



# Therapeutic Angiogenesis: From Single-Factor Failures to Precision Vascular Regeneration

Habeeb Akorede Lawal<sup>1,2</sup>, Aisha Eniola Olayiwola<sup>1,3\*</sup>, Abdulquadir Abdulhafeez<sup>4</sup>, Adedolapo Aishat Bakare<sup>5</sup>, Nimatallahi Olamide Tajudeen<sup>6</sup>, Ibrahim Ahmed Bashir<sup>2,7</sup>, Zainab Ajoke Suleiman<sup>1,8</sup>, Wahab Muiz<sup>9</sup>, Abdulrahman Olamilekan Raji<sup>1,8</sup>, Abdulmajeed Opeyemi Agboola<sup>6</sup>, Olalekan John Okesanya<sup>10,11</sup>, Olalere Oluwaseun Olaniyi<sup>12</sup>, Tolutope Adebimpe Oso<sup>10,13</sup>

## Abstract

Ischemic vascular diseases, including peripheral artery disease, chronic limb-threatening ischemia, ischemic heart disease, diabetic ulcers, and stroke, remain major causes of morbidity, mortality, disability, and healthcare expenditure worldwide. Despite significant advances in surgical and endovascular revascularization, a substantial proportion of patients remain unsuitable for conventional interventions, creating an urgent need for regenerative strategies capable of restoring tissue perfusion and promoting functional repair. Therapeutic angiogenesis, the controlled induction of new blood vessel formation, has emerged as a promising approach for addressing this unmet clinical need. However, early angiogenic therapies based primarily on single growth-factor delivery produced inconsistent clinical outcomes, highlighting the complexity of vascular regeneration and the limitations of reductionist therapeutic designs. This review critically examines the biological foundations, historical evolution, translational progress, and public health relevance of therapeutic angiogenesis. Particular emphasis is placed on recent advances in gene-based therapies, stem and progenitor cell approaches, engineered extracellular vesicles, biomaterial-assisted delivery systems, hypoxia-

responsive platforms, and metabolic and immune regulatory mechanisms that collectively shape angiogenic responses. We further discuss disease-specific applications in chronic limb-threatening ischemia, diabetic wound healing, myocardial repair, bone regeneration, and other ischemic disorders, while highlighting contexts in which angiogenic stimulation may be detrimental, such as retinal neovascular diseases. Emerging evidence indicates that successful vascular regeneration requires coordinated modulation of endothelial signaling, immune responses, extracellular matrix remodeling, metabolic adaptation, and vessel maturation rather than isolated stimulation of endothelial proliferation. Finally, we evaluate key translational challenges, including safety concerns, delivery efficiency, manufacturing scalability, patient stratification, regulatory considerations, and implementation in resource-limited settings. Collectively, current evidence suggests that next-generation, multimodal, and precision-guided angiogenic therapies may overcome historical barriers and enable clinically meaningful vascular regeneration, positioning therapeutic angiogenesis as an increasingly important component of future regenerative medicine and public health strategies.

**Keywords:** Chronic limb-threatening ischemia; extracellular vesicles; ischemic disease; peripheral artery disease; therapeutic angiogenesis.

**Significance** | Advances multimodal, precision-guided therapeutic angiogenesis strategies addressing ischemic vascular diseases, offering regenerative solutions where conventional revascularization fails, guiding future clinical translation.

\*Correspondence. Aisha Eniola Olayiwola, Faculty of Science, Department of Biochemistry, Mahidol University, Bangkok, Thailand. Division of Vaccine Design and Pharmacotherapies Development, Helix Biogen Institute, Ogbomoso, Nigeria. E-mail:

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## Author Affiliation.

- <sup>1</sup> Department of Biochemistry, Kwara State University, Malete, Nigeria.
- <sup>2</sup> Faculty of Science, Department of Biochemistry, Mahidol University, Bangkok, Thailand.
- <sup>3</sup> Division of Vaccine Design and Pharmacotherapies Development, Helix Biogen Institute, Ogbomoso, Nigeria.
- <sup>4</sup> Department of Biochemistry and Molecular Biology, Usmanu Danfodiyo University, Sokoto, Nigeria.
- <sup>5</sup> Department of Zoology and Environmental Biology, Olabisi Onabanjo University, Ago-Iwoye, Nigeria.
- <sup>6</sup> Department of Public Health Science, Kwara State University, Malete, Nigeria.
- <sup>7</sup> Faculty of Life Sciences, Department of Biochemistry, Ahmadu Bello University, Zaria, Nigeria.
- <sup>8</sup> Eagles' Research Laboratory, Ladoko Akintola University of Technology, Ogbomoso, Oyo State, Nigeria.
- <sup>9</sup> Department of Industrial Chemistry, Federal University Dutsin-Ma, Katsina State, Nigeria.
- <sup>10</sup> Department of Medical Laboratory Science, Neuropsychiatric Hospital, Aro, Abokuta, Nigeria.
- <sup>11</sup> Faculty of Medicine, Department of Public Health and Maritime Transport, University of Thessaly, Volos, Greece.
- <sup>12</sup> Institute of Parasitology, McGill University, Montreal, Quebec H3A 0G4, Canada.
- <sup>13</sup> Department of Medical Laboratory Science, McPherson University, Seriki Sotayo, Ogun State, Nigeria.

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## 1. Introduction

Ischemic vascular diseases, including peripheral artery disease (PAD), chronic limb-threatening ischemia (CLTI), ischemic heart disease, diabetic ulcers, and stroke, remain major contributors to global morbidity, mortality, disability, and healthcare expenditure (Biscetti & Flex, 2023). The increasing prevalence of aging, diabetes mellitus, obesity, and metabolic syndrome has further intensified the burden of impaired tissue perfusion and chronic ischemia, particularly in low- and middle-income countries where access to advanced vascular interventions remains limited (Jude & Wang, 2026). These challenges have renewed interest in regenerative vascular strategies capable of restoring blood flow and promoting tissue repair. Angiogenesis, the process through which new blood vessels form from pre-existing vasculature, is a tightly regulated and evolutionarily conserved mechanism essential for tissue growth, repair, oxygen delivery, and maintenance of vascular homeostasis (Larionova et al., 2021). This process is regulated by a dynamic balance between pro-angiogenic mediators—including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and the angiopoietin–Tie2 signaling axis—and endogenous inhibitors such as thrombospondin-1 and angiostatin (Izadpanah et al., 2025). Under physiological conditions, angiogenesis is spatially and temporally controlled, supporting processes such as embryogenesis, wound healing, and reproductive cycling (Dudley & Griffioen, 2023). In contrast, dysregulated or pathological angiogenesis contributes to disease progression in cancer, diabetic retinopathy, chronic inflammation, and atherosclerosis. Therapeutic angiogenesis, therefore, seeks to harness and precisely modulate this biological process to restore perfusion in ischemic tissues while minimizing the risks associated with uncontrolled vascular growth. Although early therapeutic angiogenesis trials yielded inconsistent clinical outcomes, advances in biomaterials, gene delivery systems, engineered extracellular vesicles, stem-cell-based therapies, and precision targeting technologies have renewed optimism in the field. These developments suggest that previous translational failures reflected limitations in therapeutic design and biological control rather than invalidation of angiogenesis as a regenerative strategy (Wang et al., 2025).

At the opposite end of the angiogenic spectrum are diseases characterized by insufficient vascularization, in which endogenous vascular repair mechanisms fail to adequately restore tissue perfusion, resulting in chronic ischemia and progressive tissue damage. PAD currently affects more than 230 million individuals worldwide, with prevalence continuing to rise because of aging populations, diabetes, smoking, and metabolic disease burden (Song et al., 2019). The most advanced form of PAD, chronic limb-threatening ischemia (CLTI), is associated with severe morbidity, major amputation risk, impaired quality of life, and high mortality. Contemporary epidemiological data indicate that CLTI

carries one-year mortality rates approaching 20–25% and five-year mortality exceeding 50%, comparable to or worse than many malignancies (Conte et al., 2019). Major amputation rates remain substantial, particularly among patients with diabetes mellitus, renal insufficiency, and delayed vascular intervention, with reported limb loss rates ranging from 10–40% depending on disease severity and access to care (Conte et al., 2019). Beyond mortality and limb loss, PAD and CLTI impose profound economic and healthcare-system burdens. Recurrent hospitalizations, revascularization procedures, wound management, rehabilitation, and long-term disability contribute significantly to healthcare expenditure worldwide. In the United States alone, PAD-related healthcare costs account for billions of dollars annually, with CLTI representing the most resource-intensive subgroup because of repeated admissions, infection management, and amputation-associated care (Akintoye et al., 2018). The burden is especially pronounced in low- and middle-income countries, where delayed diagnosis and limited access to vascular surgery or endovascular intervention worsen outcomes. In this context, therapeutic angiogenesis has emerged as a potentially valuable regenerative strategy aimed at improving tissue perfusion, reducing amputation risk, enhancing functional recovery, and alleviating the long-term public-health burden associated with ischemic vascular disease.

Despite early enthusiasm, initial clinical efforts in therapeutic angiogenesis, particularly those centered on single-agent VEGF delivery, failed to produce durable and clinically meaningful outcomes. However, these failures should not be interpreted as evidence that therapeutic angiogenesis is biologically invalid; rather, they revealed critical limitations in the design and implementation of first-generation strategies. Earlier approaches relied on oversimplified assumptions that administration of a single pro-angiogenic factor could adequately restore perfusion in chronically ischemic tissues, without sufficient consideration of dosage optimization, spatial localization, temporal regulation, vessel maturation, immune modulation, or patient-specific disease context. In many studies, poor delivery efficiency, transient gene expression, inadequate tissue targeting, and failure to support vascular stabilization resulted in the formation of immature or nonfunctional vessels (Peeters et al., 2024). Furthermore, the inclusion of patients with advanced-stage disease and extensive tissue fibrosis limited the regenerative capacity of ischemic tissues, thereby contributing to inconsistent therapeutic outcomes. The renewed interest in therapeutic angiogenesis during the 2024–2026 era reflects not merely technological improvement, but a broader conceptual shift in how vascular regeneration is understood and therapeutically approached. Emerging evidence now supports the view that angiogenesis is a systems-level and microenvironment-dependent process requiring coordinated regulation of endothelial signaling, inflammatory responses, metabolic adaptation,

extracellular matrix remodeling, and vessel maturation ([Sabra et al., 2021](#)). Therefore, newer therapeutic platforms are designed to address the fundamental shortcomings of earlier interventions through combinatorial and precision-oriented strategies. These include engineered extracellular vesicles (EVs) with targeted pro-angiogenic cargo, hypoxia-responsive biomaterials capable of controlled spatiotemporal factor release, advanced gene therapy vectors with tissue-specific and regulatable promoters, and mesenchymal stem/stromal cell-based therapies that exert both regenerative and immunomodulatory effects (Wang et al., 2025; Deshmukh & Chong, 2023). Collectively, these innovations represent a transition from simplistic vessel induction toward integrated vascular regeneration strategies that emphasize functionality, stability, immune compatibility, and tissue-context responsiveness. This review aims to critically evaluate the evolving landscape of therapeutic angiogenesis within the broader context of public health and translational medicine. Beyond summarizing foundational concepts, this review specifically integrates recent advances including emerging clinical and preclinical evidence involving engineered extracellular vesicles, hypoxia-responsive delivery platforms, biomaterial-assisted angiogenesis, and angiogenesis-immune-metabolic crosstalk. In addition, this review uniquely emphasizes the translational and implementation challenges associated with deploying angiogenic therapies in low-resource and high-burden healthcare settings, where the unmet need for cost-effective vascular regenerative strategies remains particularly urgent. By synthesizing historical lessons, current innovations, and public-health considerations, this review provides a more comprehensive and forward-looking framework for understanding how therapeutic angiogenesis can be optimized for safe, durable, and clinically meaningful vascular regeneration.

