# Teleost fish – powerful models for studying development, function and diseases of the human eye

**Satish Srinivas Kitambi[1,2,4,*], Gayathri Chandrasekar[1,2] and Vamsi Krishna Addanki[3]**

[1]School of Lifesciences, Södertörns Högskola
[2]Department of Biosciences and Medical Nutrition, Karolinska Institutet, Stockholm, Sweden 14157
[3]Department of Biotechnology, Ministry of Science and Technology, Government of India, New Delhi 110 003, India
[4]Present address: Department of Medical Biochemistry and Biophysics, Division of Molecular Neurobiology, Scheeles Väg2, Karolinska Institutet, Stockholm, Sweden 17177

**The human eye is a highly specialized structure and defects in its development or functioning process have an impact on the quality of life. Different animal models, especially murine models, have been used to identify the key molecular players required for the normal functioning of the eye. This review highlights the importance of the teleost model in dissecting the development, functioning process and diseases of the human eye.**

**A high degree of conservation is seen in the development, organization and function of the eye throughout vertebrates. Vertebrate teleost models, zebrafish and medaka, have become popular to study various aspects of developmental biology and genetics. Teleost eye shows high similarity to that of the mammalian eye; for example, as seen in mammals, the retina of zebrafish and medaka shows six types of neurons and one type of glia arranged in three layers. In addition, rapid embryonic development, transparency during early development, and the availability of various biochemical, molecular and genetic techniques applicable on these models facilitate in dissecting the developmental and functioning processes of the eye. The availability of mutants with eye defects in zebrafish and medaka allows the possibility of utilizing these two species as comparative models in gaining rapid understanding of the developmental events of various human diseases. The small size of these fish embryos and their availability in large numbers allow performing medically relevant chemical screens to identify potential drug and/or drug targets for different human eye conditions.**

**Keywords:** Development and functioning process, diseases, drug screen, human eye, teleost model.

## Eye development

### *The vertebrate eye and its early development*

IN ANIMALS, light has been an important governing factor in the development and functioning of the eyes. From a primitive sensory system sensing the intensity and direction of light, the eye has evolved into a highly specialized structure with different wavelength sensitivity, zoom and depth perception, thereby providing visual communication with the external world[1]. The external world or the environment has been an important selective force in the development and functioning of the eye as a sensory organ. In invertebrates, the eyes display a wide variety in number, location and function, whereas vertebrates have paired chambered eyes, inverted retinal layers and the image is formed by refraction of light by the lens and cornea[1–6].

*For correspondence. (e-mail: Satish.Kitambi@ki.se)

The vertebrate eye development is highly conserved and it presents an excellent system to study the structural and functional complexity of an organ. During vertebrate embryonic development, the eye is specified as the eye field, a centrally located region in the prospective forebrain (Figure 1). The growth of the forebrain moves the eyefield forward to form the optic groove[6,7]. The optic groove induces the formation of the lens placode on the ectodermal surface upon contact[8]. The lens placode formed on the surface ectoderm, invaginates and pinches off to form the lens vesicle; this process also creates the optic cup, thereby establishing the first shape of the eye[8,9]. The surface ectoderm overlying the lens vesicle forms the cornea, whereas the optic cup gives rise to the neural retina (NR – inner layer of optic cup) and the retinal pigment epithelium (RPE – outer layer of optic cup). The outer lip of the optic cup, where NR and RPE meet, gives rise to the iris and ciliary body[6,8–12].

The developing optic vesicle exhibits a defined axis pattern. For example, RPE forms from the dorsal region of the optic vesicle and the retina from the ventral region[7,8]. The vertebrate lens placode formation coincides with the expression of crystalline protein, which is

required to maintain transparency of the lens vesicle[9]. The lens vesicle shows polarity, which can be readily seen in the formation of lens fibres. The primary fibre cell mass is formed by the posterior part of the lens, whereas the secondary fibres are formed at the transitional zone to the proliferating anterior cells[10,11]. The ventral portion of the optic vesicle forms a groove due to the invagination process. This groove runs from the neural retina to the junction of the neural tube and provides a channel for the blood vessels to enter the retina and the axons to exit the retina. Lateral edges of the groove near the optic vesicle fuse to form the choriod fissure[7,12].

