International Journal of Science and Research Archive

eISSN: 2582-8185

Cross Ref DOI: 10.30574/ijsra

Journal homepage: https://ijsra.net/

(REVIEW ARTICLE)

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Zebrafish as a comprehensive model of neurological diseases

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International Journal of Science and Research Archive, 2023, 10(01), 018–052

Publication history: Received on 18 July 2023; revised on 30 August 2023; accepted on 01 September 2023

Article DOI: https://doi.org/10.30574/ijsra.2023.10.1.0696

Abstract

Neurological diseases play an important role in world health and require new treatments. In recent years, the zebrafish (*Danio rerio*) has emerged as a powerful and versatile animal model to study many neurological diseases and facilitate drug discovery. This article provides an overview of the use of zebrafish models in neuro drug discovery and clinical evaluation and highlights the challenges in translating these findings into clinical practice. Researchers are using the zebrafish model to study various neurological diseases such as Alzheimer's, Parkinson's, epilepsy and autism spectrum disorders. These models provide insight into disease processes and allow the identification of drug targets and therapeutic agents. However, several challenges prevent the zebrafish-based findings from being translated for clinical use. First, the difference in brain complexity between zebrafish and animals requires careful validation of results in more complex models. In addition, it is difficult to understand drug pharmacokinetics and kinetics in zebrafish and to determine their relationship to human physiology. In addition, the need for qualitative behavioral tests and quantitative neurological readouts present significant challenges for assessing the efficacy of drugs in zebrafish models. Overcoming these challenges requires the optimization of experiments and the integration of advanced techniques to improve data accuracy and reproducibility.

Keywords: Zebrafish; Neurological Disorders; Neuroanatomy; Genetic tractability; Drug Screening; Challenges

1. Introduction

Neurological diseases represent an important role in world health, affecting millions of people worldwide and presenting difficult problems for scientists and doctors. Understanding the mechanisms underlying these diseases and their potential treatments requires new and effective experimental designs. In recent years, the zebrafish (*Danio rerio*) has emerged as a powerful and versatile organism that can be used to study a variety of neurological diseases. The zebrafish model has many advantages over animal models, including small size, rapid growth, high fecundity and transparency of early life. Additionally, zebrafish share similar genes with humans, with up to 70% of their genes homologous to humans, making zebrafish relevant for studying the genetics of insects. (Howe K, 2013). In addition, the regenerative capacity of the nervous system provides a unique platform for studying repair and recovery of the nervous system after injury, which is important for potential therapeutic interventions (Kroehne V, 2011). Researchers have successfully used the zebrafish model to study a variety of neurological diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), epilepsy, and autism spectrum disorder (ASD), among others. By introducing disease-related genes or causing specific mutations in zebrafish embryos, researchers can assess the effects of genetic changes on the brain and habit development. Additionally, the transparency of zebrafish larvae enables the timing of neural activity, providing a better understanding of changes in neural circuits (Arrenberg AB, 2010). Additionally, the zebrafish model makes it useful for drug screening, as hundreds of larvae can be tested simultaneously in a small well. This accelerates the identification of potential therapeutic agents, enabling rapid translation of research findings into clinical applications (Barbazuk WB, 2000). One of the reasons that hinders the discovery of new drugs is the lack of knowledge about the genetics and neurobiology of diseases. Further research into the etiology of mental disorders, guided by a

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combination of human genetic studies and animal models, and considering the need for intervention to improve drug therapy and improve early intervention (before symptoms Appear) to prevent, prevent or delay environmental onset of disease (H.J.Norton, 2013) In this review, we explore the utility of zebrafish models for the study of a variety of brain diseases, focusing on recent findings and those that are improving our understanding of these challenging diseases. We will also highlight the challenges and limitations of the zebrafish model and discuss how zebrafish research can be integrated with other models to better understand neurological diseases.

2. Zebrafish models in neurological diseases

The zebrafish (*Danio rerio*) has emerged as a powerful model organism for studying various aspects of neurological diseases. Some advantages of using the zebrafish model in neurological disease research is given below.

2.1. Conserved Neurological Processes

Zebrafish share genetic and physiological similarities with humans, particularly in terms of neurodevelopmental processes and molecular involvement in neurological diseases. This protection allows scientists to study the mechanisms underlying these diseases. For example, zebrafish have been used to study neurogenesis, axon guidance, synaptic plasticity, and neuroinflammation (Scholpp, 2004).

2.2. High Genetic Accessibility

Zebrafish have transparent embryos that allow unobstructed views of their developing neural structures. This allows researchers to observe neuron migration, axon pathway finding, and synapse formation over time. In addition, zebrafish are characterized by a short lifespan, small size and ability to perform genetic manipulation, making them ideal for clinical research genetic size (Megason SG, 2007).

2.3. Behavioral Assays

Zebrafish exhibit a wide variety of behaviors, including working, learning and social behavior, all of which can be measured quantitatively. Behavioral analysis of zebrafish provides insight into genetic and environmental influences on neural function. (S. Ahmed, 2023). They have been used to model various neurological disorders, such as autism spectrum disorder, epilepsy, and anxiety (R, 2010).

2.4. Drug Screening Platform

The zebrafish model has been used as the most advanced screening method for drug discovery in neurological diseases. Because of their small size and rapid growth, zebrafish larvae can be exposed to many compounds and their effects on neural phenotypes can be well evaluated. Zebrafish-based drug screening yields promising results in identifying therapeutic candidates (Zon LI, 2005).

2.5. Regeneration and Repair

Zebrafish have the ability to regenerate themselves, including the ability to regenerate damaged tissue. This feature allows scientists to study the process of nerve regeneration and repair. Zebrafish models have been used to study neurodegenerative diseases, spinal cord injuries and brain injuries and provide insight into potential treatments (Becker CG B. T., 2008).

2.6. High fecundity and rapid development

Zebrafish reproduce quickly, with each female producing hundreds of embryos per week. Also, their transparent embryos develop on the outside, allowing for easy visualization and monitoring of early neural development. Rapid development of zebrafish facilitates disease research and drug screening in the short term (Becker CG B. T., 2019; Kaslin, 2001).

2.7. Neuroanatomical and physiological similarities

Zebrafish have well-preserved vertebrate neuroanatomy and exhibit neuronal cells and circuits similar to humans. They also report on neurotransmitters and exhibit behaviors associated with neurological diseases. This similarity allows researchers to study disease processes and evaluate treatment strategies (Becker CG B. T., 2019; Ahrens MB, 2012).

2.8. Optical transparency

Zebrafish embryos and larvae are transparent, allowing for non-invasive imaging such as fluorescent microscopy and in vivo imaging of neuronal activity. This provides real-time visualization of neurodevelopmental processes, neuronal connections, and changes in the brain in response to disease or treatment (Becker CG B. T., 2019; Kyritsis N, 2012).

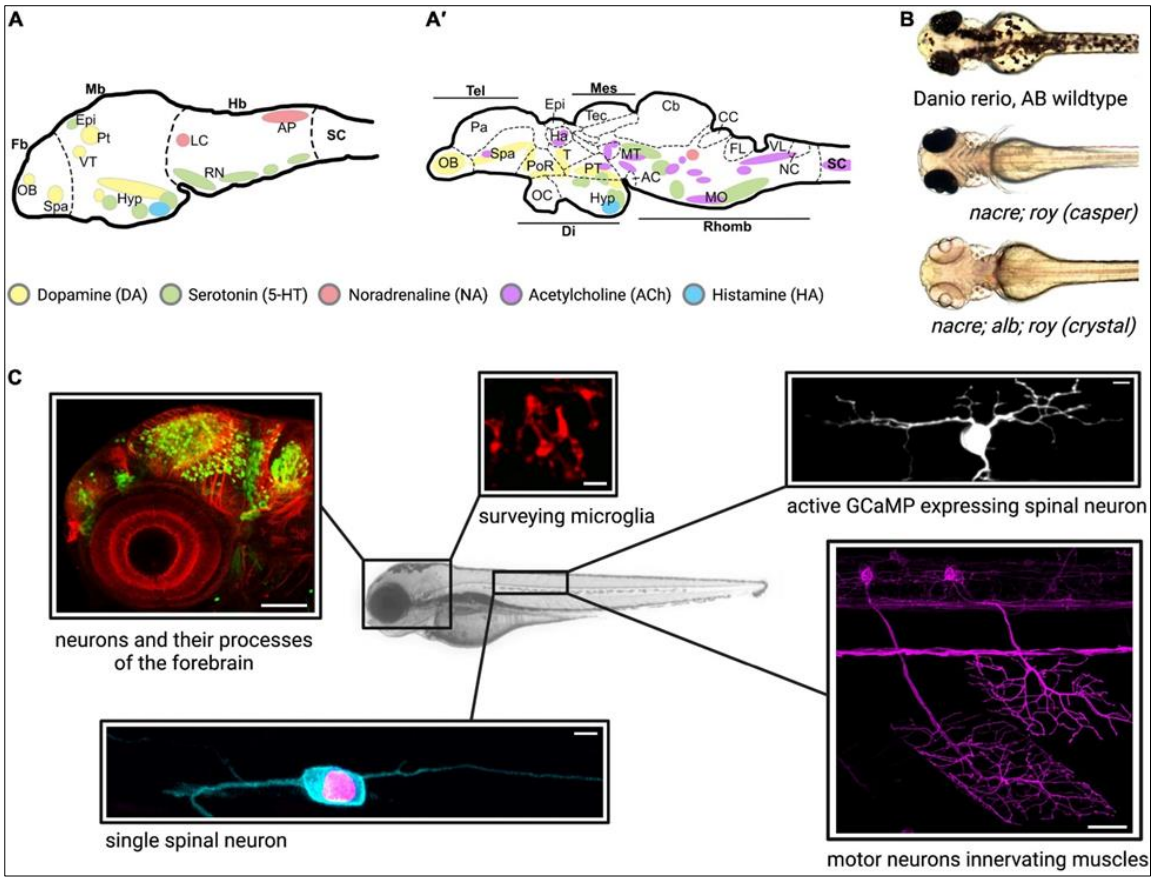

Figure 1 (A, A') Schematic of the monoaminergic regions and temporal lobes in the zebrafish brain. The monoaminergic system of zebrafish is well developed, specific regions of the neuronal regions responsible for different neurotransmitters in the brain: dopamine (yellow), norepinephrine (red), serotonin (green), acetylcholine (green) and Amines group (blue). (A) The brain of zebrafish larvae is developed as early as 3 dpf with high activity in the central nervous system. (A') Schematic side view of an adult zebrafish brain showing the well-defined and complex structure. Schematic and annotations adapted from (A) (Alunni et al., 2017)., 2013) and (B) Wullimann et al. (2011), Parker et al. (2013). AC, crochet; AP, posterior region; Cb, cerebellum; CC, cerebellar crest; Di, diencephalon; Epi, epiphysis; Fb, forebrain; FL, frontal lobe; Oh, undress; Hb, hindbrain; Hyp, hypothalamus; LC, blue dot; Mb, midbrain; Mes, midbrain; MO, medulla oblongata; MT, middle membranes; NC, commissural nucleus; OB, olfactory bulb; area; point, protection; PT, posterior tubercle; rhombic, rhombic cells; RN, raphe nucleus SC, spinal cord; spa, lining; T, room; you, the roof; Wire, telencephalon; VT, ventral thalamus; VL, vagal lobe. (B) Zebrafish are optically clear during the first week of development.

Unhindered in vivo imaging was enabled by creating mutant gene sequences that control cell color production (nacrew2/w2, roya9/a9) as well as melanin production (albb4/b4). The image in (B) was taken and adapted from Antinucci and Hindges (2016) gp. (C) Representative images of neuronal cell types in zebrafish larvae. Neurons and processes in the forebrain [Dlx:GFP (green), tubulin (red) scale bar 100 μm]. Side view of a zebrafish embryo: Monica Folgueira and Steve Wilson, Wellcome Collection, microglia (mpeg: mCherry) scale bar 10 μm, active spinal cord neurons (GCaMP7s) scale bar 5 μm, motor neurons (nefma: Kalt4UAS Scarlett) scale bar 2 μm, only (Chia K, 2022).