## 2. Conceptual and Biological Foundation

Angiogenesis occurs through two primary mechanisms: sprouting and intussusceptive angiogenesis. Sprouting angiogenesis results from endothelial sprouts extending from parental vessels, while intussusceptive angiogenesis, also known as non-sprouting microvascular growth, emerges from the splitting of existing vessels by insertion of a tissue pillar via the lumen (Ribatti & Crivellato, 2012). The stages of sprouting angiogenesis are stated to involve the activation phase, which requires vasodilation by increasing vascular permeability and activation of endothelial cells, pericytes, CD34+, and other inflammatory cells at the sprouting site. Then the sprouting phase, which involves anastomosis formation of capillary loops, migration, tubulogenesis, and proliferation of the key cellular players, and then the stabilization stage, known to be the remodelling phase, where endothelial cells become inactive, pericytes contribute to the new vessel walls, and the basement membrane is reconstructed ("Morphofunctional Basis of the

Different Types of Angiogenesis," 2017; Ribatti & Crivellato, 2012). In short, it is classified as the neovessel growth and neovessel stabilization stage.

### 2.1 Cellular and Molecular Regulators of Therapeutic Angiogenesis

- Endothelial Cell:** This is known to be the primary effector cell with the central key role in the angiogenesis process. This cell is functionally specialized into 3 distinct subtypes, which are tip cells, stalk cells, and phalanx cells. These cells specialize in the leading of sprout via filopodia, elongation, and quiescence, respectively, and are highly regulated by VEGF/VEGFR-2 signaling and DLL4/Notch signaling (Ribatti & Crivellato, 2012; "Targeting Angiogenesis and Growth Factor Pathways," 2024). Tip cells drive the process of angiogenesis in colorectal cancer. It is reported that an increase in the density of tip cells is correlated with CRC occurrence and progression ([Xie et al., 2024](#)). This also corroborates the fact that tip EC takes the lead in migration and proliferation, while stalk EC comes behind the tip.
- Pericyte:** Recruited via PDGF-B/PDGFR $\beta$ , Ang1/Tie2, TGF- $\beta$ , and ECM cues, pericytes provide vessel stability and enhance the proliferation of the sprouted tube from endothelial cells. A recent study interested in drug targets states the importance of pericytes as an angiogenesis regulator and in blood vessel functionality (Gerhardt & Betsholtz, 2003). Pericyte damage has been reported to lead to edema, diabetic retinopathy, and embryonic lethality, resulting from vessels that are hemorrhagic and hyperdilated (Bergers & Song, 2005). Pericytes are smooth muscle-like cells found in capillaries, where they regulate the morphology and functionality of the vessels ([Hellberg et al., 2010](#)).
- Macrophage and Immune Cell:** Within the angiogenic cascade — sprouting, vascular plexus modeling, and maturation — macrophages orchestrate all cascading stages (Du Cheyne et al., 2020). Macrophages are reported to take part in normal physiological processes like menstruation and the maternal-fetal interface during gestation ([Thiruchelvam et al., 2013](#)). Macrophage interactions are implicated during pathological processes; for instance, pro-inflammatory macrophage presence is regarded as a crucial component of dysregulated angiogenesis seen in atherosclerosis (Malecic & Young, 2017), and cancer progression toward malignancy is associated with macrophage-enhanced vasculature ([Williams et al., 2016](#)). The evidence above critically proves the key functional role of macrophages in angiogenesis at all cascaded stages.
- Fibroblast and Stroma Cell:** Cancer-associated fibroblasts, such as stromal myofibroblasts, are a wide-ranging source of growth factors (IL-8, VEGF, TGF- $\beta$ , PDGF, and CTGF),

extracellular matrix remodeling enzymes, and inflammatory cytokines and chemokines, which enhance tumorigenic angiogenesis ([Dong et al., 2004](#)).

- **Progenitor Cell:** The discovery of adult vasculature-forming endothelial progenitor cells has debunked the perception that vasculogenesis is restricted to embryonic development (Käßmeyer et al., 2009). Progenitors are needed to create the cell mass required for the angiogenesis process, which involves activation, neovascular growth, and contribution to the angiogenic microenvironment either directly or indirectly (Fang & Salven, 2015).

Table 1 provides an overview of different cellular and molecular regulators of therapeutic angiogenesis, including their meaning and functional roles. Evidence has proven the centralized functionality of angiogenesis, arteriogenesis, and vasculogenesis to be involved in two main opposing disorders: insufficient blood supply, as in ischemic disorders, and excessive vasculature leading to more blood supply, as in cancer, retinopathy, and other disorders (Selvapriithviraj et al., 2017; Yoo & Kwon, 2013). Angiogenesis is reported to be a therapeutic simulation of neovascularization in less vascularized tissues — essential in wound healing and ischemic injuries, but pathological in tumor progression and diabetic retinopathy (Selvapriithviraj et al., 2017; Yoo & Kwon, 2013; Semenza, 2007). Vasculogenesis, particularly in adults, involves the differentiation of bone marrow-derived progenitor endothelial stem cells to develop new blood vasculature driven by the growth factor VEGF ([Semenza, 2007](#)).

Therapeutic angiogenesis and arteriogenesis are pictured to perform similar functions, however, in different vascular structures (as seen in Table 2). Therapeutic angiogenesis involves building new microvasculature at ischemic tissue, whereas arteriogenesis involves enlargement of pre-existing collateral arteries to achieve greater bypass blood flow ([Selvapriithviraj et al., 2017](#)). The vascular structure of these two processes has played a significant role in their clinical interventions. Angiogenesis is driven by hypoxia and angiogenic factors, while arteriogenesis is triggered by shear stress, inflammation, and recruited circulating cells ([Spadaccio et al., 2022](#)). Studies have identified arteriogenesis as a clinically relevant therapeutic induction, while many human angiogenesis trials have been inconsistent and unencouraging despite extensive preclinical studies showing growth-factor-triggered effects. However, arteriogenesis may be physiologically relevant for restoring perfusion in occlusive diseases, but it is yet to be established as a reliable therapeutic induction due to limited evidence (Grundmann et al., 2007; Van Oostrom et al., 2008; Lekas et al., 2006).

### 3.0 Public Health Relevance of Therapeutic Angiogenesis

Ischemic diseases, including coronary artery disease, stroke, and peripheral artery disease (PAD), are among the deadliest causes of

death globally. Therapeutic angiogenesis offers an alternative for patients who are not candidates for standard revascularization operations. By encouraging neovascularization, it improves blood flow to ischemic regions and decreases disease burden (Giacca & Zacchigna, 2012). From a public health viewpoint, this is critical because cardiovascular illnesses account for a considerable share of mortality in low- and middle-income nations, including Nigeria.

#### 3.1 Improvement in Quality of Life and Disability Reduction

Amputations, ulceration, and persistent discomfort are common outcomes of conditions like critical limb ischemia. Restoring perfusion and preventing limb loss by therapeutic angiogenesis has been shown to improve mobility and quality of life ([Ouma et al., 2012](#)). The public health objectives of lowering years lived with disability (YLDs) and raising population productivity are in line with the reduction of disability. Regenerative medicine relies heavily on therapeutic angiogenesis, especially for wound healing and tissue engineering. It improves healing in chronic wounds like diabetic ulcers and makes it easier for engineered tissues to vascularize ([Gianni-Barrera et al., 2020](#)). By lowering long-term care expenses and hospital burden related to chronic non-healing illnesses, this has implications for improving health systems.

#### 3.2 Addressing Non-Communicable Disease (NCD) Epidemic

The need for novel treatments has increased due to the rise in NCDs, particularly diabetes and cardiovascular illnesses. Instead of treating symptoms, therapeutic angiogenesis addresses the underlying pathology, inadequate vascularization (Zachary & Morgan, 2011). Recent findings demonstrate the pleiotropic effects of angiogenic factors such as vascular endothelial growth factor (VEGF), which enhance neuronal survival and regeneration in addition to stimulating blood vessel expansion ([Shibuya, 2011](#)). This broadens its use to neurodegenerative illnesses and stroke, which are becoming more widely acknowledged as significant public health issues. Advanced gene and stem cell therapies have replaced protein-based therapies in therapeutic angiogenesis. Clinical trials have demonstrated the potential of gene transfer methods employing VEGF and other growth factors, providing focused and long-lasting therapeutic effects ([Shibuya, 2011](#)). Furthermore, cutting-edge precision medicine therapies such as bone marrow-derived cells and endothelial progenitor cells are being investigated for vascular regeneration (Murayama & Asahara, 2002). These developments support the global progress of health technology development and biomedical research. Therapeutic angiogenesis may eventually reduce healthcare expenses by lowering the necessity for costly surgical procedures (such as amputations and bypass surgery). However, issues including gene therapy costs, scalability, and accessibility continue to be important factors for decision-makers (Giacca & Zacchigna, 2012). To guarantee equal access, public health systems must assess cost-effectiveness, particularly in environments with limited resources.