The entire process of eye development is a tightly regulated one (Figure 1), with genes involved in bone morphogenetic protein (BMP)[13,14] and WNT signalling pathways[15], PAX6 (refs 16–19), playing important roles in its early development. Loss of function of *Pax6* in mice, *pax6* in zebrafish produces ocular defects[20–22]. In humans, loss of function or missense mutation in *PAX6* is characterized by defects in iris, cornea, lens and hypoplasia of the retina and iris[23–25]. In addition, expression of genes like *RX*, *SOX2*, *SIX3*, *OPTX2* is also required for proper patterning of the eye and retina and their loss in humans is characterized by microophthalmia or anophthalmia and holoprosencephaly[25–29]. The expression of OTX1, a homeodomain containing protein, regulates the development of iris and ciliary body, and its loss of expression results in the absence or malformation of iris and ciliary body[30].

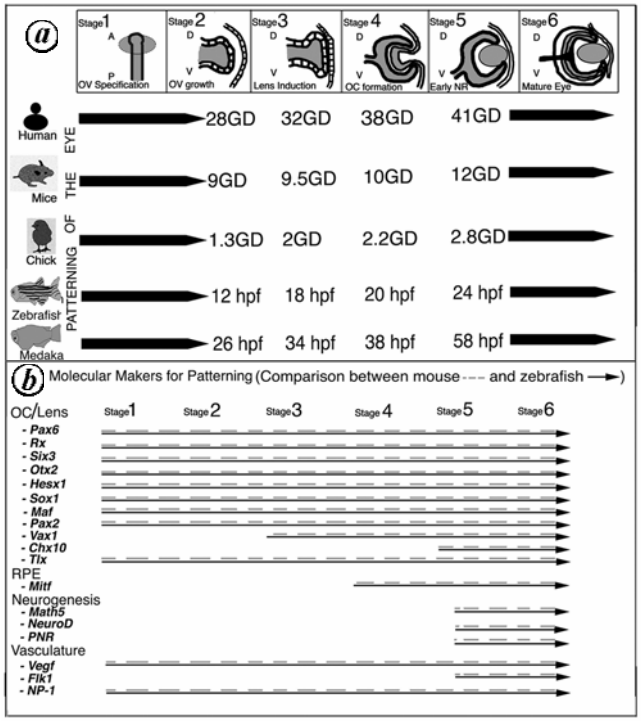


**Figure 1.** Early eye development in different species. ***a***, Early eye development, classified into six stages (Stages 1–6). The approximate time required by humans, mice and chicks to reach the stage are represented by gestation days (GD), and by zebrafish and medaka are shown in hours post fertilization (hpf). ***b***, Comparison of the expression time line of various eye markers from zebrafish (black arrow) and mouse (grey broken lines). A, Anterior; P, Posterior; D, Dorsal; V, Ventral; OV, Optic vesicle; OC, Optic cup; NR, Neural retina and RPE, Retinal pigment epithelium.

