10^7 pfu of the virus, diluted in enough DMEM without FBS, pH sensor or antibiotics to cover the cell monolayer. A three hour period for virus adsorption shaking every thirty minutes was allowed, before adding media. Seven days post-infection, supernatant was collected and centrifuged at 4°C for 3 minutes at 2000 rpm. The supernatant was then filtered using a 0.45 µg filter bottle and concentrated to 25% of its original volume (Thermoscientific, #88533). Concentrated viral stock was maintained at -80°C.

Subsequent propagations of the virus were performed in C6/36 cells.

2.3.3 Virus titration

CCL81 cells were seeded in a six-well plate. When confluent, they were challenged with ten-fold serial dilutions of the viral stock. They were incubated at 37°C for 90 minutes, lightly shaking them every 15 minutes. Supernatant was then replaced with 3% carbomethylcellulose. After 5 days incubating at 37°C, cells were fixed in 4% paraformaldehyde (PFA) in phosphate buffer saline (PBS). PFA was replaced with 1% w/v crystal violet solution in 20% ethanol and incubated for 15-20 minutes, after which the cells were carefully washed with miliQ water and left to dry before counting plaque forming units (pfu).

2.3.4 Virus strains

MR766 (African lineage) was used for the experiments described. This stock was kindly gifted by Professor Alfredo Castello.

2.4 Detection of *Wolbachia*

Wolbachia is an endosymbiotic bacteria, transmitted vertically, which is very frequently carried by insects in the wild. It is also present in many laboratory fly stocks. *Wolbachia* can confer resistance to infection, including with ZIKV, to its insect host (Cogni et al. 2021; Teixeira, Ferreira, and Ashburner 2008; Stevanovic, Arnold, and Johnson 2015; Minwuyelet et al. 2023; Tafesh-Edwards and Eleftherianos 2023). Therefore, all flies used in infection experiments were periodically tested for presence of *Wolbachia* by extracting genomic DNA and performing a PCR. Fly stocks found to be infected with the bacteria were treated with tetracyclin 0.3% for two generations and retested. Primer sequences can be found in the Appendix.

2.5 Genomic DNA extraction and PCR

2.5.1 DNA extraction

Two male and two female adult flies were collected and washed first in 70% ethanol and then in water. Flies were then homogenised in 50 μ L TNES buffer (10 mM Tris-Cl pH 7.5, 400 mM NaCl, 100 mM EDTA, 0.6% SDS) and 4 μ L proteinase K (20 mg/mL). After incubating at 55°C for three hours, 146 μ L TNES buffer were added, as well as 67 μ L of 5M NaCl, to a final concentration of 1.25M. Samples were centrifuged at 24000 g at room temperature for 10 minutes. After adding 270 μ L of ice cold 100% ethanol, samples were centrifuged at 24000g for 10 minutes again, this time at 4°C. The supernatant was discarded, and the DNA pellet was washed gently with 900 μ L of 100% ethanol. Samples were centrifuged 5 minutes at 24000 g, and after discarding the supernatant, washed a second time in 70% ethanol. After centrifuging for 5 minutes at 24000 g and discarding the second wash, the pellets were left to air dry open on a hot block at 35°C for 10-15 minutes. They were resuspended in TE buffer and stored at -20°C.

2.5.2 DNA amplification

For *Wolbachia* detection, PCR was performed according to the manufacturer's instructions using the Taq PCR kit (NEB #E5000S). 100 ng of DNA were added to each reaction. Other PCR reactions were performed using the MyTaq Red Mix kit from Meridian Bioscience (BIO-25043), according to the manufacturer's instructions, adding 200 ng of genetic material to each reaction.

The following base thermocycling program differed depending on the primers used, and can be found in each chapter. Primer sequences can be found in the Appendix. The resulting amplified genetic material was run through an agarose gel and stained using ethidium bromide.

2.6 Detection of viral RNA

To allow digestion and emptying of the gut, larvae were collected and left to feed in PBS for 30 minutes. Then they were washed five to ten times in PBS before flash-freezing them in dry ice. Similarly, adults were collected and left in a vial without food for three hours before freezing them.

2.6.1 RNA extraction

RNA was extracted following a modified protocol for TRIzol (Invitrogen #15596026) (Allen 2016). 250 μ L TRIzol were added directly to the frozen sample, which was immediately homogenised with a disposable pestle and a motorized chuck (90 seconds for adult flies and full larvae, 30 seconds for dissected soft tissues). 250 μ L TRIzol were added before centrifuging at 12000 g for 10 minutes at 4°C. In samples of adult flies, the supernatant is covered by a fatty layer, which was removed carefully before collecting it and incubating it for 3 minutes at room temperature. 0.1 mL chloroform was added to each sample, shaking the mix by hand after securely capping the tube.

Samples were then centrifuged at 12000 g for 15 minutes at 4°C, which results in a low red-phenol phase, an interphase and an upper colourless aqueous phase with the RNA. The upper phase was collected, and 250 µL isopropanol and GlycoBlue to a final concentration of 100 µg/mL were added. Samples were incubated for an hour at room temperature and then centrifuged at 12000 g for 30 minutes at 4°C, which causes the RNA to form a pellet. The pellet was washed with 0.5 mL 75% ethanol, vortexed to be dislodged, and centrifuged 7500 g for 5 minutes at 4°C. The ethanol was then discarded, and the pellet allowed to air dry open on the bench for 5-10 minutes. RNA was resuspended in RNase-free water and diluted to a concentration of 50 ng/µL. Samples were stored at -80°C.

2.6.2 RT-qPCR

RT-qPCR was performed according to manufacturer's instructions using a Luna Universal One-Step RT-qPCR kit (NEB #E3005). 25 ng RNA were added to each 10 µL reaction. The thermocycler was programmed to hold 55°C for 10 minutes, then 95°C for 1 minute, followed by 45 cycles of 10 seconds at 95°C and 30 seconds at 60°C before reading the plate. The melt curve was measured between 60°C and 95°C at 0.5°C intervals. Relative fold expression was calculated using the $2^{-\Delta\Delta C_t}$ method. Housekeeping gene rp49 was used for normalising. The primers used can be found in the Appendix.

2.7 *Drosophila* oral infection with ZIKV

2.7.1 Larval infection

2.7.1.1 Egg collection and dechoriation

Before infection, egg laying was synchronised. For this, 100-150 adult flies were placed in cages with apple juice agar plates and a dollop of yeast paste, which were kept at 25°C in the dark for twenty-four hours. After this time had passed, apple juice agar plates were changed and the cages moved to the light. After three hours, embryos were collected from the plates with a soft brush and water.

Embryos were poured into a sieve and washed with 14% bleach for 45 seconds, until most of the embryos were floating. Bleach was washed away thoroughly with water, and the dechorionated embryos were transferred to fresh apple juice agar plates with a soft brush. They were incubated at 25°C for sixteen to twenty-four hours.

2.7.1.2 Infection and gut microbiota ablation

A paste containing 0.1 g of yeast, water, 10^6 pfu of ZIKV (or the equivalent volume of DMEM for mock conditions) and an antibiotic cocktail (128 µg Ampicillin, 128 µg Doxacyclin, 200 µg Kanamycin, 40 µg Rifampicin) was placed in the apple juice agar plates. These were incubated at 25°C for twenty-four hours, when infection was refreshed by adding the same amount of virus (or DMEM) and enough yeast to avoid drowning the larvae. After eight hours, the yeast paste and crawling larvae were scooped into a standard cornmeal food vial, which was maintained at 25°C.

To confirm gut microbiota ablation, larvae guts were dissected in PBS and homogenised in 50% glycerol. They were plated onto an MRS agar plate and incubated at 30°C for forty-eight hours.

2.7.2 Adult fly infection

Oral infection of adults was performed adapting previously described protocols (Segrist et al. 2021; Sansone et al. 2015; Xu et al. 2013). First, ingestion of the virus was synchronised by starving three- to five-day old mated females, placing them on a water-only diet overnight and then starving them for three hours. For infection, a whatman paper was soaked in a 5% sucrose solution with 10^6 pfu of ZIKV (or the equivalent volume of DMEM for mock conditions) and introduced into the vial. Flies were kept for three days at 25°C before being transferred to standard cornmeal food vials. The day of the transfer was considered DPI0.

2.8 Tissue dissections

2.8.1 Larvae

Before dissection of any tissue, larvae were transferred to vials of PBS for at least 30 minutes to empty their gut. Afterwards, they were thoroughly washed by repeatedly replacing the PBS a minimum of five times until it was transparent.

2.8.1.1 Fillet prep

Larvae were dissected as described by (Titlow et al. 2018). L3 larvae were collected and placed dorsal side up on a Sylgard plate, where they were pinned at the end of the tail and covered in cold PBS. A second pin was placed between the brain and the mouthpiece, holding the larvae in place about 80% extended. Using microdissection scissors, a small incision was made perpendicular to the larva, on the dorsal side. The tip of the microdissection scissors were then inserted into the incision, cutting the cuticle along the dorsal side from tail to head, adding two small diagonal cuts on the sides of the head and the tail to avoid damaging the body wall when pulling the sides open. The gut was pulled out with the help of forceps, and two more pins were added to each side, pinning the larva body wall open flat with a total of six pins on the surface of the plate. Any remainder of the gut or other internal organs were carefully cleaned using forceps, until only the nervous system and the body wall remained.

When specified, brain and nerves were pulled out to allow clearer imaging of NMJs by gently grabbing the end of the VNC with forceps and pulling towards the tail.

2.8.1.2 Brain

Brains were imaged *in situ* in fillet prepped-larvae. For RNA extraction and qPCR, they were separated from the rest of the larvae by aspirating them with a pipette tip after the larvae was cleaned from gut and other debris and pinned open on the plate.

They were collected into a 1.5 mL tube, which was centrifuged and the supernatant discarded before flash-freezing the tissue in dry ice.

2.8.1.3 Gut

For RNA extraction and qPCR, larvae gut was collected into a 1.5 mL tube during fillet prep dissection. It was placed in a 1.5 mL tube and centrifuged. Supernatant was discarded and the tissue was flash-frozen in dry ice. As specified before, larvae were fed on PBS for at least thirty minutes to empty their gut.

2.8.1.4 Salivary glands

Salivary glands were collected by placing the larvae in a Sylgard plate and submerging it in PBS before gently holding it down and pulling at the mouthpiece with a forceps until the mouth and the glands were out. They were placed in a 1.5 mL tube and centrifuged before flash-freezing them once the supernatant was discarded.

2.8.1.5 Haemocytes

Before collecting haemocytes, we made sure the larvae were thoroughly washed of food debris by putting them in 1.5 mL tubes and rinsing them repeatedly with PBS. Clean larvae were placed on a Sylgard plate and covered with PBS before puncturing them lightly on the side with microdissection scissors. The haemocytes can be seen through the dissection microscope, and they were aspirated with a pipette tip and transferred to a clean 1.5 mL tube. To separate the cells from the PBS, they were centrifuged until a small pellet had formed. The supernatant was discarded and the samples were flash-frozen in dry ice.

2.8.2 Adults

Before dissection, flies were transferred to empty vials for three hours to allow digestion and gut emptying. Flies were anaesthetised either with a CO₂ gun or by putting their vials in ice for at least ten minutes. Individual flies were collected by the wings and submerged in 70% ice cold ethanol for twenty seconds and then dried with a paper towel. They were then transferred to a cold glass dish with a drop of PBS.

2.8.2.1 Heads

The wings were cut off using dissection scissors and disposed of. Dissection scissors were also used to cut the head at the narrowest point of connection to the thorax. The head was collected into a 1.5 mL microtube containing 10 μ L of PBS.

2.8.2.2 Haemocytes

Adult haemocytes extraction was modified from Ghosh, Mandal, and Mandal 2018. Beheaded, wingless flies were held by their legs with a fine point dissection forcep, and another one was used to lightly scrape the lateral sides of the thorax, lifting the

cuticle without damaging the abdomen or disturbing any further than the cuticle. Flies were placed with their dorsal side on the PBS drop and left to bleed for two to five minutes before the PBS containing the haemocytes was collected.

2.8.2.3 Salivary glands

Salivary gland dissection was performed as described in Palmer et al. 2020. A forcep was used to lightly grip the thorax, while another one gripped the boundary between the thorax and the abdomen and pulled tightly. Separation of the thorax and abdomen resulted in the proventriculus of the gut and the salivary glands being exposed. The gut was pulled out of the thorax carefully, and the salivary glands were separated from it with the forcep.

2.8.2.4 Gut

On beheaded flies, the thorax was held with a fine point forcep while the boundary between the thorax and the abdomen was tightly pulled with another forcep, exposing the gut, which was gently pulled and separated from the thorax. Holding the side of the abdomen carefully, the 7th segment was gripped tightly and pulled from the anus, leaving the gut loose but still inside the abdominal cuticle. To fully separate the gut from the abdomen, the left forcep was used to grip the side of the cuticle while the right forcep grabbed the top and bottom edges of the ventral side of the abdominal cuticle, scrunching it together carefully not to press into the organs inside. Once the abdomen was tightly held with the right forcep, the left forcep was used to pull apart the ventral side of the cuticle, exposing the inside of the abdomen. The ovaries and gut were extracted and separated, and malpighian tubes and other debris cleared from the gut.

2.9 Fluorescent imaging

2.9.1 smFISH

2.9.1.1 Probe design

Probes for smFISH were designed using the Stellaris probe designer tool (Biosearch technologies), including a 3 nucleotide spacing between probes and avoiding intron-exon junctions. 48 oligos were designed against each gene. Oligos were stored at -20°C resuspended in IDTE buffer (10 mM Tris pH 8.0, 0.1 mM EDTA). A full list of the sequences used can be found in the Appendix.

2.9.1.2 Probe synthesis

Conjugation with fluorophores was performed following a protocol adapted from (Gaspar, Wippich, and Ephrussi 2017). First, dideoxy uridine triphosphate (ddUTP) was reconstituted to 10 mM in 0.1M NaHCO₂ with pH 8.3. The dye (Sulfo-Cy3 or AlexaFluor647) were reconstituted to 20 mM in anhydrous DMSO. 20 µL of dye were mixed with 20 µL of amino-ddUTP, and the mixture was incubated on a rotating

platform for three hours at room temperature, covered from light. 0.4 μL 1M Tris-HCl were added to quench unreacted NHS ester groups. Nuclease-free water was added to adjust the concentration to 1 mM. Aliquots were stored at -20°C .

5 μL of pooled oligos (prepared mixing 10 μL each from an original concentration of 200 μM) were mixed with the prepared dye-ddUTP (2.5 μL of Sulfo-Cy3 or 5 μL of AlexaFluor647), 3 μL 5X TdT buffer, 0.6 μL TdT enzyme and nuclease-free water to a total reaction volume of 15 μL . The reaction mixture was incubated overnight at 37°C .

For purification, Zymo Oligo clean and concentrator kit (#D4060) was used as instructed by the manufacturer. Briefly, 100 μL oligo binding buffer were added directly to the reaction mix, followed by 400 μL 95% ethanol. The sample was transferred to the column and centrifuged for 1 minute, discarding the flow through. 750 μL DNA wash buffer were added to the column, which was then centrifuged a second time, discarding the flow through. 15 μL TE buffer were then added to elute the probes.

After calculating the degree of labelling and concentration using the spreadsheet provided by (Gaspar, Wippich, and Ephrussi 2017), TE buffer was added to store the probes at a final concentration of 25 μM , at -20°C protected from light.

2.9.1.3 Staining

Immediately after dissection, tissues were fixed in PBTX 0.3% (0.3% TritonX in 1X PBS) and 4% PFA for an hour with gentle rocking. Samples were rinsed three times in PBTX 0.3%, followed by two 20 minutes washes. PBTX 0.3% was removed and the samples rinsed three times with wash buffer (2X SSC, 10% deionized formamide, nuclease-free water). This was followed by a 30 minute incubation at 38°C in wash buffer. Incubation took place at 30°C overnight in Hybe buffer (2X SSC, 10% deionized formamide, 10% dextran sulfate, 250 nM smFISH probes and, if staining neurons, HRP-Dylight 0.003 $\mu\text{g}/\mu\text{L}$). The next day, Hybe buffer was rinsed three times with wash buffer. For nuclear staining, samples were incubated at 38°C in wash buffer with DAPI 0.02 $\mu\text{g}/\mu\text{L}$ or To-Pro-3 1:500 for 30 minutes. Samples were then washed in wash buffer for 45 minutes at room temperature.

Before mounting, samples were incubated for 30 minutes in SlowFade Diamond mounting medium (Thermo Fisher Scientific, #S36967).

2.9.2 HCR

HCR was performed as described in our methods paper (Olivares-Abril et al. 2024). Details of the method optimisation can be found in Chapter 5.

2.9.2.1 Probe design

Probes were designed using a custom probe designer pipeline, which can be found in an associated Zenodo repository <https://zenodo.org/records/12518278>. Briefly, the sequences of the genes of interest were downloaded from the UCSC genome browser (Nassar et al. 2023) in a FASTA format, excluding introns. All possible 52

nucleotide-long probes were generated, avoiding splice junctions. Thermodynamic parameters (melting temperature, Gibb's free energy and GC content) for each potential probe were calculated, considering the HCR hybridisation conditions. These were used to filter the probes, eliminating those that did not fit within a melting temperature of 30 to 90 °C, a Gibb's free energy range of -75 to -50 or a GC content between 0.4 and 0.7. Potential probes within these ranges were then filtered for potential off-target hits by screening their sequences against a custom *Drosophila melanogaster* transcriptome database generated from *D. mel* ENSEMBL version99 data. The optimal probes according to all criteria are then split into two 25 nucleotide halves, which are then attached to the desired HCR-B initiator sequences. Probes with no off-target hits were selected at random from regions of the gene shared across all isoforms. Sequences for all probes and initiators can be found in Appendix.

2.9.2.2 Staining

After dissection, tissues were fixed for 30 minutes at room temperature in 4% PFA in 0.3% PBSTx (0.3% TritonX in PBS), with gentle rocking. PFA was rinsed three times with 0.3% PBSTx, followed by two 20 minutes incubations at room temperature in 0.3% PBSTx. Samples were then rinsed once with 5X SSCT (5X SSC, 0.1% Tween) and then incubated for five minutes at room temperature in 5X SSCT. This was followed by a 10 minute wash at 37°C with wash solution (5X SSC, 30% formamide, 0.1% Tween). Samples were pre-hybridised twice in hybridisation solution (5X SSC, 30% formamide, 10% dextran sulfate, 0.1% Tween) for 20 minutes at 37°C. Hybridisation took place overnight at 37°C, incubating the samples in hybridisation solution containing the primary probes at a final concentration of 10 nM.

The next day, samples were washed in wash buffer at 37°C four times for 15 minutes each, then washed in 5X SSCT at room temperature twice for 5 minutes each. Probes were pre-amplified in amplification solution (5X SSC, 10% dextran sulfate, 0.1% Tween) at room temperature for 30 minutes. While the pre-amplification step took place, the hairpins were prepared for amplification by calculating the necessary volume of each hairpin for a final concentration of 6-60 nM and pipetting this amount to individual PCR tubes, which were heated to 95°C for 90 seconds before immediate transfer to room temperature. The hairpins were cooled for thirty minutes hidden from light and pooled in amplification solution, which was used to incubate the samples overnight at 37°C.

After amplification, samples were rinsed three times in 5X SSCT, and then washed in 5X SSCT twice for 30 minutes at room temperature. They were stained with HRP-Dylight (0.003 µg/µL in 5X SSCT at 37°C for two hours, after which DAPI (0.02 µg/µL) was added and incubation continued for one more hour. Then, samples were rinsed twice with 5X SSC and incubated twice for 20 minutes in 5X SSC at room temperature. They were then incubated in SlowFade Diamond mounting media (Thermo Fisher Scientific, #S36967) for 10 minutes at room temperature before mounting onto slides.

2.9.3 Immunofluorescence

After dissection, tissues were fixed in 4% PFA in 0.1% PBSTx (0.1% TritonX in PBS), incubating for an hour at room temperature with gentle shaking. Samples were rinsed twice in 0.1%PBSTx, followed by two 5 minutes washes in 0.1% PBSTx. Samples were blocked for two hours in 1.5% BSA in 0.1% PBSTx before incubating overnight with primary antibody in 1.5% BSA with gentle rocking, sealing the tubes or glass dishes with parafilm or using a wet chamber.

The next day, samples were rinsed with 4% NaCl in 0.1% PBSTx. Sequential washes with 4% NaCl in 0.1% PBSTx (5 minutes, 20 minutes, 15 minutes) followed. After the washes, samples were incubated with secondary antibody diluted in 0.1% PBSTx for two hours with gentle rocking. Incubation was followed by a rinse with 0.1% PBSTx and three sequential washes with 0.1% PBSTx (5 minutes, 20 minutes, 15 minutes, 5 minutes). After one last rinse in 0.1% PBSTx, samples were incubated with nuclear stain To-Pro-3 (1:500, Invitrogen) for 20 minutes. Samples were washed twice with PBS for 5 minutes before mounting.

The full list of primary and secondary antibodies used follows.

Antibody	Source
anti ZIKV envelope (rabbit)	Invitrogen (HL1699)
Goat anti-rabbit AlexaFluor 546	Abcam (175471)

Table 2.2: List of primary and secondary antibodies used.

2.9.4 Mounting

While samples were incubating in mounting media (Vectashield or SlowFade Diamond), a drop of the corresponding mounting media was placed on top of a slide, flanked by two 3-5 mm wide stripes of double-sided tape. Samples were placed dorsal side down on the drop and covered with a glass coverslip, which was sealed using nail varnish.

2.9.5 Polylysine treatment

Some samples (adult tissues, Chapter 4) were very delicate, so they were stained and imaged in polylysine-treated slides to reduce manipulation as much as possible. For this, a 10X stock solution containing 1g of polylysine (Sigma P1524) was emptied into a beaker, along with 170 mL double distilled water used to rinse it. A magnetic stirrer was used to fully dissolve the polylysine. 10X stock solution was kept at -20°C. 30mL of the stock solution were added to 170 mL double distilled water and 1.5 mL kodak Photo-Flo to create a working solution, which was stored at 4°C but used at room temperature.

Clean frosted slides were loaded into a glass staining rack in pairs, before rinsing with double distilled water. They were then covered with working solution and left in a rocker for ten minutes at room temperature. The working solution was transferred to a beaker, and the slides were moved to a 60°C oven for drying. The

treatment-drying cycle was repeated three times, reusing the same working solution, before air-drying for an hour.

Slides were dried and stored at 4°C. Before use, a well was created using a hydrophobic pen (ImmEdge Hydrophobic Barrier pen, Vector laboratories H-4000), where the samples were placed in a drop of PBS before fixing and stained as described.

2.9.6 Microscope specifications

smFISH and HCR experiments were imaged using an Olympus/Evident SpinSR10 spinning disk confocal system equipped with Prime BSI and Prime 95B sCMOS cameras. The objectives used were a 60X oil immersion objective (1.5 NA, UPLAPOHR60X) or a 100X oil immersion objective (1.45NA, UPLXAPO100XO). Images were acquired with Olympus/Evident cellSense Dimension software.

Immunofluorescence experiments were imaged using a Leica SP5 confocal microscope and the LAS X software, using a 63X oil immersion objective.

2.9.7 Image analysis

Images were visualised using Fiji/ImageJ. RNA quantification was performed using a custom pipeline <https://github.com/jefflee1103/Image-analysis/tree/main/BigFISH> based on BigFISH (Imbert et al. 2022).

2.10 DNase and RNase treatments

In some HCR experiments, samples were treated with DNase or RNase before staining. Immediately after permeabilisation with PBSTx, samples were washed 5 minutes with PBS Tween (0.1%). For the DNase experiment, this was followed by a 10 minutes wash in DNase TURBO buffer (TURBO DNase buffer, AM2238). Samples were incubated at 37°C overnight with the DNase (TURBO DNase, AM2238, 0.02 U/mL) in DNase buffer and 1mM magnesium chloride.

For RNase treatment, the PBS Tween (0.1%) wash was followed directly by an overnight incubation at 37°C with RNase T1 (EN0541, 20U/mL) and RNase III (AM2290, 0.02U/mL) in PBS Tween (1%) and 1mM magnesium chloride.

The HCR protocol was continued as normal the next day, starting with the first 5X SSCT wash.

2.11 Behavioural assays

2.11.1 Larval crawling

Vials were left in the room where the behavioural assay would take place for 20 minutes to acclimate before starting the assay, which was performed at room temperature. L3 crawling stage larvae were collected and transferred with a wet brush to the centre of a 9 cm diameter 1% agarose plate. Plates were placed over a white

light box and filmed as they crawled for 3 minutes. Crawling behaviour analysis is described in detail in the appropriate chapters.

2.11.2 Adult climbing

Adult flies were collected between 10 and 11 am into a completely empty transparent food vial, which was closed using a second empty vial, sticking them together at their opening using transparent tape to create a long, enclosed, transparent tube. Flies were left to acclimate for thirty minutes in the room where the assay would take place before starting the assay.

A white background was placed behind the vial, and a phone camera was placed so that the full vial would be in the frame. The vial was tapped six times rapidly to ensure all flies would fall to the bottom of the vial before tracking their climbing. A customised version of the FlyTracker program (Callan Sharples, 2024, unpublished data) was used to track and analyse the movement of flies live.

2.12 Enrichment analysis

A list of orthologs for *Drosophila melanogaster* and *Aedes aegypti* was downloaded from OrthoDB (Kuznetsov et al. 2023). Datasets containing expression data and gene ontology data were obtained from Flybase (Öztürk-Çolak et al. 2024) and the Gene Ontology Consortium (Ashburner et al. 2000; Aleksander et al. 2023) and collated to the ortholog list. Enrichment analysis was performed using Fisher’s exact test (Mi et al. 2020) and Benjamini-Hochberg correction. Analysis was executed and plotted using a custom python pipeline.

Chapter 3

ZIKV infection of *Drosophila melanogaster* larvae

3.1 Introduction

Drosophila melanogaster has been extensively used to understand innate immunity (reviewed in Yu et al. 2022). This is mainly due to insects lacking adaptive immunity, which eliminates its confounding effects and allows us to dissect individual immune pathways cleanly (Cheung et al. 2022). Innate immunity pathway components are also highly conserved across the tree of life (reviewed in Ulianova et al. 2026), and the wide availability of genetic tools for *Drosophila melanogaster* as well as its low maintenance cost and high throughput makes it an ideal model organism for the study of this field.

There are three main innate immunity pathways in *Drosophila melanogaster*: the Toll pathway, the IMmune Deficiency (IMD) pathway, and the RNAi pathway (Figure 3.1). Toll and IMD both act via NF- κ B and ultimately result in regulation of transcriptional responses, including the synthesis and secretion of antimicrobial peptides (AMPs) and the accumulation of reactive oxygen species (ROS) (reviewed in Ulianova et al. 2026). The Toll pathway (Figure 3.1A) has been studied mainly in the context of immunity against fungal and bacterial infections (Lemaitre and Hoffmann 2007), where the pathogen is sensed extracellularly by a variety of mechanisms that ultimately result in cleavage of pro-Spätzle. Cleaved Spätzle (Spz), a Nerve Growth Factor homologue, can bind one of the Toll receptors (Toll-1), triggering a signalling cascade that translocates NF- κ B transcription factors Dif and Dorsal into the nucleus, where they control the expression of target genes (Valanne, Wang, and Rämét 2011; Uttenweiler-Joseph et al. 1998), including inducing expression of secreted antimicrobial peptides (AMPs) (Drosomycins, Metchnikowins, Drosocins, Cecropins, Defensins, Yu et al. 2022; Hanson and Lemaitre 2020) and other effectors such as Bomanins (Clemmons, Lindsay, and Wasserman 2015), Daisho proteins (Cohen et al. 2020) and Baramicins (Hanson et al. 2021). The mechanism of action of these effectors varies greatly (reviewed in Hanson et al. 2025), with classical AMPs generally directly targeting pathogens extracellularly and other effector genes providing the fly with additional protection, such as bomanins targeting toxins in the context of fungal infections (Huang et al. 2023a). Toll activation also regulates cellular pro-

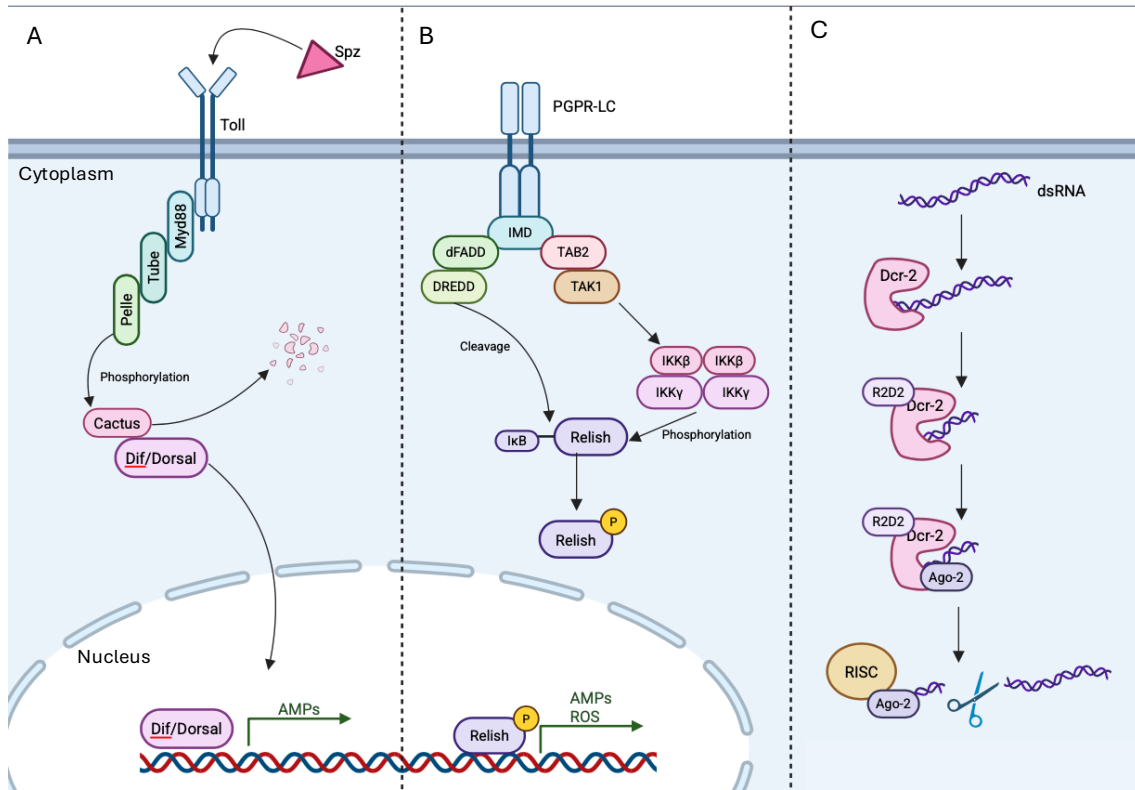


Figure 3.1: Innate immunity pathways in *Drosophila melanogaster*. **A: Toll pathway.** Spz is extracellularly cleaved upon detection of bacteria. Cleaved Spz can bind the Toll receptor, which dimerises to bind Myd88, Tube and Pelle. The protein complex formed can phosphorylate Cactus, which is then targeted for degradation, releasing the NF- κ B transcription factors Dif and Dorsal. Dif and Dorsal can then be translocated to the nucleus, where they regulate NF- κ B-dependent expression of immune effectors, including AMPs. **B: IMD pathway.** The IMD pathway is activated by PGRP receptors, which, upon detection of bacterial pathogens, recruits and activates a complex formed by IMD, dFADD, DREDD, TAB2 and TAK1. After activation of the complex, DREDD cleaves the C-terminal domain of Relish, and TAB2/TAK1 phosphorylate its N-terminal domain via IKK- β and IKK- γ . Cleaved, phosphorylated Relish translocates to the nucleus, where in a NF- κ B-dependent manner, it controls expression of immune effector genes, including AMPs and reactive oxygen species producing enzymes. **C:** The RNAi antiviral immune pathway is activated upon detection by Dcr-2 of foreign genetic material, in particular double-stranded RNA. Dcr-2 is able to process this RNA into a 21-nucleotide-long small interfering RNA (siRNA), which, aided by R2D2, is used to form a RISC complex along with Ago-2. Ago-2 then uses the nucleotide sequence to detect and degrade viral RNA.

cess such as survival and proliferation (Zettervall et al. 2004; Sorrentino, Melk, and Govind 2004; Matova and Anderson 2010; Udayakumar 2023) and differentiation (Louradour et al. 2017; Hao and Jin 2017; Lemaitre et al. 1995a)

The IMD pathway (Figure 3.1B) has also been studied largely against bacterial infections. Upon detection of the pathogen and consequent activation of PGRP membrane receptors, IMD is recruited to be cleaved, activating a signalling cascade that ends with the translocation of NF- κ B transcription factor Relish (Rel) to the nucleus, where it controls expression of target genes. Similarly to the Toll pathway, IMD pathway activation effects also include expression of classical AMPs (Diptericins, Attacins, Cecropins) (Yu et al. 2022), as well as maintaining gut microbiota homeostasis (Guo et al. 2014; Ryu et al. 2008), cell proliferation and survival (Buchon et al. 2009; Petkau et al. 2017; Georgel et al. 2001; He et al. 2017). In ad-

dition, IMD controls gut peristalsis to excrete bacteria (Hori, Kurata, and Kuraishi 2018).

In contrast, the RNAi response (figure 3.1C) works directly against viruses by cleaving viral RNA, thus inhibiting viral replication (reviewed in Luan 2025). In the immune RNAi response, Dicer-2 produces a small interfering RNA (siRNA) from exogenous (viral) double-stranded RNA found inside the cell. Along with R2D2 and Argonaute2 (AGO2), they form an RNA-induced silencing complex (RISC), which is able to degrade viral RNA by targeting the complementary sequence to the siRNA (Wang et al. 2006; Faria et al. 2021; Kemp et al. 2013; Rij et al. 2006; Galiana-Arnoux et al. 2006).

Although the RNAi response is the most well-understood antiviral innate immune response, there is mounting evidence that NF- κ B-dependent pathways, including Toll and IMD, are also involved (reviewed in Cheung et al. 2022). Both Toll and IMD pathway components are upregulated upon infection with a variety of viruses (Avadhanula et al. 2009; Huang et al. 2013; Zambon et al. 2005; Costa et al. 2009; Angleró-Rodríguez et al. 2017; Barletta et al. 2017; Xi, Ramirez, and Dimopoulos 2008; Luplertlop et al. 2011). In most cases the activation of Toll, IMD and even NF- κ Bmediation is only inferred from increased expression of classical pathway components or of AMPs, and these might instead be the result of alternative immune pathways or be acting independently of NF- κ B. In addition, activation of immune pathways and the details of the response are largely pathogen-dependent, therefore our understanding of non-RNAi-dependent antiviral immunity is very fragmented: for example, it was shown that Toll receptors can directly bind vesicular stomatitis virus (VSV), but the result of this interaction is not well-understood further than it not resulting in expression of AMPs (Nakamoto et al. 2012); conversely, DENV has been shown to trigger expression of AMPs after being recognised by scavenger receptor C (SR-C), with the rest of the pathway remaining unknown (Xiao et al. 2014).

