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Zebrafish in Biomedical Research and Drug Discovery

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Review Article

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ABSTRACT

Many model organisms like yeast (Saccharomyces), Drosophila, zebrafish, mouse, rats, hamsters, rabbits, cat, chicken, monkey etc. are being used in biomedical research. Invertebrate models like yeast, Drosophila etc. are used to study genetic functions. On the other hand vertebrate model systems like mouse, rats, hamsters, rabbits, cat, chicken, monkey preferred models for research in diseased conditions when compared to invertebrate model organisms but vertebrate models are the more complex model systems. Zebrafish though a vertebrate with physiological and anatomical characteristics of higher organism it also provides the ease of use of a lower organisms. Hence zebrafish offers an important model system which can connect development, disease, and toxicological studies.

INTRODUCTION

The zebrafish (*Danio rerio*) is a freshwater fish found in tropical environment a native of Himalayan region and is commonly kept in aquaria in India. It belongs to the Cyprinidae family and Cypriniformes order. Initially it is studied for vertebrate development and it is the first vertebrate organism to be cloned. Over the period of time large number of zebrafish models has been developed for investigating different human diseases and toxicity studies. Both embryos and the adult zebrafish are widely being used in the research.

The use of zebrafish as an experimental animal model is increasing these days. This model is gaining popularity in the fields of biomedical research and toxicology. The reason behind wide acceptance of zebrafish as animal model is because of exceptional characteristics which are discussed below.

Zebrafish have a fully mapped genome with 400 distinct genes and >2000 microsatellite markers which is found significantly homologous to the human genome (about 75% Similar), including noncoding regions which suggests that many genes involved in human diseases can be matched with zebrafish genome. Signaling pathways of both zebrafish and humans are highly conserved with high genomic homology. Gene function assessment can be performed in zebrafish with ease by transgenic development and knockdown experiments making it a handy model for analytical studies [1-6].

Zebrafish possess high fecundity produce large number of embryos. On an average female spawn around 300 eggs per week under optimal conditions. It is found that the hatching of eggs and organogenesis occurs rapidly [7-14]. In contrast to other mammalian models they develop outside uterus which makes it possible to raise them in petri dishes or in multi- well plates containing water. They can be used for larval experiments from 3rd days post fertilization (dpf). The embryos are transparent (Figure 1) upto 7 dfp, and all cells cells can be observed since intial larval stage. In addition to it tissues and organs can also be visualized *in vivo* the transparency can be extended to up to 9-14 dpf by adding melanocyte inhibitor like phenylthiourea. Moreover, recently transparent adult zebrafish like the Casper line (Figure 2) is produced which provides new imaging possibilities. Additionally the use of sophisticated fluorescent technologies to indicate signaling proteins and cellular entities help in making time-lapse imaging of biological processes and diseases possible (Figure 3).

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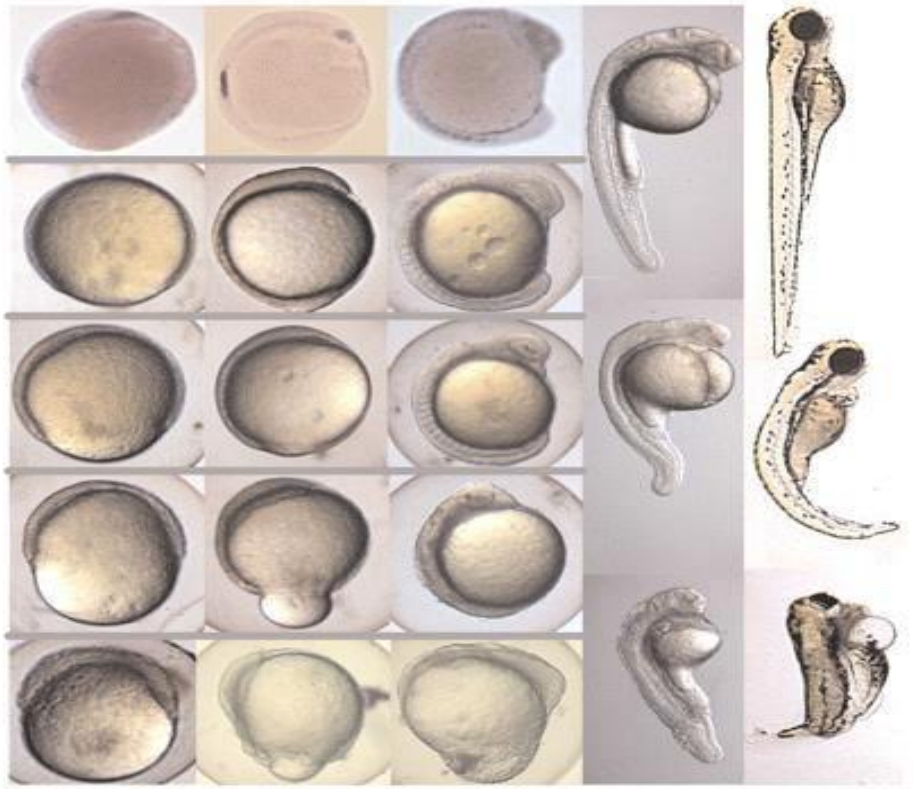

