Review

Zebrafish-based platform for emerging bio-contaminants and virus inactivation research

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HIGHLIGHTS

- Emerging contaminants have affected economic and environmental settings globally.
- High costs and ethical concerns are limitations when using existing animal models.
- Zebrafish can be used for risk assessment due to their amenable characteristics.
- Coronaviruses and poxviruses can be explored using zebrafish as an infection model.
- Zebrafish can be utilized to monitor emerging bio-contaminants.

GRAPHICAL ABSTRACT
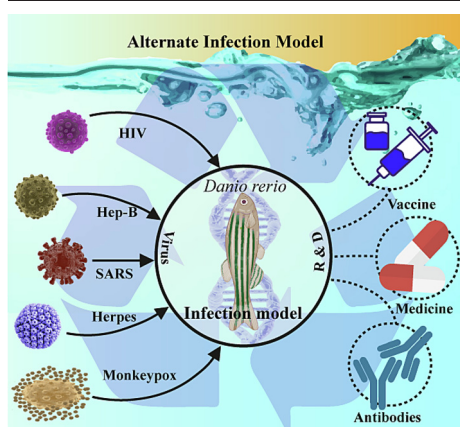
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ABSTRACT

Emerging bio-contaminants such as viruses have affected health and environment settings of every country. Viruses are the minuscule entities resulting in severe contagious diseases like SARS, MERS, Ebola, and avian influenza. Recent epidemic like the SARS-CoV-2, the virus has undergone mutations strengthen them and allowing to escape from the remedies. Comprehensive knowledge of viruses is essential for the development of targeted therapeutic and vaccination treatments. Animal models mimicking human biology like non-human primates, rats, mice, and rabbits offer competitive advantage to assess risk of viral infections, chemical toxins, nanoparticles, and microbes. However, their economic maintenance has always been an issue. Furthermore, the redundancy of experimental results due to aforementioned aspects is also in examine. Hence, exploration for the alternative animal models is crucial for risk assessments. The current review examines zebrafish traits and explores the possibilities to monitor emerging bio-contaminants. Additionally, a comprehensive picture of the bio contaminant and virus particle invasion and abatement mechanisms in zebrafish and human cells is presented. Moreover, a zebrafish model to investigate the emerging viruses such as coronaviridae and poxviridae has been suggested.

Contents

1. Introduction

Contagious infections are a major hazard to public health, causing more years of life to be lost due to early death than any other disease process (WHO, 2009, 2008). Until the nineteenth century, artists and authors typically did a better job of describing infectious syndromes than scientists. This began to change as bacteria became increasingly understood, and many ancient infections such as polio, measles, and smallpox have been explained and handled during the last 150 years. During the last three decades, however, there has been a continual stream of newly discovered illnesses that have drawn increasing interest. In 1992, emerging infections were defined as "new, re-emerging, or drug-resistant illnesses whose incidence in humans has grown during the last 20 years or whose incidence threatens to increase in the near future" by the expert committee that produced the Institute of Medicine report on emerging infections (Watkins, 2018). Changes in human demographics, technological advances, changes in industry practices, economic development, increase in international tourism, microbial adaptation, and breakdown in public health capacity were presented as some major key contributors to the diseases (Hughes, 2001). Furthermore, most of the emerging contaminants like chemical toxins, plastic components, flame retardants, surfactants, fragrances, pesticides and dissemination of nanoparticles in natural surroundings thorough cosmetic and daily products have always been a topic of concern. However, recent years 2020 and 2021 demonstrated that biological contaminants (virus) possess immediate threat that could wipe out huge population within few weeks. SARS-CoV, Zika, MARS-CoV, Rift Valley fever virus, human coronaviruses, avian influenza A, Heartland and Bourbon viruses, Nipah virus, Hendra virus, Ebola virus, MarV disease, Crimean-Congo hemorrhagic fever, and Lassa fever (Dabbu Kumar et al., 2018; Israel Nii-Trebi, 2017; Wigginton et al., 2015), are some WHO highlighted emerging biological contaminants that has the potential to cause epidemics in the future (LP and V, 2021; Watkins, 2018).

Viruses are ubiquitous entities and are the most diverse microbes on the planet. For billions of years, they have been a component of life's evolution (Nasir and Caetano-Anollés, 2015). They are found in all ecosystems and can infect a wide variety of living organisms, including animals, people, plants, and microorganisms (Couch, 1981). Viruses have aided in the evolution of life on Earth and can help preserve ecosystems and crucial natural cycles, such as the carbon cycle in the oceans (Wilhelm and Suttle, 1999). However, pathogenic viruses cause a great deal of hospitalization, animal sickness, animal fatalities, and agricultural losses. Thereby creating tremendous social, economic, and biological burden (Filipić et al., 2020). Due to their adaptability, they currently exist in all environmental conditions. They can also be passed directly from one sick person to another by contaminated intermediaries, such as surfaces, objects, air, food, and water. According to several epidemiological studies, the most important vectors of viral infections are water and air (Martínez-Montelongo et al., 2020; Mehle and Ravnikar, 2012; Shrestha et al., 2018; World Economic Forum, 2021).

Viruses comprise of two main components; a nucleic acid genome made up of double-helix DNA, or single-helix RNA, and a capsid. The capsid,

which encases and protects the viral genome, is a highly symmetrical structure composed of many copies of a few proteins expressed by the viral genome (Domingo, 2020). However, it is renowned for being multi-functional, involved in cell entrance, genome uncoating, and intracellular trafficking (Freire et al., 2015; Mateu, 2013). Some viruses have an additional layer of protection, known as an envelope, in addition to the capsid, commonly comprising a lipid or glycoprotein covering. Lipid envelopes originate from the cell membrane of the infected host, whereas glycoprotein envelopes are usually programmed by the viral genome. Which finally assembles to form a virion (Banerjee and Mukhopadhyay, 2016). The viral genome also contains proteins that aid viral particle multiplication and assembly. Although most viruses have common structural features, such as symmetric capsid proteins, they are genetically heterogeneous.

Evidence suggests that viruses present in animal pools have now spread to humans and are responsible for serious illnesses. Cases such as 2019 novel coronavirus (Li et al., 2020), yellow fever in 1901, Spanish flu in 1918, Ebola outbreak in 2014 caused by flavivirus (Frierson, 2010; Taubenberger, 2006) and Ebola virus (Cdc.gov, 2022). As such, there is rekindled interest in creating methods for quicker prevention, treatment, and management of newly emerging and re-emerging viruses with significant outbreak capability.

One of the major aspects of virology is understanding how viruses multiply and cause symptoms in individuals. Understanding the processes underlying *in vivo* viral characteristics is vital for virologists who research viruses that are hazardous to humans. To do this, investigations using animal models are crucial for generating both accurate *in vivo* analyses and effective viral infection prevention strategies. The manner in which a virus behaves in its natural host frequently differs from its behavior in humans. Viruses that cause major illnesses in humans frequently show no symptoms in their native hosts. Consequently, the use of natural hosts as animal models has been limited. Studies on these viruses have been conducted using animal models by examining the host features of the viruses—their ability to reproduce, cellular tropisms, pathogenicity, and transmission—and by creating vaccines and antivirals. No animal can be an exact clone of a human. Certain animal models may be better able to depict viral infection but still have drawbacks in other areas. As a result, the optimal animal model may be determined by experimental questions, and studies should be designed such that the results acquired from animal models can be transferred to humans.

Animals that serve as natural reservoirs for influenza A viruses include swine and bird species, whereas bats and dromedary camels serve as reservoirs for MERS-CoVs (Cui et al., 2013; Mohd et al., 2016; Peck et al., 2015). Flu, Heartland, and Bourbon viruses have been studied using animal models including ferrets, mice, guinea pigs, cats, Syrian hamsters, rabbits, raccoons, chickens, and non-human primates (Bosco-Lauth et al., 2016; Bouvier, 2015; Godsey et al., 2021; Kwon et al., 2009; Lowen et al., 2006; O'Donnell and Subbarao, 2011; Van Der Laan et al., 2008; Van Hoeven et al., 2009). Mouse models, guinea pig models, and non-human primate models (marmoset, rhesus monkey, and cynomolgus macaque) have been used to study Lassa fever (Bell et al., 2017; Carrion et al., 2007; Cashman et al., 2017, 2011; Flatz et al., 2010; H et al., 1975; Jahrling et al., 1982; Oestereich et al., 2016; NE et al., 2016; Rieger et al., 2013; Sattler et al., 2020; Uckun et al., 2004; Walker et al., 1982, 1975; Yun et al., 2013, 2012). In addition, hDPP4-mice and non-human primates have been used to study MERS-CoV viruses (Agrawal et al., 2015; Cockrell et al., 2016; J et al., 2014). Large animals, such as rhesus macaques and, to a lesser extent, cynomolgus macaques, are species of non-human primate that are predominantly used as Zika virus research models (Code and Beaverton, 2008; Lindsey, 2016). A variety of immunocompetent mice, immunodeficient mice, hamsters, strain 13 guinea pigs, outbred guinea pigs, macaques, African green monkeys, marmosets, baboons, rhesus macaques, and cynomolgus macaques (Bente et al., 2009; Bird et al., 2015; Patterson and Carrion, 2005; Perry et al., 2012; V et al., 2012) have been used for EboV research. Moreover, immunocompetent mice, immunocompromised mice, guinea pigs, and cynomolgus macaques (Cross et al., 2015; DA et al., 2010; LE et al., 2011; Marzi et al., 2016; Warfield et al., 2009) have been

used to study the Marburg virus. Hendra virus research employs mice, syrian golden hamsters, ferrets, squirrel monkeys and African green monkeys (B et al., 2011, 2010; J. et al., 2012; Pallister et al., 2011; V et al., 2009). Research on Rift Valley fever virus includes animal models of mice, rats, sheep, claves (<1-month-old), and primates (Anderson et al., 1991; Anderson and Smith, 1987; Davenport et al., 1953; Ikegami and Makino, 2009; Jensen and Francis, 1953; Peters et al., 1988; Peters and Slone, 1982; Rippy et al., 1992; Ross et al., 2012; Smith et al., 2010). Crimean-Congo hemorrhagic fever virus models include mice and immunocompetent non-human primates (Bente et al., 2010; Bereczky et al., 2010; Farzani et al., 2019; Garrison et al., 2017; Golden et al., 2019; Haddock et al., 2018; Lindquist et al., 2018; Smith et al., 2019; Spengler et al., 2017; Tignor and Hanham, 1993). The Nipah virus models include pigs, Syrian hamsters, ferrets, African green monkeys, cats, and mice (BA et al., 2006; de Wit et al., 2011; Geisbert et al., 2010; KN et al., 2009; KP et al., 2013; Middleton et al., 2002). Finally, recent models used for research on SARS-CoV-2 include human Angiotensin-converting enzyme 2 (hACE2) mice, Golden Syrian hamsters, ferrets, cats, rhesus monkeys, cynomolgus macaques, marmosets, African green monkeys, and tree shrew (Johansen et al., 2020; Zhang et al., 2021).

Animal models of viral infection are essential for exploring viral pathogenesis and host responses. Important traits for viral studies include support for viral replication, susceptibility to viral infection, and a summary of clinical symptoms of human sickness. There are numerous viral models, as has already been indicated, and each has advantages and shortcomings that should be considered. Scientists investigating infectious diseases utilize small animals including rats, mice, and guinea pigs. The mouse model is beneficial for establishing immunological response, signal-transduction, inflammatory pathway, and effectiveness research; however, it has its limitations as a rodent model. Due to various host-range restrictions, mice are frequently difficult to infect with human viruses. If the circumstances are right, it is possible to study immune responses but not viral multiplication and dissemination. Additionally, all strains of mice lack the Mx protein, which is essential for viral replication and is caused by a faulty Mx1 gene (Zhou et al., 1999). Which further causes aberration in IFN response. Moreover, the pathogenesis and immunological responses of different inbred strains can also differ from those of humans, which may affect experimental results and restrict their predictive usefulness for research of pharmacological intervention techniques (Guénet, 2005; Rivera and Tessarollo, 2008). While transgenic mice are incredibly useful for researching pathophysiology, antivirals, and developing vaccines. Nevertheless, due to variations in immunopathology and disease severity caused by cell or tissue selectivity and/or degrees of transgenic expression among various transgenic mice lines, effectively replicating viral illness in humans has remained a challenge (Koike et al., 1994). An investigation revealed that human poliovirus receptor CD155 did not effectively invade when delivered orally, but did so when administered intravenously and intraperitoneally (Zhang and Racaniello, 1997). Post entry inhibition of HIV-1 replication exhibited, when the virus was administered in transgenic mice resulted in infecting limited number of cells (Mariani et al., 2000). Aforementioned studies explain the lack of permittivity or difference in pathophysiology could be due to absence of co-receptors or co-factors, or due to host-range restriction factor. Due to a mutation in the DNA repair enzyme prkdc (protein kinase, DNA activated, catalytic polypeptide), SCID (severe combined immunodeficient) suffer from a continuous *de novo* multilineage hematopoiesis defect and a total absence of the human immune system, making them unsuitable for studying the human immune response to virus infection and the effectiveness of vaccines (GC et al., 1983; Shultz et al., 2007). Although numerous factors (such as HIS functioning and engraftment variability) in humanized immunodeficient mice continue to hinder the investigation of immunopathogenesis of human virus, progress is still being made. Guinea pig has always been intermediary model (secondary) between mice and NHPs. The establishment of deadly disease models in guinea pigs frequently necessitates host adaptation of infections, such as guinea pig-adapted Ebola. The drawback of this model is that it doesn't have readily available commercial reagents, which makes it difficult to describe illnesses in

these models (Nguyen et al., 2021). Hamsters offer an intriguing option for small animal disease models and their use in the field of emerging viral pathogens research. Infected hamster by paramyxoviruses Nipah and Hendra, could result in neurological or respiratory symptoms that are comparable to those in humans (B et al., 2012, 2011). The pathological presentations seen in hamster models seem to more accurately mimic the human situation as compared to mice and guinea pigs. Syrian hamsters are outbred, despite the fact that little is known about their genetic makeup and immune systems. It's possible that hamsters lack some host defensive systems and have suppressed inducible nitric oxide (Saldarriaga et al., 2012), both of which might boost the virulence of infection by specific viruses infection or human viruses. To assess host immune response, antiviral drug and vaccine efficacy against influenza virus, ferrets has been a pivotal animal model. However, lack of reagents such as ferret-specific monoclonal antibody for analysis of immune response, high cost, size and husbandry requirements are few reasons making this model in assessable to researcher. Furthermore, this inaccessibility might lead to misinterpretation of the results (Nguyen et al., 2021). Small animal models are less similar to humans than large animal model such as non-human primates (NHPs) and pigs in terms of morphology, specialized lymphoid tissues at mucosal sites, and peripheral immune system development (Hein and Griebel, 2003). Even though the use of NHPs is clearly supported by our phylogenetic and evolutionary connections to humans (F. et al., 2005). However, the intricacy of animal husbandry and scientific investigation, ethical issues, expensive and the accessibility of immunoreagents is a challenge. Due to aforementioned limitation their usage drastically reduced or limited to researches with hepatitis B, C, E virus (Bettauer, 2010). Macaques being 93–99 % similarities in protein level for several cytokine with human and relatively small in size, is the most used NHPs in virus research (F. et al., 2005). Despite having similitude with humans, there are limitations to its usage. In contrast to humans, changes in pathophysiology, MHC-restricted immune responses, and disease manifestation might result from species differences (such as MHC polymorphisms), even if they are minimal (Bontrop and Watkins, 2005; Kaiser et al., 2007). It should be emphasized that there are variations in the susceptibility and pathogenicity of NHPs among species or subspecies (Ten Haaft et al., 2001). NHPs are rigorously controlled and numbered in their experimental uses. Owing to the outbreeding of NHPs, genetic variability might cause confounding and skewed results in (statistical) studies. Pigs are good animal models for studying influenza virus, however they are not the best choice due to their high cost, challenges with housing, handling, and waste management. Aside from the major category of animals, many other animals, including cats, rabbits, chickens, goats, and raccoons, are used as animal models for viral research. However, these creatures are not suitable for high-throughput drug screening or the visualization of host-pathogen interactions due to their high maintenance requirements, complex animal husbandry procedures, ethical considerations, or experimental limitations (Dycke et al., 2019; Gabor et al., 2014). Therefore, a simpler, more robust, and widely accessible viral replication model is urgently needed. It is critical to create a paradigm that allows large-scale chemical and genetic screening to corroborate bio-contaminants studies.

Zebrafish are superior to small and large animal models in various ways for studying emerging contaminants as well as bio-contaminants. Due to which our knowledge of the interactions between the host and pathogen has improved considerably. The ability of this species' embryos to grow outside the mother's body and their transparency, which is one of the most frequent reasons for choosing this animal model, make it more desirable to researchers even if it is generally not the first option. Despite the widespread use of small animal models by researchers, SARS-CoV-2 susceptibility in models like rats and mice is negligible due to intrinsic characteristics (variation in the amino acid sequence encoding ACE2 receptor) (Chan et al., 2020). Transgenic mice overexpressing human ACE2 have been constructed to address this issue, however they have some limitations, such as the inability to conduct long-term studies due to the scarcity of breeding and the high mortality rate, which reported 7 days after infection, and distribution facilities. Conducting experimentation on animal models such as

mice, ferret, golden hamster and large animals possess limitation such as high maintenance costs, several weeks to produce offsprings sophisticated animal husbandry protocols, and many more which has been mentioned above (Chan et al., 2020; Johansen et al., 2020; Kim et al., 2020; Munnink et al., 2020). Non-human primates (NHPs), for instance, are the nearest animal species to the pathophysiology of humans, and their research has FDA permission. However, not all non-human primates exhibit complete susceptibility to infection or exhibit all COVID-19 symptoms of humans (Johansen et al., 2020). Zebrafish possess several inherent characteristics that make them excellent biological model system include a high fecundity rate, clear embryos, cheap maintenance cost, easy husbandry routine (Choi et al., 2021; Dycke et al., 2019; Gabor et al., 2014; Laghi et al., 2022; Lama et al., 2022); in some cases, no ethical permission is necessary for zebrafish embryos/larvae up to 120 h postfertilization (Strähle et al., 2012). The presence of alpha2,3- and alpha2-6-linked sialic acid receptor in zebrafish, makes them susceptible to H1N1 and influenza A virus. As human virus can be infected in zebrafish which possible give opportunity to examine viral infection and host inflammatory response in human (Gabor et al., 2014). In case of SARS-CoV-2, zebrafish has shown infectivity when injected in swim bladder, without overexpressing human ACE2 receptors (Laghi et al., 2022). In another study, when exploring SARS-CoV-2 host cell entry, ACE2 and TPC2 founded to be the major player in translocation of virus through endolysosomal when entered through peripheral sense organs (Choi et al., 2022). However, SARS-CoV-2-infected to dog, pig, tree shrew, and chicken animal models, respectively, had very few effects and no animals showed symptoms (Johansen et al., 2020). Zebrafish model may be used to perform toxicity and immunological tests, including embryotoxicity, hepatotoxicity, endocrine toxicity, genotoxicity, neurotoxicity, hematological analysis, differential white cell count, and immunological studies (Fukushima et al., 2020, 2017; McFetridge et al., 2015). Small animal models like rodents have been used for these tests till date, but recent studies show zebrafish model has proved to be an important tool in the studies of infection and immunological responses. In addition, due to their transparent embryo and larvae observation can be made in real-time allowing for the monitoring of embryogenesis. Similarly, the zebrafish model has helped in explaining bacterial infection in humans, as well as freshwater pathogens in fishes. Various freshwater pathogens (bacteria, viruses, and parasites) associated with fish diseases have already been investigated using the *Danio rerio* model (von Jørgensen and G., 2020; Rakus et al., 2019). Bacterial pathogens such as *Mycobacterium marinum*, *Vibrio anguillarum*, *Aeromonas salmonicida*, *Yersinia ruckeri*, and *Flavobacterium psychrophilum*; enteric bacteria such as *Vibrio*, *Listeria*, *Shigella Salmonella*, and *E. coli*; viruses such as infectious hematopoietic necrosis virus (IHNV), viral hemorrhagic septicemia virus (VHSV), spring viremia carp virus (SVCV), and infectious pancreatic necrosis virus (IPNV), Chikungunya virus (CHIKV), human norovirus (HuNoV), influenza A virus, and herpes simplex virus type-1 (HSV-1); and parasites such as *I. multifiliis* and *Trypanosoma carassii* have all been demonstrated to infect zebrafish larvae (Burgos et al., 2008; Dycke et al., 2019; Gabor et al., 2014; Palha et al., 2013; Kanther and Rawls, 2010). This paper discusses in detail about benefits of utilizing zebrafish in research as well as their potential applications in developing infection models. We mostly focused on the disadvantages as well as advantages of using current animal models for investigations and emphasized how zebrafish could offer several benefits over other models at the moment. Secondarily, this paper discusses how numerous zebrafish aspects are applied to the development of disease models that might closely resemble human disease, toxicity testing, and models to research bio-contaminants. We also went into further detail on evaluations of entry routes and mechanism of bio-contamination in zebrafish and how it pertains to human cells. This paper also discusses several cell mechanisms and strategies for preventing viral replication. The use of *Danio rerio* as a model organism for studies on the Sars-CoV-2 virus has been reviewed. Finally, we discuss the potential application of this model system to study the recently reported monkeypox virus. In our opinion, this review has the opportunity to educate researchers about the utilization of zebrafish models, encourage them to switch to using zebrafish model systems for research

involving infectious diseases, environmental pollutants, and toxicological studies of contaminants, and minimize the use of certain existing models, which are typically time-consuming and difficult. This review's main argument is that zebrafish models can be used to study various bio-contaminants that might cause pandemics, and that doing so could be analogous to conducting so on humans.

2. Methodology

The systematic literature review that formed the basis of this study was conducted utilizing resources including Google Scholar, Science Direct, the Zebrafish Information Network database, and PubMed. The focus was on obtaining literature by utilizing terms like zebrafish model, bio-contaminants, toxicity, infection model, SARS-CoV-2, monkeypox virus, viral entrance mechanism, and contemporary animal models. The relevance of the zebrafish model's applicability for evaluating viruses and different emerging bio-contaminants studies was taken into consideration while choosing the papers referenced here. The papers in this list include original research articles, critical essays review and perspectives that have been published in prestigious worldwide scientific publications. Lastly, the citation was included with Mendeley program.

