Narrative Review Article

Zebrafish as a Model Organism for Anti-Angiogenesis Cancer Drug Screening

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ABSTRACT

Angiogenesis is a critical biological process in development and disease, particularly in cancer progression, where it supports tumor growth and metastasis. Vascular endothelial growth factor (VEGF) signaling plays a central role in angiogenesis, making VEGF pathway inhibitors key therapeutic targets. The zebrafish model provides a valuable platform for studying VEGF-driven angiogenesis and screening anti-angiogenic compounds due to its optical transparency, rapid vascular development and genetic similarity to humans. Several VEGF inhibitors, including SU5416 (Semaxanib) and PTK787 (Vatalanib), have been widely used in zebrafish assays and consistently demonstrate dose-dependent inhibition of intersegmental vessel formation. More selective inhibitors such as DMH4 show promising activity with reduced off-target effects. Clinically approved or repurposed agents, including sorafenib and rosuvastatin, exhibit variable inhibitory effects, while natural compounds such as baicalein offer potential lower-toxicity alternatives with modest efficacy. Overall, the zebrafish model provides a rapid, cost-effective, and biologically relevant in vivo system for evaluating anti-angiogenic agents. This narrative review summarizes current advances in zebrafish-based anti-angiogenic drug discovery, highlighting both established inhibitors and emerging or repurposed compounds. Future studies should combine zebrafish screening with molecular profiling and prioritize validation in mammalian systems to enhance clinical translation.

Keywords: Angiogenesis; Vascular endothelial growth factor; Zebrafish; drug discovery; Anti-Angiogenic Compounds; in-vivo screening; Drug Repurposing

INTRODUCTION

Angiogenesis, the process by which new blood vessels form from pre-existing vasculature, plays a fundamental role in cancer progression. As tumors expand beyond a minimal size of approximately 1–2 mm^3, diffusion alone becomes insufficient to meet metabolic demands, necessitating the induction of neovascularization to supply oxygen and nutrients and to remove metabolic waste products (1). Furthermore, angiogenesis is essential for tumor invasion and metastasis, providing a conduit through which cancer cells can disseminate to distant organs (2).

Tumor cells frequently exploit endogenous pro-angiogenic signaling pathways to sustain aberrant vascular growth. Among the most prominent of these pathways are those mediated by vascular endothelial growth factors (VEGF), fibroblast growth factors (FGFs), and angiopoietins, which collectively promote endothelial cell proliferation, migration, and vessel

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stabilization (3-5). Dysregulated activation of these pathways results in excessive, tortuous, and poorly organized tumor vasculature, a hallmark of malignant tissues (6). Therapeutic strategies targeting angiogenesis have therefore become an integral component of modern oncology. VEGF-directed therapies, including monoclonal antibodies and small-molecule tyrosine kinase inhibitors (TKIs), have demonstrated clinical benefit across multiple cancer types by suppressing tumor vascularization and delaying disease progression (7, 8).

Despite these advances, the clinical efficacy of current anti-angiogenic therapies remains limited by intrinsic and acquired resistance, activation of compensatory pathways such as FGF and angiopoietin signaling, and dose-limiting toxicities associated with chronic VEGFR inhibition. Moreover, responses are often transient, underscoring the need for next-generation agents with improved selectivity, multi-pathway targeting capacity, and optimized pharmacologic profiles (9). Efficient development of such compounds requires physiologically relevant in vivo platforms that enable rapid and quantitative assessment of angiogenic phenotypes while maintaining scalability for drug screening.

The zebrafish (*Danio rerio*) has emerged as a powerful and versatile in vivo model for angiogenesis research and for the phenotypic screening of small-molecule anti-angiogenic compounds. Zebrafish embryos and larvae readily absorb chemical agents directly from the surrounding water, enabling rapid, non-invasive, and dose-controlled evaluation of candidate drugs in a whole-organism context (10, 11). Their optical transparency, combined with well-established transgenic lines expressing fluorescent reporters in vascular endothelial cells, permits real-time visualization of vascular development and tumor-induced angiogenesis at single-vessel resolution (12). Importantly, the molecular pathways governing angiogenesis are highly conserved between zebrafish and humans, supporting the translational relevance of zebrafish-based findings (13-15).

