ACCSCIENCE PUBLISHING

Global Translational Medicine

REVIEW ARTICLE

Vascular organoids in cardiovascular medicine: From stem cell biology to precision medicine

Qiuyue Gao[1†], Caihua Long[2†], Anjun Zhong[2], and Baoqi Yu[1,3*]

[1]Department of Physiology and Pathophysiology, School of Basic Medical Sciences, Capital Medical University, Beijing, China

[2]Department of Basic Medical Sciences, School of Basic Medical Sciences, Capital Medical University, Beijing, China

[3]Department of Cardiology, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

Abstract

Cardiovascular diseases remain the leading cause of death worldwide. However, conventional therapies incompletely address disease heterogeneity, and conventional *in vitro* models do not accurately recapitulate the complex vascular microenvironment. Embryonic stem cells, induced pluripotent stem cells, and adult stem cells, including adipose-derived mesenchymal stem cells and bone marrow mesenchymal stem cells, provide a robust cellular foundation for constructing functional vascular networks through multidirectional differentiation and paracrine signaling. Advanced technologies for generating vascularized organoids, including co-culture systems, bioprinting, and growth factor modulation, have markedly enhanced organoid survival, structural stability, and physiological fidelity. These organoids have enabled the formation of functional vascular networks in multiple organ systems, including the brain, kidney, and heart, while faithfully reproducing both disease-associated pathological features and normal physiological functions. As a result, they serve as versatile platforms for investigating mechanisms of vascular disease, performing high-throughput drug screening, evaluating drug efficacy and toxicity, and developing personalized therapeutic strategies. Furthermore, vascularized organoids facilitate mechanistic studies on angiogenesis, vascular remodeling, and cell–cell interactions within physiologically relevant three-dimensional contexts, offering insights that are difficult to obtain from conventional two-dimensional cultures or animal models. This review systematically summarizes the roles of various stem cells in angiogenesis, outlines strategies for constructing vascularized organoids, and highlights their emerging applications in modeling vascular-associated diseases and regenerative therapy, providing a comprehensive reference for advancing both basic research and clinical translation in vascular medicine.

Keywords: Vascularized organoid; Stem cell; Angiogenesis; Vascular remodeling; Cardiovascular disease; Precision medicine

†*These authors contributed equally to this work.*

***Corresponding author:**
Baoqi Yu
(baoqiyu@ccmu.edu.cn)

Citation: Gao Q, Long C, Zhong A, Yu B. Vascular organoids in cardiovascular medicine: From stem cell biology to precision medicine. *Global Transl Med*. doi: 10.36922/GTM025350068

Received: August 31, 2025

Revised: December 31, 2025

Accepted: January 29, 2026

Published online: July 21, 2026

1. Introduction

Vascular lesions represent a broad spectrum of diseases characterized by structural or functional abnormalities of blood vessels. As the leading cause of death worldwide,

cardiovascular diseases account for more than 34.9% of global mortality annually.[1] According to the Global Burden of Disease study, cardiovascular diseases are among the leading contributors to global disability-adjusted life years, with major vascular disorders imposing a profound healthcare and socioeconomic burden worldwide.[2] Despite advances in pharmacological therapies, clinical treatment still faces significant challenges. Current drugs can delay disease progression or reduce the incidence of high-risk events; however, limitations remain, including incomplete understanding of disease mechanisms, insufficient long-term safety data, and variable individual responses.[3] In addition, many existing clinical and preclinical studies are subject to population-related biases, including the underrepresentation of females, younger individuals, and certain racial or ethnic groups. These limitations may further constrain the generalizability of current findings.[4]

The pathological mechanisms of vascular diseases, such as atherosclerosis, have shifted from the early hypothesis of endothelial dysfunction to complex systemic disorders involving multicellular communication networks.[5] Traditional *in vitro* models, such as two-dimensional cell culture, are overly simplified and fail to recapitulate the *in vivo* microenvironment. Similarly, animal models suffer from interspecies differences, leading to limited clinical translatability.[6]

Organoid technology offers a promising strategy to overcome these limitations. Organoids are self-organizing three-dimensional multicellular structures generated *in vitro* that can partially recapitulate the architecture and functions of their corresponding organs. The successful establishment and long-term maintenance of organoids rely heavily on pluripotent stem cells, which provide a self-renewing and multipotent cell source essential for mimicking organ development and function. The advent of human pluripotent stem cells has further advanced organoid research and regenerative medicine. Since the first derivation of human embryonic stem cells (hESCs) in 1998, their self-renewal and pluripotency have opened new avenues for disease modeling. However, ethical concerns, immune rejection, and limited availability have restricted the clinical utility of hESCs. The emergence of induced pluripotent stem cell (iPSC) technology in 2007 addressed these issues, enabling patient-specific therapies through somatic cell reprogramming. When combined with gene-editing tools such as clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9, iPSCs have greatly facilitated mechanistic studies and drug discovery.[7]

In parallel, organoid technology has expanded the applications of stem cells. Organoids derived from ESCs/iPSCs are established through developmental protocols that mimic embryogenesis, making them suitable for early developmental and disease studies. In contrast, adult stem cell-derived organoids are obtained directly from mature tissues[8]; by supplementing with niche-specific growth factors, these models can replicate tissue homeostasis, investigate normal physiological processes, and establish disease models for precision medicine. Collectively, these advances provide an integrated platform that bridges basic research and clinical translation.

This narrative review is based on targeted searches of PubMed and Web of Science, focusing on recent peer-reviewed studies relevant to vascular organoids and stem cell-based vascularization strategies.

2. Cellular basis of vasculogenesis

Pluripotent stem cells, such as ESCs and iPSCs, are key for organoid development due to their self-renewal and differentiation capabilities, with iPSCs offering ethical advantages for disease modeling and translational research. In addition to PSCs, adipose-derived mesenchymal stem cells (ASCs) maintain tissue-specific differentiation potential and can generate organoids that recapitulate the structure and function of their original tissue when cultured under defined growth factor conditions. While mesenchymal stem cells (MSCs) are rarely used as the sole cellular source for organoid formation, they are frequently integrated as supportive elements, contributing to stromal organization, paracrine signaling, and microenvironmental regulation. Notably, the choice of stem cell source not only determines organoid lineage commitment and maturation but also significantly affects the processes through which vascularization is achieved within organoids. As a result, distinct vascularization strategies are observed between PSC-derived and ASC-derived organoid systems.

Angiogenesis within organoids involves two related but distinct processes: vasculogenesis, the *de novo* formation of blood vessels from angioblasts that aggregate into a primitive vascular plexus and angiogenesis, the subsequent remodeling of these vessels through sprouting, migration, and pruning to form a functional vascular network. The balance between these mechanisms varies depending on organoid type and culture conditions. In iPSC/ESC-derived organoids (e.g., brain or cardiac organoids), mesodermal precursor cells such as angioblasts can self-organize into primitive capillary-like networks that

recapitulate key aspects of early embryonic vasculogenesis. In contrast, ASC-derived organoids (e.g., intestinal or tumor organoids) rely on pre-existing endothelial cells, which respond to vascular endothelial growth factor (VEGF) and other signaling pathways, thus resembling the angiogenic processes typically observed in adult tissues.[9]

2.1. Embryonic stem cells

Embryonic stem cells, derived from the inner cell mass, possess pluripotency and have demonstrated substantial value in regenerative medicine. Their robust trilineage differentiation potential and stable long-term expansion capacity make them particularly promising for endothelial cell generation and vascular regeneration therapies. ESCs can be directed toward endothelial lineages, with differentiation confirmed by endothelial markers such as fetal liver kinase 1 and VE-cadherin, and can form vascular sprouts under the induction of bone morphogenetic protein family members, a phenomenon confirmed to be stable and durable *in vivo*.[10,11] Park *et al.*[12] further demonstrated that hESC-derived endothelial progenitor cells (EPCs) exhibit superior proliferative and secretory functions compared to cord blood-derived EPCs.

With advances in gene-editing technologies, ESC-based strategies for angiogenesis have focused on enriching endothelial subtypes and designing immune-evasive cells. For instance, iPSC-derived $CD157^+$ endothelial cells (day 14) display enhanced angiogenic potential and improved blood flow recovery in murine ischemic models.[13] In parallel, immune-evasion designs such as beta-2-microglobulin/class II transactivator knockout combined with CD24 overexpression have shown promise in reducing transplant rejection risks in ESC-derived endothelial cells.[14] Nevertheless, the clinical application of ESCs remains constrained by several challenges, including potential immunogenicity, tumorigenic risk, as well as ethical, legal, and regulatory concerns. These limitations have further spurred interest in iPSC-based technologies as alternative approaches. Currently, most human organoid studies are not subject to the same rigorous ethical oversight frameworks that apply to embryonic or pluripotent stem cell research. However, the International Society for Stem Cell Research has recommended that institutional-level prospective ethical review, similar to embryo research oversight, should be implemented for embryo-like or complex organoid systems possessing overall developmental potential. It also underscores the importance of avoiding overstatement as these technologies advance toward clinical use.[15]

2.2. Induced pluripotent stem cells

Induced pluripotent stem cells are a class of pluripotent stem cells generated by reprogramming somatic cells, such as dermal fibroblasts.[16] This technology was pioneered by Takahashi *et al.*[17] in 2006 through the introduction of four transcription factors—Oct3/4, Sox2, Klf4, and c-Myc. Compared with ESCs, iPSCs circumvent ethical concerns and the risk of immune rejection, while also possessing unlimited expansion capacity.[18]

In terms of differentiation potential, iPSCs can give rise to all three germ layers, including endothelial cells with angiogenic functions. For example, ECs derived from porcine iPSCs have demonstrated vascularization capacity both *in vitro* and *in vivo* using Matrigel transplantation assays.[19] In tissue engineering, iPSC-derived cells, such as EPCs or co-grafting systems of endothelial cells and smooth muscle cells (SMCs), have been shown to markedly enhance neovascularization in diabetic wound models.[20] Notably, iPSC-derived microvesicles act as paracrine mediators that accelerate angiogenesis by upregulating pro-angiogenic signaling.[21] Similarly, conditioned medium from iPSCs has been reported to promote the proliferation, tube formation, and metabolic activity of human umbilical vein endothelial cells via extracellular signal-regulated kinase pathway activation, outperforming medium derived from umbilical cord MSCs.[22]

Collectively, evidence indicates that iPSCs enhance angiogenesis through multiple mechanisms, including direct cell transplantation, scaffold-based delivery, and paracrine effects. Moreover, iPSC-derived organoids are widely used for *in vitro* disease modeling. Importantly, iPSCs can differentiate into endothelial cells, pericytes, and SMCs (Figure 1), all of which are critical for angiogenesis and vascular network formation.