Figure 1. Figure showing different stages of transparent zebrafish embryo.

Figure 2. Figure showing transparent zebrafish (Casper line).

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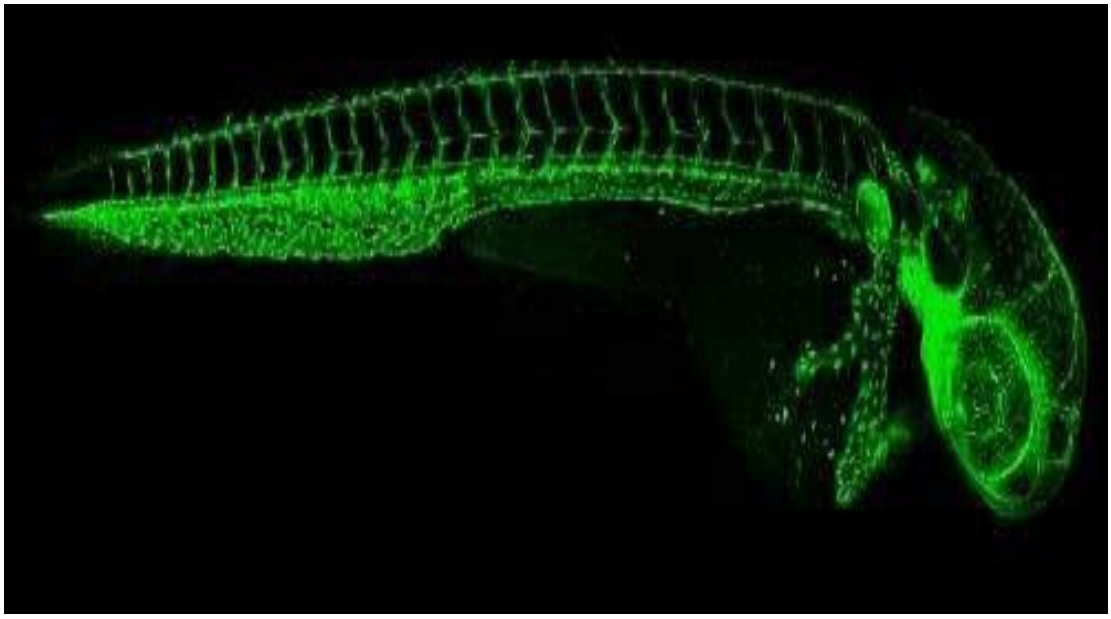

Figure 3. Genetically modified zebrafish with circulatory system glowing with a green fluorescence to study the development of circulatory system.

Drugs can be administered systemically to zebrafish just by adding it to the water in the aquarium on the other hand if embryos are used, then the test compound is added to water in the petri plates that holds the embryo [16-20]. Hence these models can be preferred to test scarce or expensive compounds. Drugs can also be locally delivered into the tissues with the use of surgical implants or electrophoresis. Animal breeding, developing and maintaining animal house facilities involve high cost whereas zebrafish with their smaller size, high fecundity, simple and rapid lifecycle and developemental stages make them ideal for reliable rapid and economic screenings during pre-regulatory phases and toxicity studies [21-31].