## *Patterning, neurogenesis and vasculature of the vertebrate eye*

Early embryonic retina is simply a neuroepithelial layer made up of progenitor cells which proliferate and expand in cell number; this event is necessary to achieve the right size and proportion of different cell types[7,8,31]. The neural epithelial progenitor cells undergo patterning to generate six different types of neurons and one type of glia arranged in three laminar layers. The three laminar layers are retinal ganglion cells (RGC) and displaced amacrine cells in the ganglion cell layer (GCL); biopolar, amacrine, horizontal and muller glia cells in the inner nuclear layer (INL), and rod and cone photoreceptor cells in the outer nuclear layer (ONL)[32–34]. The cell proliferation, neuronal development and gliogenesis are regulated by multiple transcription factors, mostly bHLH factors[34]. For example, in mice, *Tll*, *Hes1* and *Hes5* act to maintain the progenitor cells in undifferentiated state and play an important role in maintaining an adequate supply of retinal progenitors[35–37]. Then, the expression of neural bHLH genes like *Math5*, *Math3* and *NeuroD* in mice, regulates retinal cell fate specification and neurogenesis. The retinal cell fate specification and neurogenesis are highly regulated processes governing the proper time, position and number of different types of neurons in the retina. In mice, from E10.5 onwards, the retinal progenitors generate neurons, with the RGC appearing first and the muller glia cells appearing last[12,34,38–42].

Developing eye is vascularized by the process of angiogenesis[43,44], which also plays a role in different pathological conditions like proliferative diabetic retinopathy and wound healing[43]. Vasculature is one of the earliest organs formed and plays a major role in supplying oxygen and nutrient during development. Many signalling pathways, and Vegf in particular, play an important role in vasculature development. The primitive vascular network in the developing embryo is actively remodelled to form the mature vasculature[45–47].

Similar to other tissues of the body, oxygen and nutrients to the mammalian eye are supplied via three different vasculature systems. They are hyaloid, choroid and retinal vasculature[43]. While choroid and retinal vasculature are the main systems in the adult retina, the developing retina initially receives oxygen and nutrients via the hyaloid vasculature. The hyaloid vasculature is a transient vasculature system and is later replaced by the mature retinal vasculature. Proper regulation of the vascular system of the eye is important for its normal functioning; failure of it during development, as seen in a human condition of

persistent foetal vasculature or in various pathological conditions like proliferative diabetic retinopathy, venous occlusion and retinopathy of prematurity (ROP)[43,44,46–49].

### *Teleost models and teleost eye*

In recent years teleost models, zebrafish and medaka, have become popular to study various aspects of developmental biology and genetics of the eye[32,50,51]. The rapid external development, transparency of embryos, housing many fish together and the ease of obtaining a large number of offspring are advantages readily offered by these models. The possibility of performing toxicity and efficacy screening of chemicals, pharmaceuticals and pesticides that can be correlated in terms of human health risks are propelling this model as a choice for toxicological or pharmacological screens[52–62]. Small-molecule screening to identify and characterize a molecule that produced eye-specific effects has been successfully performed before[63].

The zebrafish, *Danio rerio*, has been more extensively used than medaka to study development. Zebrafish eye shows a high degree of anatomical and physiological homology to that of other higher order vertebrates and also has highly similar cellular structure, signalling processes and cognitive behaviour[59,64–66].

The medaka, *Oryzias latipes* is similar to the zebrafish in its anatomy and physiology. Medaka and zebrafish evolutionary lineages have been separated for around 110 million year ago (MYA)[3,51]. This separation offers a unique opportunity to uncover conserved and divergent pathways guiding various developmental and metabolic processes of the eye, as shown earlier for the photoreceptor patterning[67]. The collection of various mutant lines with defects in the development and functioning of the eye, and the development of various biochemical, molecular and genetic techniques facilitate studying developmental biology, metabolism and physiology of the eye in terms of various human ocular conditions[54,56,68–70] (Figure 2). The identification of teleost mutants with defects in the development of optic lobe, patterning and neurogenesis of the retina, development of lens, cornea or regulation of the intraocular pressure has aided in our further understanding of various human ocular defects such as microopthalmia, photoreceptor degeneration, cataract, glaucoma (as summarized in Figure 2).

The eye of the zebrafish and medaka displays high similarity to that of mammalian eyes[65,67]. Similar to other vertebrates, the teleost retina is made up of six different types of neurons and one type of glia cells. The RGC are the first neurons to be generated followed by other classes of neurons. The similarity to other vertebrates, rapid development of the eye and availability of many mutants showing defects in the development and functioning of the eye make these models ideal for elucidating the underlying genetic pathways in retina development[66,67,71–74].