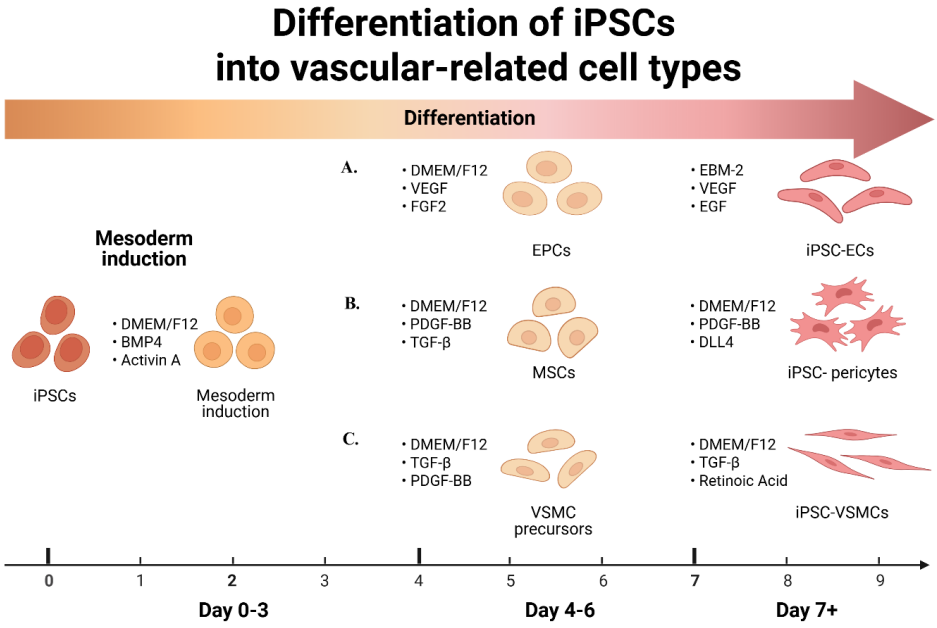

Figure 1. Differentiation of iPSCs into vascular-related cell types. This figure illustrates the differentiation of iPSCs through the mesodermal stage into three vascular-related cell types: ECs, PCs, and SMCs. All differentiation pathways start with mesoderm induction using BMP4 and Activin A.[23] (A) EC differentiation: endothelial progenitors are induced by VEGF and FGF2, followed by maturation with VEGF and EGF.[24,25] (B) Pericyte differentiation: mesenchymal stem cells are induced by PDGF-BB and TGF-β, with Notch ligands promoting maturation.[26,27] (C) SMC differentiation: progenitors are induced by TGF-β and PDGF-BB, followed by maturation with retinoic acid. Created in BioRender. Yu, B. (2026) https://BioRender.com/jpc58jk.
Abbreviations: BMP4: Bone morphogenetic protein 4; EC: Endothelial cell; EGF: Epidermal growth factor; FGF2: Fibroblast growth factor 2; iPSC: Induced pluripotent stem cell; PC: Pericyte; PDGF-BB: Platelet-derived growth factor-BB; SMC: Smooth muscle cell; TGF-β: Transforming growth factor beta; VEGF: Vascular endothelial growth factor.

2.3. Adipose-derived mesenchymal stem cells

Adipose-derived MSCs exhibit distinct therapeutic potential in angiogenesis. Owing to the lack of major histocompatibility complex class II antigen expression on their surface, they possess notable immunosuppressive properties, providing a natural advantage in allogeneic transplantation. The International Federation for Adipose Therapeutics and Science defines ASCs as a multipotent cell population with plastic adherence capacity within adipose tissue. Their discovery can be traced back to the pioneering work of Rodbell's group in the 1960s, and was further validated by Zuk *et al.*[28] in human fat aspirates in 2001. ASCs are primarily localized in the stromal vascular fraction of adipose tissue, which also contains vascular SMCs, endothelial cells, and other cellular components. Importantly, although both white and brown adipose tissues can serve as ASC sources, the derived cells differ significantly in their biological properties.[29] Compared with other stem cell types, ASCs offer several advantages, including easy accessibility, absence of ethical controversy, strong proliferative capacity *in vitro*, high genetic stability, and multipotent differentiation potential, making them highly valuable in tissue engineering and regenerative medicine.

In angiogenesis, ASCs act mainly through two complementary mechanisms: (i) direct differentiation into endothelial cells to participate in vascular construction, and (ii) paracrine secretion of pro-angiogenic factors. Transplanted ASCs not only integrate into vascular networks to form functional endothelial cells but also continuously secrete growth factors such as VEGF, transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), and hepatocyte growth factor, thereby improving blood perfusion in ischemic tissues.[30-34] Furthermore, ASC-derived exosomes carrying small RNAs (e.g., miR-21) have been shown to markedly enhance endothelial cells' angiogenic capacity.[35] Under hypoxic conditions, these exosomes further promote neovascularization through activation of the protein kinase A signaling pathway and the VEGF/VEGF-R system.[36] Collectively, these findings provide a strong theoretical basis for the clinical application of ASCs in ischemic disease therapy.

2.4. Bone marrow mesenchymal stem cells

Bone marrow (BM) is one of the primary sources of MSCs in humans. Within BM, two major stem cell populations coexist: hematopoietic stem cells, which give rise to all blood lineages, and stromal stem cells, which differentiate into adipocytes, chondrocytes, and osteocytes. BM-MSCs belong to the latter population, namely stromal stem cells, and are characterized by their remarkable multidirectional differentiation potential. They are capable of differentiating into cells of all three germ layers: ectoderm, mesoderm, and endoderm. The pioneering work of Friedenstein *et al.*[37], who first successfully isolated and characterized BM-MSCs, laid a crucial foundation for subsequent research in this field.

Bone marrow MSCs play a pivotal role in angiogenesis, particularly in promoting neovascularization and accelerating wound healing. Compared with dermal fibroblasts, BM-MSCs secrete significantly higher levels of collagen, fibroblast growth factor (FGF), and VEGF *in vitro*. Beyond their ability to directly differentiate into endothelial cells and contribute to vessel formation, BM-MSCs exert substantial paracrine effects through their secretome. They release a wide array of pro-angiogenic factors, including angiopoietin, angiopoietin-1, CXCL16, endothelin-1, FGF7, heparin-binding EGF, and pentraxin-3.[38-40] These secreted factors act on multiple vascular-associated cell types, while BM-MSC-derived exosomes provide natural targeting for precise delivery, thereby minimizing systemic side effects. Furthermore, exosomes mediate synergistic regulation of angiogenesis, anti-inflammatory responses, and antioxidative processes.[41]

3. Construction of vascularized organoids

In vivo, vascular networks are indispensable for maintaining physiological functions such as nutrient and oxygen delivery, waste clearance, and growth factor transport. In recent years, organoid technology has advanced rapidly, providing powerful platforms for studying human organ development, disease modeling, and drug screening (Figure 2). However, before organoids can be broadly applied in preclinical research and clinical translation,