3. Neuroendocrinological diseases

It is important to think outside the "box" for experimental modeling of brain dysfunction in Zebrafish (Kalueff A. V., 2008). The hypothalamic-pituitary-adrenal (HPA) axis mediates the endocrine response to stress in humans and animals (Alsop, 2008) under stress, the paraventricular nucleus of the hypothalamus produces corticotropin-releasing factor (CRF), which is transported to the anterior pituitary via the hypothalamus-pituitary portal vasculature (Suzuki, 2009). CRF stimulates the anterior pituitary gland and causes adrenocorticotropic hormone (ACTH) to be released into the bloodstream (Tsigos, 2002) when stimulated by ACTH, the adrenal cortex synthesizes glucocorticoids that regulate the stress response (Dedovic, 2009). A similar protection. The mechanism exists in zebrafish, where the hypothalamic-pituitary-interrenal (HPI) axis is homologous to the HPA axis. According to (Winberg, 1997) cortisol is a mediator of the body's response to stress, zebrafish may be an excellent model for endocrine research (Winberg, 1997) to illustrate the results developed by our laboratory from several experiments that most recently caused severe stress in zebrafish. The consistency of increased cortisol levels following stress is consistent with behavioral data collected in these studies and previous studies (Egan, 2009). Such ability to parallel physiological responses with behavioral phenotypes provides researchers with an important tool for investigating stress-related phenomena. A study investigated the gene expression changes in male zebrafish exposed to two anti-androgenic compounds, cyproterone acetate and vinclozolin, which can disrupt the normal functioning of androgen hormones (Filby, 2010). Investigated the impact of Endocrine disrupting chemicals (EDCs) on the HPA axis in adult zebrafish. They observed changes in stress-related gene expression and behavior following exposure to certain EDCs. The researchers found that early-life exposure to PBDE-47 altered the neuroendocrine system, rendering adult male zebrafish more sensitive to the effects of an estrogenic compound. This study demonstrated how early-life neuroendocrine disruption can have long-lasting consequences on adult endocrine function (Zhang J. C., 2019).

Some synthetic or artificial substances naturally interact with hormone signaling pathways to modulate or block the action of natural hormones. Examples of (EDCs) that interfere with the functioning of the endocrine system, including neuroendocrine diseases, include bisphenol A (BPA), phthalates, pesticides, and pharmaceuticals. They cause changes in hormones and disrupt normal physiological processes, causing abnormal growth and reproduction. (Stolte et al., 2017) used zebrafish embryos to evaluate the effects of endocrine disrupting compounds on thyroid hormone signaling. They found that exposure to certain drugs causes changes in thyroid hormones and disrupts normal growth (Palaniappan, 2018). Some types of endocrine disruption are discussed here using the zebrafish model.

3.1. Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysregulation

The HPA axis is an important neuroendocrine system involved in stress management. Dysregulation of this axis can lead to chronic stress, anxiety, and depression. (Stewart A. M., 2014).

3.2. Thyroid Hormone Disruptions

Thyroid hormones play a vital role in metabolism, development, and growth. (Gholizadeh, 2021). A study was conducted on zebrafish to understand the effects of environmental pollution on neurotransmitter systems and behavior. They proved that exposure to specific pollutants causes changes in neurotransmitters and abnormal behavior. Too much thyroid hormone can cause growth abnormalities and affect metabolism.

3.3. Gonadal Hormone Disruptions

These disruptions affect the production and regulation of sex hormones such as estrogen and testosterone, leading to reproductive and developmental issues. Developmental exposure to low-dose PBDE-47 increases male zebrafish susceptibility to the effects of an estrogen analog in adulthood (Lema, 2007).

3.4. Neurodevelopmental Disorders

Autism Spectrum Disorder (ASD) and *Attention Deficit Hyperactivity Disorder* (ADHD) are neurodevelopmental disorders often linked to exposure to environmental toxins. Zebrafish models have been employed to investigate the effects of chemicals like bisphenol A (BPA) on behavior and neurodevelopment, providing insights into potential mechanisms involved (Kaur, 2019).

3.5. Neurodegenerative Diseases

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the loss of dopaminergic neurons. Zebrafish models have been used to explore the impact of pesticides and other environmental toxins on dopaminergic neurons

and behavior, providing insights into potential links between environmental exposures and PD pathogenesis (Teixeira da Costa, 2020).

3.6. Anxiety and Depression

Exposure to certain environmental chemicals, such as endocrine-disrupting compounds, has been associated with increased anxiety and depressive-like behaviors. Zebrafish models have been utilized to study the effects of these substances on the neuroendocrine system and behavior, offering valuable information on the potential impact of these compounds on mental health (Stewart A. M., 2014).

3.7. Endocrine-related Cancers

Some neuroendocrine disruptors have been linked to an increased risk of endocrine-related cancers, such as breast and prostate cancers. Zebrafish models have been employed to study the effects of these chemicals on the endocrine system and cancer development, contributing to our understanding of the mechanisms involved (Incardona, 2005).

3.8. Neuroendocrine tumors

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms that arise from neuroendocrine cells in various organs. These tumors can disrupt the normal balance of hormones in the body. Zebrafish models have been used to study the development and progression of NETs and to explore potential therapeutic interventions. (Schlueter, 2018).

3.9. Stress-related neuroendocrine disruptions

Chronic stress can dysregulate the neuroendocrine system, leading to alterations in hormone levels, metabolism, and behavior. Zebrafish models have been employed to study the effects of stress on neuroendocrine function and to investigate potential stress-alleviating interventions (Barcellos, 2019).

3.10. Neuroendocrine disruptions in neurodevelopmental disorders

Neuroendocrine disruptions refer to the disturbances in the normal functioning of the neuroendocrine system, which is responsible for regulating hormone production and secretion. These disruptions can have adverse effects on various physiological processes, including development, reproduction, metabolism, and behavior (Panula P. C., 2017). There are several types of neuroendocrine disruptions, and zebrafish models have been used extensively to study these phenomena due to their similarities with humans in terms of genetic, molecular, and physiological aspects such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD), are associated with alterations in neuroendocrine signaling pathways (Colman, 2009). Zebrafish models have been utilized to study the genetic and environmental factors contributing to neuroendocrine disruptions.

4. Depression

Although no attempt has been made to induce depression in zebrafish to date, some attempts have been made to induce bipolar depression in mice. Such a model is based on the administration of one drug followed by another that results in different behavioral effects. (Adam Stewart, 2010). An anxiety-inducing dose of psychostimulant, such as amphetamine or methamphetamine, is used to measure the effectiveness of antimanic treatments such as lithium and valproate. In addition, behavioral disorders caused by repeated use of psychostimulants such as amphetamine, methamphetamine, and cocaine have also been used as a model of bipolar disorder in mice. (Kato, 2007). Since repeated exposure to cocaine can induce an oscillation or cycling in a variety of neurochemical and physiological systems (Antelman, 1998), For example, we say that it is also possible to induce 'bipolar' behavior in zebrafish using cocaine and anti-inflammatory drugs since the Zebrafish models are increasingly used in depression research to explore the behavioral, genetic, and neurobiological aspects of the disease. Many stress-like behaviors can be observed in zebrafish, including the 'new tank test' or 'swim test' to quantify the zebrafish's response to stress and to measure the time of inactivity as a sign of despair. (Barcelos RC, 2019). This represents a decreased interest in fun activities. This behavior can be measured using the 'new tank dive test' or 'new tank test with food' (Stewart AM, 2015). Zebrafish are social animals, and changes in their behavior may indicate a stressful situation. There are tests such as the 'Social Preference Test' (Kyzar EJ, 2017). Researchers can analyze zebrafish activity patterns to study sleep patterns often seen in depressed patients (Mathur P, 2010).

5. Serotonin syndrome

With the rapid increase in clinical use of serotonin reuptake inhibitors (SSRIs), their toxicity has also become an important biomedical problem. Serotonin Syndrome (SS) is an adverse drug reaction characterized by altered mental status, functional impairment, and neuromuscular abnormalities (Adam Stewart, 2010). SS symptoms include restlessness, delirium, coma, mydriasis, sweating, hyperthermia, and tachycardia, changes in blood pressure, tremor, stiffness, myoclonus, and seizures. Although mild pain usually resolves within 24-72 hours (Martin T. G., 1996), SS is particularly difficult to diagnose and can develop rapidly (Boyer, 2005) While SS was modeled in mice (Gingrich, 2001), this was not observed in zebrafish with a positive serotonergic system. Here we show that when trying to model SS in zebrafish, we should choose a behavior (such as anxiety, weakness) and focus on the toxicity of several serotonin compounds together (as it would not be reliable and valid as an agent) to support SS. For example, monoamine oxidase inhibitors combined with SSRIs should induce an SS-like state in zebrafish, similar to the SS-like state induced by these two drugs in mice or humans. Drugs that show promise for this effect include fluoxetine, tranylcypromine, olanzapine, or clomipramine. In line with behavioral abnormalities, endocrine and/or neurochemical (e.g., brain serotonin levels) endo phenotypes can be evaluated more than in fish such as SS.

6. Alzheimer's disease

Aβ is produced by APP, a type I transmembrane glycoprotein. β- and γ-secretases are involved in the cleavage of APPβ to form Aβ peptides, while α- and y-secretases are involved in the formation of P3 peptides from *APPa*. Various Aβ isoforms of varying lengths are produced, particularly the toxic peptides Aβ42 and Aβ40. Oligomers, fibrils, and fibrils formed by Aβ deposition eventually led to the formation of Aβ plaques. Zebrafish Ventricular Microinjection of Aβ42 Induces Aβ Protein Accumulation, Apoptosis, Microglial Activation, and Synaptic Degeneration (Bhattarai P. T., 2017) Islet amyloid polypeptide (IAPP) or Aβ microinjection into zebrafish embryos can produce an AD-like animal model to study amyloidosis (Nery L. R., 2014). This approach provides a serious AD model for future cost-effective neuropathology research and drug screening. Swedish mutant *APP* is known to cause familial AD, and zebrafish have two genes *(APPa* and *APPb)* similar to human APP (Musa, 2001). Although the *APP* gene is evolutionarily conserved in vertebrates, the function of *APPb* is more important than that of *APPa*, because the loss of *APPb* not only impairs motor behavior, motor neuron structure and formation, growth of Mauthner cell activity, but also inhibits the early developmental process in zebrafish cell adhesion (Abramsson, 2013; Banote, 2020) Tg Swedish mutant APP zebrafish with the *APPb* promoter efficiently expresses disease-causing proteins in the brain, heart, eye and vasculature. This model exhibits AD-like behavioral symptoms and brain β-amyloidosis, as well as brain tissue loss and perivascular space development (Pu, 2017). Definitive characterization of gene duplication in zebrafish will pave the way for discovering mechanisms of disease-associated subterranean genes that can be fatal in mammals.

