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REVIEW ARTICLE

A Review of the Ethological Model of Zebrafish Larvae for Use in Medicinal Screening and Pre-clinical Trials

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ABSTRACT
Robust biological systems are essential for accurate data generation in drug development and research, whether investigating novel compounds or assessing the toxicity and biological activity of pharmaceuticals. The zebrafish has become an essential model for drug screening and biological research. In order to treat complicated illnesses, phenotype-based screenings can use multi-target approaches to capture the organism's compensatory processes. Because of the zebrafish's close resemblance to mammals in terms of neuro-anatomical, physiological, and behavioral features, it is easier to create useful and realistic experimental models for researching neurological illnesses. Zebrafish exhibit highly conserved physiological pathways found in higher vertebrates, including mammals, and have a diverse behavioral repertoire. Furthermore, they exhibit strong pharmacological and environmental sensitivity, both larvae and adults display similar behavioral traits. This paper highlights important behavioral domains investigated in zebrafish larvae and their neurotransmitter systems, and it thoroughly reviews existing techniques for evaluating and measuring zebrafish larvae behavior in lab experiments.
Keywords: *alternative model, 3Rs, behavioural repertoire, drug discovery, neurological drugs, neurotransmitters, anxiety-like behaviour*

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INTRODUCTION

Zebrafish Modelling for Phenotypic-Based Screening:

Sixty-two present of first-in-class medications approved by the FDA between 1999 and 2008 were found through phenotype-based screening, in which the assay generates an organic/functional phenotype that combines various biochemical signals from the biological system [1]. By observing a whole animal and the interactions between various cell types, phenotype-based screening combines generic morphological screening for anomalies in embryonic development with observations of animal behaviour. The selected hits have increased biomedical applicability as a result during the process [2]. The apparent advantage of phenotype-based screening versus target-based screening, which begins with a particular molecular target thought to be crucial in disease, can be attributed to a number of causes. First, even in the absence of a validated target, phenotypic screening can find potent medicines. Second, it can spot drugs that operate simultaneously on several targets and have therapeutic effects. Third, phenotypic screening frequently combines screening and counter-screening in a single assay, identifying chemicals that have the desired impact while examining undesired characteristics. In direct consequence, drugs that advance via phenotype-based screening are typically safer, more efficient, and with less side effects when compared to those produced from in vitro cell culture studies employing target-based screens [3].The teleost fish known as the zebrafish (*Daniorerio*) shares 70% of its genes with humans and has highly conserved molecular targets and physiological pathways among vertebrates [4]. Its neuroanatomical characteristics, neuronal cell morphology, and circuitry are very similar to those of mammals [5]. Zebrafish-based screening, which is a tiny but expanding portion of phenotype-based screening, is used to