Zebrafish are even used in high-throughput screening (HTS) of drug libraries. Zebrafish embryos or larvae, in the same development stage, are loaded into multi well plates, and are then screened with chemical compounds at different concentrations. Robotics and automated fluid handling systems are also used in HTS [32-35].

ZEBRA FISH AS DISEASE MODELS

Alzheimer's Disease

Though rodents are more closely related to human physiology than fish, Zebrafish whose embryos are easily manipulable because of their large size, their ready availability and the ease of gene manipulation even in their development for assay of particular gene activities make zebrafish embryos a felicitous vertebrate system to examine the cellular and molecular functions of genes implicated in Alzheimer's Disease [36-40].

Depression

Because of neuroanatomical, neuroendocrine, neurochemical and genetic homology to mammals, chemical genetic screens, zebrafish offers ideal experimental models of depression helps in discovering novel therapeutics. Behavioral testing models like–cognitive, avoidance and social paradigms are available in zebrafish and can be used to identify depression in zebrafish by exposing them to physiological, environmental, genetic, and/or psychopharmacological alterations. Moreover they are highly sensitive to commonly used psychotropic drugs [41-45].

Anxiety

All the "classic" neurotransmitters present in vertebrates are possessed by Zebrafish and its neuroendocrine system shows different physiological stress responses. Two important methods namely light/dark test and the novel tank test are demonstrated successfully in zebrafish to study anxiety disorders [46-49].

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Immune System

Zebrafish possess an innate immune system composed of NK cells, neutrophils, and macrophages/monocyte which starts functioning from 2 dpf and an adaptive immune system that is functioning during 4–6 weeks post fertilization which is highly similar to that of mammalian, with T lymphocytes and B lymphocytes that have Rag-dependent V(D)J recombination which makes zebrafish a suitable animal model for immune system [50,51].

Cancer

Stanton, et al. in 1960s first used Zebrafish in cancer research to test the effects of carcinogens. Though it have a very low rate of spontaneous neoplasia, which account to about only 10% of zebrafish develop a tumour in lifetime, when exposed to carcinogenic agents likes MNNG (N-methyl-N-nitro-N-nitrosoguanidine), DMBA (7,12-dimethylbenz(a)anthracene) and DENA (diethylnitrosamine) they develop cancer. It has been proved to be an ideal model to study the malignancy of many tumours by using tumour transplantation assays. They were found to be robust and have an additional advantage of high fecundity as discussed earlier which provide donor and recipient fish in large numbers. Many types of cancers like melanoma, leukemia, endocrine or liver cancer are studied using zebrafish. Moreover by using xenotransplantation of human tumor cells into zebrafish embryos (xenografts) phenomena like metastasis, tumor cell migration, angiogenesis can be studied. Availability of forward and reverse genetic tools, the non-invasive *in vivo* imaging technology, and the above characteristics made it an ideal vertebrate model to study cancer [52-54].

Diabetes and Lipid Diseases

Because of accessibility of zebrafish for developmental studies, a complete description of pancreatic development and morphogenesis is available which led to the understanding of extrinsic signaling molecules, like Shh, retinoic acid and FGF, in influencing intrinsic transcriptional programs. These studies made zebrafish an alternative model to study the onset of diabetes along with its treatment. Hypoglycaemia can be induced in zebrafish by exposing it to high glucose and even retinopathies are developed with prolonged high blood sugar levels. All these makes it suitable model for diabetes.

Zebrafish possess many similarities with mammals in terms of lipid absorption, processing and metabolism, moreover application of new imaging methods with subcellular resolution to whole organism and the use of fluorescent lipid. It is even used in obesity studies [55-63].

Gastrointestinal Disorders

The gastrointestinal system of zebrafish is highly homologous to mammalian counterpart, which contains a liver, gall bladder, pancreas and a linearly segmented intestine with secretory and absorptive functions. The intestinal epithelium possess similar proximal-distal functional specification and many of same epithelial cell lineages like goblet cells, enteroendocrine cells and absorptive enterocytes. With the help of all these similarities zebrafish are used to model numerous gastrointestinal pathologies [64].