3. Relevance of zebrafish attributes

The selection criteria for animal models are intimately connected to the study's ultimate objective. Zebrafish model use within the scientific community has increased dramatically, despite small and big animal models being the most often used research animal models globally. Thanks to the Streisinger's work, Zebrafish rose to the top of the list of NIH-funded biological models (Driever et al., 1996; Eisen and Grunwald, 2002; Haffter et al., 1996; Kinth et al., 2013). And are favored above other species and are used frequently as animal models due of these benefits (Fig. 1). Primarily, zebrafish was widely accessible, simple to produce, and, they are less expensive to maintain than mice (Burke, 2016a). These tiny cyprinids, which reach adulthood at a length of 2–4 cm, are found in warm, slowly flowing streams, ponds, and flooded rice fields in Southern and South-Eastern Asia (Parichy, 2015). Under controlled environment zebrafish can produce approximately 200 eggs at a time and spawn daily throughout the year in a laboratory setting. Daylight period is the main activity hours for the fishes (Miller and Gerlai, 2011). In the lab, larvae hatch 72 h after fertilization and mature after 3 months, however in the wild they may take longer than six months to fertilize (Khan and Alhewairini, 2019). During mating and spawning seasons, violent behavior associated to dominance may only occur, or at least be significantly more prevalent (generally during early morning) (Khan and Alhewairini, 2019; Miller and Gerlai, 2011).

Secondly, this model is a vertebrate, therefore it has structural and physiological similarities to humans (Burke, 2016a). In comparison to the human genome, which has 25,000 protein coding regions spread across 23 pairs of chromosomes, the zebrafish genome has 26,000 protein coding regions when it was evaluated (Costa et al., 2021), and also shows that zebrafish and humans have been shown to share 70 % of the same genes (orthologous proteins are 70 % similar in terms of their amino acid residue sequence) (Animals Facts, 2015). Zebrafish contain equivalents to about 80–84 % of the genes linked to human illness (Animals Facts, 2015; Galindo-Villegas, 2020). When compared to mouse editing, zebrafish gene editing is less complicated. Another study revealed that the zebrafish homebox gene and the mouse hox-2.1 domain have a multitude of similarity amino acid sequences (Costa et al., 2021). Moreover, many other genes similarities were found between both the organisms. Study conducted to examine HSV-1 entry through 3-O sulfated heparan sulfate demonstrated the presence of human homologs receptors in zebrafish (Hubbard et al., 2010; Yakoub et al., 2014). Most commonly mutation in BRAF gene in human melanoma has been successfully created in zebrafish to make a knock-in model. Due to which other

potential cancer-causing mutations have been able to identify such as SETDB1 (Burke, 2016b). Dystrophin, a muscular weakness in humans, the loss of dystrophin gene gradually leads to necrotic muscle fibers in zebrafish as well (Burke, 2016b).

The capacity to expose fish embryos to various drug/chemicals to develop or relieve specific trait can be undertaken on a big scale, as zebrafish produces hundreds of offspring at a regular interval, giving scientist a plentiful supply of embryos to analyze when studying diseases associated with human. *Ex situ* development enables the exposure of zebrafish embryos to drugs by putting them in an embryo support medium (Burke, 2016a; Khan and Alhewairini, 2019). The drugs do not undergo through the mother's metabolism before reaching the growing embryo, unlike placental animals. Additionally, because there are many zebrafish embryos accessible, it is easy to arrange them in microtitre dishes for exposure to various drugs, dosages, and treatment combinations. A different approach to comprehend the biology of drug response is to utilize genetic screening to identify mutants that are specifically sensitive or resilient to the effects of a certain compounds (Lardelli, 2008). When Growth rate is compared with human embryos zebrafish embryos grow incredibly quickly; they develop as much in one day as an embryonic human does in one month. Zebrafish embryos are transparent, making it simple for scientists to study the growth of interior components. Contrary to *C. elegans*, zebrafish have most of the major vertebrate organ systems, including the heart, eyes, and kidneys, allowing the study of organ development (Gehrig et al., 2018; Teame et al., 2019). Zebrafish have a special capacity for heart muscle healing. For instance, if a portion of their heart is removed, they may quickly regenerate it again (Beffagna, 2019; Karra et al., 2015; Sande-Melón et al., 2019). Zebrafish are incredibly useful for recent day researches because of their well-characterized genes, which allow for the targeting of individual genes, their ability to be turned "OFF"/"ON", or the ability to introduce exogenous gene into the organism (Avcı, 2014). Concerning bacterial pathogenesis investigations, a recent work by Cao et al., demonstrated the functional properties of the anti-apoptotic protein BIRC2 (cIAP1) in response to *Edwardsiella piscicida* (a significant bacterial pathogen) in zebrafish (Cao et al., 2021). This study claims that piscine BIRC2 inhibits caspases and accumulates the p53 gene in a p53 transcription-dependent and -independent way in response to the *E. piscicida* infection, acting as a negative regulator for the antibacterial immune response. A significant family of host pattern recognition receptors (PRRs) called toll-like receptors (TLRs) may detect a wide range of molecular patterns associated with pathogens (PAMP). Currently, the zebrafish genome has 24 TLRs (Sullivan and Kim, 2008). Zebrafish TLRs have been investigated in response to viral and bacterial stimuli. Tlr3, Tlr7, Tlr8a/b, Tlr9, and Tlr22, which are specific to fish, have been linked to the response to viruses in zebrafish. According to Pietretti and Wiegertjes (2014), Tlr3 and Tlr22 exhibit striking similarities in their cellular location and molecular functions and have the ability to detect viral replication by binding to double-stranded RNA (dsRNA) or its counterpart poly I:C (a synthetic polyinosinic-polycytidylic acid dsRNA). In response to infection with the ssRNA virus snakehead rhabdovirus (SHRV), zebrafish tlr3 transcripts were up-regulated (Phelan et al., 2005a). Additionally, Tlr3 was up-regulated following infections with the viral hemorrhagic septicemia virus (VHSV) (Novoa et al., 2006), and the single-stranded RNA (ssRNA) virus popularly known as spring viremia of carp virus (SVCV), was found to infect zebrafish larvae systemically (López-Muñoz et al., 2010; Varela et al., 2014). Furthermore, a group of researchers demonstrated large similarities of chromosome between mammalians and zebrafish when mapped 144 gene of zebrafish (Postlethwait et al., 1998). Researchers have used zebrafish to study a variety of human ailments, including bio-contamination, infectious diseases, diabetes, cancer, cardiovascular disease, and renal disease. This is due to the fact that zebrafish and humans share high physiological and morphological similarity in terms of their central nervous system, adipose tissue, kidneys, skeletal muscles, and white blood cells (T-lymphocytes, erythrocytes, and myeloid cells) (Kandasamy et al., 2022). It is reasonable to anticipate that more human viral disease models will manifest in zebrafish over the next few years given the potential of zebrafish for the study of viral diseases in
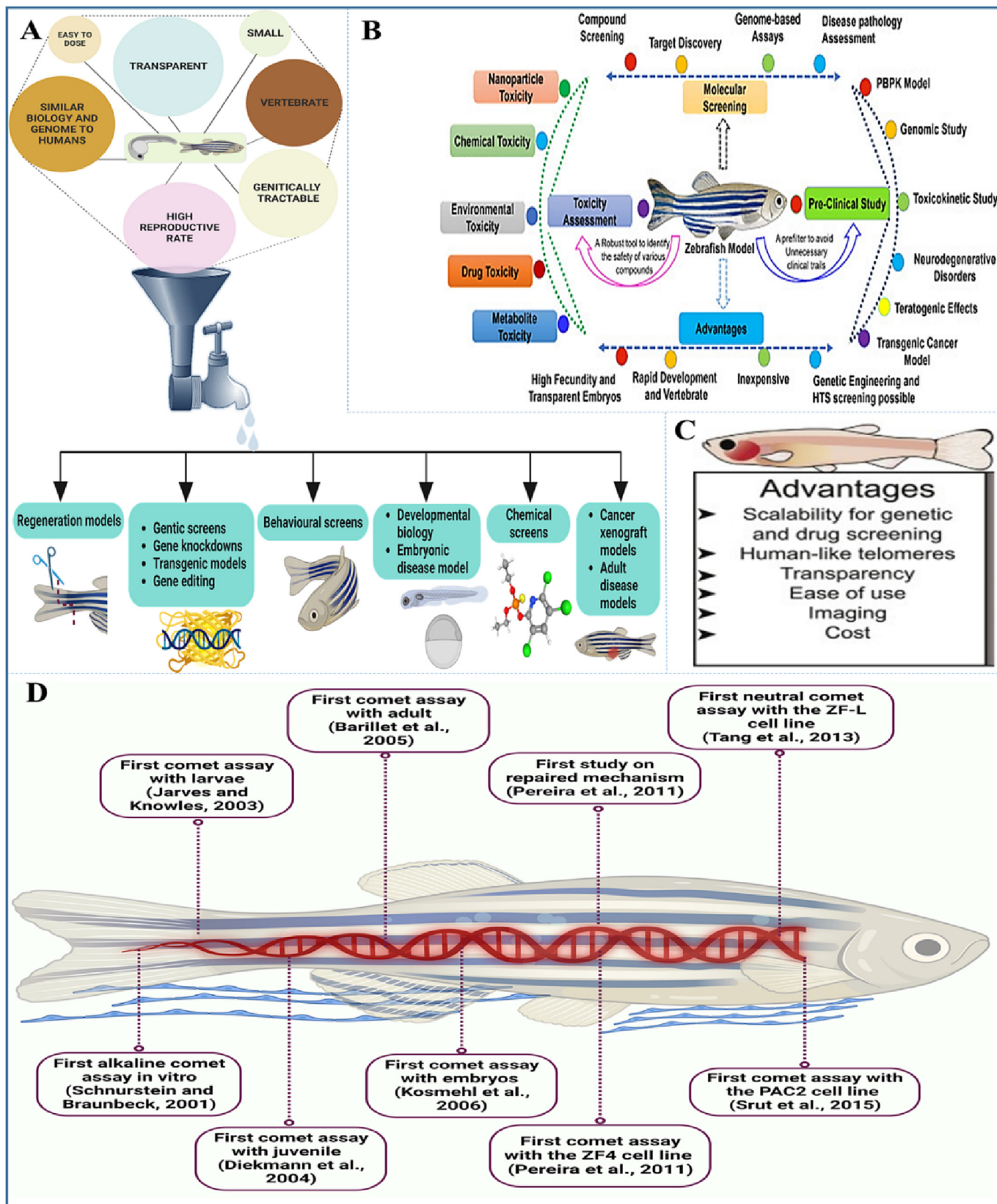
Fig. 1. Importance of *Danio rerio* model in scientific arenas.

humans. This will result in the advancement of research into new vaccines and antiviral agents with potential biomedical applications, as well as the comprehension of viral diseases and host-pathogen interactions will also get more prominent.

4. Myriad of scientific arenas embracing zebrafish model

Early on, scientists understood the significance of zebrafish and a huge, thriving community of researchers employing zebrafish and other

aquarium fish models because of the work done at 1970s by George Streisinger and fellow colleagues (Collodi, 2004). There are 101 different topic areas covered by zebrafish research. Developmental biology, biochemistry/molecular biology, cell biology, and neurology/neuroscience were the four subject categories with the highest percentages, according to a publication on zebrafish survey (2013). Anatomy, zoology, science technology, toxicology, genetics, life sciences and biomedicine were the next four most popular subject categories (Fig. 2) (Kinth et al., 2013).

4.1. Implementation in various scientific arenas

4.1.1. Developmental biology

Zebrafish, having high genomic similarities with humans, are useful model to understand the pathways that control development and complex processes of development. It allows for the typical invertebrate genetic screening to be performed in a vertebrate model. The percentage of genetic similarity between humans and zebrafish is as high as 70 %. The first vertebrate to undergo ongoing genetic testing to detect developmental mutations (Driever et al., 1996). Numerous developmental genes have been found since the full-scale genetic screening (Amsterdam et al., 2004a; Golling et al., 2002; Haffter et al., 1996). Understanding how these genes are expressed and operate in space is being revealed using transgenic reporter lines, gene regulation, and precision gene editing. In addition to the desirable phenotypes, the model's genetic tractability is useful for studying developmental biology. In light of the zebrafish model's significance, the following systems and processes have been utilized to monitor their development: development of the brain, the enteric nervous system, the processes of angiogenesis, gastrulation, neurogenesis, neurulation, eye development, organogenesis, and regeneration (Fig. 3) (Khan and Alhewairini, 2019; Roper and Tanguay, 2018).

4.1.2. Cancer biology

Cancer is a general word encompassing a variety of genetically heterogeneous ailments that have similar cellular and molecular characteristics. Considering that intratumor heterogeneity amplifies inter-individual variations, tumor diversity is regarded as one of the major complications in treating cancer patients. Clinically and pathologically every vertebrate species, including humans, fish, and other mammals, is affected by this dreadful ailment. Though humans and fish are not related by blood, the biochemistry of cancer is analogous in both groups, making the zebrafish an excellent model to research cancer (Fig. 4). Zebrafish are particularly well-suited to observe tumor formation, metastasis, and microenvironmental interactions because of their optical transparency, which has dramatically improved the capacity to see internal cell biology using fluorescent reporters. Chemical carcinogenesis, transgenic lines, mutant lines, and xenotransplantation are all methods for inducing cancer in fish (Tables 1, 2). Skin, testicles, GI tract, liver, pancreas, muscles, and vasculature are some organs that could be used to develop tumor (Basten et al., 2013; Mizgireuv and Revskoy, 2006; Siew et al., 2006; Spitsbergen et al., 2000a, 2000b). stat3^{ia23}, *Bymb*, mr^{ia32}, Tg(tg:mCherry)^{ulb1}, gr^{ia30}, Tg(tg:nlsEGFP)^{ulb4}, pigmentless Casper strain (Facchinello et al., 2017; Opitz et al., 2012; Peron et al., 2020; S et al., 2005; Shepard et al., 2005; White et al., 2008), kRASG12D solid tumor models, TEL-AML1 leukemia models, BRAFV600E melanoma models, Myc, kRASG12D embryonic rhabdomyosarcoma models and MYCN are few examples of zebrafish mutant lines and transgenic lines (Stoletov and Klemke, 2008). The most common technique for modeling cancer in zebrafish is *via* xenotransplanting human cancer cells. Additionally, fish are known to be susceptible to and spontaneously acquire cancer (White et al., 2013). Yolk, hindbrain, duct of cuvier and caudal vein are few most common sites for xenotransplantation for generating cancer model example breast (MDA-MB-231, MDA-MB435), prostate (PC3), Sarcoma (U20S, TC32), pancreatic (patient-derived pancreatic tumor tissue, PaTu, Panc-1), neuroblastoma (U87-L), melanoma (WM-266-4), jurkat, NB-4, colorectal (SW620), leukemia
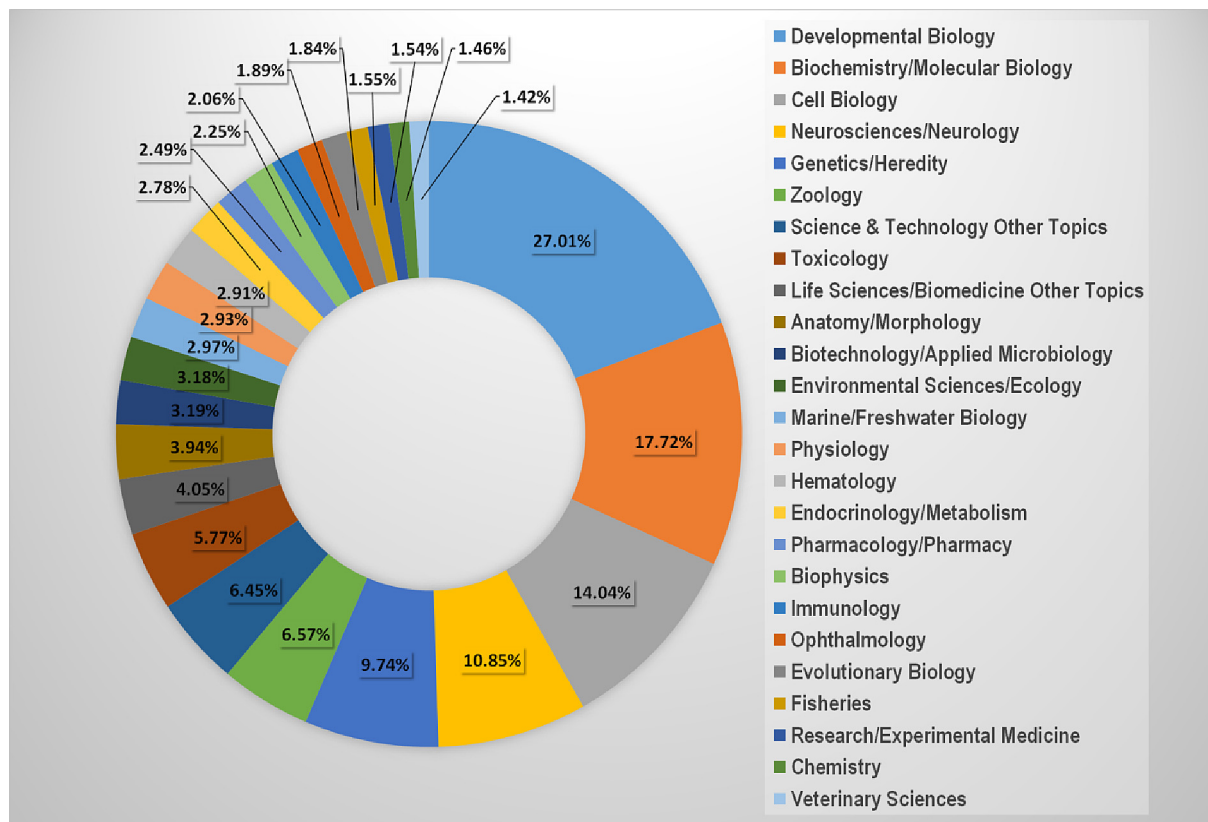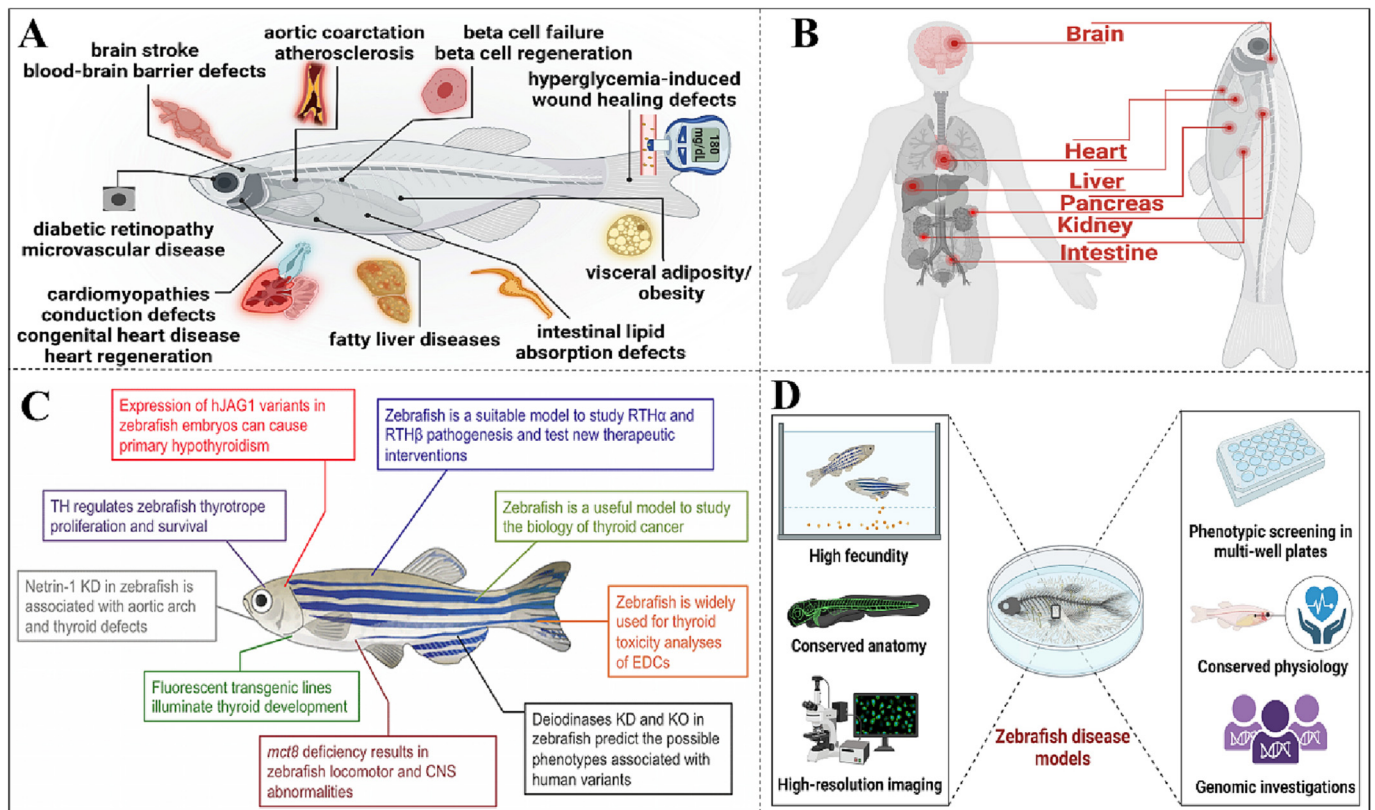

Fig. 2. Major research area where zebrafish are being used (Kinth et al., 2013).

Fig. 3. (A) Similarities in anatomy between higher vertebrates zebrafish could be potential model to investigate wide range of cardiovascular and metabolic diseases (Gut et al., 2017). (B) Corresponding organs in human and zebrafish. (C) Recent discoveries on thyroid hormone action and development that were acquired utilizing zebrafish as a model system shown schematically (Persani and Marelli, 2017) (KO: knock out, EDC: endocrine disruptor chemical, CNS: central nervous system, RTH: resistance to thyroid hormone, MCT8: monocarboxylate transporter 8 and KD: knock down). (D) The diagram demonstrates ways zebrafish are utilized for a range of genomic, physiological, image analysis, and small-molecule forms of assessment (Gut et al., 2017).

(Kt562, patient-derived leukemia samples) and ovarian (OVCA-433) (Veinotte et al., 2014).

4.1.3. Toxicology model

More than 200 different cell types work together in the body's intricate structure to create highly specialized organ systems, including the immune system. However, no *in vitro* or artificial model can precisely depict how a human internal system would react to the introduction of a medicine, chemical, nanomaterial, or any other foreign material because of the infinite number of biological processes that occur naturally in a human body. Zebrafish might therefore be used to investigate toxicity, evaluate the eco-environment, and assess various contaminants (*i.e.* Nano materials, toxic heavy metals, endocrine disruptors and organic pollutants) (Fig. 5) (Table 3) (García-Cambero et al., 2019; Khezri et al., 2017; Verma et al., 2021; Zhang et al., 2003).