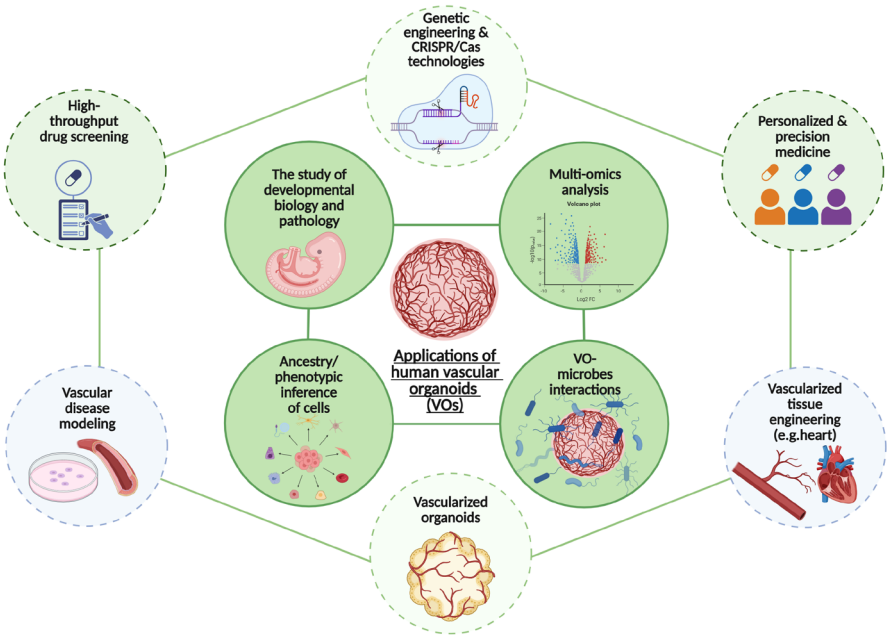

Figure 2. Key technologies and applications of vascularized organoids. This diagram outlines the principal applications and enabling technologies for vasculature-on-a-chip organoids (VOs)—miniaturized models of vascularized tissues. Enabling technologies: High-throughput drug screening, CRISPR/Cas9-based genetic engineering, and multi-omics analysis support the selection of specialized vascular cell types (e.g., endothelial cells, SMCs), optimize vascularization strategies (e.g., three-dimensional scaffold design, angiogenic factor modulation), and validate VO functionality for downstream clinical applications. Core applications: VOs provide robust *in vitro* platforms to (i) elucidate how specific vascular cell types contribute to developmental processes and pathological remodeling in vascular diseases; (ii) uncover ancestry-associated phenotypic traits of vascular cells and their influence on vascularization efficiency; (iii) explore interactions between VOs and microbes, including their effects on vascular homeostasis; and (iv) generate vascularized tissues (e.g., cardiac microtissues) by integrating defined cell type combinations with targeted vascularization strategies for disease modeling and preclinical evaluation. Created in BioRender. Yu, B. (2026) https://BioRender.com/ozvx9jh.
Abbreviations: CRISPR/Cas9: Clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9; SMCs: Smooth muscle cells.

significant challenges remain. A major limitation is the lack of intrinsic vasculature, which restricts oxygen and nutrient diffusion, leading to necrotic core formation and premature cell differentiation. Beyond this, the limited and poorly defined extracellular matrix complexity—often relying on animal-derived matrices—further restricts organoid maturation and translational applicability.[42] Thus, establishing vascularized organoids with functional vascular systems is critical for enhancing their long-term survival, recapitulating complex *in vivo* physiological processes, and facilitating clinical applications.

Induced pluripotent stem cells represent a promising cell source for *in vitro* modeling and play a central role in organoid vascularization. Current vascularization strategies can be broadly divided into four categories. First, *in vivo* implantation, in which organoids cultured *in vitro* are transplanted into immunodeficient hosts (e.g., mice or pigs), allowing host vasculature to infiltrate and establish a functional vascular network. Second, modulation of angiogenic factor expression, achieved by gene editing to enhance VEGF levels, or by manipulating physical cues such as fluid shear stress and interstitial flow within the culture environment. Third, co-culture systems, where organoids are cultured together with endothelial cells or pre-vascularized organoids to promote vascular network formation and integration. Fourth, engineering-based approaches, including organ-on-a-chip platforms for generating perfusable microvasculature to sustain organoids, or three-dimensional bioprinting to fabricate pre-designed vascular scaffolds that endow organoids with vascular functionality. Taken together, these strategies provide complementary avenues that can be strategically chosen or combined to meet diverse clinical and experimental objectives, from long-term *in vivo* functional validation, precise modulation of vascular growth, and rapid network integration, to scalable platforms for drug testing and translational research.

These emerging vascularization strategies have markedly advanced the application of organoids in fields such as disease modeling, drug discovery, and regenerative medicine.

3.1. Vascularization of brain organoids

Brain organoids are derived from the ectoderm and, due to their lack of intrinsic vasculature, face severe limitations in oxygen and nutrient diffusion during *in vitro* culture. As a result, necrotic regions typically appear after only a few months of survival.[43] Current vascularization strategies for brain organoids primarily involve two approaches: *in vivo* transplantation and *in vitro* co-culture.

Mansour *et al.*[44] demonstrated that transplanting human brain organoids into the brains of adult mice enables the establishment of vascularized, functional brain organoid models *in vivo*. Alternatively, co-culture approaches using iPSC-derived endothelial cells have been widely adopted. For instance, Pham *et al.*[45] generated vascularized brain organoids by differentiating patient-specific iPSCs into both endothelial cells and brain organoids, embedding endothelial cells with Matrigel at day 34 of organoid culture, and subsequently obtaining vascularized structures by day 54. These organoids contained neurons, astrocytes, and neural progenitor cells.[46] Upon transplantation into immunodeficient mouse brains, $CD31^+$ vessels were observed within and surrounding neural rosettes, confirming functional vascular integration.[47]

In addition, Ham *et al.*[48] reported that supplementing culture media with VEGF significantly promoted endothelial cell formation and enhanced angiogenesis in brain organoids without interfering with neuronal marker expression. Moreover, the combined administration of VEGF and Wnt7a at later differentiation stages further augmented vascularization levels. Collectively, these findings establish an essential foundation for applying vascularized brain organoids to studies of human brain development and neuropsychiatric disorders.

3.2. Vascularization of renal organoids

The kidney possesses a highly intricate vascular network that participates in blood pressure regulation, filtration, and endocrine activity.[49] Therefore, establishing vascularized kidney organoids is essential for faithfully recapitulating renal physiology. Although kidney organoids theoretically retain angiogenic potential, their practical application is still hampered by restricted vascular outgrowth and immature tubular development. To address these limitations, multiple *in vitro* vascularization strategies have been developed to promote vascular network formation in human kidney organoids. These include chip-based platforms to enhance fluid dynamics[50,51], decellularization or recellularization of extracellular matrix scaffolds[52], bioprinting, subcapsular transplantation, supplementation with VEGF, and time-dependent modulation of Wnt family member 1 (WNT1) and FGF9.[53-55]

A major breakthrough was reported by Maggiore *et al.*[49], who integrated iETV2-hiPSCs, an inducible human iPSC line expressing the transcription factor ETS translocation variant 2, which plays a key role in directing endothelial cell differentiation, into a bioreactor culture system for human kidney organoids. This approach successfully reconstructed an endothelial niche that

developed in synchrony with renal organogenesis. Their findings demonstrated that iETV2-hiPSCs can sense microenvironmental cues from developing kidney organoids, thereby generating kidney-specific vascular networks and promoting epithelial maturation.[49] Of particular significance, the newly formed endothelial network exhibited classical fenestrated ultrastructural features—namely, regularly arranged nanoscale pores on the surface of endothelial cells, which are essential for glomerular selective filtration. This achievement marks a substantial technological advance in the vascularization of renal organoids and exemplifies the co-culture strategy for organoid vascularization.

3.3. Vascularization of cardiac organoids

Research on cardiac organoids has progressed relatively slowly, owing to the complexity of cardiac development and the organ's reliance on precise structure–function relationships. As one of the most densely vascularized organs in the human body, the heart's elaborate vascular network directly reflects its exceptionally high metabolic demands. This anatomical and physiological feature dictates that the success of cardiac organoid culture *in vitro* critically depends on the degree of vascularization.

In 2020, Kupfer *et al.*[56] introduced an innovative bioink by optimizing the photocrosslinking formulation of natural extracellular matrix proteins, enabling the three-dimensional bioprinting of human iPSC-derived cardiac structures. The biomimetic construct was designed with dual chambers and fluidic channels to resemble the multi-chamber architecture of the heart. Following directed differentiation, the engineered tissue exhibited hallmark cardiac functions, including continuous action potential propagation, responsiveness to pharmacological and electrical stimulation, coordinated chamber-specific pumping, and pressure–volume loop dynamics.[56] This demonstrated the potential of biomaterials and three-dimensional printing in advancing vascularized cardiac organoid engineering.

Nevertheless, self-vascularization of cardiac organoids remains a formidable challenge due to the heart's intricate architecture and functional complexity. A major advance was achieved in 2021 by Drakhlis and colleagues[57], who embedded human pluripotent stem cell aggregates into a stromal matrix and induced cardiac differentiation using biphasic WNT pathway modulation. This approach yielded complex, highly organized three-dimensional heart-forming organoids containing endocardioid cells, septum-like vascular structures, and both anterior and posterior endodermal tissues. Importantly, these heart-forming organoids developed vascular networks with distinct spatial and molecular characteristics, representing a significant step toward modeling functional vascularized cardiac tissue *in vitro*[57] (Table 1).