Beyond their biological relevance, zebrafish offer substantial practical advantages for drug discovery. Their rapid external development, small size, and compatibility with microplate-based assays facilitate high-throughput screening of chemical libraries at relatively low cost. Quantitative assessment of vessel formation, branching, remodeling, and regression can be readily performed using fluorescent vascular reporter lines, while zebrafish tumor xenograft models enable direct visualization of cancer–vasculature interactions in a living organism. Collectively, these features position zebrafish as an effective intermediate platform that bridges the gap between in-vitro assays and mammalian preclinical studies, accelerating the identification and optimization of orally relevant small-molecule anti-angiogenic agents. This review examines the role of zebrafish as an in vivo platform for anti-angiogenic drug discovery, with particular emphasis on VEGF signaling inhibitors, repurposed pharmaceuticals, and natural compounds, while also discussing the current limitations and future directions of zebrafish-based screening approaches in cancer therapeutics.

ANGIOGENESIS AND ITS ROLE IN CANCER

Angiogenesis is the physiological process by which new blood vessels form from existing vasculature. In normal tissues, angiogenesis is essential for embryonic development, wound healing and tissue repair, and is tightly regulated by a balance between pro-angiogenic factors, such as VEGF, FGF, and platelet-derived growth factor (PDGF), and anti-angiogenic signals that maintain vascular stability and prevent excessive or aberrant vessel formation (16). Under healthy conditions, pro-angiogenic signaling is transient and occurs only when required to restore oxygenation and structural integrity. When this balance is disturbed, abnormal vessel growth can result (17).

In cancer, this regulatory equilibrium is disrupted. As tumors enlarge, their centers frequently become hypoxic. Hypoxia stimulates hypoxia-inducible factor-1 (HIF-1), which then upregulates the expression of pro-angiogenic factors such as VEGF (18). Elevated VEGF levels stimulate endothelial cell proliferation, migration, and capillary sprouting toward the tumor mass. The resulting neovasculature supplies oxygen and essential nutrients that sustain continued tumor growth, while simultaneously providing access to the systemic circulation, thereby facilitating metastatic dissemination (16).

Because angiogenesis is central to tumor progression and metastasis, anti-angiogenic therapies have become a major strategy in oncology. Many anti-angiogenic agents target the VEGF/VEGFR signaling pathway, either by neutralizing the VEGF ligand or by inhibiting VEGFR tyrosine kinase activity downstream. For example, bevacizumab, a monoclonal antibody that binds VEGF, prevents its interaction with VEGFR on endothelial cells, thereby inhibiting neovascularization (19).

Zebrafish as a Model for Angiogenesis Drug Screening

Zebrafish is a well-validated in-vivo model for angiogenesis research and anti-angiogenic drug discovery. The utility of zebrafish in vascular biology was first recognized in 1999 when Serbedzija and colleagues first proposed the zebrafish embryo as a tractable model for pharmacological screening of angiogenesis (20). Since then, the model has been substantially refined and widely adopted across both academic and translational research settings (21).

One of the most important biological features of zebrafish is the optical transparency of their embryos and early larvae, which enables direct and real-time visualization of developing blood vessels (20, 21). This transparency is further leveraged through the use of stable transgenic reporter lines expressing fluorescent proteins under endothelial cell–specific promoters. In these lines, specific cell populations are genetically engineered to fluoresce under microscopic imaging, making the vascular network directly visible in living embryos. Among these, the Tg(fli:EGFP) line is the most widely utilized. In this model, enhanced green fluorescent protein (EGFP) is expressed under the control of the fli1a promoter, marking endothelial and hematopoietic progenitor cells (13, 21) (Figure 1). This line has become a standard tool for in vivo vascular imaging in zebrafish, enabling high-resolution quantification of vascular sprouting, intersegmental vessel (ISV) formation, subintestinal vessel (SIV) plexus development, and overall vascular patterning throughout embryogenesis (13, 21).