find novel compounds (Figure 1). Zebrafish screenings have been effective for finding new applications for medicines already on the market, in addition to uncovering novel compounds with therapeutic promise. In addition to the conventional benefits of phenotype-based tests, zebrafish screenings have the special benefit of being carried out on a vertebrate creature, embryo, or larva. Relevant examples of characteristics that are visible in zebrafish but inaccessible in cell culture include pain, drowsiness, tumour metastasis, vascular tone, and intestinal motility. The zebrafish embryo-larval stage can replace other vertebrates in investigations involving all organic systems and fits the 3Rs idea of replacement, reduction, and refining well [6]. Independent feeding in zebrafish requires multiple characteristics, including a fully developed digestive system, the ability to swim for prey or food, and entire yolk depletion. These physiological events take place between 120 and 144 hpf [7]. By 96 hpf, zebrafish have developed substantial neuromodulator systems and are capable of displaying coordinated behaviour in response to various stimuli [8,9]. Thus, after they are designated as non-protected under the EU Directive of animal welfare (EU 2010/63/EU), larvae below 120 hpf are regarded as an alternative model to animal research, according to Strahle et al. (2012) [6]. However, research utilizing zebrafish at an early stage of life continues to adhere to the 3Rs principle [10]. With the complexity of cell-cell interactions and endocrine signalling, neurologic drug discovery makes use of intact animals as the focus of screening particularly advantageous. Additionally, behaviour analysis can be combined with transgenic strains using techniques to produce targeted genetic modification, such as CRISPR/Cas9, RNA interference (RNAi), zinc-finger nucleases (ZFNs), and antisense Oligonucleotide morpholions [11]. As zebrafish larvae have functional livers, kidneys, blood-brain (BBB) and blood-retinal barriers (BRB) [12,13], as well as drug-metabolizing enzymes and metabolic rates comparable to humans [14], zebrafish screenings reveal insights into these pharmacological characteristics, in contrast to cell-based assays that only provide limited information on the absorption, distribution, metabolism, excretion, and toxicity (ADME-Tox) of substances. Compounds must have the capacity to be absorbed, reach target tissue, and escape fast metabolism and excretion in order to produce phenotypes in vivo in zebrafish tests.This finding may help to explain the observation that a number of compounds found in zebrafish screenings were quickly and with limited pharmacological property optimization translated to mammalian models in vivo. In terms of brain patterning and the structure and operation of a number of neurological and physiological systems, including the stress-regulating axis, zebrafish and other vertebrate species (including rats and humans) have a great deal of similarities [15]. In the larval stage, the zebrafish neurological system develops between 72 and 120 hpf. Three embryonic layers (endoderm, mesoderm, and ectoderm) are produced throughout development from which neural tissue develops. The anterior neural tube divides into the forebrain, midbrain, and hindbrain as a result of a series of curves and constrictions, which enables it to settle into the skull. The development of a constriction at the midbrain-hindbrain boundary is the first morphogenetic event. The opening of the cerebral ventricles is another crucial stage in brain morphogenesis [4, 16]. By 24 hpf, zebrafish primary neurons are visible, and early embryogenesis shows few axonal tracts and commissures. The BBB is present before the end of embryogenesis (72 hpf), when the morphological development of the CNS is complete [17]. The zebrafish brain has a remarkable capacity for regeneration, in contrast to that of mammals [18], which is another benefit in studying the processes underlying neuro-protection, neuro-genesis, and functional integration of developing neural cells as well as the development of new drugs to treat neurodegenerative or neuro-developmental disorders. Chemical screens rely on biological models that are typically well-studied and applicable to other vertebrates. For accurate findings, using models with proven methodologies is ideal. Since the neural system is still developing and various neurocircuits may be missing or undeveloped, the behavioural repertoire of zebrafish larvae is constrained. As a result, although zebrafish larvae are unquestionably a suitable biomedical model, they might not exhibit some complicated behaviour. Only after the transition to adulthood can behaviours like schooling, aggressive confrontations, and mating arise. These behaviours make up social behaviour domains, which in adult fishes are fully formed [9,19].
When it is intended to link behavioural traits, like as cognition, social relationships, and locomotor activity, with physiological evidence of a particular illness, zebrafish have been used. In the past ten years, various approaches and disease-relevant models, capable of generating trustworthy data for behavioural pharmacology, have been created and tailored for zebrafish use in neurological drug screening [20–23]. Neurobehavioral measures such as swimming ability and the efficiency of the motor, sensory, and stress-regulating systems can be used to evaluate the effects of various novel substances on brain development.

Zebrafish Neurotransmitter Systems

The zebrafish larval brain has neuromodulator circuits similar to those in mammals. Major neurotransmitter systems are conserved among vertebrates, and zebrafish have well-characterized