The first sign of eye development in zebrafish occurs with the process evagination of the optic lobe from the diencephalon, whereas the early optic bud is seen as a bilateral evagination at around 11 hours post fertilization (hpf)[65,66]. The growth of the optic bud towards the overlying epithelium triggers lens induction. Following the lens induction at around 16 hpf, the invagination of lens vesicle and formation of the optic cup is seen. By 18 hpf the first eye shape is established with a distinct lens, retina and retinal pigment epithelium[32,50,65,66,75] (Figure 1). The first postmitotic neurons are already distinguishable between 28 and 32 hpf, and similar to other vertebrates the retinal ganglion cells are the first to become postmitotic[31]. Neurogenesis of the zebrafish retina starts at the ventronasal region, and spreads dorsally and temporally in a wave-like fashion. Histologically, by 48 hpf, lamination of almost the entire retina, and maturation of lens and cornea begin. Zebrafish exhibits complete visual function by 72 hpf[32,50,71]. The development of vasculature of the zebrafish eye also starts early (around 24 hpf). Endothelial cells can be seen entering the eye via the choroid fissure. These cells then form a network of vessels arround the lens and exit via the surface of the retina by 48 hpf[63]. This early vasculature is termed as intraocular vasculature and is similar to the hyaloid vasculature of the mammalian counterpart[76]. By 55 hpf, blood circulation via the intraocular vasculature is seen. But unlike mammalian, there is no hyaloid regression[63,76]; instead the intraocular vessels detach from the lens and fall on the bed of the retina forming the mature vasculature of the eye by 30 days post fertilization (dpf)[63,76]. The intraretinal vasculature seen in mammals is also absent in the zebrafish retina. Apart from the retinal vasculature, choriod and surface vasculature are also developed by 9 dpf and 72 hpf respectively[63]. The rapid development of the vascular system of the zebrafish eye and the ease with which compounds are permeable into the eye has been taken advantage of to conduct small-molecule screens to identify compounds affecting the eye vasculature specifically[63].

In comparison to zebrafish, the development of medaka eye is relatively slow; however the sequence of events governing the eye development is largely similar (Figure 1)[67]. Medaka early eye primordium can be first seen at around 26 hpf on either side of the rostral neural tube[77]. This event is almost about 14 h later than the appearance of the optic primordium in zebrafish[67]. Following the appearance of the optic primordium, grooving and depression of the optic bud is seen, which then leads to the formation of the first shape of the eye. Around 30 hpf, the early lens and the optic cup are clearly visible[77]. The optic cup is a simple neuroepithelial sheet with the inner surface forming the neural retina and the outer surface forming the pigmented epithelium[67]. Early medaka retina undergoes dynamic changes, from a simple neuroepithelial sheet at 30 hpf to a fully patterned retina by 9 dpf[67]. At around 58 hpf, the earliest signs of retinal