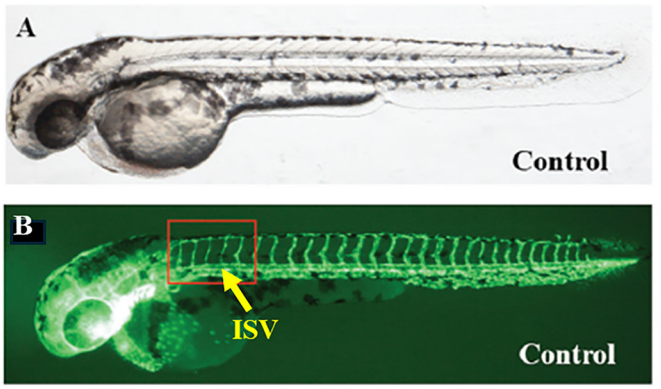

Figure 1. *Representative images of zebrafish embryos (35). (A) Brightfield image showing normal embryonic morphology. (B) Fluorescence image of a Tg(fli1:EGFP) transgenic zebrafish embryo highlighting endothelial cells and developing vasculature. Intersegmental vessels (ISV) are clearly visible along the trunk region (boxed area).*

Furthermore, the zebrafish vascular system undergoes rapid development. The primary axial vessels are established by approximately 24 hours post-fertilization (hpf) with active angiogenic sprouting of ISVs occurring between 20 and 30 hpf (20, 21). This accelerated developmental timeline enables timely and efficient evaluation of angiogenic processes within a whole-organism context, substantially reducing the experimental duration compared with rodent models. Because angiogenesis is tightly regulated in a spatiotemporal manner during early embryogenesis, pharmacological disruption of relevant signaling pathways results in readily detectable and quantifiable morphological defects in vessel growth, branching, and patterning (13). Such defects provide robust phenotypic readouts suitable for both qualitative observation and quantitative measurement.

Zebrafish share a high degree of evolutionary conservation with humans in key vascular signaling pathways, thereby enhancing their translational relevance in angiogenesis research. The principal regulators of endothelial cell proliferation, migration and tubulogenesis, like VEGF signaling, are functionally conserved between zebrafish and mammals (21, 22). This molecular conservation ensures that compounds identified as active in zebrafish vascular assays are likely to work in human endothelial biology, substantially strengthening the translational value of zebrafish-derived pharmacological data for the development of therapeutics targeting human tumor vascularization (22).

Beyond their biological relevance, zebrafish confer considerable practical advantages that make them particularly well suited to large-scale chemical screening programs. Their small body size and prolific reproductive capacity, with a single breeding pair capable of generating hundreds of embryos per clutch, enable the production of large, genetically uniform embryo cohorts. In addition, relatively low husbandry costs further support scalability. These embryos can be arrayed in 96- or 384-well microplate formats that are compatible with automated liquid handling systems and high-content imaging platforms (13, 23). The permeability of the zebrafish chorion and integument to small hydrophilic and amphiphilic molecules permits non-invasive compound administration through direct addition to the embryo medium. Phenotypic endpoints can be rapidly assessed using fluorescence microscopy. These include ISV length, SIV plexus area, vessel branching complexity, and fluorescence intensity in transgenic lines. Increasingly, these measurements are

quantified using automated image-analysis algorithms. This approach enables high-throughput analysis across large compound libraries (13, 23).

A particularly important feature of the zebrafish whole-organism screening platform is the capacity for simultaneous assessment of anti-angiogenic efficacy and systemic developmental toxicity within a single experimental assay. Zebrafish embryos integrate compound effects across multiple organ systems, enabling early-stage identification of compounds with acceptable therapeutic potential while eliminating those that exhibit unacceptable systemic toxicity or teratogenicity prior to mammalian studies (22, 23). This capacity to generate preliminary safety and efficacy data in parallel within a vertebrate organism represents a significant advantage over conventional in vitro approaches.

Collectively, literature demonstrates that zebrafish provide a robust, cost-effective, and biologically relevant platform for anti-angiogenic drug discovery, enabling rapid in vivo screening, mechanistic characterization, and preliminary safety profiling of candidate therapeutic agents. The model has been instrumental in the identification and validation of numerous small-molecule inhibitors, repurposed clinical drugs, and natural product-derived compounds with anti-angiogenic activity.