NTF, another important marker of AD, contains hyperphosphorylated tau protein. Tau is a microtubule-associated protein involved in the regulation of microtubule assembly and stability (Uddin, 2020) Hyper phosphorylated tau proteins Appear to produce NTFs that affect microtubule function, microtubule dynamics and axonal transport (Sonawane, 2018) Stable Tg zebrafish models with mutations in the tau-encoding gene *MAPT* (microtubule-associated protein tau), such as Tau-P301L and Tau-A152T, have been established to demonstrate the main features of AD tauopathies. These changes are present in AD patients with frontotemporal dementia. The Tg zebrafish model under the control of the neuron-specific HuC promoter is used to study AD pathogenesis and drug discovery. Gal4/UAS-based human Tau-P301L-Tg zebrafish exhibits tau hyper phosphorylation, aggregation, denaturation, and behavioral defects (Paquet, 2009) Gal4/UAS-based human Tau-A152T-Tg zebrafish, tau phosphorylation High, neurodegeneration, and impaired test work see This type is involved in the elimination of autophagy in Tg. (Lopez, 2017) Zebrafish orthologs of PSEN1 and PSEN2 are *psen1* and *psen2.* Loss of *psen1* in zebrafish leads to loss of histamine neurons, and histaminergic cells are thought to mediate cognition in AD (Sundvik, 2013) *psen1* splicing interference in zebrafish can induce early-onset AD phenotypes, such as cognitive deficit, Aβ42 aggregation and synaptic reduction (Nery L. R., 2017) blocks *psen2* translation, causes defects in central nervous system zebrafish embryonic development, and interferes with Notch signaling (Nornes, 2009) . In addition, the zebrafish genome is edited to resemble the human PSEN2 heterozygous for the K115fos mutation in the brain. Activation of the immune system associated with microglia does not affect histopathology (Hin, 2020). Further evidence of PSEN1 and PSEN2 function in zebrafish is needed to allow the application of this Tg model in drug discovery. Using environmental neurotoxins that cause AD-like progression is a good way to study the etiology of AD. Cholinergic dysfunction and loss of cholinergic neurons have been observed in the brains of AD patients. Thus, one hypothesis for the development of AD is a decrease in the synthesis of the neurotransmitter acetylcholine. Scopolamine, an acetylcholine muscarinic receptor antagonist, has been used to model neurotoxin-induced AD in zebrafish. (Kim Y. H., 2010).

7. Amyotrophic lateral sclerosis

Mutations in *SOD1* (copper/zinc superoxide dismutase 1), *TARDBP* (*TAR* DNA-binding protein 43), *FUS/TLS* (fusion in sarcoma/translocation in liposarcoma), and *C9ORF72* have been identified in ALS patients. *SOD1* is an enzyme that catalyzes the detoxification of superoxide. The *SOD1-G93A* mutation affects zebrafish motor neuron development, axon branching, NMJ integrity, motor neuron survival, and motor function. *SOD1-G93R* mutation shows gradual motor degeneration without muscle denervation in zebrafish (Sakowski, 2012; Morrice, 2018) Good representation of ALS phenotype in zebrafish carrying these two mutations suggests a latent model for further drug screening. TDP43 is a nuclear protein which is associated with protein aggregation of motor neurons in ALS patients and is involved in axonal transport. *TARDBP-A315T* mutation in zebrafish shows motor dysfunction and motor axon abnormality (Morrice, 2018). Knockdown of *TDP43* ortholog tdp-43 in zebrafish not only causes early defects of motor phenotype with NMJ disassembly, but also decreases AChE expression in total fish (Campanari, 2021) (Overexpression of tdp-43 in spinal motor neurons halts axonal outgrowth coupled with protein *TDP-43* cytoplasmic mis-localization instead of aggregation (Asakawa, 2020) *FUS/TLS* gene encodes sarcoma fusion protein, which is responsible for RNA-binding. A truncated mutation of FUS-R495X in zebrafish leads to cytoplasmic protein accumulation in motor neurons as well as oxidative stress (Bosco, 2010). Deletion of the *FUS* ortholog in a zebrafish model results in key features of ALS pathophysiology, including functional impairment, shortened motor neuron length, and NMJ fragmentation. The *C9ORF72* gene has an intronic hexanucleotide repeat (GGGGCC) expansion that leads to the synthesis of the DPR (dipeptide repeat) protein, which causes neuronal damage (Kramer, 2018). Shaw *et al.* generated two zebrafish lines expressing *C9orf72* hexanucleotide repeat expansion were generated and their ALS-like symptoms were confirmed. Zebrafish from another group that stably expressed 100 Gly-Arg repeats associated with *C9orf72* in motoneurons also showed reduced motoneuron length and buoyancy (Swaminathan, 2018).

Environmental factors such as β-N-methylamino-l-alanine (BMAA) and bisphenol A (BPA) have been demonstrated to be involved in ALS etiology (Gois, 2020) BPA is an industrial plasticizer which is thought to be a potential trigger in ALS pathogenesis. It can cause motor neuron degeneration, affect locomotor activity, reduce neuromuscular junction (NMJ) integrity and motor neuron-specific cell death in zebrafish embryos (Morrice, 2018) BMAA is a non-proteinogenic neurotoxic amino acid produced by cyanobacteria. Zebrafish show neurodegeneration symptoms when exposed to BMAA, including neural development disruption and learning and memory ability deficiency (Chiu, 2011; Wang, 2020) The mixture of cyanotoxins, BMAA and microcystin leucine and arginine (MCLR), cause severe neurotoxicity and upregulation of TDP-43 in zebrafish than individual toxins (Martin R. M., 2021) together, this suggesting a link between cyanotoxins and ALS. Furthermore, the combined effects of ALS causative genes and environmental factors have also been investigated in ALS zebrafish models. Exposure to BPMM changes the motor neuron growth characteristics in zebrafish with G93R-SOD1 mutation (Sher, 2017) However, neurotoxin-induced ALS-like models are used less than Tg models in drug discovery.

8. Parkinson's disease

Although neurotoxicity models have the potential to identify beneficial effects for drug development, modeling the molecular pathogenesis of PD is challenging. A family study found more than 20 genetic risk factors linked to PH (Blauwendraat, 2020) In recent years, genome-wide association studies (GWAS) have also identified 90 independent risk variants which contribute to sporadic PD (Blauwendraat, 2020) The easiest way to study loss of transfection in zebrafish is to inject antisense morpholino oligonucleotides. Subsequently, genetically derived Tg and viral zebrafish models have been widely used to study PD pathology and assess therapeutic potential.

SNCA (encoding the α-syn required for LB) was the first gene found to be associated with familial PD. Although zebrafish do not express α-syn orthologs, they do express β-, γ1- and γ2-synuclein, and γ1-synuclein has similar functions to α-syn. Knockdown of β- and γ1-synucleins leads to abnormal development of dopaminergic neurons and decreased DA levels, amplifying the human α-syn expression phenotype in zebrafish. (Milanese, 2012). Along with the neurotoxic model, a recent study showed that human α-syn deficiency increases cytoplasmic peroxide flux and oxidative stress, leading to abnormalities that have previously led to neuronal loss (Kang, 2018; Van Laar, 2020) α-syn remains an attractive target for disease modification in PD. However, all current zebrafish PD models can develop a dopaminergic cell loss phenotype and none of the resulting LB formation. Mutations in the leucine-rich repeat kinase 2 *(LRRK2)* gene are associated with familial and sporadic cases of PD, and the most common is the *LRRK2-G2019S* mutation (Blauwendraat, 2020) Zebrafish display a homologue of the human *LRRK2* gene. All functions. Disruption of *LRRK2* in zebrafish leads to developmental abnormalities and neuronal damage (Prabhudesai, 2016). However, studies have not shown consistent results regarding the effect of removing the WD40 domain of *LRRK2*. (Sheng, 2010; Ren, 2011) To

date, no zebrafish model has been generated to elucidate the effects of increased kinase activity of *LRRK2* which is highly relevant to PD etiology.

Parkin is an E3 ubiquitous ligase encoded by the *PARK2* gene. It mediates the ubiquitination of many proteins, including α-syn, and promotes proteasome-dependent degradation and mitophagy. Therefore, parkin plays an important role in the removal of damaged and misfolded proteins. Decreased parkin activity in zebrafish leads to a reduction in the number of dopaminergic neurons, and parkin-knockdown zebrafish embryos show degradation of the mitochondrial respiratory chain complex1. (Flinn, 2013; Fett, 2010) Furthermore, increased expression of parkin protected zebrafish from cell death (Fett, 2010) DJ-1 (encoded by *PARK7*) Appears to have diverse roles in protecting neurons from oxidative stress, and loss of this protein may rarely lead to early PD formation. Knockdown of DJ-1 using antisense morpholino oligonucleotides in zebrafish embryos does not reduce the number of dopaminergic neurons but increases the sensitivity of dopaminergic neurons to H2O2 (Bretaud, 2007) Loss of *DJ-1* in mice does not reduce dopaminergic neuron counts and motor function; however, *PARK7* knockout in zebrafish results in a strong PD phenotype (Edson, 2019) *PINK1* is another mitochondrial-associated gene associated with early-onset PD. Like *PARK7*, deactivation of *PINK*1 alone leads to a reduction in dopaminergic neurons in zebrafish, and when combined with other PH risk factors, it can reach model PH pathology (Zhang Y. L., 2017) A fish line with an early mutation (Y431*) in the Pink1 kinase domain that causes mitochondrial dysfunction and loss of dopaminergic neurons has also been identified (Flinn, 2013) The zebrafish Tg model is the most closely related genes. Dysfunction of the PARLA gene mainly reduces dopaminergic neurons in the olfactory eye (Merhi, 2021) VPS41 knockout causes lysosomal abnormalities with microglial and cerebellar dysfunction Motor deficiencies caused by exit defects (Yu S.-H. W., 2021). Zebrafish Tg models tend to be an effective tool to classify PD into different subtypes according to different pathogenic factors.

Table 1 Overview of zebrafish model compared to human disease condition

Diseases	**Human**	**Zebrafish**
Alzheimer's Disease	Neuronal death cognitive deficits	Neuronal cell death N cognitive test assays
	Increase numbers of activated microglia	Increase numbers of activated microglia
	Tau hyperphosphorylation and NFT formation	Hyperphosphorylation and aggregation of transgenic human tau only in the spinal cord
	Aβ plaques	Plaques formation of injected human Aβ
Parkinson's Disease	Death of Dopaminergic neurons	Death of Dopaminergic neurons
	α- synuclein accumulation in Lewy Bodies	Aggregation of transgenic human α- synuclein
	Increased numbers of activated microglia	Increased numbers of activated microglia
	Locomotor dysfunctions	Swimming deficits
Huntington's Disease	Neuronal death in stratum and cortex	Neuronal cell death in brain regions ortholog to the striatum
	Misfolded and aggregated huntingtin -polyQ expansions	Aggregation of transgenic human mHTT
	Increased numbers of activated microglia	Not investigated
	Progressive movement disorder	Inability to swim
Amyotrophic Lateral Sclerosis	Motor neuron axonopathy loss, cell death	Motor neuron axonopathy loss, cell death
	TDP-43 aggregation	Aggregation of transgenic human TDP-43
	Increased numbers of activated microglia	Increased numbers of activated microglia
	Muscle atrophy and progressive locomotor deficiencies	Reduced swim distance, duration and velocity

9. Huntington's disease

Huntington's disease (HD) is a monogenic neurodegenerative disease caused by a mutation encoding an abnormal trinucleotide on the hunting protein (HTT) that causes expansion of glutamine (CAG) (Walker, 2007). HTT deficiency in zebrafish leads to various developmental defects and disruption of iron homeostasis (Lumsden, 2007) to determine the physiological function of HTT, several research groups investigated the effects of HTT depletion on zebrafish early development. The zebrafish homologue of human HTT encodes a 3,121 amino acid protein that shares 70% identity with mammalian HTT, but contains only four glutamines, compared to seven glutamines in mice and up to 35 in humans (Karlovich, 1998). Zebrafish embryos exhibit extensive polyglutamine repeats leading to a variety of pathologies, including premature cell death and neurodegeneration. Overexpression of the C-terminal Hsp70 interacting protein (CHIP) can prevent the accumulation and toxicity of HTT fragments (Nieznanska H., 2018) The zebrafish HD model has also been used to study molecular chaperones that protect against prion aggregation and toxicity (Schiffer, 2007) As in humans, HTT is ubiquitous in the zebrafish brain and is important for the formation of telencephalic progenitors and pro-placode cells (Lumsden, 2007; Henshall, 2009) The zebrafish telencephalon is considered the mammalian equivalent (Rink E, 2002). In addition, tissue loss from plate, including olfactory and lateral sensory neurons in zebrafish, is consistent with clinical observations of developmental anosmia in humans. (Mitchell, 2005) We hope the HD zebrafish model will be very good for our understanding of the disease and to contribute to the development of new drug research for HD.