Cardio Vascular Diseases

The development of the zebrafish cardiovascular system is thoroughly studied and characterized, which provides great insights in cardiac development, vasculogenesis and angiogenesis. Some outstanding features like external embryological development, its optical clarity of embryo, closed cardiovascular system and similar cardiac cycle to that of humans make the sequential observation of the developing blood vessels and heart possible without invasive technique. Researchers have studied the origins of defects in heart shape, size and function. All these make zebrafish model useful in cardiovascular research [65-69].

Renal Disorders

Zebrafish provides a promising model for studying kidney development it provides many advantages which make it suitable model for genetic research, like the generation of offsprings in large numbers (exutero) with rapid development, low maintenance and ease of genetic modification. Use of genome editing techniques, like TALENs

and CRISPR/Cas9 for modeling human genetic disease in zebrafish is making progress moreover zebrafish larvae during 2-3 dpf possess a pronephros which is a simple reflection of human nephron [70-75].

CONCLUSION

Animal models are being used in medical research since ages among which the most commonly and successful models are that of rodents [76-101]. Though a lot of knowledge is attained from this models few factors like long gestation time of about 2-3 weeks, sexual maturation rate of 6–8 weeks and expensive housing and breeding techniques lead to search for other model organisms. The zebrafish appears as a model organism with large amounts of untapped potential. As it provides comparative anatomy and physiology, genome to that of humans this models can be used to study initial genetic or drug target information before scaling up to expensive systems moreover the transparent, larval zebrafish models can be used to study of human disease, and enables rapid physiologically relevant *in vivo* screening. The transparency of zebrafish also allows real-time imaging of pathogenesis, which can provide insights into the molecular mechanisms. Furthermore the amenability of this model for high throughput screening and different human disease makes it more helpful to researchers. However the utility of this vertebrate model though cannot replace mammalian models in the drug development mostly in the later stages where regulatory authorities demands mammalian studies and clinical trials it will provide a powerful complement to the murine system.

REFERENCES

1. Carneiro MC, et al. Telomeres in aging and disease: lessons from zebrafish. Dis Model Mech. 2016;9:737-48.
2. Goldsmith JR and Christian J. Think Small: Zebrafish as a Model System of Human Pathology. J Biomed Biotechnol. 2012.
3. Chitramuthu BP. Modeling Human Disease and Development in Zebrafish. Human Genet Embryol. 2013;3:e108.
4. Chatterjee PK. Trapping enhancers by transgenic expression of BACs in zebrafish. J Mol Genet Med. 2014;8:3.
5. Kishi S, et al. Zebrafish as a genetic model in biological and behavioral gerontology: where development meets aging in vertebrates--a mini-review. Gerontology. 2009;55:430-441.
6. Schartl M. Beyond the zebrafish: diverse fish species for modeling human disease. Dis Model Mech. 2014;7:181-192.
7. J Aquac. Effects of rearing conditions on fish growth and sex ratios: Epigenetic and transcriptomic studies in zebrafish and European sea bass. Res Development. 2015;6:6.
8. Christopher L Antos, et al. Calcineurin instructs when to stop regenerating once the correct size of zebrafish appendages is reached. J Tissue Sci Eng. 2015;6:2.
9. Ingham PW. The power of the zebrafish for disease analysis. Hum Mol Genet. 2009;18:R107-R112.
10. Zon LI. Zebrafish: a new model for human disease. Genome Res. 1999;9:99-100.
11. Gootenberg DB and Turnbaugh PJ. Companion animals symposium: humanized animal models of the microbiome. J Anim Sci. 2011;89:1531-1537.
12. Tavares B and Santos Lopes S. The importance of Zebrafish in biomedical research. Acta Med Port. 2013;26:583-592.
13. Deo RC and MacRae CA. The zebrafish: scalable in vivo modeling for systems biology. Wiley Interdiscip Rev Syst Biol Med. 2011;3:335-346.
14. Okamoto H and Ishioka A. Zebrafish research in Japan and the National BioResource Project. Exp Anim. 2010;59:9-12.
15. Marshall RA and Osborn DP. Zebrafish: a vertebrate tool for studying basal body biogenesis, structure, and function. Cilia. 2016;5:16.
16. Gioacchini G, et al. Effects of Probiotics on Zebrafish Reproduction. J Aquac Res Development. 2011;S1:S2.
17. Sahoo TP and Oikari A. Use of Early Juvenile Zebrafish Danio Rerio for In-Vivo Assessment of Endocrine Modulation by Xenoestrogens. J Environ Anal Toxicol. 2013;4:202.
18. Jan de Sonneville. Use of zebrafish embryos to elucidate and target disease mechanisms in vivo. J Cell Sci Ther. 2012;3:7.
19. Barreiro-Iglesias A. Transgenic Zebrafish Lines as Valuable Tools to Understand Successful Spinal Cord Regeneration. Clon Transgen. 2013;3:118.