Table 1. Vascularization strategies and functional characteristics of brain, kidney, and cardiac organoids

Organoid category	Organoid system	Common vascularization strategy	Vascularization efficiency and features	Functional assessment	*In vitro* longevity	References
Brain	Conventional brain organoids	No dedicated vascularization strategy; relies on host vessel ingrowth after transplantation	Delayed vascularization (typically within 2 weeks post-transplantation); low vessel density	Cell viability, neuronal maturation, synapse formation, electrophysiological activity	Several months (e.g., up to 8 months)	44,45,58-60
	Vascularized brain organoids	Co-culture with human umbilical vein endothelial cells or stem cell-derived endothelial cells	Early vascularization (within 14 days post-transplantation); higher vessel density; earlier anastomosis with host vasculature	Reduced apoptosis; enhanced electrophysiological maturation; $CD31^+$ vascular marker expression	>100 days *in vitro* (DIV)	
	Brain organoids on microfluidic chips	Dynamic nutrient and gas exchange via microfluidic systems	Markedly reduced necrotic cores; enhanced angiogenesis, neurogenesis, and corticogenesis	Improved neuronal structural continuity; stronger electrical activity; increased vascular marker expression	>120 days	

(*Cont'd...*)

Table 1. (*Continued*)

Organoid category	Organoid system	Common vascularization strategy	Vascularization efficiency and features	Functional assessment	*In vitro* longevity	References
Kidney	Renal cancer organoids	-	Vascularization promotes organoid maturation while preserving tumor proliferation and invasive capacity	Intact glomerular filtration and proximal tubule reabsorption (validated by intravital imaging window)	Not clearly defined *in vitro*; long-term maintenance after *in vivo* transplantation	61-63
	Kidney organoids	Transplantation under the renal capsule of immunodeficient mice	Vascularization facilitates maturation and formation of functional nephron-like units	Glomerular filtration and proximal tubule function validated by in vivo imaging	Limited *in vitro* culture; long-term survival and functional maturation after transplantation	
	High endothelial venule (HEV) organoids	Co-culture with fibroblastic reticular cells followed by implantation into mice	Formation of lymph node-like structures; enhanced adaptive immune responses and antitumor activity	Recruitment of antigen-presenting cells and lymphocytes; enhanced immune activation		
Heart	Self-organized cardiac organoids	Spontaneous self-assembly or induction via endothelial cell co-culture	Formation of endogenous vascular networks and chamber-like structures; recapitulates cardiac development	Spontaneous beating; calcium transients; chamber-specific gene expression; drug responses	Stable beating ≥ 8 weeks	64-72
	Engineered cardiac tissues	Co-encapsulation of cardiomyocytes and endothelial cells within biomaterial scaffolds	Scaffold-guided angiogenesis; controllable architecture with relatively low complexity	Contractile force; electrophysiological signals; cardiomyocyte maturation markers	Several weeks *in vitro*; months after transplantation	
	Heart-on-a-chip	Construction of vascularized tissues or simulation of blood flow within microfluidic channels	Precise control of microenvironment (e.g., oxygen gradients); enables functional vascularization	Real-time multiparametric monitoring (contraction, electrophysiology, metabolic consumption)	Long-term dynamic culture (weeks to months)	
	Cardiac assembloids	Assembly of cardiac organoids with vascular organoids	Functional integration of cardiac tissue with vascular networks; promotes maturation	Cell–cell interactions and activation of signaling pathways at the assembly interface	Primarily short-term studies (several weeks)	

3.4. Vascularization of other organoids

In liver organoids, vascularization is critical for promoting the coordinated development of multiple cell types, including hepatocytes, endothelial cells, bile duct cells, liver mesothelial cells, hepatic stellate cells, macrophages, mesenchymal cells, and numerous blood cell lineages. This enables liver organoids to more faithfully recapitulate human liver development and physiological functions. Velazquez *et al.*[73] demonstrated that overexpression of the *PROX1* gene enhanced angiogenic factor expression and promoted vascularization in liver organoids by systematically analyzing gene regulatory networks.[74]

Although intestinal organoids represent one of the earliest and most widely used human organoid models, their vascularization remains insufficiently explored. Using single-cell RNA sequencing, Holloway *et al.*[75] identified endothelial cell populations emerging at the early stage of intestinal organoid differentiation, which progressively declined during culture. By optimizing the culture medium to expand and preserve endothelial cell populations,

the team successfully generated vascularized intestinal organoids.[75] Beyond liver and intestine, vascularization strategies have also been applied to other tissue-specific organoids. Dailamy and colleagues[76] constructed vascularized human tissues by integrating transcription factor-mediated cellular reprogramming with chemically directed organoid differentiation. Their approach yielded neurovascular and muscular vascular organoids that preserved both neural and vascular functions for up to 45 days.[76]

4. Applications of vascular organoids in modeling and therapeutic strategies for vascular and cardiometabolic diseases

The vascular system is fundamental for maintaining body homeostasis and contributes critically to the development of various disorders, including cardiovascular and cerebrovascular diseases as well as diabetes. The onset and progression of vascular diseases are driven by multiple factors—such as cellular dysfunction, lipid accumulation, inflammatory mediators, and mechanical stress—yet current investigations still rely heavily on animal models. However, species-specific differences in genotype and phenotype restrict the translational potential of these findings. Thus, there is an urgent need for reliable *in vitro* models. The iPSC-derived blood vessel organoids (BVOs) can self-organize into three-dimensional vascular networks composed of endothelial cells, SMCs/pericytes, and basement membrane, while faithfully recapitulating disease phenotypes within pathological microenvironments. This makes BVOs a promising platform for disease modeling and drug screening (Table 2). To better recapitulate the *in vivo* vascular microenvironment, vascularized organoids are increasingly combined with microfluidic organ-on-a-chip platforms, which enable controlled perfusion, shear stress, and dynamic biochemical gradients. This integration enhances vascular maturation and improves physiological relevance, providing a more translatable platform for disease modeling and drug screening.[77]

Table 2. Applications of induced pluripotent stem cell-derived models in vascular and cardiac diseases

Disease	Method	Culture medium and growth factors	Application	References
Atherosclerosis	iPSC-ECs, iPSC-VSMCs co-cultured with macrophages in a flow system, shear stress loading in 3D fibrin hydrogel, or using a BVO (vascular organoid) model	Differentiation: VEGF, FGF2, BMP-4; Modeling: high-concentration oxidized LDL, TNF-α, IL-1β	Study plaque formation mechanism, endothelial inflammation, drug screening (e.g., lipid-lowering and anti-inflammatory drugs)	78,79
Hypertension	iPSC-VSMCs in 2D or 3D culture, with mechanical stretch stimulation or vascular tension measurement devices	Differentiation: PDGF-BB, TGF-β; Modeling: vascular tension, Ang II, endothelin-1	Study vascular contraction/relaxation function, vascular remodeling, antihypertensive drug efficacy	80
Marfan syndrome	iPSCs from patients carrying *FBN1* mutation, differentiated into VSMCs for 2D or 3D culture	Differentiation: PDGF-BB, TGF-β; Analysis: no need for additional external factors, mainly gene mutation expression itself	Study aortic aneurysm/dissection pathogenesis (e.g., abnormal TGF-β signaling, ECM remodeling); validation of gene therapy (CRISPR correction)	81

Abbreviations: 2D: Two-dimensional; 3D: Three-dimensional; Ang II: Angiotensin II; BMP-4: Bone morphogenetic protein 4; BVO: Blood vessel organoid; CRISPR: Clustered regularly interspaced short palindromic repeats; ECM: Extracellular matrix; EC: Endothelial cell; FBN1: Fibrillin-1; FGF2: Fibroblast growth factor 2; IL: Interleukin; iPSC: Induced pluripotent stem cell; LDL: Low-density lipoprotein; PDGF-BB: Platelet-derived growth factor-BB; TGF-β: Transforming growth factor beta; TNF-α: Tumor necrosis factor alpha; VEGF: Vascular endothelial growth factor; VSMC: Vascular smooth muscle cell.

4.1. Vascular diseases

Despite significant advances in pharmacological interventions for cardiovascular diseases such as atherosclerosis, hypertension, and aortic disorders, therapeutic efficacy remains constrained by individual variability and limited drug targets. Statins form the cornerstone of atherosclerosis treatment, and in 2008, Ridker and colleagues[82] demonstrated that their

low-density lipoprotein cholesterol-lowering effects significantly reduced cardiovascular events.[83] More recently, anti-inflammatory strategies have attracted attention: the interleukin 1-beta antibody canakinumab was confirmed in a 2025 meta-analysis of the CANTOS trial to reduce cardiovascular mortality.[84] With iPSC technology, Cayo and colleagues[85] showed that iPSC-derived hepatocyte-like cells could be applied to screen compounds suppressing ApoB production, such as cardiac glycosides, while iPSC-derived endothelial cells and vascular SMCs have been employed to model plaque formation and facilitate anti-inflammatory drug testing. Moreover, Kong and collaborators[86] established an atherosclerotic BVO that reproduced hallmark pathological features—including endothelial dysfunction, inflammation, foam cell formation, fibrous plaque development, and calcification—under conditions of shear stress, low-density lipoprotein exposure, pro-inflammatory cytokines, and monocyte co-culture, and further validated the model by demonstrating phenotype attenuation following lovastatin treatment.

