Artificial Lungs: Current Status and Future Directions

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Abstract

Purpose of Review Although lung transplantation can be used to treat lung failure, limited donor organ availability creates a pressing need for improved artificial lung technology. This review discusses recent developments and future research pathways for respiratory assist devices and regenerative therapies intended to treat advanced lung disease.

Recent Findings Hollow fiber membrane gas exchangers can be used to bridge lung failure patients to transplantation. Engineering improvements to such devices are on the verge of enabling longer term wearable systems that simplify and improve support. Progress with microchannel-based devices provides hope of smaller, more biomimetic devices that may even enable implantation; however, further development and testing are needed. Advances in cell-based technologies and tissue engineering have enabled early proof of concept of bioartificial lungs with properties similar to the native organ.

Summary Recent progress with artificial lungs has enabled better treatment as a bridge therapy. Continued advances in both engineering and biology will be necessary to achieve a truly implantable artificial lung capable of destination therapy.

Keywords Artificial lungs · Oxygenator · Lung disease · Lung transplantation · Extracorporeal membrane oxygenation

Introduction

Lung transplantation remains the most effective treatment option for patients suffering from advanced stage lung disease with over 2000 lung transplants performed annually in the USA [1]. Despite the success of transplantation, there is a tremendous unmet need for advanced therapies for lung failure. Evidence demonstrates that only a fraction of those patients with end-stage lung disease receive a transplant and that over 150,000 Americans die every year from lung failure [2]. This disparity between organ need and availability has created

vigorous research efforts toward the development of artificial lung technology for lung failure including both regenerative technologies and extracorporeal and intracorporeal gas exchange devices.

Contrary to the tremendous progress that has been achieved with ventricular assist devices (VADs) for destination therapy in advanced heart failure, no such platform exists with regard to end-stage lung disease. Thus, similar to the current state of VADs, the pursuit of artificial lung technology capable of destination therapy or bridge to recovery/transplantation has the potential to significantly improve outcomes and quality of life for those suffering from advanced lung failure. Successes obtained with extracorporeal membrane oxygenation (ECMO) have revitalized research interest into the development of artificial lung technologies and several devices have advanced to clinical trials in recent years. Herein, we will review the current state of artificial lung development and related therapies as well as the direction of the field moving forward.

Extracorporeal Devices

Extracorporeal gas exchangers draw venous blood from the vascular system and achieve oxygen and carbon dioxide

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(CO₂) transfer outside the body. Gas transfer is accomplished in present-day devices via the use of hollow fiber membranes (HFMs) in which blood flows over the fiber exterior while oxygen-rich sweep gas flows through the fiber lumen. Oxygen and CO₂ diffuse through the microporous HFM wall along their respective concentration gradients. To achieve physiological exchange rates, clinical devices incorporate thousands of fibers into a bundle with a total membrane surface area sufficient to maintain normal gas partial pressures within blood. Gas exchangers may operate with or without the assistance of a blood pump depending on the points of connection to the vascular system and resistance to blood flow created by the HFM bundle.

Extracorporeal gas exchangers are currently used during ECMO to bridge advanced lung failure patients to transplantation. In a recent study published from the University of Pittsburgh, Hayanga and colleagues showed that 1-year survival for patients bridged with ECMO to transplantation increased from 25% for the period spanning 2000–2002 to 75% for 2009–2011 [3•]. These findings support the increased utilization of ECMO-based technology as a platform for the development of artificial lung systems. In this regard, ambulatory ECMO as a bridge to transplantation is clearly advantageous as it allows patients to be awake, ambulatory and off of mechanical ventilation while being bridged to transplantation [4]. In a single institution study from Columbia University Medical Center, 55.6% of patients bridged with ECMO were successfully transplanted while only 12.5% died while awaiting transplant [5•]. Of those transplanted, 80% were on ambulatory ECMO. This is an important point as rehabilitation is facilitated in ambulatory ECMO patients thus allowing preservation of the physiologic capacity and strength needed to undergo successful transplantation. Similar findings were reported from the group at Hannover wherein patients bridged with ambulatory ECMO had less ventilator dependence and shorter intensive care unit (ICU) stays [6]. Although most reports describe support durations of approximately 1–2 weeks, isolated cases of ambulatory ECMO support for a matter of months prior to successful transplantation have been reported [7]. These studies clearly demonstrate the clinical benefit of ambulation during respiratory assist and identify this as a critical priority in the development of a “true” artificial lung.