Table 1: Cellular and Molecular Regulators of Therapeutic Angiogenesis: Meaning and Functions

| Term                         | Meaning                                                                    | Function                                                                                 | Reference(s)                                        |
|------------------------------|----------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-----------------------------------------------------|
| FGF                          | Fibroblast growth factor                                                   | Promotes endothelial cell growth, migration, and new vessel formation                    | (Dong et al., 2004)                                 |
| PDGF                         | Platelet-derived growth factor                                             | Recruits pericytes and smooth muscle cells; supports vessel maturation                   | (Gerhardt & Betsholtz, 2003; Hellberg et al., 2010) |
| Angiopoietin/Tie2            | Angiopoietin family and its endothelial receptor Tie2                      | Regulates vessel stability, quiescence, and remodeling                                   | (Thurston & Daly, 2012)                             |
| HIF-1α                       | Hypoxia-inducible factor 1-alpha                                           | Turns on hypoxia-response genes, including pro-angiogenic signals                        | (Ziello et al., 2007)                               |
| PI3K/AKT/eNOS                | Signaling pathway linking PI3K, AKT, and endothelial nitric oxide synthase | Supports endothelial survival, migration, and nitric oxide production                    | (Zhang et al., 2014)                                |
| Notch/Dll4                   | Notch signaling activated by Delta-like ligand 4                           | Helps specify tip vs. stalk endothelial cells during sprouting                           | (Suchting et al., 2007)                             |
| TGF-β                        | Transforming growth factor beta                                            | Controls proliferation, differentiation, extracellular matrix production, and remodeling | (Tie et al., 2022)                                  |
| Integrins and ECM remodeling | Cell-adhesion receptors and extracellular matrix changes                   | Let cells attach, migrate, and reorganize tissue during vessel growth                    | (Schwartz, 2010)                                    |

Table 2: Comparison of Angiogenesis and Arteriogenesis: Triggers, Vessel Types, Cellular Dominance, and Clinical Relevance in PAD/CLTI

| Process                                        | Trigger                                                                                                                                                        | Vessel Type                                                         | Dominant Cell                                                                                                                                 | Clinical Endpoints                                                        | Relevance to PAD/CLTI                                                                                                                                                                     |
|------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Angiogenesis</b><br>(Malhi et al., 2023)    | Hypoxia/ischemia and local pro-angiogenic signaling are impaired in PAD/CLTI                                                                                   | New capillaries/microvessels from existing endothelium              | Endothelial tip and stalk cells; in translational work, endothelial cells and angiogenic cell therapies are central                           | Microvascular sprouting, perfusion recovery, wound healing                | Major therapeutic target in PAD/CLTI, but clinical benefit has been limited; revascularization remains primary therapy                                                                    |
| <b>Arteriogenesis</b><br>(Gornik et al., 2024) | Increased shear stress/flow redistribution after arterial occlusion; collateral recruitment                                                                    | Pre-existing arterioles enlarge into functional collateral arteries | Monocytes/macrophages and vascular smooth muscle cell remodeling are key; the 2024 update treats it as a distinct revascularization mechanism | Formation of higher-conductance collateral arteries that bypass occlusion | Highly relevant in PAD because large-vessel obstruction is the core lesion; collateral growth is one route to limb salvage when revascularization is incomplete or not possible           |
| <b>Vasculogenesis</b><br>(Annex & Cooke, 2021) | Progenitor-cell recruitment and assembly of vessels; in adult ischemic disease discussed as a regenerative strategy rather than the main native repair program | De novo vessel formation/progenitor-derived microvascular networks  | Endothelial progenitor cells, stem/progenitor cells, and in some therapeutic approaches mesenchymal stem cells or angiogenic cell products    | New microvascular network formation and tissue perfusion support          | Important mainly as a regenerative or cell-therapy concept in PAD/CLTI; reviews emphasize promise, but clinical translation has been modest and no-option CLTI remains a major unmet need |

#### 4. Historical Evolution of Therapeutic Angiogenesis

The concept of therapeutic angiogenesis gained significant momentum in the late 20th and early 21st centuries, driven by the discovery of potent pro-angiogenic growth factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factors (FGFs) ([Carmeliet et al., 1996](#)). These molecules were identified as central regulators of endothelial cell proliferation, migration, and new vessel formation, leading to the hypothesis that exogenous delivery of a single angiogenic factor could restore perfusion in ischemic tissues ([Carmeliet, 2005](#)). To contextualize the historical evolution of therapeutic angiogenesis, Table 3 summarizes major milestones in the field, from the discovery of key angiogenic growth factors and early clinical trials to the translational setbacks that reshaped subsequent research directions and the recent resurgence of next-generation angiogenic platforms. As shown below, advances in delivery systems, regenerative medicine, and microenvironmental control have progressively transformed therapeutic angiogenesis from a simplistic single-factor strategy into a more integrated and precision-oriented field.

In the 1990s, seminal work demonstrated that intramuscular or local VEGF administration in rabbit or murine hindlimb-ischemia models yielded functional neo vessels and improved perfusion, generating the idea that a single pro-angiogenic factor might "rescue" ischemic tissue in humans ([Engler, 1996](#)). This early success rapidly translated into clinical trials employing recombinant proteins, plasmid DNA, and viral vectors encoding VEGF or FGF. Initial findings suggested modest improvements in perfusion and symptom relief in patients with peripheral artery disease and ischemic heart disease ([Ferrara, 2004](#)).

##### 4.1 Lessons from failed or modestly effective early trials

By the early 2000s, several randomized trials revealed that VEGF- or FGF-based monotherapy often failed to achieve meaningful benefit on primary clinical endpoints such as exercise capacity, myocardial perfusion, or major adverse cardiovascular events (Ferrara & Kerbel, 2005). For example, the VIVA (Vascular endothelial growth factor in Ischemia for Vascular Angiogenesis) and FIRST (FGF Initiating Revascularization Trial) trials in coronary disease showed only modest/inconsistent improvements, raising doubts about the strength of single-agent angiogenic therapy ([Stewart et al., 2009](#)). While some studies reported transient improvements in surrogate endpoints such as perfusion indices or exercise tolerance, these effects were often not durable or reproducible across larger populations ([Vincent et al., 2007](#)). A key lesson from these trials was that simply increasing vessel number does not necessarily translate into effective tissue perfusion, particularly when newly formed vessels are structurally immature or poorly integrated into existing vascular networks ([Henry et al., 2003](#)).

##### 4.2 Why first-generation approaches underperformed

The limited success of early therapeutic angiogenesis strategies can be attributed to a combination of biological, technical, and clinical factors. A major limitation was poor delivery efficiency, as early systems such as plasmid DNA and first-generation viral vectors exhibited low transfection rates and inadequate tissue penetration, resulting in insufficient local concentrations of angiogenic factors ([Annex, 2013](#)). Even in cases where delivery was achieved, gene and protein expression were often short-lived, producing only transient angiogenic signals that were inadequate for the formation of stable and functional vascular networks (Ferrara & Kerbel, 2005). In addition, many clinical trials suffered from inadequate patient selection, enrolling heterogeneous populations without molecular or genetic stratification, thereby masking potential therapeutic benefits in responsive subgroups ([Simons et al., 2000](#)). The challenge was further compounded by the inclusion of patients with advanced-stage disease, where extensive tissue damage, fibrosis, and impaired cellular responsiveness limited the capacity for vascular regeneration ([Annex, 2013](#)). Finally, reliance on weak or surrogate endpoints such as perfusion imaging or vessel density rather than robust clinical outcomes reduced the ability to accurately assess therapeutic efficacy and clinical relevance ([Stewart et al., 2009](#)). Collectively, these challenges revealed that early approaches were based on an oversimplified view of angiogenesis, failing to account for the complex, context-dependent, and multi-factorial nature of vascular growth.

##### 4.3 Transition to next-generation angiogenic therapeutics

The 2020s have seen a shift toward next-generation angiogenic platforms that acknowledge angiogenesis as a systems-level process requiring tight spatial, temporal, and immune-context control. Rather than relying on a single bolus of VEGF or FGF, newer strategies include:

- Controlled-release biomaterials that provide sustained, graded delivery of multiple angiogenic factors (Chu & Wang, 2012).
- Gene- and cell-based therapies engineered for longer-term expression and better targeting of ischemic microenvironments ([Moccia et al., 2021](#)).
- Combinatorial approaches that couple VEGF with angiopoietins, HGF, or other modulators to improve vessel maturity and stability (Silva & Mooney, 2010).
- Microenvironment-modulating regimens that integrate growth-factor therapy with anti-inflammatory or matrix-remodeling agents to support functional network formation rather than just capillary sprouting ([Moccia et al., 2021](#)).

Next-generation strategies incorporate advances in gene therapy, biomaterials, stem cell biology, and immunomodulation to overcome earlier limitations. For instance, engineered delivery systems now enable sustained and localized release of angiogenic

factors, while combinatorial approaches target multiple signaling pathways simultaneously to promote vessel stability and functionality ([Sabra et al., 2021](#)).

These innovations reflect a more holistic understanding of vascular regeneration, recognizing that successful therapeutic angiogenesis requires integration of endothelial, stromal, and immune components within a supportive microenvironment. Thus, the field has evolved from reductionist, single-factor interventions to multifaceted, precision-driven strategies, marking a critical transition toward more effective and clinically translatable therapies ([Henry et al., 2003](#)). To better illustrate the progression of therapeutic angiogenesis strategies over time, Table 4 provides a comparative overview of first-generation and next-generation approaches, highlighting key differences in conceptual framework, delivery systems, biological targets, and clinical performance. As shown in the table below, the field has evolved from simplistic single-factor interventions toward more sophisticated, precision-driven, and systems-level therapeutic strategies.

## 5.0 Therapeutic Strategies for Inducing Angiogenesis

Therapeutic angiogenesis has evolved from early single-factor approaches toward increasingly sophisticated, multi-modal strategies that integrate molecular, cellular, and biomaterial-based platforms. While initial efforts focused on exogenous delivery of angiogenic growth factors, inconsistent clinical outcomes have driven the development of gene-based, cell-based, and acellular systems with improved spatial and temporal control. Emerging evidence (2024–2026) strongly supports combinatorial and context-adapted approaches as the most promising direction for clinical translation ([Wang et al., 2025](#)).

### 5.1 Growth Factor-Based Therapies

Growth factor delivery represents the earliest strategy for therapeutic angiogenesis, primarily targeting endothelial cell proliferation, migration, and survival. Vascular endothelial growth factor (VEGF) is the most extensively studied angiogenic mediator. VEGF is crucial for vascular growth and a key target in therapeutic angiogenesis, but clinical trials have been disappointing due to a narrow therapeutic window and the need for sustained expression to achieve stable, persistent vessels ([Uccelli et al., 2019](#)). Fibroblast growth factor (FGF) and hepatocyte growth factor (HGF) have broader mitogenic and cytoprotective effects. FGF promotes endothelial and smooth muscle cell proliferation ([Izadpanah et al., 2025](#)), whereas HGF enhances angiogenesis via c-Met signaling and anti-apoptotic pathways ([Muppala, 2021](#)).