10. Dementia

We focus on two familial forms of dementia: Alzheimer's disease (AD) and frontotemporal lobe degeneration (*FTLD*). For familial AD, mutations have been identified in three genes: amyloid precursor protein (*APP*), *presenilin* 1 (*PSEN1*) and *presenilin 2* (*PSEN2*). More importantly, orthologs of AD family-related genes have been identified in zebrafish (Amores A, 1998; Nornes S, 2003). The transcript for psen1 is expressed by the mother, while the transcript for *psen2* is expressed post-transplantation in zygotes. There is compelling evidence that *presenilin* interacts with the Notch signaling pathway, which is also found in zebrafish. Recent studies have shown a direct link between early development and late life neurodegeneration, because both Notch and APP are substrates of *presenilin.* All molecular components that process APP are conserved in zebrafish, allowing research to explore the in vivo function and regulation of *presenilin* (Rob Willemsen, 2011). In fact, the MO strategy was used to study the zebrafish *presenilin* function. Zebrafish embryos microinjected with MO to inhibit *Psen1* mRNA translation showed defects in somite formation (Amores A, 1998). Similar problems were observed in Psen1 knockout mice. Elucidating the molecular mechanisms underlying the processing of *presenilin* substrates such as the membrane proteins Notch and APP will provide insight into signal transduction pathways. Another idea is to create a transgenic zebrafish that expresses one of the genes with the AD mutation. More importantly, these transgenic fish must survive and have an adult-like phenotype. The first step to examine the effect of mutant human APP expression on AD development was achieved by breeding transgenic zebrafish that express EGFP as a control element of the zebrafish application gene (Lee JA, 2007). EGFP expression was found in the lower regions of the brain and spinal cord. Expression in the brain begins in the first days of development and increases in intensity after development. Strikingly, EGFP expression is also present in the developing and adult vasculature. Of course, the next step is to use this vector to clone PCR products containing mutant human APP (Rob Willemsen, 2011). Expression of mutant human APP can induce Aβ plaque formation depending on the early expression level. Additionally, in this way, the effects of environmental toxicants and natural and synthetic products on AD susceptibility and development can be evaluated in a high-throughput manner by exposure to compounds at the embryonic stage or later. Additionally, FTLD-related genes have been found in zebrafish. It is unclear how mutations in the gene encoding microtubule-associated tau (MAPT) are associated with neuronal and glial tau pathology.

11. Prion diseases

They are characterized by the accumulation of the harmful form of the toxic prion protein *(PrP).* In addition, evidence suggests that *PrP* may be responsible for protein aggregation and play an important role in the pathogenesis of other neurodegenerative diseases (Watts JC, 2018). Using the zebrafish genetic model, the researchers found that APP can regulate neuronal activation through its interaction with the prion protein (Richard Kanyo, 2020) Long Aβ oligomers or fibrils can also bind directly to *PrP* to maintain synapses (Um JW, 2012). Inhibition of attachment inhibits sleep induction in zebrafish, leading to light exposure leading to AD development (Özcan GG, 2020). Taken together, *PrP* proteins could be a drug target for the treatment of prion disease and other neurodegenerative diseases. (Nelson PT, 2008) The zebrafish model has many advantages for prion disease research, such as its rapid development, transparency of initial stages, and ease of genetic control. Zebrafish can express prion proteins *(PrP)* from other species such as humans and can be used to study the toxic effects of misfolded prion proteins. Researchers can introduce

mutations or diseases associated with *PrPs* into zebrafish to study their effects on neurodevelopment and function (Scheckel C., 2018) By misexpressing *PrP* in certain tissues or at different stages of development, researchers can observe how the disease develops and affects the nervous system (Kovač V, 2022). Zebrafish models enable rapid and cost-effective drug screening. Researchers can analyze many compounds to identify drug candidates that can alter prion protein aggregation or improve symptoms of the disease (Nieznanska H., 2018). The transparency of zebrafish embryos enables real-time imaging of neurodegenerative processes. This feature allows researchers to see how prion proteins affect the brain and monitor disease development (Pollock NM, 2021) Zebrafish embryos are amenable to genetic manipulation, such as knocking out or destroying certain genes involved in prion disease pathogenesis. This helps scientists understand the role of many genes in the development of the disease. They exhibit complex behaviors, including social and academic. Researchers can use the zebrafish model to study how prion disease affects behavior and cognition.

12. Schizophrenia

Experimental approaches to model schizophrenia in animals include dopamine agonist-mediated hyperactivity and measurement of responses to antipsychotic dopaminergic antagonists, including dopamine metabolites, dihydroxyphenyl acetic acid and homovanillic acid (in the cerebrospinal cord of human patients). We suggest that administration of the same antipsychotics (such as haloperidol, clozapine, risperidone, and olanzapine) used in rats can produce similar responses in zebrafish (Adam Stewart, 2010). Clearly, more zebrafish models for schizophrenia are needed. The only current model to date has been successfully developed using sensory processing by Burgess and Granato; it has been shown in this model that anti-inflammatory drugs can inhibit the dopamine agonist-induced effects of zebrafish PPI (Burgess & Granato, 2007) The number of genes involved in zebrafish, including Disc1, provides new insights into the function of these genes. (De Rienzo, 2011) demonstrated that disc1 has an important role in both canonical (β-catenin-mediated) and non-canonical *Wnt* signaling during embryonic development.

Other examples including the link between Akt signaling, dopaminergic neurotransmission and schizophrenia have been examined. (Cheng, 2013) used zebrafish to study rgs4, a regulator of the G protein signaling family, which is expressed in the developing brain. Loss of gene function results in poor neurite outgrowth as well as reduced motor performance in the hindbrain and spinal cord. Activation of Akt signaling rescues the developmental phenotype in the spinal cord but not the hindbrain, suggesting that Akt signaling is required for some RGS4-mediated axon formation (Cheng, 2013; Souza, 2011) Neurotransmission in the developing brain. Since changes in Akt signaling are also associated with schizophrenia, this supports the idea that changes in dopaminergic signaling during development may be at the root of the disease. Other human genetic diseases have also been studied. Knockdown of the synaptically expressed schizophrenia susceptibility gene kinesin 17 (kif17) causes severe phenotypes in zebrafish embryos, including growth retardation and the curled tail phenotype; this indicates that kif17 is active during embryonic development (Tarabeux, 2010 MKDA receptor) triggered many behavioral changes such as schizophrenia-like (Tarabeux, 2010) Finally, treatment of zebrafish with the NMDA receptor antagonist MK-801 causes several behavioral alterations including changes to social interaction, hyperactivity, and amnesia, which have been interpreted as being schizophreniform (schizophrenia-like (Chen M. M., 2009; Seibt, 2011) social changes, hyperactivity and amnesia, and similar behavioral changes from psychopathies in rodents.

13. Autism spectrum disorder

Many of the behavioral abnormalities associated with autism spectrum disorders (ASD) are difficult to model in animals. However, previous experiments have shown that it is possible to model social imbalances and developmental and cellular deficiencies that affect such symptoms in zebrafish. For example, zebrafish homologues of ASD-related genes such as *neurexins, reelin, mecp2*, and *Meet* have been identified and experiments have been developed to assess the association (Colman, 2009). Thus, like mice, zebrafish will also lead to new experiments and genetic models related to the autism spectrum due to the ease of genetic control. ASD-related genes include the fragile X gene *FRAGILE X* mental disorder 1 (*FMR1*), the *GABAA β3* subunit gene *GABRB3* and *SHANK3, TSC1*, *NEUROLIGIN3* and *NEUROLIGIN4*, *PTEN* and *CNTNAP2* (Cook, 2008; Geschwind D. H., 2008; Lord C. E., 2010) The neurobiology of autism spectrum disorder is unknown, but it may be related to the brain's need to control behavior and language. For example, changing the connection between the frontal lobe (orbitofrontal cortex) and the frontal cortex (including the frontal lobe and frontal lobe) may improve some symptoms of the disease (Geschwind D. H., 2011). Other important brain regions include the cerebellum, brainstem, and limbic region, as well as the hippocampus, amygdala, septal nucleus, and anterior cingulate cortex (Lord C. C., 2000). Finally, autism has also been associated with megalencephaly, an increase in patients' total brain size. In one study, (Golzio, 2012) identified 24 genes involved in this *CNV* and one gene *KCDT13* was identified as the most likely cause of the disease. This study demonstrates how zebrafish can be used to identify genes that cause

variation in large genomic regions. (Gauthier, 2010) used morpholinos to knockdown *SHANK3*, a gene associated with schizophrenia and ASD, in human patients. *SHANK3* mutant zebrafish exhibit reduced swimming activity after being touched; this is a phenotype that can be rescued by wild-type (but not mutant) expression of the gene. Thus, this study confirms that mutations in *SHANK3* are important for controlling behavior associated with both schizophrenia and autism spectrum disorders.

14. Epilepsy

It has a pathological mechanism that is poorly understood and is a complex brain disorder with many fundamental causes (Galanopoulou. et al. 2012). Zebrafish have lots of brains, good manners, and are prone to seizures. Adult zebrafish have many learnable behaviors, making them unique for modelling. Pentilentetrazolium (PTZ)-induced seizures in zebrafish were used to study the seizure mechanism. Endurance in larval and adult zebrafish is also useful and allows ontogenesis to examine many epilepsy-related events. Today, various genetic modifications are used to study behavior and brain functions related to epilepsy. Zebrafish (~5–7 dpf) are typically placed in multiple wells and monitored using video surveillance software and recorded continuously by a video camera. Mutations in two families, the potassium voltage-gated channel subfamily Q member 2 (KCNQ2) and the potassium voltage-gated channel subfamily Q member 3 (KCNQ3), are associated with neonatal diabetes such as seizures. For example, benign familial neonatal epilepsy. This gene is highly expressed in zebrafish and supports the use of vertebrate models for epilepsy studies (Desmond, et al., 2012).

15. Psychosis

Psychosis manifests as disturbances in cognition, affect, motor function, and social functioning (American Psychiatric Association, 2013) and is often accompanied by alternative glutamate signaling (Merritt K, 2013). The glutamate NMDA receptor antagonists phencyclidine and ketamine produce psychotic symptoms in healthy volunteers and ameliorate positive, negative and cognitive symptoms in schizophrenia (Merritt K, 2013) MK-801 is a potent NMDA antagonist for schizophrenia in mice, zebrafish and other animals. Similarly, pre-stimulus inhibition (PPI) is the reduction of the initial response, that is, a weak response preceded by a negative stimulus (Moghaddam B, 2003). Likewise, pre-pulse inhibition (PPI) is the attenuation of startle response, when a weak non-startling response is presented before the startling stimulus (Swerdlow NR, 2001). Patients with schizophrenia show a negative PPI that can be salvaged by antipsychotics (Geyer MA, 2001). PPI reproduces reliably in zebrafish larvae with currently available genetic mutants with reduced PPI. Overall, the similarities in zebrafish neural pathways and innate responses suggest that they are useful as an unbiased platform for the discovery of gene regulators and drugs for the treatment of diabetes mellitus (Kanza M Khan, 2017).

16. Sleep disorders

Although zebrafish do not sleep like humans, they show reduced activity and relaxation time that can be used as a model to study sleep and illness. The zebrafish model has been used to study insomnia (Yokogawa, 2007) using zebrafish mutants to identify a gene called period 2, which is involved in the regulation of sleep and wakefulness in zebrafish, similar to its role in animals. (Zhang Y. L., 2017) This study shows that interruption of the time 2 gene causes insomnia-like behaviors in zebrafish (Zhdanova, 2001) induced sleep apnea-like conditions in zebrafish by exposing them to intermittent hypoxia, which resulted in disrupted sleep patterns and behavioral changes associated with sleep deprivation.