In addition to the classical IMD and Toll pathways, other RNAi-independent antiviral immunity pathways has been discovered: the Janus kinase-signal transducer and activator of transcription (Jak-STAT) signalling pathway has an antiviral role (Dostert et al. 2005; Souza-Neto, Sim, and Dimopoulos 2009; Merkling et al. 2015a; Huang et al. 2023b; Zhang et al. 2023), where both under- and over-activation of the pathway can have detrimental effects on insect survival (Shen et al. 2022). Even the heat shock response has been shown to restrict viral replication in *Drosophila* (Merkling et al. 2015b). There are also alternative, non-canonical immune activators of NF- κ B-mediated responses, such as VINR, a long non-coding RNA that detects *Drosophila* C virus (DCV) and prevents degradation of Cactin, therefore allowing the I κ B homologue Cactus to release Dif and Dorsal for their subsequent entry into the nucleus to activate expression of AMP and other effector genes (Huang et al. 2013). Combined evidence supports a model where NF- κ B-dependent immune pathways, including IMD and Toll, are important for antiviral immunity, often through non-classical pathways, in a very pathogen-specific manner.

One such non-canonical antiviral immune pathways is controlled by the protein stimulator of interferon genes (Sting), which was recently discovered to activate an NF- κ B-mediated antiviral immune reaction (Figure 3.2). Upon detection of

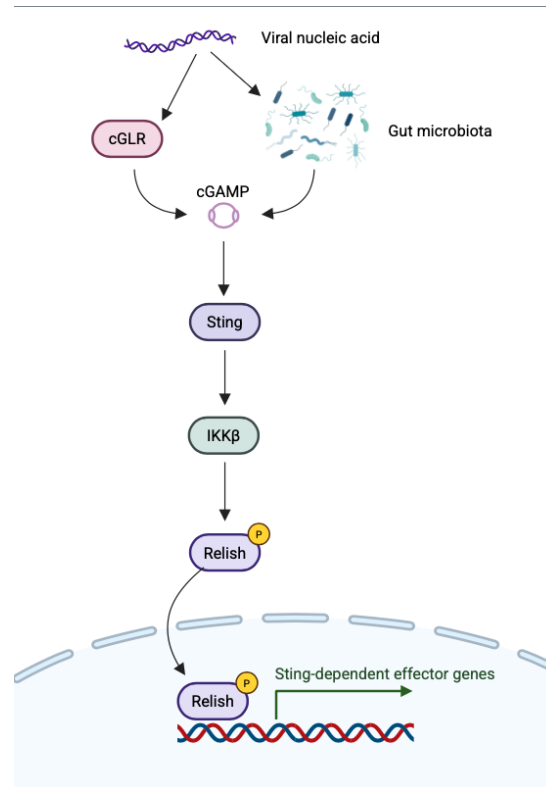


Figure 3.2: Sting pathway as described by Goto et al. 2018 and Segrist et al. 2021. Detection of viral nucleic acids, either intracellularly via cGMRs or through the gut microbiota, results in activation of Sting via production of cyclic dinucleotides. Sting activation results in $IKK\beta$ translocation of activated Relish to the nucleus, where it controls expression of Sting-dependent immune effectors.

intracellular RNA, cyclic GMP-AMP synthase(cGAS)-like receptors (cGMRs) have been shown to activate Sting (Holleufer et al. 2021), which in turn triggers expression of immune genes known to be controlled by $NF-\kappa B$ (Goto et al. 2018; Cai et al. 2020). Although the full pathway is not yet understood, studies have identified IMD pathway components Relish and $IKK\beta$ to work downstream of Sting (Holleufer et al. 2021; Cai et al. 2020; Slavik et al. 2021). However, this response is separate from the classical IMD pathway, as Sting-dependent activation of Relish results in expression of a different group of genes from those expressed as a result of canonical IMD activation (Goto et al. 2018; Ai et al. 2024; Hédelin et al. 2024), despite their expression also being mediated by $NF-\kappa B$ (Liu et al. 2018b; Cai et al. 2020). A recent study using oral infection of *Drosophila melanogaster* with SINV found that the pathway was activated by cyclic dinucleotides secreted by gut microbiota (Segrist et al. 2021), which adds further complexity to the understanding of this pathway in immunity due to potential differences between tissues. Sting is still understudied, with the rest of the pathway and effectors remaining unknown. This is underscored by how pathogen-specific the antiviral innate immune response has been shown to be.

Sting has been shown to play a role in infection with ZIKV (Liu et al. 2018b), SINV (Segrist et al. 2021), *Drosophila* A virus (DAV, Nigg et al. 2024), and very likely also with *Drosophila* C virus (DCV) and Nora virus (Nigg et al. 2024). In the context of ZIKV specifically, Liu et al. showed that Sting limits infection of

the brain in systemically infected *Drosophila* (Liu et al. 2018b). **This highlights a trend in viral infection research using flies, where most studies use systemic infection, injecting the pathogen directly into the thorax of the insect. However, this method bypasses the first natural line of defence, the physical barrier of the gut, as it introduces the pathogen directly into the haemocoel.**

Therefore, injection can make an active infection more likely, establishing the virus and thus facilitating studies that dissect specific interactions between host and the pathogen. However, it is less well-suited for research focusing on vector-pathogen interaction, as oral infection is more representative of how insects get infected in nature (for arboviruses). Segrist et al. showed differences in Sting-dependent immune system activation in flies infected systemically and orally with SINV (Segrist et al. 2021), indicating that, while systemic infection studies can be very helpful for zoomed-in analysis of pathogen interactions with an organism, their results might not be fully representative of vector-pathogen interactions in the wild.

Since Sting-deficient *Drosophila melanogaster* has been shown to be susceptible to ZIKV systemic infection, in this chapter I explore the possibility of using this model organism to study oral infection with the virus.

3.1.1 Aims and Objectives

- Determine whether Sting-deficient *Drosophila melanogaster* larvae show increased susceptibility to ZIKV infection when challenged orally as they do when systemically infected. Optimise an oral infection protocol, exploring potential variables such as gut microbiota.
- Study the viral tropism of the orally infected larvae by imaging the viral RNA in dissected samples and performing qPCR of different tissues.

3.2 Materials and methods

3.2.1 Virus production and titration

MR766 strain of ZIKV was produced and quantified as described in the Materials and Methods section. Virus used in this chapter was generated in Vero CCL81 cells, maintained in Dulbecco's modified Eagle Medium (DMEM) supplemented with 10% foetal bovine serum (FBS) and 1% penicillin-streptomycin in a 5% CO₂ incubator at 37°C.

3.2.2 *Drosophila melanogaster* lines

Flies were maintained as described in the Materials and Methods section. The fly lines used in this chapter are:

Line	Genotype	Description	Source
W ¹¹¹⁸	W ¹¹¹⁸	Wild type background	Davis lab stocks
Sting ^{EY06491}	;Sting ^{EY06491} ;	Transgenic insertion stock with decreased expression of Sting (Liu et al. 2018b)	BDSC(16729)

Table 3.1: List of *Drosophila melanogaster* stocks used in this chapter.

3.2.3 Detection of *Wolbachia*

Fly stocks were periodically tested for presence of *Wolbachia*. Lines positive for *Wolbachia* were treated with tetracyclin 0.3% for two generations before retesting.

3.2.3.1 Genomic DNA extraction and amplification

DNA extraction was performed as described in the Materials and Methods section.

PCR was performed according to the manufacturer’s instructions using the Taq PCR kit (NEB #E5000S). 100 ng of DNA were added to each reaction. Thermocycler program was as follows: an initial denaturation step at 95°C for 30 seconds, 40 cycles of 98 °C for 10 seconds, 50°C for 30 seconds and 72°C for 30 seconds, and a final extension step at 72°C for 10 minutes before holding at 4° until gel electrophoresis. *Wolbachia* primer sequences can be found in the Appendix.

Samples were mixed with purple gel loading dye (NEB #B7024S). Gel electrophoresis was performed on a 0.8% agarose gel prepared in TAE buffer and stained with Midori Green, which was ran for 30 minutes at 120 V.

3.2.4 RNA extraction and qPCR

RNA was extracted using TRIzol reagent (invitrogen #15596026) as described in the Materials and Methods section.

The Luna Universal One-Step RT-qPCR kit (NEB #E3005) was used for RT-qPCR. The thermocycler was programmed to hold 55°C for 10 minutes, 95°C for 1 minute, then 45 cycles of 10 seconds at 95°C and 30 seconds at 60°C before plate reading. The melt curve was measured at 0.5 °C intervals between 60°C and 95°C. Relative fold expression was calculated using the $2^{-\Delta\Delta C_t}$ method, and RNA was normalised against housekeeping gene rp49. Primer sequences can be found in the Appendix.

3.2.5 Larval oral infection

Larval infection was performed as described in the Materials and Methods section.

3.2.6 Gut microbiota ablation

Eggs laid on an apple juice agar plate during a 4 hour window were collected with a wet brush and placed inside a disposable cell sieve and dechorionated by submerging in 14% bleach for 45 seconds before rinsing with abundant distilled water. The dechorionated eggs were retrieved using a wet brush and placed into a new apple juice agar plate.

When making the yeast paste with virus solution for oral infection, a cocktail of antibiotics (128 µg Ampicillin, 128 µg Doxacyclin, 200 µg Kanamycin, 40 µg Rifampicin, Segrist et al. 2021) was added to the yeast paste. The paste was refreshed with virus the next day, but not with antibiotic.

Gut microbiota ablation was confirmed by dissecting five empty larvae guts from each condition, which were homogenised in 50% glycerol and plated onto an MRS agar plate, which were incubated for two days at 30°C.

3.2.7 Dissection

Larvae were dissected as described in the Materials and Methods section.

When preparing tissues for RT-qPCR of different tissues, dissected tissues were placed in a 1.5 mL tube containing 20 µL of PBS, except for the hemocytes, which were collected directly in 20 µL PBS and transferred to an empty 1.5 mL tube. Samples were centrifugated for 20 minutes at 4°C at 10000 RPM and the PBS supernatant was removed before freezing at -80°C.

When dissecting larvae for smFISH staining, they were fixed while still pinned to the Sylgard plate, and then transferred to a 1.5 mL tube for the rest of the staining process.

3.2.8 Staining

3.2.8.1 Cell culture

In preparation for staining, CCL81 cells were grown directly on clean glass coverslips using a six well plate. They were infected when confluent and fixed two days later using 4% formaldehyde in PBS for 20 minutes before gently retrieving the coverslip. During the staining process, a wet chamber was made using a clean pipette tip box with the rack covered with parafilm. For staining, coverslips were placed cell side down on top of a drop of the appropriate reagent which was deposited on top of the parafilm. The staining protocol, including number and timing of washes and concentrations of reagents was the same for cell culture as for whole larvae.

3.2.8.2 Larvae

Larvae were dissected and stained using smFISH against viral RNA as described in the Materials and Methods section. Custom DNA probes were designed using the stellaris probe designer <https://oligos.biosearchtech.com/products/rna-fish/stellaris-probe-designer> and their sequences can be found in the

Appendix. Probes were ordered from IDT and conjugated with the fluorophores as described in the Materials and Methods section.

3.2.9 Imaging

Samples were mounted using SlowFade Diamond mounting media (invitrogen #S36967). For the experiments described in this chapter, frosted slides (not treated with polylysine) were used.

3.2.10 Larval crawling behavioural assay

Vials were left to acclimate for 20 minutes before the assay. Individual L3 larvae were collected with a wet brush and placed in the centre of a 9 cm diameter 1% agarose plate, which was washed with 70% ethanol and water between samples. Larvae were left to acclimate to the plate for 20 to 30 seconds before pushing them to the centre again. Crawling was filmed parallel to the plate, which was placed on top of a white lightbox, for 3 minutes. A custom python pipeline was used to track the movement of the larvae, obtaining the following metrics: mean velocity, mean acceleration, mean angle, speed regularity (standard deviation of the speed) and directional regularity (standard deviation of the angle).

3.2.10.1 Unsupervised clustering

All six variables extracted from the videos were used for unsupervised clustering, which was performed on the Orange software (Demšar et al. 2013) using Louvain clustering. Data was visualised using t-SNE.

3.2.10.2 Correlation analysis

For Spearman correlation analysis, each of the behavioural variables, measured in different units, was standardised using z-scoring to be weighted equally in the analysis. Each larvae was assigned a composite z-score (the average of the z-scores for each behavioural trait). Because of the type of data I collected, a lower composite z-score indicates lower mobility and more sluggish behaviour compared to other larvae. The relationship between the composite z-score and the ZIKV RNA load was assessed using a Spearman correlation.

3.3 Results

3.3.1 Oral infection of *Drosophila melanogaster* larvae

Sting-deficient *Drosophila melanogaster* line Sting^{EY06491} has been shown to display increased susceptibility to viral infection via injection, specifically to SINV and ZIKV (Liu et al. 2018b). It has also been infected orally with SINV, which also resulted in increased viral load compared to wild type adult flies (Segrist et al. 2021). I wanted to test whether the increased susceptibility to ZIKV infection of this line extended

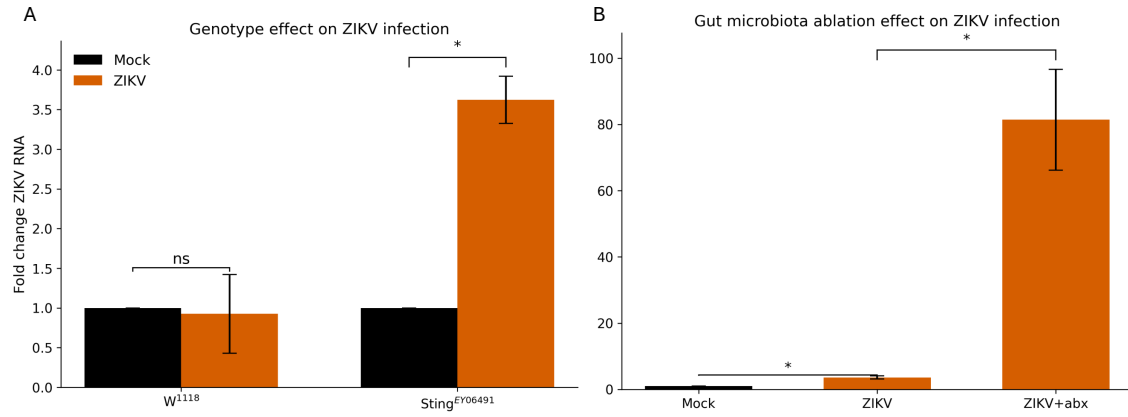


Figure 3.3: A: Effect of genotype on oral ZIKV infection. Relative ZIKV RNA abundance as detected with qPCR in three pooled orally challenged *W¹¹¹⁸* and *Sting^{EY06491}* L3 larvae (n=3; Mean $\pm$ SEM; *, p<0.05) **B: Effect of gut microbiota ablation on oral ZIKV infection.** Relative ZIKV RNA abundance as detected with qPCR three pooled orally challenged *Sting^{EY06491}* L3 larvae, either untreated (ZIKV) or dechorionated and treated with antibiotics (ZIKV + abx) to ablate the gut microbiota. (n=2; Mean $\pm$ SEM; *, p<0.05)

to oral infection, therefore devising an oral infection protocol that involved feeding the virus to larvae in a yeast paste as soon as they emerge from the egg. Comparing infected L3 *Sting^{EY06491}* larvae with that of infected wild type background *W¹¹¹⁸* via qPCR showed a moderate but significant increase in ZIKV RNA load (Figure 3.3.A) in the *Sting* deficient larvae, confirming the maintenance of the increased susceptibility to infection to orally infected larvae.

3.3.2 Effect of gut microbiota ablation on larval oral infection

Drosophila melanogaster gut microbiota were shown to secrete cyclic dinucleotides (CDN) upon infection with SINV, which resulted in a sting-dependent activation of the antiviral immune response. Gut microbiota ablation resulted in an increase in susceptibility to the virus, which could be returned to normal levels by feeding the flies CDNs (Segrist et al. 2021). Therefore, I tested the effect of ablating the gut microbiota of larvae on oral ZIKV infection, to assess whether the mechanism by which the immune response against ZIKV is activated is similar to that against SINV. qPCR of orally infected larvae showed ZIKV RNA levels were 80 times higher in *Drosophila* larvae that had their gut microbiota ablated by egg dechorionation and antibiotic feeding compared to those with intact gut microbiota, thus suggesting the mechanism by which the immune response against oral infection of ZIKV and SINV are conserved.

3.3.3 smFISH imaging of ZIKV of orally infected *Drosophila melanogaster* larvae

Since *Sting^{EY06491}* larvae were more susceptible to infection with ZIKV than wild type larvae, I attempted to study the oral infection process of this genotype further.

For this, I designed and conjugated smFISH probes against ZIKV RNA, which I tested in mammalian tissue culture infected and uninfected with the virus (Figure 3.4A). I was able to detect fluorescence in the infected cells in a pattern similar to previous studies that infected cells from the same cell line with MR766 ZIKV (Cortese et al. 2017), and found no signal in the mock-infected cells, therefore validating the probes.

L3 *Drosophila* larvae were dissected and stained with the tested probes to detect the virus in different tissues (Figure 3.4B-F). The result showed ZIKV RNA was absent from the nervous system, both from the brain and from the neuromuscular junctions (NMJ) in the peripheral nervous system. However, I was able to find a strong signal coming from haemocytes and the fat body.

3.3.4 ZIKV tropism in orally infected L3 *Drosophila* larvae

In order to gather an improved overview of viral tropism on orally infected L3 larvae, I dissected and collected tissues from infected and mock-infected larvae and performed qPCR on them (Figure 3.4G). This experiment showed the highest amount of viral RNA to be in the larval haemocytes, which is consistent with the smFISH experiment results. There was also a slight, non-significant detection of viral RNA in the gut. Interestingly, qPCR also detected a slight, non-significant amount of ZIKV RNA in the brain, even though the smFISH experiments did not detect any viral RNA in this tissue. The other tissues assessed (salivary glands, body wall) did not display a difference in viral RNA load compared to their mock conditions.

3.3.5 Viral RNA load of individual larvae and relationship to crawling behaviour

There is a very high variability in rates of mosquito infection (where virus can be extracted from the body), dissemination (where virus can be found in tissues other than the abdomen, suggesting the virus has crossed the gut barrier and infected other organs) and transmission (where the virus can be detected in the saliva) across studies (reviewed in Gutiérrez-López, Figuerola, and Martínez-de la Puente 2023). To account for this possible variability, I performed qPCR on individual larvae, ensuring I was collecting them all to avoid inadvertently selecting those with better crawling abilities. A randomised selection of the collected larvae was homogenised and RNA extraction was performed. The result showed 53% of larvae to have higher viral loads than the mock-infected larvae, however the fold change did not show a large difference, with all the larvae displaying values below 3-fold increase; and only one biological repeat of this experiment was performed, so it is not possible to know whether these larvae were infected or if the differences in viral load were caused by noise. Attempting to infect mammalian tissue culture with the larvae homogenised in the appropriate media and FBS (Chouin-Carneiro et al. 2020), would provide a high resolution, quantitative answer to this question.

Before freezing and homogenizing the larvae for RNA extraction, I performed a

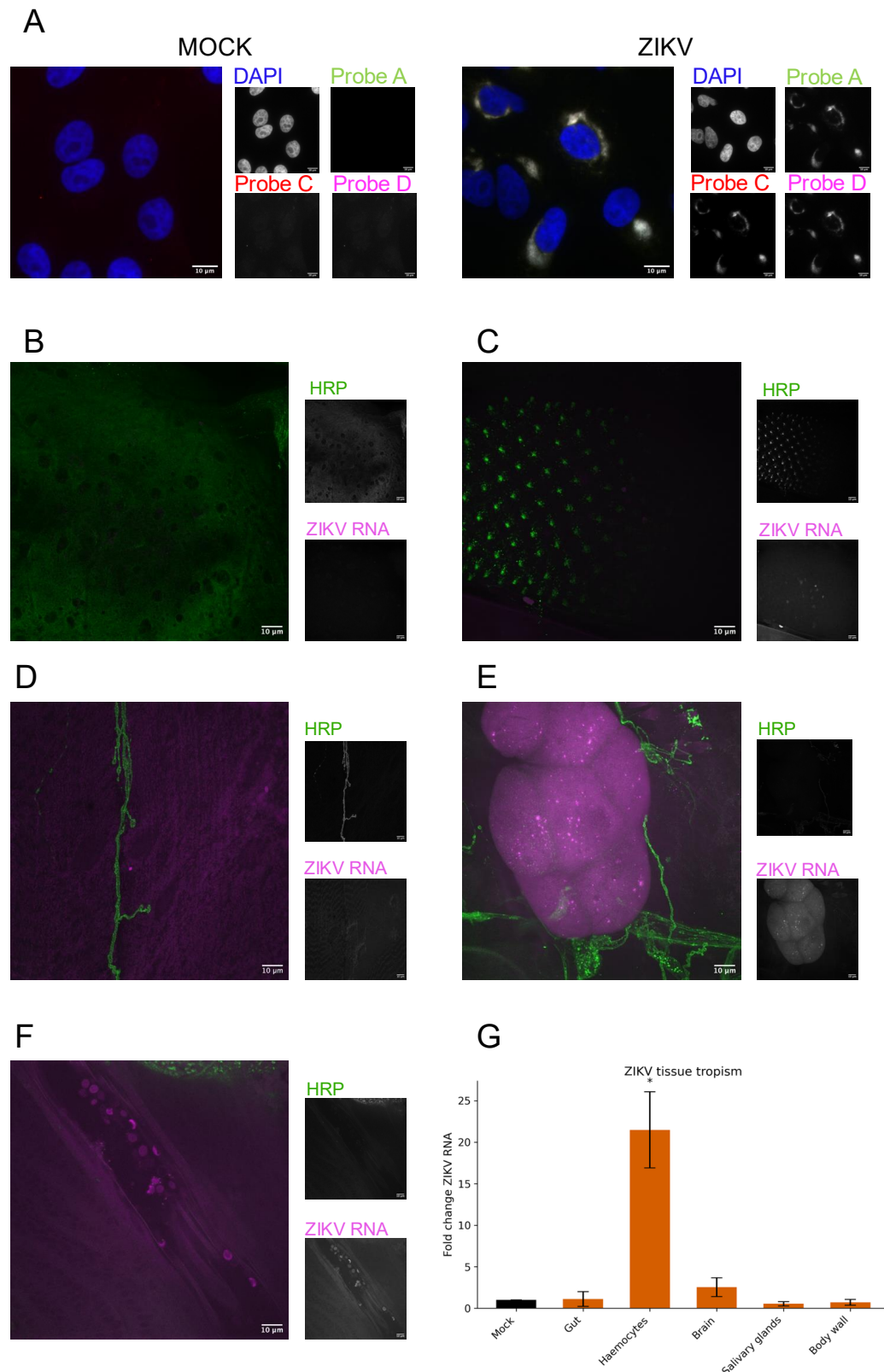


Figure 3.4: A: Validation of smFISH probes against ZIKV RNA in mammalian tissue culture. Representative images of mock-infected and ZIKV infected CCL81 cells stained with smFISH probes against ZIKV RNA (Probe A, ATTO488; Probe B, Cy3; Probe C, ATTO647. Nuclei are stained with DAPI. Scale bar: 10 μ m). **B-F: Larval tissue stained with smFISH probes against ZIKV RNA.** B,C: brain, D: neuromuscular junction, E: fat body, and F: haemocytetes. (ZIKV RNA probe, ATTO647, neurons stained with HRP-GFP. Scale bar: 10 μ m) **G: Tissue tropism of ZIKV in larvae as detected by qPCR.** Relative ZIKV RNA abundance as detected with qPCR in tissue dissected from five orally challenged *Sting^{EY06491}* L3 larvae, pooled after dissection (n=2; Mean $\pm$ SEM; *, p<0.05).

crawling assay, filming individual larvae crawling on a clear agar plate for three minutes with the intention to find any potential behavioural patterns associated to higher viral loads. Any patterns found would allow me to train an algorithm that detected infected larvae before dissection, thus allowing any future experiments to always be performed on infected larvae. The crawling assay was performed on all the larvae from the vial to avoid inadvertently selecting against any crawling behaviour patterns. A custom analysis software was used to measure five variables: mean speed (pixels per second), mean acceleration (change in speed each second), mean angle (change in vector direction per second), speed regularity (standard deviation of speed) and directional regularity (standard deviation of the angle). Individual larvae were grouped by unsupervised clustering using the Louvain algorithm, which produced four clusters with distinct behavioural patterns (Figure 3.5A). The behavioural patterns of each cluster are described in Figure 3.5B-F.

I attempted to find a relationship between viral load and cluster using the qPCR data from individual larvae, however I was not able to find a clear association between ZIKV RNA load and any of the clusters, with the differences in viral load being non-significant between all the clusters (Figure 3.6A). However, I noticed that the cluster with the highest mean viral load (C4) was also the one with the lowest scores for all the variables measured in the crawling assay (Figure 3.5B-F). Therefore, I assessed whether there was a correlation between higher viral load and lower motility. For this, I generated each individual larvae's composite behavioural z-score to standardise all the behavioural variables regardless of units, and performed a Spearman correlation analysis using this composite score and the ZIKV RNA load (Figure 3.6B). The result showed there was a significant negative association between the viral load and the overall behavioural z-score.

3.4 Discussion

In this chapter, I studied oral infection of Sting deficient *Drosophila melanogaster* larvae. The vast majority of studies of arboviral infection in insects have relied on microinjection to introduce the virus (Liu et al. 2018b; Palmer et al. 2020, among others). However, orally challenging the insect instead can allow us to improve our understanding of how the different innate immunity pathways of the insect interact with the virus in the different tissues, as injection bypasses the natural barriers to infection by introducing the virus directly into the insect. A *Drosophila melanogaster* line deficient for Sting, Sting^{EY06491}, has been found to be more susceptible to systemic infection with ZIKV than wild type controls, therefore suggesting a role for this innate immunity pathway in infection with this virus (Liu et al. 2018b). Orally challenging larvae from this same genotype with ZIKV resulted in increased viral load compared to the control, suggesting this protein has a role in defending the insect from the virus both when systemically and orally challenged. Antiviral innate immunity is less well-understood than antibacterial, with most of the research focusing on the RNAi pathway. Achieving oral infection with ZIKV in Sting-deficient larvae suggests that Sting is important in restricting entrance of the virus into the insect, with the intact RNAi pathway not being able to protect the larvae from infection in the absence of this protein. This supports recent research highlighting the importance of the Toll and IMD pathways for innate antiviral immunity (Cheung

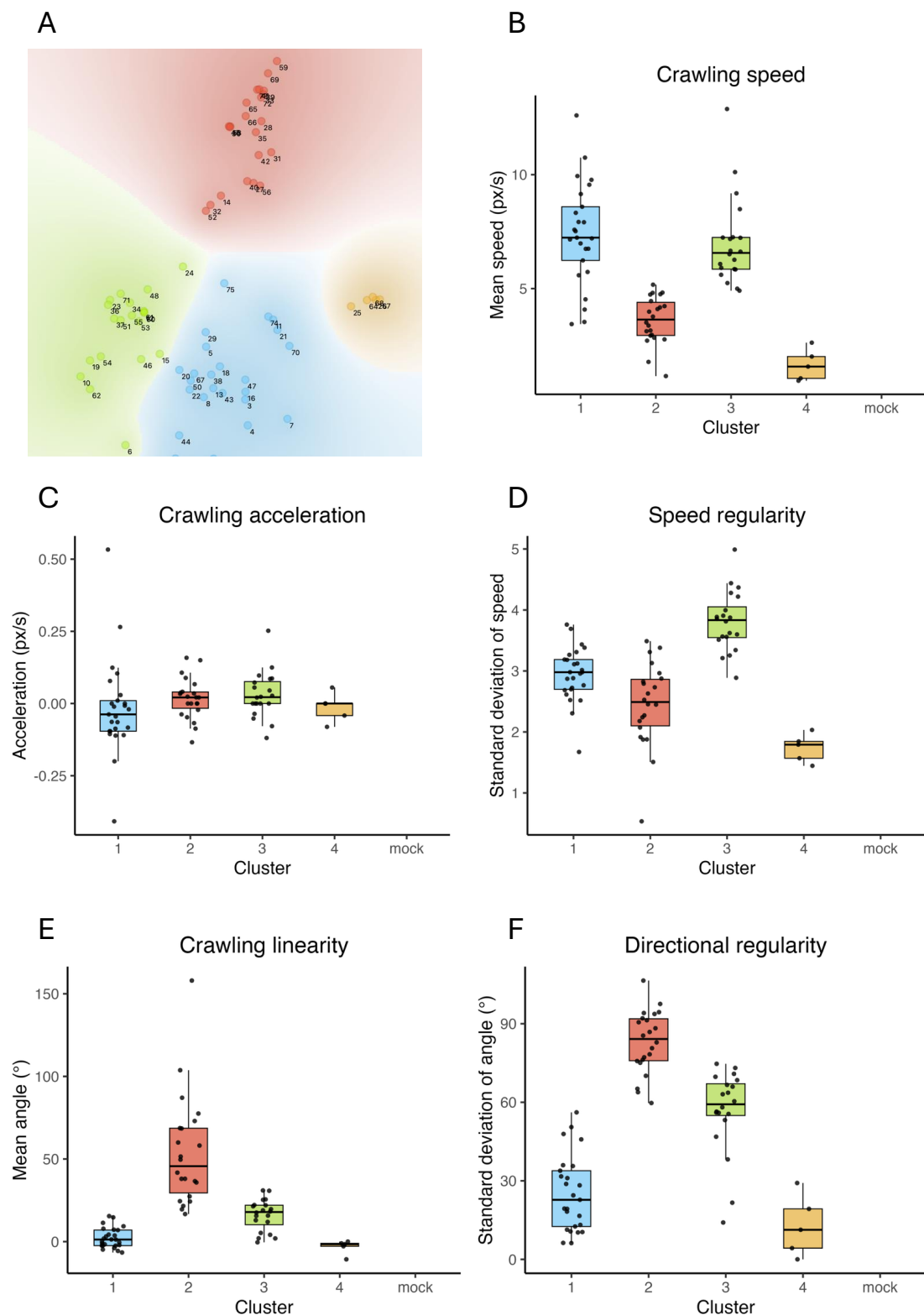


Figure 3.5: A: Unsupervised clustering of crawling behavioural patterns of orally challenged larvae. Louvain clustering was performed on 5 principal components. Representation was performed using a t-SNE algorithm (perplexity, 32; exaggeration, 2). Larvae were identified with a numerical ID. **B-F: behavioural patterns of each cluster.** Each dot represents an individual larvae (n=75). Boxplots show the median and interquartile range.

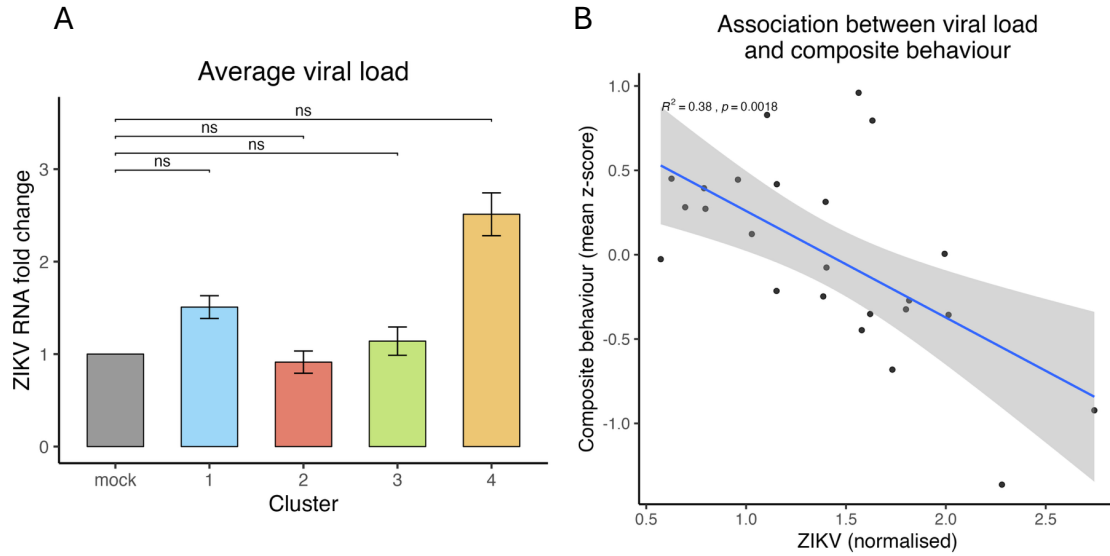


Figure 3.6: Association between viral load and composite behaviour of larvae. **A:** Mean viral load of individual larvae from each behavioural cluster ($n=26$; Mean *, $p<0.05$). **B:** Spearman correlation of composite behavioural z-score of individual larvae and viral load. Each larva is represented by a dot: viral load was quantified by qPCR, and the composite behaviour score was determined as the mean z-score of the different behaviour metrics (speed, acceleration, linearity, speed regularity and directional regularity). The blue line represents the best fit linear regression, and the shaded area is the 95% confidence interval. The strength of association was calculated using Spearman's correlation ($n=26$)

et al. 2022).

Part of the reason why antiviral innate immunity is so understudied is its complexity: the response is tissue- and virus-specific, and many factors, including microbiota, have been shown to play a role (Barletta et al. 2017; Ansaldo, Farley, and Belkaid 2021; Sansone et al. 2015; Mantilla-Granados, Castellanos, and Velandia-Romero 2024). Since the gut microbiota are able to activate Sting by secreting cyclic dinucleotides after oral challenge with SINV (Segrist et al. 2021) and SINV is very closely related to ZIKV, I ablated the gut microbiota of larvae before infection to study whether this had an effect on infection. The result showed an increase in ZIKV RNA load compared to the untreated infected control, and this increase in viral load was much greater than in Sting-deficient larvae. This suggests there is a mechanism for oral infection restriction induced by the gut microbiota in addition to Sting, as otherwise gut microbiota ablation would result in the same level of viral RNA load as in the Sting-deficient larvae, regardless of the presence or absence of gut microbiota. More research needs to be done in this area.

It is important to note that Sting expression is not completely eliminated in Sting^{EY06491} flies (Liu et al. 2018b), therefore there might still some activation of the pathway. This is particularly relevant to the results of the oral infection of Sting-deficient flies with their gut microbiota ablated, where the viral RNA level was much higher than that of orally infected Sting deficient flies with normal gut microbiota. Repeating the experiments with a different line, such as Sting^{Roxanne}, which contains a deletion of the Sting gene (Goto et al. 2018), will help elucidate whether the difference is

caused by activation of small amounts of Sting present in the Sting^{EY06491} flies, or whether it is due to the gut microbiota activating other immune pathways against ZIKV independently of Sting.