While VEGF signaling drives endothelial sprouting and early angiogenic expansion, it is insufficient for the formation of stable vasculature. In contrast, PDGF-B/PDGFR $\beta$  signaling mediates pericyte recruitment, proliferation, and vessel coverage, which are essential for vascular maturation and stabilization, highlighting the

necessity of coordinated multi-factor signaling in functional angiogenesis ([Izadpanah et al., 2025](#); [Li et al., 2025](#)).

### 5.2 Gene-Based Therapeutic Angiogenesis

Gene-based therapeutic angiogenesis delivers pro-angiogenic genes to ischemic tissues via platforms including plasmid DNA, adenoviral vectors, adeno-associated viruses (AAVs), mRNA systems, and emerging genome-engineering technologies to promote collateral vessel formation and tissue reperfusion ([Wang et al., 2025](#)). Plasmid DNA vectors are attractive for their low immunogenicity, favourable safety profile, and scalability, though therapeutic efficacy is often limited by low transfection efficiency and transient gene expression. In contrast, adenoviral vectors provide rapid, robust transgene expression in both dividing and non-dividing cells but are constrained by strong host immune responses and limited long-term applicability ([Aday et al., 2021](#)). AAV-based systems offer prolonged expression and improved tissue specificity, with relatively low immunogenicity; however, pre-existing anti-AAV immunity and limited cargo capacity remain translational barriers ([Wang et al., 2024](#)). More recently, mRNA-based delivery has emerged as a transient, non-integrating alternative with improved biosafety and controllable expression kinetics. In parallel, CRISPRa and epigenome-editing platforms are being explored as preclinical strategies to modulate endogenous angiogenic pathways, including HIF-1 $\alpha$  and VEGF signaling, without permanent genomic modification ([Li et al., 2025](#); [Kantor et al., 2024](#)).

Controlled gene expression systems encompass regulated transgenes, modulation of endogenous genes, tissue-specific promoters, inducible systems, epigenome editing, and synthetic genetic circuits, all under development to enable precise modulation of gene expression for therapeutic applications such as angiogenesis ([Butterfield et al., 2025](#)). A study by [Masumoto et al. \(2021\)](#) reported that hypoxia-responsive gene expression systems enable condition-dependent VEGF production, allowing precise, localized angiogenic signaling that improves vascularization and the survival of engineered tissues.

### 5.3 Cell-based therapies

Cell-based approaches aim to supply or stimulate angiogenic cells within ischemic tissues directly.

#### 5.3.1 Endothelial progenitor cells

The term endothelial progenitor cells (EPCs) remains controversial because it encompasses heterogeneous circulating and bone marrow-derived cell populations with distinct biological properties. Current classifications broadly distinguish early EPCs, also referred to as circulating angiogenic cells (CACs), which predominantly promote angiogenesis through paracrine signaling, from endothelial colony-forming cells (ECFCs), which possess robust proliferative potential and can directly contribute to endothelial lining formation and neovascularization ([Liu et al., 2024](#);

Table 3: Historical Timeline of Therapeutic Angiogenesis Development

| Period           | Major Milestone                                        | Key Advancement                                                                                                                                                        | Translational Impact                                             |
|------------------|--------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|
| 1970s–1980s      | Discovery of angiogenesis regulators                   | Identification of angiogenesis as a biologically regulated process (Sherwood et al., 1971)                                                                             | Established angiogenesis as a therapeutic target                 |
| 1989             | Discovery of VEGF                                      | VEGF identified as a potent endothelial growth factor (Leung et al., 1989)                                                                                             | Sparked interest in pro-angiogenic therapy                       |
| 1990s            | FGF and VEGF preclinical studies                       | Demonstrated improved perfusion and neovascularization in ischemic animal models (Carmeliet et al., 1996)                                                              | Generated strong optimism for clinical translation               |
| Late 1990s–2000s | Early VEGF/FGF clinical trials                         | Use of recombinant proteins, plasmids, and viral vectors in peripheral artery disease and ischemic heart disease (Rosengart et al., 1999)                              | Produced modest and inconsistent clinical outcomes               |
| 2000s            | Recognition of trial limitations                       | Poor delivery efficiency, transient expression, weak endpoint selection, and advanced disease-stage intervention identified as major barriers (Henry et al., 2003)     | Shifted focus toward systems-level angiogenic regulation         |
| 2010s            | Emergence of regenerative and combinatorial approaches | Integration of stem cells, biomaterials, controlled-release systems, and tissue engineering platforms (Silva & Mooney, 2010)                                           | Improved vessel stability, targeting, and regenerative potential |
| 2024–2026        | Resurgence of next-generation therapeutic angiogenesis | Development of HGF plasmids, engineered extracellular vesicles (EVs), immune-context modulation, and smart biomaterials for precision angiogenesis (Wang et al., 2025) | Renewed translational and clinical momentum                      |

Table 4: Comparison Between First-Generation and Next-Generation Therapeutic Angiogenesis Strategies

| Feature                | First-Generation Approaches                                                   | Next-Generation Approaches                                                          |
|------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Core Concept           | Single growth factor (e.g., VEGF, FGF) (Vincent et al., 2007)                 | Multi-factor, systems-level modulation (Peirce et al., 2004)                        |
| Delivery Method        | Plasmid DNA, early viral vectors, recombinant proteins (Filion & Popel, 2005) | Advanced viral vectors, nanoparticles, biomaterial scaffolds (Silva & Mooney, 2010) |
| Expression Profile     | Short-term, poorly controlled (Ferrara, 2004)                                 | Sustained, tunable, spatially targeted (Chu & Wang, 2012)                           |
| Biological Focus       | Endothelial cell stimulation only (Ferrara, 2004)                             | Endothelial + stromal + immune interactions (Wang et al., 2025)                     |
| Clinical Outcomes      | Modest, inconsistent, non-durable (Stewart et al., 2009)                      | Improved efficacy, emerging evidence (Moccia et al., 2021)                          |
| Patient Selection      | Broad, non-stratified (Henry et al., 2003)                                    | Biomarker-guided, precision-based (Wang et al., 2025)                               |
| Disease Stage Targeted | Often late-stage disease (Annex, 2013)                                        | Earlier intervention + regenerative window consideration (Wang et al., 2025)        |
| Therapeutic Strategy   | Monotherapy (Ferrara, 2004)                                                   | Combination therapy (genes, cells, biomaterials) (Wang et al., 2025)                |

Table 5: Combinatorial Strategies for Therapeutic Angiogenesis: Mechanisms, Outcomes, and Translational Advantages

| Combination Strategy                                       | Mechanistic Rationale                                                                        | Key Therapeutic Outcome                                                 | Translational Advantage                                          | Reference               |
|------------------------------------------------------------|----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|------------------------------------------------------------------|-------------------------|
| Cells + biomaterials                                       | Biomaterials enhance cell retention, survival, and support vascularized tissue formation     | Improved angiogenesis and tissue regeneration                           | Overcomes poor cell engraftment and microenvironment limitations | (Wang et al., 2022)     |
| EVs + scaffolds                                            | Scaffolds enable sustained and localized release of EV cargo (miRNA, proteins)               | Prolonged angiogenic signaling and enhanced tissue repair               | Improves targeting and stability of EV-based therapies           | (Zarubova et al., 2022) |
| Gene + matrix delivery                                     | Biomaterial matrices provide spatially controlled and sustained gene expression              | Enhanced angiogenesis with reduced off-target effects                   | Enables precise spatiotemporal gene regulation                   | (Zhang et al., 2024)    |
| Angiogenesis + immunomodulation                            | Modulation of immune response (e.g., macrophage polarization) enhances vascular regeneration | Reduced inflammation and improved tissue repair outcomes                | Addresses inflammatory barriers to angiogenesis                  | (Abedi et al., 2025)    |
| Angiogenesis + osteogenesis                                | Coupled vascular and bone formation pathways promote integrated tissue regeneration          | Accelerated bone healing and vascular integration                       | Critical for large bone defect repair                            | (Qin et al., 2025)      |
| Immunomodulation + osteogenesis + angiogenesis (tri-modal) | Coordinated regulation of immune, vascular, and bone pathways                                | Synergistic enhancement of regeneration and microenvironment remodeling | Represents next-generation multi-functional scaffolds            | (Wu et al., 2023)       |

Table 6: Disease-Specific Comparison of Therapeutic Angiogenesis

| Disease Area                  | Target Tissue                                                       | Preferred Platform                                                     | Primary Endpoint                                                              | Translational Maturity                                  | Major Safety Concern                                                          |
|-------------------------------|---------------------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------|-------------------------------------------------------------------------------|
| PAD / CLTI                    | Skeletal muscle; ischemic limb vasculature                          | HGF plasmid; MSCs; peripheral blood mononuclear cells                  | Amputation-free survival; ABI; TcPO <sub>2</sub> ; QoL                        | Phase II–III (HGF); Phase I–II (MSC)                    | Ectopic VEGF expression; oedema; occult tumour promotion                      |
| Diabetic Foot Ulcers          | Dermal microvascular bed; wound bed                                 | MSC-derived EVs; placenta-derived cells; secretome products            | Complete wound closure (4-week durability); amputation prevention; QoL        | Phase I–II multi-centre trials                          | Infection propagation; vessel destabilisation in neuropathic tissue           |
| Myocardial Ischemia / Post-MI | Infarcted and peri-infarct myocardium                               | Adenoviral VEGF-A isoforms (XC001); epicardial biomaterial delivery    | LVEF; myocardial perfusion reserve; MACE; QoL                                 | Phase I/II safety data; EXACT CABG ongoing              | Pathological angiogenesis in fibrotic scar; arrhythmia; vascular leakage      |
| Bone Regeneration / ONFH      | Femoral head; fracture non-union site; cortical and trabecular bone | Dual angiogenic–osteogenic scaffolds; exosome-laden acellular matrices | Radiological healing score; collapse prevention; pain; functional recovery    | Predominantly preclinical; early-phase data emerging    | Heterotopic ossification; over-vascularisation of remodelling tissue          |
| Ophthalmic (AMD / PDR)        | Retinal pigment epithelium; choroidal vasculature                   | Anti-VEGF intravitreal injection (cautionary/anti-angiogenic model)    | Visual acuity; central retinal thickness; lesion regression; injection burden | Established clinical standard; multiple approved agents | Repeated injection burden; sex-specific adverse effects; efficacy attenuation |

Hassanpour et al., 2023). ECFCs are increasingly regarded as the "true" endothelial progenitor population because of their clonogenicity and vessel-forming capacity, whereas early EPCs largely consist of hematopoietic or monocyte-derived cells that support vascular repair indirectly by secreting angiogenic mediators (Vincent et al., 2007; Tariq et al., 2024). Despite promising preclinical and translational findings in ischemic diseases, variability in EPC nomenclature, isolation protocols, donor heterogeneity, and functional characterization continues to limit standardization and clinical reproducibility in therapeutic angiogenesis.