Nevertheless, zebrafish have also been employed in several other types of toxicology studies, including those examining the effects of toxins on the reproductive system, nervous system, circulatory system, eyes, brain, and behavior, as well as cardiotoxic effects.

4.1.4. Human disease model

For the advancement of biomedical research, several animal species play crucial roles as experimental models. Research outcomes are reliable and consistent when using animal models. The fully sequenced genome, accessibility of genetic manipulation, quick growth, high fertility, and practically transparent embryo of the zebrafish have made it a popular animal model. As a result of these traits, it is a special model organism for the investigation of numerous biological and human ailments. Zebrafish are perfect subjects to study various human ailments such as dyslipidemia, hematopoietic disorder, type 2 diabetes mellitus, cardiovascular disorder (CVD), non-alcoholic fatty liver disease (NAFLD), atherosclerosis, kidney disorder,

Obesity, and holoprosencephaly (HPE), as they have all the same major organs as humans (Gongal and Waskiewicz, 2008; Konantz et al., 2019; Morales and Wingert, 2017; Teame et al., 2019).

5. Zebrafish: a versatile infection paradigm to study host-pathogen interaction *in vivo*

Why zebrafish should be utilized as a model for infection in research? Developmental biologists have used this paradigm to bridge the gap between mammalian evolution and that of lesser living forms. Zebrafish are vertebrates, making them more similar to humans in terms of evolution than other models like fruit flies or nematodes. They are also simpler to work with and research than small animal models. Zebrafish are 21st century animal model (*in-vivo*) for a myriad of infections such as bacteria, viruses, fungus, protozoan, metazoan and parasites, due to advantageous traits such as ex utero, genetic accessibility, optical accessibility, whole sequence genome, and high genomic similarity with humans. Zebrafish infection models have real-time visualization and genetic screening over other vertebrate infection models like rats and mice. Forward genetic screening, which is only achievable in vertebrates, can be used in conjunction with reverse genetics.

When conditions are natural, pathogens are thought to enter zebrafish through the gills, the digestive tract, or a damaged surface (O'Toole et al., 2004). However, parasites can occasionally act as an infection source. Co-incubation or incubation in medium containing the pathogen, is a method for experimentally infecting zebrafish with diverse pathogens (Chen et al., 2015; Laghi et al., 2022; Liew et al., 2017; Rendueles et al., 2012). Adult fish and its embryos have both been treated using this technique. However, experimental infections are often administered into sedated fish by injection (Akle et al., 2017; Benard et al., 2012). Both the embryonic and adult phases of development are appropriate for administering the injection
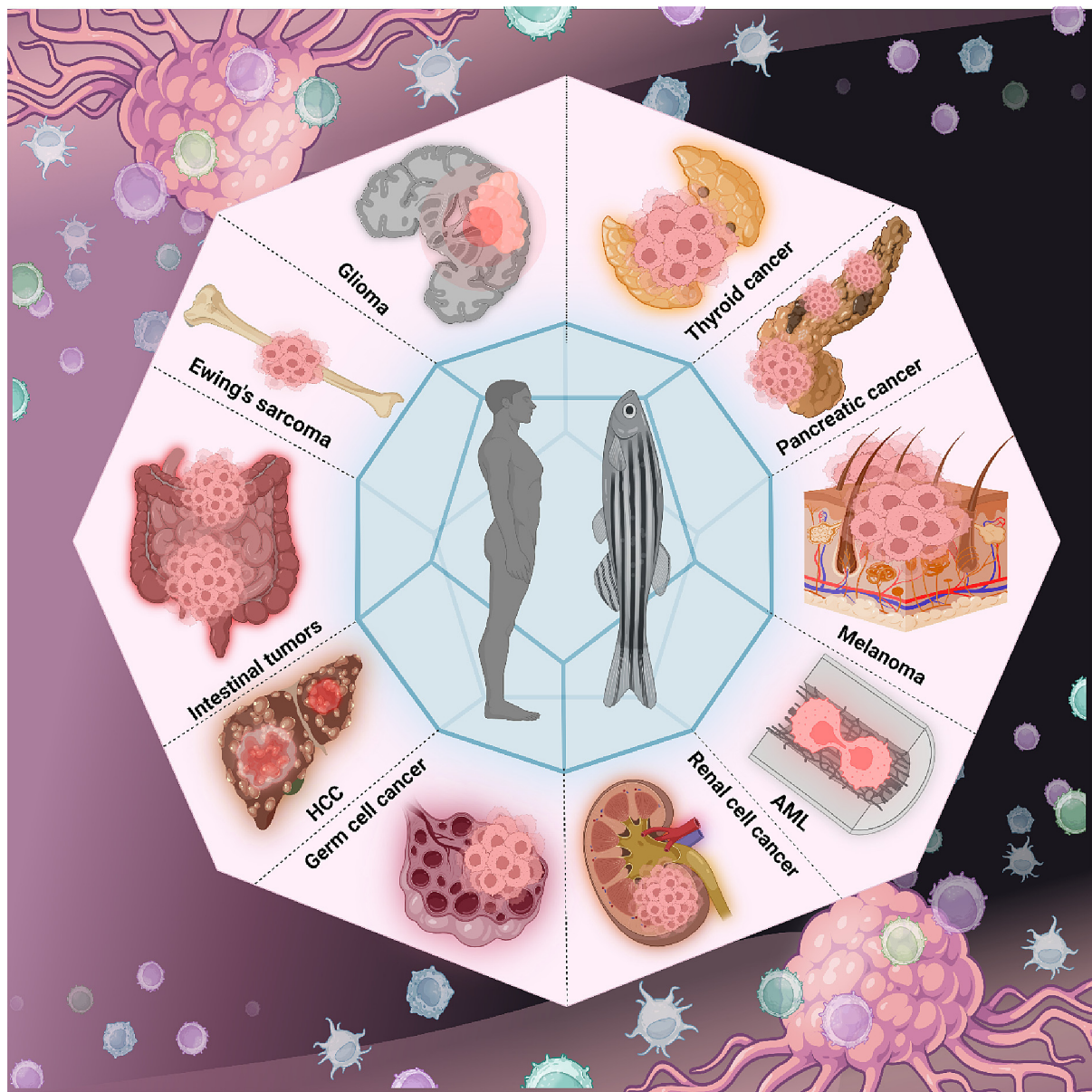
Fig. 4. Several cancers that have been studied using zebrafish model.

(Figs. 6, 7). A 29-gauge needle is used together with a syringe to inject a bacterial solution into an adult fish after it has been given tricane (anesthesia) in order to make it unconscious (Phelps et al., 2009). The bacterial solution is then loaded in the embryo using a glass capillary under micromanipulator (Davis et al., 2002) or microscope (Fig. 6).

Several different infections that are known to impact fish and mammals have previously been exploited, despite the fact that the zebrafish infection model is still relatively young. The benefit of a naturally occurring fish pathogen is that it has evolved with its host, leading to a dynamic interplay. The temperature of incubation may be a challenge for the utilization of mammalian pathogens. In order to preserve viability, zebrafish are typically kept between 26 °C and 29 °C. Mammalian pathogens, on the other hand, are adapted to their host's temperature (27 °C), and many of them, such as *Salmonella arizonae* and *S. typhimurium*, only express virulence factors at this temperature.

5.1. Bacteria

A wide range of human ailments causative bacteria, including *Listeria*, *Flavobacterium*, *Aeromonas*, *Salmonella*, *Pseudomonas*, *Streptococci*, *Listonella*, *Burkholderia*, *Edwardsiella*, *Shigella*, *Staphylococcus*, and *Mycobacteria*, have been established as zebrafish infection models (Figs. 6, 7).

5.1.1. Edwardsiella tarda

One day post fertilized zebrafish embryos were susceptible to *Edwardsiella tarda* infection using static immersion, showing an average mortality of 31 %, when compared to control fish 11 % (Pressley et al., 2005). Adult zebrafish treated to the bacteria by static immersion after being scraped revealed a death rate between 45 and 95 %, depending on the infection dose (Pressley et al., 2005). Adults had a mortality rate of between 30 and 60 % when infected by intraperitoneal injection. They even displayed lesions, perianal edemas, and abdominal distention at the site of injection (Pressley et al., 2005). Infected embryos' histopathological analyses revealed the presence of bacteria along with significant nerve tissue deterioration, abundant black cell nuclei in the retina and brain, indication of cell death by necrosis or apoptosis, and disorganized fin axis (Pressley et al., 2005). Adults fishes injected with bacteria showed deteriorated secondary oocytes and ruptured yolk sacs, according to further investigation of their ovaries (Pressley et al., 2005). Exposed fishes showed high

Table 1
Various transgenic model of cancer using zebrafish (McConnell et al., 2020).

Cancer type	Gene mutated	References
MPNST	$brca2^{Q658X/Q658X}$; $tp53^{M214K/+}$ $rp+/-$ (rps8a, rps15a, rpl7, rpl35, rpl36, rpl36a, rpl13, rpl23a, rps7, rps18, rps29) $rp^{+/-}$ or $p53^{M214K}$ $sox10{:}mCherry)$; $nf1a^{+/-}$; $nf1b^{-/-}$; $p53^{m/m}$ Tg(sox10:PDGFRA; sox10:mCherry); Tg(mitfa:atg5^{K130R}); $p53^{M214K/+}$ Tg(sox10:PDGFRAmut; $nf1a^{+/-}$; $nf1b^{-/-}$; $p53^{m/m}$	(Amsterdam et al., 2004b; Ki et al., 2017; Lee et al., 2016; Oppel et al., 2019; Shive et al., 2014; Zhang et al., 2013)
Thyroid cancer	Tg(tg:BRAF^{V600E}-TOM)	(Anelli et al., 2017)
Ewing's sarcoma	Tg(β-actin:EWS-FLI1:IRES-GFP) $+/- p53^-$ Tg(hsp70:EWS-FLI1) $+/- p53^-$ Tg(hsp70:EWS-FLI1:IRES-GFP) $+/- p53^-$	(Leacock et al., 2012; Park et al., 2016)
AML	Tg(spi1::loxP-EGFP-loxP:: NUP98-HOXA9) IDH1-R132H, idh1−/− Tg (ß-actin-LoxP-EGFP-LoxP-KRAS^{G12D}; hsp70-Cre) stat8.1^{N646H} or stat8.1$^{H298R/N714F}$ irf8$^{-/-}$ Tg(spi1:MYST3/NCOA2-EGFP) RUNX1-CBF2T1 Tg(spi1:FLT3-ITD-2A-EGFP/CG2) $+/-$ spi1:NPM1-Mut-PA/CG2	(Forrester et al., 2011; Kalev-Zylinska et al., 2002; Le et al., 2007; Lewis et al., 2006; Lu et al., 2016; Shi et al., 2014; Zhao et al., 2018; Zhuravleva et al., 2008)
Germ cell	ns1402 Tg(flck:TAg) dnaaf1^{hu255h} ENU mutagenesis lrrc50^{Hu255h}	(Basten et al., 2013; Gill et al., 2010; Litchfield et al., 2016; Neumann et al., 2009; Shimizu and Matsuda, 2019)
Rhabdomyosarcoma	Tg(fli1:GFP2A-PAX3FOXO1) Tg(β-actin: LoxP-EGFP-LoxP-KRAS^{G12D}) Tg(cdh15:KRAS^{G12D}) Tg(mitfa:GFP2A-PAX3FOXO1) Tg(rag2:KRAS^{G12D}) $+/- p53^-$ Tg(ubi:GFP2A-PAX3FOXO1) Tg(CMV:GFP2A-PAX3FOXO1) Tg(mylz2:KRAS^{G12D})	(Ignatius et al., 2018; Kendall et al., 2018; Langenau et al., 2007; Le et al., 2007; Storer et al., 2013)
Glioma	Tg(gfap:Gal4VP16; UAS: mCherry-KRAS^{G12V}) Tg(zic4:Gal4TA4; UAS:mCherry; UAS:Xmrk) Tg(zic4:Gal4TA4; UAS:mCherry; UAS:AKT-BFP) Tg(sox10:mCherry-NRAS^{wt}) $+/- p53^{M214K}$ Tg(ptf1:Gal4; UAS:GFP; UAS: DA-RAC1) Tg(zic4:Gal4TA4; UAS:mCherry; UAS:YAP^{S5A}) Tg(sox10:mCherry-NRAS^{S17N}) $+/- p53^{M214K}$ Tg(krt5:Gal4VP16; UAS: mCherry-KRAS^{G12V})	(Ju et al., 2015; Jung et al., 2013; M et al., 2017; Modzelewska et al., 2016)
Melanoma	Tg(kita:HRAS^{G12V}) Tg(mitfa:BRAF^{V600E}); $p53^{-/-}$ Tg(mitfa:EGFP:NRAS^{Q61K}); $p53^{-/-}$ Tg(mitfa:NRAS^{Q61R}) Tg(mitfa:BRAF^{V600E}); $p53^{-/-}$; mitfa$^{-/-}$ + MiniCoopR	(Ceol et al., 2011; Dovey et al., 2009; McConnell et al., 2019; Patton et al., 2005; Santoriello et al., 2010)
CML	Tg(hsp70:p210$^{BCR/ABL1}$)	(Xu et al., 2020)
Liver cancer	Tg(fabp10a:tTA; pT2-TRE-gankyrin-HcRed) Tg(fabp10:TA; TRE:Myc) Tg(pLF2.8-HCV-core) Tg(fabp10:LexPR; LexA:Cre; fabp10: loxP-mCherry-loxP-EGFP-KRAS^{G12V}) Tg(fabp10:TA; TRE:xmrk) apc$^{+/-}$ Tg(fabp10:NRAS^{Q61K})	(Haramis et al., 2006; Huang et al., 2017; Li et al., 2013; Z. Li et al., 2016; Nguyen et al., 2016, 2011; Rekha et al., 2008; Wang et al., 2017)

Table 1 (*continued*)

Cancer type	Gene mutated	References
	Tg(fabp10:EGFP-KRAS^{G12V}) $+/-$ $p53^{M214K}$	
Renal cell	vhl$^{-/-}$	(Van Rooijen et al., 2009)
Neuroblastoma	Tg(dβh:ptpn11^{E69K}-EGFP; dβh: EGFP-MYCN) Tg(dβh:MYCN; dβh:EGFP) Tg(dbh:Gab2wt; dβh:EGFP; dβh: EGFP-MYCN) Tg(dβh:EGFP-MYCN) Tg(dβh:MYC) Tg(dβh:EGFP-MYCN); nf1a$^{-/-}$; nf1b$^{+/-}$ Tg(dβh:EGFP; dβh:ALK^{F1174L}) Tg(dβh:EGFP-MYCN; dβh:LMO1; dβh:mCherry)	(He et al., 2016; Tao et al., 2017; Zhang et al., 2017; S. Zhu et al., 2012; Zhu et al., 2017; Zimmerman et al., 2018)
Liposarcoma	Tg(krt4:Has.myrAkt1)^{cy18} Tg(rag2:myr-mAkt2) $+/- p53^{M214K}$	(Chu et al., 2012; Gutierrez et al., 2011b)
ALL	TEL-AML1 Tg(rag2:EGFP-mMyc) Tg(rag2:cMyc) Tg(rag2-ICN1-EGFP) Tg(rag2:MYC-ER)	(Arceci, 2008; Chen et al., 2007; Gutierrez et al., 2011a; Langenau et al., 2005; Langenau et al., 2003)
Pancreatic cancer	Tg(ubb: Lox-Nuc-mCherry-stop-Lox-GFP:: KRAS^{G12D}) z-myod:MYCN, core-z-myod:MYCN rpl36$^{+/-}$; Tg(ptf1a:gal4VP16; UAS: GFP-KRAS^{G12V}) Tg(ptf1a:eGFP-KRAS^{G12V}) Tg(ptf1a:gal4VP16; UAS: GFP-KRAS^{mut})	(Hong et al., 2004; Oh and Park, 2019; Park et al., 2015, 2008; Provost et al., 2014)

Footnote: ALL-acute lymphoblastic leukemia; AML-acute myeloid leukemia; DA-dominant active; CML-chronic myeloid leukemia; MPNST-malignant peripheral nerve sheath tumor.

level of TNFα and IL-1β mRNA level through cytokine analysis (Pressley et al., 2005).

5.1.2. Streptococcus

5.1.2.1. Streptococcus iniae. **Meningoencephalitis** is the predominant symptom of a systemic, invasive sickness caused by the naturally occurring bacterial fish pathogen *streptococcus iniae* in fish. *Streptococcus iniae* infections in fish are similar to those caused by many streptococcal species in humans. *S. iniae* has a relatively low LD50 (lethal dosage) for adult zebrafish following intraperitoneal injection (10^3) (Neely et al., 2002). After 26 h post-infection, bacteria spread widely throughout the body and typically result in death within a few days. However, *S. pyogenes*, a human pathogen, has a comparable LD50 in zebrafish, demonstrating that fish are also susceptible to the virulence of these bacteria (Neely et al., 2002). Additionally investigated in adult zebrafish were two *S. pyogenes* mutants that showed signs of attenuation in a mouse infection model. In contrast to one of these mutants with a damaged RopB regulatory gene, the glutathione peroxidase mutant did not show decreased pathogenicity (Brenot et al., 2004; Neely et al., 2002). This finding suggests that while the zebrafish infected model may be utilized to identify virulence mutations, the outcomes need to be confirmed in other infection models. Additionally, two other potential virulence factors for *S. pyogenes*—ATP-binding cassette transporter and peptidoglycan-modifying enzyme—were discovered using zebrafish (Neely et al., 2002).

5.1.2.2. Streptococcus agalactiae. The gram-positive bacterium "*Streptococcus agalactiae*" (also known as GBS: group B streptococcus) infects a wide range of species, including both aquatic and terrestrial organisms (Delannoy et al., 2013). The primary source of infection in the newborn is due to GBS (Le Doare and Heath, 2013). Some of the typical clinical effects of a GBS infection include pneumonia, sepsis, and meningitis (Le Doare and
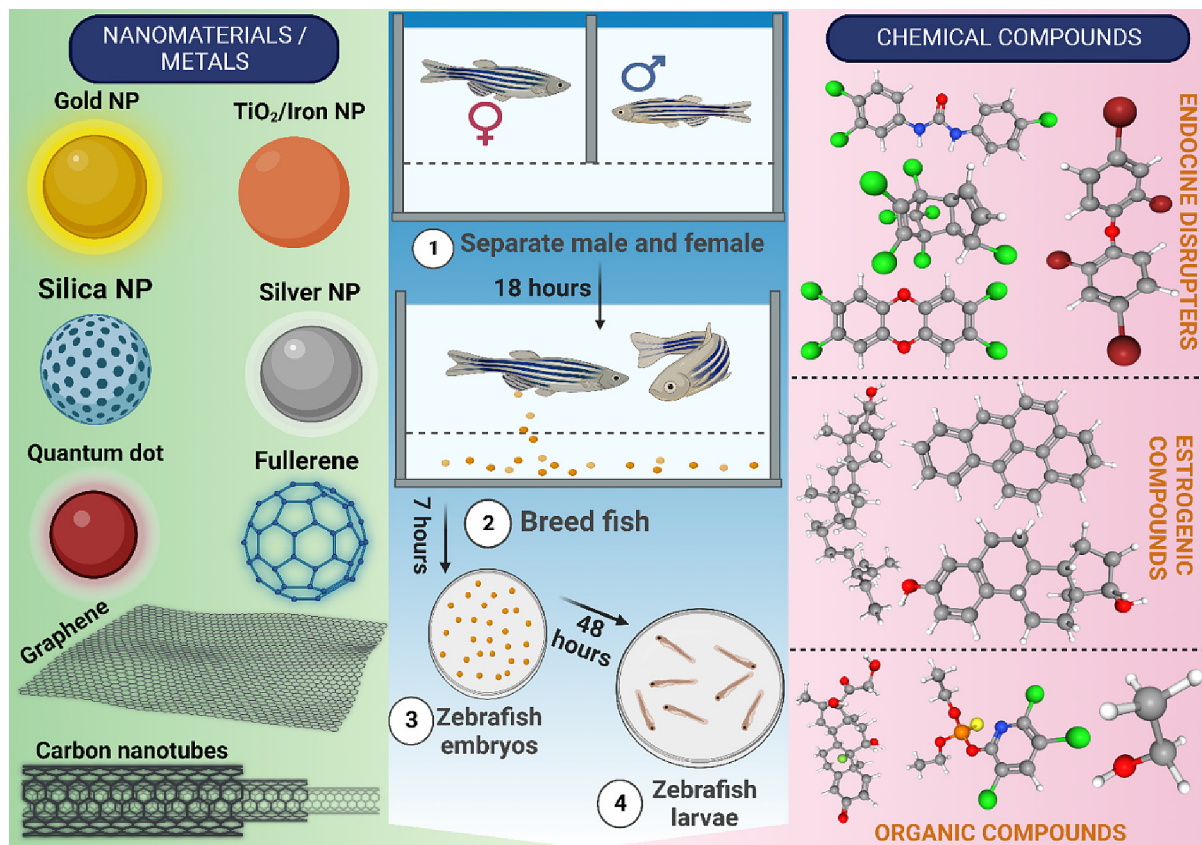
Table 2

Various zebrafish cancer genetic model (Hason and Bartůněk, 2019).