Focusing on the Sting-deficient larvae, I used qPCR to assess the viral tropism. I was not able to show viral presence in the nervous system, despite systemic infection via injection in adult flies showing ZIKV presence in the brain (Liu et al. 2018b). This could be due to the virus needing more time to disseminate through the organism, as the peak in ZIKV brain infection was reached on DPI 20 in adults (Liu et al. 2018b), while larvae can only be studied for three to four days after oral challenge, when they pupate. Another possibility I considered was that very few cells in the brain were infected, therefore not showing a significant presence of viral RNA by qPCR. However, I was not able to find viral RNA in the nervous system using smFISH against viral RNA either. Interestingly, I was able to detect a correlation between higher levels of viral RNA and more sluggish larvae, suggesting there is variability in larval susceptibility to infection and/or dissemination speed, and that the virus might be affecting the nervous system either very specifically or to very few larvae, and further research needs to be done.

In addition to the brain, I also assessed the abundance of viral RNA in other tissues via qPCR and smFISH. There was a slightly higher amount of viral RNA in the gut compared to the control, suggesting the viral infection is either transient or the virus infects very few cells, both of which are possible and have been shown in other viruses (Girard, Klingler, and Higgs 2004; Chen et al. 2024; Encarnação Sá-Guimarães et al. 2021; Whitfield, Murphy, and Sudia 1973; Scholle et al. 2004; Smith et al. 2008). I did not image infected larval guts or looked at different time points of infection, therefore it is not possible to identify the reason.

The tissue that displayed the highest ZIKV tropism as detected by qPCR was the haemocytes, which was corroborated in the smFISH images. This is interesting, as the haemocytes have been hypothesised to function as a means of viral dissemination through insect vector before (Parikh, Oliver, and Bartholomay 2009). This result, along with the rest of the tissue tropism experiment, seems to replicate what we know of oral infection of insect vectors after an infected blood meal: the virus first enters the gut, which it crosses to disseminate, potentially via haemocytes, through the rest of the organism, ultimately establishing a low-grade infection in the salivary glands, from where it can be injected into a mammalian host (Franz et al. 2015). *Drosophila melanogaster* is very closely related to ZIKV natural vectors, mosquitoes *Aedes spp.*, and since it is a well-established model organism, it is well-understood and there are a wide availability of genetic tools. Therefore, I decided to, infecting adults instead of larvae, study the potential of using this insect to model oral infection with ZIKV in mosquitoes.

Chapter 4

ZIKV infection of *Drosophila melanogaster* adult females

4.1 Introduction

Drosophila melanogaster has been used as a model to study disease almost since its establishment as a model organism, with the first hyperproliferative mutation associated to cancer being discovered in 1938 (Hadorn 1938; Gateff 1978). 65-70% of human disease-associated genes are present in *Drosophila*, but there is less genetic redundancy in the fly, which makes it easier to study the role of individual genes in health and disease without interference. However, the vast majority of research of diseases in *Drosophila* has been on neurodegeneration, cancer and developmental disorders, and in comparison little work has been done on infectious diseases (reviewed in Victor Atoki et al. 2025 and Harnish, Link, and Yamamoto 2021), despite the fly being the main model of innate immunity (Lemaitre and Hoffmann 2007).

Even less work has made use of *Drosophila* as a model for mosquito infection, despite the similarities between both species, which belong to the *Diptera* order (Waterhouse et al. 2007; Sieglaff et al. 2009; Severson et al. 2004). The fly has been used to elucidate host factors required for growth of different species of malaria *Plasmodium* in mosquito (Brandt et al. 2008), and many studies have used the wide range of genetic tools for *Drosophila* to detect innate immunity pathways involved in infection control (Palmer et al. 2020; Liu et al. 2018b; Harsh et al. 2018a; Nigg et al. 2024; Sherri et al. 2018; Shelly et al. 2009), as well as to study how pathogens' interactions with the host can cause certain symptoms of a disease (Harsh et al. 2020; Link et al. 2019; Chen et al. 2007; Macke et al. 2020; Jacob et al. 2022). However, the majority of these studies do not have the specific intention of using the fly to model mosquito.

Experimental infection of mosquitoes themselves has been more frequent, especially with Dengue virus (DENV). Research in mosquitoes has mainly focused on the immune response against viruses (reviewed in Li et al. 2024), but also on molecular interactions between the pathogen and the vector, such as exploring entry factors (reviewed in Liu et al. 2024; De Caluwé, Ariën, and Bartholomeeusen 2021), viral

determinants (reviewed in Lewis et al. 2023) or effects of infection on the vector's normal biological functions (reviewed in Ratnayake et al. 2023; Maire, Lambrechts, and Hol 2024; Nanaware et al. 2021; Sharma, Vrati, and Kalia 2021; Cardoso-Jaime et al. 2022; Ahmed, Varga, and Yang 2025; Sinha et al. 2024 and others); -omics studies to assay changes in the mosquito post-infection; vector competence, such as dosage studies and population genetics (reviewed in Couderc, Lambrechts, and Merklings 2025); microbiome and symbiotic interactions and their role in infection (reviewed in Mantilla-Granados, Castellanos, and Velandia-Romero 2024; Li et al. 2024; Minwuyet et al. 2023; Shi, Yu, and Cheng 2023), and, of course, potential interventions for pathogen control (reviewed in Côrtes et al. 2023; Wang et al. 2021; Zhang et al. 2024; Wang, Hoffmann, and Champer 2025 and others). However, the increased difficulty and cost of rearing and maintaining mosquito stocks in the lab and increased health and safety needs, added to the lack of easily available and abundant genetic tools for this species, still make *Drosophila* an underutilised, useful candidate to use as a model.

From the experiments presented in Chapter 3, I was able to show that the tissue tropism of Sting-deficient L3 *Drosophila melanogaster* larvae orally infected with ZIKV mirrors what we know of dissemination of other arboviruses inside the insect vector, where after entering the gut lumen through a bloodmeal, the virus first enters and infects only a few cells in the gut (Girard, Klingler, and Higgs 2004; Whitfield, Murphy, and Sudia 1973; Smith et al. 2008) before escaping to other tissues (fat bodies, muscle, nervous tissue or, in the case of my experiment, haemocytes) and, ultimately, reaching the salivary glands, from where it can be injected into a new host along with the mosquito saliva. The tissues it can infect and use to replicate vary from virus to virus, and most studies focus on some tissues and/or time points post-infection, resulting in incomplete tropism data: Dengue (DENV), West Nile Virus (WNV), and ZIKV are all found in the fat body, while only WNV and Venezuelan Equine encephalitis virus (VEEV) have been shown to infect the muscle of the mosquito. WNV was also found in nervous tissue (Girard, Klingler, and Higgs 2004; Weaver 1986; Zhang et al. 2010; Encarnação Sá-Guimarães et al. 2021). Haemocytes have been shown to both control infection (Lamiabale et al. 2016; Tassetto, Kunitomi, and Andino 2017; Nainu et al. 2015) and to get infected at very large numbers, hypothetically providing a site for viral replication (Parikh, Oliver, and Bartholomay 2009). Both can sometimes occur in the context of infection with the same virus (Leite et al. 2021), highlighting the bidirectional relationship between pathogens and their hosts. However, these results once again differ greatly depending on the virus used and on the infection method, with most studies using injection to infect even in mosquitoes, which is not representative of the normal tropism or timeline of infection with viruses in nature.

In the particular case of haemocytes and ZIKV, the larval tissue tropism data presented in chapter 3 showed very high viral load in haemocytes, suggesting that in oral ZIKV infection of the insect, this cells could be used to generate and disseminate large amounts of the virus. Very recently, this hypothesis was proved in a study by Hall et al., which proved that, in the case of ZIKV, haemocytes are not only able to get infected, but that their depletion reduces viral dissemination, pointing towards this cell type acting as one of the main ways the virus spreads across the different tissues (Hall et al. 2025), as I proposed in Chapter 3 and further show

in this chapter.

Since my previous experiments were performed in larvae, I decided to try to orally infect adult *Sting* deficient flies with ZIKV instead. This is a more relevant model of mosquito infection, since only adult females consume the viraemic blood that results in infection. I am particularly interested in the initial stages of infection, the viral escape from the gut. This stage of mosquito infection is not well-understood: viruses must not only enter (or otherwise bypass) the epithelia, but also cross the basal lamina: a dense, fibrous extracellular matrix that lines the gut.

Although the basal lamina has pores, these have been shown to be too small for viral particles to cross directly (Houk, Hardy, and Chiles 1981). Hence, several hypotheses for viral crossing have been presented: the pores become larger or deformed either upon infection, for example by inducing cellular damage that disrupts maintenance of the basal lamina (Weaver et al. 1988; Ayers et al. 2021) or by the distension caused by the blood meal, which can last for days after the blood has been digested (Cui et al. 2019; Romoser et al. 2004; Kantor et al. 2018). Research in Rift Valley Fever Virus (RVFV) suggests a second theory: while not exclusive of midgut infection, viral infection in the foregut, where the basal lamina is more porous, could explain the ability of this virus to escape the gut (Romoser, Faran, and Bailey 1987; Lerdthusnee et al. 1995). However, this theory might apply only to certain viruses, as it was disproved in WNV and Dengue infections (Girard, Klingler, and Higgs 2004; Salazar et al. 2007). It is also possible that the virus escapes via infecting a different tissue directly, such as haemocytes or the trachea (Salazar et al. 2007; Romoser et al. 2004; Romoser et al. 2005).

Viral particles, other molecules of similar size and even red blood cells have been found in the mosquito haemocoel before viral replication could have occurred (Paquette et al. 2015; Weaver et al. 1991; Boorman 1960; Cui et al. 2019), suggesting intercellular escape routes that do not rely on viral replication inside the gut cells. However, other studies have shown that increasing or reducing viral replication results in changes in viral spread in the mosquito, therefore suggesting a mechanism reliant on viral replication is also involved in gut escape, even if in combination with an intercellular one (Carpenter et al. 2021; Franz et al. 2006; Khoo et al. 2010). In the case of Western Equine Encephalitis Virus (WEEV) and ZIKV, there is evidence that the virus needs to reach a certain threshold to cross the gut, whereas for others, such as DENV, there is no such threshold (Dickson et al. 2014; Bosio, Beaty, and Black 1998; Vazeille et al. 2019; Kramer et al. 1981), further demonstrating that the relationship with the vector differs between viruses.

The gut in fruit flies and mosquitoes is very similar morphologically even when the mosquito gut has specialised for blood digestion. It is divided into foregut, midgut and hindgut in both species. Although not exclusively, in both flies and mosquitoes the midgut is the region of the gut where digestion occurs, and it is also the initial site of infection in most cases (Franz et al. 2015). The *Drosophila* midgut is further divided into several regions with defined morphological and physiological characteristics (Marianes and Spradling 2013; Buchon et al. 2013; Miguel-Aliaga, Jasper, and Lemaitre 2018; Liu and Jin 2017), however the most general and widely used distinction divides the midgut into anterior, middle and posterior midgut (Tafesh-Edwards and Eleftherianos 2023, Figure 4.1).

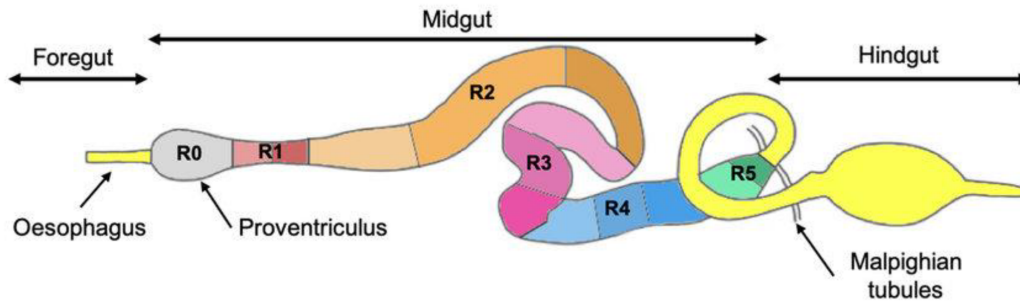


Figure 4.1: Anatomy of the *Drosophila* gut. The different regions have distinct morphological and physiological features. The posterior midgut is comprised of regions R4 and 5. Figure from Capo, Wilson, and Di Cara 2019

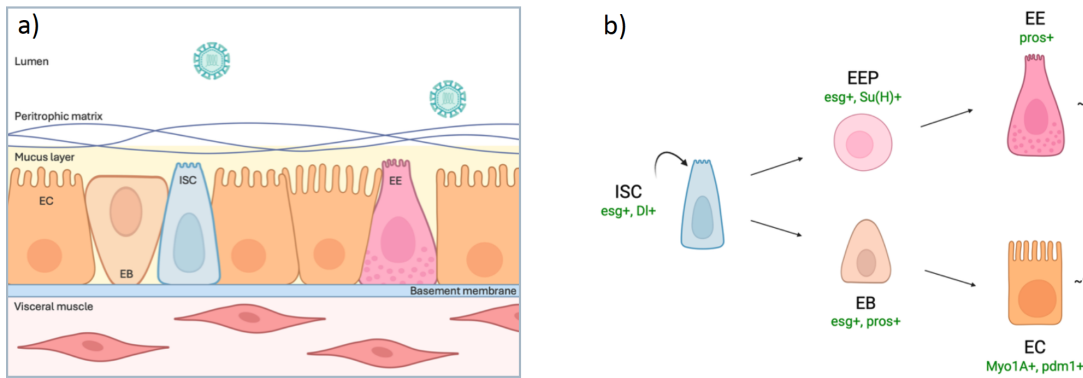


Figure 4.2: A: Structure of the *Drosophila* midgut. The gut epithelium is a polar structure, with the apical side of the cells separated from the lumen by the peritrophic matrix and a mucus layer, and the basal side protected by the basement membrane and wrapped with visceral muscle. Viral particles entering the gut lumen encounter the peritrophic matrix first. **Cell lineage of the *Drosophila* midgut epithelia.** ISCs divide symmetrically and asymmetrically, which produces transient progenitors EBs and EEPs. EBs will differentiate into ECs, which compose approximately 90% of the cells. EEPs will differentiate into EEs. Genetic markers for each cell type are highlighted in green.

Regardless of this compartmentalisation, the basic architecture of the tissue is consistent through the midgut. It is formed by an epithelium layer, which is wrapped by muscle, neurons and trachea (Figure 4.2A, Tafesh-Edwards and Eleftherianos 2023). The epithelium is separated from the muscle by the basal membrane, which forms a mesh-like extracellular matrix (Shanbhag and Tripathi 2009), and the lumen of the gut is protected by a chitinous layer: the peritrophic matrix (Hegedus et al. 2009). The epithelium is maintained by a pool of pluripotent intestinal stem cells (ISCs), which can divide asymmetrically into enteroblasts (EBs) or enteroendocrine progenitor cells (EEPs). EBs and EEPs are transient progenitors which further differentiate into absorptive enterocytes (ECs) and secretory enteroendocrine cells (EEs), respectively (Figure 4.2B). ECs are the most abundant cell type in the gut. Figure by Hope O'Brien.

While the gut physiology and dynamics of *Drosophila* midgut are relatively well-understood, there is little information available on its mosquito equivalent. However,

a recent single-cell RNA sequencing study was able to match cell type clusters from *Drosophila melanogaster* and *Aedes aegypti*, thus pointing to a highly conserved system where the main differences are a result of the mosquito's adaptations for blood feeding (Cui and Franz 2020).

Mosquito blood feeding is an essential part of their life cycle, triggering a transition from a sugar-feeding state to a reproductive state. The blood meal has effects on the whole organism, which remain largely unexplored. A 2025 study by Vial et al. found some physiological changes to the gut post-blood meal, including increased growth and differentiation of EC subtypes that secrete digestive enzymes (Vial et al. 2025). The nutrients present in the blood result in growth of the gut microbiota (Rodgers et al. 2020; Dong, Manfredini, and Dimopoulos 2009; Demaio et al. 1996), which is controlled by increased expression of antimicrobial peptides (Vial et al. 2025; Meister et al. 2009). This activation of the immune response has been shown to have an effect on resistance to DENV (Ramirez et al. 2012) and malaria parasite growth (Cai and Christophides 2024; Garver, Almeida Oliveira, and Barillas-Mury 2013; Isaacs et al. 2011). In contrast, digestion of the high content of proteins in blood produces glutamic acid, which has been shown to activation of the GABAergic system, which in turn reduces activation of antiviral immunity pathways, thus facilitating arbovirus infection with both ZIKV and DENV (Zhu et al. 2017). Blood meals also have physiological effects on other tissues: hemocytes proliferate as a result of insulin-like peptide expression and ovary ecdysteroidogenic hormone (Samantsidis, Karim, and Smith 2025; Martinson et al. 2022; Ling and Raikhel 2023; Castillo, Brown, and Strand 2011), which could help the virus disseminate to other tissues. Orally challenging *Drosophila* with isolated virus does not replicate the effects of a blood meal on the mosquito physiology, and therefore results obtained using the fly as a model need to be considered taking into account these differences.

Another important consideration for this chapter is that the larvae used in Chapter 3 were deficient for Sting. This genotype has been shown to have increased susceptibility to viral infection, including with ZIKV, when infected systemically via injection (Liu et al. 2018b). Sting has also been shown to drive antiviral immunity when infecting flies orally with *Drosophila* C virus (DCV) and Sindbis virus (SINV) (Segrist et al. 2021). Importantly, Sting is not conserved in mosquitoes, which makes the sting deficient *Drosophila melanogaster* a promising, biologically relevant model to study ZIKV infection of insects.

4.1.1 Aims and objectives

- Compare gene homology between *Drosophila melanogaster* and *Aedes spp.* mosquitoes.
- Confirm Sting deficiency is sufficient to create a permissive condition for ZIKV oral infection in adult female *Drosophila melanogaster*
- Establish a timeline of infection.
- Study viral tropism through time, detecting which tissues are more susceptible to ZIKV infection at different time points post-infection.
- Identify cell type tropism of ZIKV in the fly gut.

- Detect potential effects of ZIKV on lifespan, healthspan and behaviour of infected flies.
- Begin to investigate potential mechanisms for viral gut barrier escape.

4.2 Materials and methods

4.2.1 Enrichment analysis

The OrthoDB API was used to download the list of orthologs between *Drosophila melanogaster* and *Aedes aegypti* from the latest available versions of the *Drosophila melanogaster* NCBI RefSeq assembly (GCF_000001215.4, Hoskins et al. 2015) and *Aedes aegypti* NCBI RefSeq assembly (GCF_002204515.2 Matthews et al. 2018). Protein-coding genes that had no orthologs were added from the FlyBase gene_snapshots_fb_2025_ file.

Gene ontology (GO) IDs were added using the Gene Association File (GAF, gene_association.fb.gz), also available from Flybase (Öztürk-Çolak et al. 2024). The resulting dataset was collated with the Gene Ontology Resource core ontology annotations dataset (go-basic.obo, Ashburner et al. 2000; Aleksander et al. 2023), to obtain a readable description of the alphanumeric GO term ID. To simplify the list of GO terms, they were classified into high-level functional groups using generic GO Slim categories from the *Drosophila*-specific Slim subset (goslim_drosophila.obo, available from the Gene Ontology Consortium).

GO enrichment analysis to identify over- and under-represented terms was performed using Fisher's exact test (Mi et al. 2020) on the Slim categories, applying the Benjamini-Hochberg correction to calculate the false discovery rate (FDR). For the background gene count calculation, only genes with any GO slim annotation were counted, to avoid over-representation of background genes. GO terms arising from the "cellular component" root term were removed, as these only describe where the genes associated are active. GO slim terms arising from the root "molecular function" were also removed, as this root denotes non-specific activity, such as "kinase activity" or "DNA-binding" but do not specify the context of the activity. Data was analysed and plotted using a custom Python pipeline and Matplotlib.

To analyse immune-related GO term enrichment, enrichment analysis was performed on GO terms instead of slim terms as previously described. GO terms were filtered to select those associated with immunity by finding those with a "is a" or "part of" relationship with GO terms "immune system process", "immune response", "defense response" or "immune effector process". To protect for unlikely but potential orphan terms, the following keywords were also searched within the GO term names in the dataset: "immun", "immune", "defense", "antimicrob", "antigen", "inflamm", "hemocyte", "phagocyto", "antiviral" and "cytokin". To remove overly general terms, GO terms with root terms "cellular component" and "molecular function" were removed. To further simplify the list and remove any redundant terms, although GO terms that contained unique genes not present in any other GO term were maintained, when a parent-child GO term pair had both members present in the dataset only the one within root depths 3-6 was kept. If both or none of the

members were within this range, the more distant to the root (more specific and generally better annotated) was retained. Lastly, GO terms that had two or less genes in the foreground or background and three or less genes in total were considered too specific and removed.

To compare whether genes expressed in certain tissues are more conserved than others, tissue RNA expression data was added from the curated expression dataset curated_expression_fb_2025_04.tsv.gz file, also available from FlyBase. The anatomical structure data was assigned to each gene, and then grouped into nervous system, digestive system, salivary glands and haemocytes by searching for the following terms within the expression information: for the nervous system: "neuron", "nerve", "glia", "brain", "glial", "sensory", "neuro", "neuronal", "neuroblast", "NMJ", "bouton", "photoreceptor", "nervous", "cerebrum", "mushroom body", "neuromuscular", "optic", "sense"; for the digestive system: "midgut", "gut", "crop", "foregut", "intestine", "intestinal", "micropyle", "digestive", "proventriculus", "pylorus", "enteroendocrine"; for the salivary glands: "salivary", and for the haemocytes "hemolymph", "crystal cell", "hemocyte", "plasmatocyte", "hemocoel", "circulatory".

Enrichment was calculated the same way as before, using Fisher's exact test on the broad tissue data and applying the Benjamini-Hochberg correction to calculate the FDR. To avoid over-representation of background genes, only those with any tissue expression annotations were considered.

4.2.2 ZIKV strains, production and titration

ZIKV was produced on Vero CCL81 cells or C6/36 cells as described in the Materials and Methods section. The viral strain MR766 was used in this chapter.

4.2.3 *Drosophila* stocks

The fly lines used in this chapter are:

Line	Genotype	Description
W ¹¹¹⁸	W ¹¹¹⁸	Wild type background
Sting ^{EY06491}	;Sting ^{EY06491} ;	Transgenic insertion stock with decreased expression of Sting (Liu et al. 2018b)
esg ^{ts}	;esg-Gal4, UAS-GFP, Tub-Gal80 ^{ts} ;	Gut progenitor cells (escargot positive) marked with GFP

Table 4.1: List of *Drosophila melanogaster* stocks used in this chapter.

Flies were maintained at 25°C as described in the Materials and Methods section, except esg^{ts}, which were maintained at 18°C and transferred to 29°C as specified for each experiment.

Fly lines used were Wolbachia-free, tested as described in the Materials and Methods section.

4.2.4 DNA extraction and PCR

DNA extraction was performed as described in the Materials and Methods section. PCR was performed using the MyTaq Red Mix kit from Meridian Biosciences (BIO-25043) according to the instructions provided by the manufacturer. 200 ng of genetic material were loaded per sample. The primers used in this chapter can be found in the Appendix. The thermocycling conditions were as follows: an initial denaturation step for one minute at 95°C, followed by 35 cycles of a fifteen second denaturation step at 95°C, a fifteen second annealing step at 56°C, and a ten second extension step at 72 °C, followed by a longer extension step, where 72 °C were maintained for ten minutes. Samples were maintained at 4°C until ready for gel electrophoresis, which was performed on a 1% agarose in 1X TAE buffer.

4.2.5 RNA extraction and qPCR

RNA was extracted as described in the Materials and Methods section, using TRIzol reagent (invitrogen #15596026).

RT-qPCR was performed using the Luna Universal One-Step RT-qPCR kit (NEB #E3005). The thermocycler was programmed to hold 55°C for 10 minutes, then 95°C for 1 minute, followed by 45 cycles of 10 seconds at 95°C and 30 seconds at 60°C before reading the plate. The melt curve was measured between 60°C and 95°C at 0.5°C intervals. Relative fold expression was calculated using the $2^{-\Delta\Delta C_t}$ method. RNA levels were normalised against housekeeping gene rp49. Primer sequences can be found in the Appendix.

4.2.6 ZIKV infection of adult *Drosophila*

Fly vials were emptied of adults, and pupa left to emerge for three days. On day three, mated female adults (aged 1-3 days old) were transferred to a fresh vial, and left to age two more days, therefore becoming 5-2 day old adults. These were transferred to an empty vial in the evening of day five, along with a 5cm diameter Whatman paper soaked in distilled water to starve them. Vials were kept inside a customised wet chamber. To ensure virus ingestion synchronisation, the Whatman paper was removed the morning after, and the walls of the vial were carefully cleaned of water condensation, and the flies were left for three hours in an empty, dry vial, outside of the wet chamber.

The virus (4×10^6 pfu) was introduced in a DMEM solution containing 10% FBS and 5% sucrose, which was used to soak a Whatman paper. The equivalent volume of DMEM and sucrose was used for the Mock infection condition. Infected fly vials were kept inside a wet chamber for three days. In the evening of day 3 (day post infection 0, or DPI0), flies were transferred to standard food vials.

4.2.7 Collection of infected samples

Full infected flies were collected at the same time every day. They were left for three hours to empty their gut before being dissected or, for full body infection experiments, directly flash-frozen at -80°C .

4.2.8 Tissue dissection and collection for qPCR

At least three flies per condition were dissected sequentially on a drop of PBS placed on a glass dish, pre-chilled to avoid evaporation. Collected tissues were transferred into a 1.5 mL tube containing 20 μL of PBS and kept on ice. The full dissection method for each tissue can be found in the Materials and Methods section.

Sequential dissection started by removing the head. To ensure the haemocytes were retrieved as cleanly as possible, the PBS drop was replaced by a 20 μL amount. Beheaded flies were bled for three minutes to collect haemocytes into the PBS, which was transferred into an empty 1.5 mL tube and placed on ice. Flies were subsequently dissected to separate the salivary glands, gut and abdominal wall and ovaries. The thorax was not collected, as it contains haematopoietic hubs.

4.2.9 Tissue dissection and collection for imaging

At least three flies per condition were dissected sequentially as described in the section above.

Brains were extracted from collected heads using two forceps: one to hold the fly by the proboscis, the other one to peel away the eyes, one at a time, releasing the brain.

For imaging, flies were bled directly onto the microscopy slide, treated with polylysine. A 20 μL drop was placed in the centre of an area limited with a hydrophobic pen (ImmEdge Hydrophobic Barrier pen, Vector laboratories H-4000). The slides were kept inside a wet chamber while the rest of the tissues were dissected, leaving approximately thirty minutes for the haemocytes to settle before fixing.

After bleeding, flies were returned to the glass dish, where the salivary glands and gut were extracted and placed into polylysine-treated slides for staining and imaging.

4.2.10 Immunofluorescence staining

Antibody staining was performed as described in the materials and methods section. Tissues were placed on a drop of PBS on a polylysine plate immediately after dissection, and kept in a wet chamber during the staining process. The antibodies used in this chapter and their concentrations are:

Antibody	Concentration	Source
anti ZIKV envelope (rabbit)	1:200	Invitrogen (HL1699)
Goat anti-rabbit AlexaFluor 546	1:500	Abcam (175471) (

Table 4.2: List of primary and secondary antibodies used in this chapter.

4.2.11 Lifespan assay

Infected and mock-infected flies were maintained as described above. Every two days, flies were tipped into a fresh food vial, and dead flies counted and collected and flash-frozen for RNA extraction and qPCR.

4.2.12 Smurf assay

The smurf assay is a validated method to assay gut permeability in *Drosophila* and other organisms (Martins et al. 2018). Flies were maintained as described above, but on alternating days between 10-11 am, they were transferred to a food vial containing a 5 mm diameter Whatman paper soaked with 20 μ L of a solution containing 10% glucose and 2.5% Brilliant Blue FCF dye (Merck #80717) in distilled water. Flies were left to feed for five hours before anaesthetising with CO₂ and counting. Non-smurf flies display a blue spot in their abdomen, where the food is inside the gut. Only flies where the full body had turned blue were counted as smurfs. Dead flies were rinsed in distilled water to make sure they were real smurfs and not stained with blue food had on the outside of their body. Flies were transferred back to normal food after counting.

4.2.13 Climbing assay

Climbing abilities of infected and mock-infected flies was assessed as described in the Materials and Methods section.

4.3 Results

4.3.1 Genome conservation between *Drosophila melanogaster* and *Aedes aegypti*

Although both the fruit fly and mosquitoes belong to the order Diptera, little work has been done in studying how similar their genomes are. Past studies have focused on specific regions of the genome, particularly those related to immunity (Waterhouse et al. 2007), development (Behura et al. 2011) and cis-regulatory elements (Sieglaff et al. 2009), or have a very reduced scope due to the limited resources available before the full genome sequencing of the different mosquito species (Zdobnov et al. 2002; Bolshakov et al. 2002; Matthews and Munstermann 1994; Fulton et al. 2001; Severson et al. 2004; Danchin and Pontarotti 2004). The general consensus reached by these studies is that conservation between the different species of mosquitoes included in these studies (*Aedes spp.*, *Anopheles spp.* or *Culex spp.*)

is very high, and comparisons with *Drosophila melanogaster* showed a homology between 51% (Zdobnov et al. 2002) and 85% (Waterhouse et al. 2007) of sequences considered in each study, with the highest percentage homology being in immune-related genes.

Despite recent advances, such as the improved sequencing and annotation of both the *Drosophila melanogaster* (Adams et al. 2000) and some *Aedes spp.* genomes (Matthews et al. 2018; Acharya et al. 2024; Nene et al. 2007), there have been no new studies that consider the similarities between both organisms. As my project had the intention of using *Drosophila melanogaster* to model mosquitoes, particularly using a fly genotype mutant for a gene that is not conserved in mosquitoes, I compared the most recent versions of the *Drosophila melanogaster* (NCBI RefSeq assembly GCF_000001215.4, Hoskins et al. 2015) and *Aedes aegypti* (NCBI RefSeq assembly GCF_002204515.2, Matthews et al. 2018) reference genome protein coding genes using OrthoDB (Kuznetsov et al. 2023).

Using the OrthoDB API (Kuznetsov et al. 2023) I was able to generate a list of all *Drosophila melanogaster* protein coding genes that had at least one *Aedes aegypti* ortholog. The list had a total of 14150 entries, in which 1942 fly genes appeared more than once, since they have more than one ortholog in mosquito, as was the case for 1616 mosquito genes. 9388 *Drosophila* genes appeared in the list at least once, out of the 13822 total protein coding genes in the fly (Hoskins et al. 2015). Conversely, out of the 15419 protein coding genes in the *Aedes aegypti* genome (Nene et al. 2007), 10306 have at least one *Drosophila* ortholog. This means 68% of protein coding genes from *Drosophila melanogaster* are conserved in *Aedes aegypti*, and 66% of protein coding genes from *Aedes aegypti* are conserved in *Drosophila melanogaster*.

To further explore the similarities and differences between both genomes, the ortholog list was annotated with generic gene ontology (GO) slim terms (Ashburner et al. 2000; Aleksander et al. 2023; Öztürk-Çolak et al. 2024) in order to classify the genes into broad, biologically relevant categories. Enrichment analysis was performed on these slim GO terms by comparing the number of genes within a GO term with and without an ortholog and the overall conservation of the genome using Fisher’s exact test. GO terms were systematically filtered for biological functions that were neither too broad nor too specific, resulting in 53 significantly enriched (45) or depleted (8) categories (Figure 4.3). The most significantly enriched term was nervous system development, followed by cell differentiation and morphogenesis. Eight out of the 45 significantly enriched terms were related to development. Terms related to the nervous system were also present several times, with synaptic organisation and signalling both appearing as highly enriched, along with nervous system development and cognition. Salivary gland development was also significantly enriched.

Interestingly, the slim GO term for immune response appeared to be significantly under-represented. To further explore this, I analysed enrichment of GO terms related to the immune response (Figure 4.4). It is important to note that barely any GO terms demonstrated significant enrichment or depletion when using the full *Drosophila* genome ortholog count as a background, due to the number of genes present in each category was very low (2-200, with a mean of 20 and a median of

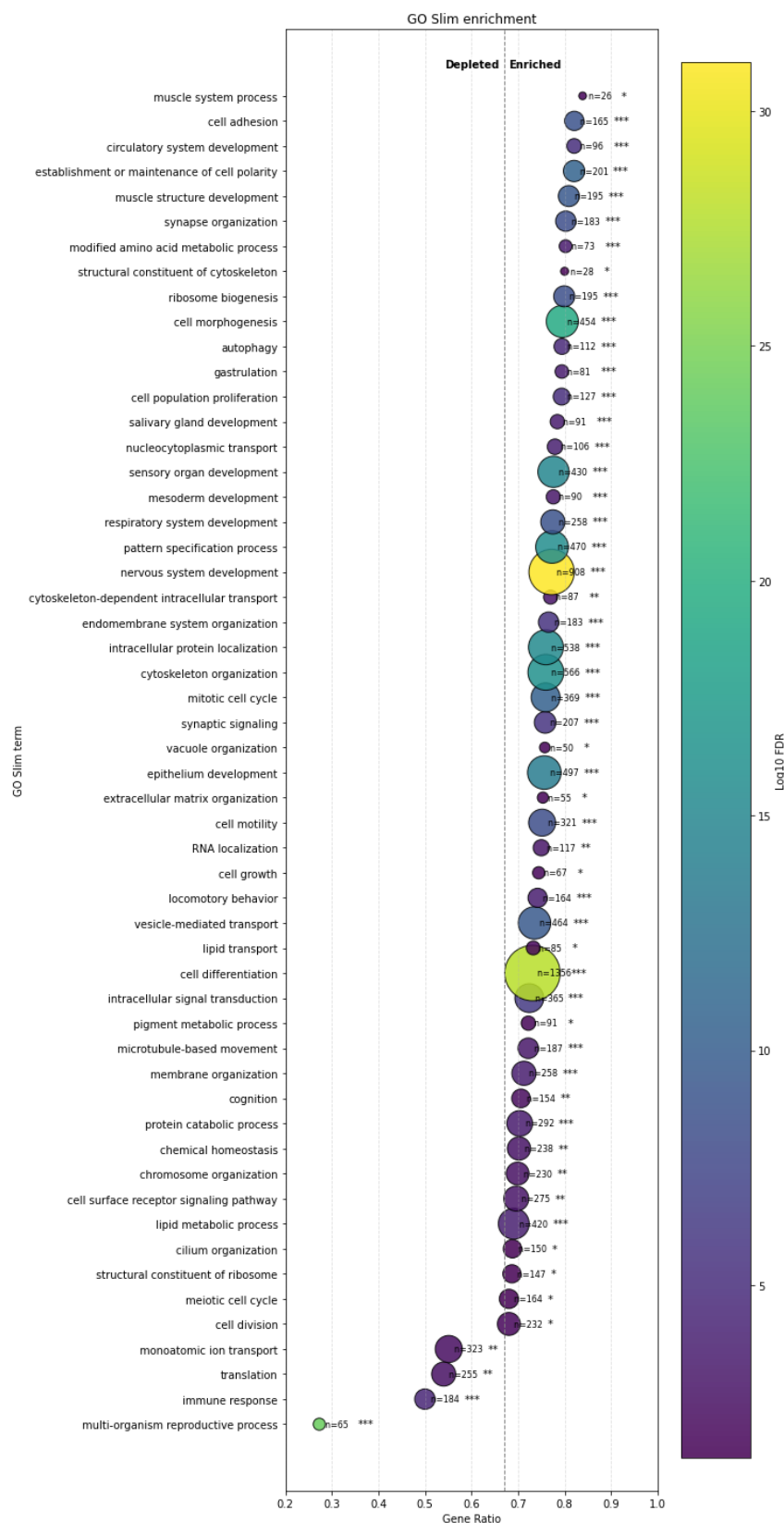


Figure 4.3: GO Slim term enrichment in *Drosophila melanogaster* genes with orthologs in *Aedes aegypti*. GO terms are listed on the left, ranked by gene ratio (proportion of genes within that term that have an ortholog). The size of the dot represents the number of genes within the term that have an ortholog. The colour of the dot represents the $-\text{Log}_{10}$ false discovery rate. (*, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.005$, ****, $p < 0.001$)

11. Two of the terms with the most genes were very vague, "immune response" and "innate immune response", and removing them resulted in a mean of 15). All of the 51 GO terms remaining after filtering had at least one conserved ortholog in *Aedes aegypti*, and 19 of them were under-represented compared to 32 enriched.