glutamate, gamma-amino butyric acid (GABA), acetylcholine, dopamine, serotonin (hydroxytryptamine or 5-HT), noradrenaline, and histamine systems [24]. Neurological diseases are associated with changes in transmission patterns [25]. Glutamate is the primary excitatory neurotransmitter in vertebrates, controlling synaptic transmission and neuronal excitability. Vesicular glutamate transporters (VGLUT2) are present in 24hpf zebrafish larvae, and by 96 hpf, glutamate metabotropic and ionotropic receptors are expressed in the olfactory bulb, optic tectum, hypothalamus, cerebellum, and retina [26]. GABA is an inhibitory neurotransmitter that is present in both the fetal and adult phases of life [27,28]. GABA-ergic neurons can be found in the diencephalic basal plate, central optic tectum, olfactory bulb, subpallium, posterior preoptic area, torus semicircularis, ventral mesencephalic tegmentum, valvula of the cerebellum, and medulla oblongata in zebrafish [29]. Catecholamines are a significant neurotransmitter in zebrafish. The zebrafish noradrenergic system is extremely similar to mammals, and noradrenaline (NA) functions in the autonomic nervous system to regulate cognition, including learning and memory as well as arousal and reward systems [30,31]. The histaminergic system also influences memory, cognition, and circadian rhythm in a manner comparable to that of mammals [32]. Serotonin (5-HT) is a neurotransmitter that is found in the spinal cord of developing embryos as well as in the telencephalon, hindbrain, and raphe area in larval and adult zebrafish [31]. 5-HT affects behavioural processes like aggression, anxiety, cognition, and sleep. Zebrafish have all dopamine receptors, with the exception of dopamine receptor type 5D5 [33].The zebrafish larvae's dopaminergic system plays a significant role in controlling its movement. Additionally, zebrafish exhibit behavioral traits that are comparable to those of rats and humans and are then subjected to dopaminergic system alteration [34,35]. Zebrafish respond to stress by activating the hypothalamus-pituitary-interrenal (HPI) neuroendocrine axis, which results in the release of cortisol, just like in people. The glucocorticoid receptors that cortisol binds to control transcriptional responses that are involved in immunological function, ion homeostasis, glucose metabolism, and, ultimately, behaviour [36].In the adult CNS, cholinergic neurons are widely dispersed and first arise in the embryonic stage. The expression of the enzyme acetylcholinesterase (AChE) first appears in 4 hpf embryos and rises by 210-folds in 144 hpf larvae [37]. Acetylcholine operates on muscarinic and nicotinic cholinergic receptors in zebrafish, just as it does in humans, influencing cognitive functions [38,39]. The ability to reproduce complex behavioural models that mimic human neurological disorders like Alzheimer's disease [40,41], Parkinson's disease [42,43], depression and anxiety [28,44], epilepsy [45–47], and amyotrophic lateral sclerosis—ALS [48,49] is made possible by the similarity in the zebrafish neuroendocrine repertoire in addition to easy genetic and pharmacological modulation. In this approach, the study and development of CNS medications are aided by the use of behavioural models in zebrafish larvae.

Pre-clinical Assays: Neurological Functions and Behavior Models

Zebrafish are nocturnal and capable of doing behavioural tests in conditions of normal lighting. Through the incorporation of infrared cameras with programmed stimuli control, tests with zebrafish may be carried out fast, with numerous chemicals in parallel in confined testing venues. High-level automated techniques can also quantify all behavioural phenomena under experimental conditions [50,51]. In addition to producing results that are equally as good as those produced in trials with adults, it also enables a reduction in the duration of experiments and the size of the apparatus used to conduct them, making zebrafish larval research more effective. Zebrafish larvae behaviour models can be used to study neurological processes like memory, anxiety, anxiety-related behaviours, and social or illness-related behaviours that are regulated by neurotransmitters. Social behaviour (exploratory and locomotor skills) and sickness behaviour, which is characterized by lethargy, anxiety, reduced physiological function such as locomotor activity, exploratory and social interaction can be used to distinguish behavioural phenotypes found in both larval and adult stages of zebrafish [52]. Despite its complexity, escape swimming is a reflexive response to touch and sound. The lateral pallium of the zebra fish telencephalic area is where behavioral processes like memory or processing and spatial learning occur, and the habenula is where fear response occurs, similar to the hippocampus and amygdala in mammals, respectively [53–55].The main categories of learning and memory models in zebrafish larvae include sensitization, which is based on unpleasant or painful stimuli, conditioning, which entails associating a neutral stimulus with a rewarding stimulus, and social learning, which is based on the animal's preference for shoal formation [30]. Zebrafish also give new settings or items more attention than they do to familiar ones when they explore them [56, 57], while Santacà, Dadda, Petrazzini, and Bisazza claim that zebrafish can tell the difference between new and familiar objects by their differences in sizes, forms, and colours [58]. Zebrafish also exhibit a wide range of cognitive abilities, including avoidance learning, spatial learning, and reinforcement-based learning [59].Zebrafish, both as larvae and as adults, have a