Cancer	Genotype	Zebrafish background	Reference
Testicular tumor	brca2^{Q658X}	Wild type	(Shive et al., 2010)
RMS	rag2:dsRed2	tp53^{M214K}	(Langenau et al., 2008, 2007)
	rag2:KRAS^{G12D}	α-actin:GFP, Wild type	
Intestinal tumors	+ various Gal4 lines	cyp7a1^{-5} or wild type	(Enya et al., 2018)
	fabp10a:mCherry	cyp7a1^{-5} or wild type	
	5×UAS:EGFP-P2A-kras^{G12D}	cyp7a1^{-5} or wild type	
	fabp10a:mCherry-P2A-cyp7a1	cyp7a1^{-5} or wild type	
MDS	tet2$^{-/-}$	cd41:eGFP, cmyb:eGFP	(Gjini et al., 2015)
Melanoma	UAS:eGFP-HRAS^{GV12}	tp53^{M214K}, wild type	(Anelli et al., 2018; Kaufman et al., 2016; Lister
	BRAF^{V600E}mitfa^{vc7}	mitfa^{vc7}	et al., 2014; Patton et al., 2005; Santoriello et al.,
	UAS:eGFP-HRAS^{GV12}	–	2010, 2009)
	UAS:eGFP-jmjd6	tp53^{M214K}, wild type	
	BRAF^{V600E} tp53^{M214K}	tp53^{M214K}	
	hsp70I:GFP-HRAS^{G12V}	–	
	kita:Gal4TA, UAS:mCherry	tp53^{M214K}, wild type	
	BRAF^{V600E} tp53^{M214K}	tp53^{M214K}, crestin:EGFP	
	kita:GalTA4,UAS:mCherry	–	
AML	pHsFLT3-ITD-T2a-eGFP	Wild type variant	(Dayyani et al., 2008; He et al., 2014; Yeh et al.,
	hsp70:AML1-ETO	Wild type variant	2008; Zhuravleva et al., 2008)
	FLT3-ITD-T2a-mRFP	Wild type variant	
	spi1:MYST3/NCOA2-eGFP	–	
	pHsFLT3-WT-T2a-eGFP	Wild type variant	
Thyroid cancer	tg:BRAFV600E-pA	Wild type variant	(Anelli et al., 2017)
	tg:TdTomato-pA	Wild type variant	
PNST	tp53^{M214K}	tp53^{M214K}, wild type variant	(Mensah et al., 2019; S et al., 2005)
	tp53^{M214K}	Wild type variant	
	brca2^{Q658X}	tp53^{M214K}, wild type variant	
CML	spi1:tel-jak2a	Wild type variant	(Onnebo et al., 2012, 2005)
HCC	krt4:GFP	Wild type variant	(Chou et al., 2019; Li et al., 2019; Yang et al., 2019)
	TRE:Myc	Wild type variant	
	fabp10:TA	Wild type variant	
	myl7:GFP	–	
	fabp10a: RPIA	–	
	fabp10:TA	Wild type variant	
	krt4:GFP	Wild type variant	
	TRE:xmrk	Wild type variant	
	TRE2:eGFP-kras^{G12V}	lepr$^{+/-}$, wild type variant	
	fabp10:rtTA2s-M2	lepr$^{+/-}$, wild type variant	
T-ALL	spi1:tel-jak2a	Wild type variant	(Langenau et al., 2008, 2005; Langenau et al., 2003;
	rag2:GFP	Wild type variant	Onnebo et al., 2012)
	rag2:loxP-dsRED2-loxP-eGFP-mMyc	Wild type variant	
	rag2:dsRed2	Wild type variant	
	rag2:mMyc	Wild type variant	
Pancreatic cancer	ptf1a:CRE^{ERT2}	–	(Park and Leach, 2018; Park et al., 2008)
	ubb:lox-Nuc-eCFP-stop-lox-GAL4-VP16	–	
	ptf1a:eGFP-KRAS^{G12V}	Wild type variant	
	UAS:eGFP-KRAS^{G12V}	–	

Footnote: MDS-myelodysplastic syndrome, RMS-rhabdomyosarcoma, AML-acute lymphoid leukemia, PNST-peripheral nerve sheath tumor, CML-chronic myeloid leukemia, HCC-hepatocellular cancer, T-ALL-T-cell acute lymphoid leukemia.

Heath, 2013). A systemic GBS infection model using zebrafish has recently been established (Kim et al., 2015; Patterson et al., 2012). Researchers found that adult zebrafish exposed to intraperitoneal (IP) and intramuscular (IM) injections of the LD50 levels of 10^2 and 10^4 cfu, respectively, were susceptible to GBS infection (Patterson et al., 2012). The multiplication of bacteria in the blood, a high death rate, and meningoencephalitis symptoms have all been linked to intraperitoneal injections of bacteria. When the brain's bacterial burden was examined, it became clear that the bacteria had breached the blood-brain barrier (BBB) and was responsible for the model's meningitis. The GBS infection also stimulated the host's inflammatory response in adult fish, as has been observed in mice and people, as evidenced by elevation in the proinflammatory cytokines IL-1β and IL-6 (Patterson et al., 2012).

5.1.2.3. Streptococcus pneumonia. Streptococcus pneumonia (pneumococcus), a member of the *Streptococcus* genus, is frequently linked to adverse clinical outcomes and an invasive illness in humans (Krzyściak et al., 2013). Although pneumococcal vaccinations have improved, this pathogen still accounts for most infectious disease-related fatalities. Zebrafish larval and adult models for pneumococcal infection have been developed to explore the condition more thoroughly (Rounioja et al., 2012; Saralahti et al., 2014). The introduction of pneumococci into the bloodstream of zebrafish larvae at 2dpf demonstrated their susceptibility to pneumococcal infection, this resulted in a dose-dependent infection that was fatal within 48 h (Rounioja et al., 2012). Pneumococcus was able to multiply in this host as evidenced by the rising bacterial counts in the infected larvae, and the high bacterial levels were linked to the larvae's demise. Studies using the zebrafish embryo model for pneumococcal infection also applicable to adult zebrafish (Saralahti et al., 2014). Pneumococcus appears to be less virulent than other streptococci in adult zebrafish since an intraperitoneal infection with just 2.5×10^6 cfu was enough to kill half the people (Saralahti et al., 2014). Pneumolysin, autolysin, and pilus defective mutants infected adult fish led to a comparatively mild illness. The wild-type pneumococcus, on the other hand, induced a severe systemic infection that spread to the fish's brain when it was injected intraperitoneally into adult fish (Saralahti et al., 2014). This paradigm has a considerable advantage over the larval one because adult zebrafish exhibit both innate and adaptive responses. However, investigating the role of the adaptive immunity in a pneumococcal infection utilizing mutant zebrafish line Rag1hu1999, which is devoid of activated lymphocytes, revealed that the adaptive

Fig. 5. Diagrammatic representation of different chemical compounds and metals/nanomaterials-induced toxicity profiling using the *Danio rerio* model (NP: nanoparticles).

immune system plays no part in a severe pneumococcal infection in adult zebrafish (Saralahti et al., 2014).

5.1.2.4. Streptococcus pyogenes. *S. pyogenes* (also known as GAS: group A streptococcus), which causes over than 700 million infections yearly, is the most common source of human illness (Krzyściak et al., 2013). Although *S. pyogenes* generally does not infect fish, it has been shown that it may infect adult zebrafish *via* intramuscular (IM) and intraperitoneal (IP) injections (Neely et al., 2002). *S. pyogenes* when injected intramuscularly, the outcome closely resembles human necrotizing fasciitis because to its constrained nature and severe muscle tissue destruction at the site of infection (Miller, 2004; Phelps and Neely, 2007). Demise of zebrafish has been observed in 36–48 h after being intramuscularly injected with *S. pyogenes* at a dose equal to its lethal dose (LD50) (3×10^4), which causes the fish to acquire broad hypopigmented lesions where the injection was performed (Neely et al., 2002). According to reports, the dorsal muscle is the only location where *S. pyogenes* infection persists in adult zebrafish, which is aligned with results from murine models of infections (Miller, 2004). In a study by Montanez et al. (Montañez et al., 2005), the adult zebrafish model was used to explore the role of iron absorption channels, which are surprisingly preserved across various species of streptococcal. Researchers used *S. pyogenes* mutant with an inactive Siu transporter gene to demonstrate the significance of iron uptake for the pathogenicity of *S. pyogenes* (Montañez et al., 2005). Another study by Brenot et al. (2004) using a zebrafish model, Brenot et al. and his group indicated that the inflammatory response is required for *S. pyogenes* to survive in the host in order for it to produce the enzyme glutathione peroxidase.

5.1.3. Mycobacteria
Numerous mycobacterial pathogens, including *Mycobacterium fortuitum*, *Mycobacterium chelonae*, and *Mycobacterium abscessus*, can infect zebrafish (Astrofsky et al., 2000). Furthermore, *M. marinum*, a closely related species of *M. tuberculosis*, is the most potent agent of fish tuberculosis

(Stinear et al., 2008). *M. marinum* can sporadically infect humans and spreads through water, although most often, the illness just affects the skin (Linell and Norden, 1954). Compared to *M. tuberculosis*, *M. marinum* is less dangerous to handle and replicates more quickly. Since *M. marinum* infection in zebrafish serves as a model for TB, these facts have motivated a number of researchers to explore it (Decostere et al., 2004; Tobin and Ramakrishnan, 2008). *M. marinum* can live and proliferate in adult zebrafish, as predicted, and depending on the inoculum employed, can cause an acute or chronic illness. Zebrafish are a beneficial choice for *M. marinum*'s host organism in a laboratory environment for a number of reasons: Zebrafish embryos and adults may both be infected using the multiple infection approach (Benard et al., 2012). Due to the embryos' transparency, advanced *in vivo* real-time imaging methods, such as the use of many leukocyte and macrophage fluorescent reporter lines, are possible (Renshaw et al., 2006; Wittamer et al., 2011). All the embryonic defenses in zebrafish are innate. Post one or two day fertilization appearance of functional neutrophils and macrophages occurs, whereas, Lymphocyte development begins four days after conception, and adaptive immunity is fully developed four weeks after fertilization (Langenau et al., 2004). Based on genetic fingerprinting, there are two groups of *M. marinum* strains, and the group of *M. marinum* that encompasses the most lethal strains simultaneously holds the bulk of the mycobacteria found in individuals with *M. marinum*-caused skin infections (Van Der Sar et al., 2004), However, the zebrafish embryo model has shown the most intriguing results with zebrafish *M. marinum* infections. According to research by Davis et al. (Davis et al., 2002), *M. marinum* infected embryonic macrophages extravasate and begin to congregate. This results in the activation of certain genes that are exclusively activated in the granuloma's confined environment and not in isolated infected macrophages.

5.1.4. Shigella
A clinical process known as shigellosis is caused by the human pathovar of *E. coli, Shigella flexneri*, which causes bacillary dysentery and gastroenteritis.

Table 3

Different types of metals and chemicals evaluated for toxicity in zebrafish.

	References
Nanomaterial	
Silver (Ag) NP	(Asharani et al., 2011; Boran and Şaffak, 2020; Chao et al.,
Gold (Au) NP	2021; Cheng and Cheng, 2012; Duan et al., 2013;
Silicon dioxide (SiO2) NP	Ghobadian et al., 2015; Gu et al., 2021; Ispas et al., 2009;
Titanium dioxide (TiO2) NP	King-Heiden et al., 2009; Lee et al., 2021; Madhubala
Platinum (Pt) NP	et al., 2019; Patsiou et al., 2020; Shankar et al., 2021;
Nickel (Ni) NP	Usenko et al., 2007; Van Aerle et al., 2013; Villacis et al.,
Copper (Cu) NP	2017; Wang et al., 2016; X. Zhu et al., 2012)
Copper oxide (CuO) NP	
Nickel oxide (NiO) NP	
Zinc (Zn) NP	
Lead (Pb) NP	
Uranium (U) NP	
Magnesium (Mg) NP	
Magnesium oxide (MgO) NP	
Iron (Fe) NP	
αFe2O3 NP	
γ-Fe2O3 NP	
Al2O3 NP	
Fullerenes	
Carbon nanotubes	
Quantum dot (CdSe core/Zn shell)	
Estrogenics compounds	
Phytosterols	(Elfawy et al., 2021; Kazeto et al., 2004; Kishida et al.,
Nonylphenol	2001; Nakari and Erkomaa, 2003; Weber et al., 2003;
17Alpha-ethinylestradiol	Willey and Krone, 2001)
Ethinylestradiol	
Benzo[*a*]pyrene	
17-Beta estradiol	
Diethylstilbestrol	
Metals	
Cadmium	(Chan et al., 2006; Chan and Cheng, 2003; Dave, 1985;
Methylmercury	Dave and Xiu, 1991; Labrot et al., 1999; X. Li et al., 2012;
Cobalt	Richetti et al., 2011; Samson et al., 2001; Wu et al., 2012)
Nickel	
Lead	
Copper	
Iron	
Aluminum	
Uranium	
Zinc chloride	
Cadmium acetate	
Mercury chloride	
Lead acetate	
Arsenic	
Cd2+	
Cu2+	
Hg2+	
Cd2+	
Zn2+	
Endocrine disruptors	
DE-71	(Chen et al., 2012; Chow et al., 2013; Chunga et al., 2011;
Bisphenol A	Heiden et al., 2008; Yu et al., 2010)
BDE-47	
Tetrabromobisphenol A	
Endosulfan	
TCDD	
Methoxychlor	
Heptachlor	
Triclocarban	
Organic compounds	
Dexamethasone	(Abnet et al., 1999; Collier et al., 2004; Fåhræus-Van Ree
Doxorubicin	and Payne, 1997; Huang and Huang, 2012; Levin et al.,
Epirubicin	2003; Oulmi and Braunbeck, 1996; Todd and Van
Flavopiridol	Leeuwen, 2002; Wiegand et al., 2001; Zhang et al., 2003)
Acetaminophen	
DCA	
Didemnin B	
Ethanol	

Table 3 (*continued*)

|	References
Fujisawa peptide	
5-FU	
Vinblastine sulfate	
TCDD	
Trithiophene	
Naproxen	
Staurosporine	
SU5416	
Ibuprofen	
Methotrexate	
Chlorpyrifos	
Methyl parathion	
PCBs	
PAHs	
Sevin	
Toxaphene	
4-Chloroaniline	

Footnote: Cd-cadmium, Cu-copper, Hg-mercury, Zn-zinc, DCA-dichloroacetic acid, 5-FU-5-fluorouracil, SU5416-, PCBs-polychlorinated biphenyls, DE-71-polybrominated diphenyl ethers, PAHs-polycyclic aromatic hydrocarbons, BDE-47-2,2,4,4-tetrabromodiphenyl ether, TCDD-2,3,7,8-tetrachlorodibenzo-p-dioxin.

Our capacity to comprehend the *Shigella* infection process *in vivo* has, as of now, been constrained. Shigellosis in humans cannot be accurately simulated by any non-primate animal model. Animal model such as rabbit (Schnupf and Sansonetti, 2012), mouse model (Li et al., 2017) and guinea pig (Shim et al., 2007) are few animals where the numerous researches have been carried out. Utilizing *Danio rerio* larvae to research *Shigella* infection has several benefits. When injected into zebrafish, *Shigella* has the potential to infiltrate epithelial cells and result in symptoms similar to those of human Shigellosis, including inflammation and macrophage cell death (Mazon-Moya et al., 2017; Mostowy et al., 2013). Zebrafish study has demonstrated that the type-3 secretion system (T3SS), a crucial component in the progression of illness in humans, is absolutely necessary for Shigella absorption into nonphagocytic cells (Cossart and Sansonetti, 2004). Additionally, studies have shown that *Shigella* can escape to the cytoplasm and be picked up by the autophagy process (Mostowy et al., 2013, 2010). Study by Cossart et al. revealed that actin and septins are attracted to the phagocytic cup during the *Shigella* infection, where they form rings around the invasive bacteria (Mostowy et al., 2009). Although Depletion of SEPT2 by small interfering (si)RNA greatly decreases *Shigella* access into host cells, despite the fact that the specific function of septins during bacterial entry is unclear (Mostowy et al., 2009). Septin caging, which is the process of recruiting septins to actin-polymerizing bacteria after bacterial escape from the phagosome to the cytosol, creates cage-like structures surrounding *Shigella* that prevent cell-to-cell dissemination (Mostowy et al., 2010). SEPT2, SEPT9, or nonmuscle myosin II depletion decreases septin caging and increases the proportion of bacteria with actin tails, whereas boosting SEPT2-nonmuscle myosin II interactions with tumor necrosis factor promotes septin caging and reduces the occurrence of actin tails in bacteria (Mostowy et al., 2010). Significantly, results from studies of septin cages in zebrafish cells both *in vivo* and *in vitro* support their role as an evolutionarily conserved host defense component (Mostowy et al., 2013).

5.1.5. Salmonella

The most widespread pathogen that affects several host species is *Salmonella enterica* serovar Typhimurium, which causes gastroenteritis in humans and other animals and symptoms that resemble fever in mice (Thiennimitr et al., 2012). The majority of studies on bacterial virulence have used traditional animal models including mice, primates, and pigs (Verma and Srikanth, 2015). Nevertheless, the utilization of mammal hosts is constrained by the limited real-time analytic options and the demands for intrusive sample collection. The development of vertebrates has been widely studied using zebrafish as a model in biological research. When *S. Typhimurium* is injected into zebrafish, a typhoid-like sickness similar to that caused by *S. Typhimurium* in rodents and *S. enterica* serovar Typhi in humans is induced. According to a research, guanylate-binding protein 4
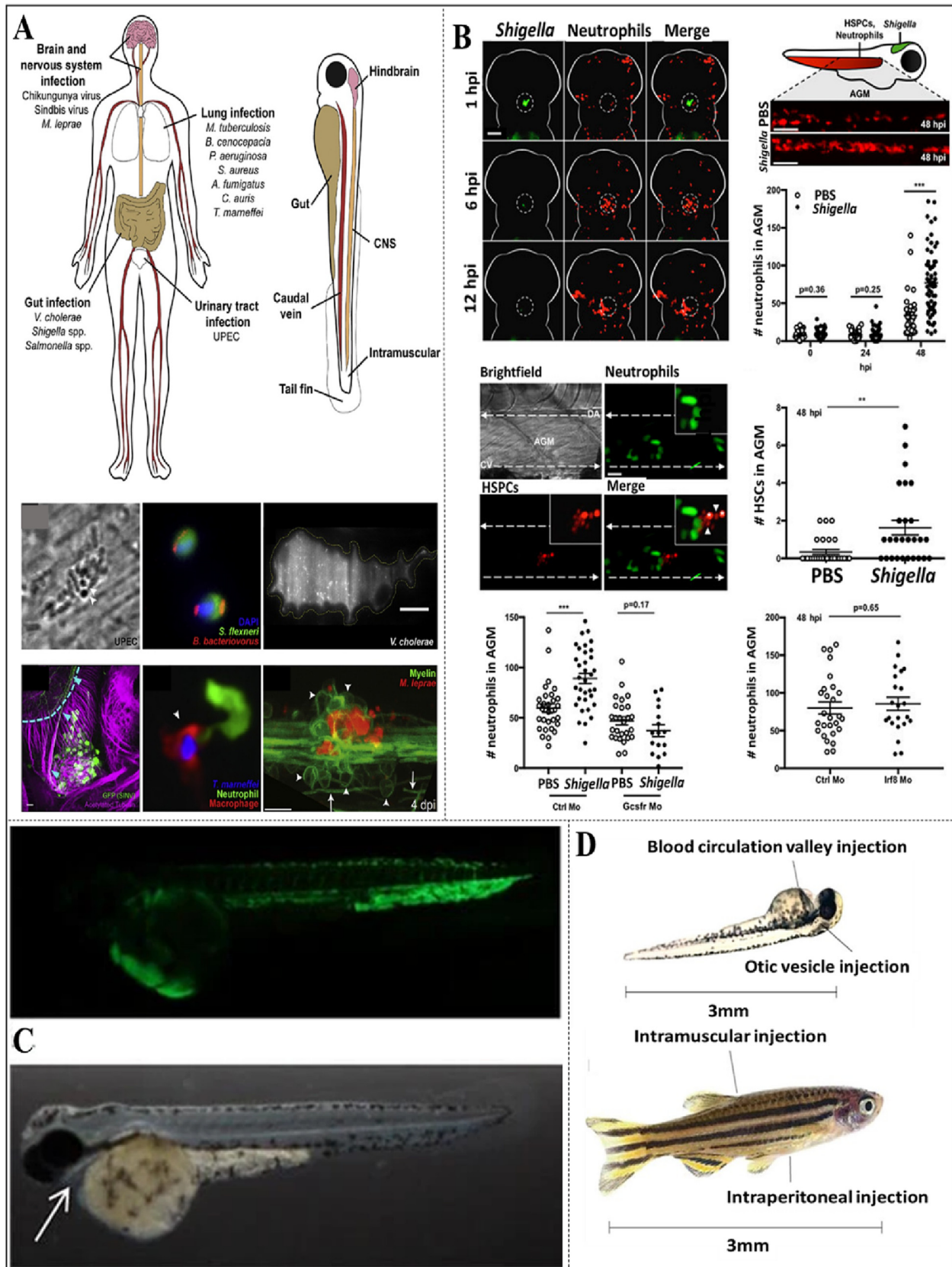
Fig. 6. (A, left) Zebrafish are being used to study the brain, lungs, bladder, nerve system, and gut, which are the four main areas of the human body where infections occur. (A, right) Central nervous system, rear brain, tail (muscles, fin), and caudal vein are among the zebrafish injection sites that are often used. (A, bottom) represents bacterial injections in different parts of zebrafish: UroPathogenic *Escherichia coli* (UPEC) administered into the tail fin, *Vibrio cholerae* populating the gut, Sindbis virus in the central nervous system, *Talaromyces marneffei conidia* in the muscle tissue and *Mycobacterium leprae* in the CNS region (Gomes and Mostowy, 2020). (B) Zebrafish model of Shigella infection used to examine granulopoiesis (Willis et al., 2018) (AGM: aorta gonad mesonephros, HSPCs: hematopoietic stem and progenitor cells). (C) Fluorescence image of zebrafish inoculated with *E. coli K46/pGEN-GFP* strain (CK et al., 2017). (D) Various injection route for infecting streptococcal infection (blood circulation in larvae and intramuscular, intraperitoneal in adult) (Saralahti and Rämet, 2015).
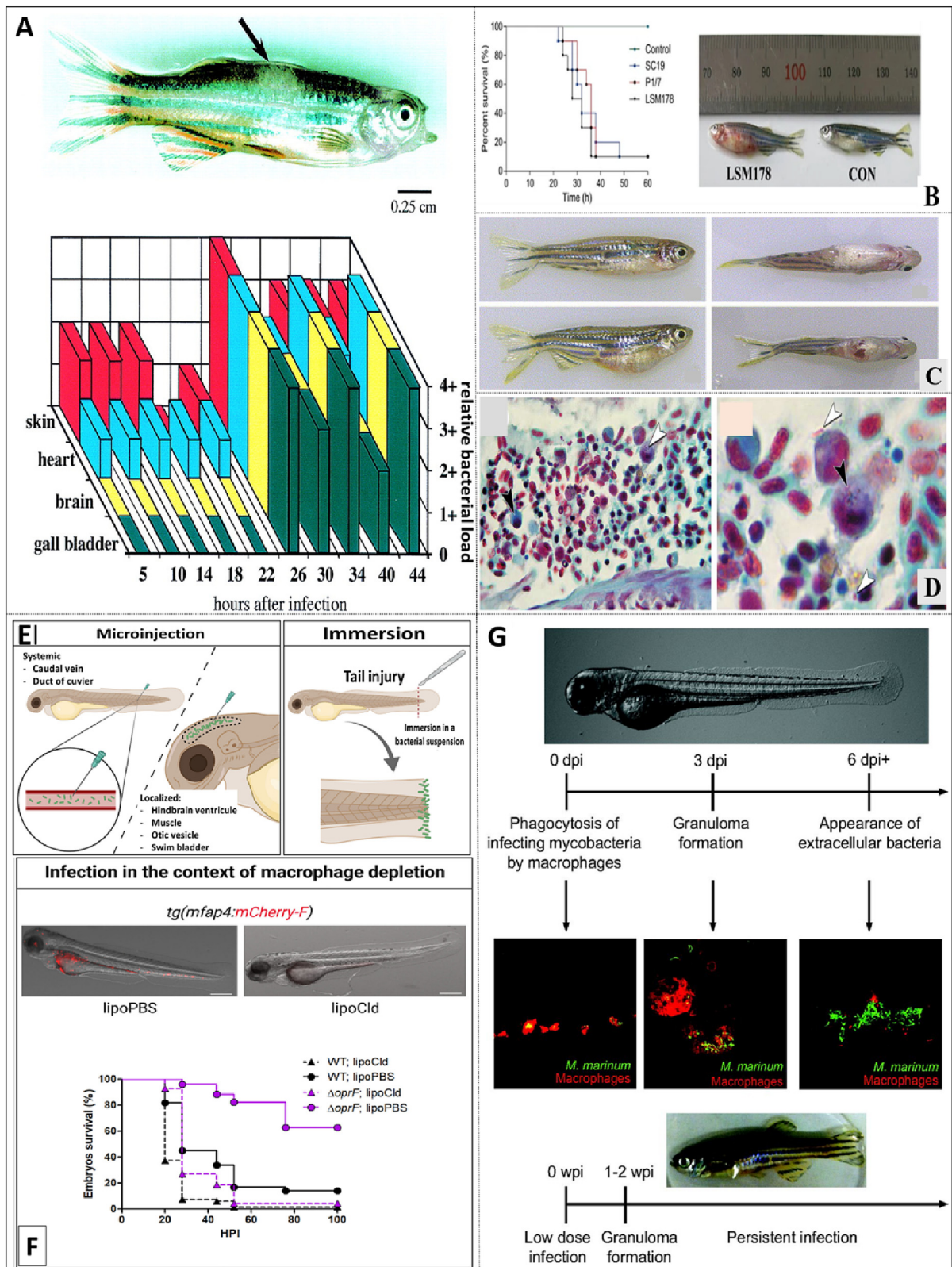
Fig. 7. (A, top) Hypopigmented lesion at the intramuscular site of zebrafish caused due to *S. iniae*. (A, bottom) Relative bacterial load of *S. iniae* in various organ of zebrafish (Neely et al., 2002). (B) Survival rate of fish infected with *Streptococcus suis* LSM178, SC19 and P1/7 strain (Y. Hu et al., 2021). (C) Infection of zebrafish with *E. tarda* (Pressley et al., 2005). (D) Histopathology investigation (Brown and Brenn Gram staining) of adult zebrafish infected with *E. tarda* (Pressley et al., 2005). (E) Various injection techniques to introduce *Pseudomonas aeruginosa* in the larvae of zebrafish (Pont and Blanc-Potard, 2021). (F) Confocal imaging representing fluorescent labelled macrophages, *P. aeruginosa* (Pont and Blanc-Potard, 2021). (G) Progression of infection of *Mycobacterium marinum* in larvae and adult zebrafish (Cronan and Tobin, 2014).