17. Addiction

A recent analysis of genetic alterations following acute or chronic exposure to drugs of abuse (Kily LJ, 2008) has identified genetic effects on drug addicts. For example, long-term treatment of zebrafish with ethanol and nicotine alters the expression of several CNS genes, some of which have been identified as components of the mammalian system (Kily LJ, 2008). Further evidence also suggests the sensitivity of zebrafish to drug withdrawal, which is the cornerstone of addictive behavior (Cachat, 2009). Additional evidence also suggests that zebrafish are vulnerable to drug withdrawal, which is the basis of behavior (Gerlai, 2009), while cocaine withdrawal evokes marked alterations in their locomotion (Lopez-Patino, 2008; Lopez Patino, 2008) Our laboratory has demonstrated that withdrawal also modulates zebrafish cortisol levels, implicating their cortisol abnormalities as a phenotype (Cachat, 2009) consistent with glucocorticoid dysregulations in human and rodent withdrawal syndrome (Borlikova, 2006; Keedwell, 2001; Lovallo, 2006) Substance use disorder (SUD) is a complex problem that involves the use of substances such as alcohol, drugs, or drugs, despite its negative consequences. Zebrafish models have been used to study many aspects of SUD, including addictive behaviors,

neural mechanisms, and the effects of drugs on the brain (et.al, 2011) Examination of the effects of ethanol using zebrafish (Steenbergen, 2011) demonstrates that acute ethanol exposure induces anxiolytic-like behavior in zebrafish, demonstrating the potential of the zebrafish model to study the effects of drugs on anxiety-related behavior. (Huang DQ, 2023) Demonstrated zebrafish as model used to examine phenotypes associated with drug use, including behavioral response to drugs, withdrawal, and drug-seeking behavior. (Stewart A. W., 2011) (Dar et al. 2012) demonstrated the ability of zebrafish to discriminate nicotine and investigate the underlying neurochemical mechanisms. drugs like Psychostimulants (e.g., Cocaine, Amphetamines). (Darland T, 2001). employed a zebrafish model to screen for cocaine sensitivity and identified mutant zebrafish lines with altered responses to cocaine, providing insights into the genetic factors underlying cocaine sensitivity. (et.al, 2011) evaluated the locomotor activity induced by cocaine and amphetamines. (Bencan Z, 2009) examined the effects of anxiolytic drugs such as Opioids (e.g., Morphine) on zebrafish using a light-dark box paradigm. The findings that zebrafish exhibited was anxiety-like behavior, Now Zebrafish models have been employed to assess the effects of opioids on behavior, withdrawal, and potential therapeutic interventions.

18. LPS response and sickness behavior

It is an animal syndrome involving cytokine-mediated disease behavior, reduced locomotor activity, inhibition of exploration of its body and social environment, reduced food and water intake, and poor learning and memory (Dantzer, 2001). Notably, zebrafish possess a wide array of cytokines, similar to humans and mice (Lieschke, 2001). Based on current knowledge that lipopolysaccharide (LPS) can induce disease-like behavior in zebrafish by inducing prionflammatory cytokines (Henry, 2008), exposure to LPS may be a model for disease behavior in zebrafish. The inflammatory response is initiated by the uptake of pathogens and their products by immune system cells, and cytokines and/or chemokines (such as TNF-α, IL-1), IL-6 and IL. -8 (Decker, 2004). While affective pathogenesis is attributed to various exogenous stressors (Nutt, 2000; Nemeroff, 2007), recent studies have directly linked affective disorders with various cytokines (Asberg, 2009; Hoge, 2009).Thus, induction of cytokine responses by LPS in zebrafish may be a good model of cytokine-mediated behavioral syndromes.

19. Fetal alcohol spectrum disorders (FASD)

Fetal Alcohol Spectrum Disorder (FASD) refers to a developmental and behavioral abnormality caused by prenatal alcohol exposure. These diseases can cause cognitive, physical, and mental disorders. The zebrafish (Danio rerio) has become a useful animal model for studying FASD due to its genetic similarity to humans and its ability to mimic certain aspects of alcohol consumption due to developmental delays. (Bilotta J, 2002) demonstrated the effects of ethanol exposure during embryonic development on visual function in zebrafish, providing insight into the effects of alcohol on brain development. Differences in the developmental response of zebrafish to ethanol exposure reveal the importance of genetics in susceptibility to FASD (Loucks E C. M., 2004) Persistent microphthalmia (small eyes) after ethanol exposure during the retinal neurogenesis mechanism of FASD-related visual deficits in zebrafish embryos. Long-term embryonic alcohol exposure, the effects of survival on coordination learning in adult zebrafish provide behavioral evidence for FASD—about mystery (Kashyap B, 2007). The long-term effects of embryonic alcohol exposure on associative learning performance in adult zebrafish, offering valuable behavioral insights into FASD-related cognitive impairments (Fernandes Y, 2014).A study investigating the role of Sonic Hedgehog *(Shh)* signaling in the development of axial defects induced by ethanol exposure in zebrafish provides insight into the molecular mechanisms underlying FASD-related deformities (Loucks E A. S., 2009).

19.1. Neurospinal diseases

The zebrafish (*Danio rerio)* is a useful animal model for studying many neurospinal diseases due to its genetic similarity to humans, rapid development and transparent embryo. The following are some neurospinal diseases that have been investigated using zebrafish models, for example:

19.2. Spinal Muscular Atrophy (SMA)

Zebrafish models help to understand the pathophysiology of SMA, a disease that has been tested with muscle weakness and atrophy illness. Zebrafish carrying mutations in the smn1 gene, homologous to the human SMN1 gene, exhibit motor neuron deficiencies similar to those seen in SMA patients ((Martinez-Carrera, 2015).

19.3. Amyotrophic Lateral Sclerosis (ALS)

Zebrafish models have provided insights into the mechanisms underlying ALS, a neurodegenerative disease affecting motor neurons. By expressing mutant forms of ALS-associated genes, such as *SOD1* or *TDP-43,* in zebrafish, researchers have observed motor neuron degeneration and functional deficits. (Babin PJ, 2014; Kabashi E, 2008) .

19.4. Spinal Cord Injury (SCI)

The zebrafish model has been used to examine ability recovery after SCI. They have the ability to regenerate spinal tissue and regenerate the body. Examining the genetic and cellular mechanisms of spinal cord regeneration in zebrafish will provide insight into developing strategies for human spinal cord injury (Michael Cronin, 2008)

19.5. Neurofibromatosis Type 1 (NF1)

A zebrafish model contributes to our understanding of NF1, a condition caused by the growth of tumors in the brain. The researchers examined the effect on neuronal development as well as tumor formation and growth by altering the nf1 gene in zebrafish (Jennifer Yen, 2014).

19.6. Spinal Muscular Dystrophy (SMD)

Zebrafish models have been used to study spinal muscular dystrophy, a group of genetic diseases that cause muscle weakness and wasting. By disrupting genes associated with muscle function in zebrafish, such as dystrophin or lamin A/C, the researchers reproduced the muscle degeneration seen in human patients (Thomas Pietri, 2013).

20. Cerebrospinal diseases

Cerebrospinal fluid disorders are diseases or conditions that affect the cerebrospinal fluid (CSF), the fluid that surrounds the brain and spinal cord. These diseases can cause abnormalities in the production, circulation, or absorption of cerebrospinal fluid and cause a variety of neurological symptoms. The zebrafish (Danio rerio) is a useful model for studying brain and spinal cord diseases due to its genetically easy domestication, transparent embryo and physical resemblance to humans. Here are some examples of cerebrospinal fluid and how zebrafish are used in research:

20.1. Hydrocephalus

Hydrocephalus is a condition characterized by an excessive accumulation of CSF within the ventricles of the brain. It can lead to increased intracranial pressure and neurological dysfunction. Zebrafish have been used to study the genetic and molecular mechanisms underlying hydrocephalus. For example, researchers have identified mutations in genes such as *L1cam* and *mpdz* that result in hydrocephalus-like phenotypes in zebrafish embryos ((Weinstein, 2017).

20.2. Chiari malformation

Chiari malformation is a structural defect in which the cerebellum extends into the spinal canal, causing compression of the brainstem and spinal cord. Zebrafish have been used to study the developmental processes and genetic factors associated with Chiari malformation. By using gene editing techniques such as CRISPR/Cas9, researchers have successfully induced Chiari-like phenotypes in zebrafish embryos by disrupting genes involved in the development of the hindbrain and spinal cord (Fisher, 2019).

20.3. Spinal muscular atrophy (SMA)

SMA is a genetic neuromuscular disorder characterized by the loss of motor neurons in the spinal cord, leading to muscle weakness and atrophy. Zebrafish have been instrumental in understanding the molecular mechanisms underlying SMA and in testing potential therapies. Zebrafish models of SMA have been generated by introducing mutations in the survival motor neuron (*smn1*) gene, which is also associated with human SMA. These models have helped elucidate the role of *smn1* in motor neuron development and have facilitated the screening of small molecules and genetic modifiers that rescue the SMA phenotype (Kariyawasam, 2019).

21. Congenital scoliosis (cs)

CS is usually caused by defects in vertebral development. Despite the difference in spinal formation and segmentation between humans and zebrafish, zebrafish can still be used to model the characteristics of CS, such as severe vertebral defects with fusion and disorganized neural and vascular arches Congenital scoliosis (CS) is a condition characterized by abnormal curvature of the spine present at birth due to vertebral malformation or fusion. Zebrafish models have been used to study CS and have provided valuable insights into the molecular and genetic mechanisms underlying this condition.

21.1. pipetail (ppt) mutant zebrafish

The ppt mutant zebrafish is a well-established model for studying CS. It exhibits a curved tail phenotype due to defects in somite segmentation and subsequent vertebral malformation. The mutation affects the *deltaC* gene, a Notch pathway component involved in somite patterning. The *ppt* mutant zebrafish has been extensively studied to understand the molecular mechanisms leading to CS (Catherine Haddon, 1998).

21.2. lft1 (lefty1) mutant zebrafish

The lft1 mutant zebrafish is another model used to study CS. The mutation disrupts the *lefty1* gene, an inhibitor of the Nodal signaling pathway. This disruption leads to abnormalities in somite development, resulting in scoliotic phenotypes. The *lft1* mutant zebrafish has provided insights into the role of Nodal signaling in vertebral column formation (E. Topczewska-Lach, 2005).

21.3. setd5 (SET domain-containing 5) mutant zebrafish

Mutations in the human *SETD5* gene have been associated with intellectual disability and CS. The zebrafish model with a mutation in the zebrafish homolog of *SETD5* exhibits spinal deformities resembling CS. This model has been instrumental in understanding the role of *SETD5* in spinal development and the molecular mechanisms underlying CS associated with *SETD5* mutations. (Voigt AP, 2019).

21.4. tbx6 (T-box 6) mutant zebrafish

The tbx6 mutant zebrafish model displays scoliotic phenotypes due to defects in somite formation and segmentation. The tbx6 gene is essential for somite development and patterning. Mutations in tbx6 have been associated with vertebral malformations and CS in humans. The zebrafish model has contributed to elucidating the role of tbx6 in spinal development and understanding the etiology of CS (Whitfield TT, 1996).

22. Cerebral amyloid angiopathy

Cerebral amyloid angiopathy (CAA) is a neurological disease caused by the deposition of amyloid-beta (Aβ) protein in the walls of small blood vessels in the brain. These conditions can cause blood vessel damage, insufficient blood flow, and in some cases, bleeding in the brain. CAA is often associated with Alzheimer's disease and other neurodegenerative diseases. The zebrafish (*Danio rerio*) has become a valuable animal model for studying many neurological diseases, allowing researchers to observe pathological changes. The CAA zebrafish model has been used to understand disease mechanisms and to test therapeutic interventions. (Paquet D S. B., 2004) investigates the role of lipid rafts in the amyloidogenic processing of amyloid beta precursor protein APP) in zebrafish, providing insights into the mechanisms of Aβ accumulation. (Bolduc DM, 2016) provided insight into the mechanism of Aβ accumulation by investigating the role of lipid rafts in the amyloidogenic process of amyloid-β precursor protein (APP) in zebrafish. (Lee Y, 2017) demonstrated the visualization of adult neural stem cells in the zebrafish brain and their response to injury, which is important for understanding the potential of CAA to affect the brain (Davis JM, 2017) not only focuses on CAA, but also provides an overview of zebrafish models of neurodegenerative diseases, including Alzheimer's disease, and how they contribute to our understanding of this disease. During a study of hydrocephalus in mice, he cites the role of LRP1 (low-density lipoprotein receptor-associated protein1) in brain development and vascular integrity, which is essential for CAA research (D'Amico L, 2010).