substantial behavioural reaction to environmental novelty [55, 60 &61]. Since the same neurotransmitters and neuroendocrine system are present as in other vertebrates, the zebrafish response to novelty is consistent with an anxiety-like behaviour [29, 62 &63].
Zebrafish response is consistent with an anxiety-like behaviour in a stressful scenario, which prompts the activation of the HPI axis and the activity of the corticotropin-releasing hormone (CRH) cascade, culminating in cortisol release [60, 61 &64]. In behavioral experiments, anxiety states are expressed by decreased exploration and zebrafish exhibit this behaviour, as well as freezing episodes and irregular movement, quite convincingly [65–67]. Next, we review current theories regarding techniques used to assess larval zebrafish behavior and talk about their uses in toxicological pre-clinical drug development (Table 1).

Behavioral Models that Relate to Anxiety

The first signs of locomotor activity show as spontaneous contractions inside the chorion at 17 hours post fertilization. Over the next hours of development, the movements become more coordinated, and the larvae are able to respond to physical contact about 21 hours after fertilization. Zebrafish larvae that are 24-48 hpf exhibit synchronized swimming as their nervous systems continue to mature, and those that are 96-120 hpf exhibit highly sophisticated brains and exhibit more robust behaviors [8].Larvae are individually placed in a plate or multi-well plate and acclimated to the experimental apparatus to determine their locomotor capacity. Then, to evaluate potential neurobehavioral effects of the treatment, all movements are tracked, and parameters of total distance travelled and mean velocity are examined [68,69].Since zebrafish respond quickly by changing locomotor parameters like distance travelled and mean velocity, which may result in changes in exploration pattern, zebrafish hyper- or hypoactivity is a valuable biological marker of environmental perturbations, whether they occur naturally or in a lab setting [70]. The 144 hpf zebrafish larval locomotor assay model has been approved by Afrikanova *et. al.* as a quick first-pass screening tool for determining a compound's anticonvulsant and/or proconvulsant activity [71]. They assessed the acute locomotor impairment in zebrafish larvae as well as their response to being mildly startled by the tail with a small needle using the automated tracking device ZebraBox™ [84]. The visual motor response (VMR) assay, which measures zebrafish larvae's ability to move and their visual capacity, is similar to a startle response test and is initiated by a sharp change in lighting conditions [72,73]. Larvae between 120 and 168 hpf exhibit more robust responses [74, 75 & 85]. Zebrafish larvae are subjected to alternate periods of light and darkness in this test, and those with a functioning visual system should react with certain swimming patterns. The larvae movement in both dark and light periods is recorded and quantified in a high-throughput manner generating reliabledata [86, 87] through automated systems such as Zebra Box™ apparatus [84] or DanioVision™ [88]. VMR is an effective instrument for noninvasively evaluating oculotoxicity and visual abnormalities as well as the physiological integrity of the neurocircuits supported by therapeutic drugs [83,89-91].
In vertebrates, including zebrafish, monoamines play a crucial role in the neurocircuits [92–94]. Pharmacological treatment with anxiolytic medications and MAOIs also supports its involvement in locomotor activity. By analysing the transcription of genes involved in serotonin, dopamine, and adrenergic transporters and receptors signalling as well as by analysing the escape behavior after touch in 80 hpf larvae, Cunha et al. (2018) examined the effect of fluoxetine in 1 hpf embryos [95]. Deprenyl, an MAOB inhibitor, was found to reduce monoamine oxidase (MAO) activity, which led to elevated levels of serotonin and dopamine that are indicative of anxiolytic-like behavior, according to Faria et al. (2021) [76].Larvae that have been exposed have a diminished reaction in behavioral paradigms assessed by visual motor response (VMR).
Recently, a number of behavioural tests were carried out on valproic acid-treated larvae (168 hpf) to measure anxiety, inattentive behaviour, and circling behaviour as surrogate parameters of autism spectrum disorder (ASD)-like characteristics [77] for quick screening of conventional medications marketed for symptomatic treatment in ASD. The authors conclude by suggesting that 7-day-old larval zebrafish be used for a preliminary therapeutic screening against VPA-induced neurodevelopmental damage [96].
The ability of zebrafish to move is indicated by locomotor measures such total distance travelled, swim speed, irregular movements, burst swimming, or freezing [97]. Non-anxious larvae typically increase exploratory activity by spending longer in the centre zone or in the bright zones (phototaxis) in behavioral light/dark preference tests without an unpleasant stimuli [98].According to Chen, Deb, Bahl, and Engert, zebrafish larvae exhibit a phototactic behaviour that entails retreating from dark places in order to control the environmental brightness to a level appropriate for their visual function. As a result, zebrafish larvae with lower levels of anxiety display positive phototaxis [99].Zebrafish larvae exposed to