#### 5.4 Cell-free therapies

Extracellular vesicles (EVs), including exosomes and microvesicles, are emerging as promising cell-free therapeutic platforms for angiogenesis due to their ability to transfer proteins, lipids, nucleic acids, and bioactive signaling molecules between cells (Skouras et al., 2023). Compared with live-cell therapies, EV-based approaches offer several advantages, including lower immunogenicity, improved biosafety, easier storage and scalability, reduced risk of tumorigenicity, and greater stability under inflammatory microenvironments (Claridge et al., 2021). Among these, mesenchymal stromal/stem cell-derived EVs (MSC-EVs) are the most extensively studied and exert potent pro-angiogenic, immunomodulatory, and anti-inflammatory effects through delivery of miRNAs, cytokines, and growth factors (Hassanzadeh et al., 2021). Platelet membrane-engineered EVs enhance therapeutic angiogenesis by inheriting platelet targeting ability and retaining EV pro-angiogenic potential (Li et al., 2021). Mechanistically, receptor-mediated EV uptake remains critical for therapeutic efficacy, as CD44-dependent internalization and FGFR2 activation have been shown to regulate exosome-mediated angiogenic signaling and vascular regeneration (Zhang et al., 2022).

#### 5.5 Biomaterials and tissue-engineering platforms

Biomaterials and tissue-engineering platforms play a critical role in therapeutic angiogenesis by providing structural support and enabling controlled delivery of pro-angiogenic cues. Hydrogels have emerged as versatile therapeutic platforms with immense potential for treating various diseases, due to their tunable properties and biocompatibility (Dong et al., 2025). Because of their excellent biochemical and mechanical properties, hydrogels have shown great potential for promoting angiogenesis. However, the current understanding of the mechanisms underlying the promotion of angiogenesis remains limited (Wang et al., 2024). Nanofibers composed of both natural and synthetic polymers are frequently used to integrate bioactive elements (such as bioactive glasses) and to load biomolecules (such as VEGF) that promote angiogenesis. In addition, the application of specific types of stem cells (such as endothelial progenitor cells) on nanofibrous scaffolds

is seen as a promising approach for stimulating angiogenesis (Nazarneshad et al., 2020).

Scaffolds mimic the extracellular matrix, promoting endothelial cell adhesion, migration, and vessel formation, while enhancing cell retention within ischemic tissues (Wang et al., 2022; Daghrery et al., 2023). Injectable matrices, including hydrogels, enable minimally invasive delivery and provide sustained release of bioactive factors, thereby enhancing local angiogenic responses (Wang et al., 2022). In addition, emerging stimuli-responsive biomaterials, including oxygen-sensitive systems, can dynamically respond to hypoxic microenvironments to regulate angiogenic factor release, enabling precise spatiotemporal control of vascularization (Wang et al., 2025; Jiang et al., 2025).

#### 5.6 Small molecules and metabolic reprogramming

Small-molecule and metabolic modulators represent an important adjunct strategy in therapeutic angiogenesis by targeting intracellular signaling and endothelial metabolic pathways. Activation of the PI3K/AKT-eNOS axis enhances endothelial survival, proliferation, and nitric oxide production, thereby promoting functional vascular growth (Wu et al., 2023; Han et al., 2024). In parallel, stabilization of hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) induces VEGF expression and broader angiogenic gene programs, enabling adaptive responses to ischemic stress (Wu et al., 2023). Recent research has revealed that endothelial glycolysis and lactate-mediated signaling, particularly through histone lactylation, play crucial roles in regulating angiogenic gene expression and vascular remodeling under hypoxic conditions (Zhang et al., 2019). Additional metabolic regulators, including NAD<sup>+</sup>/sirtuin signaling and mitochondrial reactive oxygen species (mtROS), play important roles in endothelial redox homeostasis, mitochondrial adaptation, and angiogenic function during vascular repair (Campagna et al., 2024; Luo et al., 2023). Emerging evidence also highlights GLP-1 receptor agonists, which improve endothelial function and angiogenesis through metabolic and anti-inflammatory mechanisms, particularly in diabetic conditions (Han et al., 2024). Additionally, nutraceutical and redox-active compounds modulate angiogenesis via oxidative stress regulation and PI3K/AKT signaling (Hedayati et al., 2025). Despite these benefits, their limited specificity necessitates integration with combinatorial therapeutic strategies.

#### 5.7 Combination strategies

Combination therapy is increasingly considered necessary in therapeutic angiogenesis because vascular regeneration requires coordinated endothelial sprouting, vessel maturation, immune modulation, extracellular matrix remodeling, and tissue-specific repair. Single-factor approaches often generate unstable or poorly perfused vessels, whereas combinatorial strategies better reproduce the complex microenvironment needed for functional neovascularization and long-term tissue regeneration (Wang et al.,

2025; Zarubova et al., 2022). The superiority of combinatorial approaches over single-modality therapies is increasingly evident, as these strategies integrate cellular, molecular, and microenvironmental cues to achieve sustained and functional angiogenesis (Table 5).

## 6.0 Disease-Specific Application

Therapeutic angiogenesis is not a one-size-fits-all intervention. Its clinical value is shaped entirely by the tissue in which it occurs, the biological cues already present, and the consequences of getting it wrong. The five disease contexts below illustrate why the same molecular signals that rescue an ischemic limb may destroy vision in the retina, and why each context demands its own risk-benefit calculus (Kukharchuk, 2024). A comparative overview of these disease areas is presented in Table 6.

### 6.1 Peripheral Artery Disease and Chronic Limb-Threatening Ischemia

Among patients with CLTI who have exhausted surgical and endovascular options, major amputation rates remain between 10% and 40%. The therapeutic objective extends beyond vessel proliferation; what is required is a perfusion-competent collateral network capable of sustaining viable tissue (Cressman et al., 2025). Plasmid-based HGF gene therapy has produced the most compelling recent data. In the Phase III HOPE-CLTI 2 trial, donaperminogene seltoplasmid achieved complete ulcer healing in 41.8% of patients at 180 days versus 15.8% for placebo ( $P < 0.0001$ ) (Di et al., 2025), while AMG0001 (Collatogene) cut median healing time from 280 to 84 days in the Phase II LGenD 1 study ( $P = 0.007$ ) (Armstrong et al., 2026). A critical caveat applies: wound closure is not limb salvage. Regulatory and clinical benchmarks now require amputation-free survival, major adverse limb events, quality of life, and mortality as primary endpoints, none of which have been met at the Phase III level for gene therapy. MSC-based approaches carry a solid safety record but inconsistent efficacy; a meta-analysis of peripheral blood mononuclear cell therapy in 256 diabetic CLTI patients reported a 15.7% annual amputation rate and a 62% healing rate (Rehak et al., 2024). Functional outcomes should be assessed through ABI, TcPO<sub>2</sub>, toe pressure, perfusion imaging, and validated quality-of-life instruments.

### 6.2 Diabetic Wounds and Ulcers

Diabetic foot ulcers present a microenvironment inherently hostile to vascular repair. Sustained hyperglycemia drives accumulation of advanced glycation end products, suppresses endothelial progenitor cell mobilization, and sustains sterile inflammation compounded by recurrent infection. Microvascular basement membrane thickening further limits oxygen exchange. No angiogenic therapy operates effectively without first addressing wound conditions — offloading, debridement, infection control,

glycemic optimization, pressure redistribution, and vascular assessment are prerequisite steps, particularly in low-resource settings where advanced therapies may be inaccessible. MSC-derived exosomes preconditioned with empagliflozin accelerate closure via the PTEN/AKT/VEGF axis (Wang et al., 2025). Hypoxia-conditioned extracellular vesicles from umbilical cord MSCs additionally promote M1-to-M2 macrophage polarization and reduce oxidative stress (Su et al., 2025). A Phase II trial of human placenta-derived cells (PDA-002) demonstrated complete closure in 38.5% versus 22.6% for placebo over four weeks (Pollak et al., 2025). The persistent gap between young, healthy animal models and complex human wounds, where neuropathy, sustained pressure, and polymicrobial infection each destabilize new vessels, remains the central translational challenge.

### 6.3 Myocardial Ischemia and Infarct Repair

Following myocardial infarction, the balance between capillary ingrowth and fibrotic remodelling determines long-term ventricular function. Insufficient angiogenesis permits infarct thinning and dilation; excessive or disorganized vessel ingrowth yields hyperpermeable, haemorrhage-prone tissue. Diabetes disrupts this balance by impairing eNOS activity, VEGF expression, and PI3K/Akt signaling, thereby reducing coronary collateral development and elevating post-infarction mortality (Guddeti et al., 2025). In this setting, angiogenesis must be evaluated against functional endpoints — left ventricular ejection fraction (LVEF), myocardial perfusion reserve, and major adverse cardiovascular events — rather than vessel density alone. The interplay between angiogenesis, progressive fibrosis, cardiomyocyte survival, and lymphangiogenesis must be addressed collectively; a capillary network embedded within a stiff collagen scar is unlikely to restore contractile function without coordinated anti-fibrotic and lymphatic support. The adenoviral vector XC001 (encoherminogene rezmadenovex), expressing three VEGF-A isoforms, demonstrated an acceptable safety profile and reductions in perfusion defect burden in Phase I/II evaluation; the ongoing EXACT CABG study is testing epicardial delivery in patients with incomplete surgical revascularization (Guddeti et al., 2025).

### 6.4 Bone Regeneration and Osteonecrosis

Bone is distinctive in that vascularization and regeneration are structurally coupled rather than merely concurrent. Osteoprogenitors, osteoblasts, and osteoclasts each depend on adequate perfusion, while endochondral ossification actively promotes angiogenic invasion. Osteonecrosis of the femoral head (ONFH), driven primarily by corticosteroid use and aging, represents a failure of this coupling, and with aging populations and rising corticosteroid prescriptions for inflammatory and autoimmune conditions, its public health burden continues to grow (Zhu et al., 2025). Contemporary preclinical strategies target angiogenesis and osteogenesis simultaneously. A magnesium-

scandium alloy scaffold activates Wnt/ $\beta$ -catenin signaling to reinforce this coupling in a rabbit model of steroid-induced ONFH ([Liang et al., 2025](#)). Acellular fishbone scaffolds loaded with hypoxia-conditioned osteogenic exosomes coordinate angiogenic and osteogenic gene programs within a shared regenerative window ([Zhu et al., 2025](#)). These dual-targeting approaches may represent the first disease-modifying option for early ONFH before structural collapse occurs, though prospective clinical validation remains necessary.