23. Cerebral ischemia

Cerebral ischemia, commonly known as a stroke, occurs when blood flow to the brain is cut off, resulting in a lack of oxygen and nutrients. This can lead to brain damage and is associated with dementia (Lovatt, 2017) discusses methods for inducing focal cerebral ischemia in zebrafish and how to assess neuronal damage and functional recovery following stroke. Researchers explored the use of zebrafish as a model for studying the role of autophagy (a cellular recycling process) in ischemic stroke. Zebrafish can be utilized to investigate the molecular mechanisms and potential therapeutic targets related to autophagy in stroke (Yu L. &., 2018). Zebrafish have been used to study the role of mitochondria in brain development and morphogenesis, which may provide insight into the processes involved during brain ischemia (Zea Restrepo, 2019).

24. Balance and coordination

Zebrafish have proven useful in the study of many human diseases, including those that affect balance and coordination. Explicit models of ataxia help elucidate gene function and mechanisms that cause neuronal damage. In the future, the application of gene therapy techniques will help to establish a true model of zebrafish dominant ataxia (Quelle-Regaldie A, 2021). Here are a few examples of zebrafish models used in the study of balance and coordination disorders:

24.1. Episodic ataxia 1

Episodic ataxia 1 is caused by vision loss, nonsense, and a junctional mutation in the *KCNA1* gene, resulting in potassium deficiency. Transient ataxia and sometimes seizures are symptoms of this problem (Rajakulendran S., 2007).

24.2. Ataxia Telangiectasia (A-T)

A zebrafish model was used to investigate the molecular and cellular mechanisms of A-T, a neurodegenerative disease characterized by impaired coordination and coordination. Zebrafish mutants with homologs of A-T-related genes were created, allowing researchers to study neurological diseases (Kabiraj, 2017).

24.3. Cerebellar Ataxia

Cerebellar ataxias refer to a group of problems affecting the cerebellum, causing coordination and balance problems. Zebrafish models contribute to understanding the genetic basis and neurodevelopmental processes of various cerebellar ataxias. By selectively knocking down certain genes, researchers discovered new genes and pathways involved in cerebellar development and function (Hoshijima, 2012; Quelle-Regaldie A, 2021).

24.4. Spinocerebellar Ataxia (SCA)

Spinocerebellar ataxias are a group of neurodegenerative disorders characterized by decreased balance and coordination. The zebrafish model of SCA helps identify disease-associated genes and genetic changes as well as explore therapeutic interventions. The zebrafish essential tremor model has been used to investigate the role of genetics and signaling pathways in the development of tremor and related movement disorders (Rabe, 2018).

24.5. Essential Tremor

Essential tremor is a common neurological disorder, which can affect balance and coordination. Zebrafish models of essential tremor have been used to explore the role of specific genes and signaling pathways in the development of tremors and associated motor impairments (Bhattarai S. C., 2017) these studies demonstrate the usefulness of zebrafish as a model organism for investigating balance and coordination diseases. They provide valuable insights into the underlying mechanisms of these disorders and aid in the development of potential therapeutic strategies.

24.6. X-Fragile Syndrome

Fragile X Syndrome (FXS) is a condition caused by mutations in the *FMR1* gene on the X chromosome. Symptoms of FXS include mental retardation, seizures, autism-like behavior, attention deficit hyperactivity disorder, development of large tumors, and mild pain associated with the development of dendritic spines during development (H.J.Norton, 2013). It is the most common genetic cause of mental retardation and autism spectrum disorders. FXS results from expansion of a DNA repeat sequence (called CGG trinucleotide repeat) in the *FMR1* gene (Hagerman, 2001). Typically, the *FMR1* gene contains 5 to 40 CGG repeats; however, individuals with FXS have more than 200 copies of *CGG* that result in genes. Silencing and reducing the production of *FMRP* (fragile X brain retardation protein) (Crawford D.C., 2001). *FMRP* plays an important role in brain synaptic function and protein synthesis, and its deficiency causes FXS symptoms (Coffee, 2009).

25. Hyperkinetic movement disorders

ADHD is a group of disorders caused by movement disorders. Huntington's disease and other chorea disorders may result from dysfunction of the basal ganglia pathway, including projections from the putamen to the outer globus pallidus and subthalamic nucleus. Zebrafish models of hyperkinetic movement disorders often involve the expression of genetic mutations associated with these disorders in humans. For example, mutations in genes encoding proteins involved in dopamine metabolism or neurotransmitter receptor signaling can cause zebrafish abnormalities. Mutations in this gene impair brain function and result in a hyperkinetic phenotype (Panula P. C., 2010). It allows dopaminergic dysfunction to work by controlling the expression or activity of dopamine-related genes or by administering drugs that

alter dopamine signaling. These changes can lead to hyperkinetic exercise similar to those observed in human patients (Kabashi, 2010). Deficiencies in inhibitory (GABAergic) and excitatory (glutamatergic) neurotransmission are associated with hyperkinetic movement disorders. The zebrafish model allows regulation of GABAergic and glutamatergic signaling pathways to study their roles in the development of impaired physiology. By modulating the expression or activity of GABA or glutamate receptors, the researchers were able to induce hypermobility in zebrafish (Rihel, 2010) . Hyperkinetic movement disorders are associated with disruption of neuronal circuits responsible for motor control. Because of its transparent embryos and larvae, the zebrafish model offers a unique opportunity to visualize and control neuronal diseases. Using genetic tools or drugs, scientists can selectively activate or deactivate specific populations of neurons involved in motor control, thereby identifying abnormalities that cause hyperkinetic movement (Ahrens MB, 2012). Huntington's disease is a neurodegenerative disease characterized by loss of movement control, cognitive impairment, and behavioral symptoms. Zebrafish models have been used to examine the molecular mechanisms and therapeutic strategies underlying HD (Zoghbi, 2000). Tourette's syndrome is a hyperkinetic movement disorder characterized by motor and vocal tics. Zebrafish models have been used to examine genetic and environmental factors that contribute to TS-like behavior as well as clinical outcomes (Huang, 2012). Dystonia is a disease characterized by recurrent or recurrent persistent muscle spasms. Zebrafish models have been used to examine the role of various genes and signaling pathways in the pathogenesis of dystonia (Fogel, 2010). Rett syndrome is a rare genetic disorder that mostly affects women and causes a variety of neurological and movement disorders. Zebrafish models have been used to examine the effects of specific genetic changes and treatments for Rett syndrome (Armstrong, 2012). Gilles de la Tourette syndrome is a disorder characterized by multiple motor and at least one vocal tic. Zebrafish models have been used to examine the neurobiological basis of GTS and to test potential treatments (Zhu, 2019).

26. Hypokinetic movement disorders

Hypokinetic movement disorder is characterized by a lack of movement and can be caused by many factors, including neurodegenerative diseases or the use of anti-Parkinsonian drugs. The zebrafish model (Danio rerio) was used to study the mechanism of hypokinesia and to identify therapeutic strategies investigated the role of GPR37, a Parkinson's disease-associated receptor, as an endoplasmic reticulum (ER) companion for LRP6, a protein involved in the Wnt signaling pathway in zebrafish. (Panula P. C., 2010) demonstrate the importance of the zebrafish model in understanding the molecular mechanisms of Parkinson's disease. Hypokinetic movement disorder is often associated with the destruction of dopaminergic signaling pathways, particularly in the basal ganglia. Dopamine depletion disrupts the balance between inhibitory and excitatory signals, leading to reduced motor activity (Granato M. , 2010). In hypokinesia, injection of the neurotoxin 6-OHDA into the zebrafish brain selectively targets and destroys dopaminergic neurons, similar to the loss of dopaminergic cells seen in Parkinson's disease. This model allows the study of motor deficits and the evaluation of potential neuroprotective or neurorestorative treatments (Peterson, 2014). Zebrafish models with transgenic overexpression of alpha-synuclein, a protein implicated in Parkinson's disease, can display motor abnormalities and dopaminergic neuron degeneration. These models provide insights into the role of alpha-synuclein in the pathogenesis of hypokinetic movement disorders and enable the screening of compounds that modulate its toxicity (Larson, 2016). Zebras with genetic mutations associated with human dyskinesia have been used as fish models to study the following mechanisms. For example, zebrafish carrying a mutation in a Parkinson's gene associated with early-onset Parkinson's disease results in loss of dopaminergic neurons (Schildknecht, 2017).

26.1. Ocular movements

The researchers studied the hunting behavior of zebrafish larvae in response to visual stimuli. They used a high-speed camera to record the movements of the fish while catching prey and analyzed the kinematics of the eye movements (Bianco, 2011). This study provided insight into the neural circuits and mechanisms behind visual behavior, including eye movements, in zebrafish (Bianco, 2011). Strabismus is a problem that results from misalignment of the eyes, resulting in blurred vision between the two eyes. Zebrafish mutants with impaired retinal development, such as the *lama1* and *lrp2b* mutants, have been used to study the cellular and molecular mechanisms involved in strabismus (Gao C, 2010). These studies provide insight into the role of extracellular matrix proteins and cell adhesion molecules in eye muscle development and eye control. Nystagmus is a disorder caused by visual disturbances, usually caused by rapid and repetitive vibrations. Zebrafish mutants with defects in the oculomotor system were used to study the mechanism of nystagmus. For example, belladonna (belly) mutant zebrafish lacking the function of ephrin-B1a receptors exhibit nystagmus due to disruption of brain neural circuits (Xiao T, 2011). Oculomotor apraxia is a disorder caused by the inability to control eye movement. Zebrafish have been used to study the history of the disease. Mikre oko (*mok*) mutant zebrafish lack the X-linked *Atrx* protein and exhibit eye movement defects and abnormal axonal projections from oculomotor neurons (Martins RA, 2017).

26.2. Sensorimotor integration

Sensory-motor integration refers to the process of receiving, processing, and using the information needed to produce an Appropriate response. Zebrafish have many senses, including sight, hearing, smell, and a central line that detects changes in water flow and pressure. These sensations receive external stimuli and convert them into neural signals. When necessary, information is received, it is processed in brain regions. For example, visual information is processed in the optic tectum (the mammalian equivalent of the superior colliculus), while auditory information is processed in the hindbrain and midbrain auditory nuclei (Granato H. A., 2007) . Auditory information is combined with other internal cues and sent to motor centers such as the spinal cord and hindbrain that generate the Appropriate commands. Zebrafish have a segmented spinal cord that allows for motor control (Steven Knafo, 2018). Zebrafish receive continuous feedback from their urine, enabling adaptation and learning. This feedback helps improve the integration of sensorimotor time (F., 2013). It exhibits optokinetic response (OKR), which is the reflex power of the eye used to stabilize vision as the surrounding light moves. Researchers used zebrafish to examine the neural circuits and genetic mechanisms underlying OKR and its integration with other needs (Bianco et.al, 2012). The zebrafish's external system is involved in detecting changes in water flow and pressure, helping to identify animals, avoid predators, and travel. Research has focused on understanding how zebrafish combine information from the system with other senses to generate motor responses (Bianco et.al, 2012). They exhibit a startle response, characterized by a rapid escape swim when startled by a sudden acoustic or vibrational stimulus. Researchers used zebrafish to study the neural circuits and genes involved in the fear response and how it is regulated by sensory processing (Oda, 2008).

27. Infectious diseases

Zebrafish models have also been employed to identify potential compounds with anti-infective properties. A study by Meeker et al. (2018) used zebrafish to screen a library of compounds for their ability to inhibit mycobacterial infection. They identified several compounds with anti-mycobacterial activity, demonstrating the potential of zebrafish in anti-infective drug discovery (Meeker, 2018).