Another caveat was evidenced by how "Innate immune response", which appeared significantly under-represented with 79 genes conserved and 121 not conserved, included far more genes than the broader term "immune response", which while also (non-significantly) under-represented, only contained 35 conserved genes and 39 *Drosophila*-specific. Similarly, none of the genes tagged with GO term "positive regulation of phagocytosis", which appeared as enriched (3 genes conserved, 1 *Drosophila*-specific), were tagged with broader GO term "phagocytosis", which appeared as under-represented (8 genes conserved, 8 genes *Drosophila*-specific). These differences pointed at issues with GO term annotation, indicating the rest of the data should be carefully analysed, particularly when considering these more specific GO terms rather than slim terms, since poor annotation of a single gene could result in a GO term appearing as enriched rather than under-represented. The statistical test used does account for this issue caused by a small foreground, which explains why only three GO terms had a p-value lower than 0.01.

Despite these caveats, I noted that there were 11 terms related to haemocytes enriched, compared to 5 that were under-represented. There was also one enriched term related to the antiviral response, compared to two neither over- nor under-represented ones and one under-represented, but the under-represented one ("defence response to virus") was also broader than the other three, one of which ("positive regulation of defence response to virus with host") was remarkably similar to the under-represented term. Once again, some genes were tagged only with the more specific terms but not the broader ones. As such, I cannot extract any significant conclusions from this analysis.

I also attempted to compare conservation across *Drosophila* and *Aedes* across different tissues (Figure 4.5). For this, I collated the ortholog dataset with a dataset containing curated gene expression available from Flybase, and manually classified anatomical structure data into parts of the nervous system, parts of the digestive system, the salivary glands and the haemocytes. Slim term annotations for anatomical structure were not cross-checked, but not used, as they included the haemocytes with cardiac tissue elements. The resulting enrichment analysis showed that genes expressed in both digestive and nervous tissues were enriched for presence of orthologs in *Aedes aegypti*. The digestive system in particular was very highly and significantly enriched, with 74% of genes having an ortholog and a false discovery rate of 0.000000306. Genes expressed in the nervous system also appeared to be highly enriched for the presence of orthologs, with 73% of genes expressed in the nervous system having at least one. Genes expressed in the other tissues assessed were neither significantly enriched or depleted, with 72% and 68% of the genes expressed in the salivary glands and haemocytes respectively having at least an ortholog.

While this analysis did validate that *Drosophila melanogaster* and *Aedes aegypti* are closely related and comparable species in general, it also highlighted the differences between conservation levels of different biological processes and even tissues, showcasing the need to confirm conservation of genes and biological pathways before

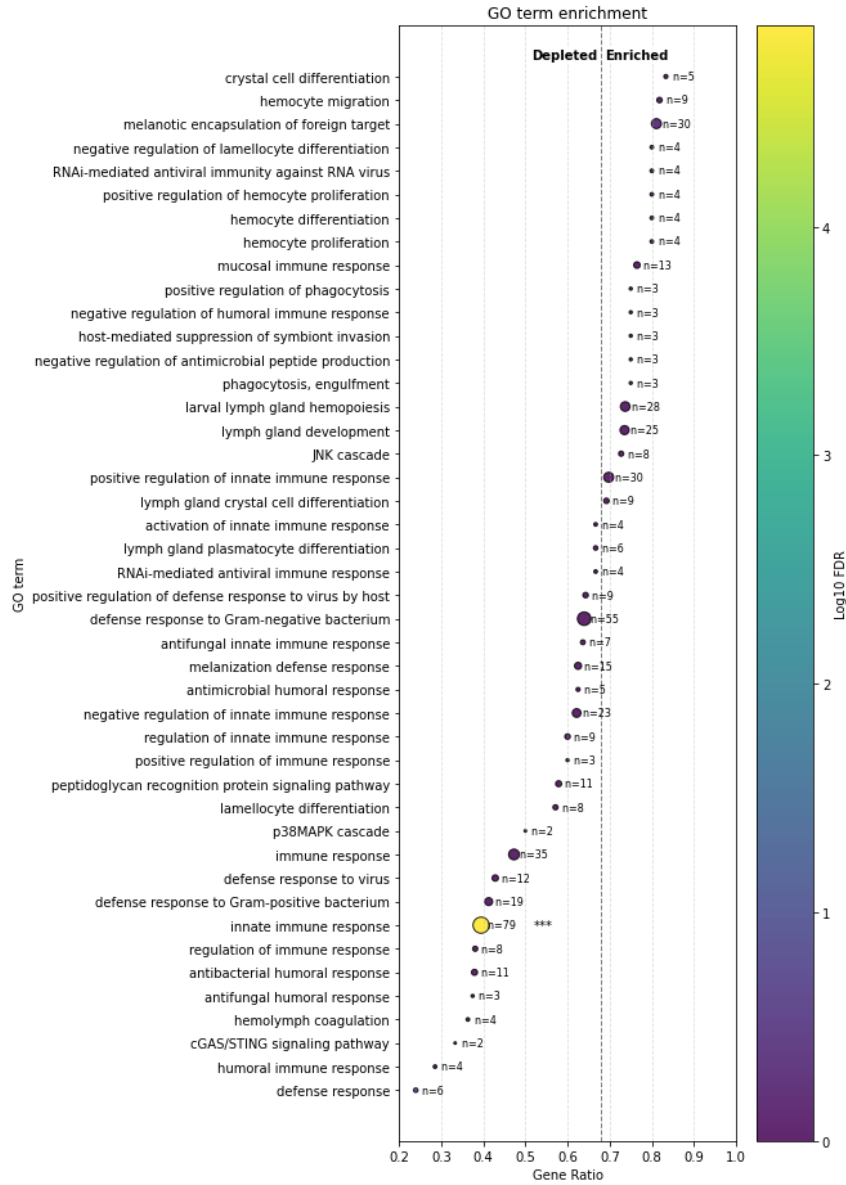


Figure 4.4: Immune GO term enrichment in *Drosophila melanogaster* genes with orthologs in *Aedes aegypti*. GO terms are listed on the left, ranked by gene ratio (proportion of genes within that term that have an ortholog). The size of the dot represents the number of genes within the term that have an ortholog. The colour of the dot represents the $-\log_{10}$ false discovery rate. (*, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.005$, ****, $p < 0.001$)

attempting to study them using a model.

4.3.2 Oral infection with ZIKV of adult *Drosophila melanogaster* flies

Drosophila melanogaster has been used in several occasions to study ZIKV infection, however in the majority of viral infection studies for ZIKV and other viruses, the viral delivery method is thoracic injection. Since, as described in Chapter 3, Sting^{EY06491} fly larvae are susceptible to oral ZIKV infection, particularly in germ-free conditions, I attempted to orally challenge adults of this same genotype. For

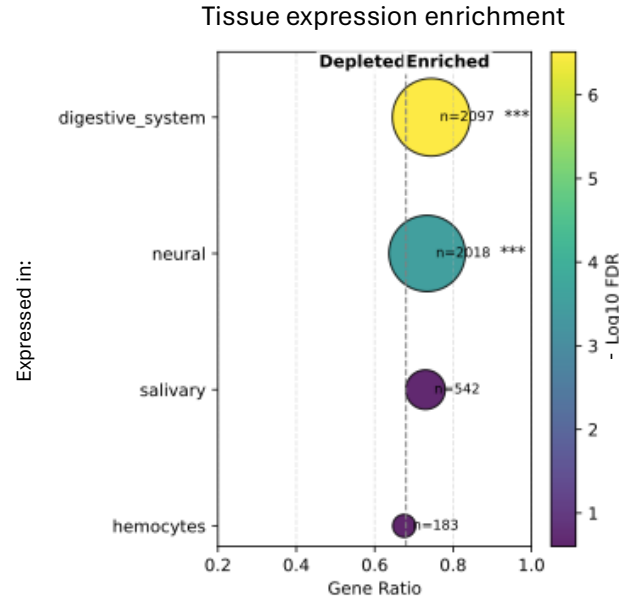


Figure 4.5: Tissue expression pattern conservation enrichment of *Drosophila melanogaster* genes with orthologs in *Aedes aegypti*. Tissues are listed on the left, ranked by gene ratio (proportion of genes within that term that have an ortholog). The size of the dot represents the number of genes within the term that have an ortholog. The colour of the dot represents the $-\text{Log}_{10}$ false discovery rate. (*, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.005$, ****, $p < 0.001$)

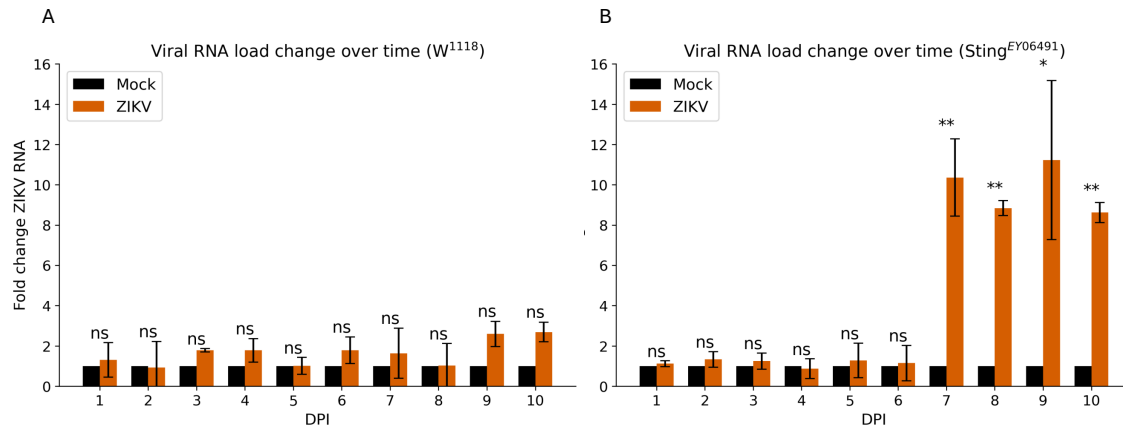


Figure 4.6: Oral infection timeline of adult flies. Relative ZIKV RNA abundance as detected with qPCR in the first 10 days post infection. Three pooled orally challenged W¹¹¹⁸ (A) and Sting^{EY06491} (B) adult flies ($n=3$; Mean $\pm$ SEM; *, $p < 0.05$; **, $p < 0.01$).

this, I starved the flies on water overnight and removed the water for three hours before infection to synchronise feeding. qPCR of whole Sting^{EY06491} adult flies on days post infection (DPI) 1 through to fourteen showed a sharp increase in viral RNA load on DPI7, which was maintained until DPI10 (Figure 4.6A).

Control W¹¹¹⁸ adult flies are susceptible to systemic ZIKV infection via injection, even if sustaining a lower viral load than Sting^{EY06491} flies (Liu et al. 2018b). However, injection is not a viral delivery method representative of natural infection, where the first challenge for ZIKV is crossing the gut barrier. Given what is known about Sting-dependent anti-viral defence after oral challenge with SINV (Segrist

et al. 2021), and after testing this same hypothesis in larvae (chapter 3), I tested whether adult W^{1118} flies were susceptible to ZIKV oral infection. The resulting qPCR showed no significant increase in viral load in DPI 1-14 (Figure 4.6B), thus highlighting a role for Sting in *Drosophila melanogaster* immunity against oral infection with ZIKV, and validating using the ZIKV-susceptible Sting^{EY06491} fly line to further study innate immunity against this virus.

4.3.3 ZIKV tissue tropism in adult flies following oral infection

The tissue-specific qPCR experiment described in chapter 3 provided a promising snapshot into ZIKV distribution through the infected organism, but of course is less biologically relevant than in adults, plus work with larvae is limited to four days, when they pupate. Therefore, I used the orally infected Sting^{EY06491} to study ZIKV distribution through the different tissues through the first two weeks post-infection. This was of particular interest as most studies of viral tropism in mosquito in general and of ZIKV in particular have ignored haemocytes, despite this cell type being shown to have a high susceptibility to the virus in systemic infection experiments (Parikh, Oliver, and Bartholomay 2009; Lamiable et al. 2016; Tassetto, Kunitomi, and Andino 2017; Cheng et al. 2022; Cheng et al. 2010). They had only been hypothesised to work as a vehicle for viral dissemination (Parikh, Oliver, and Bartholomay 2009) until very recently when that was shown (Hall et al. 2025).

To create a timeline of infection of the different insect tissues after oral challenge with ZIKV of Sting^{EY06491} adult females, I dissected and performed qPCR on different tissues (heads, haemocytes, gut, salivary glands, and ovaries and abdominal wall) on DPI 1-14 (Figure 4.7). The results were consistent with the tropism found in infected larvae, with the added temporal dimension for early infection. The gut qPCR (Figure 4.7A) showed no differences through the first two weeks of infection, indicating that the virus was not present in this tissue at a high enough concentration to be detected with qPCR. This is consistent with what is known of other arboviruses, where only a reduced number of cells in the gut are infected (Encarnação Sá-Guimarães et al. 2021).

Viral RNA load in haemocytes (Figure 4.7B), in contrast, displayed a sharp increase on DPI 7, which was maintained on DPI9 and then slowly decreased. The finding of viral RNA outside of the gut tissue shows that ZIKV is able to cross the gut barrier and disseminate to other tissues upon oral infection of Sting^{EY06491} *Drosophila melanogaster* adult females. The presence of a large viral load in haemocytes also supports the hypothesis that haemocytes are used by the virus as a means of expansion through the insect. Importantly, the increase in viral load in this cells occurs on DPI 7, which is also the time point that the full fly viral RNA qPCR had a sudden, sharp increase in viral RNA abundance.

ZIKV RNA abundance in the salivary glands (Figure 4.7C) also peaked quite sharply, but later than in haemocytes, on DPI 11. Although RNA levels decreased in this tissue after this point, they remained elevated when compared to DPI 1 until the end of the experiment. Lastly, neither fly brains (Figure 4.7D) nor the ovaries and abdominal wall (Figure 4.7E) samples resulted in noticeable differences in viral

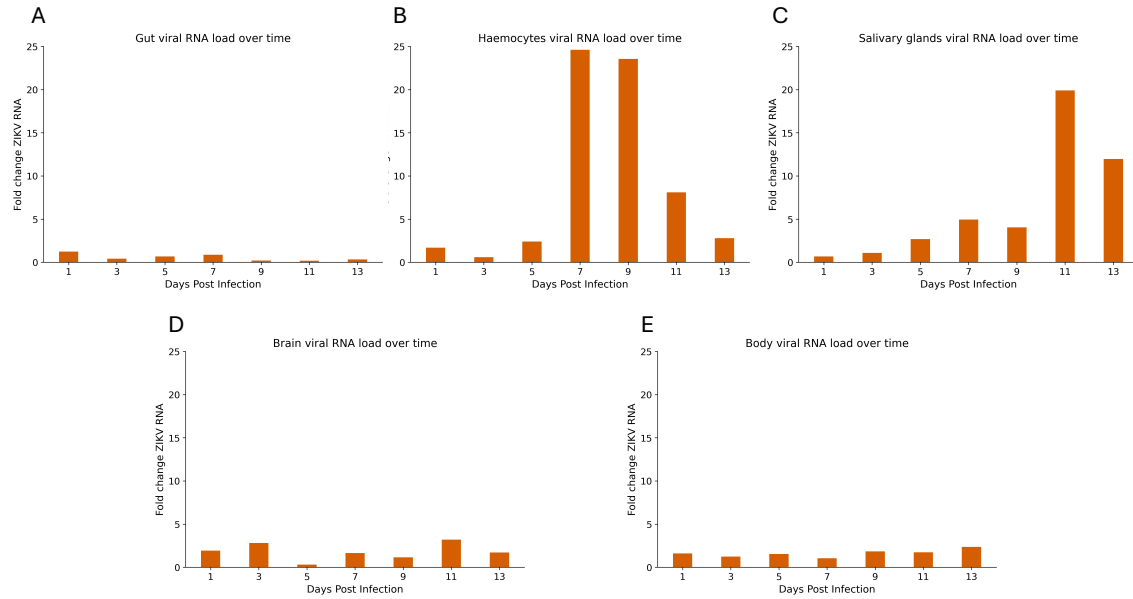


Figure 4.7: ZIKV tissue tropism the first 14 days post oral infection Relative ZIKV RNA abundance in each tissue (A: gut, B: haemocytes, C: salivary glands, D: heads, E: body wall and ovaries) as detected with qPCR in the first 14 days post infection, reported on alternating days. RNA was extracted from the pooled tissues dissected from five orally infected pooled adult flies (n=1).

RNA load through early oral infection. Due to time constraints, only one biological repeat of this experiment has been performed, therefore significance can not be assessed.

4.3.4 Imaging ZIKV during early oral ZIKV infection

To validate the results of the tissue-specific qPCR and further explore the tropism of the virus, I performed immunostaining using an antibody against ZIKV capsid in different tissues: the salivary glands and haemocytes, both of which had showed a high peak of ZIKV RNA in the second week of infection, as well as the brain and the gut. The brain and gut did not show a significant increase in viral RNA during infection on the qPCR experiment, however this could be due to the virus infecting a small selection of cells, therefore the viral RNA in the tissue not being abundant enough to be detected using qPCR.

Although I collected, fixed and stained haemocytes, due to the many manipulation steps of the immunostaining protocol, I was unable to collect images of infected haemocytes. This was most likely due to a combination of many of the collected cells being accidentally removed during the washes, and the difficulty of identifying haemocytes without a marker or specific antibody in the microscope slide. Therefore, this experiment should be repeated collecting more flies and, ideally, using fluorescent virus instead of an antibody in order to eliminate the washing steps and reduce sample manipulation as much as possible.

The images of the salivary glands, however, were consistent with the results of the

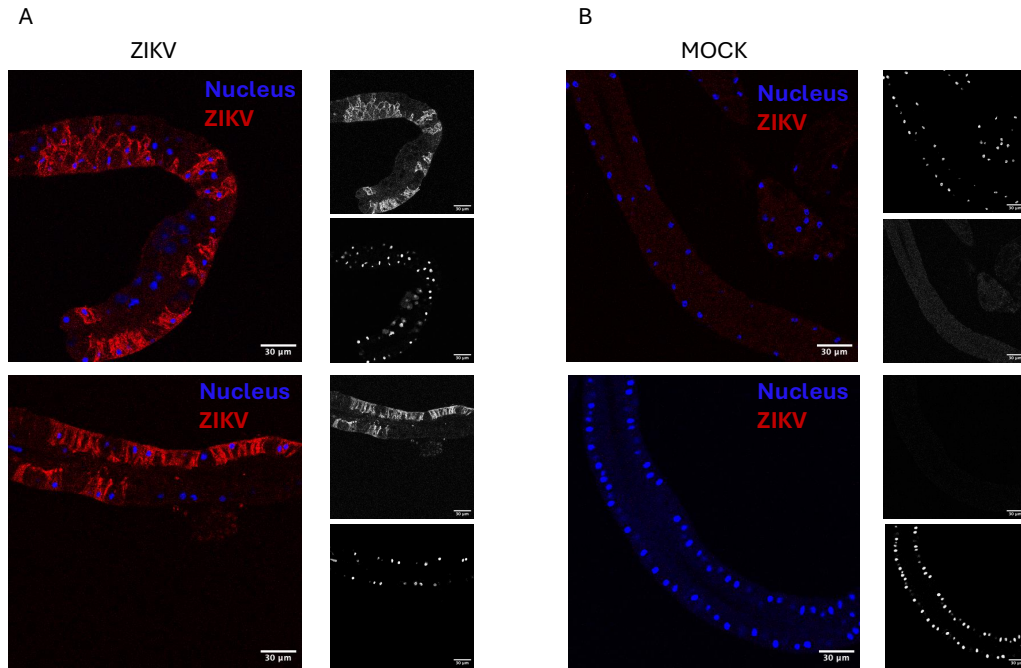


Figure 4.8: Immunostaining ZIKV in the salivary glands on DPI 10. A: salivary glands of an infected fly. Representative images of the salivary glands of a ZIKV infected fly, stained with nuclear stain (To-Pro-3, blue) and an antibody against ZIKV capsid (red). Scalebar = $30\mu\text{m}$. **B: salivary glands of a mock-infected fly.** Representative images of the salivary glands of a mock-infected fly, stained with nuclear stain (To-Pro-3, blue) and an antibody against ZIKV capsid (red). Scalebar = $30\mu\text{m}$. Three to five adults were dissected for each condition.

qPCR experiment, with the tissue showing no differences with mock until DPI 10, when very strong fluorescent signal could clearly be seen inside the cells (Figure 4.8). Interestingly, the virus seemed to affect the glands unevenly, with the fluorescent cells appearing in clusters and affecting most but not all of the infected gland.

Since the gut is the first tissue the virus enters in contact with, despite the qPCR results showing no significant differences between days, I performed immunostaining on guts from infected and mock-infected flies. A possibility was that very few cells were infected, therefore making the overall level of viral RNA not high enough to be noticeable using qPCR. Another possibility was that the virus bypassed the gut completely to infect other tissues, for example using the tracheal system (Engelhard et al. 1994; Means and Passarelli 2010). However, my imaging experiment showed some infected cells in the gut on DPI 1 (Figure 4.9). Fluorescent cells were localised to the posterior midgut region of the fly gut, and although there were no cell markers to differentiate between gut cell type, their small nuclear size and elongated or triangular morphology (Figure 4.9C) suggest these are ISCs. Not all the ISCs in the infected fly guts appeared fluorescent, with many small nuclei having no fluorescent signal around them, suggesting that only some cells of a type within a very specific region of the gut are susceptible to infection with ZIKV.

Lastly, and even though the brain-specific qPCR did not display any significant amounts of viral RNA either, I also performed immunostaining of this tissue in case the virus was infecting a very restricted number of cells, as is the case of the gut.

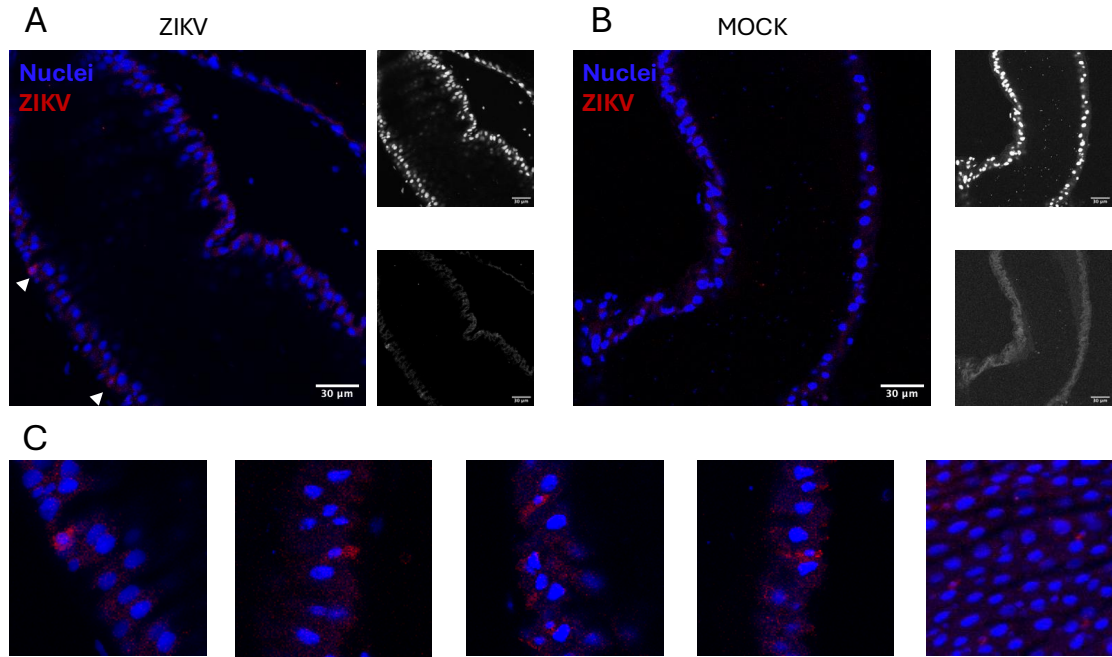


Figure 4.9: Immunostaining ZIKV in the gut on DPI 1. A: midgut of an infected fly. Representative image of the posterior midgut of a ZIKV infected fly, stained with nuclear stain (To-Pro-3, blue) and an antibody against ZIKV capsid (red). Infected cells are indicated with white arrows. Scalebar = 30μm. **B: midgut of a mock-infected fly.** Representative image of the posterior midgut of a mock-infected fly, stained with nuclear stain (To-Pro-3, blue) and an antibody against ZIKV capsid (red). Scalebar = 30μm. Three to five guts were collected for each condition. **C: Detail of the infected gut cells.** Zoomed in images from the infected guts where the morphology of the infected cells can be seen, with the cells having elongated morphology, smaller nuclei than the surrounding cells, and being placed closer to the basal membrane than to the lumen, suggesting they are ISCs. Samples were stained with nuclear stain (To-Pro-3, blue) and an antibody against ZIKV capsid (red).

ZIKV has been shown to infect the brain of *Sting*^{EY06491} *Drosophila melanogaster* flies when infecting the fly via injection (Liu et al. 2018b), therefore there was a possibility that the virus would also reach the brain when orally introduced, simply infecting very few cells, as seems to be the case in systemic infection (Liu et al. 2018b). Indeed, when assessing the stained images, I was able to find some infected cells in the brain on DPI 10 (Figure 4.10). Further work needs to be done to identify the cell type.

4.3.5 Effects of oral ZIKV infection on lifespan

Given the *Sting*^{EY06491} flies were able to sustain an infection in different tissues when orally challenged with ZIKV, I tested whether this infection was detrimental to them by conducting a lifespan assay (Figure 4.11A). Both mock-infected and ZIKV-infected *Sting*^{EY06491} adult females displayed normal distributions in death frequency, however, those infected with ZIKV showed an earlier peak frequency, with most of them dying between DPI 20-40 (median survival: 32 DPI). Uninfected *Sting*^{EY06491} flies reached their peak frequency between DPI 35-55 (median survival:

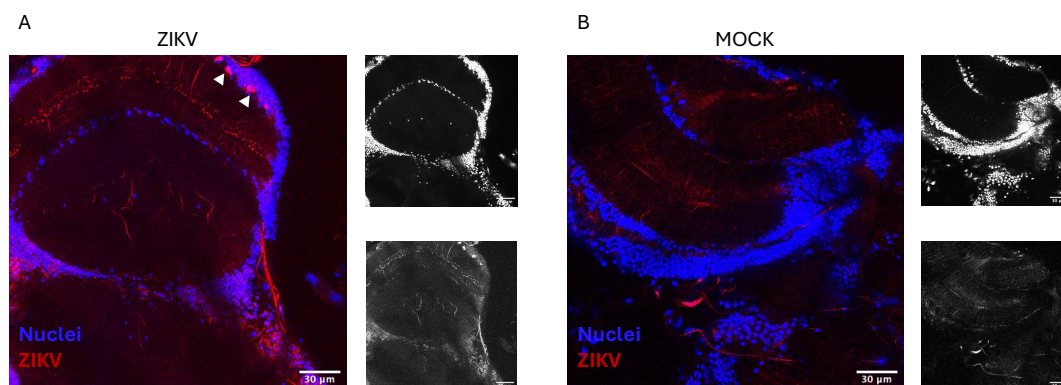


Figure 4.10: Immunostaining ZIKV in the brain on DPI 10. A: brain of an infected fly. Representative image of the brain of a ZIKV infected fly, stained with nuclear stain (To-Pro-3, blue) and an antibody against ZIKV capsid (red). Infected cells are indicated with white arrows. Scalebar = 30 μ m. **B: brain of a mock-infected fly.** Representative image of the brain of a mock-infected fly, stained with nuclear stain (To-Pro-3, blue) and an antibody against ZIKV capsid (red). Scalebar = 30 μ m. Three to five brains were collected for each condition.

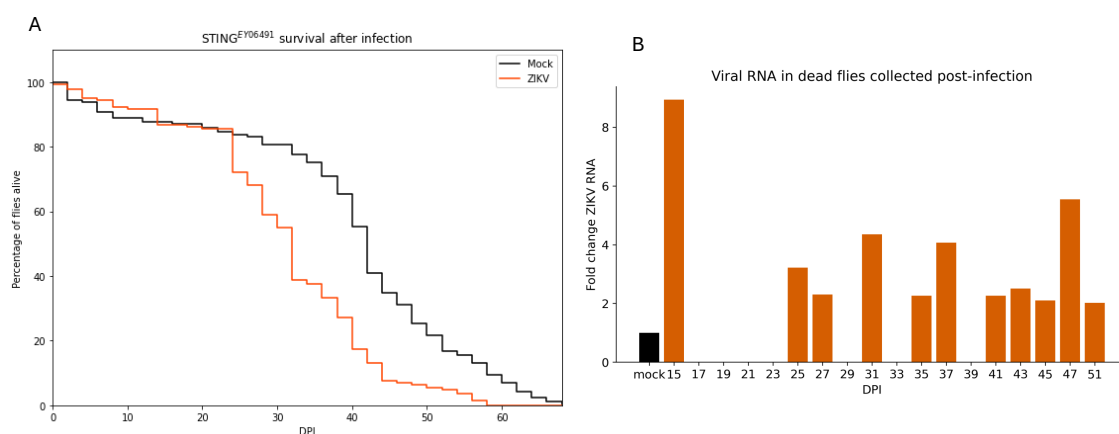


Figure 4.11: A: Survival of infected flies Survival curve of ZIKV-infected (orange) and mock-infected (black) *Sting^{EY06491}* flies. Three biological replicates with a minimum of 40 flies were analysed. Log-rank test p value was < 0.0001. **B: Relative ZIKV RNA abundance in dead infected flies.** qPCR was performed on the dead flies collected every other day after infection, until all the flies were dead. Days where no flies were dead have no bar. RNA extraction and qPCR was performed on all the flies collected that day, pooled (n=1-7). Only one biological repeat was done.

42 DPI). 90% of ZIKV infected *Sting^{EY06491}* flies had died by day 50, while mock-infected ones did not pass this threshold until DPI 60.

To test whether this effect was caused by long-term persistent ZIKV infection or by the result of a long-lasting effect on healthspan of a cleared infection, I performed qPCR to assess the amount of viral RNA in the corpses of flies collected through the two months after infection, until no flies remained alive (Fig 4.11B). The result showed the level of ZIKV RNA on the first flies that died (DPI 15) to remain quite

high (9-fold), consistent with the slow decrease in amount of viral RNA detected on live flies on DPIs 13 and 14. The rest of the dead flies, collected on or after DPI 25, displayed low but detectable levels of viral RNA, approximately 2- to 4-fold compared to mock-infected controls in the $\Delta\Delta C_t$ analysis. This suggests that the peak amount of ZIKV RNA occurs around DPI 10, and then declines until reaching a stable, very low grade infection. This can hypothetically be caused by the infection being cleared from most tissues, particularly haemocytes, once the virus has spread through the organism, but remaining in others, potentially the salivary glands and/or brain.

4.3.6 Effect of early oral ZIKV infection on climbing ability

Since I was able to find some virus in the brain in the imaging experiment, I tested whether this infection had any effect on the ability of the fly to move. My larval experiments were able to show a correlation between higher viral load in full larvae and less active crawling behaviour, despite also showing a non-significant amount of viral RNA in the heads, similar to the adult tropism results. For this, I performed a climbing assay.

Flies display negative geotaxis, an innate escape response meaning that, upon forcing the flies to fall to the bottom of the vial (for example, by tapping the vial harshly against the surface of a table), they will react by climbing the walls of the vial (Gargano et al. 2005). Their climbing performance after falling to the bottom of the vial (speed, maximum height reached) has been used before as a metric of age-related neurodegeneration (Gargano et al. 2005), but there are other age-independent factors such as brain injury, developmental defects and infection that have also caused a climbing phenotype in flies (Rogers et al. 2020; Kelly, Delventhal, and Barber 2025). To test whether ZIKV presence in the brain was associated with any neurological effects, I performed a climbing assay on infected and mock-infected flies on DPI 4 (before the virus has reached the brain) and on DPI 10 (when the virus is detectable in the brain with immunofluorescence). However, using this method, I was not able to detect a difference in neurological abilities on either date (Figure 4.12). It is possible that an effect on locomotion appears later in infection, therefore there is a need for repeating the experiment at a later time point.

4.3.7 Effects of oral ZIKV infection on gut permeability

As previously discussed in the Introduction, the mechanism by which viruses are able to cross the gut barrier is not yet fully understood. In mosquito, a blood meal causes a distension in the gut, which has been shown to alter the structure of the basal lamina and increase its permeability (Kantor et al. 2018; Romoser et al. 2004). However, Sting^{EY06491} *Drosophila* is able to get infected through the gut without its gut undergoing this structural deformation, which suggests ZIKV is able to cross the fly gut via a different mechanism, which might be acting in place of or jointly with the basal lamina distension in mosquitoes.