e-ISSN: 2322-0139
p-ISSN: 2322-0120

20. Raghupathy RK, et al. Transgenic Zebrafish Models for Understanding Retinitis Pigmentosa. Clon Transgen.2013;2:110.
21. Christopher L Antos, et al. Simplet is required for nuclear localization of beta-catenin and for progenitor cell proliferation and patterning during zebrafish early embryogenesis and tissue regeneration. J Cell Sci Ther. 2014;5:4.
22. Saputra F, et al. Toxicity Effects of the Environmental Hormone 4-Tert-Octylphenol in Zebrafish (Danio Rerio). J Marine Sci Res Dev. 2016;6:180.
23. Khan M, et al. Identification of Stress Related Molecular Biomarkers in Zebrafish Employing an In-Silico Approach to Access Toxicity based Risks in Aquaculture. Poult Fish Wildl Sci. 2015;3:137.
24. Bhusnure OG, et al. Drug Target Screening and its Validation by Zebrafish as a Novel Tool. Pharm Anal Acta. 2015;6:426.
25. Zhou W, et al. Zebrafish as a New Platform Used in Exploration of Ketamine-Induced Neurodevelopmental Toxicity. J Clin Exp Pathol. 2015;5:225.
26. Bourdineaud JP, et al. Partial Inventory of ABCB and ABCC Transporter Genes responding to Cadmium and Zinc Contamination in Zebrafish Danio Rerio. J Environ Anal Toxicol. 2015;5:276.
27. Lucia Rocco, et al. Genotoxicity in zebrafish (danio rerio) exposed to two pharmacological products from an impacted italian river. J Environment Analytic Toxicol. 2011;1:1.
28. Noor F. Advanced human cell cultures for repeated dose exposure in toxicity prediction and adverse outcome pathways studies. J Drug Metab Toxicol. 2015;6:3.
29. Rocco, et al. Genotoxicity in zebrafish (danio rerio) exposed to two pharmacological products from an impacted Italian river. J Environment Analytic Toxicol. 2011;1:2.
30. Hill AJ, et al. Zebrafish as a model vertebrate for investigating chemical toxicity. Toxicol Sci. 2005;86:6-19.
31. Antonio Planchar, et al. Advancing toxicology research using in vivo high throughput toxicology with small fish models. ALTEX. 2016.
32. Chiranjib Chakraborty, et al. Zebrafish: A complete animal model to enumerate the nanoparticle toxicity. J Nanobiotecnol. 2016;14:65
33. Mathias JR, et al. Advances in zebrafish chemical screening technologies. Future Med Chem. 2012;4:1811-1822.
34. Boyd RT. Using zebrafish for screening and development of new nicotinic and dopaminergic drugs. Mol Biol. 2012;1:e102.
35. Avsar-Ban E, et al. High-Throughput Injection System for Zebrafish Fertilized Eggs. J Data Mining Genomics Proteomics.2013;4:137.
36. Bhusnure OG, et al. Zebrafish as a model system for drug target screening and validation. J Develop Drugs. 2015;4:4.
37. Vemula PK, et al. Design and development of a novel color bias avoided and appetite conditioning T-Maze model for evaluating the memory enhancing drugs in zebrafish. Res. J. Pharm. 2014; 5:434-437.
38. Boyd RT. Therapeutic targeting of nicotinic acetylcholine receptors: From Alzheimer's to zebrafish. Biochem Anal Biochem. 2013;2:4.
39. Olivier Kah, et al. Biosensor zebrafish comes to the rescue to study effects of steroids and endocrine disruptors on brain development. Endocrinol Metab Synd. 2014;3:2.
40. Newman M, et al. Using the zebrafish model for Alzheimer's disease research. Frontiers in Genetics. 2014;5:189.
41. Newman M, et al. Zebrafish as a tool in Alzheimer's disease research. Biochimica et Biophysica Acta. 2011; 1812:346-352.
42. Fonseka TM, et al. Zebrafish models of major depressive disorders. J Neurosci Res. 2016;94:3-14.
43. Gerlai R. Zebrafish antipredatory responses: a future for translational research? Behav Brain Res. 2010;5:223-231.
44. Haesemeyer M and Schier AF. The study of psychiatric disease genes and drugs in zebrafish. Curr Opin Neurobiol. 2015;30:122-130.
45. Walcott BP and Peterson RT. Zebrafish models of cerebrovascular disease. J Cereb Blood Flow Metab. 2014;34:571-577.
46. Singh SK, et al. Proteome profile of zebrafish brain based on gel lc-esi ms/ms analysis. J Proteomics Bioinform.2010;3:135-142.