Anti-Angiogenic Compounds Identified Using Zebrafish

Several small-molecule inhibitors with anti-angiogenic activity have been identified or validated through zebrafish-based screening systems including DMH4, SU5416 (Semaxanib), and PTK787 (Vatalanib / ZK222584) (Figure 2). Zebrafish embryos, particularly transgenic Tg(fli1:EGFP) lines, provide a powerful in vivo model for angiogenesis research (13). In addition, the zebrafish vascular system forms rapidly within the first 24–48 hours post-fertilization, which enable efficient observation of vascular growth and the effects of candidate anti-angiogenic compounds.

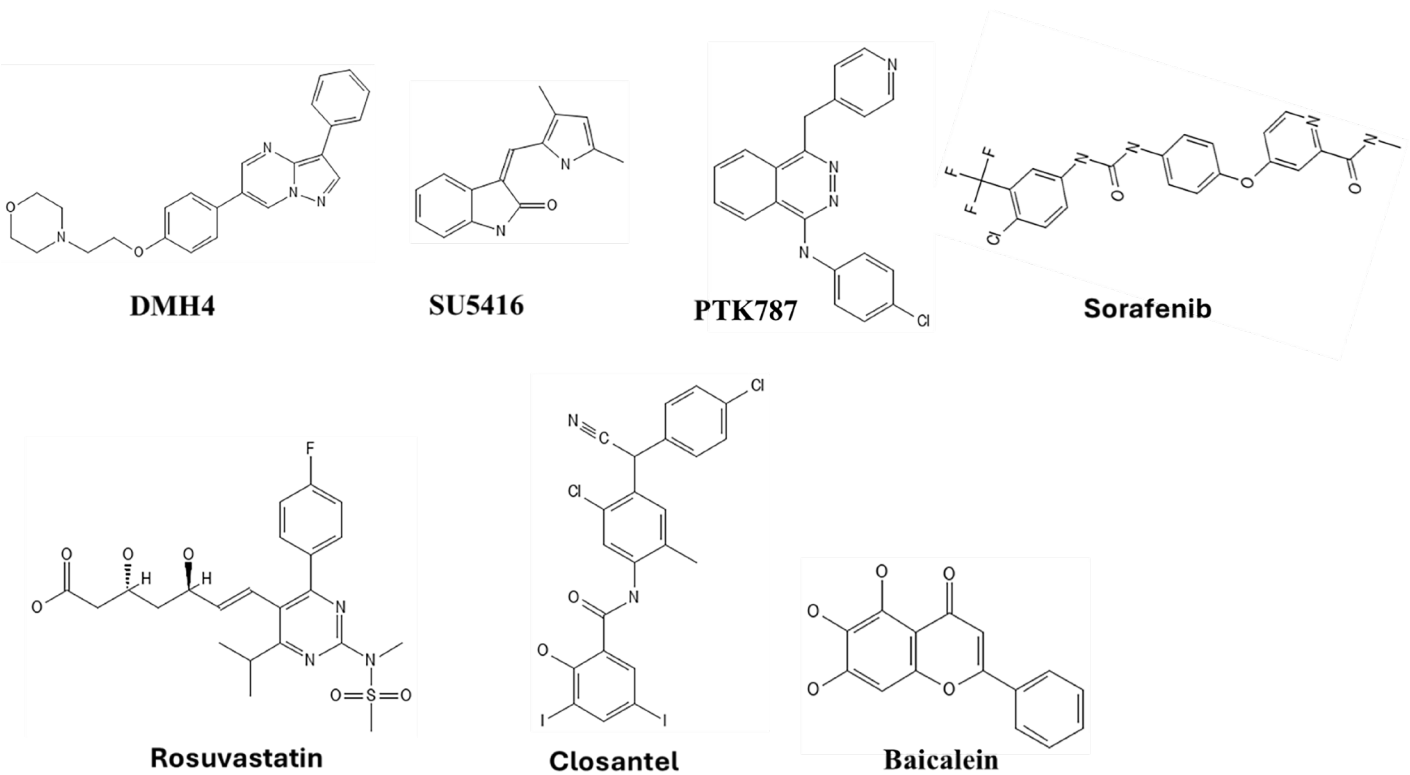

Figure 2. *Chemical structures of the anti-angiogenesis compounds identified and repurposed by using zebrafish including DMH4, SU5416 (Semaxanib), PTK787 (Vatalanib / ZK222584), rosuvastatin, Sorafenib (BAY43-9006), Closantel, and Baicalein.*