27.1. Mycobacterium marinum infection

Zebrafish model is used to study the pathogenesis of tuberculosis. Zebrafish embryos are infected with *Mycobacterium marinum*, and the infection can be visualized using fluorescently labelled bacteria (Volkman, 2013). *M. marinum,* which shares similar characteristics with *M. tuberculosis,* can invade microglia and replicate in microglia, which subsequently promote the secretion of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. *M. marinum* infection in microglia can also promote autophagy, which conversely limits the replication of *M. marinum*. Thus, pharmacological activation of autophagy by rapamycin could prevent *M. marinum* replication. Also, it provides in vivo and in vitro models to study underlying pathogenic mechanisms of tubercular meningitis by using *M. marinum* (Chen Z. S., 2018).

27.2. Streptococcal infections

Zebrafish larvae are infected with *Streptococcus pneumoniae*, causing meningitis-like symptoms. These models help to understand host interactions and test treatment strategies (Cyber 2020). Zebrafish provide an attractive environment for some Streptococci, including *Streptococcus iniae* and *Streptococcus agalactiae*, and this link has been used to develop a *Streptococcus*-zebrafish model to reveal detailed information about the same human health-causing bacteria (Kim BJ H. B., 2015; Harvie EA, 2013)**.** *Streptococci. sp*. has the potential to unlock new treatment strategies and vaccines that can be used in human clinical settings and in the ocean. At the same time, this zebrafish model provides an opportunity to demonstrate the mechanism of transmission of the virus from fish to humans (Rowe HM, 2014)**.**

27.3. Listeria monocytogenes infection

Zebrafish embryos were infected with *Listeria monocytogenes*, a bacterium that causes meningitis and encephalitis in humans. This model allows the study of host defenses and invasion of the central nervous system (Levraud, 2009). Attenuated bacteria (*Listeria monocytogenes*) vector vaccines have been shown to promote the advancement of anti-tumor drugs. New viruses, virus-directed antibodies and vaccines to heterologous antigens have given rise to more viable viruses in other areas, such as aquatic immunotherapy. In this study, we found that attenuated Lm protected zebrafish from competing with Vibrio species (Chengchao Ding, 2019).

27.4. Cryptococcus neoformans infection

Zebrafish larvae are infected with *Cryptococcus neoformans,* a fungal disease that causes meningitis. These models are useful for studying host-fungus interactions and screening for antibiotic resistance (Mylonakis, 2005). The zebrafish is a new model for studying the development and function of the blood-brain barrier (Kim BJ H. B., 2015). This study

shows that the zebrafish larvae of *Cryptococcus neoformans* migrate to the central nervous system and *Cryptococcus* mutants are known to be affected in the disruption of the blood-brain barrier in animals, and also have an effect on the invasion of the zebrafish brain (Jennifer L. Tenor, 2015).

27.5. Herpes simplex virus type 1 and type 2 infections

Zebrafish embryos are infected with herpes simplex virus type 1 (HSV-1) or HSV type 2 (HSV-2) to cause herpes encephalitis. This model leads to the study of neuroinvasion and the development of anti-inflammatory drugs (Prasad, 2013). In addition, there are human homologues of viral entry in animals such as 3-O-sulfated heparan sulfate, nectin, and tumor necrosis factor receptor superfamily member 14-like receptors, allowing time for doctors to diagnose their disease. The in vivo significance of entry provides a strong rationale for comparing the structure-function of zebrafish receptor interactions with virus entry in the zebrafish model. On the other hand, zebrafish models have been used to study inflammation and angiogenesis with or without genetic manipulation and can therefore be used to study infection-associated pathology. In addition, many transgenic lines expressing fluorescently labeled immune cells are very attractive for in vivo imaging of infected animals. In addition, the potential for immune system and receptor-specific knockout strategies further supports the use of zebrafish as a new tool to study infectious diseases. (Thessicar Evadney Antoine, 2014).

Table 2 Zebrafish Modeling for Rare Neurological Diseases

Gene Name	Related Disease	Zebrafish Phenotype	Publication
sod1	Amyotrophic Lateral Sclerosis	Motor neuron loss Muscle atrophy	(Ramesh, et al., 2010)
fus		Shortened motor neuron length Decreased neuromuscular junction Impaired motor behavior Decreased life span Increase of the smallest tau transcripts	(Bourefis & et.al, 2020)
Tardbp		Axonopathy of the motor neurons Premature of axonal branch	(Hewamadduma, et al., 2013)
c9orf72		Impaired motor behavior Cognitive impairment Muscle atrophy Motor neuron loss	(Shaw, et al., 2018)
fam50a	Armfield XLID syndrome	Abnormal neurogenesis Abnormal craniofacial patterning	(Lee, et al., 2020)
dyrk1a	Down Syndrome and Autism	Decreased brain size Increased anxiolytic behavior Impaired social interaction/cohesion	(Kim, et al., 2017)
wdr11	Idiopathic Hypogonadotropic Hypogonadism Kallmann Syndrome	Delayed puberty Impaired sense of smell	(Kim, et al., 2010)
eftud2	Mandibulofacial Dysostosis, Guion–Almeida Type	Decreased brain size Small eyes Curved body Early embryonic lethality	(Deml & Reis, 2015)

zc4h2	Miles–Carpenter Syndrome	Abnormal swimming Increased twitching Motor hyperactivity Eye movement deficits Pectoral fin contractures	(May, et al., 2015)
phf21a	Potocki–Shaffer Syndrome	Abnormal head and jaw size Change of head and face shape	(Kim, et al., 2012)
eif4a3	Richieri–Costa–Pereira Syndrome	Underdevelopment of craniofacial cartilage and bone structures	(Favaro, et al., 2014)
eif2b5	Vanishing White Matter Disease	Early embryonic lethality Loss of oligodendrocyte precursor cells Impaired motor behavior	(Keefe, et al., 2020)
eif2b3		Defected myelin gene expression Defected glial cell differentiation	(Lee, et al., 2021)
sam2	12q14.1 Deletion Syndrome	Increased of fear, anxiety-related behaviors, and autism	(Choi, et al., 2018)

Table 3 Neuro-Phenotypic Domains and Their Behavioural Paradigm In Zebrafish

Disorder	**Behaviour**	**Criterion**	**Zebrafish Phenotype**
Stress	Aggression	Live observation of two fish Mirror image test Pigment response Startle reaction	Reduction of exploration Increased avoidance Erratic behaviour Elevated cortisol
	Alarm reaction	Response to alarm substance	
	Anti-predation	Predator stimulation	
Anxiety	Fear related behaviour	Exit latency test Group preference Light/dark preference Locomotor activity Thigmotaxis Tank diving test Time in enriched T-maze chamber	
Depression Autism and schizophrenia	Locomotion	Mean velocity Number of lines crossed Total distance crossed Turning angle	Reduced activity Elevation of cortisol Assessment of memory and learning
	Audition	Response to startling noise	
	Courtship	Observation of courtship postures	Potent social behaviour
	Learning/memory	Active avoidance conditioning Delayed spatial alterations Learned alarm reactions Spatial alterations	Hyper activity Impaired cognitive process

		T-maze Visual discrimination learning	
	Olfaction	Response to amino acids	
Sleep Disorder	Sleep	Monitoring sleep postures Pigment response Locomotor inhibition	Vigorous circadian rhythms Sensitive to sleep-modulating drugs
Neurodegeneration	Locomotion	Interaction with object Total distance moved	Decline in locomotion
Reward Related Behaviour	Reward	Conditioned place preference Presence of conspecific	Rewarding stimuli, including food and abused substances

28. Mutagenesis screens transgenic and knockout zebrafish

Zebrafish are well suited for large-scale forward genetic screening to detect phenotypic defects before identifying the genes responsible for them. This is due to the high ovulation, short duration and external development of transparent embryos. In addition, an important development is the ability to freeze zebrafish sperm in future research. Three methods for inducing mutations in zebrafish include chemical mutagenesis, gamma-ray irradiation, and intervening mutagenesis (Fritz A, 1996).Chemical mutagenesis is the most favourable and efficient method applied thus far (Haffter P, 1996; Driever W, 1996) or these screens, chemical mutagenesis was performed by exposing adult zebrafish to N-ethyl-N-nitrosourea (ENU). ENU is an alkylating agent that produces genome-wide changes in pre-meiotic organisms by transferring the ethyl group in DNA captured by DNA polymerase to a single base when repeated errors occur. A second modality of change affecting the development of zebrafish is radiation, primarily gamma rays. Gamma-ray mutagenesis provides very high mutation rates of about 1:100 and is often used to screen for morphological defects (Kimmel CB, 1995). In contrast to chemical mutagenesis, gamma radiation induces high frequency translocations and large deletions in the zebrafish genome, thus chemical mutagenesis is the method of choice (Fritz A, 1996). A third alternative method to induce mutations in zebrafish is sequence transduction, which can be produced using plasmid DNA injection, mouse pseudotyped retroviruses, or P-element transposons as intervening mutagens (Amsterdam A, 2004).

Strategies for Constructing Knockout Zebrafish Using ES Cells by Transferring Relevant Functional Alleles. The only way to create a rock is mutagenesis followed by screening for mutation (*TILLING)* (Wienholds E, 2004). A pluripotent zebrafish ES cell line was developed (Fan L C. J., 2004). Recently, directed integration of plasmid DNA into cells by homologous recombination followed by in vitro chemical selection has been achieved (Fan L M. J., 2006) additionally, the authors were able to use microinjection to introduce ES cells expressing markers such as EGFP into host embryos and obtain disease outcomes. Although germline mosaicism occurs at a frequency of 2-4%, the abundance of fertilized eggs makes it possible to produce fish lines in the future (Fan L M. J., 2006). These genetic screens can identify new genes and mutants of organs or systems. After screening the phenotype by random mutagenesis, the cloning program should be used to find the mutation causing the defect. The main disadvantage of genetics is that it is slow and labor-intensive due to the cloning method. In 2002, due to the lack of a working method to generate ES cell-based knockouts (or target expression), the *TILLING* method was developed (DL, 2004) *TILLING* affects the rate of change in ENU after detecting changes in targets. The screen is enzyme-mediated (CEL-I endonuclease) recognition mismatch for detection of heterozygous germline mutations in the F1 generation. Another generation of embryos with the mutant phenotype is similar to the reproductive process described above. Cultivation can be done in high places. The only downside is that changes are introduced randomly.

Transgenic animal models are widely used to demonstrate the function of many new (disease) genes. Zebrafish have emerged as important models for the study of human diseases and similar or additional genetic methods specific to zebrafish should be developed. Methods for the production of transgenic zebrafish are pseudotyped retrovirus infection (Chen W, 2002; Linney E, 1999) , transposons (Raz E, 1998) transfection of sperm nuclei (Jesuthasan S, 2002) and DNA microinjection. The latter is the most widely used method for the generation of transgenic lines expressing flower genes. DNA microinjection can be achieved by injecting plasmid DNA or bacterial combinations (BACs) into the cytoplasm of 1-cell stage embryos. Zebrafish integrate DNA into the germline by microinjection with a frequency of 1-30% compared to mice (Udvadia AJ, 2003). Injection of I-SceI meganuclease and a construct from the known meganuclease site has been shown to improve integration in fish (Thermes V, 2002).Another way to study gene function (disease) in animal models is to inactivate or disrupt gene expression. Strategies to breed competitive zebrafish by germline transmission

into mice using ES cells of targeted loss-of-function alleles are not yet complete. The only way to generate a fragment is by (*TILLING).* Mutagenesis followed by point mutation as previously described. A pluripotent zebrafish ES cell line was developed (Fan L C. J., 2004) recently, directed integration of plasmid DNA into cells by homologous recombination followed by in vitro chemical selection has been achieved (Fan L M. J., 2006).