e-ISSN: 2322-0139
p-ISSN: 2322-0120

47. Ortiz JG. Zebrafish as a screening tool for psychoactive incenses. J Addict Res Ther. 2014;5:3.
48. Raúl Bonne Hernández, et al. Toxicogenomics analysis of zebrafish (danio rerio) embryos reveals pathways involved in manganese induced Dementia. J Drug Metab Toxicol. 2015;6:3.
49. Jesuthasan S. Fear, anxiety, and control in the zebrafish. Dev Neurobiol. 2012;72:395-403.
50. Whitfield TT. Zebrafish as a model for hearing and deafness. J Neurobiol. 2002;53:157-171.
51. Renshaw SA and Trede NS. A model 450 million years in the making: zebrafish and vertebrate immunity. Dis Model Mech. 2012;5:38-47.
52. Qing Deng. Host-pathogen interactions in zebrafish. J Bacteriol Parasitol. 2013;4:4.
53. Quintana AM, Grosveld GC. Zebrafish as a model to characterize tel2 function during development and cancer. J Carcinogene Mutagene. 2011;S1:001.
54. Barriuso J, et al. Zebrafish: a new companion for translational research in oncology. Clin Cancer Res. 2015;21:969-975.
55. Lu JW, et al. Zebrafish as a Model for the Study of Human Myeloid Malignancies. Biomed Res Int. 2015;2015:641475.
56. Norbiato G. Facing up to diabetes mellitus, epidemic of the century, with a new biological treatment based onstem cells differentiation stage factors (SCDSFs) taken from zebrafish embryos. J Diabetes Metab. 2015; 6:10.
57. Tamaru Y, et al. Molecular Characterization of Protein O-Linked Mannose ß-1,2-N-acetylglucosaminyl transferase 1 in Zebrafish. J Glycomics Lipidomics. 2014;4:111.
58. Nakatani H, et al. Characterization of N-Myristoyltransferases in Vertebrate Embryos by Using Zebrafish: Appearance of Low Molecular Weight N-Myristoyltransferase 1 in Early Development. J Glycomics Lipidomics. 2014;4:120.
59. Jerzy Adamski, et al. Zebrafish 20 α -hydroxysteroid dehydrogenase type 2 is important for glucocorticoid catabolism in stress response. Endocrinol Metab Synd. 2014;3:2.
60. Lin YP, et al. The Liver-Enriched Transcription Factors HNF-1α, HNF-3α , and C/EBPα Contribute to the Growth Hormone-Induced Transcription of the Progranulin a Gene in Zebrafish (Danio Rerio). J Aquac Res Development. 2014;5:237.
61. Rutao Liu, et al. Mechanisms and modes of lead action on SOD inactivation in zebrafish livers. J Clin Toxicol. 2015;5:3.
62. Chiou-Hwa Yuh. Establishment of Anti-hepatocellular Carcinoma drug screening platform in zebrafish. J Liver. 2015;4:3.
63. Hor-Yue Tan, et al. Preclinical Models for Investigation of Herbal Medicines in Liver Diseases: Update and Perspective. Evid Based Complement Alternat Med. 2016;2016:26.
64. Goessling W and Sadler KC. Zebrafish: an important tool for liver disease research. Gastroenterology. 2015 149:1361-1377.
65. Yang Y, et al. Could a swimming creature inform us on intestinal diseases? Lessons from zebrafish. Inflamm Bowel Dis. 2014;20:956-966.
66. Florian Ulrich, et al. Development of functional hindbrain oculomotor circuitry independent of both vascularization and neuronal activity in larval zebrafish. Curr Neurobiol. 2016;7:62-73.
67. Qi M, Chen YH. Zebrafish as a Model for Cardiac Development and Diseases. Human Genet Embryol 2015; 5:e112.
68. Zong-Yu Kuo, et al. Investigating the significant proteins of heart regeneration by comparing the PPI networks of zebrafish, MRL mouse and C57 mice via gene expression analysis. J Proteomics Bioinform. 2012;5:6.
69. Jiang Zhang. A statistically enhanced spectral counting approach to tcdd cardiac toxicity on the adult zebrafish heart. J Proteomics Bioinform. 2013;6:7.
70. Aarti Asnani and Randall T. Peterson. The zebrafish as a tool to identify novel therapies for human cardiovascular disease. Disease Models & Mechanisms. 2014;7:763-767.
71. Miceli R, et al. Molecular Mechanisms of Podocyte Development Revealed by Zebrafish Kidney Research. Cell Dev Biol. 2014;3:138.
72. Poureetezadi SJ, Wingert RA. Congenital and Acute Kidney Disease: Translational Research Insights from Zebrafish Chemical Genetics. Gen Med (Los Angel). 2013;1:112.
73. Gary F Gerlach, et al. Modeling renal progenitor development using the zebrafish kidney. J Cell Sci Ther. 2015; 6:2.

