

Review

Living Devices for Organ Replacement: The Rise of Bioartificial Organ Engineering

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Abstract

Organ failure remains one of the foremost medical and socioeconomic challenges of the twenty-first century, with global transplant waiting lists far exceeding the supply of donor organs. Chronic supportive therapies sustain life but do not restore organ function, underscoring an urgent need for curative alternatives. Bioartificial organs represent a major frontier in organ replacement, driven by converging advances in cell biology, biomaterials science, and bioengineering. By integrating living cells or biologically derived matrices with engineered devices or scaffolds, these systems aim to restore functions that purely mechanical supports cannot reproduce. This review examines the principal technological platforms underpinning the field, including cell encapsulation, decellularization and recellularization, three-dimensional bioprinting, organoids, organ-on-chip systems, and xenotransplantation, and discusses their application to kidney, liver, heart, pancreas, and lung replacement. Across organ systems, progress is advancing from experimental proof-of-concept toward modular and increasingly translational platforms, although whole-organ bioengineering remains largely preclinical for the most structurally complex targets. The major unresolved barriers include vascularization, immune compatibility, scalable cell manufacturing, durable function, and stable integration between biological and engineered components. Overall, bioartificial organ engineering is evolving toward clinically relevant therapeutic strategies capable of complementing, bridging, or eventually reducing dependence on donor-organ transplantation.

Keywords: bioartificial organs; organ replacement; tissue engineering; cell encapsulation; decellularization; 3D bioprinting; organoids; organ-on-chip; xenotransplantation; regenerative medicine



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1. Introduction

Organ failure constitutes one of the most significant medical and socioeconomic challenges of the twenty-first century. The persistent shortage of transplantable organs leaves millions of patients dependent on chronic supportive therapies such as dialysis, mechanical ventilation, and insulin administration, which are life-sustaining but do not

restore full organ function [1–5]. According to the Organ Procurement and Transplantation Network (OPTN), as of April 2026, there are more than 121,200 registrations on the U.S. transplant waiting list [6]. Kidney alone accounts for 103,655 registrations ($\approx 85\%$), followed by liver with 8973 ($\approx 7\%$), heart with 4100 ($\approx 3\%$), lung with 1018 ($\approx 1\%$), pancreas with 834 ($\approx 1\%$), and combined kidney–pancreas with 2504 ($\approx 2\%$) [6]. Although these figures derive from the U.S. transplant system, they effectively illustrate the magnitude and organ distribution of unmet transplant need in high-resource healthcare settings and reflect a broader global imbalance between organ demand and supply.

Bioartificial organs seek to address this gap by integrating living biological components, including cells, tissues, or extracellular matrix, with engineered devices or biomaterial scaffolds in order to restore or supplement organ-specific function [7–10].

Unlike purely mechanical artificial organs, these systems are intended to reproduce complex metabolic, endocrine, and biosynthetic activities that cannot be fully replicated by engineering alone [7–10].

Their development depends on the convergence of biomaterials science, stem cell biology, physiology, anatomy, and biomedical engineering, and is fundamentally constrained by three interdependent requirements: sustained cell viability and function, biocompatibility, and efficient mass transport of oxygen, nutrients, and metabolic waste [11–13]. Over the past decades, the field has expanded from early extracorporeal support systems to increasingly sophisticated strategies that include wearable devices, encapsulated cell therapies, decellularized organ scaffolds, and stem cell-based tissue engineering [14–20]. This review provides an overview of the principal bioartificial organ technologies and examines their application to the organs that currently dominate transplant demand, namely the kidney, liver, heart, pancreas, and lung (Figure 1). The literature search underlying this work was conducted primarily in PubMed/MEDLINE and Scopus, supplemented by targeted searches in Web of Science and ClinicalTrials.gov. Searches were performed between February 2026 and May 2026, with no lower time limit applied in order to capture foundational studies alongside recent developments. Search terms included combinations of the following: “bioartificial organ”, “bioengineered organ”, “organ-on-chip”, “decellularization”, “recellularization”, “cell encapsulation”, “3D bioprinting”, “organoids”, “xenotransplantation”, “bioartificial kidney”, “bioartificial liver”, “bioartificial pancreas”, “bioartificial heart”, and “bioartificial lung”. Priority was given to peer-reviewed original research articles, systematic reviews, and clinical trial reports published in English. Conference abstracts and non-peer-reviewed materials were excluded. The selection of cited works was guided by clinical relevance, methodological rigor, recency, and representativeness of the main research directions within each topic area.

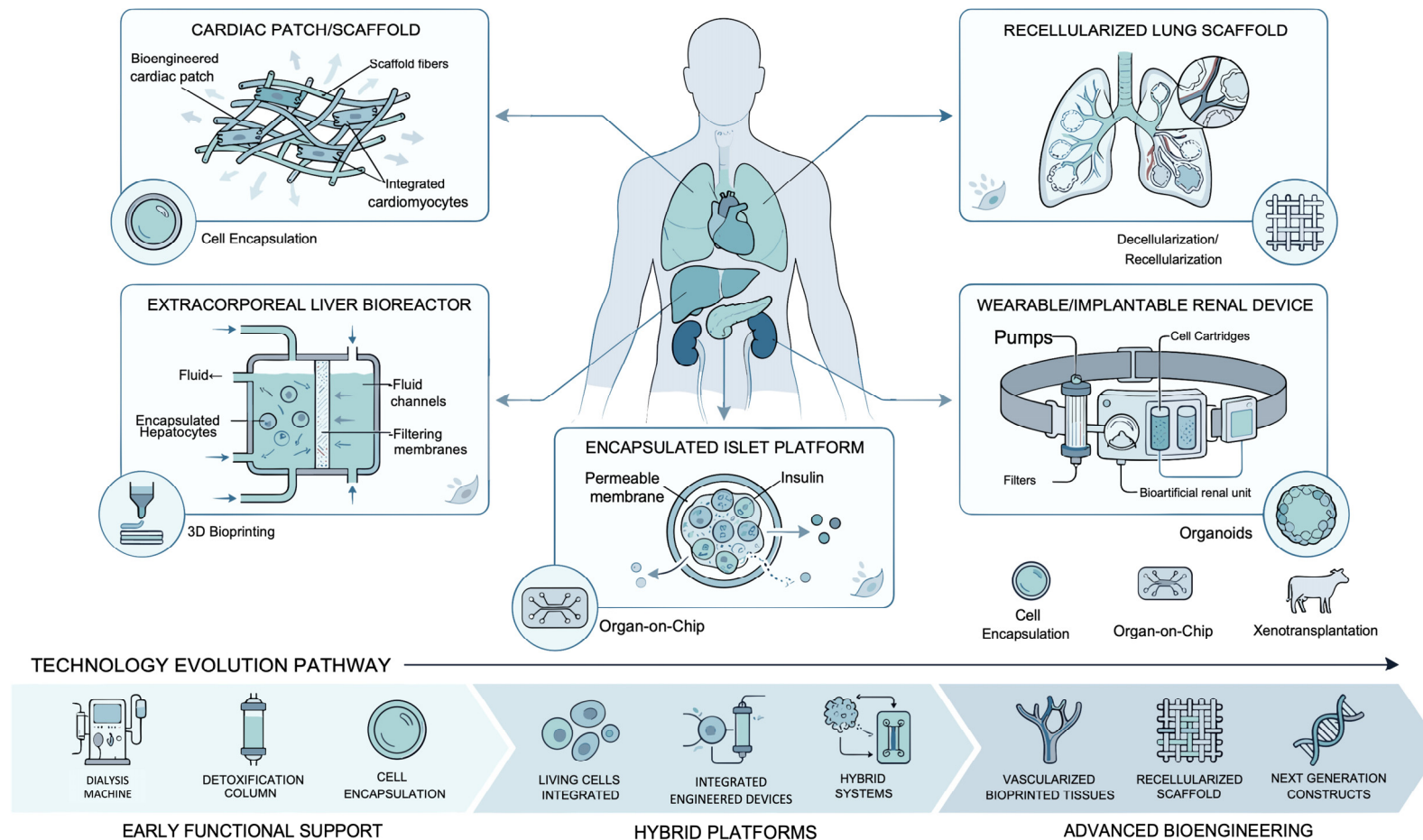


Figure 1. Schematic overview of the current landscape of bioartificial organ technologies and their translational evolution in regenerative medicine. Representative strategies targeting the heart, liver, kidney, pancreas, and lung are arranged around a central human silhouette, highlighting the organ-specific application of extracorporeal support systems, hybrid devices, scaffold-based constructs, and tissue-engineering platforms. The figure illustrates the progression from early functional support approaches toward advanced bioengineered systems integrating living cells, biomaterials, bioreactors, and organ-mimetic design principles. This visual framework emphasizes the convergence of regenerative medicine, biomaterials science, and biofabrication in the development of next-generation bioartificial organs. Clinically, these platforms may provide complementary strategies to bridge organ failure, support recovery, or reduce dependence on donor-organ transplantation.