### 6.5 Ophthalmic and Neurological Cautionary Contexts

The retina offers therapeutic angiogenesis its most instructive counterexample. In neovascular age-related macular degeneration (AMD) and proliferative diabetic retinopathy, hypoxia-driven VEGF release produces structurally deficient, hyperpermeable vessels that haemorrhage and scar, destroying photoreceptors, making anti-VEGF injection the therapeutic goal rather than angiogenic induction (Le Du & Ronco, 2025). Anti-VEGF therapy is itself imperfect: repeated injection burden, progressive efficacy attenuation, and sex-specific adverse effects remain incompletely resolved (Castellana & Chiappetta, 2025). This context crystallizes the review's central principle: therapeutic angiogenesis must be compartment-specific, inducible under controlled conditions, localized to the intended ischemic target, and reversible when the clinical context demands it. Long-term safety data from systemic angiogenic programs have not demonstrated excess rates of retinal neovascularization or malignancy, yet these reassurances rest on localized delivery and rigorous post-treatment surveillance, not on uncontrolled systemic VEGF exposure. Retinal neovascular disease thus serves simultaneously as a warning against unrestricted angiogenic stimulation and as a benchmark of the spatiotemporal precision that any responsible translational program must achieve. Table 6 provides a comparison between various disease areas of therapeutic angiogenesis, affected tissue, delivery platforms, primary endpoint, translational maturity, and major adverse effects.

## 7.0 Novel and Emerging Insights

In this section an in-depth exploration of novel and emerging trends is discussed, particularly the molecular mechanisms of metabolic control of angiogenesis, engineered EVs, and immune crosstalk.

### 7.1 Metabolic control of Angiogenesis

Lactylation is regarded as a post-translational modification process stimulated by the accumulation of lactate; it regulates metabolic reprogramming and angiogenesis in many diseases. Hence, this is regarded as a promising edge to regulate angiogenic vasculature of cancer cells, diabetic retinopathy, and also accelerate the process of wound healing. Lactylation plays a significant role in liver fibrosis, carcinogenesis, invasion, metastasis, and liver disease ([Tan et al., 2025](#)). However, targeting the production and transportation

system of lactate would be a crucial therapeutic strategy. A study on diabetic myocardial infarction mouse hearts reveals that IDH2 lactylation at lysine 272 enhances the binding of Cav1 and inhibits Cav1-eNOS interactions ([Zang et al., 2025](#)). This has linked metabolic interaction as a potential therapeutic site. Corroborated by another study where a serine/glycine-free diet inhibits colorectal cancer and stimulates the accumulation of cytotoxic T cells to enhance antitumor immunity. The study also examined the effect of lactylation on programmed death-ligand 1 in tumor cells as a mechanism of immune evasion during cytotoxic T cell-mediated antitumor response following the serine/glycine-free diet ([Tong et al., 2024](#)). Mechanistically, lactate accumulation is stimulated by hypoxia and is regulated by enzymatic writers (p300, ACT1) and erasers (HDAC1 and HDAC2). Following four distinct pathways — HIF-1 $\alpha$ , IDH2, YY1, and H3K9 lactylation — lactate is regarded as not only waste; it acts as a signaling metabolite and donor for lysine lactylation that can reshape endothelial, immune, and tumor microenvironments (Zang et al., 2025; Wang et al., 2025; Wang et al., 2023; Fan et al., 2024).

### 7.2 Engineered Extracellular Vesicle and Precision Cargo delivery

Ever since researchers recognized angiogenesis as a potential remedy for ischemic tissue diseases, extracellular vesicles that stimulate the angiogenic process have been limited by their targeting capability. Studies have now opted for engineered extracellular vesicle designs, which are reported to be highly therapeutic due to their precise targeting capacity. A study reported the design of an engineered platelet-mimetic EV (p-EV) injected into a myocardial ischemic reperfusion (MI/R) mouse model. This p-EV inherited an adhesive protein and natural targeting ability toward injured vasculature from platelets, while retaining the pro-angiogenic potential of the EV ([Li et al., 2021](#)). Surface engineering is also reported to be exceptional in its targeted therapeutic potential and systemic delivery ability. Another finding by [Mentkowski et al. \(2024\)](#) reports that EVs stimulated by cardiosphere-derived cells (CDC) enhance cardiac repair, though translational biodistribution remains limited. This led to the engineering of a cardiomyocyte-binding protein onto CDC-EVs to create CMP-EVs. The surface-engineered CMP-EV was administered to mice induced with myocardial infarction using intramyocardial and intravenous delivery. Mice treated with IV-delivered CMP-EVs demonstrated a significant improvement in LVEF and a significant reduction in remote-zone cardiomyocyte apoptosis compared with placebo. Despite the promising potential of engineered EVs, the translational challenges experienced prior to clinical intervention remain low drug-loading efficiency, poor renal targeting, and batch heterogeneity. Moreover, rapid systemic clearance and off-target accumulation have been significant hurdles. Yet, scalable manufacturing solutions and regulatory

frameworks to accelerate translation are highly recommended (Dave et al., 2025; Shi et al., 2026).

### 7.3 Angiogenesis-Immune system Crosstalk

A study demonstrated the importance of infiltrated macrophages recruited at ischemic tissue following vascular injuries by femoral arterial ligation to enhance capillary and artery growth required for blood flow restoration. The study claimed infiltrated macrophages are the main source of VEGF-A required for endothelial cell recruitment and inflammatory-mediated angiogenesis and arteriogenesis (Sharma et al., 2025). This ascertained the claim that inflammation is one of the burgeoning mechanisms to examine in post-angiogenesis development (Sharma et al., 2025; Akorede Lawal et al., 2025; Morrison et al., 2014). Moreover, the study cautioned against certain paradigms that claim inflammatory macrophages suppress the angiogenesis process in wound healing, showing instead that only alternatively activated macrophages enhance the wound-healing process and vascular repair (Zhang et al., 2021). Corroborated by other findings that show M2-like macrophages derived from young mice enhance the process of neovascularization in old mice (Chen et al., 2025). Macrophages contribute to angiogenesis and arteriogenesis, but the effect depends on phenotype, timing, cytokine milieu, and tissue context. Graney et al. (2020) reported from a study conducted using transwell coculture and a 3-D tissue-engineered human blood vessel network that M1 macrophages increased vessel formation at 1 day but caused regression at 3 days, while M2a/M2c promoted pericyte differentiation genes. However, Spiller et al. (2014) found both M1 and M2 macrophages were coordinately required for scaffold vascularization, contradicting traditional M2-only paradigms.

## 8.0 Opportunities for Public Health Impacts on Therapeutic Angiogenesis

Therapeutic angiogenesis presents a transformative opportunity for public health by addressing the growing burden of ischemic diseases, chronic wounds, and degenerative conditions. Beyond clinical applications, its integration into population health strategies offers pathways for prevention, health system strengthening, and innovation-driven care delivery.

### 8.1 Expanding Treatment Access for Non-Revascularizable Patients

A major public health opportunity lies in providing treatment options for patients who are not eligible for surgical or endovascular interventions. Many individuals with peripheral artery disease (PAD) or critical limb ischemia lack suitable vessels for revascularization. Therapeutic angiogenesis via gene, protein, or cell-based therapy can stimulate collateral vessel formation and improve perfusion (Ouma et al., 2012). This expands access to life-

and limb-saving therapies, particularly in low-resource settings where advanced surgical infrastructure is limited.

### 8.2 Integration into Chronic Disease Control Programs

The increasing burden of non-communicable diseases (NCDs), especially diabetes and cardiovascular diseases, creates an opportunity to incorporate angiogenic therapies into broader public health interventions. Ischemic vascular diseases remain among the "deadliest and most disabling conditions," necessitating innovative therapeutic strategies (Chen et al., 2023). Public health programs targeting diabetes complications (e.g., diabetic foot ulcers) could integrate therapeutic angiogenesis as an adjunct to improve outcomes and reduce amputations.

### 8.3 Strengthening Wound Care and Preventive Health Systems

Therapeutic angiogenesis has significant applications in wound healing, including chronic ulcers and burns. By promoting vascularization, it accelerates tissue repair and reduces infection risks. Emerging biomaterials and growth factor delivery systems further enhance this potential (Augustine et al., 2019). From a public health perspective, this creates opportunities to reduce hospital admissions, improve community-based wound care, and decrease long-term disability.

### 8.4 Leveraging Emerging Technologies (Gene, Cell, and Nanomedicine)

Recent advances in gene therapy, stem cell therapy, and nanotechnology offer scalable opportunities for public health innovation: gene delivery systems (e.g., VEGF plasmids) enable targeted angiogenesis, stem/progenitor cell therapies enhance vascular regeneration, and nanoparticles improve controlled delivery of angiogenic factors. These technologies have shown strong potential in preclinical and translational studies, although clinical validation is ongoing (Augustine et al., 2019). Public health systems can leverage these innovations through investment in biotechnology and translational research infrastructure. Therapeutic angiogenesis offers unique opportunities for conditions with limited treatment options, such as Buerger's disease. Traditional therapies are often ineffective, leading to high amputation rates; however, gene- and cell-based angiogenic therapies have shown promise in improving perfusion and wound healing (Ribieras et al., 2022). Therapeutic angiogenesis is central to regenerative medicine, which focuses on restoring function rather than merely treating symptoms. Its integration into national health policies could encourage innovation in biomedical research, support the development of local expertise in tissue engineering, and facilitate partnerships between academia, government, and industry (Ribieras et al., 2022). Such strategies align with global health priorities for sustainable and innovative healthcare systems.

## 9.0 Clinical and Scientific Challenges

A consistent theme across recent translational and clinical studies is that the central challenge in therapeutic angiogenesis is not merely inducing vessel growth, but achieving spatiotemporal precision, functional maturation, and systemic safety. Evidence from cardiovascular, oncologic, and ophthalmologic contexts demonstrates that angiogenesis is highly context-dependent, with heterogeneous outcomes, limited durability, and potential for pathological remodelling. Notably, lessons from anti-VEGF therapy in retinal disease underscore that dysregulated angiogenesis leads to leakage-prone, unstable vasculature, reinforcing the need for controlled induction rather than maximal stimulation (Annex & Cooke, 2021; Ngo Ntjam et al., 2021). Despite advances in gene therapy, biomaterials, and extracellular vesicles, translation remains hindered by biological variability, trial inconsistency, and regulatory complexity, suggesting that future progress will depend on precision angiogenic modulation rather than generalized pro-angiogenic strategies.

### 9.1 Risk of maladaptive or off-target angiogenesis

Therapeutic angiogenesis frequently results in non-specific vascular proliferation, raising concerns about ectopic or maladaptive vessel formation. Preclinical and clinical studies show that VEGF-driven approaches can induce disorganized, tortuous, and poorly perfused vasculature, particularly when delivered systemically or without spatial control (Annex & Cooke, 2021; Dumitru & Raica, 2024). Furthermore, angiogenic signaling pathways overlap across tissues, increasing the likelihood of off-target activation in organs such as the retina or tumor microenvironments (Tiwari et al., 2022). While biomaterial-based delivery systems aim to localize effects, variability in tissue retention and diffusion kinetics remains unresolved (Gagliardi et al., 2021). These findings highlight a persistent limitation: current strategies lack sufficient targeting specificity to reliably confine angiogenesis to intended ischemic sites.