Among these compounds, DMH4 is a representative VEGF signaling inhibitor identified through phenotypic screening in zebrafish embryos (24). In zebrafish angiogenesis assays, treatment with DMH4 produces a dose-dependent suppression of intersegmental vessel (ISV) sprouting, one of the most widely used indicators of angiogenic activity during early vascular development. This phenotype indicates that DMH4 primarily interferes with angiogenic sprouting driven by VEGF pathway. Mechanistically, DMH4 selectively inhibits VEGFR2 kinase, key regulator of endothelial cell proliferation, migration and survival during vascular development (24, 25). As a result, endothelial cells fail to extend properly from the primary vessels, leading to defective angiogenic patterning.

Other VEGF pathway inhibitors have also been extensively evaluated using zebrafish angiogenesis assays. SU5416 (Semaxanib) is a small-molecule tyrosine kinase inhibitor originally developed as anti-cancer agents that target VEGF receptor signaling. SU5416 is a selective inhibitor of VEGFR2 and blocks receptor autophosphorylation, thereby suppressing downstream signaling pathways that regulate endothelial cell proliferation, migration, and survival (26). When applied to developing zebrafish embryos, SU5416 causes a pronounced inhibition of intersegmental vessel (ISV) sprouting, often resulting in truncated or completely absent ISVs. In many cases, embryos treated with SU5416 display normal formation of the primary axial vessels—such as the dorsal aorta and posterior cardinal vein—but show severe impairment in secondary angiogenic sprouting, indicating a specific disruption of VEGF-dependent angiogenic processes (27).

Similarly, PTK787 (Vatalanib / ZK222584) is a potent inhibitor of multiple VEGF receptor tyrosine kinases including VEGFR1, VEGFR2, and VEGFR3 (27). In zebrafish angiogenesis models, PTK787 treatment significantly reduces endothelial sprouting and disrupts the formation of intersegmental vessels and dorsal longitudinal anastomotic vessels. The compound also interferes with endothelial cell migration along somite boundaries during early vascular development. Because PTK787 inhibits several VEGF receptor subtypes, its effects in zebrafish embryos often produce a broader suppression of vascular development compared with more selective inhibitors. These phenotypic changes closely resemble those observed in genetic models with impaired VEGF signaling, further validating zebrafish as a reliable model for studying angiogenic pathways.

Overall, zebrafish-based screening offers several advantages for anti-angiogenic drug discovery. The optical transparency of embryos, rapid development of the vascular network, availability of fluorescent endothelial reporter lines, and compatibility with high-throughput chemical screening allow researchers to directly observe vascular phenotypes and evaluate compound toxicity in vivo (1–3). These features have enabled the rapid identification of vascular inhibitors such as DMH4 and continue to support the discovery of new therapeutic agents targeting pathological angiogenesis.

Drug Repurposing and Natural Product Discovery Using Zebrafish Angiogenesis Models

The advantages of zebrafish-based screening, particularly whole-organism drug exposure, real-time visualization of vascular development and suitability for high-throughput assays, make it a valuable platform for both novel drug discovery and repurposing existing compounds. In contrast to traditional in-vitro systems, zebrafish embryos allow compounds to be evaluated in a living organism, where vascular responses can be observed directly and in context. This has proven particularly useful in identifying drugs with previously unrecognized anti-angiogenic effects.

Several FDA-approved drugs with previously unrecognized anti-angiogenic activity have been identified through zebrafish angiogenesis assays. For example, rosuvastatin, a widely used HMG-CoA reductase inhibitor for cholesterol management, has been shown to suppress vascular sprouting and disrupt intersegmental vessel (ISV) formation in zebrafish embryos. Although primarily prescribed for lipid lowering, rosuvastatin can influence endothelial cell function and angiogenic signaling pathways, potentially through modulation of nitric oxide production and inflammatory responses that affect endothelial cell migration and proliferation (28, 29).