the SNDRI venlafaxine were shown to be less active and travel shorter distances in a light/dark behavioural test than the controls, according to Thompson et al.'s findings [78]. Additionally, additional studies have demonstrated that the thigmotaxis was considerably reduced in zebrafish larvae as young as 120 hpf exposed to diazepam, supporting the link between the GABAergic signalling pathway and anxious behavior [79]. Through thigmotaxis behaviour, Han et al. described a neuroserpine non-anxiogenic activity [80]. Additionally, Maphanga et al. confirmed the anxiolytic-like action of *Mesembryanthemum tortuosum* L. extract, recognized for displaying the ability to treat anxiety, stress, and depression [81], using thigmotaxis behaviour in zebrafish larvae. Using the zebrafish larvae photomotor response (PMR) assay [82], Copmans *et al.* found two known isoquinoline alkaloids, TMC-120A and TMC-120B, as novel antiseizure drugs. The PMR is a characteristic behaviour of zebrafish embryos between 30 and 40 hpf that can be seen in the motions of the embryo inside the chorion and is brought on by bright light [21,100].

Visual Patterns

Zebrafish larvae are a good model to study the modulation of locomotor parameters mediated by visual stimuli, or visual behaviour. The optomotor response (OMR) and optokinetic response (OKR) are innate visual reactions in which an individual imitate a naturalistic behaviour in larval zebrafish by moving their eye (OKR) or swimming in the direction of an optic flow (OMR), with the goal of stabilizing the surrounding image [8]. The visuomotor response (VMR), another visual behaviour, assesses the zebrafish larvae's visual and locomotor abilities. Zebrafish larvae are exposed to alternate periods of light and darkness during this test, and those who have a functioning visual system should react by displaying particular swimming patterns [8]. The optical transparency of the early life stages of the zebrafish allows for two things: first, the observation of the operation of the visuo-neural circuitry, and second, the measurement and evaluation of the pattern of behaviour [90].The mature zebrafish retina, which is comparable to the human eye, is made up of three nuclear layers that are divided by outer and inner plexiform layers (OPL and IPL, respectively).The amacrine, bipolar, horizontal, and Müller glial cell bodies are found in the inner nuclear layer (INL), the ganglion cell layer (GCL), and the photoreceptor (rod and cone) cell bodies are found in the outer nuclear layer (ONL).At the plexiform layers, synapsis takes place between these nuclear layers and retinal neurons [101]. The visual system is an effective tool for evaluating medication effects in phenotype-based screenings because it exhibits rapid development [102]. VMR and other powerful visually directed reactions, for example, can be utilized to reposition already-approved medications or to find novel therapeutic compounds [83]. In zebrafish, a number of neurotransmitters work together to coordinate vision. The photoreceptor layer communicates with bipolar cells via the glutamate pathway [103]. Additionally, the visuomotor response and short-term memory to various stimuli are thought to be mediated by the dopaminergic system in the posterior tuberculum and the serotonergic system in the dorsal raphe nucleus [104-106].