In hypertension research, findings from the ALLHAT study[87] and subsequent work by Jamerson *et al.*[88] underscored the importance of individualized combination therapy. The iPSC vascular SMC models not only elucidate the underlying vascular pathology but also provide predictive platforms to optimize precision treatment.[89] Aortic diseases such as Marfan syndrome are characterized by vascular wall fragility due to collagen defects. While traditional therapies—such as β-blockers or TGF-β inhibitors—were shown to be effective in a 2003 animal model by Neptune *et al.*[90], subsequent clinical studies by Lacro *et al.*[91] revealed limited translational success. Patient-derived iPSC vascular SMC models of Marfan syndrome, established by Granata *et al.*[81] and Park *et al.*[92] in 2017, successfully recapitulated *FBN1* mutations, extracellular matrix degradation, and TGF-β signaling abnormalities, thereby advancing applications in regenerative medicine. Collado *et al.*[93] further leveraged iPSC models for biomarker discovery and small-molecule screening. In a complementary effort, Granata *et al.*[81] generated Marfan syndrome human iPSC-derived SMCs that recapitulated the pathological hallmarks of Marfan aortopathy. Mechanistic investigations identified pivotal roles of p38 mitogen-activated kinase and Krüppel-like factor 4 in SMC dysfunction, and notably, CRISPR-mediated correction of *FBN1* mutations partially rescued these abnormalities, highlighting potential therapeutic targets.[81,94]

Beyond disease modeling, vascular organoids offer unique advantages in drug screening and target discovery. Unlike conventional two-dimensional cell culture systems—often compromised by culture-induced mutations and cross-contamination—BVOs preserve patient-specific genetic and phenotypic characteristics. For instance, nanographene oxide demonstrated therapeutic potential in atherosclerotic BVOs by promoting macrophage polarization toward the M2 phenotype, thereby alleviating pathological vascular changes.[95] These findings underscore the utility of organoids not only in validating established therapies but also in evaluating novel biomaterials and identifying innovative therapeutic targets.

4.2. Cardiometabolic diseases

The development of cardiometabolic diseases is driven by a complex interplay of genetic predisposition and environmental influences. Lifestyle factors such as poor diet, smoking, chronic stress, and gut microbiome disturbances have all been implicated in accelerating disease progression.[82] Type 2 diabetes mellitus, now a global epidemic affecting more than 500 million people, is particularly concerning, as cardiovascular complications remain the leading cause of mortality in affected patients.[96] Mechanistically, type 2 diabetes mellitus impairs myocardial function through insulin resistance and pancreatic β-cell dysfunction. Moreover, hypertension and dyslipidemia associated with metabolic syndrome substantially increase cardiovascular risk, with endothelial nitric oxide dysfunction considered a key initiating factor in atherosclerosis.[97]

Induced pluripotent stem cell technology provides powerful new tools for investigating the mechanisms of metabolic cardiovascular diseases and identifying individualized therapeutic targets. Specifically, iPSC-derived cardiomyocytes cultured under high-glucose and hyperinsulinemic conditions have been widely employed to model cardiometabolic stress and disease-associated phenotypes. Notably, recent advances in bioelectronic materials optimized for cardiomyocyte culture have enabled precise electrical stimulation and real-time recording of cardiomyocyte electrophysiological signals. The integration of such bioelectronic platforms with iPSC-derived cardiomyocytes and vascularized organoid systems provides a promising strategy for functional assessment and early prognostic evaluation of vascular and cardiometabolic diseases.[98-100]

Induced pluripotent stem cell-derived cardiomyocytes exposed to high-glucose and hyperinsulinemic conditions successfully recapitulate the phenotype of diabetic cardiomyopathy, as demonstrated by Patel's group.[101] Using

this platform, Ng and colleagues[102] further showed that the sodium-glucose co-transporter 2 inhibitor empagliflozin ameliorates diabetes-induced cardiac dysfunction.[103] Earlier, Haffner's team[104] was the first to report that type 2 diabetes mellitus patients can develop diabetic cardiomyopathy independently of other risk factors, while Ding's group[105] further elucidated its pathogenic mechanisms, though targeted therapies remain lacking.

In the context of vascular complications, Wimmer and colleagues[106] developed a human iPSC-derived three-dimensional vascular organoid model that faithfully reproduced the pathological features of diabetic microangiopathy. In parallel, they identified neurogenic locus notch homolog protein 3–delta-like canonical Notch ligand 4-mediated endothelial–pericyte interactions as a critical mechanism driving diabetes-associated basement membrane thickening.[107] Together, these findings highlight that iPSC-derived organoids serve not only as robust platforms for mechanistic studies but also as valuable tools for therapeutic target discovery and drug screening, thereby supporting the advancement of precision medicine in cardiometabolic disorders.

5. Conclusion

This review summarizes the clinical challenges and research bottlenecks associated with vascular lesions, highlighting the innovative breakthroughs and application potential of organoid technology in this field. The multidirectional differentiation capacity of ESCs and iPSCs, combined with the paracrine synergy of ASCs and BM-MSCs, establishes a solid cellular foundation for constructing functional vascular networks. Utilizing advanced vascularized organoid engineering approaches, including co-culture, bioprinting, and growth factor modulation, researchers have effectively overcome the limitations of traditional models, markedly improving organoid longevity and physiological relevance, and providing robust platforms for mechanistic studies, efficient drug screening, and individualized precision therapy.

To date, vascularized organoids have successfully generated functional vascular networks in multiple organ systems, including the brain, kidney, and heart, and have demonstrated promising capabilities in recapitulating disease pathology and physiological function, offering substantial support for regenerative medicine applications.

Nevertheless, challenges remain in organoid vascularization: the functional maturation of vascular networks requires further enhancement, and the fidelity of complex human physiological microenvironments—such as hemodynamics and barrier properties—needs improvement. In particular, vascular organoids often lack the dynamic flow, mechanical cues, and cellular heterogeneity that are indispensable for faithfully recapitulating *in vivo* vascular physiology. Existing vascular organoids can recapitulate vascular-like structures composed of endothelial cells, a basement membrane, and periendothelial mural cells; however, these networks are typically not integrated with a functional circulatory system and lack sustained pulsatile perfusion. As a result, the terminal functional maturation of the vessel wall, which critically depends on mechanical stimuli, remains limited.[108] Recent studies have sought to overcome this limitation by using orthogonal transcription factor activation to simultaneously induce iPSCs to differentiate into endothelial and mural cell lineages, significantly improving the structural and functional maturity of vascular organoids and enabling successful revascularization in ischemic and transplantation models *in vivo*.[109] Nevertheless, substantial variability across induction strategies and culture systems persists, underscoring the need for further standardization to improve vascular network maturity and reproducibility. Moreover, long-term stability and scalability of these models remain unsolved technical hurdles. Despite the remarkable diversity and broad application potential of vascularized organoids, their clinical translation remains limited by protocol variability, batch-to-batch inconsistencies, and the lack of unified quality control standards.[110] At the regulatory level, the Food and Drug Administration Modernization Act 2.0 explicitly encourages the incorporation of non-animal models, including iPSCs, organoids, and microphysiological systems, into drug safety and efficacy evaluation frameworks, thereby establishing a policy foundation for the regulatory approval and industrial translation of organoid-based technologies. Although vascularized organoids have demonstrated considerable potential in "clinical trials-in-a-dish" and drug screening, their large-scale clinical application is anticipated to be a long-term process, necessitating further progress in standardization, reproducibility validation, and integration with existing clinical trial frameworks.[111] Future efforts should focus on systematic characterization and standardization of organoid cell composition, differentiation states, and tissue structure by high-throughput single-cell and spatial omics technologies, thereby enhancing reproducibility, cross-study comparability, and regulatory acceptability.[110]

Future studies should emphasize interdisciplinary and multi-system integration, encompassing disciplines such as stem cell biology, developmental biology, vascular physiology, biomaterials science, microfluidics, and computational modeling. For example, combining stem cell biology with microfluidic "organ-on-a-chip" systems can reproduce hemodynamic conditions, while integrating

biomaterials engineering with vascular physiology may provide scaffolds that enhance vessel maturation. Computational modeling and artificial intelligence further enable the prediction and optimization of vascular network formation. Leveraging cutting-edge technologies such as gene editing, advanced biomaterials, and artificial intelligence can optimize organoid models and accelerate their translation into personalized medicine. Equally important is the integration of immunology and metabolic science, which can refine organoid systems to better mimic inflammation, immune regulation, and metabolic cues relevant to vascular diseases. With continued advances in bioengineering and materials science, vascular organoids are poised to serve as a critical bridge between basic research and clinical practice, not only facilitating drug screening and disease modeling but also supporting regenerative strategies such as vascular grafting and patient-specific cell therapies. They offer transformative solutions and foundational technologies to tackle cardiovascular diseases and related major health challenges, and drive regenerative and precision medicine toward new frontiers.

Acknowledgments

None.

Funding

This work was supported by the National Natural Science Foundation of China (32271231) and the Open Research Fund Program of Beijing National Research Center for Information Science and Technology (Grant number: 04410306024).

Conflict of interest

Baoqi Yu serves as an Editorial Board Member for this journal, but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. The authors declare they have no competing interests.