2. Foundational Technologies and Emerging Frontiers

Foundational bioengineering technologies underpin the development of all bioartificial organ systems, providing core platforms that recur across different organ targets. These include cell encapsulation, decellularization and recellularization, three-dimensional bioprinting, organoids, organ-on-chip systems, and xenotransplantation, each of which offers distinct biological and engineering advantages while introducing specific translational limitations (Table 1).

Cell encapsulation involves surrounding living cells with a semipermeable membrane that permits the diffusion of small molecules—including oxygen, glucose, insulin, and metabolic waste—while shielding the encapsulated cells from host immune recognition. This strategy is central to the development of bioartificial endocrine organs, particularly the bioartificial pancreas, in which insulin-producing islet cells must be protected from autoimmune destruction without requiring systemic immunosuppression [21–25]. Three principal encapsulation architectures have been developed: microencapsulation (individual islets in hydrogel capsules of 100–400 μm diameter), macroencapsulation (larger planar or cylindrical devices), and nanoencapsulation (conformal coatings applied directly to the cell surface), each presenting distinct trade-offs between mass transport efficiency, immunoprotection, biocompatibility, and retrievability [21–25]. Hydrogel-based biomaterials—particularly alginate, polyethylene glycol (PEG), and zwitterionic polymers—have been the primary candidates for encapsulation membranes due to their biocompatibility and tunable permeability [26–28]. A major research focus has been the engineering of encapsulation materials that minimize the foreign body response, which remains a primary mechanism of device failure in vivo. In this regard, chemically modified alginates and immunomodulatory formulations have shown encouraging results in minimizing fibrotic overgrowth and improving long-term glycemic control in preclinical models [29–31].

A complementary scaffold-based strategy is decellularization, defined as the removal of cellular material from a donor organ while preserving the native three-dimensional extracellular matrix (ECM) architecture [32]. The resulting acellular scaffold retains organ-specific structural cues—vascular channels, basement membranes, bile canaliculi, glomerular structures, alveolar compartments—that provide the spatial template for subsequent repopulation with recipient-derived cells [17,32–34]. Perfusion decellularization has emerged as the most consistent method for whole-organ scaffold preparation, delivering detergent solutions through the native vasculature to achieve uniform cell removal while preserving the hierarchical vascular architecture [17,34–36]. A critical determinant of success is the balance between adequate cellular clearance and preservation of ECM composition and mechanics, as excessive detergent exposure can damage matrix proteins and compromise subsequent recellularization efficiency [37]. Although this approach has been applied successfully to heart, liver, lung, kidney, and pancreas scaffolds in preclinical settings, recellularization remains the principal bottleneck, particularly with respect to the spatial organization of multiple cell types, the generation of sufficient cell numbers for human-scale organs, and the induction of mature functional phenotypes [38–46].

An alternative bottom-up approach is three-dimensional bioprinting, which constructs tissue architectures by the layer-by-layer deposition of bioinks composed of cells, biomaterials, and signaling factors [47,48]. Unlike decellularization-based approaches, 3D bioprinting is, in principle, entirely donor-independent and can be personalised to match patient anatomy and cell biology [49–52]. Major modalities include extrusion-based printing, inkjet printing, stereolithography (SLA/DLP), and laser-assisted bioprinting, each offering different trade-offs between resolution, cell viability, printing speed, and material compatibility [53–55]. The fundamental unsolved challenge in 3D bioprinting of solid organs is vascularization, because tissues thicker than about 100–200 μm exceed the diffu-

sion limit for oxygen and nutrients and therefore require an internal perfusable vascular network to remain viable [56,57]. This limitation has been demonstrated in vascularized bioprinting studies showing that thick constructs rapidly lose viability without embedded vessels. In contrast, bioprinted tissues with perfusable channels or prevascular networks can be maintained for prolonged perfusion and support endothelialization and angiogenesis. Recent progress in vascularized bioprinting has been achieved through smart bioinks and sacrificial printing strategies. Notable examples include SWIFT (Sacrificial Writing Into Functional Tissue), in which organ building blocks are embedded in ECM matrices and sacrificial inks are used to create perfusable channel networks, as well as coaxial extrusion and embedded bioprinting approaches that enable endothelialized tubular structures and multiscale vascular architectures [58–61]. These advances are increasingly supported by artificial intelligence tools for bioink optimization and vascular design, further enhancing the precision and scalability of printed constructs [62].

Complementary biological platforms include organoids and organ-on-chip devices. Organoids are three-dimensional tissue structures generated from pluripotent or adult stem cells that self-organize to recapitulate important aspects of organ-specific cellular composition, architecture, and function [63,64]. They preserve patient-specific genetic and pathophysiological features with significantly higher fidelity than typical two-dimensional cultures, and hence provide enormous advantages for disease modeling and regenerative applications [65–67]. They are also of particular interest in bioartificial organ development, as they represent scalable sources of patient-derived functional cells for tissue assembly [68]. In contrast, organ-on-chip systems incorporate living cells into microfluidic devices designed to replicate the chemical, physical, and mechanical milieu of native tissues [69–71]. These models have gained renewed relevance with recent regulatory and institutional developments, including increasing FDA (Food and Drug Administration) openness to alternative preclinical platforms and broader support for the validation of organoid- and organ-on-chip-based approaches, which may influence future translational and regulatory pathways [72]. The emergent convergence of these two approaches in organoid-on-chip systems merges the self-organizing complexity of organoids with the engineering control of microfluidic platforms, allowing for improved vascularization, immune-cell interactions, and inter-organ connectivity [69,71,73,74].

While conceptually distinct from scaffold-based bioengineering, xenotransplantation has become increasingly relevant to bioartificial organ development because both fields must solve common immunological bottlenecks—complement regulation, coagulation compatibility, and endothelial protection—that determine the long-term viability of any biological construct in vivo. The transplantation of genetically engineered animal organs into human recipients has demonstrated that large-scale physiological support is feasible, but also highlighted the significant hurdles of innate immunity, complement activation, coagulation incompatibility, and endothelial injury [75–79]. Gene-edited pig kidney and liver grafts have provided measurable functional support in highly selected human settings [75–81], while genetically modified swine lungs have shown maintained viability without hyperacute rejection in cross-species transplantation models [82]. The results are very informative for bioartificial organ engineering, as the same strategies employed in xenotransplantation, particularly xenoantigen deletion, insertion of human complement-regulatory genes, and modulation of thromboregulatory pathways, can conceptually be applied to decrease the immunogenicity of biological components of hybrid organ constructs. Itoh et al. developed an immunodeficient porcine model that was able to incorporate artificial human vascular grafts [83], and Cravedi et al. elucidated broader immunological mechanisms of biomaterial-host interactions, such as complement activation, macrophage polarization, T-cell recruitment, and humoral immunity [84,85]. Collectively, these data position xeno-

transplantation as a translationally instructive platform for understanding and engineering immunological compatibility in next-generation bioartificial organs.