### 9.2 Cancer promotion and occult tumor risk

A major translational concern is the potential for pro-angiogenic therapies to accelerate tumor growth or activate dormant malignancies. Angiogenesis is a hallmark of cancer, and even modest increases in VEGF signaling may enhance tumor vascularization and progression (Ribatti et al., 2021). Importantly, studies in oncology demonstrate that tumors exploit angiogenic pathways with significant heterogeneity and adaptive resistance, suggesting that systemic angiogenic stimulation could unintentionally support malignant niches (Zhang et al., 2023). However, clinical evidence remains inconclusive due to limited long-term follow-up in angiogenesis trials. This creates a critical gap: the absence of robust surveillance frameworks to detect delayed oncogenic effects in treated populations.

### 9.3 Retinopathy and aberrant vascular leakage

Ocular neovascular diseases provide a cautionary paradigm, demonstrating that angiogenesis without proper regulation leads to vascular leakage, edema, and tissue damage. Anti-VEGF trials show that pathological vessels are often immature, hyperpermeable, and structurally unstable, requiring repeated intervention (Bekes & Wulff, 2019; Oronsky et al., 2012). Translationally, this raises concern that induced angiogenesis in other tissues may similarly produce non-functional or leaky vasculature, particularly in inflammatory or diabetic environments (Kolluru et al., 2012). While some studies report minimal systemic adverse events, microvascular dysfunction and permeability changes remain under-characterized, indicating a need for better functional endpoints beyond vessel density.

### 9.4 Poor durability of induced vessels

A recurring limitation across clinical trials is the transient nature of induced angiogenesis. VEGF-based therapies often produce short-lived vascular responses, with regression occurring after cessation of signaling (Annex & Cooke, 2021; Mancuso et al., 2006). Mechanistically, this reflects failure to achieve vascular maturation, including pericyte recruitment and extracellular matrix stabilization. Comparative studies suggest that multi-factor approaches (e.g., VEGF + PDGF) improve stability, yet clinical translation remains inconsistent. Furthermore, repeated dosing introduces safety and cost concerns (Tu et al., 2026). Thus, durability is not merely a biological issue but a multifactorial translational barrier involving delivery, signaling complexity, and host environment.

### 9.5 Heterogeneity of patient response

Clinical outcomes in therapeutic angiogenesis exhibit marked inter-patient variability, influenced by age, comorbidities, genetic background, and disease stage (Wang et al., 2025). For example, patients with diabetes or chronic inflammation often show impaired angiogenic responsiveness, likely due to endothelial dysfunction and altered signaling pathways. Additionally, tumor and vascular heterogeneity complicate both pro- and anti-angiogenic strategies, limiting reproducibility across trials (Liu et al., 2025). This variability underscores the inadequacy of "one-size-fits-all" approaches and highlights the need for biomarker-guided patient stratification, which remains underdeveloped in current clinical pipelines.

### 9.6 Standardization problems across trials

A major barrier to evidence synthesis is the lack of standardization in clinical trial design, including differences in delivery methods, dosing regimens, endpoints, and patient selection criteria. Reviews of angiogenesis trials reveal inconsistent outcome measures, ranging from subjective symptom improvement to imaging-based perfusion metrics (Annex & Cooke, 2021). Additionally, small sample sizes and heterogeneous populations limit statistical power and generalizability. This fragmentation has contributed to mixed

or inconclusive results, even for promising therapies (De Haro et al., 2009). Future trials should adopt harmonized clinically meaningful endpoints, including amputation-free survival, complete wound closure with durability, transcutaneous oxygen pressure, ankle-brachial index/toe pressure, perfusion imaging, pain-free walking distance, LVEF where relevant, quality of life, and long-term safety monitoring (Caradonna et al., 2025). Without harmonized protocols and validated endpoints, comparative evaluation and meta-analysis remain challenging, slowing regulatory approval and clinical adoption.

### 9.7 Regulatory complexity for biologics and engineered vesicles

Emerging angiogenic therapies, including advanced therapy medicinal products (ATMPs), biologics, gene therapies, engineered exosome/EV products, and combination products incorporating biomaterials or medical devices, face significant regulatory complexity (Bian et al., 2019). These platforms frequently blur conventional distinctions between drugs, biologics, and device-based therapeutics, resulting in inconsistent approval pathways across regulatory jurisdictions (Hanna et al., 2016; Sui et al., 2026). Regulatory agencies require rigorous demonstration of manufacturing consistency, biodistribution, potency, immunogenicity, and long-term safety, yet these parameters remain difficult to standardize for heterogeneous cell-derived products. EV-based therapies are particularly challenging because variations in isolation, cargo characterization, and storage conditions may significantly alter biological activity (Jarrige et al., 2021). In addition, combination therapies involving scaffolds or biomaterials may require dual regulatory assessment as both biologic and device products, further prolonging translational timelines. These uncertainties continue to slow clinical implementation despite encouraging preclinical efficacy.

### 9.8 Manufacturing, storage, potency, and reproducibility issues

Scaling angiogenic therapies from bench to clinic introduces significant manufacturing challenges, particularly for cell-based and vesicle-based products. Variability in cell sourcing, culture conditions, and isolation techniques leads to inconsistent potency and therapeutic efficacy (Jarrige et al., 2021). Storage and transport further affect stability, especially for biologics sensitive to temperature and handling conditions. Reproducibility remains a critical concern, as batch-to-batch variability can alter biological activity, undermining clinical reliability (Patel et al., 2025). These issues highlight the need for robust quality control frameworks and standardized production protocols, which are still evolving.

### 9.9 Ethical concerns for cell-derived products

Cell-based angiogenic therapies raise ethical and governance challenges, particularly regarding sourcing, consent, and long-term safety. The use of stem cells or genetically modified cells introduces concerns about tumorigenicity, immune reactions, and unforeseen systemic effects (Wang, 2023). Additionally, disparities in

regulatory oversight across regions complicate ethical standardization (Patel et al., 2025). These issues necessitate transparent ethical frameworks and rigorous post-marketing surveillance.

### 9.10 Cost and access inequities

Finally, the high cost of advanced angiogenic therapies, including gene therapy and biologics, poses a significant barrier to equitable access. Manufacturing complexity, regulatory requirements, and individualized treatment approaches contribute to a substantial economic burden. Evidence from regenerative medicine and extracellular vesicle therapeutics suggests that such costs may limit scalability and exacerbate healthcare disparities, particularly in low-resource settings. Without scalable and cost-effective solutions, therapeutic angiogenesis risks becoming a high-impact but low-access intervention, limiting its public health relevance.

## 10. Future Research Directions

### 10.1 Multi-omics and Single-cell Mapping of Reparative Angiogenesis:

The integration of both multi-omics and single-cell mapping provides deeper insights into specific cells having angiogenic effects, as well as combining various levels of molecular data involving genomics, transcriptomics, proteomics, and metabolomics (Subramanian et al., 2020; Traversa & Chiara, 2025). For instance, a study by Frolov et al. (2023) used RNA sequencing and ultra-high performance liquid chromatography-mass spectrometry to analyze the multi-omics data of two different endothelial cell types (human coronary endothelial cells and human internal mammary artery endothelial cells), predicted to reinforce each other's repair functionality accompanying coronary artery bypass graft surgery. However, no distinct difference was observed in the proteomics and transcriptomics profiles of these endothelial cells despite originating from different vascular beds. This showed the high potential of multi-omics to reveal different angiogenic cells involved in vascular repair; the need to integrate single-cell mapping to gain further insights into relevant subpopulation information is essential. Single-cell mapping technologies, such as single-cell RNA sequencing, have been used to uncover newly recognized specialized endothelial cells, such as aerocytes, as well as to provide novel insights into the molecular patterns of ECs in arterial, venous, and capillary beds across different organs (Wakabayashi & Naito, 2023). Further studies should investigate specific subpopulations of endothelial cells with the strongest reparative angiogenic properties and the potential of multi-omics and single-cell data to predict biomarkers of vascular regeneration.

### 10.2 Precision Angiogenesis in Diabetic and Elderly Populations:

Diabetic vasculopathy is a condition characterized by endothelial dysfunction in diabetes-associated vascular dysfunction (Zhang et al., 2012). The disruption of the endothelium in blood vessels results from metabolic disorders accompanying

diabetes mellitus, such as persistent hyperglycemia, insulin resistance, hyperinsulinemia, and excess release of free fatty acids, thereby initiating endothelial cell death, adhesion of immune cells (monocytes) to the inner membrane of blood vessels, reducing vessel relaxation ability, promoting plaque buildup (atherosclerosis), and suppressing barrier function (Zhang et al., 2012). This dysfunction results in vascular deficiency, which impedes wound-healing rates, such as in diabetic foot ulcers, highlighting the necessity of angiogenesis for tissue regeneration in diabetic wounds (Huang et al., 2025). Precision angiogenesis therapies such as stem cell therapy have been studied by Xia et al. (2024) to significantly improve wound healing in diabetic patients and elderly populations with ischemic tissue, thereby reducing amputation rates. These stem cells help promote angiogenesis, secrete growth factors, stimulate vascular differentiation, and improve collagen deposition, especially when incorporated with other therapies such as hypoxic pre-treatment and the integration of regenerative biomaterials with immunomodulatory therapies (Huang et al., 2025; Xia et al., 2024). However, they are currently limited to the preclinical phase because the type of target stem cell needed, efficacy, route of administration, and dosage are still underexplored (Xia et al., 2024), highlighting the need for further research to authenticate the safety and efficacy of this therapy. Therefore, future research should focus on investigating and identifying stem cell populations with the highest angiogenic effects and the wound-healing abilities of precision-based therapies. Also, standardized protocols guiding administration and dosage should be implemented.