74. Robert McKee. Using zebrafish to model acute kidney injury. Transl Med 2014;4:3.
75. Rebecca A Wingert. Zebrafish as an animal model to study renal regeneration after acute kidney injury. Transl Med. 2014;4:3.
76. van de Hoek G, et al. Functional models for congenital anomalies of the kidney and urinary tract. Nephron. 2015;129:62-67.
77. Ibrahim AE, et al. Elucidation of Acrylamide Genotoxicity and Neurotoxicity and the Protective Role of Gallic Acid and Green Tea. J Forensic Toxicol Pharmacol. 2015;4:1.
78. Altawil HJA, et al. Analgesic, Antipyretic and Anti-Inflammatory Activities of the Egyptian Spitting Cobra, Naja Nubiae Venom. J Forensic Toxicol Pharmacol. 2015;4:1.
79. Aboubakr M, et al. Influence of Aeromonas hdrophilia Infection on the Disposition Kinetic of Norfloxacin in Goldfish (Carassuys auratus Linnaeus). J Forensic Toxicol Pharmacol. 2014;3:1.
80. El-Bialy BES, et al. Biochemical and Histopathological Alterations as Forensic Markers of Asphyxiated Rats and the Modifying Effects of Salbutamol and/or Digoxin Pretreatment. J Forensic Toxicol Pharmacol. 2016;5:1.
81. Tsompos C, et al. The Effect of the Antioxidant Drug "U-74389G" on Uterus Inflammation during Ischemia Reperfusion Injury in Rats. J Pharm Sci Emerg Drugs. 2016;3:1.
82. Swapnil S, et al. Healing Potential of Citrullus Lanatus in Acetic Acid Induced Ulcerated Rats. J Pharm Sci Emerg Drugs.2015;3:1.
83. Balekari U and Veeresham C. Insulinotropic Agents from Medicinal Plants. J Pharm Sci Emerg Drugs. 2014;2:1.
84. Zhou Y, Gui S, et al. Therapeutic Effects of Sinomenine Microemulsion-Based Hydrogel on Adjuvant-Induced Arthritis in Rats. J Pharm Drug Deliv Res. 2014;1:3.
85. Akintunde JK, et al. Sub-Chronic Treatment of Sildernafil Citrate (Viagra) on some Enzymatic and Non-enzymatic Antioxidants in Testes and Brain of Male Rats. J Pharm Drug Deliv Res. 2012;1:2.
86. Arikawa M, et al. Donepezil, Therapeutic Acetylcholinesterase Inhibitor, Prevents the Progression of Ventricular Dysfunction by Promoting Myocardial Glucose Utilization in Rat Model of Chronic Heart Failure Following Myocardial Infarction. Cardiol Pharmacol. 2014;3:121.
87. Ferreira H, et al. Deformable Liposomes for the Transdermal Delivery of Piroxicam. J Pharm Drug Deliv Res. 2015;4:4.
88. Johnson D, et al. Effects of the ResQPod® on Maximum Concentration and Time to Maximum Concentration of Epinephrine in a Porcine Cardiac Arrest Model. Analg Resusc: Curr Res. 2013;S1.