Beyond these basic platforms, several emerging areas are likely to further expand bioartificial organ engineering. Four-dimensional bioprinting is an extension of traditional 3D bioprinting that incorporates stimuli-responsive materials that respond to environmental cues such as temperature, pH, light, or moisture to change their form, stiffness, or functionality after production [86–88]. This opens the door to dynamic constructs that respond to physiological cues, potentially enabling self-assembling vascular networks or valve-like structures responding to haemodynamic stresses. Concurrently, in situ bioprinting enables direct deposition of bioink into the wound bed or surgical area, enabling tissue creation in vivo rather than ex vivo [89]. The approach is particularly useful for partial liver or heart repair but introduces further issues of sterility, gelation kinetics, and image-guided precision during implantation [90]. Artificial intelligence and machine learning are also developing as enabling technologies across the full design pipeline of bioartificial systems [91,92]. These technologies are being used to optimize construct performance through scaffold design, vascular network configuration, bioink formulation, and bioreactor settings, decreasing empirical trial and error [47,93]. Computational methods have been shown to substantially reduce bioink optimization time, and fluid dynamics-based design algorithms are increasingly used to maximize nutrient delivery and minimize hypoxic regions within engineered tissues [94–96]. At the same time, cell viability may be monitored in real time, and automated construct quality control can be performed using image analysis based on neural networks [97,98]. Another challenge is represented by the creation of multi-organ bioartificial systems able to reproduce inter-organ metabolic interactions. This idea is particularly important in patients with complex or multiorgan failure because consecutive single-organ support may be biologically inadequate. Organoid-on-chip platforms integrating liver, kidney, and gut tissues through common microfluidic circuits are the most advanced preclinical models of inter-organ crosstalk to date, and could represent a conceptual foundation for future extracorporeal systems offering combined, biologically accurate support across different organ functions [11,66].

Table 1. Foundational technologies in bioartificial organ engineering: comparative principles, advantages, and translational limitations.

Technology	Principle	Main Advantages	Key Limitations	Key Ref.
Cell encapsulation	Enclosure of living cells within semipermeable membranes that permit nutrient, gas, and metabolite exchange while limiting immune recognition	Avoids systemic immunosuppression; minimally invasive implantation; preserves small-molecule diffusion; particularly suitable for endocrine applications	Fibrotic overgrowth; oxygen diffusion constraints; inflammatory responses; limited long-term durability	[21–23,31,99–104]
Decellularization/recellularization	Removal of donor cellular material with preservation of native ECM architecture, followed by repopulation with functional recipient-derived cells	Maintains organ-specific 3D architecture; preserves native vascular conduits and biochemical cues; strong biomimetic potential	Difficult cell scaling; incomplete or heterogeneous recellularization; challenges in maturation, storage, and logistics	[14–17,32,34–37,41,44,105–118]
3D bioprinting	Layer-by-layer deposition of cell-laden bioinks to generate spatially controlled tissue constructs	Donor-independent; customizable and patient-specific; precise spatial control; compatible with computational design optimization	Limited vascularization beyond diffusion thresholds; bioink formulation constraints; trade-off between print resolution and cell viability	[7,47,48,51–57,59,87–90,93,94,96]

Table 1. Cont.

Technology	Principle	Main Advantages	Key Limitations	Key Ref.
Organoids	Self-organizing 3D stem cell-derived tissue structures recapitulating key functional and architectural features of native organs	Patient-derived; useful for disease modeling and drug testing; scalable cell source; captures relevant biological complexity	Limited size and vascularization; incomplete maturation; restricted immediate implantability	[54,63,65–68,72–74,119–133]
Organ-on-chip	Microfluidic platforms containing living cells and engineered microenvironments that mimic tissue-level physiology	Dynamic physiological control; real-time monitoring; strong relevance for preclinical testing and regulatory validation	Generally not implantable; low cell numbers; manufacturing and scale-up challenges	[69,71,73,122,134]
Xenotransplantation	Use of genetically engineered animal organs to provide physiological support in human recipients	Full organ-level complexity; native vascularization already present; suitable size matching for clinical translation	Immune rejection; coagulation incompatibility; PERV and biosafety concerns; major ethical and regulatory issues	[75,77–80,82,135–147]

Abbreviations: ECM, extracellular matrix; PERV, porcine endogenous retrovirus; Ref., references.

3. Organ-Specific Bioartificial Platforms

Bioartificial organ development has progressed unevenly across organ systems, reflecting substantial differences in physiological complexity, clinical need, engineering feasibility, and regulatory maturity. Whereas some platforms primarily aim to replace filtration or detoxification functions, others must reproduce highly integrated endocrine, contractile, or gas-exchange activities, thereby requiring distinct combinations of living cells, biomaterials, extracorporeal circuits, and tissue-engineering strategies. To provide a coherent comparative framework, the following sections examine kidney, liver, heart, pancreas, and lung bioartificial systems with emphasis on their biological rationale, principal cell sources, bioreactor or device configurations, major functional achievements, and the main barriers to clinical implementation (Figure 2).

Figure 3 provides a complementary translational overview of these platforms, highlighting their relative maturity, near-term clinical applications, major safety and regulatory challenges, and next development priorities.

Conventional haemodialysis and peritoneal dialysis remove uraemic solutes and control fluid balance but cannot replicate the multidimensional endocrine, metabolic, and homeostatic functions of the native kidney, including erythropoietin production, calcitriol synthesis, renin secretion, prostaglandin- and kinin-mediated blood pressure regulation, and acid-base homeostasis at the cellular level [148,149]. Haemodialysis is based on diffusion and ultrafiltration across a semipermeable membrane, allowing for efficient removal of unwanted solutes from the blood. However, the endocrine and biosynthetic functions of the kidney are not reproduced by the device and must therefore be supplemented pharmacologically. Furthermore, the intermittent nature of conventional thrice-weekly sessions leads to cyclic fluctuations in uraemic toxin concentrations, which contribute to persistent cardiovascular morbidity [148–150].