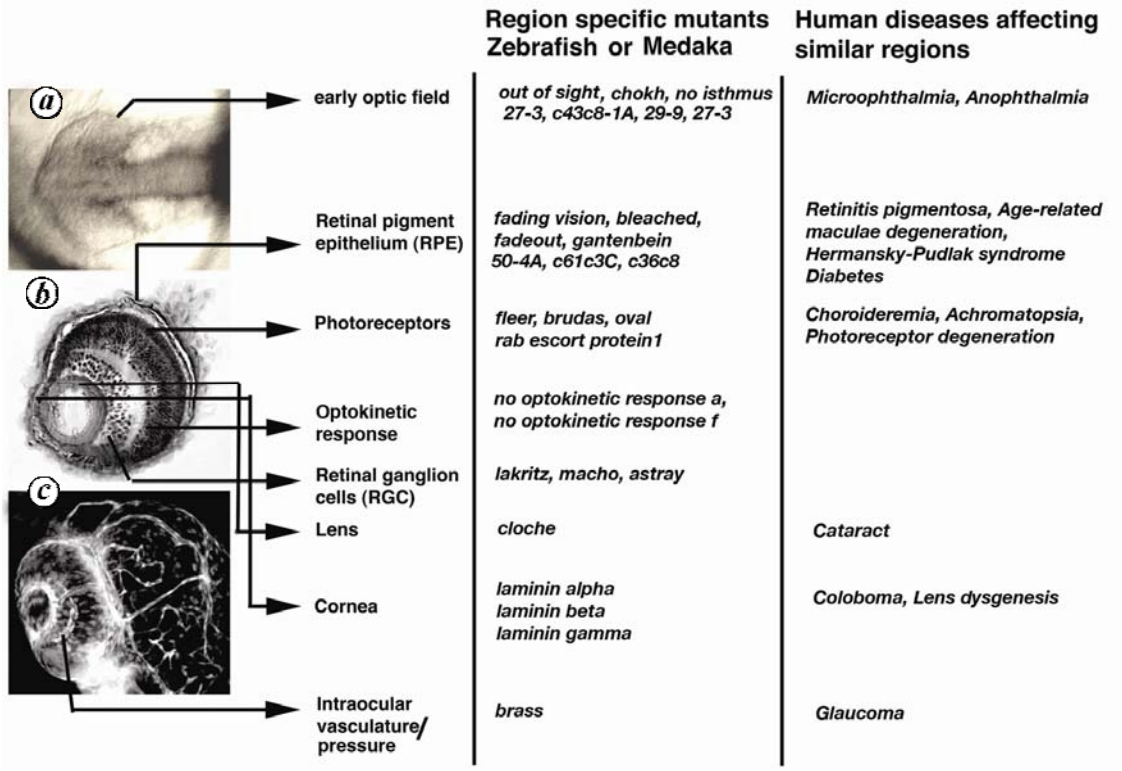


**Figure 2.** Comparison of ocular mutants identified in zebrafish and medaka to similar regions affected in human diseases. ***a***, Early optic field of eight somite zebrafish embryo; ***b***, Cross-sections of zebrafish larvae eyes at 4 days post fertilization showing different layers and regions of the eye; ***c***, Intraocular blood vessel of 72 hpf zebrafish larva.

neurogenesis can be characterized by the onset of ath5 expression[78]. Similar to other vertebrates, the expression of ath5 in medaka preceeds the differentiation of retinal ganglion cells. The expression of ath5 is seen in the central retina and as development proceeds, the expression domain expands towards the periphery and gradually disappears in the same fashion as it appeared. Immediately following the expression of ath5, neurogenesis begins in the retina[67,68,78]. Similar to that seen in zebrafish and other vertebrates, the retinal ganglion cells are the first cell type to appear at around 54 hpf[67]. At around 64 hpf, the onset of pigmentation of the retinal pigment epithelium is seen[77]. Almost about 20 h after the first appearance of the retinal ganglion cells, the retina shows signs of lamination on histology sections. By 9 dpf, the entire retina is laminated into three layers (RGC, INL, photoreceptor cell layer (PRCL)) and different cell types in these layers are arranged in the same fashion as seen in zebrafish and other vertebrates[67].

Although zebrafish and medaka are closely related species, the time taken for medaka eye development is much longer than that seen in zebrafish (Figure 1). In addition, differences can be seen in the pattern of neurogenesis and lamination of the retina. These remarkable differences between two closely related species are highly beneficial, given that they are the only two fish species widely used in genetic and embryological studies. The possibility of performing relatively fast and similar experiments in both the species creates an opportunity to understand the importance of different gene expressions for eye development. In addition, the availability of many mutants with eye defects in both species facilitates our understanding of the onset and progression of the mutant phenotype (Figure 2). Mutant phenotypes like photoreceptor degeneration, reduced eye size or disorganized retina or lens would profoundly increase our understanding of various diseases of the human eye (Figure 2).