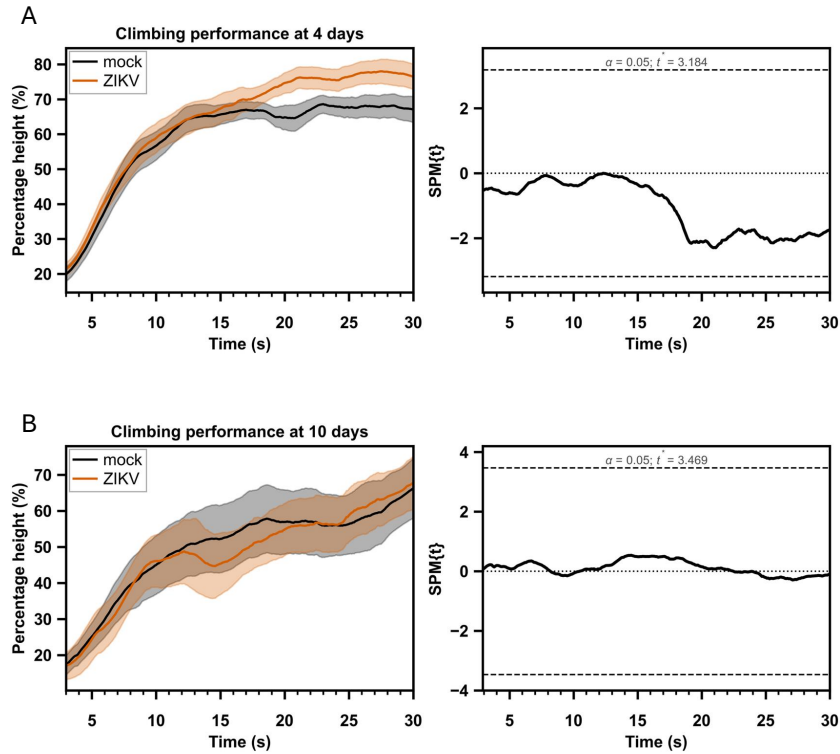


Figure 4.12: Effect of oral infection on climbing ability. **A:** Climbing ability of mock-infected (black) and ZIKV-infected flies 4 days post infection. **B:** Climbing ability of mock-infected (black) and ZIKV-infected flies 10 days post infection. For both A and B: on the left panel, the percentage of height of the vial climbed through time (Mean $\pm$ SEM). On the right panel, statistical parametric mapping (SPMt) of the results through time. Time intervals where the SPMt trajectory surpasses the horizontal threshold (t) that corresponds to the family-wise error-corrected significance level (α) indicate statistical significance. Neither time point produced statistical significant differences. Three biological replicates were used ($n=7-10$ flies per replicate). Six technical replicates were performed for each biological replicate.

As a first step, I used a Smurf assay (Martins et al. 2018) to detect damage to the gut barrier of *Sting^{EY06491}* flies, which could be achieved by means other than physical strain on the basal lamina. This assay involves feeding the flies a blue dye that can not be absorbed by the gut, therefore allowing me to identify flies with an intact gut barrier (where the dye remains localised inside the gut) and flies where the gut barrier has been compromised, due to ageing or otherwise (where the dye can escape the gut and stain the whole fly blue, which is termed a "Smurf" fly). It is possible that Smurf flies are only detected after death ("dead-as-smurf", which suggests they become Smurfs very close to the end of life.

The results showed no significant difference between the mock-infected and the infected conditions, with the mean onset of smurfiness being 51.5 DPI for the mock condition and 43 DPI for ZIKV-infected flies (Figure 4.13A). It is worth noting that this difference can be largely attributed to the fact that mock-infected flies live longer: the earliest Smurf fly found was found on DPI 36 on the mock condition and DPI 32 on the ZIKV-infected flies. No living Smurfs were detected, only dead as Smurf flies, and the difference in percentage of dead as Smurf out of total dead flies was also not significant (Figure 4.13B). This result suggests ZIKV does not affect

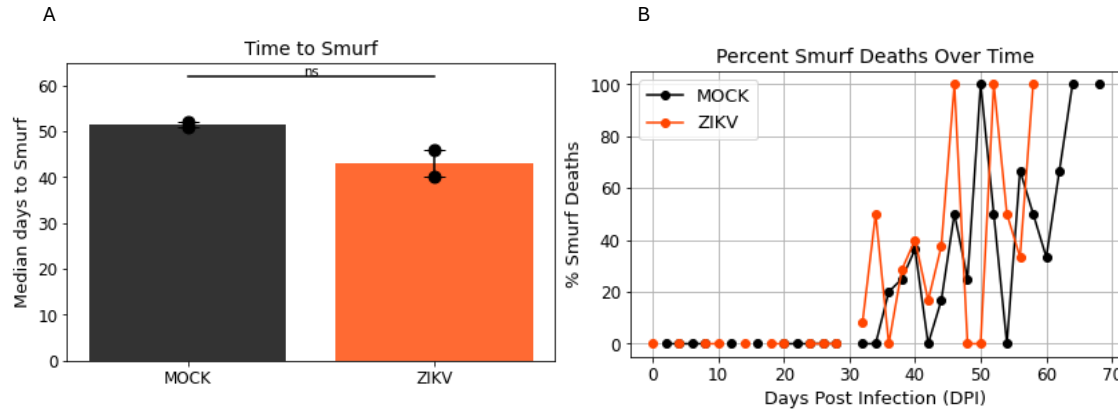


Figure 4.13: Effect of oral infection on gut plasticity, measured with the Smurf assay. **A:** Median days until the Smurf phenotype was observed in orally mock- or ZIKV-infected flies (Mean $\pm$ SEM; $p > 0.05$). **B:** Percentage of dead flies on a given day that displayed the Smurf phenotype ($p > 0.05$). For both A and B two biological repeats were performed, with a minimum of 40 flies per condition at the start of the experiment.

gut permeability as a means of escape.

4.3.8 Generation of *Drosophila melanogaster* genetic lines

Since a Sting deficiency was sufficient to allow for infection, the tissue tropism experiment showing expansion of the virus to other tissues outside of the gut, fly lines with a Gal4-UAS system driving expression of Sting RNAi in different intestinal cell types were generated, using driver *esg^{ts}/CyO* for midgut progenitor cells and *Myo1A^{ts}/CyO* for enterocytes. Oral challenge of these fly lines with ZIKV would show whether gut barrier crossing is dependent on any of the specific cell types assessed, and whether disruption of sting expression in them is enough to allow for infection of other tissues.

I also attempted to generate a fly line that was both homozygous for the Sting deficiency and expressed a fluorescent marker in the gut progenitor cells in order to continue studying the infection of the gut cells. However, as the *esg^{ts}* UAS driver and the Sting^{EY06491} P-element insertion are both on chromosome 2, the 32 stocks generated by this recombination cross will have to be assessed before using it in experiments.

4.4 Discussion

In this chapter, I explored the similarities between the genome of *Drosophila melanogaster* and *Aedes aegypti*, concluding that, while there is a high overall gene sequence conservation despite the high rate of chromosomal redistribution (Bolshakov et al. 2002), there are differences in conservation rates across functions, including some unexpected results such as immunity-related genes having less orthologs than expected from the overall conservation of the genome. These results directed me to

believe that *Drosophila melanogaster* can be used as a biologically relevant model of *Aedes spp.* mosquito to dissect individual molecular processes and interactions in the context of ZIKV oral infection, subject to confirmation that the genes and pathways involved are present in both species. During this analysis, I also noted issues with GO term annotations, where genes more often had several very narrow annotations that were not propagated to more general parent GO terms. The GO consortium has noted this disclaimer in the past, and annotations on non-mammalian models are known to be especially uneven (Lewis 2017; Troha and Buchon 2019).

Sting is one of the immune genes that is not conserved in mosquitoes, and its depletion is known to increase susceptibility to study viral infection of *Drosophila* in several viruses, including ZIKV. With the intention of using the Sting^{EY06491} Sting-deficient *Drosophila melanogaster* line to model ZIKV infection of mosquito, I first confirmed that oral infection of Sting-deficient flies with ZIKV was possible in adults as well as larvae, and that wild-type background W¹¹¹⁸ flies were not able to sustain the infection, proving that the Sting deficiency is sufficient to allow fly infection through the gut.

The timeline of infection obtained, where the levels of viral RNA peak on DPI 7-10, is consistent with what we know about arboviral infection of mosquito, with ZIKV infecting mosquitoes to detectable levels between DPI 5-10 at 25° (Winokur et al. 2020; Zimler and Alto 2021). Analysis of tissue tropism of ZIKV in orally infected Sting^{EY06491} flies was also remarkably consistent with literature on mosquitoes, with the viral load in the salivary glands peaking 10 days after infection. At 25°C, mosquitoes also need 10 days to become infective post-viral ingestion, suggesting the virus has reached the salivary glands at this time and the viral load in this tissue is high enough for it to be secreted into the saliva and injected into other mammals (Winokur et al. 2020). In addition, WNV, very closely related to ZIKV, first becomes highly detectable via antigen detection in the salivary glands of the mosquito on DPI 10 (Girard, Klingler, and Higgs 2004).

It is also now known that mosquito haemocytes are in fact infected by ZIKV outside of injection or *in vitro* experiments, with haemocyte infection providing a way for the virus to disseminate through the insect after ingestion (Hall et al. 2025); it is promising to see the high level of viral RNA in the infected *Drosophila* haemocytes before the peak in the salivary glands viral load, as this suggests this mechanism of dissemination is conserved in the fly. In the future, the haemocyte viral infection and dissemination can be dissected and better understood with the help of the genetic tools available in *Drosophila*, with several authors highlighting the difficulties of working with *Aedes spp.* due to the lack of tools available (Hall et al. 2025; Cardoso-Jaime et al. 2022). It is of particular interest to test whether gut-resident haemocytes get infected and, if so, if this infection contributes to the gut barrier crossing. Sessile gut haemocytes were shown to rapidly internalise nanobeads meant to emulate DENV, and although this is believed to be limiting the expansion of the infection, it is possible that the virus exploits this mechanism (Cardoso-Jaime et al. 2022).

The salivary gland infection was also very interesting. The virus was visible in the gland on DPI 10 but not on DPI 7, which was consistent with the tissue-specific qPCR result. The pattern of infected cells is also interesting, with infected cells in

patches. There is very little known about viral infection of the salivary glands, even though this is an essential step for transmission of arboviruses. A study studying viral infection of this tissue was published recently began to explore using *Drosophila melanogaster* to viral infection of this tissue, systemically infecting flies with a panel of arboviruses, including ZIKV. After injection with the virus, they were able to detect ZIKV in the salivary glands in a similar pattern to what I found, with the cells displaying clusters of highly infected cells, in both wild type and argonaute 2 (AGO2)-deficient flies (Palmer et al. 2020). Together with my results, this suggests that Sting is important for repressing oral infection of the insect at an earlier stage, either for gut barrier crossing or entry to haemocytes, as the virus was able to infect the salivary glands of a fly with wild type sting after being injected directly into the haemocoel, but not when orally infected. However, more research into what stages of infection and dissemination is Sting important for are essential. Achieving salivary gland infection by orally challenging Sting deficient *Drosophila* makes this model promising for studying all the stages of insect infection, including entry and, potentially, exit from the salivary glands.

The gut-specific qPCR showed the levels of viral RNA decrease through the timeline assayed. Although the timeline of gut infection is largely virus-dependent, with DENV and WNV peaking six and four days after being in first contact with the virus respectively (Salazar et al. 2007; Girard, Klingler, and Higgs 2004), in both of these studies the level of infection in the gut decreased after reaching its maximum. It is also very interesting to note that the highest peak of viral RNA level in my tropism experiment, which happens on DPI 1, is not significant, indicating that the viral load in this tissue is very low. While this is not the case for all arboviruses, with closely-related WNV infecting the midgut cells at very high levels (Girard, Klingler, and Higgs 2004), a lot of arboviruses have no need for a large number of cells to be infected for the virus to expand through the insect, and usually it is only a small number of cells that actually internalise the virus (Chen et al. 2024; Encarnação Sá-Guimarães et al. 2021; Whitfield, Murphy, and Sudia 1973; Scholle et al. 2004; Smith et al. 2008). The results of my qPCR experiment mean that ZIKV is able to disseminate after oral infection of the Sting^{EY06491} *Drosophila* model despite the gut not showing a high viral load. This was validated in my imaging experiments, which showed the virus to be constrained to very few cells in a specific region of the gut: ISCs in the posterior midgut. This is especially interesting, as the posterior midgut is where blood digestion takes place in mosquitoes (Cui and Franz 2020), but we do not have any further information on how ZIKV interacts with the mosquito gut. These experiments highlight this *Drosophila* genotype as a promising model to study this interaction outside of blood meal-induced basal lamina deformation. To begin exploring this relationship, I then tested a potential effect of infection on gut permeability. My experiment showed there was no effect on gut barrier integrity after infection, at least not to a degree that was noticeable by the Smurf assay I performed. However, this assay has been shown to be quite variable, and a study using a fly line with excised Sting detected had a mean Smurf onset time of 24.3 DPI for the mock-infected condition. However, the Smurf assay method used in this study differs from the one I performed, with their study using a much higher concentration of dye and a different Sting genotype (Nigg et al. 2024). Regardless, it seems unlikely that the low viral load detected in the gut via qPCR would be able to induce a strong effect on gut permeability: in the aforementioned paper, the

damage to the gut barrier seen in the *Drosophila* A virus (DAV) compared to mock was the result of early onset age-dependent dysplasia and no Smurfs were detected early post-infection in a way that could indicate a means of viral escape.

This study was not the only one that found oral infection of insects with arboviruses to have an effect on gut homeostasis: the cross-talk between the direct effects of infection and the immune reaction on cell division and apoptosis has been studied in the context of several viruses and insects, even suggesting that the increased apoptosis of midgut cells that occurs upon infection with ZIKV and DENV can create an opening that allows for viral crossing (Carpenter and Clem 2023; Ayers et al. 2021). Apoptosis is known to have an immune role, with mosquitoes expressing caspases and proapoptotic genes at increased levels of expression being more resistant to infection with DENV and SINV (Ocampo et al. 2013; O’Neill et al. 2015; Chen et al. 2021). While the main effect of apoptosis in this context is generally believed to be primarily protective, the full picture within the living organism is more complex: not only can high rates of apoptosis damage the gut barrier (Carpenter and Clem 2023; Ayers et al. 2021), but activation of the apoptosis pathway has been shown to inhibit the RNAi pathway in *Drosophila*, thus reducing the effectiveness of the antiviral immune response (Xie, Liang, and Birchler 2011; Wang et al. 2012).

The full picture is not yet understood, neither for arboviruses in general nor ZIKV in particular: as mentioned before, RNAseq experiments show increased expression of apoptosis-related genes (Ocampo et al. 2013; O’Neill et al. 2015; Chen et al. 2021), whereas infection experiments of tissue culture have shown insect cells to display nonlytic, persistent infection, in contrast to mammalian cell apoptosis in the same conditions (Schlesinger 1975; Stollar et al. 1975; Karpf and Brown 1998; Levine et al. 1993; Nava et al. 1998). Studies on SINV infection have suggested that the evolutionary pressure on the virus against apoptosis have led to arboviruses avoiding large-scale induction of apoptosis (O’Neill et al. 2015). In the context of ZIKV infection specifically, the virus has been shown to induce clusters of apoptosis in the mosquito midgut during very early infection (Ayers et al. 2021), thus suggesting that in the case of this arbovirus the benefits of inducing apoptosis outweigh the reduced viral spread and dissemination that can happen as a result. There have been no studies blocking apoptosis in the context of ZIKV infection, and therefore it is not known whether the effect of apoptosis has as strong an antiviral effect as is the case for other viruses. If the apoptosis clusters upon ZIKV infection are conserved in *Drosophila*, I would like to use this model to explore the possibility that the presence of these clusters is sufficient to allow for gut barrier crossing upon oral infection, and whether this hypothetical need for apoptosis is what leads to such a small viral yield in this tissue. For comparison, WNV infection of mosquito has been shown to result in very large amounts of virus in the gut (Girard, Klingler, and Higgs 2004), and a colony of its mosquito vector (*Culex pipiens*) that was not permissive to infection was assayed for potential causes and an increased rate of apoptosis in the gut was found, suggesting the apoptotic reaction was inhibiting infection establishment and viral dissemination (Vaidyanathan and Scott 2006). This opens the door to a potential situation where ZIKV needs apoptosis in order to weaken and cross the gut barrier, which comes at the cost of a lower viral yield in this tissue, whereas in the case of WNV infection, the gut barrier is crossed by a different mechanism, thus making the virus less permissible to higher rates of apoptosis.

In addition to cell death, viral infection can also induce intestinal stem cell (ISC) division. This has been shown in a variety of viruses: DAV, DCV, Nora virus and Bloomfield virus in *Drosophila* (Nigg et al. 2024) and ZIKV and DENV in *Aedes*. In DENV infection of orally infected mosquito, an increase in reactive oxygen species (ROS) abundance induced ISC proliferation, which in turn reduced susceptibility of the mosquito to infection (Taracena et al. 2018). A similar process takes place in oral ZIKV infection of *Aedes*: reduction in ability to control ROS levels resulted in increased ISC renewal, and as a result of that, the mosquito competence for ZIKV infection decreased (Bottino-Rojas et al. 2018).

In contrast, although DAV infection of *Drosophila melanogaster* also resulted in ISC proliferation, this renewal was associated with increased gut permeability and shorter lifespan (Nigg et al. 2024). It is possible that these seemingly opposed effects of viral-induced increased ISC renewal in the gut are explained by the different time points the experiments were performed: the DENV infection experiment was performed 7 days after viral ingestion (Taracena et al. 2018), and the ZIKV one, 4 days post viral ingestion (Bottino-Rojas et al. 2018), while Nigg et al. tested the entire lifespan of the fly, detecting the first detrimental effects of DAV infection on gut permeability starting 16 DPI (Nigg et al. 2024). Therefore, it is possible that increased ISC renewal has a positive effect in the early stages of infection, reducing susceptibility to the virus, but the exposure to stress has a detrimental effect later in life, when gut dysplasia becomes a predictor of early death. Overproliferation and misdifferentiation of ISCs are a symptom of normal ageing in *Drosophila* and genotypes with early intestinal dysplasia have been associating with early ageing and shortened lifespan, whereas reducing stress signalling while maintaining ISC ability to divide resulted in longer lifespan and limited dysplasia (Biteau et al. 2010).

It is also interesting to note that, while DAV infection in the gut is persistent (Nigg et al. 2024), levels of DENV in the gut seem to peak early in infection (Salazar et al. 2007), and so does ZIKV RNA load in my experiments. The long term direct exposure to DAV might be directly affecting gut homeostasis constantly, resulting in the disruptions observed, while this might not be the case in ZIKV and DENV transient infections. More research on later time points post-infection is needed, especially as ZIKV-infected flies showed a decreased lifespan, even when viral RNA peaks early in infection.

The last tissue assayed was the brain. Even though tissue-specific qPCR showed no significant increase in viral RNA on the first two weeks of infection, immunostaining of the viral capsid showed some cells to be infected on DPI 10. The *Drosophila melanogaster* brain has previously been shown to be susceptible to infection after systemic infection via injection (Liu et al. 2018b). Similarly to the salivary gland infection, this seems to suggest Sting is important for viral infection of the insect earlier in infection. How ZIKV presence in the brain affects the insect lifespan, healthspan or behaviour is yet unexplored, and I was not able to show a behavioural effect of oral ZIKV infection of adults, at least on the first two weeks of infection. However, considering the effect infection had on larval crawling and the shortened lifespan of infected adults, it is possible that extending the timeline assessed shows effects of brain infection on behaviour. It is particularly relevant to note that in injection experiments, it takes three weeks after infection for ZIKV to reach its maximum peak in the brain (Liu et al. 2018b). It is also interesting to note that

mosquito survival in the wild is shorter than the lifespan of laboratory-reared flies due to the lack of predators and controlled environment (Maciel-de-Freitas, Codeço, and Lourenço-de-Oliveira 2007), therefore any detrimental effects of infection on insect lifespan or behaviour are not subjected to strong evolutionary pressure.

To further explore the effects of the virus in the fly later in infection, I performed qPCR to detect viral RNA levels of dead flies collected during the lifespan assay, with the goal to detect whether the earlier peak of deaths was caused by high levels of infection, or if the infection was cleared and the deaths were caused by long-lasting effects on healthspan of the earlier infection. The results showed the levels of viral RNA lowered to two-fold on the third week of infection, remaining stable until all the flies were dead. This suggests the levels of viral RNA, whose peak coincided with the levels of infection of haemocytes on DPI7-10, continue to lower after DPI14, stabilising at a very low-grade infection that is maintained through the rest of the fly's life. It would be interesting to see if the detected levels of RNA post week three weeks after infection are localised to any tissues, particularly the salivary glands.

Chapter 5

Local translation of motor components in the PNS

5.1 Introduction

The roles of the nervous system cells, which have complex morphologies with long protrusions, are largely dependent on the functions carried out in the specific protrusions. In the Introduction, I described the importance of local translation of proteins for the generation of these functionally restricted distal regions of cells of the nervous system, particularly for synaptic plasticity. Previous work in the Davis lab has established a role for RNA localised to glial periphery in neuroplasticity using the *Drosophila melanogaster* third instar larval neuromuscular junction (NMJ) as a model (Gala 2023).

For this work, a list of candidate mRNAs predicted to be localised to the glial periphery (Lee et al. 2024). The list of predicted candidates was based on a meta-analysis of all published mammalian glial periphery transcriptomes, of which *Drosophila* orthologs were found. Using the Fly Cell Atlas (Li et al. 2022), the candidate list was filtered to include only glial cells. The result was a list of 1740 mRNAs predicted to localised to the periphery of glia in *Drosophila melanogaster*.

The resulting list included a number of motor proteins, involved in both kinesin- and dynein-dependent transport (Table 5.2). Given the vital role of microtubule-associated transport in cellular compartmentalisation, I sought to better understand this transport mechanism, particularly the importance of peripherally translated motor components for its correct maintenance and function.

Since nervous cell protrusions, particularly axons, can be very long, motor components age as they travel along the microtubule toward the cell periphery, especially those partaking in slow component transport modalities. For longer axons, such as the human optic nerve, it can take weeks for a molecule to be transported from the cell body to the tip of the axon (Roy 2014), and even years for a metre-long axon (Twelvetrees 2020). Although we know there is local translation of tubulin subunits along the axonal length (Gumy et al. 2011; Shigeoka et al. 2016; Hafner et al. 2019), the way the microtubule cytoskeleton and pool of motor components is maintained, replaced or degraded is not well understood yet, particularly in the

distal compartments of the cell (reviewed in Twelvetrees 2020).

As mentioned in the introduction, the main method of transport to the periphery of cells of the nervous system is microtubule-based. Proper formation of the microtubule network and effective transport along the microtubule cytoskeleton are essential for brain function, with mutations in tubulin and motor components associated with neurodegeneration (Tischfield et al. 2011; Franker and Hoogenraad 2013; Millecamps and Julien 2013). In neurons, the microtubule cytoskeleton is arranged in a polar manner along the axon, with the (-) ends toward the cell body and the (+) ends toward the cell periphery (Baas et al. 1988), although this is not maintained in dendrites. The polar arrangement of microtubules in axons is also found in oligodendrocyte protrusions (Lunn, Baas, and Duncan 1997; Fu et al. 2019; Eom et al. 2011). Although there is less research on microtubule organisation in other glial types, the importance of transport to the cell periphery is evidenced by the high stability of microtubules in cellular processes compared to those in the cell body (Eom et al. 2011).

Due to the polarity of the microtubule track, two different motor components are necessary to transport cargo in both directions: kinesin, which moves anterogradely (from the (-) to the (+) end of the microtubule, from the cell body to the periphery), and dynein, which moves retrogradely (from the (+) to the (-) end of the microtubule, from the periphery to the cell body). However, transport along the microtubule track does not occur on a continuous manner on most cases; mostly only vesicles and organelles are carried via fast transport (40-80 mm/day) (Maday et al. 2014), while other proteins and mRNAs are carried via Slow Component a (SCa, 0.1-1 mm/day) or Slow Component b (SCb, 2-4 mm/day) (Roy 2014; Wujek and Lasek 1983). Fast transport rates are consistent with motors moving continuously along the microtubule track, however, slow transport average rates are much slower than the speed motors reach when moving continuously (Vale et al. 1996; Svoboda and Block 1994), due to transport occurring in short runs with pauses in between (Roy et al. 2007).

Several explanations for this pauses have been proposed, all of which highlight the ability of a single cargo to bind several motors simultaneously in a "tug-of-war" competition (Soppina et al. 2009; Hendricks et al. 2010; Müller, Klumpp, and Lipowsky 2008). The most popular model, termed "stop and go", describes how cargo-bound kinesin motors spend most of the time in "pause" states, either on the microtubule track or off-track, disassociating from it (Trivedi, Jung, and Brown 2007; Brown, Wang, and Jung 2005). This is due to modifications to the motors or the microtubule track itself, or interactions with other proteins that recruit or disengage the motor from the track (Monroy et al. 2018; Sheng and Cai 2012; Fu and Holzbaur 2014; Verhey and Hammond 2009; McKenna et al. 2023). Another important model is the "dynamic recruitment" model, which applies mainly to proteins that are transported via larger, membrane-bound vesicles, which can disassemble and reassemble in transit and release and reattach to the motor (Scott et al. 2011). Lastly, the "kinesin-limited" model describes how the different affinities of cargo to a limited amount of kinesin molecules can affect overall speed of transport (Twelvetrees et al. 2016). Given the wide variety of cargoes, it is most likely that all models of transport are active simultaneously and competitively, the amount of motor protein a limiting factor for speed (Maiya et al. 2022).

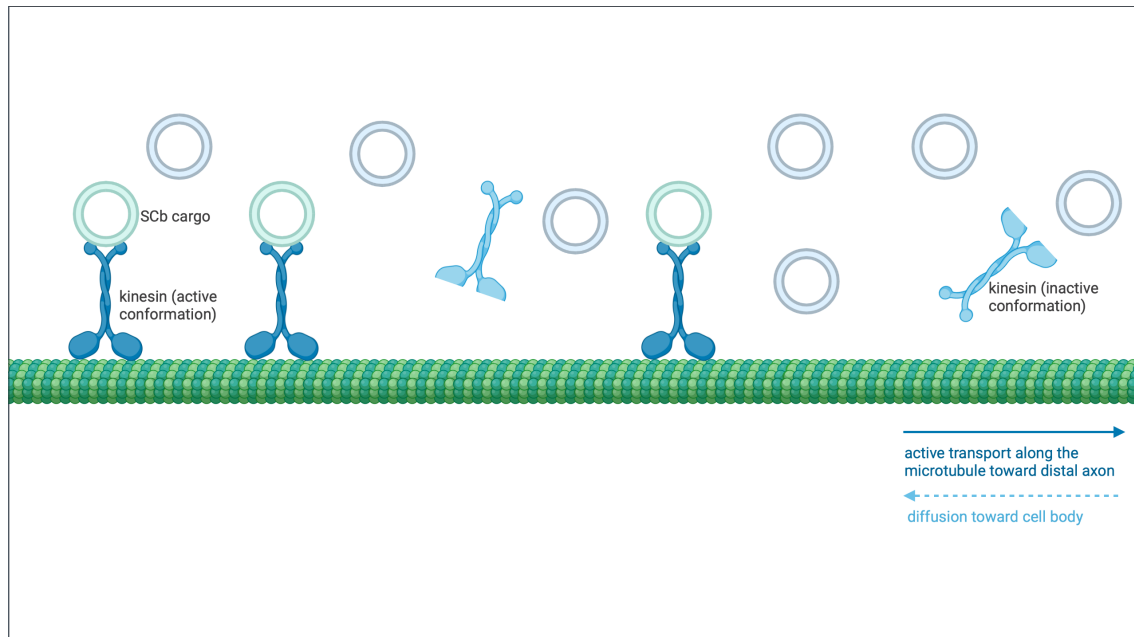


Figure 5.1: Proposed model for motor protein dynamics in cell protrusions. When bound to cargo, motors (exemplified with kinesin, but applicable to dyneins in the opposite direction) adopt their active conformation (dark blue), which has a higher affinity to the microtubule track. Bound kinesins move toward the cell periphery in short runs before the cargo disassociates. Cargo release turns the motor back to its inactive conformation (light blue), and the affinity to the microtubule track decreases. The motor disassociates from the track, diffusing toward the cell body. Since there is more cargo than motors, diffusing kinesin can bind free cargo, returning to its active conformation and able to associate to the microtubule track again, performing another short run of active transport. Made with biorender.

Most study of transport along cell protrusions has focused on the active transport carried out by the motor proteins, largely ignoring the "stop" state and assuming the cargo is either stationary or in a diffusive state. It was only recently that the importance of this diffusive state was quantified: Maiya et al. found that diffusion of cargo toward the axon tip is essential for transport to the periphery, with its effect being more important than motor number and motor-cargo interactions for bleach signal recovery (Maiya et al. 2022). Conversely, kinesin diffuses toward the cell body from the neuronal periphery (Blasius et al. 2013). However, studies of the diffusive states of both motors and cargo remain few and far apart.

In this chapter, I explore the possibility that our predicted distal local translation of motor protein components and their subsequent diffusion allows to replenish the motor protein pool from both directions (Figure 5.1), thus potentially reducing the effect of motor component ageing and thus increasing the efficiency of transport in long protrusions. Due to the lab's interest on glial cells' involvement in the synapse, I focus on this cell type, using the well-understood model of the 3rd instar larva NMJ, where the glial cells show long protrusions that contact the motor neuron and the muscle at the synapse. My ultimate goal was to study the role of distally translated motor proteins in neuroplasticity in both glial and neuronal protrusions, however, due to unforeseen circumstances and my initial screening experiments not giving any interesting results, the project was abandoned before reaching this stage.

5.1.1 Aims and objectives

- Develop a hybridisation chain reaction (HCR)-based protocol for low-cost, quantifiable imaging of single mRNA molecules at the NMJ. Validate prediction of localisation of motor protein mRNAs to the glial cell periphery.
- Using the Gal4-UAS system, screen candidate genes for effects on behaviour when absent in glial cells, which indicate an important role for the protein in this cell type. Select the candidate genes with the strongest phenotype, expecting the effect of disrupting only distal translation to have a more subtle effect.
- Discuss next steps to investigate the selected subset of candidate genes, particularly confirming they are locally translated and not only transported, identifying and disrupting their localisation sequences to study the effect of the distally translated gene, and using live imaging to tracing their movement in the cell protrusions, detecting diffusion and active transit.

5.2 Materials and methods

5.2.1 *Drosophila* stocks

In this chapter, the fly lines used to drive RNAi expression were UAS-mcd8-GFP;Repo-Gal4, used to drive expression of the in a pan-glial manner and UAS-mcd8-GFP;Mdr65-Gal4 to drive expression in subperineural glia. RNAi lines of control and motor components are listed in 5.1, and are described throughout the chapter as Repo>gene RNAi or Mdr65>gene RNAi. Fly stocks were maintained as described in the Materials and Methods section 5.2.

Line	Genotype	Description	Source
OrR	;;;	Wild type background	Davis lab stocks
Repo>GFP	UAS-mcd8-GFP/"; Repo-Gal4/TM6, tb	Expresses membrane-targeted GFP driven by repo in a pan-glial manner	Davis lab stocks
Mdr65>GFP	UAS-mcd8-GFP/"; Mdr65-Gal4/TM6, tb	Expresses membrane-targeted GFP driven by Mdr65 in subperineurial glia	Stock created by Dr D. Gala
mCh RNAi	;;UAS-mCherry-RNAi/"	Expresses dsRNA for RNAi of mCherry under UAS control	BDSC (35785)
Didum RNAi	;UAS-Didum RNAi;	Expresses dsRNA for RNAi of Didum	BDSC (55740)
DCTN1-p150 RNAi	;UAS-DCTN1-p150 RNAi/Cyo;	Expresses dsRNA for RNAi of DNCT1-p150 under UAS control	BDSC (24760)
Dlic	;UAS-Dlic RNAi;	Expresses dsRNA for RNAi of Dlic	BDSC (66981)
Khc RNAi	;UAS-khc RNAi;	Expresses dsRNA for RNAi of khc under UAS control	VDRC(44337)
Klc RNAi	;;UAS-klc RNAi	Expresses dsRNA for RNAi of klc under UAS control	BDSC (33934, stock no longer available)
Klp10A RNAi	;;UAS-Klp10A	Expresses dsRNA for RNAi of Klp10A under UAS control	BDSC (33963)
Lis-1 RNAi	;;UAS-Lis-1 RNAi	Expresses dsRNA for RNAi of Lis-1 under UAS control	BDSC (28663)
Mhcl	;UAS-Mhcl RNAi;	Expresses dsRNA for RNAi of Mhcl RNAi	BDSC (51456)
sw RNAi	;;UAS-sw RNAi	Expresses dsRNA for RNAi of sw RNAi	BDSC (30505)
unc-104 RNAi	;UAS-unc-104 RNAi;	Expresses dsRNA for RNAi of unc-104 RNAi	BDSC (53296)

Table 5.1: List of *Drosophila melanogaster* stocks used in this chapter.

5.2.2 Larval dissection

For imaging the mRNA in the NMJ, L3 stage larvae were collected and dissected before staining. Dissection was a "fillet prep", described in more detail in Materials and Methods section 5.6.1.1. Briefly, larvae were pinned on their dorsal side, their abdomen cut from anus to the head, removing the gut and other debris before pinning the sides of the cuticle to the sides, thus exposing the muscle wall and the NMJs.

5.2.3 Sample staining

smFISH and HCR staining of motor protein mRNAs was performed as described in the Materials and Methods section 5.7.1 and 5.7.2. The full optimisation of the HCR method is described in detail in this chapter (Section 5.3.2). The full sequence of the probes used can be found in the Appendix. Neuronal membranes were stained with Dylight405-conjugated HRP antibody 0.003 µg/mL.

For some HCR experiments, samples were treated with DNase or RNase before staining. The method can be found in the Materials and Methods section 5.8.

5.2.4 Mounting and imaging

Larvae were mounted as described in the Materials and Methods section 5.7.4. Imaging was performed using an Olympus/Evident SpinSR10 spinning disk confocal system with a Prime 95B sCMOS camera and a 60X oil immersion (1.5 NA, UPLAPOHR60X) objective or an Olympus/Evident SpinSR10 spinning disk confocal system, fitted with a Prime BSI sCMOS camera and a 100X oil immersion (UPLXAPO100XO 1.45NA) objective. Image acquisition was performed using Olympus/Evident cellSense Dimension software.

5.2.5 Image analysis

5.2.5.1 Quantification of spots

Images were analysed using Fiji/ImageJ (Schindelin et al. 2012) and a custom python pipeline modified from <https://github.com/JYLeeSci/Image-analysis/tree/main/BigFISH>. First, a Fiji macro was created to create masks for glia and neurons in a semi automated process. I manually selected the threshold for hysteresis for each set of images, and the macro included a function that allowed for manual deletion of regions of interest (ROIs), which allowed me to clear the masks from muscle nuclei (which were stained with DAPI and so were imaged in the same channel as neurons), nerves or other debris that might affect the quantification step.