Comparative overview of bioreactor systems for vital organ tissue engineering

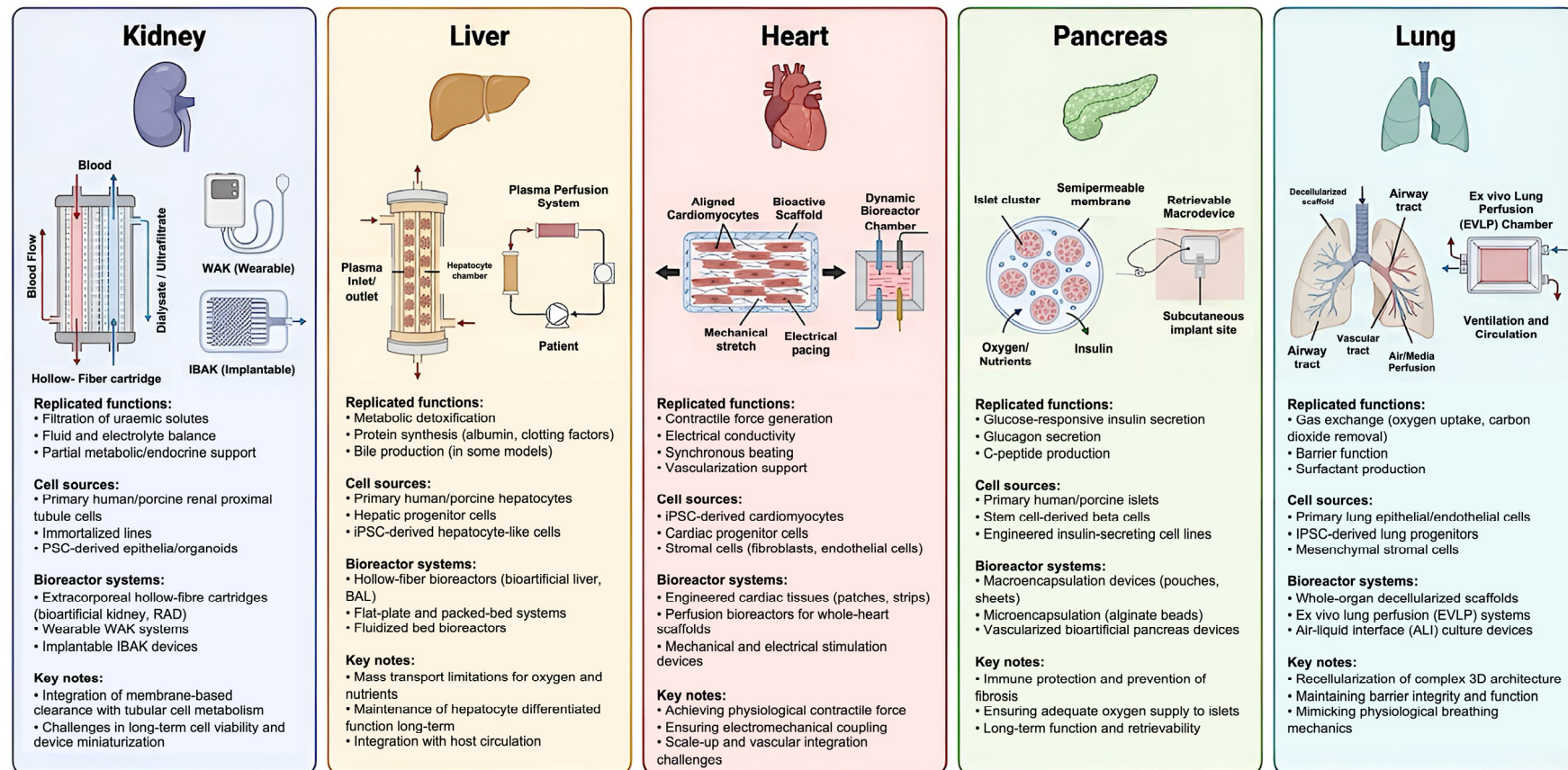


Figure 2. The figure summarizes, for kidney, liver, heart, pancreas and lung, the principal physiological functions targeted, the predominant cell sources employed, and the main bioreactor or device architectures developed to date, ranging from extracorporeal hollow-fibre cartridges and encapsulation systems to scaffold-based constructs and emerging implantable configurations. This integrated overview highlights organ-specific engineering strategies and the main technical constraints that continue to shape progress in bioartificial organ development. From a clinical perspective, these organ-specific configurations highlight how different bioartificial platforms are being tailored to address the functional deficits, translational constraints, and therapeutic priorities of each target organ. Abbreviations: WAK, wearable artificial kidney; IBAK, implantable bioartificial kidney; RAD, renal assist device; BAL, bioartificial liver; PSC, pluripotent stem cells; iPSC, induced pluripotent stem cells; EVLP, ex vivo lung perfusion; ALI, air-liquid interface.

Translational landscape of organ-specific bioartificial replacement strategies

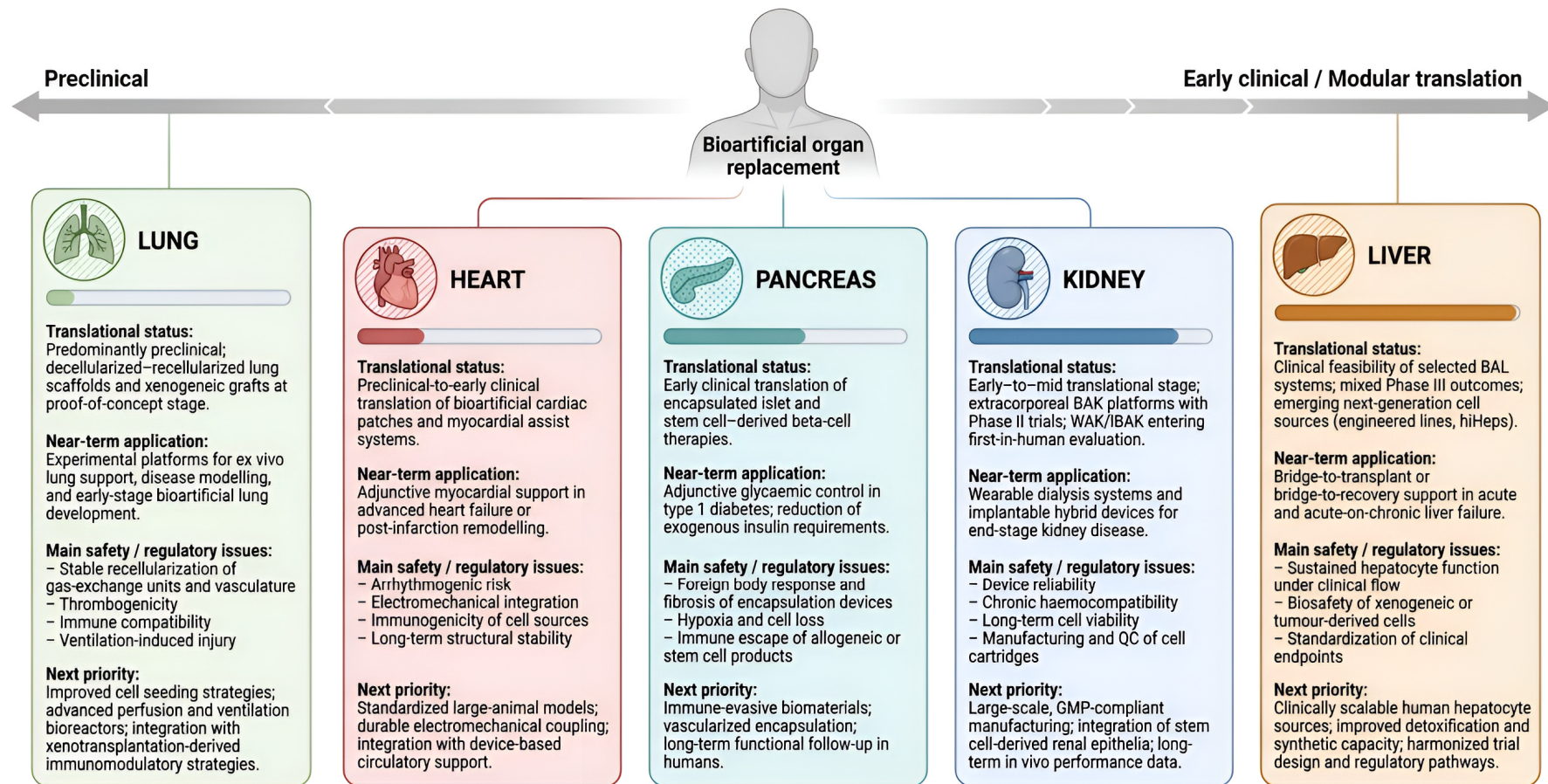


Figure 3. Translational landscape of organ-specific bioartificial replacement strategies. The figure compares kidney, liver, heart, pancreas, and lung bioartificial platforms according to translational maturity, near-term clinical application, major safety and regulatory barriers, and next development priorities. It emphasizes the more advanced modular trajectories of renal and hepatic systems, the early clinical evaluation of selected cardiac and pancreatic strategies, and the predominantly preclinical status of whole-organ heart and lung bioengineering. Clinically, this comparative overview helps identify which platforms are closest to implementation and which biological, safety, and regulatory barriers still limit broader therapeutic application. Abbreviations: BAK, bioartificial kidney; BAL, bioartificial liver; WAK, wearable artificial kidney; iBAK, implantable bioartificial kidney; hiHeps, human induced hepatocytes; GMP, good manufacturing practice; QC, quality control.

3.1. The Bioartificial Kidney

The Bioartificial Kidney (BAK) concept emerged from the recognition that cell-based renal replacement could combine the metabolic and endocrine activities of living renal tubular epithelial cells with membrane-based clearance, thereby more closely approximating a complete functional analogue of the native organ [151]. The central design premise is that biomembrane filtration and cellular metabolic support are not merely additive components but functionally interdependent pillars. While membrane separation addresses the accumulation of small uraemic toxins and extracellular volume derangement, only living renal epithelium can reconstitute the homeostatic, endocrine, and biosynthetic repertoire required for physiological organ replacement [152].

One of the first BAK platforms to show clinical feasibility was the Renal Assist Device (RAD) [153]. It consisted of a hollow-fibre cartridge containing approximately one billion human renal proximal tubule cells. The earliest designs used primary porcine renal cells and LLC-PK1 cells, but these were later replaced with human renal epithelial cells for clinical safety reasons. The device was placed in series with a standard haemofilter. In a Phase I/II study approved by the FDA, 10 critically ill patients with acute renal failure and a mean predicted hospital mortality risk of 86% were treated with the RAD. The study confirmed safety and suggested improved outcomes, with six patients surviving beyond 30 days [153].

A subsequent Phase II randomized controlled trial comparing continuous venovenous haemofiltration (CVVH) alone with CVVH plus RAD in 58 patients reported a 28-day mortality of 33% in the RAD group versus 61% in the control group, as well as a 52% reduction in the adjusted risk of death at 180 days. However, the study was underpowered for definitive conclusions, and a later Stage IIb trial failed to reproduce the same benefit. The programme was therefore not translated further into clinical practice, owing in part to major barriers in manufacturing, cell sourcing, quality control, and logistics that are intrinsic to bioartificial renal cell therapy [154,155].