Author contributions

Conceptualization: Qiuyue Gao, Caihua Long, Baoqi Yu
Visualization: Caihua Long, Qiuyue Gao
Writing–original draft: Qiuyue Gao, Caihua Long, Anjun Zhong
Writing–review & editing: Qiuyue Gao, Caihua Long, Baoqi Yu

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

1. Mensah GA, Fuster V, Murray CJL, Roth GA. Global Burden of Cardiovascular Diseases and Risks, 1990-2022. *J Am Coll Cardiol.* 2023;82(25):2350-2473.

   doi: 10.1016/j.jacc.2023.11.007

2. Vaduganathan M, Mensah GA, Turco JV, Fuster V, Roth GA. The Global Burden of Cardiovascular Diseases and Risk: A Compass for Future Health. *J Am Coll Cardiol.* 2022;80(25):2361-2371.

   doi: 10.1016/j.jacc.2022.11.005

3. Tsao CW, Aday AW, Almarzooq ZI, *et al.* Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association. *Circulation*. 2022;145(8):e153-e639.

   doi: 10.1161/cir.0000000000001052

4. Regitz-Zagrosek V, Gebhard C. Gender medicine: effects of sex and gender on cardiovascular disease manifestation and outcomes. *Nat Rev Cardiol.* 2023;20(4):236-247.

   doi: 10.1038/s41569-022-00797-4

5. Gusev E, Sarapultsev A. Atherosclerosis and Inflammation: Insights from the Theory of General Pathological Processes. *Int J Mol Sci.* 2023;24(9):7910.

   doi: 10.3390/ijms24097910

6. Jensen C, Teng Y. Is It Time to Start Transitioning From 2D to 3D Cell Culture? *Front Mol Biosci.* 2020;7:33.

   doi: 10.3389/fmolb.2020.00033

7. Hendriks D, Clevers H, Artegiani B. CRISPR-Cas Tools and Their Application in Genetic Engineering of Human Stem Cells and Organoids. *Cell Stem Cell*. 2020;27(5):705-731.

   doi: 10.1016/j.stem.2020.10.014

8. Hofer M, Lutolf MP. Engineering organoids. *Nat Rev Mater.* 2021;6(5):402-420.

   doi: 10.1038/s41578-021-00279-y

9. Harding A, Cortez-Toledo E, Magner NL, *et al.* Highly Efficient Differentiation of Endothelial Cells from Pluripotent Stem Cells Requires the MAPK and the PI3K Pathways. *Stem Cells*. 2017;35(4):909-919.

   doi: 10.1002/stem.2577

10. Li J, Stuhlmann H. In vitro imaging of angiogenesis using embryonic stem cell-derived endothelial cells. *Stem Cells Dev.* 2012;21(2):331-342.

    doi: 10.1089/scd.2010.0587

11. Wang ZZ, Au P, Chen T, *et al.* Endothelial cells derived from human embryonic stem cells form durable blood vessels in vivo. *Nat Biotechnol.* 2007;25(3):317-318.

doi: 10.1038/nbt1287

12. Park SJ, Moon SH, Lee HJ, *et al.* A comparison of human cord blood- and embryonic stem cell-derived endothelial progenitor cells in the treatment of chronic wounds. *Biomaterials*. 2013;34(4):995-1003.

doi: 10.1016/j.biomaterials.2012.10.039

13. Takii A, Tanabe Y, Li W, *et al.* CD157(+) vascular endothelial cells derived from human-induced pluripotent stem cells have high angiogenic potential. *Inflamm Regen.* 2025;45(1):14.

doi: 10.1186/s41232-025-00379-0

14. Choi J, Kim NG, Kong D, *et al.* Therapeutic effects of hypoimmunogenic universal human iPSC-derived endothelial cells in a humanized mouse model of peripheral artery disease. *Stem Cell Res Ther.* 2025;16(1):430.

doi: 10.1186/s13287-025-04554-5

15. Munsie M, Hyun I, Sugarman J. Ethical issues in human organoid and gastruloid research. *Development*. 2017;144(6):942-945.

doi: 10.1242/dev.140111

16. Stöberl N, Maguire E, Salis E, Shaw B, Hall-Roberts H. Human iPSC-derived glia models for the study of neuroinflammation. *J Neuroinflammation* 2023;20(1):231.

doi: 10.1186/s12974-023-02919-2

17. Takahashi K, Tanabe K, Ohnuki M, *et al.* Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell*. 2007;131(5):861-872.

doi: 10.1016/j.cell.2007.11.019

18. Pazzin DB, Previato TTR, Budelon Gonçalves JI, *et al.* Induced Pluripotent Stem Cells and Organoids in Advancing Neuropathology Research and Therapies. *Cells*. 2024;13(9):745.

doi: 10.3390/cells13090745

19. Li X, Yu Y, Wei R, *et al.* In vitro and in vivo study on angiogenesis of porcine induced pluripotent stem cell-derived endothelial cells. *Differentiation*. 2021;120:10-18.

doi: 10.1016/j.diff.2021.05.003

20. Shen YI, Cho H, Papa AE, *et al.* Engineered human vascularized constructs accelerate diabetic wound healing. *Biomaterials*. 2016;102:107-119.

doi: 10.1016/j.biomaterials.2016.06.009

21. Yan Y, Wu R, Bo Y, *et al.* Induced pluripotent stem cells-derived microvesicles accelerate deep second-degree burn wound healing in mice through miR-16-5p-mediated promotion of keratinocytes migration. *Theranostics*. 2020;10(22):9970-9983.

doi: 10.7150/thno.46639

22. Liang X, Lin F, Ding Y, *et al.* Conditioned medium from induced pluripotent stem cell-derived mesenchymal stem cells accelerates cutaneous wound healing through enhanced angiogenesis. *Stem Cell Res Ther.* 2021;12(1):295.

doi: 10.1186/s13287-021-02366-x

23. Zhang C, Shan Y, Lin H, *et al.* HBO1 determines SMAD action in pluripotency and mesendoderm specification. *Nucleic Acids Res.* 2024;52(9):4935-4949.

doi: 10.1093/nar/gkae158

24. Patsch C, Challet-Meylan L, Thoma EC, *et al.* Generation of vascular endothelial and smooth muscle cells from human pluripotent stem cells. *Nat Cell Biol.* 2015;17(8):994-1003.

doi: 10.1038/ncb3205

25. Kahn-Krell A, Pretorius D, Guragain B, *et al.* A three-dimensional culture system for generating cardiac spheroids composed of cardiomyocytes, endothelial cells, smooth-muscle cells, and cardiac fibroblasts derived from human induced-pluripotent stem cells. *Front Bioeng Biotechnol.* 2022;10:908848.

doi: 10.3389/fbioe.2022.908848

26. Campisi M, Shin Y, Osaki T, Hajal C, Chiono V, Kamm RD. 3D self-organized microvascular model of the human blood-brain barrier with endothelial cells, pericytes and astrocytes. *Biomaterials*. 2018;180:117-129.

doi: 10.1016/j.biomaterials.2018.07.014

27. Li X, Xu R, Tu X, *et al.* Differentiation of Neural Crest Stem Cells in Response to Matrix Stiffness and TGF-β1 in Vascular Regeneration. *Stem Cells Dev.* 2020;29(4):249-256.

doi: 10.1089/scd.2019.0161

28. Zuk PA, Zhu M, Mizuno H, *et al.* Multilineage cells from human adipose tissue: implications for cell-based therapies. *Tissue Eng.* 2001;7(2):211-228.

doi: 10.1089/107632701300062859

29. Nahmgoong H, Jeon YG, Park ES, *et al.* Distinct properties of adipose stem cell subpopulations determine fat depot-specific characteristics. *Cell Metab.* 2022;34(3):458-472.e6.

doi: 10.1016/j.cmet.2021.11.014

30. Pinheiro-Machado E, Koster C, Smink A. Modulating adipose-derived stromal cells' secretomes by culture conditions: effects on angiogenesis, collagen deposition, and immunomodulation. *Biosci Rep.* 2025;45(5):325-342.

doi: 10.1042/bsr20241389

31. Pu CM, Liu CW, Liang CJ, *et al.* Adipose-Derived Stem Cells Protect Skin Flaps against Ischemia/Reperfusion Injury via IL-6 Expression. *J Investig Dermatol.* 2017;137(6):1353-1362.

doi: 10.1016/j.jid.2016.12.030

32. Moriyama M, Sahara S, Zaiki K, *et al.* Adipose-derived stromal/stem cells improve epidermal homeostasis. *Sci Rep.*

2019;9(1):18371.

doi: 10.1038/s41598-019-54797-5

33. Rautiainen S, Laaksonen T, Koivuniemi R. Angiogenic Effects and Crosstalk of Adipose-Derived Mesenchymal Stem/Stromal Cells and Their Extracellular Vesicles with Endothelial Cells. *Int J Mol Sci.* 2021;22(19):10890.

doi: 10.3390/ijms221910890

34. Lopatina T, Bruno S, Tetta C, Kalinina N, Porta M, Camussi G. Platelet-derived growth factor regulates the secretion of extracellular vesicles by adipose mesenchymal stem cells and enhances their angiogenic potential. *Cell Commun Signal.* 2014;12(1):26.

doi: 10.1186/1478-811x-12-26

35. Wang H, Bai Z, Qiu Y, *et al.* Empagliflozin-Pretreated MSC-Derived Exosomes Enhance Angiogenesis and Wound Healing via PTEN/AKT/VEGF Pathway. *Int J Nanomed.* 2025;20:5119-5136.

doi: 10.2147/ijn.S512074

36. Xue C, Shen Y, Li X, *et al.* Exosomes Derived from Hypoxia-Treated Human Adipose Mesenchymal Stem Cells Enhance Angiogenesis Through the PKA Signaling Pathway. *Stem Cells Dev.* 2018;27(7):456-465.

doi: 10.1089/scd.2017.0296

37. Friedenstein AJ, Piatetzky-Shapiro II, Petrakova KV. Osteogenesis in transplants of bone marrow cells. *Development*. 1966;16(3):381-390.

doi: 10.1242/dev.16.3.381

38. Han SK, Yoon TH, Lee DG, Lee MA, Kim WK. Potential of human bone marrow stromal cells to accelerate wound healing in vitro. *Ann Plast Surg.* 2005;55(4):414-419.

