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# Small Fish Realm, Big Brain Dream

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## Editorial

During the process of drug discovery and development, living animal models have been widely used ranging from lead compound optimization, structure and activity relationship analyses, pharmacokinetic studies, therapeutic evaluation, to toxicity assessment [1,2]. While being applied in all the processes with large scale and high throughput advantages, cell culture models do not display the full anatomical and physiologic permeability and enzymatic barrier characteristics of physiological systems [3]. As a result, majority of the leading candidates fail in further clinical trials primarily due to the lack of studies on drug metabolic activation, distribution across physiological barrier, and off-target toxicity [4].Only feasible animal models can essentially bridge those translational gaps to the clinic, thereby providing a viable *in vivo* system to validate new drugs for therapeutic applications [2].

Zebrafish (*Danio rerio*) has been considered as a promising model organism for biomedical research and its application is rapidly growing in the past few decades [5,6]. By offering a whole physiological system, zebrafish has had multiple advantages as a model for drug discovery studies, including high fecundity, rapid development, transparency during embryonic and larval stages, available genetic tools, capable of pharmacological manipulations, and cost-effectiveness [7]. Female fish lay large numbers of eggs per week and the eggs/embryos develop quickly and externally. All the major tissues and organs such as heart, circulating blood, eyes, ears, and nervous system can be formed by one day post fertilization (dpf). By three dpf, the blood-brain barrier has been observed and fish larva have formed liver, pancreas, and a complex vascular network after five pdf [8,9]. In addition, the embryos are transparent, which makes the experiment significantly easy by visualizing the processes of morphogenesis in early developmental stages. More importantly, zebrafish has been proved to be an attractive model due to the cost-effectiveness of producing and maintaining large numbers of larvae at a low cost in laboratory settings.

Zebrafish genome has recently been fully characterized. More than 70% genes in zebrafish are found to have functionally homological similarity compared to human, and play important roles in the development of diseases [10,11].Chemical and insertional mutagenesis tools have been firstly used to model human diseases in zebrafish for small-molecule screening [12]. Antisense technology and target-selected mutagenesis approaches develop more capacity to efficiently knockdown geneand validate potential drug targets [13]. Morpholino oligonucleotides [MOs] technique is one of most commonly used anti-sense knockdowns in zebrafish. After being injected into zebrafish embryos at one to four cell stage, MOs directly inhibit translation and knockdown gene expression. In contrast, this blocking effect during the early stages of development via external injection cannot be used to study gene function in mammalian species such as mouse. Therefore, MOs technology permits a quick and easy large-scale screening, mutant phenotype verifying, and gene function validating in zebrafish [13]. Moreover, Targeting Induced Local Lesions in Genomes [TILLING] has also been used in zebrafish. Lots of loss-of-function mutations have been identified using TILLING methodology and the effectiveness of TILLING continues to be improved [14]. A Zebrafish TILLING consortium has been established to facilitate the isolation of specific mutant lines through the Zebrafish International Resource Center [ZIRC, http://zfin.org/]. More recently, the novel clustered regularly-interspaced short palindromic repeat-associated nuclease9 [crispr-cas9] gene editing technology has been evaluated in zebrafish. Cas9 recruiting specific genomic locus driven by a small guide RNA [gRNA] is complementary to the target site. In zebrafish, studies have shown that cas9 can be directed to user-defined genomic target sites via synthetic guide RNAs and edit the integration of DNA [15]. Altogether, these methods are opening new avenues for the engineering of knock-outs in zebrafish and provide promising disease models for high throughput drug target and validation. Although several mammalian organs such as breast tissue, lungs, and prostrate are not present in the zebrafish, highly conserved nature of both genetics and cell biology as higher vertebrates make zebrafish a suitable model organism for research studies in modeling human

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diseases such as cancers, renal disorders, infections, cardiovascular diseases, hearing disorders, and neurological degenerative diseases.

There is strikingly similarity between zebrafish and mammalian animal models in the brain, including both general macro-organization and cellular morphology [16]. Very relevant to human brain functioning and structures, zebrafish affective behaviors are involved with amygdala and habenula. Moreover, highly conserved across vertebrate species such as humans and rodents, zebrafish possess all major neuromodulator systems, including neurotransmitter receptors, transporters, and enzymes of synthesis and metabolism. Similar to humans, cortisol activated by the cascade of hypothalamo-putuitary hormones can mediate stress responses in zebrafish [17,18]. These advantages make zebrafish become more and more popular in the neuroscience and pharmacology studies [10]. Furthermore, zebrafish are sensitive to neurotoxins including 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP]. The exposure to MPTP neurotoxin induces a decline in dopamine content and number of detectable neurons in distinct nuclei [10,17]. Those unique brain features in addition to many available genetic methods, rapid development, cost-effectiveness, large-scale quantitative behavioral assessment, and advanced quantitative anatomical evaluation, make zebrafish an optimal organism for brain disease studies. Major brain disorders, including Alzheimer's, Parkinson's, Huntington's disease, amyotrophic lateral sclerosis [ALS], multiple sclerosis, brain cancer, stroke, brain injury, autism, lysosomal storage disorders, inherited ataxias, and blindness, have all been modeled in zebrafish [2].

Due to unique features for studying developmental processes and creating transgenic disease models, zebrafish is becoming an increasingly popular model for the drug discovery and development. In our incoming review article, tools available for researching zebrafish and current trends in using zebrafish as a model for brain disorders will be discussed. We hope the review will serve all the readers as a valuable source and inspire more researchers to investigate drug delivery and therapeutic efficacy for the treatment of brain diseases with unquestionable emergency, grand challenge, as well as considerable social and economic burden.

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