Modern BAK research has diverged into two parallel trajectories: (1) wearable artificial kidney (WAK) systems, which aim to replace conventional dialysis apparatus with portable devices; and (2) implantable bioartificial kidney (iBAK) systems, designed as permanent internal replacements. An FDA-approved human feasibility trial of the WAK showed effective uraemic solute clearance, fluid balance control, and electrolyte maintenance, but it was stopped after seven subjects because of device-related technical problems, particularly excessive carbon dioxide generation and variable blood flow [156]. These findings provided proof of concept while also highlighting key engineering limitations [156]. continuous-flow peritoneal dialysis with a sorbent-based dialysate regeneration system, reducing daily peritoneal exchanges from 4 to 6 to one. A first-in-human safety trial (NCT06314503; CORDIAL project, EU Horizon 2020) in 12 patients has evaluated the short-term clinical safety and performance of this system in a multicentre European study [157].

The most advanced iBAK programme is the Kidney Project, which aims to develop an implantable device combining a silicon nanopore membrane (SNM) haemofilter, manufactured using microelectromechanical systems (MEMS) technology, with a bioreactor containing human renal tubular epithelial cells [158,159]. A major engineering advantage of this device is that it relies solely on the patient's cardiac output to drive blood flow and therefore does not require an external pump. The SNM has pore sizes of approximately 7–11 nm, small enough to reject IgG and albumin while still allowing passage of water and small uraemic toxins. This design is intended to eliminate the need for systemic anticoagulation or immunosuppression. Key components have already been validated in vitro, including laboratory demonstration of urine formation, and the programme is advancing through preclinical development with the long-term goal of clinical feasibility testing.

Alongside membrane-based and cell-seeded implantable platforms, kidney organoids are emerging as a complementary biological strategy to provide more physiologically relevant renal cellular components for future bioartificial kidney devices. Derived mainly from pluripotent stem cells, these three-dimensional self-organizing structures recapitulate key aspects of renal development and generate nephron-like domains resembling glomerular and tubular compartments [119–121]. Their generation relies on stepwise differentiation protocols that reproduce the major signalling pathways of nephrogenesis, guiding cells through intermediate mesoderm and nephron progenitor stages toward the formation of organized renal structures in vitro [121,160]. In parallel, adult renal stem or progenitor cells have also been used to generate tubular organoid-like structures through defined growth factor-based protocols, providing an additional and experimentally practical platform for nephrotoxicity testing and preclinical investigation [161]. Beyond their established role in disease modelling and drug screening, kidney organoids are increasingly being investigated as a patient-derived and potentially scalable cell source for bioartificial kidney applications. Transplantation studies have shown that permissive extracellular environments can promote vascularization and maturation of implanted organoids, while bioengineering strategies have improved structural organization and differentiation fidelity [122–125]. Nevertheless, major limitations remain, including incomplete nephron maturation, inter-batch variability, insufficient perfusion, and the persistence of a fetal-like molecular phenotype that does not yet fully reproduce the adult kidney [119,122]. Further advances in vascular integration, immune compatibility, scalable manufacturing, and robust functional validation will therefore be required before kidney organoids can serve as reliable cellular components of clinically deployable bioartificial kidney devices [123,126,127].

In the related field of xenotransplantation, the pig has become the preferred donor species because of its morphological and physiological similarities to humans, rapid reproductive rate, and amenability to genetic modification [136–138]. The major immunological barriers [139–142], including hyperacute rejection mediated by preformed natural antibodies targeting three porcine carbohydrate xenoantigens, acute humoral and cellular rejection, coagulation dysregulation, and the risk of porcine endogenous retrovirus transmission, have been progressively addressed through combinatorial CRISPR/Cas9-based gene-editing strategies [142,162,163]. Deletion of the three principal xenoantigen enzymes (α 1,3-galactosyltransferase, CMP-N-acetylneuraminic acid hydroxylase, and β 1,4-N-acetylgalactosaminyltransferase 2), together with expression of human complement-regulatory, anticoagulant, and anti-inflammatory proteins, has enabled consistent graft survival of more than one year in pig-to-non-human primate models, with a maximum reported survival of 758 days under co-stimulation blockade [143,144]. Subsequent compassionate-use cases in living recipients with end-stage kidney disease, including one patient who remained dialysis-independent for up to eight months (271 days), have provided important proof of concept that multiplex gene-edited porcine kidneys can sustain renal function in humans and may help inform the design of future structured clinical trials [138,145,146]. These advances in xenotransplantation also inform BAK development through shared immunoprotective strategies, particularly complement regulation, coagulation stabilization, anti-phagocytic signalling via CD47, and PERV biosafety approaches that are increasingly being integrated into BAK device engineering. In addition, long-term graft function data help define the biological requirements for sustained renal replacement in immunocompromised recipients.

3.2. The Bioartificial Liver

Acute liver failure (ALF) and acute-on-chronic liver failure (ACLF) are life-threatening conditions defined by the rapid loss of hepatic biosynthetic, detoxifying, metabolic, and

biotransformation functions, which present as a clinical syndrome of jaundice, coagulopathy, hepatic encephalopathy, hepatorenal syndrome, and rapidly progressive multi-organ failure [164–166]. In the most severe grade of ACLF, 28-day mortality can exceed 50% [164,166,167]. In ALF, a double-hit mechanism underlies disease progression: primary hepatocellular apoptosis or necrosis induced by hepatotropic viruses, drugs, toxins or metabolic insults is augmented by immune-mediated injury via activation of damage-associated and pathogen-associated molecular patterns [164–167]. In ACLF, a vicious cycle of systemic inflammation, immune dysfunction, and metabolic derangements sustains progressive organ failure [164–168]. Currently, liver transplantation is the sole final therapy, but it is severely limited by donor organ scarcity and the danger of chronic rejection. Patients with grade 3 ACLF have higher 14-day waiting-list mortality than Status 1a patients, underscoring the need for effective bridging therapies [164,169].

Non-bioartificial liver (NBAL) systems, such as plasma exchange, plasma perfusion, albumin dialysis, haemofiltration, and haemodiafiltration, can temporarily substitute hepatic detoxification, ameliorate endotoxaemia, and relieve hepatic encephalopathy but cannot replicate the biosynthetic, metabolic, and biotransformation functions of native hepatocytes [169–172]. Bioartificial Liver (BAL) devices were developed to combine blood purification and living hepatocytes in an extracorporeal bioreactor to support temporary hepatic function as a bridge to transplantation or spontaneous recovery. Since their inception—beginning with Matsumura et al. in 1987, using a modified Kiil dialyser loaded with rabbit hepatocytes—the field has seen over 40 years of continuous technological evolution [173]. Despite this progress, no BAL system has been licensed for clinical use in Western markets, nor has it shown a reproducible survival benefit in large randomized trials, mainly because of challenges in sourcing enough functional cell mass, sustaining hepatocyte viability under clinical flow conditions, and ensuring robust biosafety.

Several BAL devices have progressed to advanced clinical evaluation [174,175]. Early clinical application of bioartificial liver support began in 1987, when a BAL loaded with rabbit hepatocytes was used to treat a single patient with acute liver failure, and this was followed by the first clinical experience with the ELAD system in 1991 [174,175]. However, the first large prospective, randomized, multicentre controlled efficacy trial in the field evaluated HepatAssist, an extracorporeal BAL system based on porcine hepatocytes housed in hollow-fibre cartridges [20,176]. In that study, 30-day survival in the overall cohort was 71% in the BAL group versus 62% in the control group, a difference that did not reach statistical significance. Nevertheless, the system was shown to be safe, improved biochemical parameters such as bilirubin and ammonia, and an adjusted analysis suggested a survival benefit in the subgroup with fulminant/subfulminant hepatic failure [20,176].