doi: 10.1097/01.sap.0000178809.01289.10

39. Cui B, Zhang C, Gan B, *et al.* Collagen-tussah silk fibroin hybrid scaffolds loaded with bone mesenchymal stem cells promote skin wound repair in rats. *Mater Sci Eng C.* 2020;109:110611.

doi: 10.1016/j.msec.2019.110611

40. Watt SM, Gullo F, van der Garde M, *et al.* The angiogenic properties of mesenchymal stem/stromal cells and their therapeutic potential. *Br Med Bull.* 2013;108(1):25-53.

doi: 10.1093/bmb/ldt031

41. Yu L, Qin J, Xing J, *et al.* The mechanisms of exosomes in diabetic foot ulcers healing: a detailed review. *J Mol Med.* 2023;101(10):1209-1228.

doi: 10.1007/s00109-023-02357-w

42. Gjorevski N, Sachs N, Manfrin A, *et al.* Designer matrices for intestinal stem cell and organoid culture. *Nature*. 2016;539(7630):560-564.

doi: 10.1038/nature20168

43. Li M, Gao L, Zhao L, Zou T, Xu H. Toward the next generation of vascularized human neural organoids. *Med Res Rev.* 2023;43(1):31-54.

doi: 10.1002/med.21922

44. Mansour AA, Gonçalves JT, Bloyd CW, *et al.* An in vivo model of functional and vascularized human brain organoids. *Nat Biotechnol.* 2018;36(5):432-441.

doi: 10.1038/nbt.4127

45. Pham MT, Pollock KM, Rose MD, *et al.* Generation of human vascularized brain organoids. *Neuroreport*. 2018;29(7):588-593.

doi: 10.1097/wnr.0000000000001014

46. Sabogal-Guáqueta AM, Marmolejo-Garza A, de Pádua VP, Eggen B, Boddeke E, Dolga AM. Microglia alterations in neurodegenerative diseases and their modeling with human induced pluripotent stem cell and other platforms. *Prog Neurobiol.* 2020;190:101805.

doi: 10.1016/j.pneurobio.2020.101805

47. Matsui TK, Tsuru Y, Hasegawa K, Kuwako KI. Vascularization of human brain organoids. *Stem Cells*. 2021;39(8):1017-1024.

doi: 10.1002/stem.3368

48. Ham O, Jin YB, Kim J, Lee MO. Blood vessel formation in cerebral organoids formed from human embryonic stem cells. *Biochem Biophys Res Commun.* 2020;521(1):84-90.

doi: 10.1016/j.bbrc.2019.10.079

49. Maggiore JC, LeGraw R, Przepiorski A, *et al.* A genetically inducible endothelial niche enables vascularization of human kidney organoids with multilineage maturation and emergence of renin expressing cells. *Kidney Int.* 2024;106(6):1086-1100.

doi: 10.1016/j.kint.2024.05.026

50. Gabbin B, Meraviglia V, Angenent ML, *et al.* Heart and kidney organoids maintain organ-specific function in a microfluidic system. *Mater Today Bio*. 2023;23:100818.

doi: 10.1016/j.mtbio.2023.100818

51. Bas-Cristóbal Menéndez A, Du Z, van den Bosch TPP, *et al.* Creating a kidney organoid-vasculature interaction model using a novel organ-on-chip system. *Sci Rep.* 2022;12(1):20699.

doi: 10.1038/s41598-022-24945-5

52. Kim JW, Nam SA, Yi J, *et al.* Kidney Decellularized Extracellular Matrix Enhanced the Vascularization and Maturation of Human Kidney Organoids. *Adv Sci.* 2022;9(15):e2103526.

doi: 10.1002/advs.202103526

53. Kolesky DB, Truby RL, Gladman AS, Busbee TA, Homan KA, Lewis JA. 3D bioprinting of vascularized, heterogeneous

cell-laden tissue constructs. *Adv Mater.* 2014;26(19):3124-3130.

doi: 10.1002/adma.201305506

54. Koning M, Dumas SJ, Avramut MC, *et al.* Vasculogenesis in kidney organoids upon transplantation. *npj Regen Med.* 2022;7(1):40.

doi: 10.1038/s41536-022-00237-4

55. Low JH, Li P, Chew EGY, *et al.* Generation of Human PSC-Derived Kidney Organoids with Patterned Nephron Segments and a De Novo Vascular Network. *Cell Stem Cell.* 2019;25(3):373-387.e9.

doi: 10.1016/j.stem.2019.06.009

56. Kupfer ME, Lin WH, Ravikumar V, *et al.* In Situ Expansion, Differentiation, and Electromechanical Coupling of Human Cardiac Muscle in a 3D Bioprinted, Chambered Organoid. *Circ Res.* 2020;127(2):207-224.

doi: 10.1161/circresaha.119.316155

57. Drakhlis L, Biswanath S, Farr CM, *et al.* Human heart-forming organoids recapitulate early heart and foregut development. *Nat Biotechnol.* 2021;39(6):737-746.

doi: 10.1038/s41587-021-00815-9

58. Shi Y, Sun L, Wang M, *et al.* Vascularized human cortical organoids (vOrganoids) model cortical development in vivo. *PLoS Biol.* 2020;18(5):e3000705.

doi: 10.1371/journal.pbio.3000705

59. Cho AN, Jin Y, An Y, *et al.* Microfluidic device with brain extracellular matrix promotes structural and functional maturation of human brain organoids. *Nat Commun.* 2021;12(1):4730.

doi: 10.1038/s41467-021-24775-5

60. Wang Y, Wang L, Guo Y, Zhu Y, Qin J. Engineering stem cell-derived 3D brain organoids in a perfusable organ-on-a-chip system. *RSC Adv.* 2018;8(3):1677-1685.

doi: 10.1039/c7ra11714k

61. van den Berg CW, Ritsma L, Avramut MC, *et al.* Renal Subcapsular Transplantation of PSC-Derived Kidney Organoids Induces Neo-vasculogenesis and Significant Glomerular and Tubular Maturation In Vivo. *Stem Cell Rep.* 2018;10(3):751-765.

doi: 10.1016/j.stemcr.2018.01.041

62. van den Berg CW, Koudijs A, Ritsma L, Rabelink TJ. In Vivo Assessment of Size-Selective Glomerular Sieving in Transplanted Human Induced Pluripotent Stem Cell-Derived Kidney Organoids. *J Am Soc Nephrol.* 2020;31(5):921-929.

doi: 10.1681/asn.2019060573

63. Wang X, Li X, Zhao J, *et al.* Rapid Generation of hPSC-Derived High Endothelial Venule Organoids with In Vivo Ectopic Lymphoid Tissue Capabilities. *Adv Mater.* 2024;36(15):e2308760.

doi: 10.1002/adma.202308760

64. Wu HF, Saito-Diaz K, Huang CW, *et al.* Parasympathetic neurons derived from human pluripotent stem cells model human diseases and development. *Cell Stem Cell.* 2024;31(5):734-753.e8.

doi: 10.1016/j.stem.2024.03.011

65. Yang J, Lei W, Xiao Y, *et al.* Generation of human vascularized and chambered cardiac organoids for cardiac disease modelling and drug evaluation. *Cell Prolif.* 2024;57(8):e13631.

doi: 10.1111/cpr.13631

66. Hitscherich PG, Xie LH, Del Re D, Lee EJ. The effects of macrophages on cardiomyocyte calcium-handling function using in vitro culture models. *Physiol Rep.* 2019;7(13):e14137.

doi: 10.14814/phy2.14137

67. Jian Y, Zhou X, Shan W, *et al.* Crosstalk between macrophages and cardiac cells after myocardial infarction. *Cell Commun Signal.* 2023;21(1):109.

doi: 10.1186/s12964-023-01105-4

68. Kerkering J, Muinjonov B, Rosiewicz KS, *et al.* iPSC-derived reactive astrocytes from patients with multiple sclerosis protect cocultured neurons in inflammatory conditions. *J Clin Investig.* 2023;133(13).

doi: 10.1172/jci164637

69. Van Lent J, Prior R, Pérez Siles G, *et al.* Advances and challenges in modeling inherited peripheral neuropathies using iPSCs. *Exp Mol Med.* 2024;56(6):1348-1364.

doi: 10.1038/s12276-024-01250-x

70. Sharma A, Sances S, Workman MJ, Svendsen CN. Multi-lineage Human iPSC-Derived Platforms for Disease Modeling and Drug Discovery. *Cell Stem Cell.* 2020;26(3):309-329.

doi: 10.1016/j.stem.2020.02.011

71. Vogt N. Assembloids. *Nat Methods* 2021;18(1):27.

doi: 10.1038/s41592-020-01026-x

72. Zhang J, Zhu P, Li S, Gao Y, Xing Y. From heart failure and kidney dysfunction to cardiorenal syndrome: TMAO may be a bridge. *Front Pharmacol.* 2023;14:1291922.

doi: 10.3389/fphar.2023.1291922

73. Velazquez JJ, LeGraw R, Moghadam F, *et al.* Gene Regulatory Network Analysis and Engineering Directs Development and Vascularization of Multilineage Human Liver Organoids. *Cell Syst.* 2021;12(1):41-55.e11.

doi: 10.1016/j.cels.2020.11.002

74. Post MJ, Rahimi N, Caolo V. Update on vascularization in tissue engineering. *Regen Med.* 2013;8(6):759-770.

doi: 10.2217/rme.13.74

75. Holloway EM, Wu JH, Czerwinski M, *et al.* Differentiation of Human Intestinal Organoids with Endogenous Vascular Endothelial Cells. *Dev Cell*. 2020;54(4):516-528.e7.