To quantify the spots, a file of coordinates for "real" spots was created. For this, the script uses the microscope information to estimate the size of each spot in pixels. Local maxima were used to find candidates for HCR or smFISH spots, which were then filtered according to an automatic thresholding step that uses an elbow graph to select the cut-off. Detected spots over the threshold were mapped in 3D, the end result of this step of the analysis being a file with the X, Y and Z coordinates of the detected spots.

The resulting dataset of spots was filtered using the previously created glial and neuronal masks, quantifying spots whose coordinates fall inside of the corresponding mask.

5.2.5.2 Colocalisation analysis

When comparing both staining methods, the percentage of spots that were colocalised was calculated using a custom python pipeline made by Dr Jeff Lee <https://github.com/JYLeeSci/Image-analysis/tree/main/smFISH-colocalisation>. The coordinates of the spots detected with one method were compared with the coordinates of those detected with the second method, obtaining a nearest-neighbour distance value.

5.2.5.3 Cell area calculation

Total surface area of the cell mask was calculated using a Fiji/ImageJ macro.

5.2.6 Larval crawling behavioural assay

The larval crawling assay was performed as described in Materials and Methods section 5.9. Briefly, larvae were moved from the 25°C incubator to the room where the assay would take place thirty minutes before the experiment to acclimate. Using a slightly wet brush, crawling L3 larvae were picked from the food vials and placed on a 9 cm diameter 1% agarose plate, where they were left for one minute to further acclimate before being moved to the centre of the plate. Filming took place for three minutes inside a light box built as described in Risse et al. 2013 in order to obtain high-contrast videos with no reflection. A maximum of five larvae were assayed at a time to reduce collisions. The plates were rinsed with ethanol after every experiment. Larvae arising from three different crosses were used every day, and the experiment was performed on three consecutive days. After each experiment was completed, the next genotype and repeat was chosen using a random number generator, to avoid noise arising from larvae being outside the 25°C controlled environment of the incubator for different lengths of time before the assay was performed.

5.2.6.1 Behavioural assay analysis

Analysis was performed using BioImageOperation (Cano-Ferrer et al. 2023, available at <https://joostdefolter.info/bio-research/52-bio-image-operation-new-release> using standard tracking mode. An average of the recorded video was used for background subtraction. Actual larvae (clusters) were filtered by size (minimum area 50 pixels, maximum area 300 pixels), and the position of each cluster and perimeter coordinates each frame were saved.

The R package "trajr" (McLean and Skowron Volponi 2018) was used to analyse the larval trajectories: speed, path straightness, movement linearity, and movement regularity. Speed was calculated by dividing the distance moved (in pixels) by the time elapsed. Path straightness describes the tortuosity of the path by dividing the distance in a straight line between the starting and ending points by the actual distance travelled by the larvae. The closer this value approaches one, the more linear the larval trajectory is. Movement linearity was used to assay the frequency of changes in direction by calculating the mean angular change between two consecutive frames, therefore a higher value indicating more frequent direction changes. Movement regularity describes how common are changes in the behaviour pattern of the larvae by calculating the standard deviation of the movement linearity, a higher value therefore representing a larvae that has several different movement patterns in its track.

The perimeter of the cluster at each frame was used to calculate the percentage each larva spent in curved body by comparing the perimeter of the cluster with the circumference of a circle drawn to enclose the full larvae, its diameter being the distance between the two most distant points of the larvae. Larvae were considered to be in curved body position if the perimeter of the cluster was larger or equal to 0.9 times the circumference.

Larvae stopped being analysed upon hitting the edge of the plate or colliding with each other.

5.3 Results

5.3.1 Candidate gene selection

A list of motor protein component candidate RNAs to screen was generated based on concurrently ongoing work from the lab. Dr Jeff Lee and Dr Dalia Gala performed a meta-analysis on all available mammalian glial protrusion transcriptomic datasets (Lee et al. 2024), the result of which was a cohort of 5028 transcripts present in most datasets. The resulting dataset was used to find high-confidence *Drosophila melanogaster* orthologs using a cutoff-score of 8 in DIOPT v9 (Hu et al. 2011). The Fly Cell Atlas (Li et al. 2022) was used to filter the dataset for genes present in glial clusters, producing a dataset of genes that are both transcribed in glia and predicted to have their RNA localised to the glial periphery.

In addition to collaborating on the validation of this predicted dataset by using sm-FISH to image localised RNA from some of the candidate genes, I used this dataset to perform GO term analysis (Aleksander et al. 2023) to identify a list of genes annotated with the "molecular motor activity" term from the list of candidates. The full list of candidate genes and a brief description of their role obtained from FlyBase can be found in table 5.2.

Gene name	Gene symbol	Function
Cut up	ctp	Subunit of cytoplasmic dynein and myosin (Dick et al. 1996; Williams et al. 2007)
Dilute class unconventional myosin	didum	Mitochondrial transport via microtubule, unconventional myosin (Pathak, Sepp, and Hollenbeck 2010, Pocha, Shevchenko, and Knust 2011; Tóth et al. 2005)
Drop out	dop	Predicted dynein partner (Gaudet et al. 2011)
Dynein light intermediate chain	Dlic	Dynein subunit (Amrute-Nayak and Bullock 2012; Zheng et al. 2008)
Dynein heavy chain 64C	Dhc64C	Force-generating subunit of dynein motor complex (Hays et al. 1994)
Dynactin p150 subunit	DCTN1-p150	Subunit of dynactin complex, binding motor to the cargo and enhancing its processivity (Delanoue and Davis 2005; Siller et al. 2005, Lloyd et al. 2012)
Kinesin-associated protein-3	kap3	Non-motor accessory subunit of kinesin-2 (Mattie et al. 2010; Baqri et al. 2006)
Kinesin heavy chain	khc	Force-generating subunit of Kinesin-1 (Sung et al. 2008; Ali et al. 2008, Gagliano et al. 2010; Harrison et al. 1993)
Kinesin light chain	klc	Kinesin subunit (Ali et al. 2008)
Kinesin-like protein at 10A	Klp10A	Microtubule length regulation (Rogers et al. 2004; Goshima and Vale 2005)
Lissencephaly-1	lis-1	Regulator of dynein-1 complex (Liu, Steward, and Luo 2000; Siller et al. 2005)
Milton	milt	Adapter protein for kinesin-mediated mitochondrial transport ((Glater et al. 2006; Zhang et al. 2025)
Myosin heavy chain-like	mhcl	Binds actin filaments (Guzik-Lendrum et al. 2011)
nudE	nudE	Enables microtubule binding activity (Aleksander et al. 2023)
Roadblock	robl	Dynein-associated protein (Bowman et al. 1999; Hall et al. 2010)
Short wing	sw	Non-catalytic intermediate chain subunit of dynein (Morgan, Song, and Barbar 2011; Zheng et al. 2008, Boylan and Hays 2002)
Uncoordinated-104	unc-104	Plus-end directed kinesin ATPase (Pack-Chung et al. 2007; Cao et al. 2014)
Zipper	zip	Part of myosin II complex, microtubule-binding capabilities (Ugrankar et al. 2019; Franke et al. 2006, Aleksander et al. 2023)

Table 5.2: List of candidate motor protein components

5.3.2 Optimisation of Hybridisation Chain Reaction method for imaging single mRNA molecules in *Drosophila* larvae

The first step was to confirm the localisation of the predicted motor protein mRNAs to the cell periphery in the NMJ. For this, I optimised a hybridisation chain reaction (HCR)-based method that allows for quantifiable detection of individual mRNA molecules that could be used with low-magnification objectives more cost-efficiently than single-molecule fluorescence *in-situ* hybridisation protocols. Although smFISH methods are now more accessible than ever due to the reduction in the cost of oligonucleotide synthesis, they still require synthesis of fifty to hundreds of DNA oligonucleotide probes. In addition, the protocols can be complex and result in poor sample penetrance in thick, whole-mounted samples such as *Drosophila* larvae, or in poor signal due to autofluorescence.

In contrast to these limitations of the state-of-the-art smFISH methods and make the screening of several mRNAs easier and cost-efficient, our HCR-based method has a signal amplification step, which allows for faster image acquisition and analysis even in my thick fillet-prepped whole-mount larvae. It also only requires five pairs of oligonucleotide probes for each candidate mRNA, thus reducing the cost of nucleotide synthesis by more than 75%.

The method is based on third-generation HCR applications (Choi, Beck, and Pierce 2014), which use split initiator probes (Figure 5.2A) to introduce greater specificity to the target RNA and thus results in better background suppression compared to previous techniques, which used a single initiator probe. Split initiator probes each contain half of the complementary sequence to the target RNA and half of the initiator sequence, joined by a flexible domain, while single initiator probes carry the complete target-hybridising and initiator sequences. When bound non-specifically, split probes are missing half of the initiator sequence, therefore being unable to bind the hairpins and generate an amplification signal. In contrast, when bound to the target RNA, split initiator probes are able to bind a fluorophore-bound hairpin H1, exposing its input domain and allowing for the binding of fluorophore-bound hairpin H2. Hairpins H1 and H2 polymerise, forming a self-assembling fluorescent amplification polymer that produces a brighter fluorescent signal than standard smFISH despite a much lower number of probes. This also improves the signal-to-noise ratio, permits imaging deeper into the tissue, and allows detection with lower laser power, thus slowing photobleaching. In addition, using different hairpin and initiator sequences allows for multiplexing (Figure 5.2B), and using fluorescently labelled hairpins that can be used with several initiator probes instead of conjugating fluorophores directly to the probes against the target RNA contributes to lower costs and easier experimental design.

5.3.2.1 Comparing our HCR-based method to smFISH

In order to ensure the efficacy and efficiency of our HCR-method, particularly for large-scale screening projects, the method would have to result in quantifiable signal, specific to the target RNA using the least number of probes possible. To test this, I compared samples taken using five and ten pairs of probes against *lachesin* (*lac*),

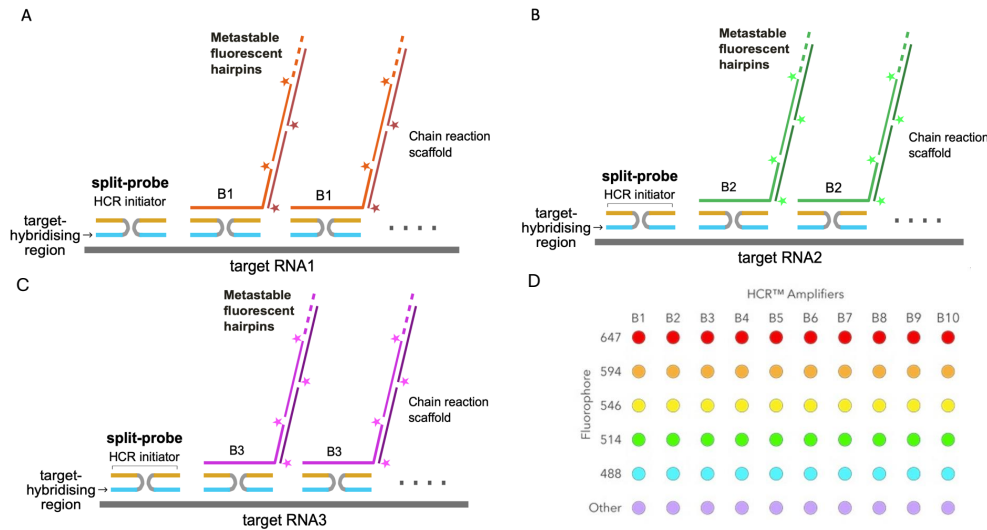


Figure 5.2: A-C: HCR mechanism. Probes are designed in three parts: in blue, the complementary sequence to the gene of interest, where it binds; in yellow, half of a HCR initiator sequence, specific to the hairpin selected (B1, B2, B3, etc.); in grey, a flexible connector. Each pair of probes binds adjoining sections of the RNA, close enough that they can reconstitute the full split HCR initiator sequence. The hairpin H1 (light red, light green, light pink), attached to a fluorophore, can then bind the corresponding reconstituted initiator sequence. Binding exposes the hairpin input domain, which allows H2 to bind along with a bound fluorophore. H1 and H2 can then form a self-assembling polymer, amplifying the fluorescent signal more with every iteration. By using different initiator and hairpin sequences with different fluorophores, it is possible to image several RNAs of interest within the same sample: in A, initiator-amplifier sequence B1 is used with a red fluorophore against gene of interest 1; in B, the amplifier sequence is B2, which is bound to a green fluorophore and hybridises with target gene of interest 2, and in C the amplifier sequence is B3, which has a far red fluorophore and detects target RNA 3. **D: possible commercially available combinations of fluorophores and amplifier sequences**, in an image reproduced from <https://www.molecularinstruments.com/straightforward-multiplexing>.

finding there was no significant difference in puncti number or localisation using five or ten pairs of probes (data not shown). Therefore, the rest of the experiments and quantifications were performed on samples stained using five pairs.

To ensure the signal was specific to the target, co-author Jana Joha performed both our HCR method, using 5 pairs of probes, and a well-established state-of-the-art smFISH method frequently used in our lab in the same sample, both targeting (*lac*) mRNA. *lac*, which encodes a cell surface protein, was previously found to be localised at the glial periphery in the NMJ by other members of the lab (Gala 2023). I then analysed the images, comparing the puncti resulting from each technique. I found that, while both smFISH and HCR resulted in very similar pictures (Figure 5.3), HCR staining resulted in more non-specific probe binding, producing an average of 10% more puncti than smFISH (HCR detected an average of 380 spots and smFISH 345). To better understand where the difference came from, I analysed the samples to find colocalised spots detected by both techniques (Figure 5.3A-B). I found that there were more smFISH puncti that colocalised with an HCR spot (76.1%) than HCR spots colocalised with smFISH signal (67.6%). Most of the difference was caused by floating self-assembled HCR initiators, identifiable under the microscope by their dimmer signal and mobility. Despite this issue, the pattern

of spots remained remarkably similar in both samples (Figure 5.2C), allowing me to conclude that the method could be used to reliably detect presence of target mRNAs in the cell periphery, particularly in the context of a screening project, in a more cost-efficient manner (this HCR method only requires 5 pairs of oligonucleotide probes, while smFISH needs 40). Due to the brighter signal resulting from the amplification step, it is possible that HCR images could be collected using a lower magnification and numerical aperture objective, however this was not tested in this project.

5.3.2.2 Studying sources of non-specific signal

To confirm that the HCR spots were the result of probe hybridisation against target mRNA, I first performed the experimental protocol on a sample without including probes against any RNAs, where any signal detected would be the result of the hairpins alone. The result of this experiment was a negligible amount of signal (Figure 5.4 A, C). I also tested the specificity of the method on samples treated with DNase, to ensure HCR spots detected were a result of the probes binding the target RNA. For this, I treated the samples with DNase, and then applied the HCR method using probes against ubiquitously present *Cam* RNA. DNase treatment resulted in a negligible reduction in number of spots, even though the nuclei were visibly less bright (Figure 5.4 B, Cc). Conversely, RNase treatment, which was performed by co-author Jana Joha, showed a clear reduction in number of spots, although they were not completely cleared according to my analysis (Figure 5.4 B, Cd). The HCR signal decreased further upon increasing the concentration of RNase and detergent, thus indicating the RNase not fully penetrating deep into the NMJ could be the reason behind the persistent HCR spots. With these controls, I was satisfied that the majority of the signal detected by the HCR method was caused by hybridisation of the fluorescent hairpins against the mRNA target.

5.3.2.3 Multiplexing

For the purpose of the screening, it was also important that the HCR method allowed for imaging several target mRNAs in the same sample, reducing sample preparation time and reagent quantities. Due to HCR using commercially available fluorophore-bound hairpins, including a different initiator sequence (B1, B2, B3... B10) in the split probe design for each target results in each target binding a specific hairpin sequence and their corresponding fluorophore. As a result, it is possible to stain several targets at once, the main limiting factor being spectral overlap. In my case, as I wanted to stain neurons and glial cells, I was limited to a maximum of three targets at one time.

To test the multiplexing capabilities of the technique, I designed HCR probes against three of my mRNAs of interest (*khc*, *kap3* and *dctn1-p150*) using initiator sequences B1, B2 and B3. The other channel in the microscope used for imaging these samples were used for neurons (stained with anti-HRP) and muscle cell nuclei (stained with DAPI). The puncti distribution differed across the three channels (Figure 5.5), thus showing it is possible to image several target RNAs in the same sample. In subsequent experiments, only two channels were used to image target mRNAs, the other two being used for neurons and cell nuclei and GFP-labelled glia.

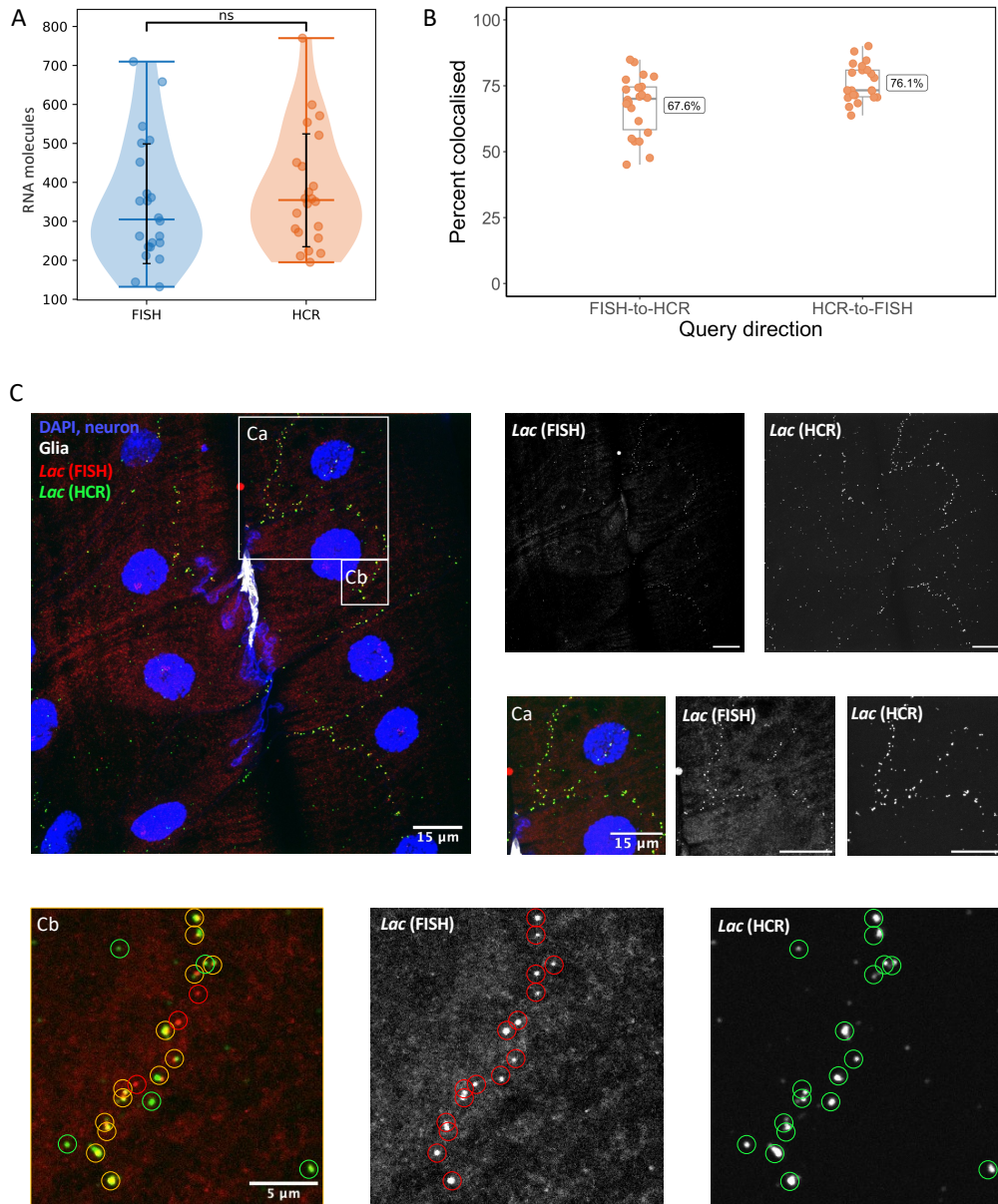


Figure 5.3: Comparison between HCR and FISH techniques. **A:** Number of *lac* RNA molecules as detected in NMJ samples stained with both smFISH and HCR probes. Each dot represents an NMJ. Horizontal line represents the median; in black, the interquartile range ($n=22$; $^*, p < 0.05$). **B:** Colocalisation analysis of smFISH and HCR against *lac* RNA in NMJ samples, showing the percentage of smFISH puncti detected within $<750\text{nm}$ of a spot detected with HCR (FISH-to-HCR) and of HCR puncti detected within the same range of a spot detected with smFISH (HCR-to-FISH). Each dot represents an individual NMJ. Horizontal bar represents the mean, boxplot represents the interquartile range ($n=22$). **C:** Representative image of a NMJ stained with both smFISH (red, Cy3) and HCR (green, AlexaFluor647) against *lac* RNA. Glia are represented in white (Mdr65>GFP), neurons (HRP-Dylight405) and cell nuclei (DAPI) in blue (scalebar = 15 μ m). **Ca** highlights a region of the image where RNA is most present (scalebar = 15 μ m). **Cb** highlights the spots detected with each technique (red: FISH, green: HCR, yellow: colocalised spots, scalebar=5 μ m).

Figure 5

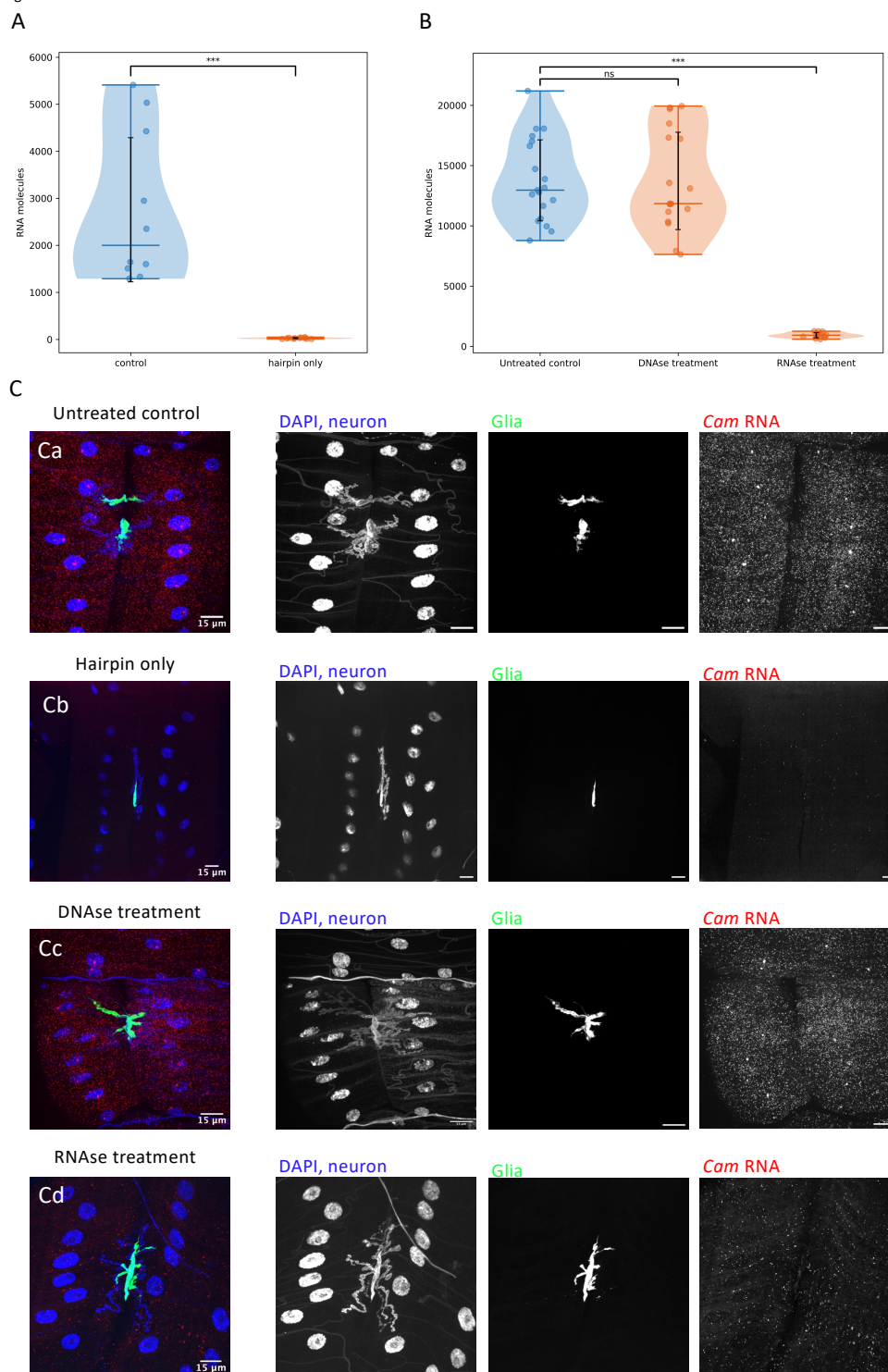


Figure 5.4: Controls of non-specific signal detected by HCR. **A:** Quantification of HCR puncti against ubiquitously expressed gene *Cam* in a control condition where the experiment was performed normally (control, n=10) and adding hairpins but no probes against the RNA (hairpin only, n=11). **B:** Quantification of HCR puncti against *Cam* RNA in a control condition (n=19), samples treated with DNase (n=16), and samples treated with RNase (n=12). In A and B, each dot represents an individual NMJ, the horizontal line is the median; the interquartile range is represented in black. **C:** Representative images of NMJs in each of the control experiments, with HCR signal in red (AlexaFluor546), glia in green (Mdr65>GFP), neurons (HRP-Dylight405) and nuclei (DAPI) in blue. **Ca** is the untreated control, where the experiment was performed normally, **Cb** was performed normally, but without including any probes, **Cc** was treated with DNase before staining, and **Cd** with RNase.

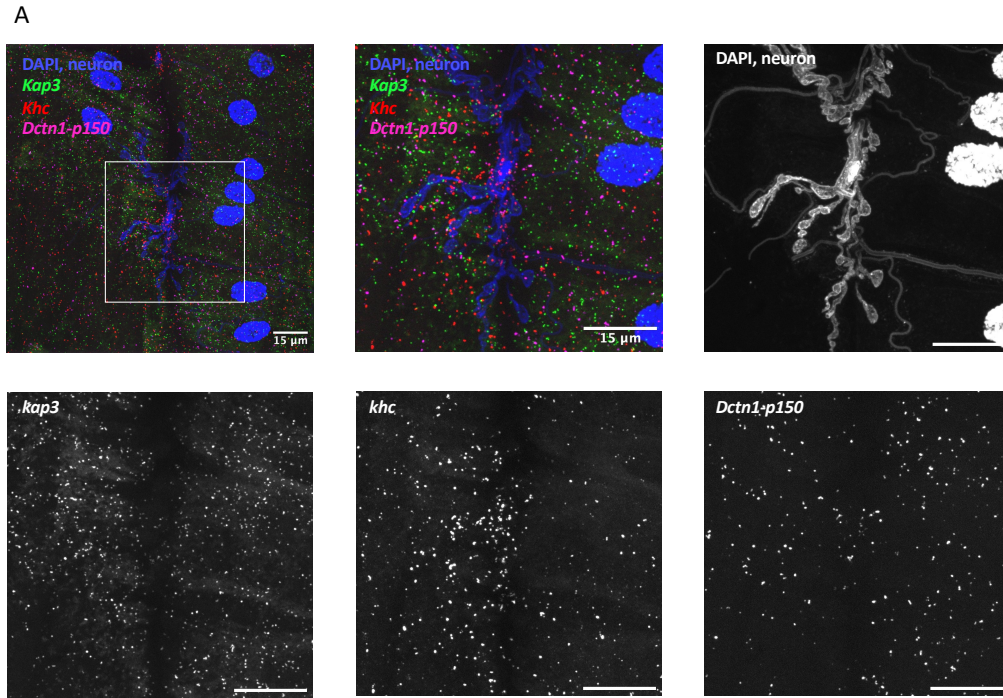


Figure 5.5: Multiplexing detection using HCR. Representative image of an NMJ stained with probes against several RNAs. HCR probes against *Kap3* appear in green (AlexaFluor488), against *khc* in red (AlexaFluor546), and against *DCTN1p150* in magenta (AlexaFluor647). Neurons and cell nuclei are represented in blue (HRP-Dylight405, DAPI). A section of the NMJ is presented zoomed in for clearer visualisation (scalebar = 15µm).

5.3.3 Localisation of candidate genes in the NMJ

Using the previously described HCR method, I designed split initiator probes against the following candidate genes: *DCTN1p150*, *Dhc64C*, *Dlic*, *ctp*, *kap3*, *khc*, *klc*, *lis-1* and *unc-104* and quantified the individual spots within the neurons and the glia (Figure 5.6A,B). All the mRNAs were found to be present distally in both cell types.

The absolute number of individual RNA molecules for the same gene was very varied (Figure 5.6A,B), even within the same type, (overall standard deviation average of 57.3 and median of 33.6) despite them being tested in the same conditions, which is consistent with the literature (Titlow et al. 2023). The localisation pattern was similar between neurons and glia, with *DCTN1p150* and *unc-104* being the most abundant RNAs in both cell types (*DCTN1p150* in neurons and *unc-104* in glia). The least abundant RNAs in glia were *Dlic* and *kap3*, whereas in neurons *Dhc64C*, *klc* and *lis-1* were all less abundant than *Dlic*. However, given the large variation in cell size, even within the same cell type, I calculated the number of spots normalised for the cell area (Figure 5.6C,D). This lowered the standard deviation from 77.7 to 10.6 in neurons, and from 35.8 to 10.38 in glia. The normalised localisation pattern was still similar between neurons and glia. Accounting for cell size variability, the most densely present mRNA in neurons as *DCTN1p150*, followed by *unc-104* and *ctp*. In glia, *unc-104* was the most abundant, followed by *DCTN1p150* and *ctp*.

Importantly, there were some differences in abundance levels of *khc* mRNA in the

cell periphery: in neurons, *khc* was proportionally more abundant than in glia. This is particularly interesting because, as described in the introduction, the cytoskeleton polarity of neurons means that transport via kinesin only occurs from the cell body toward the axon, while the microtubule architecture of glia is very likely not unilateral. This is especially interesting when comparing the abundance of *khc* to the lower density of *Dhc64c*, a dynein subunit, necessary from transport from the cell periphery to the cell body, although this is very likely due to the lower need for transport in that direction.

These results were enough to validate the prediction of genes likely to be localised to glial periphery. However, presence of the mRNA in the distal protrusions of the cell is not enough proof that the mRNA is being locally translated. For this, an assay that specifically detects nascent protein chains or interactions with the ribosome, such as a modified version of HCR which includes a split initiator against the mRNA of choice and another against ribosomal RNA to detect interactions (Fluorescence Assay to detect Ribosome Interactions with MRNA, FLARIM), should be employed.

No genes were excluded from the next steps of the candidate gene selection process.

5.3.4 Effect of candidate genes on larval crawling behaviour

Literature has come to show that locomotor behaviour is affected by local translation at the NMJ in mice (Tu et al. 2024). Our lab had also previously shown disruptions in larval crawling behaviour when disrupting glial expression of mRNA found to be localised to the cell periphery, even if this research did not target distal translation specifically, instead using a GAL4-UAS system to drive expression of RNAi against the genes of interest (Gala 2023; Lee et al. 2024).

I decided to use this behavioural assay to select genes with a noticeable phenotype, with the aim to later compare the effect on larval crawling behaviour of disrupting expression of the mRNA in the whole cell with that of disrupting locally translated mRNA specifically. This would allow me to quantitatively observe the impact of local translation of motor components in glia. Discarding those candidate genes that have no behavioural phenotype when knocked-down in the specific cell type also means it is more likely that the final candidate genes, which would have their localisation signal removed using CRISPR-cas9 in the final stages of the project, would be of interest.

For this assay, larvae expressing RNAi for the genes of interest under the control of Repo Gal4, a pan-glial promoter, were generated. I filmed the crawling behaviour of these larvae on a flat surface for three minutes, obtaining a plot of the tracks on the surface (Figure 5.7), which were later analysed in search of relevant parameters (Figures 5.8 and 5.9) such as crawling speed, path straightness, linearity of movement, and regularity of movement. The outline of the larvae was also used to calculate the percentage of time each larvae spent with their body curved, which can be an indicator of locomotor dysfunction. The same Repo-driven Gal4 flies were

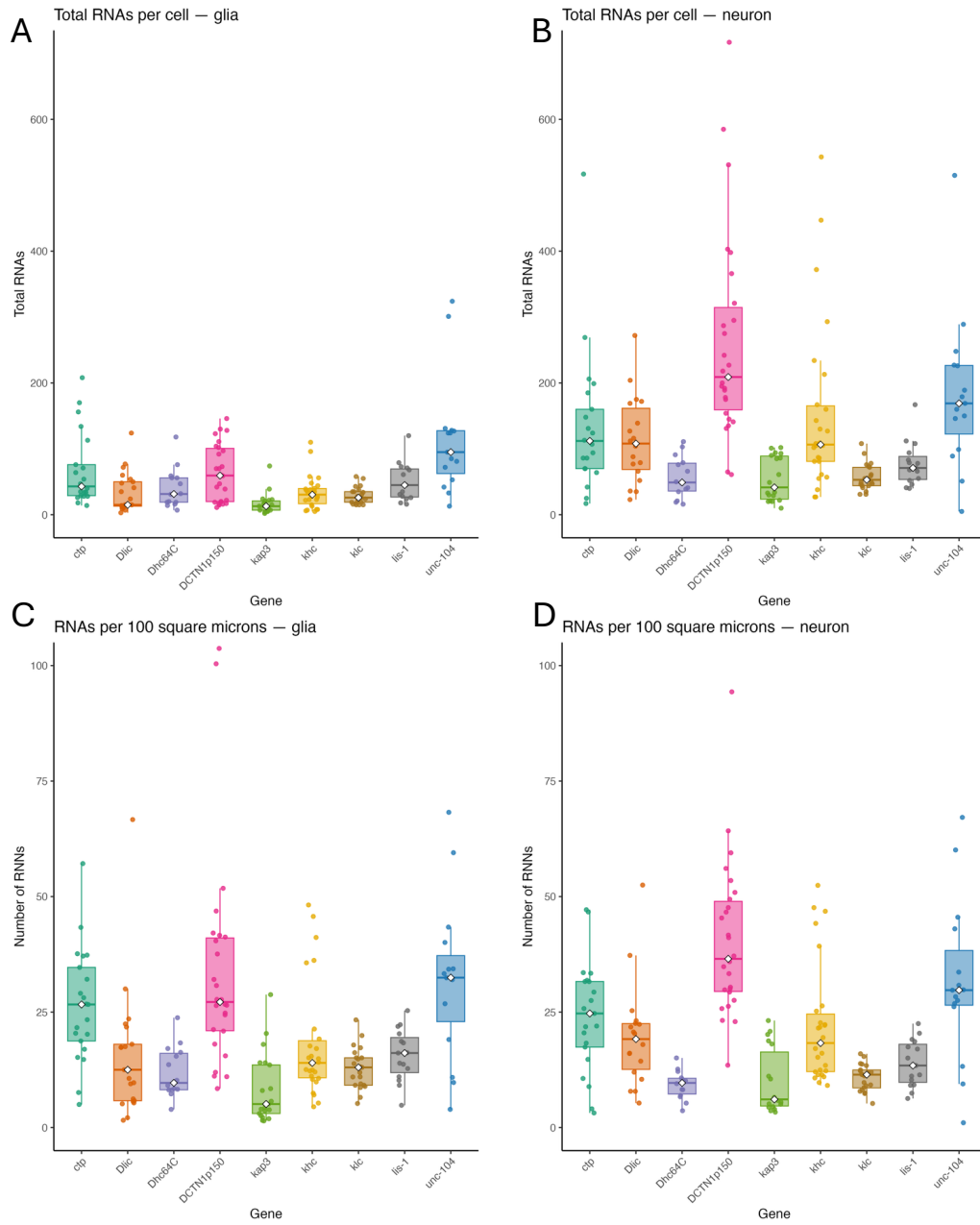


Figure 5.6: Quantification of RNA molecules of the candidate genes in the NMJ. A, B: Quantification of total RNA molecules per cell in glia (A) and neuron (B). Each dot represents the number of RNA molecules found inside a cell in one NMJ. **C, D:** Quantification of RNA molecules normalised for cell area in glia (C) and neuron (D). Each dot represents the number of RNA molecules found inside 100 square μm of the cell in one NMJ. Box plots represent the mean and the interquartile range. *ctp* n=21 , *Dlic* n=21 , *Dhc64C* n=14 , *DCTN1p150* n=26 , *kap3* n=21 , *khc* n=15 , *klc* n=21 , *lis-1* n=14 , *unc104* n=15.

crossed to a UAS-mCherry RNAi line was used as a control.