(Gbp4) activates the neutrophil inflammasome, which is essential for the removal of *S. Typhimurium* (Tyrkalska et al., 2016). Leukotriene B4 activation, an inflammatory lipid mediator, is observed to cause neutrophil chemotaxis, which results in neutrophil recruitment. Salmonella infection is eradicated as a result of the recruited neutrophils engulfing the pathogen and activating the Gbp4 inflammasome. These results highlight the critical role neutrophils play in mediating this response *in vivo*. *S. Typhimurium* strains with poor translation fidelity are rendered ineffective *in vivo* by the wild type strain and attract fewer neutrophils after colonization *via* the gastrointestinal route (Fan et al., 2019). Zebrafish larvae exposed to *S. Typhimurium* develop intestinal and cloacal inflammation, according to a research by Howlader et al. (2016) and Varas et al. (2017). It has been demonstrated that hematopoietic stem and progenitor cell (HSPC) proliferation during infection is a direct result of enhanced neutrophil production using a *Salmonella*-zebrafish infection model (Hall et al., 2012). *Salmonella* infection of zebrafish has contributed significantly to the development of novel concepts in immunometabolism, emergency granulopoiesis, and cell-autonomous immunity.

5.1.6. Pseudomonas

It has been suggested that zebrafish embryos are an effective model for studying *Pseudomonas aeruginosa* infection (Brannon et al., 2009; Clatworthy et al., 2009; Llamas et al., 2009). Patients with cystic fibrosis (CF) frequently have lung infections caused by the opportunistic bacteria *P. aeruginosa*. Embryos that are one or two days post-fertilization are often used to inject *P. aeruginosa* bacteria into the caudal vein to cause an infection. *Pseudomonas* is relatively resistant to the zebrafish, and a substantial inoculum is needed to establish infection and cause host death (Brannon et al., 2009; Clatworthy et al., 2009). Researchers may evaluate the directed migration of neutrophils and macrophages towards specific infections by administering bacteria into the hindbrain, ventricle, tail muscle and otic vesicle. The notochord is also injected with bacteria to prevent the infection from reaching the phagocytic cells (Alibaud et al., 2011). Bacteria supplied systemically can be quickly engulfed and killed by neutrophils and macrophages. *P. aeruginosa* produces elastase, phospholipase C, and exotoxin A as a few type III secretion systems as a virulence strategy to oppose host defense (Cao et al., 2001; Yahr and Wolfgang, 2006). An investigation using *P. aeruginosa* mutant T3SS revealed T3SS mutant being virulent or suppressed in host with or without phagocytes depletion. This demonstrates how interactions between phagocytes and T3SS contribute to *Pseudomonas* pathogenicity in immunocompetent hosts. Additionally, *P. aeruginosa* T3SS mutant are fatal at early stages when only macrophages have begun to form, but are diminished in the subsequent stages when both neutrophils and macrophages are involved (Clatworthy et al., 2009). When compared to healthy embryos, increased bacterial multiplication in the embryos is associated with slower blood flow, a slower heartbeat, and significant tissue damage (in the tail and brain area).

5.1.7. Escherichia

Enterohemorrhagic *Escherichia coli* (EHEC), an enteric pathogen that colonizes in the gut and causes bloody diarrhea in humans, has been effectively mimicked in zebrafish (*Danio rerio*). Following foodborne delivery by *Paramecium caudatum*, Stones et al. and his colleagues discovered that EHEC colonizes the middle intestine of zebrafish larvae, and the survival rate drops by 40 % by 4 days post infection (Stones et al., 2017). Both the colonization of the gut by EHEC in humans and cattle, as well as the emergence of adhering and effacing lesions on enterocytes, are regulated by a set of virulence genes produced by the locus of enterocyte effacement (LEE) (Elliott et al., 2000; Phillips et al., 2000). In initial gastrointestinal tract colonization in larval zebrafish, EHEC promotes the LEE, and LEE induction is necessary for successful colonization and pathogenicity. Pathogenic *E. coli* is not the only bacteria that colonizes the zebrafish intestine; nevertheless, amicable *E. coli* from healthy human gut have been utilized to colonize zebrafish and can inhibit *V. cholera* colonization by reducing intestinal pH due to glucose metabolism (Nag et al., 2018).

5.1.8. Burkholderia

A common opportunistic pathogen of individuals suffering from cystic fibrosis and chronic granulomatous disease, *Burkholderia cenocepacia* complex (BCC) bacteria may also be detected in the rhizosphere of plants (Drevinek and Mahenthiralingam, 2010; Mahenthiralingam et al., 2008). The 17 types of BCC bacteria have all been identified in CF patients (Holden et al., 2009), *Burkholderia cenocepacia* is a significant health concern for CF sufferers, just like *Pseudomonas aeruginosa*. The main colonization of *Burkholderia cenocepacia* causes progressive lung function loss, septicemia (also known as cepacia syndrome), deadly necrotizing pneumonia, abscesses and bacteremia (Saiman and Siegel, 2004). Even though BCC has a number of virulence factors, including siderophores, type 3 secretion, flagella, quorum sensing, superoxide dismutase, cable pili, and protease (Mahenthiralingam et al., 2005), the disease's molecular causes are still mostly unclear. To investigate zebrafish infection with *Burkholderia cenocepacia* has been used as a model to study *Burkholderia* pathogenesis *in vivo* (Vergunst et al., 2010). Zebrafish larvae have been shown to be very susceptible to the *B. cenocepacia* ET12 strain, despite other, less virulent members of the *B. cepacia* complex, such as (*B. vietnamiensis* and *B. stabilis*). In a zebrafish infection model, it has recently been demonstrated that macrophages are necessary for the replication of *B. cenocepacia* (Vergunst et al., 2010). This is supported by the finding that bacterial replication is limited when macrophages are reduced in larvae (Mesureur et al., 2017). IL-1beta is produced by macrophages during infection, which attracts uninfected cells to create cellular aggregates (Mesureur et al., 2017; Vergunst et al., 2010). It has been observed that *Burkholderia* administered into zebrafish interacts with neutrophils and macrophages, and that macrophages are essential for survivability and multiplication of *B. cenocepacia* (Mesureur et al., 2017; Vergunst et al., 2010). Neutrophils, in contrast, have no impact on bacterial replication or the course of a disease. A critical function of macrophages in *Burkholderia* infection was evidenced by the chemical suppression of macrophages, which greatly decreased bacterial growth and the host's vulnerability to infection (Mesureur et al., 2017). *Burkholderia* intramacrophage multiplication is necessary for the transition of a chronic condition into an acute one that is characterized by inflammation and zebrafish death. The fact that macrophages are a substantial contributor of IL-1 during *Burkholderia* infection gives credibility to this. Although decrease of IL-1 is probacterial and anakinra's regulation of IL-1 signaling is antibacterial, it is yet unknown how exactly inflammation affects *Burkholderia* susceptibility or resistance. To determine the specific involvement of inflammation in *Burkholderia* pathogenesis in the *in vivo* system, further zebrafish model application would be crucial.

5.1.9. Vibrio

Researchers now have a more complete grasp of the Vibrio infection process owing to the zebrafish model. Bacteria including *V. vulnificus*, *V. alginolyticus*, *V. cholera*, *V. parahaemolyticus*, and *V. anguillarum* have been the subject of important scientific discoveries.

5.1.9.1. Vibrio anguillarum and Vibrio alginolyticus. Hemorrhagic septicemia, often known as vibriosis, is a serious disease that affects a wide variety of fish species. *Vibrio anguillarum* is the primary cause of this disease. Through facilitating chemotactic motility, the flagellum contributes to the pathogenicity of water-borne *V. anguillarum*. However, after the pathogen is injected beyond the fish epithelial layer, the flagellum and chemotaxis are no longer necessary (O'Toole et al., 1996; Ormonde et al., 2000). According to research by Randazzo et al., zebrafish exhibit substantial histopatholoeical alterations in the gut and renal hematopoietic tissue within 48 h after receiving an intraperitoneal injection of *V. anguillarum* serotype O1. Within 7 days, the fish perished (Randazzo et al., 2015). Zebrafish were used by Zhang et al. to simulate vaccination effectiveness against *V. anguillarum*. On day 28, following immunization, wild-type pathogenic *V. anguillarum* (1×10^6 cfu/ml) were exposed to adult zebrafish by bath inoculation. When live attenuated *V. anguillarum* with 1×10^8 cfu/ml used in

the vaccination, it offered around 90 % of high relative protection (Zhang et al., 2012).

Waterborne bacteria like *Vibrio alginolyticus* can affect a wide variety of creatures, including humans and fish. Additionally, zebrafish have been employed as an infection model system for this bacterium. Another research used a zebrafish model to demonstrate the innate antibacterial action of the antimicrobial protein hepcidin (conserved in humans) against *V. alginolyticus* (Jiang et al., 2017).

5.1.9.2. Vibrio cholera. Circumventing laborious and expensive infection processes required for other animal models, *V. cholerae* inoculum can be pipetted direct into beakers containing four or five zebrafish to infect them, or zebrafish can be infected *via* immersion (Mitchell and Withey, 2018). Following the addition of the inoculum, the zebrafish devour the bacteria orally. Similar to how the human infection cycle works, infected fish can transfer the bacterium to other fish through the fecal-oral channel. The fish subsequently display the fluid, mucus-filled diarrhea that is typical of human sickness (Mitchell and Withey, 2018; Runft et al., 2014). This allows researchers to directly compare this infection's mechanism of transmission to human routes of transmission. This infection route bypasses the neutralization of stomach acid, sedation, and antibiotics, modifies the physiological environment through a pH shift, which can have an impact on the dynamics of the infection, effects on intestinal motility, or a deficiency in intact microbiota.

5.1.9.3. Vibrio parahaemolyticus. Naturally occurring as well as clinically obtained strains of *V. parahaemolyticus* may infect experimental zebrafish intraperitoneally (i.p.) in a dose-dependent form. The *tdh + trh* mutant clinical strain with lethal dose (LD50) of 5.7×10^5 cfu was intraperitoneally injected into zebrafish were fatal (Paranjpye et al., 2013). Regardless of whether the recognized hemolysins TDH and TRH were present or not, differences in zebrafish survival following infection were seen. This model may also be helpful in determining whether additional, unidentified virulence factors are present in *V. parahaemolyticus* strains and/or whether they contribute to the pathogenicity of those strains. Since abnormalities in erythrocytes were noticed in various strains of *V. parahaemolyticus* independent of the status of TDH and TRH, this model may be utilized to find the unknown variables that impact erythrocytes. The zebrafish paradigm is helpful for illustrating variations in the mortality of fish afflicted with an isogenic mutant or wild-type strain. Additionally, It also serves as a successful platform to show the pathogenicity between wild-type and isogenic mutants (Frischkorn et al., 2013).

5.1.9.4. Vibrio vulnificus. Zebrafish studies enable researchers to comprehend how infectious the bacteria are when the infected zebrafish are fed with or without protecting or stimulating substances, making them a useful tool for comprehending the *V. vulnificus* infection. An investigation by a scientist and his colleague demonstrated the antimicrobial peptide epinecidin-1 from grouper (*Epinephelus coioides*) had a protective impact on acute *V. vulnificus* infection in zebrafish. Epinecidin-1 and zebrafish infection therapy were chosen for intraperitoneal injection. In contrast to treatment with epinecidin-1, which had poor survival rate scores of 57 % and 60 %, respectively, zebrafish co-treated with epinecidin-1 and *V. vulnificus* showed survival rates score of 78 % to 97 %. Furthermore, survival rates of zebrafish after co-injection of epinecidin-1 and *V. vulnificus* ranged from 22 % to 47 %. The researchers demonstrated that epinecidin-1 altered the production of immune-responsive genes such as interferon γ, IL-10, TNF-α, and IL-1β, which abetted defense (Pan et al., 2011). In another research, *V. vulnificus* was administered intraperitoneally to two mutant zebrafish strains generated employing the Tol2 system. Fadsd6 and Elvol5a are two highly expressed Atlantic salmon enzymes present in this this strain which catalyzes the formation of docosahexaenoic acid and eicosapentaenoic acid, respectively. When compared to wild-type (WT) fish, these strains produced 2.5 times as many n-3 polyunsaturated fatty acids (PUFAs). The transgenic fish had a survival rate of 70 % compared to 20 % in WT fish 24 h after being challenged with *V. vulnificus*. Around

9 and 12 h after exposure, the production of proinflammatory genes including NF-κB, IL-1β, and TNF-α was decreased, which improved the transgenic fish's survival (Cheng et al., 2015).

5.1.10. Yersinia

Freshwater bacteria called *Y. ruckeri* affect salmonids (Kumar et al., 2015). Fish are frequently immunized against it, although there is opportunity for improvement in terms of management practices or vaccinations. Zebrafish have been used in a few investigations using *Y. ruckeri*. A GFP-tagged strain of *Y. ruckeri* was used to create an inactivated vaccine, and transparent zebrafish of various life stages were used to observe antigen absorption after bath immunization (Korbut et al., 2016). Researchers have also looked into the biology of *Y. ruckeri* infection, and they discovered that the toxic effector antifeeding prophage 18 of the translocation machinery of prophage tail-like proteins interferes with the behavior of blastomere cells in zebrafish embryos (Jank et al., 2015).

5.1.11. Listeria

Food-borne bacterium called *L. monocytogenes* may infect people and leave them with a variety of symptoms, from fever to septicemia, which can be fatal. To spread to internal organs like the liver and spleen, *L. monocytogenes* can breach the human gut epithelium. The *L. monocytogenes* model was initially utilized in investigations on the adaptive immune system's reaction to facultative intracellular infections (Pamer, 2004). Significant bacterial virulence factors including actA and listeriolysin (Gaillard et al., 1987; Kocks et al., 1992) have been discovered as a result of significant research into the virulence mechanisms of *L. monocytogenes*. Which is involved in actin-based intracellular mobility and cell-to-cell adherence of bacteria, as well as their involvement in vacuolar escape. According to a study provided by the researcher, *L. welshimeri* isolates had the highest percentage of zebrafish larval survivorship (83.0 %), preceded by *L. innocua* isolates, and *L. monocytogenes* had the least percentage (46.5 %). Selected virulence genes, the majority of which were present in *L. monocytogenes*, were detected using multiplex PCRs (*iap*, *sigB*, *plcB*, *actA*, *prfA*, *hlyA*, *luxS*, *actA2*, *inlB*, and *rrn*) (Zakrzewski et al., 2020). Additionally, 2 proteins 1) internalin (InlA) 2) InlB expressed in *L. monocytogenes* facilitating adhesion and invasion of non-phagocytic cells. The functions of both proteins are: Internalin (InlA) stimulates entrance into human epithelial cells in culture after its interaction with E-cadherin (Mengaud et al., 1996), whereas InlB promotes entry into many other cell types when Met is engaged (Shen et al., 2000). According to a study by Ying Shan et al., zebrafish are vulnerable and may be employed in a variety of ways to create microscopic infection models for *L. monocytogenes*, making them useful for future study on the interaction between bacterial pathogenicity and host immune mechanisms (Shan et al., 2015). The author demonstrated *Listeria monocytogenes* infection models in zebrafish using injection *via* the blood island, brain ventricle, and yolk sac and oral ingestion. Even when exposed to egg water containing 10^{10} cfu/ml of *L. monocytogenes* EGDe strain, zebrafish larvae were not killed, but frozen sections of the animals showed GFP-expressing bacteria in the gut lumen. Several genes that are involved in the development of the innate immune system, such as irg1l, mmp9, cyp1a, and il1b, were drastically expressed when the strains M7, innocua, and EGDe were administered orally to zebrafish (Shan et al., 2015). The major virulence factors of Listeria are Lysteriolisin O (LLO) and Act A, which aid in the creation of pores, vacuolar escape, and actin tail polymerization to weaken cellular protection. Zebrafish injections have demonstrated that blood-borne Listeria is quickly absorbed by neutrophils and macrophages (Levraud et al., 2009). ActA-dependent actin tail generation and LLO-dependent vacuole escape could both be exhibited in zebrafish, where both LLO and ActA mutations are repressed.

6. Paucity of knowledge towards viral defilement

The zebrafish has acted as a scientific model on the genetics and development of vertebrates' research. Adult zebrafish have typically only been

retained as breeding stock to create embryos for scientific study as most studies are carried out within the first few days of fertilization. To abet the investigation of cancer, immunology, infection, and hematopoiesis, scientists have recently created immunocompromised zebrafish. Compared to wild-type fish, immune-compromised zebrafish are presumably more prone to infectious viruses. Increased susceptibility is demonstrated by an increase in the mortality rate, morbidity frequency, number of clinical manifestations, and severity of histopathologic lesions. Therefore, the variability in results caused by confounding factors like inflammation and other host reactions to infection will be considerably reduced by utilizing virus-free fish. Additionally, it will also lessen the number of fish required in experimental models that use zebrafish that have compromised immune system in order to attain enough statistical power. The truth that chronic suffering and fatality in a zebrafish colony have often not hindered investigators from assembling an appropriate number of zebrafish embryos to conduct their experiments could be partially blamed for the scarcity of understanding regarding viral infections in zebrafish. As an outcome, a wide range of scientists now back the concept of tolerating a certain degree of mortality rates. Given its huge benefits as a model organism, zebrafish use has dramatically upped in biomedical research sectors, where factors caused on by unknown pathogenic organisms are a major worry, even though previously the zebrafish scientific community has not demonstrated the very same degree of importance for eradicating infectious illnesses as is now in the rats and mice scientific community. It is usually expected to maintain zebrafish alive for a significantly larger percentage of their lifespan in order to study the histopathologic changes that take place in adult animals while performing research in disciplines like cancer, infection, ageing, toxicity, and immunity. The presence of ectopic cytokines, tissue damage, a high death rate, and persistent inflammation are all indications of a natural infection. In research like this, each of these factors is likely to be a significant confounding factor (Baker, 1998; CM et al., 2002; Kent et al., 2012; Wade and Daly, 2005).

Since virions are dispersed throughout the water column, the fact that many aquatic viruses are not host-specific may indicate that they have evolved access to a greater variety of possible hosts. For instance, some freshwater and marine fish species are affected by the aquatic virus known as viral hemorrhagic septicemia virus (VHSV1). Other aquatic viruses have the capacity to spontaneously infect aquatic invertebrates, fish, and amphibians. Given how several aquatic viruses potentially infect multiple fish species, zebrafish could be prone to viral infections which have already been recognized in other marine species. In both aspects of size and variety, a large number of virus infections have been observed in innumerable teleost fishes. In order to uncover naturally occurring viruses in zebrafish, current studies should incorporate both novel viruses and viruses that have already been recognized from other teleost fishes.

Studies on viral infection that were carried out with the goal of using zebrafish as an infection model, showed that various viral family have the potential to infect zebrafish. These viral families include the *Iridoviridae*, *Birnaviridae*, *Rhabdoviridae*, SVCV: spring viremia of carp virus, SHRV, and VHSV. In addition to implying that zebrafish are frequently infected with viruses spontaneously, the likelihood of the fragility of zebrafish to experimental infections with such a diverse array of viruses increases the chance that other viral family members are present among unreported zebrafish viruses (Crim and Riley, 2012; La Patra et al., 2000; López-Muñoz et al., 2010; Lu et al., 2008; Ludwig et al., 2011; Novoa et al., 2006; Phelan et al., 2005b; Seeley et al., 1977; Xu et al., 2008).