Final Thoughts

As this review's summary shows, there are several ways to use zebrafish in behavioural study. Zebrafish larvae offer an alternate model with a number of characteristics that make them attractive for translational biomedical research. Zebrafish behaviour-controlling neurocircuits have physiological and structural characteristics with mammalian counterparts, as do the mechanisms behind medication reactions. Zebrafish larval behavioral responses, such as modifications in movement and locomotion profile, driven by intricate neural circuits involving perception, cognition, and decision-making processes, as well as visuomotor functions, can be exacerbated or diminished by various stimuli. This can be investigated by using a variety of zebrafish-specific tests and equipment. The modified behavioral repertoire can be utilized for the pre-clinical discovery and screening of potential neurological medication candidates as well as clinical translation for a variety of neurological illnesses (Figure 2)

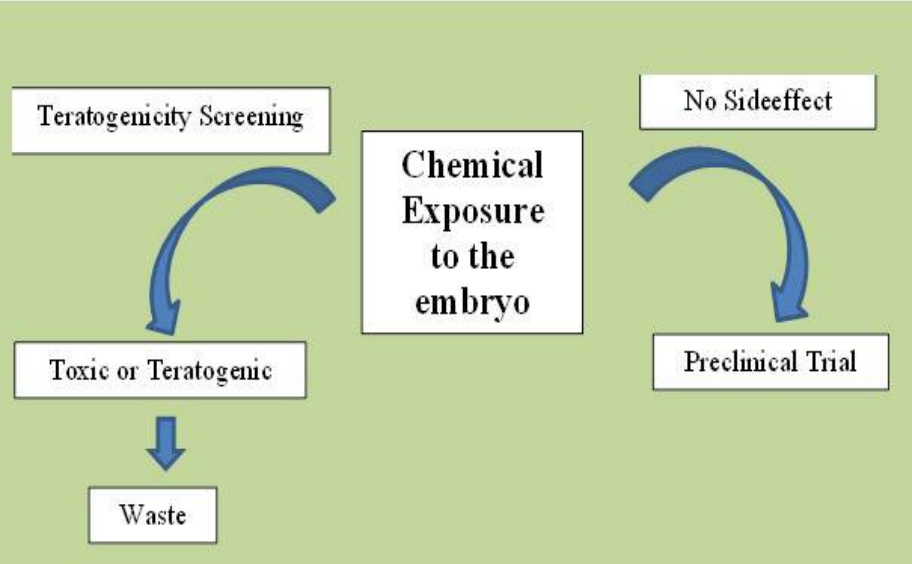

Figure 1. Development of zebrafish: In a large-scale chemical screening, zebrafish embryo-larval stages allow for the phenotypic observation of the entire organism. The larvae can be used to evaluate behavioural changes if a substance is unable to cause death or teratogenicity throughout the stage of embryonic development.

Table1 Selected studies using zebrafish larvae as experimental model in behaviour paradigms.