All of the genes assayed (DCTN1-p150, *didum*, *dlic*, *khc*, *klc*, *klp10A*, *lis-1*, *mhcl*, *staufen*, *sw*, *unc-104*) displayed significant alterations in their crawling behaviour when knocked out in a pan-glial manner compared to the control. This is noticeable in plain sight, as evidenced by their track maps, but becomes more obvious when dissecting the individual variables of their behaviour. I expected gene knockdowns to lower the ability of the larvae to move, thus decreasing their speed. However, only *sw* RNAi larvae displayed slower crawling speeds, with most of the knockdowns actually resulting in faster crawling speed than the control (from fastest to slowest: *khc*, *unc-104*, *dlic*, *klc*, *didum*, and *staufen*). Knocking down DCTN1-p150, *lis-1* had no significant effect in crawling speed.

I also assessed path straightness, which describes the tortuosity of the movement by dividing the distance between the initial and the final positions in a straight line by the actual distance travelled, its value thus approaching 1 the straighter the larval trajectory is. Overall, the RNAi larvae assayed had markedly lower median path straightness index values when compared to the control, meaning that their trajectories on the plate were more convoluted than the control. Interestingly, it was *khc* RNAi larvae which displayed the smallest difference when compared to the control. It is important to note that the path straightness indexes were not normally distributed, but rather displayed a bimodal distribution. This is especially noticeable in the control larvae, where most of the larvae moved directly towards the edges of the plate in a trajectory with few curves, while a few others moved around without reaching the edges of the plate. This results in two groups with different movement patterns, which can be seen in the path straightness boxplot (5.8). In the case of the candidate gene RNAi larvae, the majority of the larvae have curved trajectories, resulting in the median path straightness index being lower than the control, even though some larvae for all conditions had straighter trajectories. The *khc* RNAi larvae are the only other genotype where the bimodality of the data appears evident in the graph.

Following path straightness, I also calculated the movement linearity of the trajectories (for each larva, the mean angular change between two consecutive frames, therefore a higher value indicating frequent directional changes) and their movement irregularity (for each larva, the standard deviation of the movement linearity, therefore a higher value indicating more frequent changes in movement patterns). In the case of movement linearity, *klp10A*, *sw*, *klc*, *dlic* and *unc-104* all displayed significantly higher average directional change, indicating more curved trajectories. The rest of the RNAi larvae did not show any significant differences in movement linearity compared to the control. However, when considering the consistency of the movement patterns, all the genotypes (including those with no significant difference in movement linearity) had significantly higher indexes of movement irregularity, indicating that the movement patterns for all genotypes were more inconsistent than those of the control.

Lastly, I calculated the percentage of time the larvae spent with their bodies curved by comparing the size of their perimeter to the circumference of a circle whose diameter is the maximum distance in a straight line between two points of the larva. In this case, all the genotypes spent on average more time with a curved body

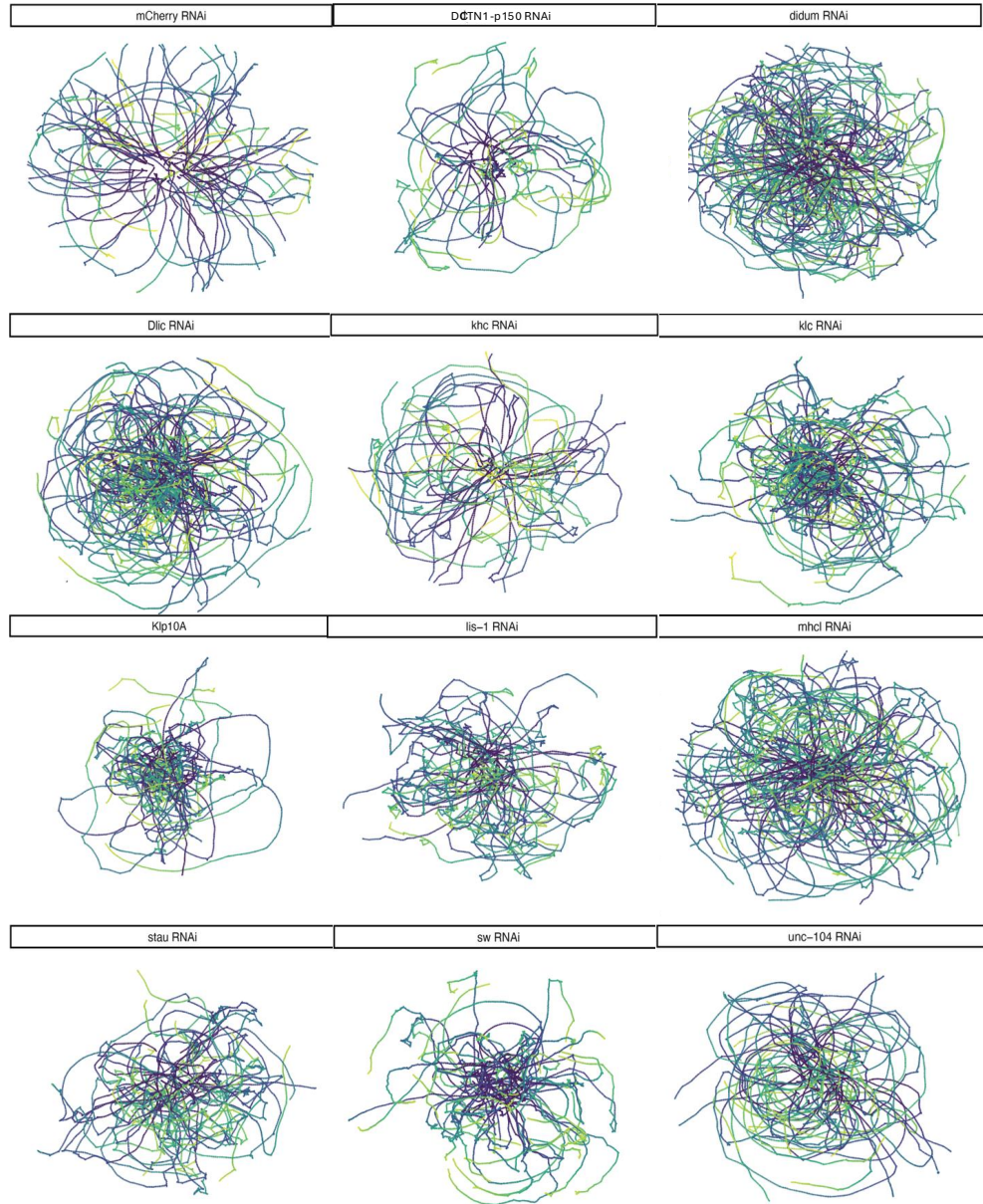


Figure 5.7: Motion tracks of crawling behaviour of glial-specific knockdown of genes of interest. The represented trajectories indicate the motion of L3 larvae on the plate during the duration of the behaviour assay (3 mins) for the glia-specific knockdowns. The RNAi specified in each label was expressed in a pan-glial manner under the control of Repo-GAL4. The control (top left) expressed mCherry RNAi (total number of larvae: control n=71, DCTN1-p150 n=42, didum n=116, dlic n=103, khc n=43, klc n=90, klp10A n=57, lis-1 n=54, mhcl n=109, stau n=49, sw n=81, unc-104 n=62).

than the control. Lis-1, stau, klc and klp in particular had the most noticeable phenotypes.

When analysing these results, khc stood out for having the least significant phenotype, this being inconsistent with published literature. It has been demonstrated that expressing khc RNAi in a pan-glial manner under the control of Repo has detrimental effects on L3 larvae motility, resulting in sluggish larvae with visibly shorter and more tortuous tracks (Schmidt et al. 2012). This can be due to the fly line used

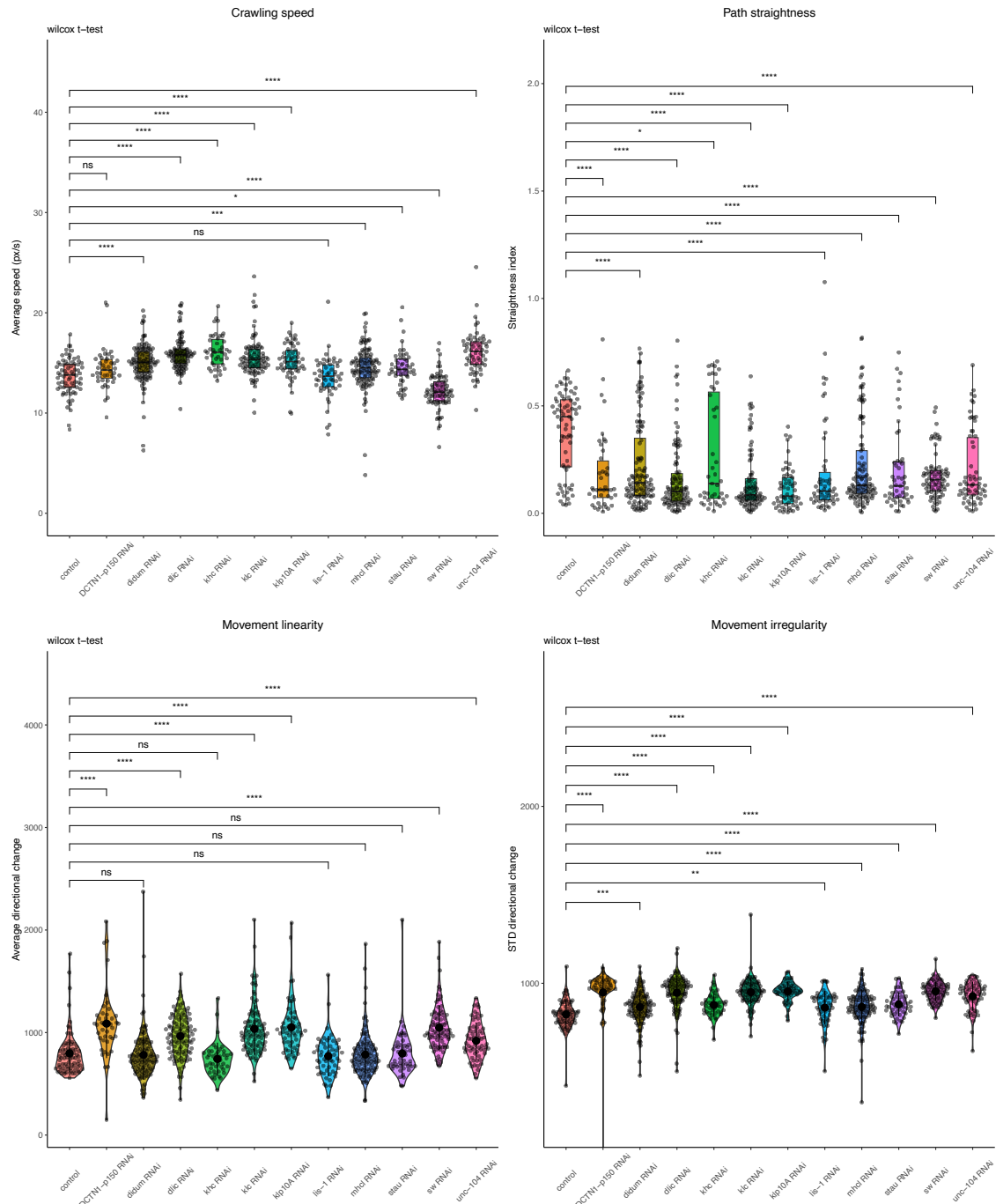


Figure 5.8: Crawling behaviour analysis in glia-specific knockdown of candidate genes.

The genes indicated are knocked down in a pan-glial manner by expression of RNAi against the genes under the control of Repo>GAL4. The control expressed mCherry RNAi instead. Each dot represents an individual larva (control n=71, DCTN1-p150 n=42, didum n=116, dlic n=103, klc n=43, klp10A n=57, lis-1 n=54, mhcl n=109, stau n=49, sw n=81, unc-104 n=62). Box-plots show the median and interquartile range (*, p<0.05, **, p<0.01, ***, p<0.005, ****, p<0.001). Continued on next page.

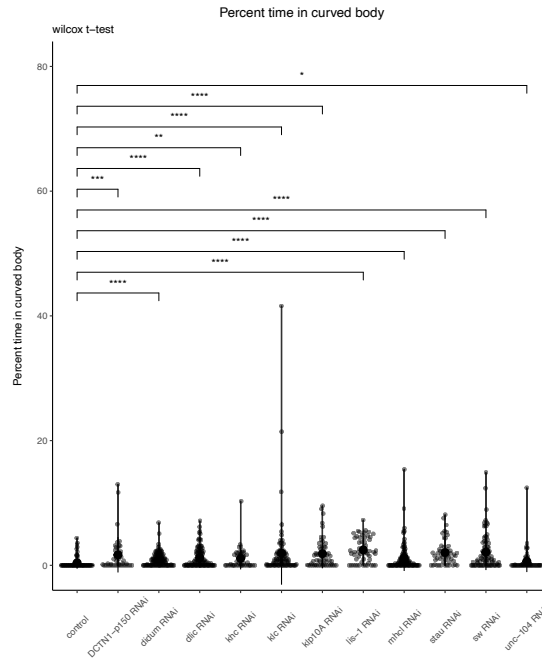


Figure 5.9: Crawling behaviour analysis in glia-specific knockdown of candidate genes (continued). The genes indicated are knocked down in a pan-glial manner by expression of RNAi against the genes under the control of Repo>GAL4. The control expressed mCherry RNAi instead. Each dot represents an individual larva (control $n=71$, DCTN1-p150 $n=42$, didum $n=116$, dlic $n=103$, klc $n=43$, klc $n=90$, klp10A $n=57$, lis-1 $n=54$, mhcl $n=109$, stau $n=49$, sw $n=81$, unc-104 $n=62$). Boxplots show the median and interquartile range (*, $p<0.05$, **, $p<0.01$, ***, $p<0.005$, ****, $p<0.001$).

for the RNAi (VDRC44337) having lower expression levels of the RNAi than the one used in the paper by Schmidt et al. (undisclosed). Experiments with an alternative line (such as VDRC44338) were not conducted due to my changing labs.

Out of all the other genotypes, dlic, klc, klp10A, sw and unc-104 displayed significant differences compared to the control's crawling behaviour in all the variables assayed. The most significantly different (all p -values <0.0001) were klp10A, sw, klc and dlic. This makes sense considering what we know about the genes: klp10A has roles in microtubule architecture, and as such its knockdown can have large effects in all molecular transport in glia. Given the tight relationship between glia and neurons at the synapse (reviewed in Liu et al. 2023), where glia aid in regulation of ions and neurotransmitter uptake (Chang et al. 2024), provide metabolic support (Bonvento and Bolaños 2021; Sodders, Das, and Bai 2025) and regulate synapse formation and neuroplasticity (Brink et al. 2012; Chang et al. 2024; Lee et al. 2024), it is very likely that its absence in glia is disrupting transport indiscriminately, as its loss will affect the microtubule track structure, which in turn can be affecting neuronal signalling at the synapse. Given the importance of molecular transport in development, it is also possible that issues in glia development affect nervous signalling, either directly by impaired glial function, or indirectly by associated issues in neuronal development and synapse formation.

As an intermediate chain subunit of dynein, sw does not generate force for the motor, but it has key roles in cargo binding, regulation of the motor and linkage to adaptor proteins (Morgan, Song, and Barbar 2011; Nyarko et al. 2004; Barbar and

Hare 2004; Nurminsky et al. 1998). Many alleles of the dynein intermediate chain are lethal (Boylan and Hays 2002), and many others, such as the one that gave the gene its name, are homozygous viable but have phenotypic effects, highlighting the importance of this gene for molecular transport. our glial knockdown might be resulting in faulty clearance of neurotransmitters or receptors (Neisch et al. 2025), or dysregulation of homeostasis needed for transport toward the cell periphery due to problems controlling the concentration of molecules along the axon (Kuznetsov and Kuznetsov 2023). In particular, effective dynein transport has been shown to be important for regulation of synaptic function by organising receptor fields in neurons (Neisch et al. 2025), and it might be performing a similar role in glia. Disruption of normal glial development due to issues with molecular transport can also have an indirect effect on neuronal development, as mentioned earlier.

Klc, like sw, is a subunit of the motor, linking cargo and adaptors to khc dimers, the force-generating subunits. It is also in charge of regulating motor activation by changing the molecular conformation of khc (Shukla et al. 2025). Disruption of this protein causes large disruptions in transport, including accumulation of cargoes (including organelles) in the cell, producing swelling and disease-like phenotypes, being essential in neurons (Gindhart et al. 1998). Its role in glia has not been studied, but given its importance for proper neuronal function, disruption in glial cells is very likely to be causing similar issues via disrupted transport, too. Importantly, reduced transport of cargo needed at the cell periphery for synaptic formation or maintenance might result in loss or weakening of the synapse, and disrupted clearing of the synapse post-firing can also have effects on connectivity.

Dlic is also a core subunit of a motor, acting as an activating adaptor by providing a binding site for motor-cargo adaptor proteins in dynein (Reck-Peterson et al. 2018). As such, it is very important for all dynein-based transport, including vesicular transport from the ER (Valenzuela et al. 2014; Roghi and Allan 1999), which can disrupt protein synthesis; mitochondria (Pilling et al. 2006), which can affect the metabolic functions of cells with long protrusions where mitochondria accumulate in areas of high energy requirements (Hollenbeck and Saxton 2005), and cytoskeletal components (Ahmad et al. 1998; Helfand et al. 2002), which can affect the overall cytoskeletal architecture, as well as RNA molecules, lipid droplets, autophagosomes and a wide variety of protein cargoes. Importantly, dynein-based transport is also required for transport in the endolysosomal pathway, meaning that disruption of dlic can be affecting signalling traffic from the cell periphery towards the cell body (Schmieg et al. 2014). As such, glial knockdown of dlic can disrupt a wide variety of cell functions, which may be affecting larval crawling behaviour by causing issues in glia-neuron signalling, metabolic support of the neuron, clearance of neurotransmitters at the synapse, cytoskeleton architecture, or even development of the synapse.

Given the important roles of these three proteins for transport, with klc, sw and dlic being components of the motor proper and klp10A affecting microtubule track architecture, it makes sense that these three genes had the most effect on the larval crawling phenotype when knocked down. In contrast, most of the genes with the less significant phenotypes overall (lis-1, stau, didum, mhcl) are not essential microtubule-based motor components, but rather adaptor proteins (lis-1, stau) or function downstream of microtubule transport for short-range delivery after

microtubule-based long-range transport (didum, mhcl; Seabrooke, Qiu, and Stewart 2010; Krauss et al. 2009). The last gene, DCTN1-p150, had a highly significant phenotype in all variables measured but one, the crawling speed. DCTN1-p150 is a core component of dynactin, which is essential for dynein function (Schroer and Sheetz 1991; Lloyd et al. 2012). Constitutive loss of DCTN1-p150 in *Drosophila* has been shown to cause some behavioural defects in larvae (number of body wall contractions increasing)(Borg et al. 2023).

The results of the behavioural assay therefore make sense, with the exception of *khc*: genes whose function is essential for core motor protein function have stronger phenotypes than adaptor proteins and other non-core motor components, with the exception of *khc*. Due to the mismatch between my detected Repo>*khc* RNAi phenotype and that reported in the literature, I decided to repeat the experiment after ordering a replacement line from VDRC. However, due to my changing labs, the experiment was not repeated.

5.3.5 Candidate gene selection and next steps

From the results displayed, I would have selected *dlic* and *klc* (as well as most likely *khc* after getting and testing a new RNAi line, as it has been shown to have a very strong behavioural phenotype when knocked down in glia). Both of these genes have their mRNA present at the glial and neuronal cell periphery, even if it is not the most abundant one. Even though DCTN1-p150 did not show a behavioural phenotype in all the variables assayed, I would have also selected it as a candidate gene to continue exploring, since it did display a highly significant phenotype in all other variables and was one of the most abundant RNAs at the cell periphery. In addition, it is another core motor protein component, and it would provide insight on dynein-based transport, thus complementing the information on kinesin-based transport provided by studying *khc* and *klc*. Lastly, although *klp10A* did have a highly significant phenotype, this is most likely due to its role in microtubule architecture organisation, which makes it a worse candidate for assaying motor dynamics. As such, it was discarded for the next stage of analysis.

This project was not continued past this point due to my moving labs. The strategy to be followed next is described in the Discussion chapter.

5.4 Discussion

In this chapter, I set out to test the role of distally translated motor protein components in the peripheral nervous system, particularly in glia. I first aimed to validate the presence of RNA at the glial cell periphery of a list of candidate genes predicted by our lab in Lee et al. 2024. For this validation, I optimised an HCR-based staining protocol (Olivares-Abril et al. 2024) to image the candidate gene RNA quantitatively and at a lower cost compared to other single-molecule RNA hybridisation methods such as smFISH. This method was developed with the intention of adopting this method for a broader screening project for the lab, and it was used to validate the distal localisation of other mRNAs. HCR imaging of my list of candidate genes, along with other candidate genes that I tested which were also localised to the glial

periphery (data not shown here but published in (Lee and Davis 2024)) helped validate the prediction of genes to have their mRNA localised to the glial periphery, as all predicted candidate mRNAs were found in the cell protrusions for both glia and neurons.

With the aim to further select functionally interesting genes to study motor dynamics, I used a Gal4-UAS system to generate flies that express RNAi for my candidate genes in a pan-glial manner, and analysed their crawling behaviour to find behavioural phenotypes caused by glial-specific knockdown of the candidate genes. All of the candidate genes produced a distinct phenotype from the control. *Khc* RNAi produced the least significant phenotype of all genes tested, which is contrary to what is shown in previously published experiments (Schmidt et al. 2012), leading me to believe the fly line used had an incomplete knockdown effect. An alternative fly line was selected to repeat the analysis on, however, due to me moving labs, the project was not continued.

Out of the other genotypes tested, I was able to select a few with significant differences in their crawling phenotypes when compared to the controls. Out of the candidate genes, which were a mix of core motor protein components and other motor-related proteins, the core motor proteins were the ones with the strongest phenotypes (except *khc*, as previously mentioned), accordingly to their function in carrying all types of cargo rather than specifically binding to a certain type.

It is important to note that some of the candidate genes were not assayed for both localisation to the cell periphery and behavioural assay (only HCR: *ctp*, *dlic*, *Dhc64C*, *kap3*, only behavioural assay: *didum*, *kpl10A*, *mhcl*, *staufen*). This was mainly due to time limitations, as well as being able to identify two components of each movement directionality that have a significant phenotype early on, which made studying the non-core motor components less of a priority.

Once selected, the four top candidate genes would have been stained using smFISH and imaged under a higher resolution microscope in addition to the here presented HCR. This is due to smFISH allowing for even higher quantitative resolution, even though it is more expensive and as such less well-suited for larger-scale screening projects. For example, due to HCR relying on assembly of a fluorescent polymer and therefore introducing higher variability in fluorescence intensity than smFISH, it is not possible to quantify RNAs if they have formed clusters. This would also allow for improved three-dimensional segmentation of the cells of the NMJ, improving the differentiation of RNA molecules inside the neuron and those inside the glial cells.

In addition to improving the resolution of the images, further experiments to assay the phenotype of the RNAi knockdown of the candidate genes are necessary. The current crawling behaviour assay does not differentiate between effects to behaviour caused by developmental effects of the knockdown, second-hand effects on neurons due to the glia failing to do its metabolic or transmission support, or effects in neuroplasticity. Some experiments to differentiate across all these include comparing the neuronal and glial structure in the knockdown flies, searching for differences in cell size and branching compared to the control, which would identify developmental effects; and performing a spaced potassium stimulation assay (Kstim), which would highlight any effects on neuroplasticity. While the behavioural assay is a time- and

resource-efficient way of screening for functionally important genes, differentiating between developmental effects and disruptions to synaptic function and neuroplasticity is essential for proceeding with the rest of the proposed experiments.

Lastly, although RNA molecules were quantified in both glia and neurons at the NMJ, the behavioural assay was only performed using a pan-glial driver. Using motor neuron driver OK6-Gal4 and repeating the behavioural assay would be a good way of determining which of the motor protein genes that localise to the neuronal periphery are most functionally important. Although the lab has an interest in glial cells and their role in synaptic plasticity, the neuronal axon might be a more interesting model for the study of motor protein dynamics, due to the longer extension of axons compared to glial protrusions, and to the fact that the microtubule track is known to be polar in neuronal axons (plus side at the cell periphery and minus side at the cell body, Baas et al. 1988), but the polarity of the microtubules in most glial types, particularly in *Drosophila melanogaster* is not known.

In conclusion, in this chapter I validated a subset of candidate genes predicted to both be localised to the cell periphery and be functionally important for crawling behaviour when expressed in glia. Further work is necessary to continue studying the role of distally translated motor proteins in the peripheral nervous system. The next steps for this project are described in the Discussion chapter.

Chapter 6

Discussion

6.1 Studying flavivirus pathogen-vector interactions using *Drosophila melanogaster* as a model

ZIKV is transmitted by *Aedes spp.* mosquitoes. Therefore, it is essential for viral transmission that the virus, which is ingested by the insect in an infected blood meal, crosses the insect midgut barrier and disseminates through the organism, ultimately establishing an infection of the salivary glands, from where it is injected into a mammalian host (Franz et al. 2015). For this, the virus needs to bypass several physical and immune barriers, including entering and exiting the gut, disseminating through the organism, and entering and exiting the salivary glands (Franz et al. 2015). Studies of these processes are fragmented, focusing on different stages of the insect infection and using a wide variety of arboviruses (reviewed in Harsh and Eleftherianos 2020; Franz et al. 2015). The complexity of working with mosquitoes (lack of genetic tools, high variability even between colonies, increased safety risks) is partly at fault for this lack of research. Given the similarities between *Aedes spp.* mosquitoes and established model organism *Drosophila melanogaster*, in chapters 3 and 4 I began to explore the bilateral interactions between ZIKV and the insect after oral infection, studying the potential use of this well-established model organism to model mosquito infection. It is important to note that the vast majority of virus studies performed in *Drosophila* have used systemic infection methods, which inject the virus directly into the insect haemocoel, bypassing the natural barriers to infection that are present in the wild, and therefore attempting oral challenge is more representative of mosquito infection in nature.

I used Sting deficient *Drosophila* stock Sting^{EY06491}, which has been shown before to display an increased susceptibility to systemic infection with ZIKV compared to controls. *Drosophila* Sting encodes a relatively under-researched protein, homologous to mammalian Sting. In the fly, this protein has been shown to have antiviral roles against several viruses (ZIKV, SINV, DAV, DCV, Noravirus, (Liu et al. 2018b; Segrist et al. 2021; Goto et al. 2018; Nigg et al. 2024)). In the context of oral infection with SINV, it has been shown to be a non-canonical activator of the IMD innate

immune pathway, triggering an antiviral immune response after activation via cyclic dinucleotides secreted by the gut microbiota in response to viral challenge.

In my initial experiments in *Drosophila melanogaster* larvae, I was able to achieve oral infection with ZIKV in Sting-deficient larvae, whereas background control W¹¹¹⁸ larvae displayed no increase in viral RNA after oral challenge, clearing the infection. This was later replicated in adults. This suggests Sting plays a role in activating an antiviral reaction against ZIKV when orally challenged.

Comparing ZIKV RNA load of orally infected larvae treated or untreated to ablate their gut microbiota also resulted in an increase in viral load, however this increase was much higher than that of the Sting-deficient larvae, suggesting the activation of the Sting pathway is not the only way the gut microbiota is involved in aiding the insect in antiviral immunity. This experiment has yet to be repeated in adults, both W¹¹¹⁸ and EY06491. In addition, gut microbiota plating of infected and mock-infected for both genotypes might help us identify any effects of viral infection on changes in the gut microbiota abundance and composition (Castelló-Sanjuán et al. 2025). Since gut microbiota are involved in control of ISC renewal and other aspects of gut homeostasis, it is important to gain a better understanding of this aspect of oral infection.

Studying the dissemination of the virus through the different larval tissues using qPCR and smFISH highlighted the similarities of ZIKV tropism with mosquito infection (Franz et al. 2015), with a slight increase in viral RNA in the gut and larval heads, and the highest abundance in haemocytes. At the time the experiments were performed, it had not yet been shown that haemocytes are used by the mosquito as a means of dissemination (Hall et al. 2025), although this was a well-established hypothesis (Parikh, Oliver, and Bartholomay 2009). Arboviruses have been shown to display a very high tropism for haemocytes, with the immune roles of this cell type, particularly their ability to phagocyte viruses, making it difficult to differentiate between the antiviral activity of the cells and their role in aiding viral dissemination (Parikh, Oliver, and Bartholomay 2009; Cardoso-Jaime et al. 2022; Lamiabile et al. 2016; Leite et al. 2021). However, the research discussing this relationship had used tissue culture or systemic infection methods until Hall et al performed oral infection of mosquitoes before collecting haemocytes from them (Hall et al. 2025).

In addition to larval haemocytes, I tested the viral tropism towards the nervous system. ZIKV has been shown to infect the *Drosophila* brain when injected into the thorax (Liu et al. 2018b), and the neuronal tropism of the virus in infected mammals, ultimately resulting in neuroblast cell death, is behind the neurodevelopmental symptoms (Yang et al. 2020; Link et al. 2019). Although the qPCR results showed a slight increase in viral RNA load in the larval heads, I was not able to find the virus in the brain using smFISH. I was however able to find a correlation between impaired, sluggish crawling behaviour and higher viral loads of individual larvae. Viral infection and dissemination has been shown to be dose-dependent (Chouin-Carneiro et al. 2020), and although all larvae are treated equally, it is possible that there are differences in feeding behaviour leading to differences in viral dose.

The data I obtained when orally infecting Sting^{EY06491} larvae was very promising, therefore I attempted to replicate the infection in adults from the same genotype. This model is more representative of mosquito infection, as both adult insects share

morphological and cellular features, particularly in the gut, which is the first tissue that the virus has to cross when orally infected (Cui and Franz 2020), and it is adult female mosquitoes that can transmit the virus after an infected blood meal.

Studying oral infection in adults has other advantages, such as that the timeline of infection can be studied for longer, assessing the dissemination of the virus across tissues on different time points post-infection. Using qPCR, I showed that levels of ZIKV RNA in the full adult fly post oral challenge peaked on DPI 7-10, which was also the time point that the haemocytes showed their peak of infection. In addition to haemocytes, I also assessed the levels of viral RNA in the gut, which was never significantly high but decreased slowly through the first two weeks post-infection; salivary glands, where it peaked after the haemocytes, on DPI 10, and the brain, where the qPCR showed no significant difference in any of the days tested.

Using an antibody against the ZIKV capsid, I attempted to find the virus in each of these tissues at different time points of infection. I was able to detect the virus in ISCs of the posterior midgut of the fly early in infection, and although a few cells appeared to contain the virus at the later time points, the number of infected cells seemed to fall later in infection, although more data is needed to confirm this prediction. I was also able to detect the virus in the haemocytes from DPI 7 onwards, as well as in the salivary glands, where it could be visible inside clusters of cells on DPI 10. I was also able to find some infected cells in the brain, despite the qPCR not detecting any. This is most likely due to too few cells being infected, making the overall abundance of the viral RNA too low to be detected by the qPCR, similar to the case of the gut. These results are very supportive of using this *Drosophila* strain as a model to study mosquito infection with arboviruses, particularly ZIKV, as the model seems to be representative of mosquito infection in nature, and the wide availability of genetic tools for the fly can be applied to study ZIKV interactions with a variety of biologically relevant tissues.

To begin understanding some of these interactions, I assessed whether oral ZIKV infection had an effect on *Drosophila* lifespan, finding that the peak of the deaths of infected flies happened earlier than in mock-infected flies. qPCR of the dead flies to assess viral load showed two-fold increase in ZIKV RNA compared to mock-infected controls after three weeks post infection, suggesting the deaths during the peak of deaths were not caused by an acute infection, but rather the product of a reduction in healthspan. The low-level infection was maintained until the last fly had died, two months post infection, suggesting there are some tissues that remain acting as viral reservoirs through the rest of the insect's life.

I also assessed gut permeability after infection, to begin studying the mechanism behind gut barrier crossing. In mosquito, the most common hypothesis for this crossing is the distension that the basal lamina of the gut undergoes after a blood-meal (Cui et al. 2019; Houk, Hardy, and Chiles 1981), however other mechanisms that can work instead of or in conjunction have also been studied (Kantor et al. 2018; Romoser, Faran, and Bailey 1987; Weaver et al. 1988; Ayers et al. 2021). The fact that dissemination of ZIKV in the fly in absence of a blood meal and the associated distension shows that there are other methods for the virus to escape the gut in addition to the escape through the distended pores, even if these might act slower. However, my smurf experiment, which assessed gut permeability by feeding the flies

a blue dye that can not be absorbed, showed no significant differences between infected and mock-infected flies. This suggests there are no infection-associated changes to the gut permeability that might be responsible for the virus crossing the gut barrier, at least in the absence of the blood meal-induced distension.