7. Ins and outs of viral invasion and abatement

7.1. Invasion mechanism involving mammalian cells

All three of the major subcategories of living things bacteria, archaea, and eukaryotic organisms have gained the capacity for viral infection. More than 3600 viruses have been identified, hundreds of which infect human cells, causing associated illnesses. Animal viruses bind to host cell receptors and enter host cell nuclei. Recent understanding on viral entry

proteins interaction with host cell receptors and the conformational changes it undergoes has opened opportunities for the development of novel therapies and vaccines (Dimitrov, 2004). Viruses, due to their high transmission rate, have been an intriguing system for delivering genes, vaccines, drugs, and peptides to cells and between cells. Furthermore, virus-based vectors and subviral systems are already being used in biotechnology and medicine. Understanding the cellular and molecular processes underlying viral entry has advanced the identification of virus receptors. Furthermore, understanding how these components assist entry, fusion of enveloped viruses with cells or breaching of cell membrane by non-enveloped viruses and what transpires after penetration is still necessary because receptor binding is only the first step (Klasse et al., 1998).

Enveloped viruses have genomes and proteins enclosed in one or more membranes. The virus receives the necessary membranes from the host cell during the assembly and budding processes. Numerous enveloped viruses, such as human immunodeficiency virus (HIV), Semliki Forest virus (*alphaviruses*), vesicular stomatitis virus (*rhabdoviruses*), influenza (*orthomyxoviruses*), and Sendai (*paramyxoviruses*), have a single membrane. Other viruses, such as the herpes virus, may undergo several steps of budding and fusing with several internal membrane compartments before eventually acquiring a single membrane *via* the exocytic route. As a member of the *Poxvirus* family, the vaccinia virus can gain numerous membranes through interactions with different membrane compartments within an infected cell. Virally encoded membrane or envelope proteins, and the lipid and protein contents of the host cell, dictate the make-up of the viral membrane(s), which differs across viruses. The Golgi apparatus, intermediate compartment, endoplasmic reticulum, and plasma membrane are just a few of the cellular locations where viruses congregate and bud during the budding mechanism, endoplasmic reticulum being the most frequent sites of viral assembly and bud development. (Bron et al., 1994; Klasse et al., 1998; Stegmann et al., 1987; Vainstein et al., 1984; Wagner et al., 1992). However, rotaviruses may briefly acquire a membrane by budding into the endoplasmic reticulum, only to lose the membrane during future maturation (Wagner et al., 1992). Once the viral genome is packed in a protein shell in the nucleoplasm of infected cells, it is then expelled from the cell either by cell lysis (Fig. 8A) or, in the case of *rotavirus*, through secretion.

Similar to enveloped viruses, non-enveloped viruses need to have the necessary molecular machinery in their outer protein shells to infiltrate cells. However, non-enveloped viruses rely on strategies other than fusion to reproduce, in contrast to enveloped viruses. In general, proteins and protein complexes cannot migrate across membranes independently; rather, sophisticated molecular mechanisms are required to enable their mobility. There is no one concept that is analogous to fusion, and the exact mechanism by which non-enveloped viral protein shells interact with cell membranes is unknown. To dock into depressions that resemble "canyons" on the surface of the virion, picornaviruses must first make connections with cell-surface components (Rossmann, 1996). Virions appear to generate holes in the endosome membrane after endocytosis. Without fully disintegrating the capsid or rupturing the endosomal membrane, these holes enable viral RNA to exit the virion and reach the cytoplasm (Prchla et al., 1995). It is plausible that receptor engagement initiates a series of processes that alter the structure of the capsid and form pores. On the other hand, adenoviruses employ fibers that protrude from the surface of the virion to bind to cellular receptors. After adhering to the cell surface, adenoviruses connect to integrins that bind vitronectin before entering the cell *via* coated vesicles, completing the endocytosis cascade. Low pH levels inside endosomes activate viral lysin, allowing the membrane of the endosome to be breached. This permits entry of the viral capsid and other endosomal components into the cytoplasm, where they are subsequently disassembles (Greber et al., 1994, 1993; Klasse et al., 1998).

Orthoreoviruses are responsible for the initiation of minor gastrointestinal diseases in a variety of mammalian species, including humans, in accordance with the original definition of reoviruses as "respiratory enteric orphan viruses". The strain designations type 1 Lang (T1L), type 2 Jones (T2J), and type 3 Dearing (T3D) are the three primary serotypes of *orthoreovirus* (Chappell et al., 2002). The sequence of the spike protein,
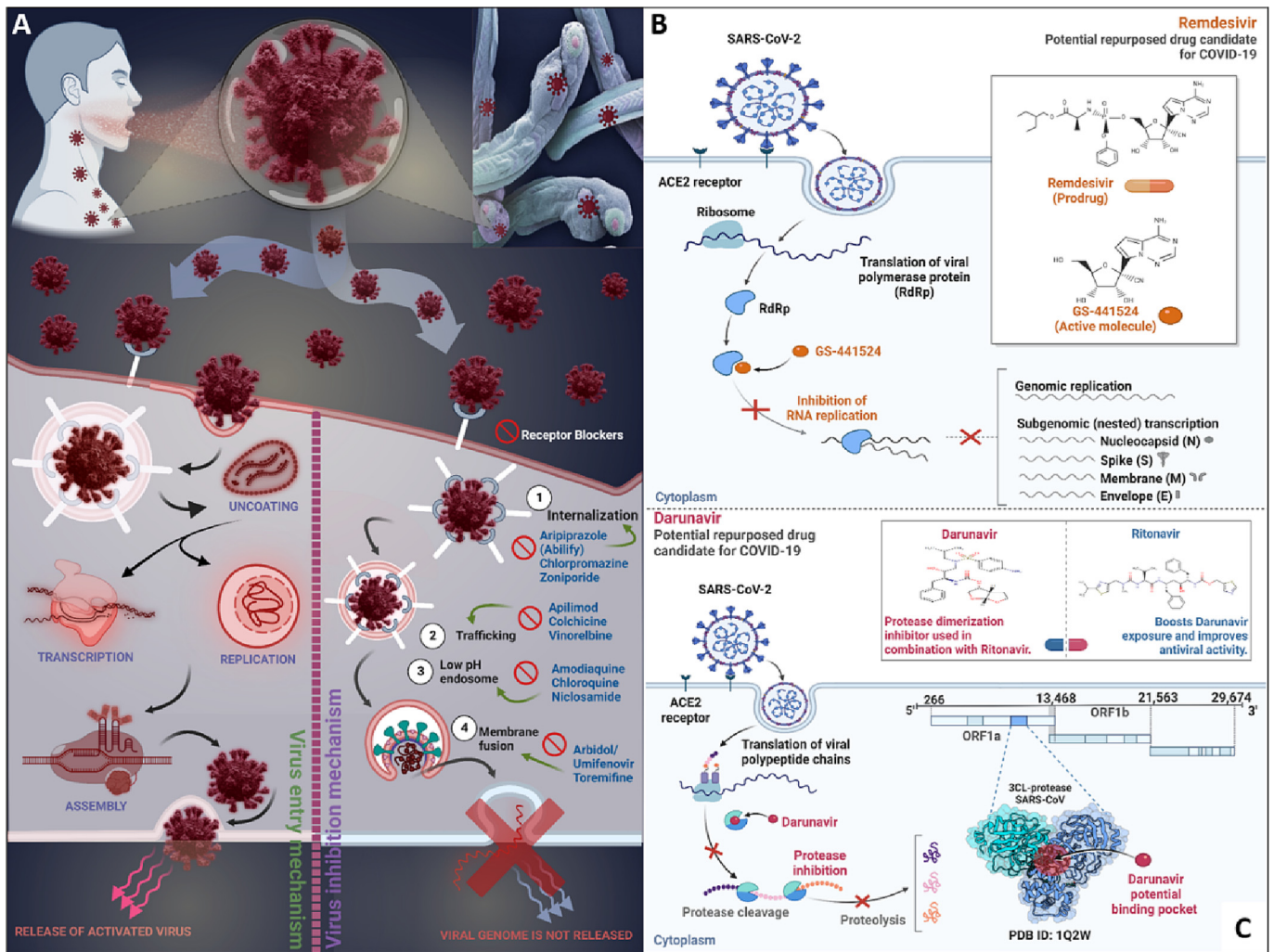
Fig. 8. (A) Viral entry and inhibition mechanism in humans and zebrafish model. (B) Mechanism of virus inhibition by Remdesivir drug. (C) Working mechanism of Darunavir: A potential drug for the inhibition of COVID-19.

which dictates the viral tropism and illness pattern, serves as the major marker for the differentiation between the three strains (Duncan et al., 1990). Mechanistic studies on *orthoreovirus* entrance, proliferation, and escape from cells have been greatly aided by the availability of primary and immortalized cell lines that permit infection *in vitro* (Roth et al., 2021). Clathrin-mediated endocytosis is thought to be the most significant uptake mechanism in both polarized and non-polarized cells, despite the observation of other entry channels, such as caveolar endocytosis (Schulz et al., 2012) and micropinocytosis (Aravamudhan et al., 2020; Boulant et al., 2013; Maginnis et al., 2008). Viral infection is identified through a series of successive interactions with the host cell. Binding to the cell surface, intracellular trafficking, membrane penetration, activation of cell signaling, and apoptosis are processes involved in these interactions. When the virions latch to the primary attachment factors, they concentrate on the cell surface, and the process begins. Prior to viral entry into the cell, secondary receptors are activated (Grove and Marsh, 2011). A core particle is delivered to the cytoplasm at the end of this procedure in the case of reoviruses. A whole double-stranded RNA genome is carried by this core particle, which is transcriptionally capable (Roth et al., 2021; Swevers et al., 2021). SARS-CoV-2 cell infection is mediated by the virus' surface spike protein. Prior to activation by human proteases through proteolysis, the SARS-CoV-2 spike protein establishes a connection with its receptor hACE2 *via* its receptor-binding domain (RBD).

7.2. Assessing virus abatement in mammalian cells

Progress in the search for viral replication inhibitors requires an understanding of the molecular mechanisms that operate during viral infections. Any of the required stages that occur throughout a virus's life cycle may be the target of an antiviral drug. Herpes virus replication is typically inhibited by medications that cause the replication chain to break. Similarly, anti-HIV medications work largely by inhibiting the HIV reverse transcriptase. Ribavirin, an antiviral drug, inhibits viral nucleic acid replication. Protease, which oversees the breakdown of polyproteins has been a point of interest in diminishing viruses such as hepatitis C virus, rhinovirus and HIV. The complicated interaction of viral entry makes it a viable target for development of virus inhibitors. Certain stages of the viral life cycle are still unclear, resulting in partial usage of antiviral strategies. For instance, RNA capping processes and membrane attachment of replication complexes (Fig. 8A), which all positive-strand RNA viruses have in common (Magden et al., 2005). The interactions between viruses and their receptors control important regulatory processes, such as the viral host range, tissue tropism, and the establishment of viral illness. Engaging with the "lock" the receptor on the cell surface, and the viral attachment protein as the "key" to unlock host cells; these "lock-and-key" relationships are necessary to effectively infiltrate host cells and gain control of the cell's vital machinery. To mediate these functions, viruses frequently target certain classes of molecules, such as sialylated glycans, immunoglobulin superfamily members, integrins, and

phosphatidylserine receptors, in formations of numerous comparable motifs in the usage of virus-receptor interactions throughout viral groups. The redundancy in receptor utilization suggests that viruses target certain receptors or "common locks" to take advantage of their biological function, which is consistent with evolutionary conservation. The importance of virus interactions with host cells in viral pathogenesis, as well as the redundant usage of viral receptors, makes the utilization of these strategies an enticing target for the development of innovative antiviral medicines (Maginnis, 2018).

The microRNA (miRNA) family is a significant post-transcriptional regulator of gene expression in mammalian cells. miRNAs have been shown to play crucial roles in viral replication and may be used by host cells to control viral infections, such as control of both lytic and latent viral replication, limitation of antiviral responses, suppression of apoptosis, and encouragement of cellular growth. A wide variety of viruses, including retroviruses, DNA viruses, and herpes viruses, express miRNAs (Grassmann and Jeang, 2008). Our immune system needs to be guided by proteins, similar to those found in mammals, which have been widely studied, to survive in virus-filled environments. Small RNA-driven antiviral immune systems can inhibit the invasion on cells by genetic material that is not native to these cells through complementary base pairing with target sequences. These RNA silencing-dependent systems are active in numerous animals. There is strong evidence that endogenous genes essential for mammalian antiviral immunity are regulated by miRNAs. Recent advances in the delivery of RNA for antiviral uses, suggests the potential for producing small non-coding RNA-directed antiviral treatments and prophylactics (Takahashi et al., 2021). The human virus adeno-associated virus (often abbreviated as AAV) has two modes of replication: an integrated provirus or a lytic infection (Atchison et al., 1965; Hoggan et al., 1966). This implies that a crucial part of AAV's life cycle is its capacity to cause latent infections. AAV frequently requires a helper virus, with a few noteworthy exceptions, to create a productive viral infection (Schlehofer et al., 1986; Yalklnoglu et al., 1988). The necessary assistance tasks can be provided by either herpes or adenovirus family members (Atchison et al., 1965; Buller et al., 1981; Hoggan et al., 1966; Melnick et al., 1965). AAV integrates into the host chromosome rather than producing progeny viruses when there is no companion virus present. AAV proviruses are stable with few variations. However, when a cell line carrying an AAV provirus is superinfected with a helper virus, the AAV genome is eradicated, and the process proceeds as if it were a typical productive infection; this process is called a "helper virus superinfection" and is a defense mechanism that enables AAV to continue living without a helper virus. This procedure enables AAV to establish a latent infection that may subsequently become active (Muzyczka, 1992).

The antiviral immunological mechanism, known as RNA interference (RNAi), has been conserved in eukaryotes. Several viruses have been shown to encode viral suppressors of RNAi (VSRs) to block the effects of antiviral RNAi. Semliki Forest virus is known to prevent RNAi in cells by entangling double-stranded RNA and short interfering RNA with the help of capsid proteins. Reverse genetics was used to inactivate VSR activity of the SFV capsid, and the resulting VSR-deficient SFV mutant showed significant replication irregularities in mammalian cells. However, blocking RNAi could reverse these abnormalities (Qian et al., 2020). The B2 protein found in short RNA viruses, such as the Nodamura virus (NoV), has been shown to function as an inhibitor of RNAi, which is triggered by either short hairpin RNAs or small interfering RNAs. NoV B2 binds to RNAs that have undergone RISC-RNA-induced silencing complex processing, as well as pre-Dicer substrate RNA. As a result, Dicer cleavage is inhibited. NoV B2 primarily binds to double-stranded RNAs that structurally match the Dicer substrates and products. Therefore, it is able to inhibit Dicer-mediated RNA cleavage in vitro, even in the absence of any other host factors (Sullivan and Ganem, 2005).

7.3. Invasion mechanism involving zebrafish

In recent years, the zebrafish has emerged as a crucial model system for the investigation of infectious disorders, notably viral infections. The outcomes of experiments utilizing adult zebrafish or embryo models as hosts for HSV-1 are intriguing because they support the theory of viral-host tropism and might test potential antiviral medications. Additionally, the presence of viral entry receptors in zebrafish, such as 3-O-sulfated heparan sulfate (HS), nectins, and the TNF receptor superfamily member 14-like receptor (with homology to its human counterpart), enables virologists to compare the structure-function basis of the virus and zebrafish receptor interaction in vivo, assessing their importance in the viral entry in a zebrafish model. The primary benefits of employing zebrafish in viral infection examination, are their completely developed immune system, opacity of the body during the early stages of life, wide accessibility to a variety of transgenic lines, and their potential for receptor-specific knockouts (Fig. 8A) (Antoine et al., 2014).

Zebrafish models have been developed for several human viruses. Both adult and embryonic zebrafish, have been used as platform for the HSV-1 infection and to discover putative receptors enabling viral entry (Antoine et al., 2014). It is important to highlight that although live imaging was not feasible, the virus's capacity to spread to the brain was observed. Recently, CHIKV a human virus causing neurological defects in newborns and acute illness in adults, have been able to propagate CHIKV in larvae of zebrafish (Palha et al., 2013). The virus was microinjected to simulate the infection caused by a typical mosquito bite. Infection in zebrafish is controlled by the host interferon (IFN) response, which is mediated by neutrophils, after a robust initial replication phase in many distinct cell types. Most of the CHIKV-infected cells disappeared, with the remarkable exception of the brain cells. Research on the tropism and transmission of viruses has also employed fish viruses, which are frequently collected from aquaculture species. For instance, when infected with infectious hematopoietic necrosis virus and rhabdovirus, zebrafish larvae died after a short period of time (3–4 days) (Ludwig et al., 2011). The main target of the infection was the endothelium of the veins, which contributed to the noticeable hemorrhagic condition. Viral damage became irreversible at a temperature of 28.8 °C, which prevented viral multiplication. The infected fish were then subjected to this temperature. Snakehead rhabdovirus (SHRV), a different fish rhabdovirus, has well-characterized pathophysiology but not tropism (Phelan et al., 2005b). Zebrafish have been observed to contract the SVCV by the immersion technique, which can cause acute illness in goldfish or carp. The SVCV statistical approach was used to examine the unique characteristics of several type I IFNs (López-Muñoz et al., 2010, 2009). Furthermore, by employing loss-of-function tests with morpholino antagonists targeting putative cytokine receptors in the context of infections produced by SVCV or IHNV, zebrafish IFN receptors could be discovered. The variety of IFN-stimulated genes (ISGs) in zebrafish has been investigated using fish viruses, as well as the more potent IFN inducer, CHIKV. The antiviral effects of zebrafish IFNs have been established in vivo, whereas those of zebrafish ISGs—including ISG15, IRF7, and the fish-specific dreI/Gig2—have only been confirmed in vitro thus far (Langevin et al., 2013; S. Li et al., 2012; Xiang et al., 2010). ISGs respond less favorably to morpholino antagonist-mediated in vivo suppression than non-inducible, genes, such as those encoding IFN receptors or mitochondrial antiviral signaling protein. The viability of antiviral drug screening has been demonstrated in a system where a vector harboring hepatitis C virus (HCV) sub-replicon was injected into zebrafish zygotes, resulting in the production of HCV core RNA and protein and triggering transcriptome alterations comparable to those in human hepatocytes. Oxymatrine and ribavirin, two well-known anti-HCV drugs, drastically reduced the production of HCV core RNA and protein during drug testing in fluorescent zebrafish larvae (Ding et al., 2011). Zebrafish have endogenous retroviruses in addition to exogenous retroviruses, which is helpful in research on how these elements affect genome changes in tumors and the relevance of their function in the regulation of antiviral immunity (Frazer et al., 2012; Levraud et al., 2014; Shen and Steiner, 2004). The mechanism of zebrafish c-reactive proteins (CRP1–7) and their antiviral effectiveness against SVCV were recently studied by Perez et al. These results did not directly demonstrate either activation of the host's interferon system, reduction of G-protein fusion activity or binding steps of attachment or blockage of the viral replication cycle. Further

investigation revealed that the antiviral defense provided by CRP1–7 was mostly due to the protein's capacity to obstruct autophagy-related mechanisms. To further describe the action of CRP, methyl-cyclodextrin, a cholesterol-complexing agent, and 25-hydroxycholesterol, a cholesterol molecule with antiviral characteristics, were used. This was accomplished owing to the strong affinity of CRPs for cholesterol and the recently discovered impact of the lipid raft cholesterol balance on autophagy. The results of additional research indicate that CRP prevents autophagy by disrupting cholesterol ratios in the host cell membranes. Moreover, reactive oxygen species (ROS) are negatively regulated inside the cell, which increases the pH of lysosomes. It was hypothesized that these pH variations prevent SVCV replication directly by interfering with the capacity of viral glycoprotein G to fuse membranes in response to changes in pH. This trait enables the virus to escape from endosomes and enter the cytoplasm during the entrance phase of its life cycle (Bello-Perez et al., 2020).

7.4. Assessing virus abatement using the zebrafish model

RIG-I-like receptors, commonly referred to as RLRs, control the innate immune system signaling pathway, hence play a vital role in the host's response to viral infections. To achieve an immunological balance between antiviral responses and virus survival, both the host and virus tightly regulate the RLR signaling pathway. Zebrafish TRIM25 (zbTRIM25) as a positive regulator of the RLR signaling pathway when infected with the red spotted grouper neurological necrosis virus (RGNNV). zbTRIM25 expression diminished after infection with RGNNV, and its ectopic expression increased the expression of genes associated with the RLR signaling pathway. zbTRIM25 increased zebrafish RIG-I (zbRIG-I)-mediated IFN signaling, which inhibited RGNNV replication, according to overexpression and knockdown analyses. zbTRIM25 bound to zbRIG-I, and the SPRY domain of zbTRIM25 interacted with the tandem caspase activation and recruitment domains (2CARD) and repressor domain (RD) sections of zbRIG-I. zbTRIM25 assisted K63 polyubiquitination of zbRIG-I, 2CARD and RD regions. Additionally, zbTRIM25-mediated zbRIG-I polyubiquitination was significant for RIG-I-triggered IFN production, as shown by the enhancement of zbRIG-I-mediated IFN synthesis activation by K63-linked ubiquitin. These findings indicate an unidentified mechanism through which zbTRIM25 favorably affects the innate immune response and the process involved in targeting and enhancing K63-linked polyubiquitination of zbRIG-I (Lu et al., 2021).

Various forms of IFNs, including virus-induced IFNs, as well as IL-10 and its related cytokines (IL-20, IL-22, and IL-26), are all included in fish type II helical cytokines. These cytokines may bind to various receptors. Three genes have been found in zebrafish that, when triggered by a virus, generate IFNs. A fourth IFN gene was discovered on chromosome 12, in addition to genes that are clustered together on chromosome 3. Each of these genes possesses the exons and introns found in mammalian IFN genes, where IFN-1 and IFN-2 offer protection. All of these compounds increased the expression of reporter antiviral genes in zebrafish larvae. Not all zebrafish IFNs bind the same receptors. Two subgroups of fish virus induced IFNs have been identified based on the conservation of cysteines, a common short-chain receptor (CRFB5) and a long-chain receptor specific to each receptor complex are present in both receptor complexes (CRFB1 or CRFB2) (Hamming et al., 2011). Based on the receptors they engage, IFNs in mammals can be divided into three types: type I (consisting of one exon), type II and type III IFN genes consisting of four and five exons, respectively. Furthermore, IFNs of types I and III collectively known as "virus-induced IFNs" (Haller et al., 2007). They differ from INF type II because they can be triggered by viral infection (Zhang et al., 2008).