### *Human eye diseases and teleost models*

Developmental ocular malformations in humans are caused by abnormalities in the normal programme of eye development. Mutations in various genes like CHX10, PAX6, BCOR, SOX2, OTX2 are heavily implicated in the failure of normal eye development[79]. Although the duration of eye development between human, mouse, chick, zebrafish and medaka is different (Figure 1), the sequence, spatial and temporal expression of molecular markers governing the development and patterning are highly conserved (Figure 1). Mutations in *Gdf6* gene in zebrafish mutant, *out of sight* (Figure 2), causes severe eye developmental abnormalities similar to the phenotype seen in human *GDF6* gene[80,81]. In zebrafish mutations in *rx3*, *pax6* and morpholino knockdown experiments of

**Table 1.** Examples of markers routinely used to study eye development in teleost fish, zebrafish or medaka. The region of the eye is indicated in the column to the left that is followed by the RNA probe or antibody against genes specifically expressed in that region

| Area | RNA probe | Antibody |
|---|---|---|
| Eye primordium | Retinal homeobox (rx) gene 1, 2, 3, paired homeobox gene (pax) 2a, ventral anterior homeobox gene (vax)1, vax2, sine oculis homeobox gene (six)3a, six3b | pax2 |
| Retinal ganglion cells | Atonal gene (ath)5, activated leukocyte cell adhesion molecule (alcam), brain3b, brain3a | zn-5, zn-8 |
| Inner nuclear layer | Tyrosine hydroxylase (Th), gamma-amino butyric acid (GABA), visual system homeobox (vsx)1, vsx2, pax6a | Islet-1, pax6a, Th, serotonin, Chat, parvalbumin, GABA, Glutamic acid decarboxylase (GAD)67, Glial Fibrillary Acidic Protein (GFAP) |
| Photoreceptor cell layer | Rod opsin, UV opsin, red opsin, blue opsin, green opsin | zpr1, zpr3, zs-4 |
| Inner plexiform layer | | Synaptosomal-associated protein 25 (snap-25), synaptic vesicle (SV2), sybtaxin-3 |
| Retinal pigment epithelium | Microophthalmia-associated transcription factor a (mitfa), tyrosine related protein 1 (tyrp1) | |
| Lens | Fibroblast growth factor (fgf) 19, musculoaponeurotic fibrosarcoma oncogene homologue B (mafb), beta-1,3-N-acetylglucosaminyltransferase 5 (b3gnt5), $\alpha$ and $\beta$ crystalline, prospero-related homeobox gene (prox) 1 | zl-1, $\alpha$-crystalline, Lengsin |
| Cornea | Lumican, scinderin a, scinderin b | Keratin 3, transforming growth factor, beta-induced (BIGH3), keratinsulfate proteoglycan |
| Blood vessels | ETS transcription factor (fli1), vascular endothelial growth factor receptor 2 (flk1), angiomotin (amot) l1 | amotl1 |

*six3*, *otx2*, *chx10* cause ocular malformation similar to that seen in mutations of the corresponding genes in humans[81–87]. Zebrafish mutants affecting neurogenesis, patterning and optokinetics also correlate to various human diseases as summarized in Figure 2.

## Advantages of teleost model

### *Gene expression analyses*

Basic understanding of the spatio-temporal expression pattern is a straightforward approach in linking the role of a gene during development or disease. In zebrafish and medaka models, chromogenic or flurogenic whole-mount *in situ* hybridization is widely used (Table 1)[67,71]. The possibility of performing single or multicolour *in situ* hybridization along with immunohistochemistry allows rapid characterization of gene expression in these teleost models. Whole-mount *in situ* hybridization and immunohistochemistry has been effectively used to characterize various genes required for the specification, patterning and maintainance of the teleost eye (Table 1). Gene expression analyses have been effectively used in mutagenic screens and chemical genetics in zebrafish and medaka[70,88,89]. Simple comparison of gene expression analyses of opsin in zebrafish and medaka identified two different signalling centres for photoreceptor patterning in the medaka retina[67].