89. Hudson Aet al. Comparing Resuscitative Measures for Bupivacaine Toxicity Utilizing Lipid Emulsions in a swine model (Sus scrofa). Analg Resusc: Curr Res. 2013;S1.
90. Johnson, et al. The Effects Vasopressin and Epinephrine on Cardiac Arrest Following Desipramine Overdose in a Porcine Model Analg Resusc: Curr Res. 2013;S1.
91. Trabelsi W, et al. Dexamethasone Provides Longer Analgesia than Tramadol when Added to Lidocaine after Ultrasound Guided Supraclavicular Brachial Plexus Block. A Randomized, Controlled, Double Blinded Study. Analg Resusc: Curr Res. 2013;2:2.
92. Han H, et al. Diabetic Feet Scald with Popliteal Artery Ligation - A New Study Rat Model, Represent Human Diabetic Foot Ulceration. J Mol Genet Med. 2015;9:149.
93. Jorum OH, et al. Effects of Dichloromethane-Methanolic Leaf Extracts of Carissa edulis (Forssk) Vahl on Serum Lipid Profiles in Normal Rat Models. J Hypertens. 2016;5:217.
94. Hughes FM, et al. The NACHT, LRR and PYD Domains-Containing Protein 3 (NLRP3) Inflammasome Mediates Inflammation and Voiding Dysfunction in a Lipopolysaccharide-Induced Rat Model of Cystitis. J Clin Cell Immunol. 2016;7:396.
95. Jorum OH, et al. Haematological Effects of Dichloromethane-Methanolic Leaf Extracts of Carissa edulis (Forssk.) Vahl in Normal Rat Models. J Hematol Thrombo Dis. 2016;4:232.
96. Annibali S, et al. Histomorphometric Evaluation of Bone Regeneration Induced by Biodegradable Scaffolds as Carriers for Dental Pulp Stem Cells in a Rat Model of Calvarial "Critical Size" Defect. J Stem Cell Res Therm. 2016;6:322.
97. Dias C, et al. Cardiac Analysis of Autologous Transplantation of Cocultured Skeletal Myoblasts and Mesenchymal Cells in a Rat Model Doxorubicin-Induced Cardiotoxicity: Histopathological and Functional Studies. J Clin Exp Cardiolog. 2015;6:407.
98. Mohamed EA. The Protective Effect of Melatonin vs. Vitamin E in the Ischemic/Reperfused Skeletal Muscle in the Adult Male Rat Model. J Cytol Histol. 2015;S3:005.

e-ISSN: 2322-0139
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99. Framroze B, et al. A Comparative Study of the Impact of Dietary Calcium Sources on Serum Calcium and Bone Reformation Using an Ovariectomized Sprague-Dawley Rat Model. J Nutr Food Sci. 2015;5:348.
100. Ichimura M, et al. An SHR/NDmcr-cp Rat Model of Non-alcoholic Steatohepatitis with Advanced Fibrosis Induced by a High-fat, High-cholesterol Diet. J Obes Weight Loss Ther. 2015;5:244.
101. Lu B, et al. Therapeutic Potential of Topical Fenofibrate Eyedrops in Diabetic Retinopathy and AMD Rat Models. J Clin Exp Ophthalmol. 2014;5:347.