Type I and type III IFNs both stimulate the same transcription factor, IFN-stimulated gene factor 3, as well as activates same sets of genes (Doyle et al., 2006; Marcello et al., 2006). Interestingly, the majority of organisms have a wide variety of IFNs that are generated in response to viral infections (13 beta, 1 beta, and 3 beta in humans). Mammalian type I IFN systems must be active for them to be able to withstand viral infections. The more recently discovered type III IFNs are crucial for preventing

influenza infection through the nasal passageway (Mordstein et al., 2008), and some viral proteins also target this subtype, even though their exact role is not fully understood. Even though IFN-like behaviors have been observed in fish for many years, it was not until recently that fish IFNs could be identified due to developments in genome sequencing. IFNs cloned from fish were shown to have antiviral effects in 2003 (Lutfalla et al., 2003; Robertsen et al., 2003). Most teleost species include several genes that create IFNs through viral infection (Sun et al., 2009). Stein et al. argued, as fish virus-induced IFNs display traits common to both type I and type III mammalian IFNs, they should be assigned the IFN designation. IFNs serve critical functions at the nexus of innate and acquired immunity, making it challenging to distinguish their particular contributions to either kind of immunity (Stein et al., 2007). Zebrafish embryos or larvae are an appealing model for the study of innate immunity in vertebrates, as acquired immunity does not fully develop until 4–6 weeks of development (Fig. 8A). As young zebrafish allow simple genetic alterations, gain- and loss-of-function studies can be used to evaluate how certain cytokines contribute to particular innate immune pathways. Diversity of IFNs caused by fish viruses, is greater than previously believed, as demonstrated by Zou et al., where researchers were able to cloned three IFNs in rainbow trout in addition to discovering two more zebrafish genes *in silico*, IFN2 and IFN3 (Zou et al., 2007). They emphasized the division of these genes into two distinct subgroups (groups I and II), each of which could be distinguished by the presence of two or four conserved cysteines, respectively, in the protein sequence. IFN-1 belongs to group I of zebrafish, whereas IFN-2 and IFN-3 belong to group II. All three zebrafish IFNs have antiviral action in adult fish (López-Muñoz et al., 2010). Study by researchers examined four IFN cDNAs, that were cloned to look for potential new IFNs gene in the current zebrafish genome. Then, IFNs were administered or overexpressed using a variety of techniques in growing zebrafish embryos to examine *in vivo* biological functions, such as viral infection resistance. Depending on the subgroup to which they belong, zebrafish IFNs have been shown to bind to one of two different receptor complexes (Aggad et al., 2009). The antiviral defenses in mammals include ISG15, a protein that is activated by IFNs, is highly conserved among vertebrates. Viral infection and IFN treatment induce ISG15 expression in fish, similar to that in mammals. Fish also have ISG15's two ubiquitin-like domains and a consensus LRLRGG sequence, which is necessary for covalent conjugation to a substrate protein in the C-terminal region. When EPC cells (epithelioma papulosum cyprini cells) overexpressed with zebrafish ISG15 (zf-ISG15) were exposed to RNA and DNA viruses genus (Novirhabdovirus, Birnavirus and Iridovirus), a declining/inhibition in viral infection was observed. ISGylation of both phosphoproteins and non-virion proteins has been proven by co-expression experiments with IHNV proteins. Mutation of glycine residues in the consensus LRLRGG motif establishes a link between ISGylation and ISG15-dependent viral restriction. This affects both cellular defense against viral infection and the removal of zf-ISG15 conjugation to these proteins. The expression of RIG-I, viperin, and, to a lesser extent, IFN genes, also increases in response to an increase in zf-ISG15 expression levels. These findings demonstrate the antiviral properties of ISG15, and vertebrates, have a similar ISGylation mechanism that was presumably created to combat viral infections. Research further revealed that zf-ISG15 affects the IFN system at several levels and complex processes that regulate the innate antiviral response in vertebrate cells (Langevin et al., 2013).

8. Comprehending the SARS-CoV-2 mechanism of hijacking and its arrest utilizing zebrafish

SARS-CoV-2 virus is anticipated to last for years; even though vaccination is now underway (WHO, 2022), as its variants possess an unpredictability concern. To understand its diverse pathophysiology and provide novel medications and vaccines, research efforts must continue. It is a highly pathogenic bio-contaminant (virus) belonging to *Coronaviridae* family, causing respiratory tract infection (Singh and Yi, 2021). Respiratory tract infections are also caused by severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus

(MERS-CoV) (B. Hu et al., 2021). The surface of the SARS-CoV-2 virus consists of spike (S) protein, which gives it the appearance of a "crown" (Wu et al., 2022). This protein is essential for the infection process because it causes the cell membrane to fuse (Yang and Rao, 2021). Spike protein, a trimeric protein belonging to class I fusion protein, consists of S1 and S2 components which assist during entry of the virus into the cell. The S1 component facilitates the adherence of the host cell's angiotensin-converting enzyme 2 (ACE2) receptor with the virus, while the S2 component facilitates the fusion of the viral and cellular membranes (Tai et al., 2020). Additionally, the spike protein has been regarded as a potential antigen for the development of COVID-19 vaccines (Fig. 8B and C) (Albanese et al., 2022; Tai et al., 2020).

Expediting the development of medication and vaccine testing requires the establishment of laboratory animal models that accurately depict the molecular mechanisms. Rhesus macaques, cynomolgus macaques, ferrets, cats, and Syrian hamsters are few lab-compatible animal species that are biologically vulnerable to SARS-CoV-2 (Bertzbach et al., 2021; Blair et al., 2021; Browne et al., 2020; Driouich et al., 2021; Qiao et al., 2021; Wang et al., 2020; Yuan et al., 2020). However, mice that express the human ACE2 receptor serve as an effective animal model because they are not naturally receptive to the virus (Muhl et al., 2022; Piplani et al., 2021). To assess the immune responses to interactions between SARS-CoV-2 and other hosts and pathogens, each of these mammalian models has certain benefits and drawbacks, but none of them offer prompt, whole-organismal, maximum throughput. Furthermore, are expensive for preliminary testing of drugs and immunotherapies.

Zebrafish due to its experimental friendly attributes, for instances compatible for human disease model studies, comparable adaptive and innate immune systems with human, makes them perfect candidate to study the signaling cascades, interaction with chemical mediators, and host-virus interaction on mucosal surfaces. Furthermore, the ACE2 protein, which the virus employs as a receptor and authorizes to enter human cells, was shown to exist in developing zebrafish (Kim et al., 2021; Laghi et al., 2022; Postlethwait et al., 2021). Intraperitoneal (IP) injection of the rSpike protein has negative effects on the liver, kidney, ovary, and brain tissue, as well as the survival rate (Ventura Fernandes et al., 2022). Researchers have shown that intramuscular injection of SARS-CoV-2 spike protein into zebrafish might cause behavioral abnormalities, skin hemorrhages, kidney necrosis, and inflammation in the swim bladder. Additionally, they investigated *Withania somnifera* extract on reduction of clinically significant pathogenic characteristics (Balkrishna et al., 2021b). In a different study, the SARS-CoV-2 spike protein was injected into human alveolar epithelial cells (A549) to create humanized zebrafish. The spike protein has been shown to cause cytokine release, morphological and cellular abnormalities, apoptosis of macrophages and granulocytes in the swim bladder, and behavioral fever in fish. Furthermore, they evaluate a tri-herbal drug "Coronil" effects on infected zebrafish, where they observed reduction of pathogenic characteristic brought on by SARS-CoV-2 spike protein (Balkrishna et al., 2020). Additionally, studies have revealed that Coronil efficiently prevents the interaction of ACE2 with the S-protein, including its variation (SD614G), which is more widespread and contagious, as well as another mutant (SW436R), which has a substantially greater affinity for ACE2. Treatment with Coronil substantially and dose-dependently decreased the elevated levels of TNF-α, IL-6, and IL-β in A549 cells exposed to various S-protein variations. Another study used human lung epithelial cells transplanted into a swim bladder that had received spike-protein injections to induce pro-inflammatory as well as macrophage and granulocyte invasion into the swim bladder. This resulted in heightened systemic impairment, as determined by kidney tissue damage and behavioral fever. When *Tinospora cordifolia* was used to treat these pathological characteristics, it was less pronounced (Balkrishna et al., 2021a). Another study suggested that spike RBD binds to the non-sensory epithelium of the olfactory organ when administered intranasally and causes considerable histopathology, as indicated by cilia loss, edema, and hemorrhages. Electrophysiological recordings showed deterioration of smelling ability towards bile and food odorants when spike RBD was

administered intranasally in animals. Furthermore, single-cell RNA-seq revealed significant olfactory receptor loss, myeloid cell cluster, and inflammatory effects in sustentacular adult zebrafish, as well as decreased numbers of T_{regs} (Kraus et al., 2022). Reduction in S-protein binding to ACE2, 3CL protease activity, and SARS-CoV-2 pseudovirus entrance into the cell has been observed, when exposed to an extract of Polygoni Multiflori Radix (PMR). With IC50 values ranging from 25 to 500 g/ml (Wang et al., 2022). Zheng et al. studied the connection between the SARS-COV-2 spike protein and blood coagulation and found that the S protein can competitively prevent antithrombin and heparin cofactor II from binding to heparin/HS, leading to an unexpected rise in thrombin activity. Zebrafish embryos can directly experience blood coagulation and thrombosis when exposed to SARS-CoV-2 S protein at a concentration (10 g/ml) comparable to the viral load in severely ill patients. In contrast to the injection of S protein alone, S protein when co-injection with heparin/HS considerably lengthened the bleeding duration in zebrafish embryos (Zheng et al., 2021). In a study by Laghi et al., wild-type zebrafish embryo and larvae were used to microinject SARS-CoV-2 into the coelom, pericardium, brain ventricle, and blood stream. The wild-type larvae, exhibited a sharp decline in SARS-CoV-2 RNA levels. However, after 24 h, the viral RNA stabilized when it was injected into the swim bladder. According to immunohistochemistry, epithelial cells in the swim bladder wall area were found to possess the SARS-CoV-2 nucleoprotein. The results of this investigation showed that wild-type zebrafish larvae had an abortive infection of the swim bladder, an aerial organ that is similar to the mammalian lung, and appeared non-permissive to SARS-CoV-2 (Laghi et al., 2022).

9. Transportation routes of bio-contaminants and contaminants

Aquatic ecosystem is gravely affected due to number bio-contaminants as well as contaminants caused by rapid advancement and industrialization. There is a considerable danger of biomagnification due to the fact that water pollution has affected the fish population and that these contaminants and bio-contaminants may aggregate or colonize fish internal organs where they may then go on to higher food chains (humans). Around 1400 types of microbes, including as bacteria, protozoa, protozoan parasites, parasitic worms, fungus, and viruses, have been discovered by scientists to be potentially harmful (Bashir et al., 2020). In addition, sewage treatment plant effluents include certain harmful microorganisms, and such litters and pollutants are found to have the potential harmful ecotoxicological impacts. As a result of such adverse effects, toxin surveillance, identification of adverse effects of exposure, and comprehension of the transportation routes have become imperative. In the current scientific era, experiments where the fish acting as the vector itself can provide the knowledge to improve investigations which may further allow to study target infection more effectively. Primary organs such as ocular and oral system, nasal, anal, auricle, and the epidermal layer of the skin are the possible route of these pathogen through which it enters fishes. Tenor et al., performed live imaging of the cranial blood arteries of zebrafish larvae infected with a fungal pathogen known as *Cryptococcus neoformans* (Tenor et al., 2015). Interestingly, post intravenous infection, it was found that *C. neoformans* can enter the zebrafish brain. In another study by Wen et al., the zebrafish model was used to investigate sepsis-associated acute kidney damage (Wen et al., 2018). In this investigation, *Edwardsiella tarda* was microinjected into the Cuvier duct of the zebrafish larvae, which further led to dose-dependent death and long-lasting bacterial infection. Mortality rate from moderate *E. tarda* infection was over 50 % in larvae and 20 % in adults. Larval pericardial edema and renal failure were also observed in both larval and adult zebrafish. Studies have also revealed that the ocular system of the zebrafish model may also assist in the investigation of routes for bacterial pathogenesis. For example, Takaki et al., developed the *Mycobacterium marinum*-infected zebrafish larva as a model to examine the early pathophysiology of ocular tuberculosis (Takaki et al., 2018). In this investigation, tricaine was used as a medium for anesthesia, and the larvae at specific developmental stages (2 or 3 dpf) were injected with *M. marinum*. This study

concluded that, despite a functioning blood retinal barrier, hematogenous bacteria can seed the zebrafish eye. Also, *M. marinum* infected eye led to the formation of prototypical early granulomas. Virology based investigations for exploring the routes of infection is a major concern, several experiments have supported such circumstances. Using the zebrafish model, Widziolek et al. assessed the pathogenicity of tilapia lake (TiL) virus infection (Widziolek et al., 2021). The duct of Cuvier was selected as the route

for injecting TiL Virus, further this study revealed that TiLV infection led to an increase in the expression of immune-related genes that code for pathogen recognition receptors for viral dsRNA (*rig-I* (*ddx58*), *tlr3*, *tlr22*), transcription factors (*irf3*, *irf7*), type I interferon (*infϕ1*), antiviral protein (*mxa*), and pro-inflammatory cytokine (*il-1β*). Another study by Passoni et al. discussed the various methods through which alphaviruses, such as the chikungunya virus (CHIKV) and the Sindbis virus (SINV), could
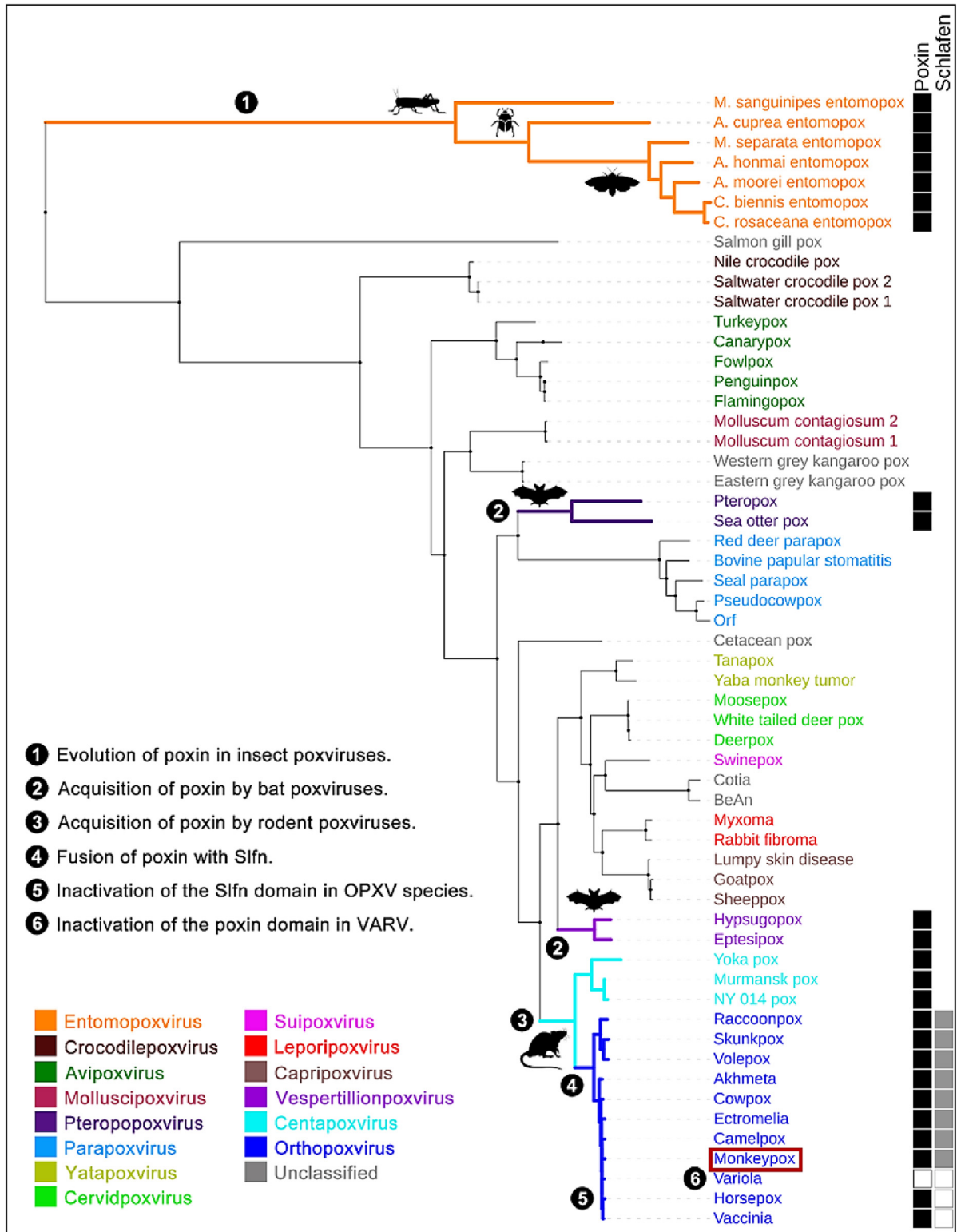
Fig. 9. Representation of phylogenetic tree of the Poxviridae family (Motesi, 2021).

infiltrate the central nervous system (CNS) (Passoni et al., 2017). It was found that the endothelial cells of the brain's vasculature are always infected by CHIKV but not by SINV. In contrast, axonal transport between neural tissues and from the periphery to the CNS was significantly more effective with SINV than CHIKV. Along with the bio-contaminants, the pathway followed by the transport routes of the industrial contaminants must be investigated. Recent reports discussed the prevalence of COVID-19-related litter in various ecosystems, wildlife contact with such objects, and the pollutants that can be discharged from such protective gear (Patrício Silva et al., 2021). Sendra et al., used RNA-Sequencing technique in the zebrafish larvae to analyze the toxicogenomic effects of face masks at various phases of water degradation (Sendra et al., 2022). Larvae were given three treatments over the course of ten days: 1) early stage fragmented face mask (poorly degraded masks, or PDM); 2) advanced stage degraded face mask (highly degraded masks, or HDM); and 3) water obtained from HDM (W-HDM). According to transcriptome analyses, the three treatments caused the downregulation of genes involved in reproduction, particularly the HDM products, which raises the possibility that breakdown products from face masks may have endocrine disrupting properties. The afflicted genes have a role in a number of reproductive processes, including gametogenesis, sperm-egg binding and recognition, or fertilization. The treatments also had varying effects on genes involved in metabolism and the immune system. Furthermore, developmental toxicity of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) has been thoroughly researched; TCDD poisoning typically comprises pericardial and yolk-sac edemas in the zebrafish model (Antkiewicz et al., 2006; Teraoka et al., 2003). Studies on phenotypic mechanisms in zebrafish have made it possible to analyze the AHR (aryl hydrocarbon receptor) pathway's role in developmental toxicity (Goodale et al., 2012; Prasch et al., 2003). Studies of complex mixtures like those found in oil spills (such as Mississippi Canyon 252 oil from the Deep Water Horizon and Alaska North Slope crude oil from the Exxon Valdez) identified polycyclic aromatic cardio toxicants in zebrafish that caused cardiac edema, defective heart looping, hemorrhage, and reduction in arteriovenous circulation, which were consistent with observations by others that dioxins and dioxin-like substances activate the aryl hydrocarbon pathway. Further research may pave a path for comprehensible conclusions on the mobility route for the bio-contaminants and contaminants in the aquatic animals like fishes.

10. Leveraging the zebrafish model to understand the holistic invasion mechanism and possible deterrent of monkeypox virus: future prospective

In 1958, two occurrences of a disease that resembled the pox spread among colonies of monkeys kept for research were reported. As the disease was first identified in monkeys, hence the name "monkeypox". During a period of increased efforts to eradicate smallpox, the first incidence of monkeypox in humans was discovered in the Democratic Republic of Congo in 1970. Several additional central and western African nations, including the Central African Republic, Liberia, Nigeria, Sierra Leone, Democratic Republic of Congo, Republic of Congo, Gabon, Cote d'Ivoire, and Cameroon, have reported cases of monkeypox among their citizens. These cases have been related to foreign travel or the importation of animals.

The WHO declared a public health emergency of international concern (PHEIC) on July 23, 2022, due to the worldwide monkeypox outbreak. Monkeypox is an uncommon illness caused by exposure to the monkeypox virus. Viruses with double-stranded DNA belong to the genus *Orthopoxvirus* and the family *Poxviridae*. This genus also includes viruses such as variola (smallpox), vaccinia (used in smallpox vaccines), and cowpox (Fig. 9). The monkeypox virus has been shown to affect several animal species. These include dormice, non-human primates, tree squirrels, Gambian pouched rats, rope squirrels, and other species. Although rodents are most likely the source of monkeypox, the natural source has not yet been discovered.

When an individual comes into contact with the virus from an infected animal, an afflicted human, or virus-contaminated items, the virus that causes monkeypox may be disseminated. The virus can potentially pass from the mother's placenta to the fetus. It may also be transferred from animals to humans through an infected animal bite or scratch. Direct contact with bodily fluids, sores on an infected person, or objects that come into contact with bodily fluids or sores, such as clothing or linens, can also spread the virus. Direct contact with bodily fluids is the main mechanism by which diseases spread between individuals. When there is lengthy face-to-face contact, they can also be transferred through respiratory secretions. Kissing, snuggling, or touching areas of the body with monkeypox symptoms might help to transmit the virus. Intimate contact between
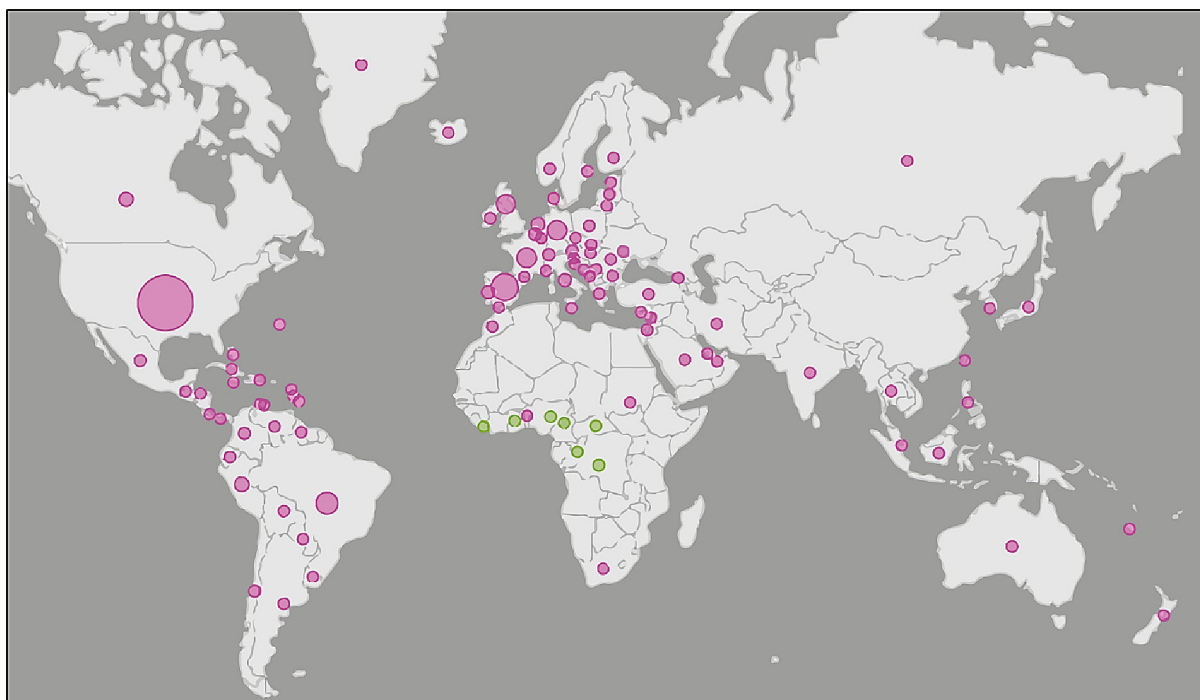

Fig. 10. Monkeypox (MPVX) outbreak global map till 16th September 2022 ("2022 Monkeypox Outbreak Global Map _ Monkeypox _ Poxvirus _ CDC," 2022). (Pink and green circle depicting countries with MPVX cases.)

individuals, particularly during coitus, may also contribute to this phenomenon.