Lastly, I assessed the effect of the brain infection in climbing behaviour. Interestingly, despite the larval crawling being affected only three days post infection, I was not able to detect differences in climbing behaviour for the first two weeks after infection, suggesting work on the flies for more than two weeks post-infection might be necessary to obtain more information on the long-term effects of ZIKV oral infection in insects. It is possible that the differences in timings of infection spreads are caused by the different cell composition of the developing gut compared to the adult one: the *Drosophila* gut is not fully developed until metamorphosis, where transient niches of adult midgut progenitors separate from the proliferating clusters of undifferentiated cells to separate proliferative islands that give rise to the adult midgut cell types and structure (Miguel-Aliaga, Jasper, and Lemaitre 2018; Takashima et al. 2011; Jiang et al. 2019). If the larval gut tissue is more susceptible for viral barrier crossing, it is possible that ZIKV is able to reach other tissues faster, hence the earlier spread to other tissues.

Overall, the results presented in Chapters 3 and 4 suggest that oral ZIKV infection in Sting-deficient *Drosophila melanogaster* follows a dissemination trajectory that closely resembles the data available for mosquitoes (6.1). In mosquitoes, successful transmission depends on the virus overcoming a series of physiological and immune barriers: crossing of the midgut after a blood meal, dissemination into the haemocoel, spread to secondary tissues and, eventually, infection of the salivary glands. Although there are anatomical and physiological differences between flies and mosquitoes, as evidenced by the GO term enrichment analysis described in Chapter 4, the overall pattern observed after oral infection in larvae and adults is remarkably similar. These results indicate that the major determinants of vector infection with ZIKV can be modelled in the genetically tractable, well-established fruit fly, providing an opportunity to study arbovirus–vector interactions without the added difficulty of working with mosquitoes. This can be of special relevance when studying the mechanism of each of the steps of infection (entry and exit into the gut, entry and exit into the haemocytes, and entry and potential secretion into the saliva of the salivary glands), which are essential steps for virus transmission and yet very under researched.

Table 6.1: Arbovirus dissemination timelines across studies.

Virus	Gut	Hemocytes	Salivary glands	Other dissemination information	Temperature	Experimental design	Detection method	Study
ZIKV	Detected in a few cells DPI1-10 (IF)	Detected DPI 7-14 (qPCR) and DPI 7-10 (IF)	Detected DPI 10-14 (qPCR) and DPI 10 (IF)	DPI 10: brain cells detected by immunofluorescence; brain qPCR not significant	25°C	<i>Drosophila melanogaster</i> (Sting ^{EY06491}); oral sucrose infection	qPCR; immunofluorescence	This work
ZIKV	Detected DPI 1-5			No dissemination detected until DPI 5	28°C	<i>Aedes aegypti</i> ; infected blood meal	Plaque assay, immunofluorescence	Cui et al. 2019
ZIKV			DPI 10 (detected in saliva in 50% of mosquitoes), DPI15 (detected in saliva in 90% of mosquitoes)		26°C	infected blood meal	qPCR of saliva	Winokur et al. 2020
ZIKV		DPI 6-10	DPI 10-12		27°C	Infected blood meal	qRT-PCR	Hall et al. 2025
ZIKV			DPI 14-21 (detected in saliva of 80% of mosquitoes, no earlier time points tested)		28°C	Infected blood meal	Plaque assay	Chouin-Carneiro et al. 2020
ZIKV	DPI 1-14 show midgut infection high by TCID ₅₀		DPI 5: salivary glands positive in 62% of mosquitoes; DPI 10: all salivary glands positive		29°C	<i>Aedes aegypti</i> ; oral blood meal	TCID ₅₀ assay	Li et al. 2012
ZIKV	DPI 3: viral particles in midgut by TEM; orally infected females also RT-qPCR positive			DPI 3: eggs RT-qPCR positive, supporting vertical transmission	28°C	<i>Aedes aegypti</i> ; oral blood meal	TEM; RT-qPCR	Encarnação Sá-Guimarães et al. 2021
DENV		DPI 6-10	DPI 10-12		27°C	Infected blood meal	qRT-PCR	Hall et al. 2025
DENV	DPI 2-DPI 10		DPI 4 in >30% of mosquitoes in one strain; DPI 10 in the other strain		28°C	Infected blood meal	Immunofluorescence	Salazar et al. 2007
WNV	DPI 2-27		DPI 8-21	Virus consistently detected in fat body (DPI 8-21) and nervous system (DPI 8-21)	28°C	Infected blood meal	Immunofluorescence	(Girard, Klingler, and Higgs 2004)

Continued on next page

Virus	Gut	Hemocytes	Salivary glands	Other dissemination information	Temperature	Experimental design	Detection method	Study
WNV	DPI 3-14		DPI 14: one pair of salivary glands positive	Head tissue dissemination was delayed by GFP cassette; mice exposed to infected mosquitoes developed viremia	28°C	Infected blood meal	imaging of GFP-virus construct	McGee et al. 2010

Besides providing promising data for future uses of this model, the work also resulted in preliminary insight into how ZIKV may balance replication and persistence within the insect host. Viral RNA peaked relatively early after infection before declining, but low levels of virus remained detectable by qPCR in infected flies, collected after they died. Infection was also associated with reduced lifespan, and I began assessing other potential effects of infection on the insect fitness such as climbing abilities. As previously discussed, research on potential effects of infection on mosquitoes other than those related to viral transmission is very sparse, therefore making direct comparisons difficult. However, the orally infected Sting-deficient *Drosophila* can also provide a model to study these, which can help elucidate more information on the effects of persistent viral infection in mosquitoes.

Due to the fact that most studies on vector-arbovirus interactions focus on one specific virus, in one or few specific tissues, at one specific timepoint, the information we have on this topic is sparse and difficult to combine. This is worsened by the large genetic variability between mosquito strains, which makes studies on vector biology hard to apply across to other strains. While using a model from a different species does come with its own clear disadvantages in this regard, which are addressed in Section 6.1.1, the wide availability of tools and genetic tractability of the fly do provide us with a useful, stable platform for investigating this area. Any relevant findings will have to be assessed in a number of mosquito species and strains in order to confirm their translatability, however the data produced during my thesis was promising in this regard.

6.1.1 Limitations of the study and future perspectives

Using *Drosophila melanogaster* to model mosquito infection with arboviruses has many advantages, namely genetic tractability and widely available tools. However, mosquitoes are a highly heterogeneous group even within a single genus, therefore limiting how generalisable results are. The mosquito genome in *Aedes spp.* is composed 40% of transposable elements, which explains why despite the high homology in gene sequence, the synteny conservation with *Drosophila melanogaster* is low (Severson et al. 2004), and there is also large diversity of single nucleotide polymorphisms (Gloria-Soria et al. 2019). Even within the *Aedes spp.*, comparisons between lab strains and field colonies display stark differences, and even strains that originated from the same stock but have been maintained in different labs have diverged through time (Gloria-Soria et al. 2019).

This genetic variability can have important effects on susceptibility to infection: for example, two colonies of the same *Culex pipiens* mosquito displayed different susceptibilities to infection with WNV, the resistance caused by increased levels of apoptosis in the gut in the resistant colony compared to the susceptible one (Vaidyanathan and Scott 2006). Therefore, it is very difficult to extrapolate findings between mosquito strains, or to generalise findings from *Drosophila melanogaster* to mosquitoes.

Another factor that might be influencing how translatable research in *Drosophila* is to mosquitoes is their genetic differences. In my research, I exploited a Sting

deficiency to achieve oral infection: since *Aedes spp.* lack a homolog for this gene, this fly model can be considered more representative of the mosquito than a wild type fly. However, and especially since non RNAi-based immunity against viruses is not well understood, it is highly likely that there are other differences in the pathways interacting with ZIKV between the mosquito and the fly that we are not aware of. Despite these caveats, the susceptibility of this fly to infection still opens the door to further studies that can help us grow our understanding of ZIKV interactions with the different insect barriers to oral infection.

One very important caveat when using *Drosophila*, a non-blood-feeding organism, to study vector-arbovirus interactions is the lack of blood meal-induced changes that accompany virus ingestion. The oral ZIKV infection protocol followed in this work is more biologically relevant than injecting the virus directly into the haemocoel, which bypasses the gut barrier and potentially introduces a higher load of virus faster than is the case in nature. However, it is still missing the important biological context of the blood meal and associated physiological changes. While the extent of these changes has not yet been fully understood, with research focusing on the gut microbiota (Cai and Christophides 2024; Ramirez et al. 2012), some cell composition variation in the gut (Vial et al. 2025) and effects on metabolism (Carvalho et al. 2026), effects on immune pathway activation (Cai and Christophides 2024), haemocyte number (Castillo, Brown, and Strand 2011) and possibly also midgut cell differentiation are very likely to play a role in controlling or increasing permissiveness to arbovirus infection. Therefore, while the *Drosophila* model can be very useful to dissect individual processes in the future (for example, determining entry factors to specific cells in the insect gut), the full extent of the oral infection process cannot be replicated due to the lack of blood meal.

Another important consideration is that the Sting^{EY06491} genotype does not contain a deletion of the gene but an insertion in its promoter sequence, therefore the Sting gene is still being expressed albeit at a very low level (Liu et al. 2018b). Using a CRISPR deletion of the Sting gene or the Sting^{Roxanne} genotype, which contains a deletion of Sting, could provide a more complete picture.

In order to obtain more information on other pathways that might be important for ZIKV immunity in insects, the lab has attempted to orally infect adult flies mutant for a variety of innate immunity pathways. Due to time constraints, lines with deficiencies in the RNAi pathway have not been tested yet. The RNAi pathway is the main insect antiviral pathway, and it has been shown to be implicated in ZIKV antiviral response in systemically infected *Drosophila melanogaster* (Harsh et al. 2018a). It would be very interesting to test whether the increased susceptibility to infection displayed by the Dicer-2 and AGO-2 mutants tested in this study is maintained when challenging the flies orally instead of via injection, and whether disrupting this pathway will be sufficient for the virus to cross the midgut barrier and establish a persistent infection in the fly the way it does in the Sting-deficient flies, or whether the Sting deficiency is an essential step for establishment of infection.

Although the RNAi pathway remains untested, the lab has tested oral infection of members of the Toll and IMD pathways, none of which showed a significant difference in ZIKV RNA load after oral infection compared to the mock (O'Brien 2025). Interestingly, this was also the case when infecting Relish mutant fly line Rel^E, despite

Relish having been shown to be implicated in Sting-dependent immunity against viral systemic infection with picorna-like viruses and ZIKV (Liu et al. 2018b; Goto et al. 2018). Antiviral immunity has been shown to be highly tissue-specific: in oral *Drosophila* infection with DCV and SINV, Sting is activated by cyclic dinucleotides, which results in Sting-dependent expression immune effectors and protection against infection. In contrast, when systemically infecting flies with DCV, Sting activation resulted in a different set of effectors being expressed, and Sting was not able to clear SINV when administered systemically. This suggests the mechanism of Sting-dependent immunity can be different in the gut compared to other tissues, even against the same viruses (Segrist et al. 2021). Therefore, it is possible that Relish is important for antiviral immunity in other tissues, but its absence is not sufficient for establishing an infection orally: while Relish-deficient flies have been shown to have increased ZIKV viral load in the brain compared to controls, this was tested in systemically infected flies, therefore any effect of Relish on inhibiting establishment of infection via an oral route is negated (Liu et al. 2018b).

It would be interesting to generate a Sting-Relish double mutant line and compare viral yield with the Sting^{EY06491} flies. If this line is more permissive to infection than the Sting single mutant, this might indicate that Relish is active in other tissues, dependently or independently of Sting. The fact that the Relish mutant is not permissive for establishment of infection via an oral route indicates that, at least in the gut, Sting is acting through a different downstream signalling protein.

RNAseq of different tissues after oral infection might shine some light on other effectors of Sting immunity upon oral infection: for example, to assess whether Relish expression is less upregulated in the gut upon oral infection when compared to other tissues, and whether other pathways of the Toll or IMD pathways might be involved in the Sting-dependent immune reaction, either upstream or downstream. For identification of the upstream members of the pathway, another important experiment would be to attempt oral infection of fly lines deficient for cGAS-like receptors, which have been identified as activators of Sting in the context of antiviral immunity (Segrist et al. 2021; Goto et al. 2018; Slavik et al. 2021; Cai et al. 2020).

The relationship between viral infection, particularly with ZIKV, and gut microbiota is also very understudied and complex. While I did test gut microbiota ablation in larvae, finding that germ-free larvae displayed a much higher viral load, I did not yet confirm whether this increased susceptibility to infection is maintained in adult flies. In addition to performing oral infection of adult germ-free flies to assess the role of their microbiota in activating an antiviral immune response, comparing the gut microbiota of infected and mock-infected flies might provide some insight into the other direction of the relationship. Oral infection with ZIKV in mosquitoes has been associated with changes to the gut microbiota density and composition (Cansado-Utrilla et al. 2025), and so has infecting *Drosophila melanogaster* with DAV, DCV, Bloomfeld virus and Noravirus (Castelló-Sanjuán et al. 2025). This could open the door for new lines of research, studying the relationship of specific types of commensals with ZIKV in the insect gut, but is beyond the scope of a direct follow-up to this project.

More direct follow-up experiments start by improving on the quantitation of the ZIKV infection kinetics and tissue tropism. qPCR can be very noisy and not able

to detect viral RNA if this is present in very few cells, as was the case of the brain and gut, where there were no significant amounts of viral RNA detected but the viral capsid could be detected using immunofluorescence. In addition, qPCR of viral RNA can amplify fragments of viral RNA that are damaged or not part of the infective particle. By performing plaque assays from filtered homogenised *Drosophila*, it is possible to verify active infection and quantitate infective virions (Chouin-Carneiro et al. 2020). In addition, although qPCR of viral RNA is the standard for detecting viral infection, it is very common to see some non-specific amplification after too many cycles (aprox. 37) despite the primers being optimised for temperature and duration of the cycles, and BLASTed against other arboviruses and the full *Drosophila melanogaster* genome. As a result, the mock-infected and the tissues with no virus can show some amplification when compared to the control (1- to 3-fold in my data), despite this amplification not being due to the virus. Sequencing the amplicons obtained from a selection of my mock-infected samples would prove that there is no off-target amplification causing the variability in RNA load of the uninfected samples.

Despite the noise in the low-grade infection as detected by qPCR, I was able to validate my data imaging in both larvae and adults. There were some limitations to this as well: as this was an initial, exploratory imaging experiment, I did not use markers for cell types in the tissues. Using the cross I generated that has both the Sting^{EY06491} insertion and expresses GFP specifically in ISCs under the control of the esg-GAL4 driver would allow me to confirm that the infected cell type is in fact ISCs, and the drivers Repo-GAL4 and elav-GAL4 would do the same in the brain, to differentiate whether the infected cell type is glia or neurons. In addition, using lines that express Sting RNAi under the control of different drivers would help elucidate in which cell types is Sting important for controlling ZIKV infection or dissemination. We are currently working on assessing oral ZIKV infection of esg-GAL4>UAS-Sting RNAi, which will let us know whether Sting absence in ISCs is sufficient for allowing viral gut barrier crossing, and whether once bypassed, the virus will behave as if injected, infecting other tissues even in presence of Sting. This can be repeated with Sting RNAi, but also with other members of the innate immunity pathways, in order to dissect the interaction between different pathways and the virus at the different barriers for ZIKV entry and exit into the tissue.

Given the absence of Sting seems to be particularly important at the stage of gut barrier crossing, I believe we can use the Sting^{EY06491} model to further study the interactions of the virus with the gut early in infection, for example studying apoptosis in the gut after oral infection. DENV and ZIKV have been shown to induce clusters of apoptosis in the mosquito gut (Carpenter and Clem 2023; Ayers et al. 2021), which have been hypothesised to weaken the gut barrier thus allowing viral crossing. I would be very interested to test whether this pattern is conserved in orally infected flies using a TUNEL assay, and whether blocking apoptosis by using a p53 or dronc mutant stocks protects the fly from infection even in the presence of Sting (Garcia-Arias et al. 2023; Martin, Perez-Garijo, and Morata 2009).

Lastly, a common caveat of insect infection experiments is that infection is only followed briefly after the challenge. Although for the experiments in adult infection I collected data for a minimum of two weeks after infection, the results point towards more interesting findings becoming apparent even later in infection. This is the

case of any potential climbing behaviour differences, which were not detected two weeks post infection but might appear later. The qPCR of the flies collected dead suggested that, after oral challenge, the fly remains persistently infected, even if at a low grade. Imaging the virus in the different tissues at later time points could help us identify where the persistent infection of the insect resides, particularly whether it is cleared from the gut and haemocytes, which are infected earlier, and whether the brain and salivary glands remain infected (Bartholomay et al. 2010). Although *Drosophila melanogaster* saliva is most frequently collected and studied from larvae, saliva has been collected from other non-blood feeding insects such as butterflies (Pometto 2015), therefore it might be possible to optimise the protocol to extract the saliva of adult flies to study salivary gland exit using this model, too.

Overall, my work orally infecting Sting^{EY06491} *Drosophila melanogaster* with ZIKV has highlighted many similarities with mosquito infection. Given the ease of working with the fly and the wide availability of tools readily available, this is a model of mosquito vector infection worth exploring further, starting with deepening our understanding of gut barrier crossing, but also later infection stages such as salivary gland infection, which is also understudied and vital for the insect to be able to transmit the virus to a new mammalian host.

6.2 Local translation of RNA in the peripheral nervous system (PNS)

The work presented in Chapter 5 set out to investigate the role of RNA localisation in the PNS, with a particular focus on motor protein transcripts in neurons and glial cells at the larval NMJ. Over the past two decades, RNA localisation has gained importance as an energy-efficient mechanism of cellular organisation in highly polarised cells (Biever, Donlin-Asp, and Schuman 2019), as local translation provides cells with a mechanism to respond rapidly and autonomously to local stimuli, reducing the temporal and energetic constraints associated with long-distance protein transport (Fonkeu et al. 2019). Advances in transcriptomic and imaging approaches have highlighted the large numbers of mRNAs that localise away from the cell body in neurons, where local translation contributes to processes including axon guidance, synaptic plasticity, neuronal maintenance and regeneration following injury (Middleton, Eberwine, and Kim 2019; Biever, Donlin-Asp, and Schuman 2019; Glock, Heumüller, and Schuman 2017). More recently, evidence has begun to accumulate that RNA localisation and local translation are also important in glial cells, although this area remains considerably less studied than in neurons (Lee et al. 2024; Gala 2023).

Drosophila melanogaster larval NMJ is a well-established model of neuroplasticity (Bai and Suzuki 2020). Its location and relative ease of access allow us to image the interactions between the neurons, glia and muscle cells at the junction, and since it is possible to dissect the larvae to expose the NMJ without killing the insect, a spaced potassium stimulation assay can be used to study the strengthening of synapses with relative ease (Gala 2023). Since the dissection exposes individual synapses, it is also possible to use microscopy to assess other variables, like the cellular morphology and protein or mRNA localisation inside each cell (Titlow et al. 2023).

Therefore, the larval NMJ provides a good system for studying local translation, which I set out to use to study motor protein dynamics. Motor proteins such as kinesins and dynein are known to coordinate the movement of diverse cargoes, including organelles, proteins and ribonucleoprotein complexes, and are essential for maintaining the organisation and function of highly polarised cells such as neurons (Hirokawa 2006; Twelvetrees 2020). However, the exact dynamics by which motor proteins associate and disassociate from the microtubule track and their cargo are not yet fully understood. The long cellular protrusions of neurons and glia, visible at the NMJ, can be assessed for local translation of motor proteins, ultimately intending to assess the role of motor diffusion towards the cell body in transport efficiency through the protrusion.

Using this model, in chapter 5 I began to examine the purpose of local translation of motor protein components in the distal ends of neurons and glia, hypothesising that their expression on both ends of the microtubule track would allow them to diffuse along the axon or glial protrusion, replenishing the pool of motors without need for them to be actively carried in the opposite direction. My objective was to select two or three motor components that were both locally translated at the periphery and had a visible phenotype when disrupted in glia or neurons, to ultimately disrupt the localisation of the mRNA and therefore local expression of the gene, allowing me to observe the effect on the phenotypes of normal translation of the gene in the cell body and disrupted expression in the periphery.

For this, I started by analysing a dataset produced by other lab members (Lee et al. 2024) that predicted which mRNAs would localise to the glial periphery in *Drosophila melanogaster*, selecting those with molecular motor activity. This produced a list of 18 candidate genes: *ctp*, *didum*, *dop*, *Dlic*, *Dhc64C*, *DCTN1-p150*, *kap3*, *khc*, *klc*, *Klp10A*, *lis-1*, *milt*, *mhcl*, *nudE*, *robl*, *sw*, *unc-104* and *zip*. As this was part of a broader lab project that involved validating the localisation of the mRNA to the glial periphery as was predicted, I optimised an HCR-based protocol for a quantifiable method of imaging mRNA molecules in the fly larvae that used less nucleotide probes than the gold standard, smFISH. This was tested for specificity of the signal, multiplexing and compared to smFISH along with lab member Jana Joha (Olivares-Abril et al. 2024). Once optimised, I designed probes against the candidate mRNAs and used the HCR method to test whether they were localised to the glial and neuronal periphery in the NMJ, finding that the prediction was correct and all the genes were present in the cell periphery.

In order to assess the importance of local translation from the cell periphery in the nervous system, I needed to assess the effect of fully disrupting expression of the genes of interest in each cell type, starting with glia, which would provide a baseline to compare when disrupting specifically local translation of the gene. For this, I crossed fly lines to obtain larvae that expressed an RNAi against each of my genes of interest specifically in glia, and I used a larval crawling behaviour assay to measure several variables (speed, linearity, regularity, straightness and time spent in curved body) that have been shown before to be affected by glia-specific impaired motor transport (Schmidt et al. 2012). All of the assessed genes showed significant differences with the control in at least one of the measured variable, with *klp10A*, *sw*, *klc* and *dlic* showing the highest difference overall.

Overall, although this section of the work was left unfinished, the findings described support the growing importance of RNA localisation as a fundamental mechanism for maintaining cellular asymmetry in the nervous system, extending beyond neurons to include glial cells. While previous studies have largely focused on local translation in neurons and its role in development and synaptic plasticity, my results demonstrate that multiple motor-related transcripts localise to the periphery of both neurons and glia, and that disruption of several of these genes in glia is sufficient to affect behaviour. While the local translation of motor proteins in order to examine the importance of diffusion from the distal end toward the cell body is better suited to be assessed in neurons due to the polar structure of their cytoskeleton, the fact that these RNAs were also localised to the periphery in glial cells suggests future studies should also consider this cell type when studying local translation, especially due to the growing interest in this cell type and its role in neurotransmission and synaptic plasticity. The set of candidate genes screened, particularly the main motor components (DCTN1-p150, *khc*, *klc*) can be used for future mechanistic studies.

6.2.1 Limitations and future perspectives

This project was not continued due to my changing research groups. Therefore, some of the candidate genes have only been assessed for either mRNA localisation (HCR) or crawling phenotype (behavioural assay), and the behavioural assay had not yet been performed in larvae where the RNAi expression was driven in neurons, therefore providing an incomplete picture. However, the data I did have time to collect was enough for me to select four candidate genes (*dlic*, DCTN1-p150, *klc*, in addition to *khc*). These were main motor protein components, compared to adaptor and other accessory proteins which had generally less significant differences with the control. This makes sense, as main motor components are involved in transport of the vast majority of molecules inside the cell, whereas adapters are only necessary to transport subsets of cargo specific to the adapter. Therefore, continuing the research focusing on these would be the most appropriate course of action.

One of the main caveats of my data is the lack of severity of the *Repo>khc* RNAi phenotype. This genotype has been previously described to result in very impaired larval crawling (Schmidt et al. 2012), therefore my results suggest the RNAi line I used is not fully silencing the *khc* gene. Therefore, before advancing any further, repeating the experiment with a different line containing a UAS-*khc* RNAi, such as VDRC44337, is necessary.

Once chosen, the localisation of the final selection of candidate mRNAs would need to be tested again, this time using smFISH instead of HCR. This is due to HCR being better suited for screening projects, since it results in a brighter signal that can be detected with a lower magnification objective, and especially due to its lower cost since it relies on five pairs of probes instead of forty. However, smFISH remains the gold-standard, and since the fluorescent signal in HCR comes from a self-assembling polymer, the fluorescent intensity of each spot is more variable and cannot be used to extrapolate number of RNA molecules when too close together, unlike in smFISH. Therefore, using smFISH and a high-resolution objective, it would be possible to fully quantify the RNA molecules in the cells of the NMJ more accurately than with

HCR. This is especially important for separating signal arising from RNA molecules in the regions where the neuron and the glia overlap. Despite the Fiji macro used to make the masks for image analysis using a 3D hysteresis algorithm, due to the microscope resolution not being high enough, in the regions where both cells overlap, it was difficult to say with certainty in which cell the mRNA molecule detected with HCR was. The chances of this happening can be reduced by using a higher resolution microscope.

In addition to improving the quantitation of distally localised mRNA, it is important to note that simply because the RNA molecule is localised is not enough proof that the protein is being distally produced. Therefore, confirming local translation of the localised mRNA is an essential next step. This can be achieved by labelling nascent peptides in the cells of the NMJ (Erdmann et al. 2015; Sambandan et al. 2017; Yuet et al. 2015; Tom Dieck et al. 2015; Shigeoka et al. 2016), or using FLARIM, another HCR-based system that includes probes against ribosomal RNA in its initiator sequence to mark locations where the mRNA of interest is in very close proximity to the ribosome (Richer, Speese, and Logan 2021).

Once confirmed that the mRNA for the candidate genes are not just transported to the cell periphery, but also actively translated distally, further experiments to characterise their role in glia and neurons using Repo>RNAi and OK6>RNAi would also be useful. In particular, quantification of cell morphology (area and branching) as well as testing effects on neuroplasticity using the KStim assay would be helpful to compare the effect of knocking each candidate gene out completely in each cell type with that of only eliminating the locally translated one.

At this stage, we would attempt to disrupt the localisation signal of the mRNA, in order to test specifically the role of the locally translated gene. This might not be possible for all candidates, as we have limited knowledge of RNA localisation sequences. A first step for this would be to compare the gene UTR sequence with databases of consensus binding sequences for RNA-binding proteins such as oRNAment (Benoit Bouvrette et al. 2020), searching for matches with target sequences for proteins known to transport RNA to the cell periphery, such as staufer (Gardioli and St Johnston 2014), IGF2 mRNA-binding protein (Imp) (Munroe and Doe 2023), Syncrin (syp) (Lee 2022; Vijayakumar et al. 2019) or Dm NXF1 (sbr) (Mamon et al. 2021). Comparison with other mRNAs that show similar localisation patterns may also result in finding a candidate localisation signal (Van De Bor et al. 2005). As a last resort, completely replacing the 3' or 5' UTR with that of a gene that is not locally translated might be successful, although this method might have undesired effects such as disrupting cell body translation levels, too. The lab has shown this is a potentially successful, relatively easier method for disrupting RNA localisation: after *lac* RNA was found to be localised to the glial periphery (Gala 2023), lab member Dominika Syska was able to generate fly lines containing the GFP gene sequence flanked by either the 3' or 5' UTR regions of the *lac* gene (whose mRNA localises to the glial periphery) or the *hsp83* gene (whose mRNA does not localise to the glial periphery). Performing smFISH against the GFP mRNA on these flies, I was able to demonstrate that the *lac* 5' UTR sequence is sufficient to localise an mRNA to the glial periphery, whereas the 3' UTR had no effect (unpublished data).

Once a candidate sequence in the UTR (or the entire UTR) have been identified,

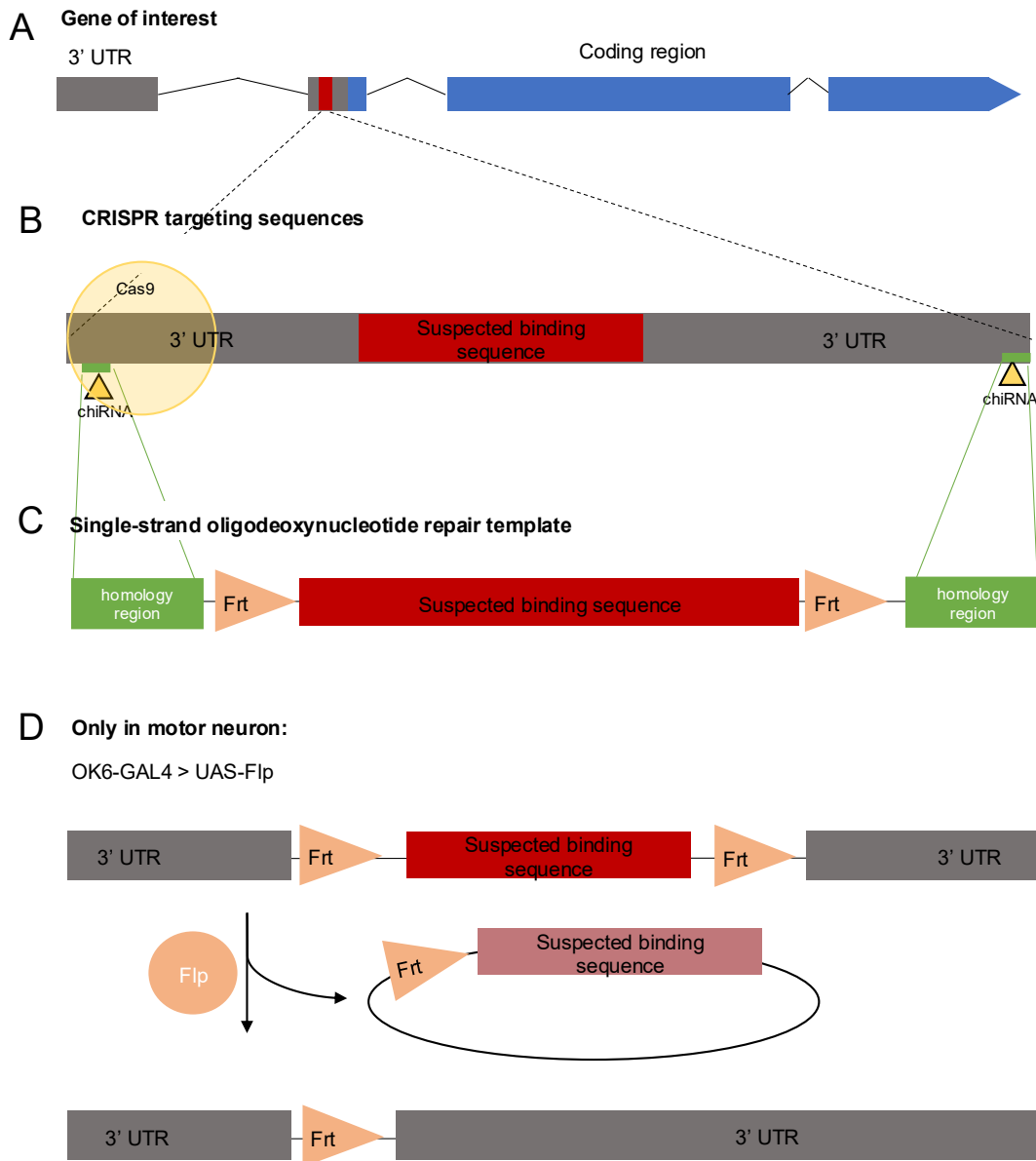


Figure 6.1: Scheme representing the proposed transgene generation for cell type-specific disruption of RNA localisation. **A:** The suspected RNA binding protein sequence (red) is located within the UTR (grey). **B:** Using CRISPR-cas9 and guide RNAs that flank the suspected binding sequence, two double-stranded breaks can be induced, allowing replacement of the sequence. **C:** A repair template containing the same suspected binding sequence, but flanked by FRT sites, would be used to repair the double-stranded break. **D:** By expressing Flt recombinase exclusively in motor neurons under the control of OK6-GAL4, in that cell type the recombinase will target the Frt sites and excise the suspected binding sequence.

CRISPR-cas9 could be used as described in Figure 6.1 to disrupt the localisation signal specifically in one cell type: neurons or glia. Briefly, by inserting FRT sites on both ends of the candidate localisation sequence, the sequence will be excised in tissues that express FLP recombinase, which can be controlled by a GAL4-UAS system. smFISH would be used to confirm that removing the localisation sequence eliminated transport of the mRNA.

Since the polar architecture of the microtubule cytoskeleton in neurons has been demonstrated (Baas et al. 1988), but we do not yet know if this is conserved in glia, particularly in *Drosophila* (Weigel, Wang, and Fu 2021; Lunn, Baas, and Duncan 1997; Fu et al. 2019; Eom et al. 2011), performing the experiment in neurons might result in a stronger phenotype. This is due to the motors only being able to use the microtubule track to move in one direction along the neuronal axon: either from the cell body to the synapse in the case of kinesin and from the synapse to the cell body in the case of dynein. Therefore, without local translation of dynein, the only way for this motor to arrive at the cell periphery is by diffusion or if actively transported by kinesin; and the kinesin motor pool is not renewed distally, which might result in depletion of the transporter pool and accumulation of aged motors, less efficient at active transport. In contrast, if the microtubule track is not organised in a polar manner, newly translated motors from both the kinesin and dynein families can join the microtubule track and participate in active transport in both directions, therefore likely resulting in a less significant effect on molecular transport dynamics. To assess this, larvae with disrupted cell-type specific distal expression of the motors would have their crawling behaviour, cell morphology and neuroplasticity compared to the larvae with the cell-wide knockdown. This would help elucidate the part of the phenotype caused by the local expression of the candidate gene as opposed to expression in the cell body.

Lastly, to study the dynamics of the locally translated motor components, testing whether they are indeed diffusing toward the cell body to replenish the motor protein pool from both ends of the protrusion, I would perform *in vivo* imaging of the larval NMJ, using a fluorescently labelled version of the candidate proteins and photobleaching the NMJ before imaging to ensure only newly synthesised proteins are considered. Proteins diffusing toward the cell body could be identified as their traces along the cell protrusion will be disorganised, compared to those being actively transported along the microtubule track, whose traces will be parallel lines along the microtubule (Bercier et al. 2019; Sleight, Tosolini, and Schiavo 2020).

Overall, the experiments performed in Chapter 5 validated a subset of the RNAs predicted to be localised to the glial periphery. Their presence distally in both neurons and glia highlighted the (still not well-understood) importance of local translation of motor protein components. The results open the door to better understand motor protein dynamics in long cellular protrusions, such as those in glia and neurons.

Appendix A

List of primers

Wolbachia:

Forward: CCTTATCTTAAAGGAGGAAA

Reverse: AATCCTTTATGAGCTTTTGC

ZIKV:

Forward: ACTTGGTGGTGCAGCTTATC

Reverse: CACTTTCTCTGGCTTCCTCAA

Rp49 (Titlow et al. 2020):

Forward: AAGAAGCGCACCAAGCACTTCATC

Reverse: TCTGTTGTGCGATACCCTTGGGCTT

Appendix A

List of probes

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