The ELAD system, derived from the human C3A hepatoblastoma cell line, has been evaluated in three phase III trials. VTIC-301 enrolled Chinese patients with hepatitis B-associated ACLF [177], whereas VTI-208 and VTL-308 focused on severe alcoholic hepatitis in Western populations; the more encouraging signal observed in the former, compared with the negative results of the latter studies, may reflect both aetiological differences between the enrolled populations and intrinsic functional limitations of the C3A cell line [178]. This interpretation is biologically plausible because C3A cells can produce urea but do not provide effective ammonia detoxification, highlighting a major limitation of tumour-derived BAL cell sources. These limitations have contributed to the shift toward next-generation cell sources [179,180], although recent studies have explored genetic restoration of urea-cycle and bilirubin-handling pathways in HepG2/C3A derivatives, suggesting that engineered tumour lines might still serve as transitional BAL cell sources [181,182]. In parallel, newer BAL platforms based on both biological and non-biological principles of liver support have continued to emerge [183,184]. Nevertheless, recent reviews still describe

a limited clinical evidence base, with relatively few informative studies and conflicting survival data, indicating that clinical translation remains incomplete [185].

The source of hepatocytes is of utmost importance for the biological potency of any BAL system. Primary human hepatocytes (PHHs) represent the functional gold standard, but are constrained by rivalry with liver transplantation, donor scarcity, and the necessity for high-quality cells for each treatment [185]. Most PHHs are, in practice, isolated from marginal livers, which are not suitable for transplantation [128,129,186]. Porcine hepatocytes are broadly available and less costly but have risks of xenogeneic immune responses and PERV transmission. Active development of strategies for targeted deletion of immunodominant carbohydrate antigens and inactivation of PERV using CRISPR–Cas9 is underway to enable safer sources [147,187]. In addition to cell identification, practical deployment of BALs also requires strong expansion, 3D culture, microencapsulation, and cryopreservation procedures that can provide off-the-shelf hepatocytes at scale [188,189]. Tumour-derived cell lines such as HepG2 and C3A are easy to expand and readily available, but they do not reproduce the full metabolic repertoire of native hepatocytes; notably, although C3A cells produce urea, they do not provide effective ammonia detoxification, a limitation that is thought to have contributed to the restricted clinical performance of the ELAD programme [178,190,191].

The field is therefore moving toward directly reprogrammed and stem cell-derived hepatocytes. GMP-grade human induced hepatocytes (hiHeps), generated by direct fibroblast transdifferentiation, have shown several therapeutic advantages in preclinical models, including improvement of liver function, reduction in ammonia and bilirubin levels, and stimulation of liver regeneration [192–194]. Furthermore, hiHeps-based BAL platforms have advanced toward early clinical translation [192,194]. In the SRBAL (spheroid reservoir BAL) system, human iPSC-derived hepatic spheroids rescued all pigs in a randomized porcine post-hepatectomy ALF model at a cell dose of approximately 10^9 , with reduced ammonia and bilirubin levels, earlier liver regeneration, and no evidence of PERV transmission [195,196]. Another scalable strategy derived from PHHs is represented by expandable primary human hepatocyte lines, such as ProliHH, which have also shown therapeutic efficacy in mouse models of liver failure [130,189].

The most conceptually novel recent advance is the UTOPiA system, which combines HLA-A/B/CIITA triple-knockout iPSC-derived hepatocyte-like cells (iHLCs) with a granulocyte-monocyte apheresis (GMA) column in a tandem whole blood extracorporeal circuit for simultaneous hepatic support and direct immunomodulation [131]. This approach tackles the two pillars of ACLF pathogenesis, hepatic failure and systemic inflammation. In a rat ACLF model, this strategy was associated with an 88.9% survival rate after a single 2 h treatment, although validation in larger animal models remains necessary. However, functional immaturity of iHLCs compared to PHHs, especially in urea production, and the necessity for validation in large animal models still pose major translational challenges [131].

The second main pillar of BAL design is bioreactor engineering. Major topologies include hollow-fibre bioreactors, fluidised-bed systems (including choanoid arrangements for increased mass exchange), scaffold-based constructs and microfluidic liver-on-chip platforms [197]. These bioreactors separate blood or plasma from the cell compartment by semipermeable membranes, which permit the management of shear stress [174]. The development of bioreactor design is trending toward dynamic ecological systems with the integration of 3D bioprinting, biomimetic scaffolds, and liver chips that more closely resemble the hepatic milieu and promote intercellular mass transfer [198].

Future clinical trials should include next-generation GMP cell sources, biomimetic reactor designs and prospectively stratified patient enrolment by aetiology and residual liver

function, as well as composite endpoints that include organ failure reversal, amelioration of hepatic encephalopathy and intensive-care-unit-free days, to demonstrate the survival benefit that has so far proved elusive for the field.

3.3. The Bioartificial Heart

Heart failure is a progressive and debilitating syndrome affecting more than 64 million people worldwide and is associated with a mortality of approximately 50% within five years of diagnosis [199]. In advanced stages, it may progress to irreversible biventricular dysfunction, leaving heart transplantation or durable mechanical circulatory support as the only life-saving therapeutic options [200]. This unmet clinical need has driven the development of total artificial hearts and, more recently, bioartificial and biohybrid cardiac platforms designed to improve haemocompatibility, physiological integration, and long-term haemodynamic support.

The SynCardia Total Artificial Heart (TAH) is a durable, pneumatically driven biventricular mechanical support device that replaces the native ventricles and is primarily used in patients with end-stage biventricular heart failure who are not suitable for conventional left ventricular assist device support [201–203]. It remains the only approved total artificial heart for clinical use and is most commonly implanted as a bridge-to-transplant, particularly in patients with severe right ventricular dysfunction or complex conditions such as ventricular thrombosis, restrictive cardiomyopathy, or congenital heart disease [201–203]. Although fully implantable, the system requires percutaneous drivelines connected to an external pneumatic driver, which may adversely affect quality of life, and device failure can result in immediate haemodynamic collapse [201–203].

The CARMAT Aeson bioprosthetic artificial heart represents a more explicitly bioartificial configuration because it combines bovine pericardium blood-contacting surfaces with self-regulating haemodynamic control through embedded sensors [204,205]. It received CE Mark approval in Europe and is being evaluated in an FDA-approved early feasibility study in the United States, illustrating the gradual clinical translation of selected biohybrid cardiac replacement systems [206].

Beyond durable mechanical replacement, the concept of the bioartificial heart has progressively expanded toward tissue-engineered constructs designed to reproduce not only pump function but also the structural, vascular, and biological complexity of native myocardium. Decellularised whole-heart scaffolds preserve native extracellular matrix architecture and can be recellularised with cardiomyocytes to generate coordinated contractile activity, establishing the proof of principle for whole-heart bioengineering [106–108,207,208]. Whole-heart decellularization also retains key anatomical features, including chamber geometry, valvular structures, and the coronary vascular tree, making these scaffolds attractive templates for repopulation with cardiomyocytes, endothelial cells, and supportive stromal populations [106–108,207,208].

However, functional performance remains far from clinical applicability, as early recellularised rat hearts generated only about 25% of neonatal systolic pressure, corresponding to approximately 15 mmHg [209–211]. Bioartificial hearts and large-scale cardiac constructs, therefore, remain confined to preclinical development, with *in vitro* studies showing very limited haemodynamic output and unstable electrophysiological behaviour. Heterotopic transplantation experiments in large animals have further highlighted persistent barriers, including thrombosis, vascular occlusion, and inflammatory infiltration after implantation [210,212,213].

Cardiac patches currently represent the most clinically advanced branch of bioartificial cardiac research because they aim to reinforce injured ventricular regions, deliver reparative cells or bioactive factors, and stimulate endogenous myocardial regeneration without

requiring replacement of the whole organ [214–216]. Most published work in this area has focused on cardiac patches, whereas only a small minority of studies have addressed whole-heart constructs or biohybrid ventricular assist strategies, underscoring the translational preference for modular and surgically manageable approaches [215–219]. Most current preclinical and early clinical evidence suggest that the main therapeutic effect of these constructs is paracrine rather than directly contractile, mediated through the release of growth factors, cytokines, extracellular vesicles, and other regenerative signals [220–222].

Engineered heart muscle allografts derived from iPSC-cardiomyocytes and stromal cells achieved remuscularisation in non-human primates and subsequently supported transition toward first-in-human clinical evaluation [223]. Early clinical experience with allogeneic iPSC-derived cardiomyocyte patches in ischemic cardiomyopathy has also suggested an acceptable safety profile, with no tumorigenesis or severe arrhythmia reported during follow-up, although efficacy data remain preliminary and based on very small cohorts [224–226].