### *Knockdown or overexpression of gene expression*

The rapid development of the teleost embryos has allowed the usage of nuclease-resistant modified oligonucleoides called morpholino to achieve effective knockdown of gene expression. Morpholino oligonucleotides designed against the splice site or initiation of transcriptional start site of the gene of interest can be microinjected to achieve efficient knockdown[90]. Morpholino knockdown is transient and the gene expression is quickly restored as the morpholino gets diluted with cell division. Recent advances in the development of photoactivatable caged morpholino allow us to perform time and area-specific knockdown[91]. Morpholino knockdown technology has provided a quick and efficient way in understanding the role of many genes implicated in various human ocular diseases[54,92]. Over expression of the gene of interest can be simply achieved by injecting *in vitro* transcribed capped mRNA of the gene of interest. Over expression can be achieved at specific time points using the Gal4 : UAS system, where transcription of the gene of interest can be controlled via the binding of the transcription activator (Gal4) to the upstream activation sequence (UAS), or over expression is also achieved via heat shock construct, where the gene of interest is placed under heat shock promoter (*hsp70*) and its transcription induced by incubating the embryos at a higher temperature[92,93].

### *Transgenic development*

Transgenic technology has found enormous potential in agriculture, medicine and biotech industry. The ease with which this technology can be applied to teleost model has allowed the development of transient assays, enhancer trapping, high content/high throughput screens, cell migration/lineage studies, tissue-specific expression, targeted mis-expression and mutagenesis screen[54,94,95]. The rapid development and possibility of obtaining large quantity of embryos allows performing these assays/experiments in a relatively short time compared to other vertebrate models[52].

In teleost fish, simple microinjection of the linearized plasmid results in a low integration into the genome. Using transposons like Tol2 (ref. 96), or retroviral vectors[97], or electroporation[98] increases the efficiency of integration. Various transgenic lines expressing fluorescent proteins in different parts of the teleost eye are available. For example, fluorescent protein expression driven by brn3a (in RGC layer)[99], GFAP (in the INL layer), opsin (photoreceptor layer) and Fli1 (eye vasculature) promoters has been effectively used in targeted screens and mutant phenotype/cell migration analyses[96].

### *Cell shape changes and migration*

Precise changes in cell shape, volume and size are necessary for events like gastrulation, germ-layer formation, segmentation, optic cup formation, etc. to occur[100]. Although there are qualitative descriptive data on these events, an accurate measurement of cell dynamics during these events is necessary to understand development and developmental disorders. The early embryonic transparency and the possibility of using chemical like *N*-phenylthiourea to suppress pigmentation have allowed reconstructing various developmental events at cellular level. Imaging techniques employing parallelized linear microscopy, point scanning two-photon microscopy, label-free nonlinear microscopy and time-lapse microscopy have allowed precise mapping and cell lineage reconstruction of early events in zebrafish model[100–102]. These approaches can not only be adopted for studying normal development, but also in understanding various disease processes.

### *Mutagenesis*

Mutagenesis using chemicals, radiation, and retrovirus has been successfully performed, and genes important for development and normal homeostasis have been identified via this process[54,56,59,103,104]. Various ocular mutants have been isolated via *N*-ethyl-*N*-nitrosourea (ENU) mutagenesis and have proved to be a preferred method in both forward and reverse genetics[54,74]. ENU-induced random mutagenesis followed by morphological/behavioural screens have been used to identify various genes required for regulating eye development and/or function[59]. Genetic lesions in the gene of interest have also been successfully performed to generate ocular mutants using targeting induced local lesions in genome (TILLING) methodology, which utilizes either *Cel*1 enzyme that cleaves heteroduplex DNA at all possible single-nucleotide mismatches or by direct resequencing of the target genes from a single mutagenized fish[105]. Emerging gene knockout technology using zinc finger nucleases in zebrafish has allowed inducing mutation in a gene-specific manner at a high frequency. This methodology utilizes zinc finger nucleases engineered to bind to a specific sequence of DNA of the gene of interest and introduce a double strand break. The double strand breaks are repaired by non-homologous end joining pathway, which introduces new nucleotides causing frame shifts[106].