Sorafenib (BAY43-9006), a multi-kinase inhibitor targeting VEGFR, PDGFR, and RAF kinases, also exhibits strong anti-angiogenic effects in zebrafish angiogenesis assays. Treatment with sorafenib results in reduced endothelial cell proliferation and significant inhibition of vascular development, consistent with its clinical role as a targeted therapy for cancers such as hepatocellular carcinoma and renal cell carcinoma (30, 31). Similarly, tivozanib (AV-951), a highly selective VEGFR inhibitor, has been evaluated in zebrafish angiogenesis models and produces marked suppression of vascular sprouting and ISV formation by blocking VEGF-mediated endothelial signaling(31).

Zebrafish screening has also revealed anti-angiogenic properties in compounds originally developed for other therapeutic purposes. Closantel, an antiparasitic drug used primarily in veterinary medicine, has been reported to inhibit vascular development in zebrafish embryos, resulting in reduced ISV growth and impaired endothelial cell migration (32). The identification of such compounds highlights the value of zebrafish models for drug repurposing and for uncovering previously unrecognized biological activities in existing pharmacological agents.

Natural products have likewise emerged as promising sources of anti-angiogenic compounds identified through zebrafish screening. Baicalein, a flavonoid derived from the medicinal plant *Scutellaria baicalensis*, and its derivatives have demonstrated significant inhibition of angiogenic sprouting in zebrafish embryos. Treatment with baicalein results in reduced ISV formation and impaired endothelial cell migration. Mechanistic studies suggest that these effects may involve suppression of VEGF signaling pathways and modulation of oxidative stress responses in endothelial cells (33, 34). The ability of zebrafish assays to rapidly evaluate natural compounds further supports their usefulness in identifying novel anti-angiogenic drug candidates.

In summary, these studies have demonstrated how zebrafish-based screening provides a practical and biologically relevant platform for both drug repurposing and natural product discovery. By enabling rapid in vivo evaluation of vascular responses, zebrafish models help bridge early-stage screening and translational research, supporting the development of new anti-angiogenic therapies.

CONCLUSION

Zebrafish phenotype-based screening has emerged as a valuable platform for the discovery of new potential drugs including anti-angiogenic compounds as it enables rapid, cost-effective, and in vivo evaluation of vascular development. Compared with traditional in-vitro systems, zebrafish models provide a more physiologically relevant environment in which endothelial behavior, vessel sprouting, and drug responses can be directly observed in the context of a living organism. The availability of transparent embryos and fluorescent transgenic lines has further strengthened the usefulness of this model for identifying compounds that interfere with angiogenic pathways such as VEGF signaling, making zebrafish an important bridge between early-stage drug discovery and later high-order animal studies.

Despite these advantages, several limitations must be considered when interpreting results from zebrafish-based assays. Biological differences between zebrafish and humans may influence the translational relevance of certain findings, particularly in the areas of metabolism, pharmacokinetics, and tissue-specific responses. Drug absorption and exposure can also vary depending on compound properties and administration methods, which may affect the consistency of screening outcomes. In addition, although zebrafish are highly effective for initial phenotypic discovery, follow-up validation in mammalian systems remains necessary to confirm therapeutic efficacy, toxicity, and clinical potential.

Future advances are expected to further enhance the role of zebrafish in anti-angiogenic drug discovery. Automated high-throughput screening platforms may improve efficiency and reproducibility, while advances in imaging technologies could allow more precise visualization and quantification of vascular changes. In the longer term, zebrafish models may also contribute to more personalized approaches to drug screening by enabling faster evaluation of candidate therapeutics in disease-relevant contexts. Overall, zebrafish phenotype-based screening represents a powerful and evolving tool for identifying anti-angiogenic agents and holds strong promise for accelerating the development of therapies targeting angiogenesis-related diseases.

CONFLICT OF INTEREST

The author declares no conflicts of interest related to this work.

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