780 laboratory-confirmed cases of monkeypox had been reported to or recognized by WHO as of 13 May and 2 June 2022 from 27 Member States in four WHO zones where the monkeypox virus is not infrequent. Up to this point, no deaths related have been documented. The West African clade was determined to be the source of infection in every instance, whose samples were verified by PCR. The monkeypox virus driving the epidemic is a close match to cases that were transferred from Nigeria to Singapore, the UK, and Israel in 2018 and 2019. This information was obtained from genome sequencing of a swab sample from a confirmed case in Portugal.

According to a recent study, on September 16, 2022, there were 61,282 verified cases of monkeypox from approximately 104 areas worldwide (Fig. 10), and 20 deaths were recorded.

Humans and other species routinely exchange viruses with each other. For instance, SARS-CoV-2 virus is commonly believed to have jumped from a bat or pangolins. While entering host cells, poxviruses employ 11 viral proteins that form entrance fusion complexes, in addition to four attachment proteins (Fig. 11). These proteins are conserved across all poxviruses. This is in contrast to SARS-CoV-2, which uses a single transmembrane protein (spike protein) (Moss, 2012). To transport their genetic material into host cells, the entry fusion complex (EFC) proteins form complexes and interact with the host cell. Infectious virions can be divided into two fundamental categories: mature virions (MV) (Fig. 11), which have a single membrane, and extracellular virions (EV) (Fig. 11), which have a second outer membrane that is ruptured before fusion (Moss, 2012). Unique sets of transmembrane proteins are found in MVs and EVs, which help the virus affix to the host cell. The outer transmembrane proteins found in EVs include A33R, B5R, A34R, F13L, A56R, A36R, and F12L (Benhnia et al., 2013; Law et al., 2006; Pickup, 2015; Wagenaar and Moss, 2009), while the MV contains just a few transmembrane proteins, including D8, H3, A26, and A27 (Chung et al., 1998; Hsiao et al., 1999, 1998; Lin et al., 2000; Singh et al., 2016). Nonetheless, the entry-fusion complex, which is mainly composed of proteins A16, A21, A28, F9, G3, G9, H2, J5, L1, L5, and O3, is used in both virions to carry out viral fusion with the host cell (Fig. 12) (Foo et al., 2009; Moss, 2016; Senkevich et al., 2005). The four attachment proteins, A26, A27, D8, and H3, present in the MV have been found to interact with laminin, glycosaminoglycan (GAG), chondroitin sulfate proteoglycan (CSPG), and heparin, similar to the spike protein and its interaction with the ACE2 receptor (Chung et al., 1998; Hsiao et al., 1999, 1998; Lin et al., 2000). It has been observed that EV outer transmembrane proteins (A33R, B5R, A34R, F13L, A56R, A36R, and F12L) interact with GAG before the EV membrane separates (Moss, 2016; Roberts et al., 2009). Utilizing zebrafish model system, it may be possible to study the interaction and suppression of poxviruses using these transmembrane proteins. Studies have shown that zebrafish also have the receptors that the monkeypox virus needs in order to enter cells (Farwell et al., 2017; Lee et al., 2020; Sztal et al., 2011; Zhang et al., 2009).
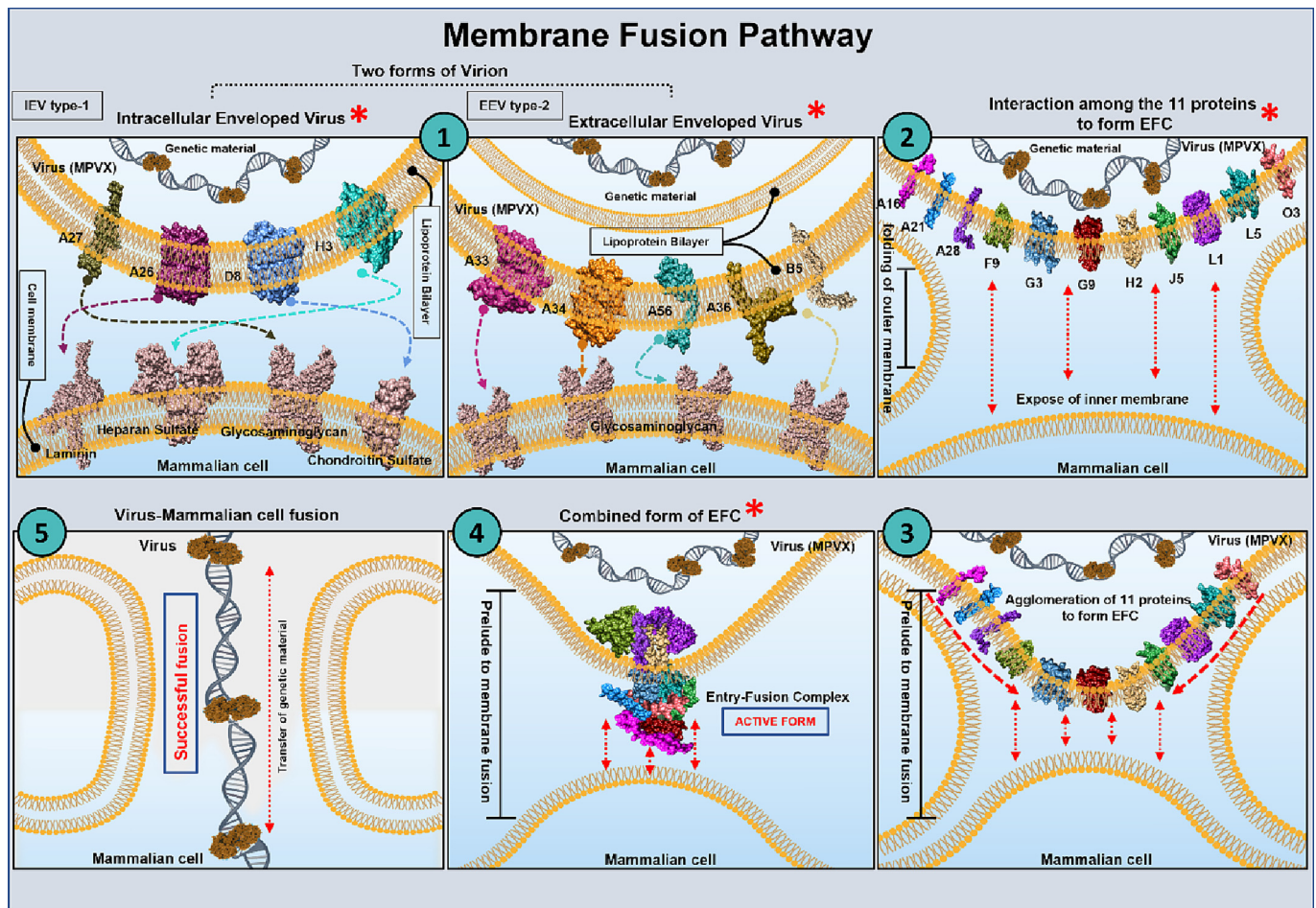

Fig. 11. Picture above illustrating the complete membrane fusion of Orthopoxvirus (monkeypox virus) with mammalian cells. (1, left) representing IEV with a single lipoprotein bilayer consisting of 4 receptors interacting with the mammalian cell counterpart. (1, right) representing EEV with double lipoprotein bilayer and (5) receptors containing in the outer layer of the virion interacting with mammalian counterparts. (2, 3 & 4) Exposure of the 11 types of protein to the inner membrane layer of mammalian cells, which forms a complex which further assists in the membrane fusion. 5 illustrating a successful membrane fusion between virus and mammalian cells resulting in the transfer of the genetic material. Panels with (red asterix) showing crucial steps where the virus could potentially be checked and could be stopped from fusing with mammalian cells.
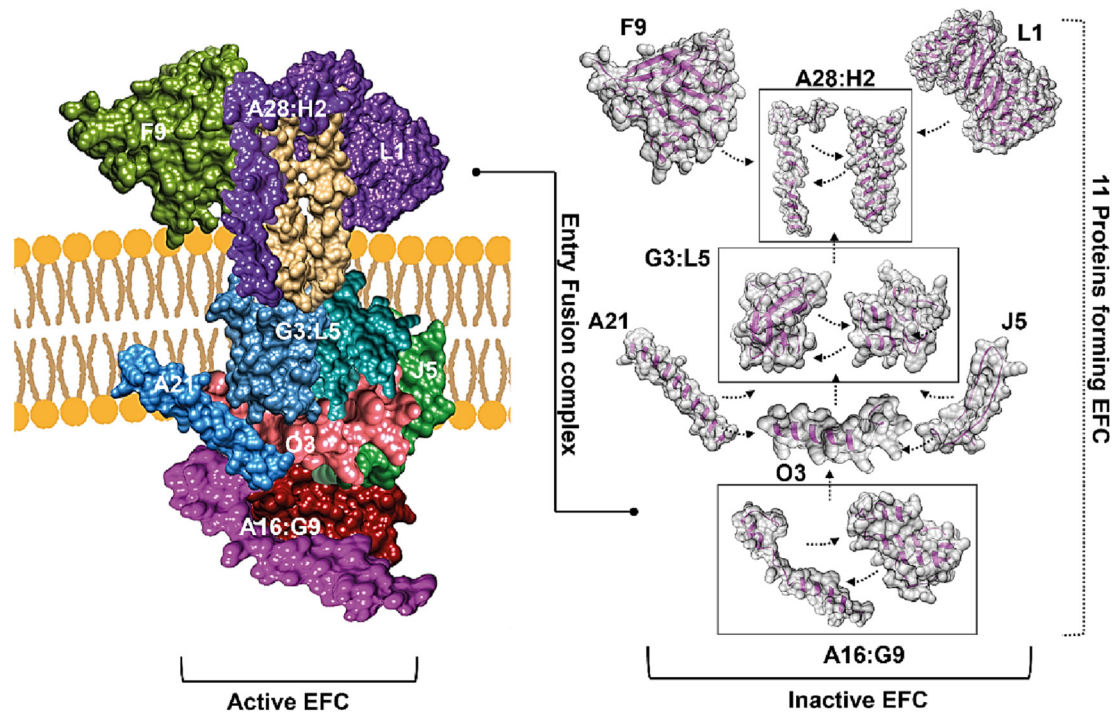
Fig. 12. Image representing the active form of entry fusion complex (EFC).

The first draft genome of the monkeypox virus has already been published by a group of experts (Isidro et al., 2022) and could be used to identify more suitable protein targets. Further work must be done before any firm conclusions can be made since this is still a very early draft. A variety of animal models have been employed to investigate the effects of viruses from the *orthopoxvirus* family (monkey virus, variola virus, Ectromelia virus, Vaccinia virus, rabbitpox virus, and cowpox virus), such as macaques (species/strain: cynomolgus), macaques (species/strain: cynomolgus, rhesus), ground squirrels (species/strain:13-lined), prairie dogs (species/strain: black-tailed), dormice (species/strain: Kellner's), rabbits, rats (cotton rats), and mice (C57BL/6, A.J, BALB/c, DBA/2, and C3H). *Orthopoxvirus* models have benefits in terms of anatomy and immunology that are comparable to those of humans; however, utilizing non-human primates, rabbits, mice, and rats is more expensive, requires a larger living area, and can be physically demanding and risky to manage. Under biocontainment circumstances, when space is at a premium and people must use specific protective gear that makes even the simplest activity more challenging to complete, housing and handling concerns take on particular significance. As a workaround for these problems, we suggest using a zebrafish model for viral infection research. Zebrafish are a particularly useful and desirable model for the study of infectious diseases and immunity because of the similarities between their immune systems and those of mammals, their ability to study specific immune system components at various stages of immunologic development, and the availability of molecular, genetic, and imaging tools for this species. As zebrafish are vertebrates and the human reference genome can be compared, it has been shown that over 70 % of human genes have at least one clear zebrafish orthologous gene. The recent transmission of the monkeypox virus in humans (from animal to human) is a growing threat. Thus, zebrafish are a useful model for checking virus-host interactions.

11. Conclusions

In this study, we emphasized the novel use of zebrafish model as a platform to study various chemical toxins, nanoparticles toxicity as well as bio-contaminants such as fungus, protozoan, metazoan, parasites, bacteria and viruses, viruses being the most important of. We have also evaluated the benefits and drawbacks of the current model organisms, and how zebrafish outperform these models in this review. This evaluation also addresses numerous gene manipulation of zebrafish model which allows researchers to replicate or establish human disease model, infectious disease model/bio-contaminants model, and investigate its mechanisms. Furthermore, we have highlighted various routes and processes by which viruses infect zebrafish and how they are analogous to human systems, as well as how these viruses may be eliminated by employing this model. A thorough explanation of how this model been used to research the recent pandemic COVIOD-19 caused by SARS-CoV-2, as well as how it could potentially be applied to research other possible pandemic-causing viruses like MPVX (monkeypox virus), is also provided. As a potential tool, zebrafish are affordable, simple to use, less difficult to handle, and capable of having a large sample size. Furthermore, unique characteristics (transparent embryos, *ex situ* development, and rapid embryo development) give the researcher an advantage to see how viruses interact with various organs under a microscope and comprehend how the body reacts to a specific viral infection, including the phenotypic characteristics that result. In conclusion, the zebrafish model has not yet reached its full potential for studying human viruses. Zebrafish are not meant to replace other vertebrate models, such as mice; however, they avoid the issues that arise when working with vertebrate models and may reveal important concepts in viral pathogenesis and host defense, which may help in the creation of groundbreaking cures for recently emerging viruses.

Abbreviations

SARS	Severe acute respiratory syndrome
MERS	Middle East respiratory syndrome
SARS-CoV-2	
Severe acute respiratory syndrome coronavirus 2	
MARS-CoV	
Middle East respiratory syndrome coronavirus	
229E	Human coronavirus 229E
OC43	Human coronavirus OC43
NL63	Human coronavirus NL63
HKU1	Human coronavirus HKU1
H7N9	Asian lineage avian influenza A
DNA	Deoxyribonucleic acid
RNA	Ribonucleic acid

hDPP4	Human dipeptidyl peptidase 4
SCID	Severe combined immunodeficient
prkdc	Protein kinase, DNA activated, catalytic polypeptide
EboV	Zaire ebolavirus
ACI	August Copenhagen Irish Rat
MAXX	Inbred stain of rats
hACE2	Human angiotensin-converting enzyme 2
IHNV	Infectious hematopoietic necrosis virus
VHSV	Viral hemorrhagic septicemia virus
SVCV	Spring viremia carp virus
IPNV	Infectious pancreatic necrosis virus
E. coli	*Escherichia coli*
CHIKV	Chikungunya virus
HuNoV	Human norovirus
HSV-1	Herpes simplex virus type-1
I. multifiliis	Ichthyophthirius multifiliis
NIH	National Institutes of Health
KO	Knock out
EDC	Endocrine disruptor chemical
CNS	Central nervous system
RTH	Resistance to thyroid hormone
MCT8	Monocarboxylate transporter 8
KD	Knock down
GI	Gastrointestinal
PRRs	Pattern recognition receptors
C. elegans	*Caenorhabditis elegans*
kRASG12D solid tumor models	Kirsten rat sarcoma viral oncogene homolog G12D
MDA-MB-231	M.D. Anderson - Metastatic Breast 231
MDA-MB435	M.D. Anderson - Metastatic Breast 435
PC3	Human prostate cancer
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
DA	Dominant active
CML	Chronic myeloid leukemia
MPNST	Malignant peripheral nerve sheath tumor
MDS	Myelodysplastic syndrome
RMS	Rhabdomyosarcoma
PNST	Peripheral nerve sheath tumor
HCC	Hepatocellular cancer
T-ALL	T-cell acute lymphoid leukemia
Cd	Cadmium
Cu	Copper
Hg	Mercury
Zn	Zinc
DCA	Dichloroacetic acid
5-FU	5-Fluorouracil
PCBs	Polychlorinated biphenyls
DE-71	Polybrominated diphenyl ethers
PAHs	Polycyclic aromatic hydrocarbons
BDE-47	2,2,4,4-Tetrabromodiphenyl ether
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
CVD	Cardiovascular disorder
NAFLD	Non-alcoholic fatty liver disease
HPE	Holoprosencephaly
UPEC	UroPathogenic *Escherichia coli*
AGM	Aorta gonad mesonephros
HSPCs	Hematopoietic stem and progenitor cells
S. typhimurium	*Salmonella typhimurium*
TNFα	Tumor necrosis factor alpha
IL-1β	Interleukin 1 beta
mRNA	Messenger RNA
LD50	Lethal dosage
S. pyogenes	*Streptococcus pyogenes*
ATP	Adenosine triphosphate
GBS	Group B streptococcus
IP	Intraperitoneal
IM	Intramuscular
cfu	Colony-forming unit
BBB	Blood-brain barrier
IL	Interleukins
dpf	Days post fertilization
GAS	Group A streptococcus
M. marinum	*Mycobacterium marinum*
M. tuberculosis	*Mycobacterium tuberculosis*
TB	Tuberculosis
T3SS	Type-3 secretion system
(si)RNA	Small interfering RNA
SEPT	Septin
S. Typhimurium	*Salmonella typhimurium*
S. enterica	*Salmonella enterica*
Gbp4	Guanylate-binding protein 4
HSPC	Hematopoietic stem and progenitor cell
CF	Cystic fibrosis
P. aeruginosa	*Pseudomonas aeruginosa*
HEC	Enterohemorrhagic *Escherichia coli*
LEE	Locus of enterocyte effacement
V. cholera	*Vibrio cholerae*
pH	Potential of hydrogen
BCC	*Burkholderia cenocepacia* complex
B. cenocepacia	*Burkholderia cenocepacia*
B. vietnamiensis	*Burkholderia vietnamiensis*
B. stabilis	*Burkholderia stabilis*
V. vulnificus	*Vibrio vulnificus*
V. alginolyticus	*Vibrio alginolyticus*
V. parahaemolyticus	*Vibrio parahaemolyticus*
V. anguillarum	*Vibrio anguillarum*
TDH	Thermostable direct hemolysin
TRH	TDH-related hemolysin
Fadsd6	Δ-6 fatty acyl desaturase
Elvol5a	Elongase
WT	Wild type
PUFAs	Polyunsaturated fatty acids
Y. ruckeri	*Yersinia ruckeri*
GFP	Green fluorescent protein
L. monocytogenes	*Listeria monocytogenes*
L. welshimeri	*Listeria welshimeri*
L. innocua	*Listeria innocua*
InlA	Internalin A
InlB	Internalin B
S. iniae	*Streptococcus iniae*
E. tarda	*Edwardsiella tarda*
LLO	Lysteriolisin O
SHRV	Viral hemorrhagic septicemia Virus
HIV	Human immunodeficiency virus
T1L	Type 1 Lang
T2J	Type 2 Jones
T3D	Type 3 Dearing
RBD	Receptor-binding domain
miRNA	MicroRNA
AAV	Adeno-associated viruses
RNAi	RNA interference
VSRs	Viral suppressors of RNAi
SFV	Semliki Forest virus
NoV	Nodamura virus
RISC	RNA-induced silencing complex
HSV	Herpes simplex virus
HS	Heparan sulfate
ISGs	IFN-stimulated genes
HCV	Hepatitis C virus

CRP	C-reactive proteins
ROS	Reactive oxygen species
RLRs	RIG-I-like receptors
zbTRIM25	Zebrafish tripartite motif containing 25
RGNNV	Red spotted grouper neurological necrosis virus
zbRIG-I	Zebrafish retinoic acid-inducible gene I
SPRY	SPla and the RYanodine Receptor
CARD	Caspase activation and recruitment domains
RD	Repressor domain
CRFB	Cytokine receptor family B
kDa	Kilodaltons
EPC	Epithelioma papulosum cyprini
S protein	Spike protein
rSpike	Recombinant SARS-CoV-2 spike proteins
VSVppSARS-2S	
SARS-CoV-2 S-protein pseudotyped vesicular stomatitis virus	
T_{regs}	Regulatory T cells
PMR	Polygoni Multiflori Radix
IC50	Half maximal inhibitory concentration
g/ml	Grams per milliliters
h	Hours
PHEIC	Public health emergency of international concern
WHO	World health organization
PCR	Polymerase chain reaction
MPVX	Monkeypox virus
EFC	Entry fusion complex
MV	Mature virions
EV	Extracellular virions
GAG	Glycosaminoglycan
CSPG	Chondroitin sulfate proteoglycan
IEV	Intracellular enveloped virus
EEV	Extracellular enveloped virus
TLRs	Toll-like receptors
PAMP	Patterns associated with

CRediT authorship contribution statement

P.P., N.K.K., N.K. and E.H.C. conceived the manuscript with inputs from all authors. P.P., N.K. and A.N. contributed to drawing diagrams on biorender and adobe illustrator software. S.K.V., A.N., N.K. and M.S. contributed substantially to writing and review of the manuscript. N.K.K., N.K., S.K.V., E.H.C. and M.S. revised the paper. All authors read and approved the final manuscript.

Data availability

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no competing interests.

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