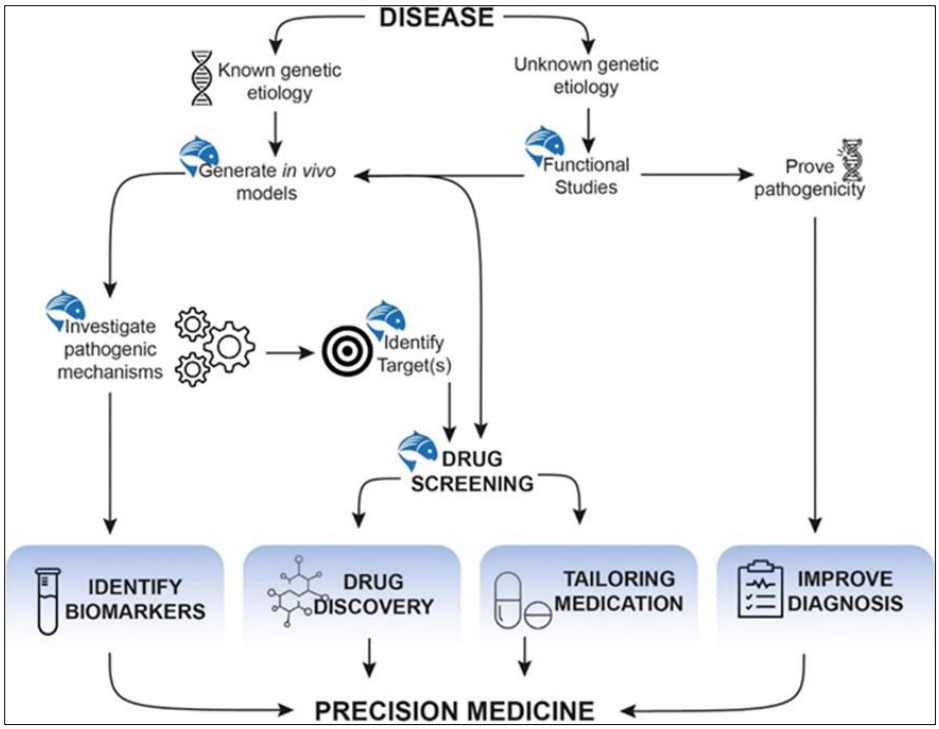

Figure 2 Accelerating the development of precision medicine approaches using zebrafish

29. Neurological drug screening and automated imaging

There have been several successful drug discovery studies using zebrafish models of neurological disorders, leading to the identification of potential therapeutic compounds. Phenotype-based drug discovery in the zebrafish is an exciting new approach for identifying psychiatric drug prototypes that may act on previously unidentified therapeutic targets (Peterson RT, 2004). The first known small-molecule inhibitor of BMP signalling, dorsomorphin, was recently identified based on its ability to perturb dorso-ventral axis formation in embryonic zebrafish (Yu PB, 2008). Because conserved molecular pathways mediate axis formation in fish and iron homeostasis in humans, this drug may have therapeutic value for treating anaemia (Yu PB, 2008). Phenotype-based chemical screens in the zebrafish have also been used to identify molecules that suppress cancer-related and cardiovascular disease phenotypes (Murphey RD, 2006). It is likely only a matter of time before high-throughput behaviour-based chemical screens in zebrafish are applied to neurological drug discovery. Some examples are given below

29.1. Drug Discovery of Fragile X Syndrome (FXS)

Studies highlight the role of Fragile X Mental Retardation Protein (FMRP) in zebrafish and its potential as a target for therapeutic interventions. The researchers discuss how zebrafish models can help identify small molecules that can restore FMRP function and mitigate the symptoms associated with FXS (Sharma, 2019; Pardo-Martin, 2013).

29.2. High-Throughput Drug Screening

Zebrafish have emerged as a valuable model for drug screening due to their small size and high reproductive rate. Automated platforms allow researchers to screen large libraries of compounds for potential therapeutic effects on neurological disorders in zebrafish models (Kokel, 2010).

29.3. Multi-Electrode Array (MEA) Recordings

MEA recordings allow simultaneous extracellular recordings from multiple regions of the zebrafish brain, providing insights into neural network activity and functional connectivity associated with neurological disorders. (Shih.et.al, 2015).

30. Limitations and challenges

Zebrafish (Danio rerio) have emerged as an important model organism for studying various aspects of biology, including neurodevelopment and neurological disorders. While zebrafish models offer several advantages such as genetic tractability, high fecundity, transparent embryos, and relatively low maintenance costs, they also come with certain limitations and challenges when it comes to studying neurological disorders. Here, we will discuss some of these limitations and challenges.

30.1. Complexity of the human brain

One of the major challenges in using zebrafish models for studying neurological disorders is the difference in complexity between the zebrafish brain and the human brain. The zebrafish brain is less complex and lacks certain brain regions present in humans, such as the neocortex. The neocortex is involved in higher-order cognitive functions and is implicated in many neurological disorders. Therefore, some aspects of human neurological disorders may not be fully recapitulated in zebrafish models (Kalueff A. V., 2016).

30.2. Behavioral and cognitive deficits

Zebrafish exhibit simpler behavioral and cognitive abilities compared to mammals, including humans. While zebrafish display basic locomotor and sensory responses, their cognitive capabilities are limited. This makes it challenging to model complex behavioral phenotypes associated with neurological disorders, such as learning and memory deficits or social interactions (Stewart A. M., 2012) or other human neurological disorders might not be fully achievable in zebrafish models (Baraban et al., 2013).

30.3. Disease manifestation and progression

Another limitation of zebrafish model is that they may not fully replicate the progressive nature and long-term manifestations of human neurological disorders. Some disorders, like Alzheimer's disease, Parkinson's disease, or amyotrophic lateral sclerosis (ALS), have complex pathologies that develop over an extended period, which is difficult to reproduce in the relatively short lifespan of zebrafish (Baraban et al., 2013). However, zebrafish can still provide insights into the early stages of disease pathogenesis and underlying molecular mechanisms (Becker, 2012).

30.4. Lack of genetic similarity

While zebrafish share a significant portion of their genetic makeup with humans, they also have notable differences. Zebrafish lack certain disease-associated genes found in humans and may possess gene duplicates or functional equivalents that can complicate the interpretation of experimental results (Baraban, 2013). These genetic differences can limit the direct translation of findings from zebrafish models to human conditions (Norton W. , 2018).

30.5. Limited modeling of higher brain functions

Zebrafish models primarily offer opportunities to study early developmental processes and basic neuronal functions. They may not be suitable for investigating complex higher brain functions associated with certain neurological disorders, such as language, executive functions, or decision-making processes. These aspects are more prominent in mammals and particularly in humans (Maximino, 2010). though zebrafish models have seen advances in genetic manipulation techniques like CRISPR/Cas9, they still have more limited tools and resources for studying the nervous system compared to mammalian models (Rubinstein, 2003).

30.6. Ethical considerations

While zebrafish models are considered a more ethically acceptable alternative to mammals, they still raise ethical concerns regarding animal welfare. Researchers need to carefully consider the potential impact on zebrafish well-being and ensure proper ethical guidelines are followed (Rubinstein, 2003)

30.7. Pharmacokinetics and drug screening

Zebrafish have different pharmacokinetics and drug metabolism compared to humans, making it challenging to directly translate drug effects observed in zebrafish to humans. This can limit the utility of zebrafish models in drug screening for neurological disorders (Norton W. &.-C., 2010).

30.8. Environmental factors

Zebrafish models are sensitive to changes in the environment, and variations in environmental conditions can influence experimental outcomes, leading to potential inconsistencies and difficulties in replicating results (Norton W. &.-C., 2010). Despite these limitations, zebrafish models continue to provide valuable insights into various aspects of neurodevelopment and neurological disorders. They are particularly useful for studying early embryonic development, neural circuitry, and drug screening (Panula P. e., 2010). Integrating zebrafish models with other complementary model systems and approaches can help overcome some of these limitations and provide a more comprehensive understanding of neurological disorders.

31. Future directions

While zebrafish research has greatly contributed to our understanding of various neurological diseases, there are some aspects and challenges that need to be addressed in the future. Here are some key areas: As we've discussed, early embryonic and larval cultures of zebrafish can provide insight into many processes and treatments of human diseases. Zebrafish-based assays enable bioassay-guided quantification of many bioactive extracts found in these in vivo screens, allowing the isolation of a variety of bioactive natural products – often ideal aluminum compounds. Develop new, effective drugs. These preliminary studies support the potential of zebrafish to help solve an important problem in nanoparticle detection by allowing rapid in vivo, microgram-scale, bioassay-guided fractionation analysis and de-replication techniques. Research on a variety of natural extracts (Arjun Pitchai, 2019).

31.1. Advanced Behavioral Analysis

Enhancing behavioral analysis techniques in zebrafish is crucial for studying neurological disorders (Randlett O, 2015) . Development of automated, high-throughput behavioral assays can provide detailed insights into disease phenotypes, drug responses, and genetic interactions. Integration of computer vision and machine learning approaches can help extract quantitative data from complex behaviors (Blum AL, 2019).

31.2. Disease Modeling

Improving zebrafish models to recapitulate the complexity of neurological disorders is crucial. Utilizing advanced genome editing tools such as *CRISPR/Cas9* allows precise manipulation of zebrafish genomes to introduce disease-associated mutations. Additionally, developing inducible and cell-specific gene expression systems can help mimic disease progression and investigate specific cell types involved. (Paquet D K. D., 2016; Arrenberg AB, 2010)

31.3. High-Resolution Imaging Techniques

Advancements in imaging technologies allow for better visualization and analysis of zebrafish neural circuits. Combining light-sheet microscopy, calcium imaging, and optogenetics enables researchers to investigate the functional dynamics of neural circuits with high spatiotemporal resolution (Ahrens, 2013; Nguyen JP, 2016).

31.4. Drug Screening and Discovery

Zebrafish models offer the opportunity for large-scale drug screening to identify potential therapeutics for neurological disorders. Developing robust assays that assess disease-specific phenotypes and utilizing chemical libraries can help identify novel drug candidates and repurpose existing drugs (Rihel J, 2010; Kokel, 2010).

31.5. Data Integration and Systems Biology

Integrating data from zebrafish research with human genetic and clinical data can provide valuable insights into disease mechanisms. Employing systems biology approaches', such as network analysis and pathway modeling, can help elucidate the underlying molecular pathways involved in neurological disorders (Kimmel CB, 1995; Hartman AL, 2018).

Overall, these future directions and challenges in zebrafish research hold great promise for advancing our understanding of neurological disorders and facilitating the development of effective therapeutic strategies.

32. Conclusion

Zebrafish models have emerged as valuable and versatile tools in the study of neurological disorders. Their genetic tractability, high reproducibility, and physiological relevance offer unique advantages that have contributed to significant advancements in our understanding of disease mechanisms, drug discovery, genetic validation, and behavioral phenotyping. Zebrafish models provide insights into the molecular and cellular basis of neurological disorders, facilitate the identification of potential therapeutic compounds, and allow for the validation of disease-associated genes and pathways. While zebrafish models have their limitations and challenges, they continue to drive innovation and provide new avenues for research. By addressing these limitations and incorporating emerging techniques and technologies, zebrafish-based research can overcome existing challenges and further enhance its impact on neurological disorder research. The potential impact of zebrafish models on understanding and treating neurological disorders is substantial. Their contributions to unraveling disease mechanisms, identifying therapeutic targets, and accelerating drug discovery hold promise for the development of personalized medicine approaches and improved treatments for patients. As zebrafish models continue to be integrated into multi-modal and translational research strategies, they have the potential to bridge the gap between basic research and clinical applications, ultimately benefiting individuals affected by neurological disorders. Overall, zebrafish models have proven to be powerful and transformative tools, bringing us closer to unraveling the complexities of neurological disorders and paving the way for novel therapeutic interventions. Their continued utilization and advancement in neurological research hold great promise for improving patient outcomes and quality of life in the future.

Compliance with ethical standards

Acknowledgments

We would like to extend our heartfelt gratitude to Mr. Sai D. Prasad, the esteemed CEO of RCC Laboratories India Private Limited, for his invaluable support and encouragement throughout the research process. And our TFM, Ms. Babitha Joseph for her support and assistance during research and preparation of the manuscript.

Disclosure of conflict of interest

The authors of this article declare that they have no conflicts of interest that could potentially influence the results or interpretations presented herein.

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