### *Chemical screen*

Small molecules, drug candidates, plant extracts, metabolites, xenobiotics, toxic compounds or pollutants can be easily evaluated using teleost models[60–62,107,108]. For example, the toxicity of heavy metals such as cadmium on retinogenesis during zebrafish embryonic development has been well characterized[109]. The rapid external development, small size, early transparent development and the possibility of obtaining large amounts of embryo from a single cross have greatly added to the use of zebrafish or medaka model as an *in vivo* vertebrate screening tool. Chemical genetic screens have been successfully carried out using zebrafish model to identify target pathways and disease phenotype rescue[110]. The availability of transgenic animals has created an easy readout for the screens, as seen in the identification of compounds that specifically affect the retinal vasculature in zebrafish[63].

### *Evolutionary and comparative genomics studies*

The Fugu genome project, initiated in 1989 was the second vertebrate genome to be fully sequenced[111]. This vertebrate teleost fish with genome size almost one-eightof the human genome has proved be a useful reference genome to identify and annotate many genes from the human genome[111–113]. The availability of genomic sequences of zebrafish and medaka and the fact that their respective genomes have independently evolved for almost 100 MYA offers a good platform for evolutionary and comparative genomics studies[51,114]. In addition to the availability of genomic sequence, the teleost genome has undergone whole genome duplication[114], which provides a good scaffold to identify the convergent and divergent signalling processes in the eye development. For example, the identification of multiple Hox clusters, *pax6*, *rx*, *brn3a* genes in zebrafish and their characterization has

allowed us to decipher their importance in eye development and disease[115–118]. The comparative genomics also helps in the identification of the importance of various signalling process required for eye development in different species in evolution, as seen in the case of eye loss of cave fish[119]. The possibility of performing wet laboratory experiments in zebrafish and medaka, to confirm the data from the genomic comparison offers a good platform to understand eye development, patterning and neurogenesis. For example, comparison of different opsins followed by characterizing their expression in zebrafish and medaka has identified two independent areas of photoreceptor patterning in medaka retina compared to zebrafish[67].

Zebrafish and medaka have ciliary marginal zones in the eye where continous proliferation occurs[66,78,120,121]. This feature of the eye allows the teleost to repair and/or regenerate the retina[122]. The regenerative property can be exploited to gain insights and develop various tools aiding in regenerative medicine, stem-cell therapy and injury repair of the human eye.

## Conclusion

The advantages offered by zebrafish and medaka makes them important models to gain rapid understanding of different human ocular conditions. The low cost, small size and the ease with which these vertebrate models can be handled make them a perfect choice to conduct large-scale chemical and mutagenesis screens. While many mutants in zebrafish or medaka corresponding to the disease-causing loci of the human eye are not available, continuous screening efforts are underway in many laboratories to identify more mutants causing defects during early development and in adult stage. The analyses of currently identified ocular mutants in these models would provide insights into a better understanding of the disease process and mechanisms leading to dysfunction of the eye. Another advantage with the zebrafish and medaka models would be the possibility of conducting small molecule or drug screens designed to rescue or alleviate the mutant phenotype. For example, screens to identify small molecules that would rescue photoreceptor loss in many photoreceptor mutants or decrease the intraocular pressure in the mutants with elevated ocular pressure would have direct clinical implications. The zebrafish and medaka models would not only strengthen the effort put into understanding the molecular pathways leading to various human ocular conditions, but would also complement other models, thereby proving to be powerful tools in understanding the development, functioning process and diseases of the human eye.

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