Despite this progress, several critical barriers still hinder the transition from experimental constructs to a clinically effective bioartificial heart. These include the need to generate a sufficient mass of mature cardiomyocytes for human-scale support, establish stable electromechanical synchronization across the construct, and ensure rapid and durable vascular integration capable of sustaining the high metabolic demands of cardiac tissue [227–229]. Bioartificial heart technologies are also likely to face more complex translational pathways than conventional mechanical circulatory support devices because they combine high-risk implantable hardware with biologically active materials, engineered tissues, or living cells.

Future development will therefore require integrated evidence on mechanical reliability, haemodynamic efficacy, hemocompatibility, thrombogenicity, immunogenicity, sterility, long-term scaffold stability, and, where applicable, arrhythmogenic and tumorigenic risk. For this reason, the field is likely to progress stepwise, from acellular or minimally cellular biomaterial patches to vascularised and electrically integrated myocardial grafts, and only later toward chamber-scale or whole-heart bioengineering strategies. In this translational continuum, cardiac patches currently represent the most realistic intermediate platform bridging conventional mechanical circulatory support and the long-term goal of a fully implantable bioartificial heart.

3.4. The Bioartificial Pancreas

Type 1 diabetes mellitus is an autoimmune disease characterized by selective destruction of pancreatic beta cells, resulting in absolute insulin deficiency and lifelong dependence on exogenous insulin therapy [230–232]. Existing treatments like multiple daily injections, continuous subcutaneous insulin infusion and closed-loop artificial pancreas systems improve glycaemic control but do not eradicate long-term complications or risk of hypoglycaemia and impose a continuous daily burden of management [233,234]. In addition to these established complications, chronic hyperglycaemia contributes to diabetic nephropathy, neuropathy, and retinopathy, substantially increasing both patient morbidity and the socioeconomic burden of the disease [235].

Pancreatic islet transplantation via the Edmonton Protocol has demonstrated that beta-cell replacement can achieve insulin independence, but is severely limited by donor availability and the need for lifelong immunosuppression, which carries substantial toxicity, including increased risk of infection and malignancy [236–238]. Since the landmark Edmonton Protocol was reported in 2000, approximately 400 pancreatic islet transplantations were performed worldwide between 1999 and 2005, confirming clinical reproducibility while also underscoring the persistent shortage of donor pancreases [238].

The bioartificial pancreas (BAP) is designed to address both limitations by encapsulating insulin-producing cells within an immunoprotective device, thereby providing physiological glucose-stimulated insulin secretion without systemic immunosuppression [239]. A BAP device consists of a semipermeable membrane that allows the diffusion of oxygen, nutrients, and glucose to the encapsulated cells and permits insulin release in response to glucose levels, while physically blocking immune cells, antibodies, and complement components that would otherwise destroy the graft [100,101,135,240]. The islets of Langerhans are complex multicellular micro-organs (70–250 μm in diameter), supplied by two or three afferent arterioles and composed of beta, alpha, delta, and PP cells [241]. This intricate architecture and the highly dynamic blood supply make precise replication within an encapsulation device exceptionally challenging [100]. Three principal encapsulation architectures are under active development [100,132,242]. Macroencapsulation devices are larger planar, cylindrical, or disc-shaped constructs, often several centimetres in diameter, that house hundreds to thousands of islets. They are retrievable and can incorporate ports for cell refilling, but the central cells are vulnerable to hypoxia because diffusion distances may exceed 200 μm , and these devices are also prone to a brisk foreign body response, resulting in fibrotic encapsulation [102,103,243]. In animal models, macroencapsulated devices have maintained blood glucose control for more than three years in allogeneic canine transplants [103,244], but progressive fibroblast overgrowth on the device surface reduces oxygen and nutrient delivery and ultimately impairs glucose responsiveness [103,244].

Microencapsulation involves the individual encapsulation of islets within hydrogel beads of 300–800 μm , providing a high surface-area-to-volume ratio and enabling minimally invasive intraperitoneal delivery. Using alginate-poly-L-lysine microcapsules, barium-cross-linked alginate, and agarose hydrogel formulations, sustained blood glucose control has been demonstrated for more than 350 days with allogeneic islets and more than 140 days with fetal porcine islets in preclinical models [99,239,245]. In clinical studies using human pancreatic islets encapsulated in alginate-poly-L-lysine, some patients achieved insulin independence for up to nine months, with improved quality of life and no device-related complications [246–248]. However, consistency of performance, pericapsular fibrosis, and long-term cell survival remain major challenges [249,250].

Nanoencapsulation and conformal coating apply ultrathin protective layers directly onto the cell surface, minimizing diffusion distances and enabling transplantation into highly vascularised sites such as the liver via portal vein infusion [27,104,251].

For the bioartificial pancreas, oxygen supply and fibrosis prevention remain the two principal unresolved challenges for clinical translation [252,253]. The blood-perfusion type of BAP, in which the device is connected to an arteriovenous shunt and insulin-secreting cells are cultured within the device septum, offers favourable glucose responsiveness because blood flows directly through the device, facilitating rapid oxygen and nutrient exchange [254]. However, this design carries an increased risk of embolism due to blood clot formation and requires invasive surgical connection, thereby limiting long-term use [254]. Subcutaneous implantation is preferred for patient quality of life, but subcutaneous sites lack adequate blood flow; strategies involving pre-vascularization with basic fibroblast growth factor (bFGF) have demonstrated excellent induction of new blood vessels around implanted devices, enabling sustained islet function in animal models. The choice of implantation site, including intraperitoneal, epididymal, intramuscular, subcutaneous, and intermuscular locations, remains an active area of investigation, with intramuscular prevascularization emerging as a particularly promising strategy [254,255].

Alongside implantation-site optimization, decellularised pancreatic ECM has also emerged as a relevant proof-of-concept for ECM-based bioartificial pancreas development, given its ability to support beta-cell function and insulin secretion [109]. Incorporation

of CXCL12 into purified alginate microcapsules enhanced glucose-stimulated insulin secretion and beta-cell function while preventing pericapsular fibrosis, enabling long-term glycaemic control for up to 174 days in diabetic mice without immunosuppression [256]. The β Air device (Betalin Therapeutics) is a subcutaneous macroencapsulation device with an integrated oxygen supply chamber, which is refuelled via subdermally implanted access ports, and provides a direct approach to the oxygen supply problem [257]. In an open-label pilot investigation (NCT02064309), it showed safety and partial islet function over 6 months, but with low C-peptide levels and limited efficacy due to inflammatory and fibrotic responses [257].

Among the cell sources, the most transformative innovation is the use of iPSC-derived beta cells [258,259]. Reprogramming of patient-derived somatic cells yields glucose-responsive, insulin-producing cells that theoretically overcome donor scarcity and reduce immune rejection [260–262]. Embryonic and adult stem cells are being actively studied. Although differentiation into insulin-secreting cells has been achieved in vitro, the generation of efficient and tightly regulated human pancreatic beta-cell lines remains an unresolved challenge [263–265]. Zimislecel (VX-880) has shown promising first-in-class clinical results, although longer follow-up, broader patient experience, and the ongoing need for immunosuppression remain important limitations for wider implementation [266]. In a Phase 1/2 trial (NCT04786262), all 12 recipients of a full-dose single infusion of hESC-derived islets reached ADA-recommended HbA1c (<7.0%) and time-in-range (>70%) targets at one year; 10 of 12 (83%) achieved insulin independence, and all remained free from severe hypoglycaemic events from day 90 onward [266]. These findings supported continued development, with zimislecel entering Phase III in November 2024 as the first stem cell-derived islet therapy to reach this milestone [267,268].

The need for ongoing immunosuppression is a critical restriction [267,268]. Attempts to abrogate immunosuppression by macroencapsulation have met with limited success to date. VX-264, a macroencapsulated allogeneic stem cell-derived islet therapy, was terminated in early 2025 after failing to meet its efficacy endpoint, highlighting that encapsulation-mediated immune evasion without functional compromise is yet to be achieved [25,269]. In parallel, CRISPR-based hypoimmune engineering has emerged as a promising encapsulation-free strategy for allogeneic beta-cell transplantation by suppressing HLA class I and II expression via B2M and CIITA knockout and limiting NK cell-mediated cytotoxicity via CD47 overexpression [270]. This approach achieved graft survival and glycaemic control without immunosuppression in immunocompetent non-human primates in 2024 and has encouraged further clinical development, including ongoing early-phase evaluation of VCTX211 (NCT05565248) [271–274].