**10.3 Engineered Extracellular Vesicles (EVs):** EVs are the likely next translational frontier, as recent advances in tissue bioengineering and regenerative medicine have shown their high therapeutic delivery potential. These extracellular vesicles possess the innate ability to transport proteins, nucleic acids, and lipids between cells, which enhances intercellular communication, thereby promoting tissue healing through immune system regulation, cell proliferation enhancement, and aiding remodeling processes (Shi et al., 2026; Arbade et al., 2024). EVs, especially those produced from cell-free stem cells, have been studied to have several advantages over stem cell therapy itself, including lower immunogenicity, a higher safety profile, and the ability to cross biological barriers (Shi et al., 2026; Arbade et al., 2024). A study reported that EVs are promising therapeutic tools due to their high biodistribution level, reaching the brain, which suggests that they may be promising vesicles for diseases relating to the central nervous system, among others. Another study by Guo et al. (2025) highlighted the angiogenic and cardioprotective effects of EVs in the myocardial infarction microenvironment, achieved by enhancing cardiac function, reducing infarct size, and mitigating remodeling in recovering MI patients. Hence, the use of EVs as

therapeutic tools may offer safer, more effective angiogenic effects across various diseases, given their versatility. Further research should optimize tissue specificity and biodistribution of EVs, as well as compare their therapeutic efficacy and long-term adverse effects with traditional therapies in clinical settings.

**10.4 Hybrid Biomaterial–EV–Gene Systems:** The integration of EVs with engineered biomaterials, such as hydrogels and multi-responsive intelligent dressings, has significantly enhanced the angiogenic effects of EVs (Wang et al., 2022; Yang et al., 2024). These biomaterials help modulate dynamic communication between cells, enhance the rate of wound healing in both acute and chronic conditions, and increase the half-life of EVs, resulting in more effective therapeutic outcomes (Yang et al., 2024). Although therapies involving mesenchymal stem cells and their exosomes have been discovered to be potential therapeutic tools in modulating immune responses, as well as enhancing angiogenesis and tissue repair, several limitations pose a significant threat to this approach (Rafati et al., 2026). These limitations — including low survival of transplanted stem cells, high exosome clearance rates, loss of function in severe pathological conditions, and low precision due to uncontrolled release of therapeutic molecules — are counteracted through the use of modern delivery systems such as hydrogels to enhance stability and bioavailability (Rafati et al., 2026). In a study by Han et al. (2022), the multifunctional ability of a hydrogel was described through the use of a NAGA/GelMA/Laponite/glycerol hydrogel wound dressing designed to release periosteum-derived EVs to promote angiogenesis and wound healing. Several functions, including physical barrier formation, tissue adhesion, and enhanced angiogenesis, were observed and confirmed in vivo as responsible for the improved wound-healing outcomes achieved by stimulating angiogenic processes. Hence, the use of hybrid materials combining EVs with other therapies, particularly in conditions like diabetic wounds and ischemic disease, may offer more stable and sustained vascular regeneration and tissue repair. New research should focus on determining the most functional biomaterial type with the highest EV retention and controlled release, and investigate its ability to significantly improve long-term vascular regeneration.

**10.5 AI-assisted Patient Stratification and Biomarker Discovery:** The use of AI, especially in big data analysis, has helped in understanding dysregulation and complex interactions between biological processes, such as angiogenesis and inflammation, which are significantly involved in diseases such as cardiovascular disease ("Artificial Intelligence in Advance Angiogenesis and Inflammation Research," 2024). Recently, the use of AI-based methods and algorithms (such as neural networks) has been extensively explored in wound care (diabetic foot ulcer) research, thereby improving personalized treatment outcomes in patients (Liu et al., 2025). AI enhances precision by analyzing wound image information to

classify wound type, wound depth, and wound tissue type, thereby assisting in selecting patients with feasible angiogenic potential and improving accuracy in personalized treatment (Liu et al., 2025; Garmany & Terzic, 2024). For instance, a study by [Grigorean et al. \(2026\)](#) highlighted the importance of precision regenerative strategies, which help monitor changes in the molecular and cellular components of ischemic cells over the long term. The use of emerging technologies such as glymphatic imaging, single-cell and spatial multi-omics, and extracellular vesicle profiling helps in the early identification of biomarkers in patients with a high probability of benefiting from therapeutic angiogenesis and vascular regeneration. AI-assisted biomarker discovery also helps improve specificity, reduce workload, and detect cancerous cells more accurately than radiologists' readings. A more effective advancement of AI in improving personalized cancer care involves the integration of multi-omics, imaging, and AI, although clinical translation requires better interpretation, validation, and gaining patients' trust ([Marouf et al., 2025](#)). Hence, future research should ensure improved interpretability and transparency of AI systems to enhance full adoption into precision regenerative medicine in clinical settings.

**10.6 Safety Frameworks for Long-Term Neovascular Surveillance:** Despite the significantly improved treatment outcomes of therapies such as cell and gene therapies in neurodegenerative diseases, autoimmune diseases, and cancer, the safety profiles of these therapies are often compromised in the long term due to prolonged biological activity, systemic immune engagement, and genomic alterations ([Youssef et al., 2026](#)). The importance of long-term reliability surveillance of these pharmacological therapies is illustrated in a study by [Deev et al. \(2018\)](#), where tolerability with prolonged exposure to a plasmid VEGF165-gene therapy drug for chronic lower limb ischemia was monitored over a period of five years. This long-term monitoring ascertained that the use of the plasmid VEGF165-gene therapy drug showed no significant adverse effects during this period, but rather a persistent angiogenic effect. This underscores the need for surveillance frameworks and the need to evolve from traditional surveillance models into proactive, data-driven frameworks to monitor the entire lifespan of these products (Youssef et al., 2026; Rosengart et al., 2013).

To address this gap, we propose a multilayered Long-Term Neovascular Surveillance Framework (LT-NSF), a six-component integrated system designed to monitor neovascular progression in retinal diseases such as diabetic retinopathy. This framework includes:

- **Risk Stratification:** For instance, in cases involving diabetic retinopathy, deep learning-based stratification methods show a higher level of accuracy in prioritizing retinopathy follow-ups compared to traditional clinical

methods, by identifying patients with higher progression risk ([Bora et al., 2023](#)).

- **Centralized Registry-Based Follow-Up System:** Regulated routine data collection, according to the Common Terminology Criteria for Adverse Events (CTCAE), allows the grading of the patient's diagnosis history, treatment exposure, and medical conditions, which enables the building of a centralized and standardized registry system ([Oth et al., 2022](#)). This helps generate real-world longitudinal data that can be used in long-term survivorship surveillance (e.g., detecting late-onset events).
- **Standardized Imaging Surveillance Protocols:** Aside from therapy, the use of Optical Coherence Tomography Angiography (OCTA) imaging should be incorporated into the surveillance system for quantitative detection of neovascular lesion growth, classification of disease progression, and interpretation of imaging outcomes linked to disease advancement ([Xu et al., 2018](#)).
- **Adverse Event Taxonomy for Gene/Cell Therapies:** A standardized classification system is required to categorize delayed toxicity, immune-mediated responses, off-target angiogenesis, oncogenic transformation signals, and therapy-related vascular abnormalities.
- **Pharmacovigilance and Safety Monitoring:** A longitudinal and systemic collection of both clinical and imaging data is required to detect and stratify long-term effects, treatment-based adverse effects, and individual-based therapeutic response variability in real-world applications ([Xu et al., 2018](#)).
- **Minimum 3–5 Year Structured Follow-Up Mandate:** Given the persistent biological activity of gene and cell-based interventions, a minimum follow-up period of 3–5 years is essential to capture delayed adverse events while also evaluating the long-term therapeutic durability of the product.

Therefore, further studies should investigate whether the use of a standardized registry system enables the early detection of therapy-related adverse effects and determine which molecular and imaging biomarkers best predict neovascular complications.

**10.7 Public-health implementation science for regenerative vascular therapies:** The timely and effective translation of research findings into clinical use is mostly hindered by the long-term processing of therapies, resulting in expensive healthcare services, limited effectiveness, and inequitable delivery, especially to individuals in low-resource settings (Galaviz & Barnes, 2021). To resolve these challenges, implementation science focuses on bridging evidence-based research findings to clinical use by identifying the evidence-based practice of choice, factors

influencing its use, designing implementation strategies to address barriers, and measuring the effectiveness of outcomes through adoption, implementation, and continued use (Galaviz & Barnes, 2021). The statement made by the American Heart Association on implementation science, used in a study by [Moise et al. \(2022\)](#), was structured into four steps addressing the implementation strategies noted above. In this context, implementation frameworks such as CFIR (Consolidated Framework for Implementation Research) and RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) should be employed to determine feasibility, acceptability, affordability, adoption, fidelity, scalability, and equity in clinical settings, especially in low-resource settings ([Moise et al., 2022](#)). RE-AIM helps determine how well an intervention is adopted and its efficiency in the real world, and CFIR highlights the reasons for successful implementation or failure in the adoption of a therapeutic intervention. Forward-looking research should investigate the barriers hindering the implementation of regenerative vascular therapies in low-resource settings, as well as the affordability and scalability of these interventions. From a public health and policy perspective, the future success of therapeutic angiogenesis will depend not only on scientific innovation but also on equitable accessibility, affordability, regulatory preparedness, and integration into healthcare systems, particularly in low- and middle-income countries disproportionately affected by diabetes, peripheral artery disease, chronic wounds, and ischemic complications. Policymakers, clinicians, and researchers must therefore collaborate to develop evidence-based translational frameworks, ethical governance structures, and cost-effective implementation strategies that can transform therapeutic angiogenesis from an experimental regenerative concept into a scalable and clinically impactful public health intervention.

## 11. Conclusion

Therapeutic angiogenesis has again become recognized as an effective approach for addressing diseases characterized by impaired vascularization, with relevance extending across cardiovascular, metabolic, and regenerative health contexts. Collectively, the available evidence shows that angiogenesis is not a single biological event but a tightly regulated, multistage process coordinated by endothelial activation, vessel maturation, and microenvironmental integration. The development of next-generation strategies has been informed by early limitations associated with single-factor approaches, including gene-based therapies, cell-derived products, extracellular vesicles, and biomaterial-associated delivery systems, which aim to achieve sustained and functional vascular regeneration.

Despite these advances, major challenges remain. The risk of maladaptive or off-target angiogenesis, limited durability of

induced vessels, interpatient variability, and unresolved regulatory and cost barriers continue to inhibit clinical translation. These constraints indicate that the main challenge is not merely inducing angiogenesis, but achieving precise, context-dependent vascular repair. From a public health and regenerative medicine perspective, therapeutic angiogenesis holds substantial potential to reduce disability, improve wound healing, and enhance tissue regeneration. Future progress will depend on precision-guided, scalable, and equitable approaches that align biological efficacy with real-world clinical and population health needs.

## Author contributions

H.A.L. and A.E.O. conceptualized and designed the study. A.A, A.A.B, T.O.N, I.A.B, Z.A.S, and W.B conducted the literature review. All authors wrote the first draft of the manuscript. H.A.L., A.O.R, A.O.A, O.O.O., and T.A.O. critically revised the manuscript for important intellectual content. O.J.O supervised the study. All authors have read and approved the final manuscript.

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## Competing financial interests

The authors H.A.L. et al., declare that they have no conflicts of interest

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