BEHAVIORAL TEST	ENDPOINTS	REFERENCE
LIGHT-DARK TEST	Total distance travelled	[68]
VISUAL MOTOR RESPONSE	Velocity, total distance moved, and mobility time	[69]
LOCOMOTOR ACTIVITY	Velocity, total distance moved, and mobility time	[70]
LOCOMOTOR ACTIVITY	Total distance travelled	[71]
ACOUSTIC STARTLE RESPONSE	Head angle	[72]
VISUAL MOTOR RESPONSE	Total distance travelled	[73]
VISUAL MOTOR RESPONSE	Average distance travelled	[74]
VISUAL MOTOR RESPONSE	Burst swim	[75]
VISUAL MOTOR RESPONSE	Total distance travelled	[76]
VIBRATIONAL STARTLE RESPONSE	Total distance travelled	[76]
LOCOMOTOR ACTIVITY	Total distance travelled, mean speed, turn angle	[77]
THIGMOTAXIS	Entries in outer area	[77]
LIGHT-DARK TEST	Total distance travelled	[78]
THIGMOTAXIS	Distance travelled in outer area	[78]
THIGMOTAXIS	Percentage of distance moved in outer zone	[79]
VISUAL MOTOR RESPONSE	Total distance travelled	[80]
THIGMOTAXIS	Distance travelled/time spent in each zone	[80]
THIGMOTAXIS	Percentage of distance moved in outer zone	[81]
LOCOMOTOR ACTIVITY	Average distance travelled	[81]
PHOTOMOTOR RESPONSE	Movements/5 min	[82]
LOCOMOTOR ACTIVITY	Total distance travelled	[82]
VISUAL MOTOR RESPONSE	Total distance travelled	[83]

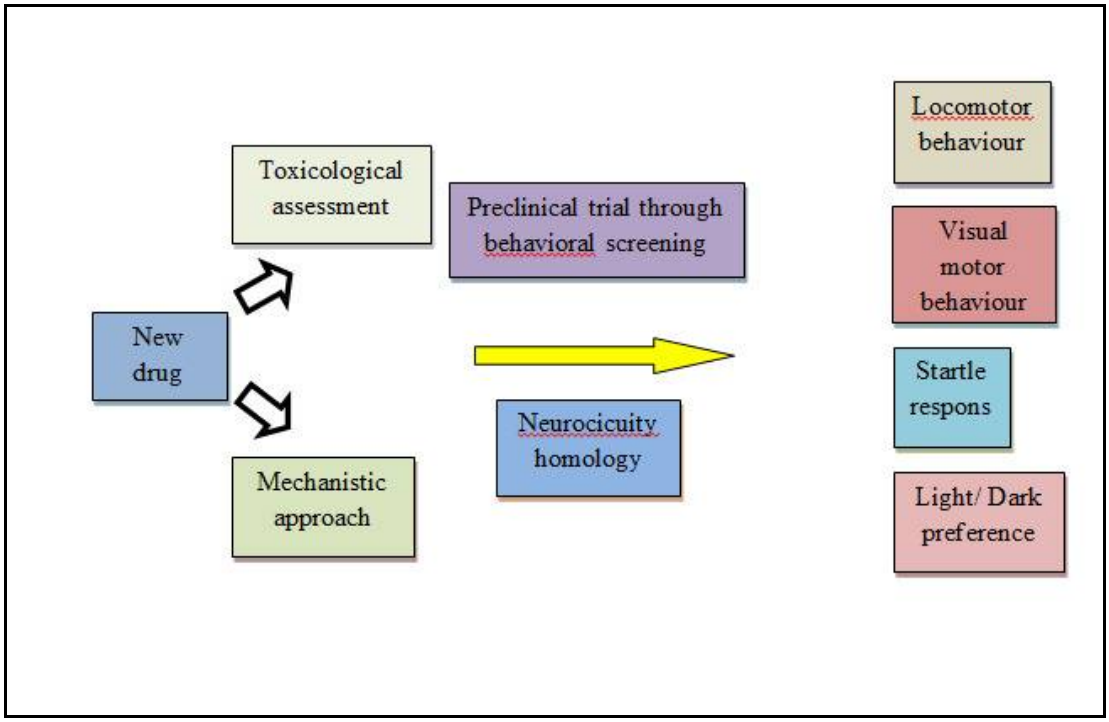

Figure2. Reaction in zebrafish larvae's behavior. In the pre-clinical stage of development, changes in movement and locomotion profile that are caused by intricate brain circuits that encompass visuomotor, cognitive, and perception processes can be used to screen and uncover potential neurological drug candidates.

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