Complex regulatory issues at the intersection of combination products have persisted for cell treatment and medical devices. Constructs of bioartificial pancreas in Europe are classed as Advanced Therapy Medicinal Products (ATMPs) in accordance with Regulation (EC) No 1394/2007 [275]. Hybrid bioartificial products that combine the mode of action of cell therapy with the functionality of a medical device highlight a basic regulatory gap, as they do not satisfactorily fit into ATMP or medical device regulatory models. This has led to calls for updated, product-specific guidance from the EMA and national competent authorities [276]. The European Commission-funded VANGUARD project developed a vascularised and immune-protected bioartificial pancreas for transplantation in type 1 diabetes, with the aim of restoring glucose control without lifelong immunosuppression [277,278].

3.5. The Bioartificial Lung

The lung remains one of the most challenging targets in bioartificial organ engineering because effective replacement requires not only structural reconstruction, but also

coordinated restoration of ventilation, perfusion, and an ultra-thin gas-exchange interface [134,279–283]. This challenge is particularly relevant in light of the persistent limitations of conventional lung transplantation: donor shortage remains severe, only a minority of donated lungs are suitable for clinical use, and long-term outcomes are still constrained by chronic rejection and the adverse effects of immunosuppressive therapy [6].

Decellularization of whole lungs has therefore emerged as a central strategy in lung bioengineering, because perfusion-based approaches can remove cellular components while preserving much of the native extracellular matrix, the airway branching pattern, and the vascular framework, thereby providing a biologically instructive scaffold that remains difficult to reproduce with fully synthetic systems [110–113,284]. However, successful lung bioengineering depends not only on scaffold preservation but also on effective and anatomically appropriate recellularization with the main pulmonary cell compartments, including alveolar epithelial cells, endothelial cells, and mesenchymal support cells, whose reciprocal interactions are essential for tissue organization, repair, and functional integration [105,285–289].

In particular, alveolar type I pneumocytes are required to re-establish the extremely thin air-blood interface necessary for oxygen and carbon dioxide exchange, whereas alveolar type II pneumocytes are essential for surfactant production, epithelial repair, and maintenance of alveolar homeostasis, also acting as progenitor cells in the adult lung [290,291]. Pioneering proof-of-concept studies demonstrated that decellularized rat lungs could be recellularized, orthotopically transplanted, and transiently support *in vivo* gas exchange, thereby establishing the feasibility of whole-lung bioengineering at the experimental level [292–294]. Subsequent studies extended decellularization protocols to porcine and human lungs, bringing the field closer to a clinically relevant scale and confirming that large-animal and human scaffolds can retain structural and matrix characteristics suitable for recellularization and *ex vivo* investigation of lung regeneration [114–116,295].

Despite this progress, clinical translation remains limited by incomplete endothelialization, thrombogenicity, and insufficient functional maturation after implantation [117,296]. As a complementary strategy, organ-specific extracellular matrix-derived scaffolds and acellular lung matrices have been used to support lung cell attachment and differentiation, although the generation of a fully functional organ-scale graft remains a major challenge [118,295]. Accordingly, major priorities include preservation of matrix properties during decellularization, more controlled epithelial and endothelial repopulation, improved bioreactor systems, and the use of pluripotent patient-specific cell sources [297,298].

In parallel with scaffold-based approaches, extracorporeal and device-driven strategies represent a clinically more immediate dimension of lung bioengineering. Although not strictly classifiable as bioartificial organs, these extracorporeal support strategies are considered here for completeness, given their direct relevance to the translational landscape of lung replacement. Extracorporeal membrane oxygenation (ECMO) currently provides the most advanced level of temporary gas-exchange support available in clinical practice, serving as a bridge to transplantation or recovery in patients with refractory respiratory failure [299–302]. However, ECMO carries substantial risks of bleeding, thromboembolism, infection, and end-organ damage with prolonged use, and does not replicate the metabolic or immunological functions of the native lung [299–303]. Next-generation artificial lung devices aim to address these limitations by reducing circuit complexity, improving hemocompatibility, and enabling longer-duration ambulatory support [304,305]. Biohybrid approaches represent a promising intermediate strategy: by seeding gas-exchange hollow-fiber membranes with autologous endothelial cells, these devices aim to reduce thrombogenicity and inflammatory activation at the blood-membrane interface, potentially extending the safe duration of extracorporeal respiratory support [299,303–305]. Lung-on-

chip platforms also provide a relevant complementary perspective in this field [306,307]. By recreating key features of the alveolar-capillary interface within microfluidic systems lined with human lung epithelial and endothelial cells, these models can reproduce important aspects of pulmonary mechanics, inflammatory signalling, and drug transport with greater physiological relevance than conventional two-dimensional cultures [306–308]. Although they are not intended as implantable replacement platforms, their growing translational value as advanced preclinical models has increased in parallel with broader regulatory and scientific interest in organ-on-chip technologies. In the same vein, pulmonary organoid models contribute complementary insight by offering patient-derived three-dimensional representations of airway and alveolar biology, thereby supporting disease modelling, mechanistic investigation, and future cell-source development for lung bioengineering [309,310].

Collectively, lung bioengineering is progressing through a combination of complementary approaches, with the most direct translational advances currently arising from scaffold-based strategies and extracorporeal or biohybrid support systems, while microfluidic lung models continue to provide important preclinical and mechanistic insight. In the near term, the clinical impact of the field is most likely to emerge from incremental improvements in extracorporeal support and biohybrid devices, whereas whole-lung recellularization remains a longer-term objective that still depends on overcoming major challenges in vascularization, innervation, and immunological integration.

4. Conclusions

Bioartificial organ research has evolved into a broad translational field in which progress differs substantially among target organs. The most advanced opportunities currently lie in modular or hybrid platforms, including extracorporeal liver support systems, wearable or implantable renal devices, stem cell-based endocrine replacement strategies, and tissue-engineered cardiac repair constructs. By contrast, whole-organ engineering of highly vascularized and structurally complex organs, particularly the heart and lung, remains largely preclinical. Across all organ systems, durable clinical translation will depend on solving a common set of challenges, especially vascularization, immune protection, long-term functional maturation, scalable cell manufacturing, and regulatory validation. In addition, meaningful clinical impact will require GMP-compliant scale-up, robust preservation and supply-chain strategies for living cell-based products, and clearer regulatory and reimbursement pathways to support adoption in real-world healthcare systems. The near-term future of the field is therefore more likely to be defined by stepwise and indication-specific clinical applications than by the immediate replacement of fully bioengineered solid organs.

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Abbreviations

The following abbreviations are used in this manuscript:

ACLF	Acute-on-chronic liver failure
ATMP	Advanced Therapy Medicinal Product
AI	Artificial intelligence
ALF	Acute liver failure
BAK	Bioartificial kidney
BAL	Bioartificial liver
CD47	Cluster of differentiation 47
bFGF	Basic fibroblast growth factor
CO ₂	Carbon dioxide
CORDIS	Community Research and Development Information Service
CORDIAL	Chronic Online peritoneal dialysis tReatment with a wearable Intelligent Automated Loop device
CVVH	Continuous venovenous haemofiltration
DLP	Digital light processing
ECM	Extracellular matrix
ECMO	Extracorporeal membrane oxygenation
ELAD	Extracorporeal Liver Assist Device
EU	European Union
FDA	Food and Drug Administration
GMP	Good manufacturing practice
hiHeps	Human induced hepatocytes
IgG	Immunoglobulin G
iBAK	Implantable bioartificial kidney
MEMS	Microelectromechanical systems
NBAL	Non-bioartificial liver
NIH	National Institutes of Health
OOC	Organ-on-chip
OPTN	Organ Procurement and Transplantation Network
PERV	Porcine endogenous retrovirus
PEG	Polyethylene glycol
PHHs	Primary human hepatocytes
PSC	Pluripotent stem cells
QC	Quality control
RAD	Renal Assist Device
SDS	Sodium dodecyl sulfate
SLA	Stereolithography
SNM	Silicon nanopore membrane
SWIFT	Sacrificial Writing Into Functional Tissue
WAK	Wearable artificial kidney

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