doi: 10.1016/j.devcel.2020.07.023

76. Dailamy A, Parekh U, Katrekar D, *et al.* Programmatic introduction of parenchymal cell types into blood vessel organoids. *Stem Cell Rep*. 2021;16(10):2432-2441.

doi: 10.1016/j.stemcr.2021.08.014

77. Bhatia SN, Ingber DE. Microfluidic organs-on-chips. *Nat Biotechnol*. 2014;32(8):760-772.

doi: 10.1038/nbt.2989

78. Gao G, Park W, Kim BS, *et al.* Construction of a Novel In Vitro Atherosclerotic Model from Geometry-Tunable Artery Equivalents Engineered via In-Bath Coaxial Cell Printing. *Adv Funct Mater.* 2020;31(10).

doi: 10.1002/adfm.202008878

79. Toyohara T, Roudnicky F, Florido MHC, *et al.* Patient hiPSCs Identify Vascular Smooth Muscle Arylacetamide Deacetylase as Protective against Atherosclerosis. *Cell Stem Cell*. 2020;27(1):147-157.e7.

doi: 10.1016/j.stem.2020.04.018

80. Biel NM, Santostefano KE, DiVita BB, *et al.* Vascular Smooth Muscle Cells From Hypertensive Patient-Derived Induced Pluripotent Stem Cells to Advance Hypertension Pharmacogenomics. *Stem Cells Transl Med.* 2015;4(12):1380-1390.

doi: 10.5966/sctm.2015-0126

81. Granata A, Serrano F, Bernard WG, *et al.* An iPSC-derived vascular model of Marfan syndrome identifies key mediators of smooth muscle cell death. *Nat Genet.* 2017;49(1):97-109.

doi: 10.1038/ng.3723

82. Ridker PM, Danielson E, Fonseca FA, *et al.* Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *New Engl J Med.* 2008;359(21):2195-2207.

doi: 10.1056/NEJMoa0807646

83. Menon T, Chahil V, Patel D, Grancorvitz C, Vijayraghavan K. Inflammation and cardiovascular disease – Part II: Anti-inflammatory therapy in cardiovascular disease. *Glob Transl Med.* 2025;4(3):12.

doi: 10.36922/gtm025100024

84. Samuel M, Berry C, Dubé MP, *et al.* Long-term trials of colchicine for secondary prevention of vascular events: a meta-analysis. *Eur Heart J.* 2025;46(26):2552-2563.

doi: 10.1093/eurheartj/ehaf174

85. Cayo MA, Mallanna SK, Di Furio F, *et al.* A Drug Screen using Human iPSC-Derived Hepatocyte-like Cells Reveals Cardiac Glycosides as a Potential Treatment for Hypercholesterolemia. *Cell Stem Cell*. 2017;20(4):478-489.e5.

doi: 10.1016/j.stem.2017.01.011

86. Kong D, Ryu JC, Shin N, *et al.* In Vitro Modeling of Atherosclerosis Using iPSC-Derived Blood Vessel Organoids. *Adv Healthc Mater.* 2025;14(1):e2400919.

doi: 10.1002/adhm.202400919

87. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288(23):2981-2997.

doi: 10.1001/jama.288.23.2981

88. Jamerson K, Weber MA, Bakris GL, *et al.* Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *New Engl J Med.* 2008;359(23):2417-2428.

doi: 10.1056/NEJMoa0806182

89. Kwartler CS, Esparza Pinelo JE. Use of iPSC-Derived Smooth Muscle Cells to Model Physiology and Pathology. *Arterioscler Thromb Vasc Biol.* 2024;44(7):1523-1536.

doi: 10.1161/atvbaha.123.319703

90. Neptune ER, Frischmeyer PA, Arking DE, *et al.* Dysregulation of TGF-beta activation contributes to pathogenesis in Marfan syndrome. *Nat Genet.* 2003;33(3):407-411.

doi: 10.1038/ng1116

91. Lacro RV, Dietz HC, Sleeper LA, *et al.* Atenolol versus losartan in children and young adults with Marfan's syndrome. *New Engl J Med.* 2014;371(22):2061-2071.

doi: 10.1056/NEJMoa1404731

92. Park JW, Yan L, Stoddard C, *et al.* Recapitulating and Correcting Marfan Syndrome in a Cellular Model. *Int J Biol Sci.* 2017;13(5):588-603.

doi: 10.7150/ijbs.19517

93. Collado MS, Cole BK, Figler RA, *et al.* Exposure of Induced Pluripotent Stem Cell-Derived Vascular Endothelial and Smooth Muscle Cells in Coculture to Hemodynamics Induces Primary Vascular Cell-Like Phenotypes. *Stem Cells Transl Med.* 2017;6(8):1673-1683.

doi: 10.1002/sctm.17-0004

94. Han X, Li Y, Wang E, *et al.* Exploring Origin-Dependent Susceptibility of Smooth Muscle Cells to Aortic

Diseases Through Intersectional Genetics. *Circulation*. 2025;151(17):1248-1267.

doi: 10.1161/circulationaha.124.070782

95. Zhang X, Bishawi M, Zhang G, *et al.* Modeling early stage atherosclerosis in a primary human vascular microphysiological system. *Nat Commun*. 2020;11(1):5426.

doi: 10.1038/s41467-020-19197-8

96. Over 250 million people worldwide unaware they have diabetes, according to new research from the International Diabetes Federation (IDF). *Diabetes Res Clin Pract.* 2025;223:112176.

doi: 10.1016/j.diabres.2025.112176

97. Arcaro G, Cretti A, Balzano S, *et al.* Insulin causes endothelial dysfunction in humans: sites and mechanisms. *Circulation*. 2002;105(5):576-582.

doi: 10.1161/hc0502.103333

98. Cai D, Yuan Q, Sun P, *et al.* Enhanced intracellular recording in cardiomyocytes via soft ionic-electronic conductive interfaces of PEDOT: PSS-modified electrodes. *Biosens Bioelectron.* 2025;290:117999.

doi: 10.1016/j.bios.2025.117999

99. Lopez-Buenafe GdR, Alonso-Cabrera JA, Marcuello C, *et al.* Fabrication and Characterization of PEDOT:PSS-Based Microstructured Electrodes for In Vitro Cell Culture. *Adv Mater Interfaces*. 2025;12(20).

doi: 10.1002/admi.202500097

100. Yu X, Liu C, Kuang Z, Song S, Tian L, Wang Y. Islet organoids: a new hope for islet transplantation in diabetes. *Front Immunol.* 2024;15:1540209.

doi: 10.3389/fimmu.2024.1540209

101. Patel L, Marzullo BP, Barlow J, *et al.* Substrate stiffness-dependent metabolic reprogramming of iPSC-derived cardiomyocytes on physiological PDMS polymers. *Metab Eng Commun.* 2025;21:e00266.

doi: 10.1016/j.mec.2025.e00266

102. Ng KM, Lau YM, Dhandhania V, *et al.* Empagliflozin Ammeliorates High Glucose Induced-Cardiac Dysfuntion in Human iPSC-Derived Cardiomyocytes. *Sci Rep.* 2018;8(1):14872.

doi: 10.1038/s41598-018-33293-2

103. Sugiura T. Cardiac regenerative therapy using induced pluripotent stem cells. *GTM*. 2024;3(3):3586.

doi: 10.36922/gtm.3586

104. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *New Engl J Med.* 1998;339(4):229-234.

doi: 10.1056/nejm199807233390404

105. Ding M, Shi R, Du Y, *et al.* O-GlcNAcylation-mediated endothelial metabolic memory contributes to cardiac damage via small extracellular vesicles. *Cell Metab.* 2025;37(6):1344-1363.e6.

doi: 10.1016/j.cmet.2025.03.006

106. Wimmer RA, Leopoldi A, Aichinger M, *et al.* Human blood vessel organoids as a model of diabetic vasculopathy. *Nature*. 2019;565(7740):505-510.

doi: 10.1038/s41586-018-0858-8

107. Le Bras A. A new organoid model to study diabetic vasculopathy. *Nat Rev Cardiol.* 2019;16(3):131.

doi: 10.1038/s41569-019-0165-6

108. Wörsdörfer P, Rockel A, Alt Y, Kern A, Ergün S. Generation of Vascularized Neural Organoids by Co-culturing with Mesodermal Progenitor Cells. *STAR Protoc.* 2020;1(1):100041.

doi: 10.1016/j.xpro.2020.100041

109. Gong L, Zhang Y, Zhu Y, *et al.* Rapid generation of functional vascular organoids via simultaneous transcription factor activation of endothelial and mural lineages. *Cell Stem Cell*. 2025;32(8):1200-1217.e6.

doi: 10.1016/j.stem.2025.05.014

110. Bock C, Boutros M, Camp JG, *et al.* The Organoid Cell Atlas. *Nat Biotechnol.* 2021;39(1):13-17.

doi: 10.1038/s41587-020-00762-x

111. Wu X, Swanson K, Yildirim Z, Liu W, Liao R, Wu JC. Clinical trials in-a-dish for cardiovascular medicine. *Eur Heart J.* 2024;45(40):4275-4290.

doi: 10.1093/eurheartj/ehae519