Although patient ambulation during support is feasible with currently available ECMO systems, the large size and cumbersome nature of the support circuits make it challenging. Mobilization of an ECMO patient requires a cart carrying the circuit components to be rolled alongside the patient as well as a team of highly trained medical professionals [8]. Considering this, multiple research groups are pursuing the development of a wearable artificial lung system that could more easily enable patient ambulation during support. Griffith and colleagues have developed an artificial pump lung (APL)

meant to be worn on the patient and allow for ambulatory respiratory or cardiopulmonary support. The APL is an ultra-compact pump-oxygenator consisting of an annular HFM bundle integrated with a magnetically levitated centrifugal pump. During preclinical testing in an ovine model, the device provided an average oxygen transfer rate of 148 mL/min at a blood flow rate of approximately 3 L/min with stable performance over the 30-day study period. Of the five long-term trials, two had isolated clots in the space between the device housing and the outer layer of the fiber bundle with no hemodynamic compromise [9•]. Thirty-day use of the APL also demonstrated good hemocompatibility with limited device-induced platelet activation and no significant hemolysis [10]. This group has also developed a smaller version of the device for use in pediatric patients (5–20 kg) termed the pediatric pump-lung (PediPL). The PediPL utilizes a similar HFM bundle and pump design as the APL and has also shown positive preclinical performance out to 30 days [11]. In an ovine model of acute respiratory failure, the PediPL demonstrated the ability to successfully treat both hypoxia and hypercapnia [12].

Federspiel and colleagues at the University of Pittsburgh have also made substantial progress toward the development of a wearable artificial lung. The Modular Extracorporeal Lung Assist System (ModELAS) integrates a pivot-bearing centrifugal pump with a HFM bundle and is intended to be worn on the patient during long-term support. The modular device design enables its configuration with HFM bundles of varying size, thereby allowing the ModELAS to be used in a variety of respiratory assist applications. A unique cylindrical, stacked-type HFM bundle design that enhances gas exchange efficiency enables full respiratory support with a considerably smaller HFM surface area (0.65 m²) relative to other devices [13]. A smaller HFM surface area should both decrease the likelihood of thrombotic complications and minimize overall device size. Preclinical ovine trials have demonstrated consistent blood flow and gas exchange rates over a 5-day period without any device-related complications. Blood outflow measurements showed full oxygen saturation for inlet saturations ranging from 50 to 59% at a blood flow rate of 2 L/min. Hemodynamics were adequate with minimal increases in HFM bundle resistance measured over the 5-day period [14]. Promising performance for the ModELAS in the settings of pediatric support and low-flow extracorporeal CO₂ removal (ECCO₂R) has also been shown in benchtop and acute in vivo studies [15–17]. These preclinical evaluations of fully integrated and wearable pump-lungs from multiple groups are promising, and clinical implementation of such devices is likely in the near future. These devices should enable safer and more convenient ambulation during respiratory support and are a first step toward enabling such treatment outside of the ICU.

In patients with sufficient cardiac function and hemodynamic stability, pumpless gas exchangers can be connected

to the vascular system such that blood flow is driven by the native heart. Pumpless devices may ease the burden of ambulatory support due to the smaller device size that is achievable without a pump. The absence of a pump may also improve performance by avoiding supraphysiological blood shear stresses that are inherent to rotary blood pumps. The Novalung (Xenios, Germany) is a low-resistance gas exchanger that can be used without a pump. In a recent report by Hoetzenecker, the authors report on their experience using ECMO as a bridge to lung transplantation. Among the cohort were 17 patients supported with the pumpless Novalung (8 in a femorofemoral [fem-fem] arteriovenous configuration and 9 in a pulmonary artery to left atrium [PA-LA] configuration) who were successfully bridged to transplantation with a median survival of 31 (fem-fem) and 39 (PA-LA) months [18]. Although the Novalung exhibits a low resistance to blood flow (~ 5 mmHg/[L/min]) relative to other commercially available gas exchangers, this resistance is still approximately 5-fold greater than that of the native lung [19]. Low resistance to blood flow is critically important for a pumpless gas exchanger in order to both maintain sufficiently large device blood flow rates and avoid detrimental effects on the right heart. Thus, ultra-low resistance gas exchangers have been pursued extensively over the past decade [20–23]. Cook and colleagues recently reported development of a compliant thoracic artificial lung (cTAL) with a measured blood flow resistance of 1 mmHg/(L/min). Preclinical testing in an ovine model demonstrated stable performance over a 14-day period with minimal increase in resistance and a low degree of intra-bundle thrombus formation [24]. Bartlett et al. at the University of Michigan are working toward the development of a pumpless artificial lung intended for use in pediatric patients with pulmonary hypertension [25, 26]. The most recent design iteration of this device utilizes a unique concentrically gated HFM bundle design to increase gas exchange efficiency and has shown positive benchtop performance [25]. Low-resistance, pumpless artificial lungs are attractive due to simplified device management and maintenance of low shear stresses within the blood. The absence of a pump, however, results in less control over device blood flow rates and thus overall support.

ECCO₂R is the use of extracorporeal gas exchangers with low blood flow rates (< 1 L/min) to achieve the primary therapeutic goal of CO₂ removal. Although oxygen and CO₂ transfer within a HFM occurs via the same diffusion process, therapeutic levels of CO₂ removal can be accomplished at much lower blood flow rates relative to those needed for oxygenation. This is primarily due to the large amount of CO₂ carried per volume of venous blood relative to the amount of oxygen that can be added per volume of venous blood. The lower blood flow rates used during ECCO₂R enable the use of smaller bore cannula (typically 13–22-Fr dual-lumen cannulas) and less invasive

cannulation strategies relative to traditional ECMO. This therapy can be particularly useful in managing hypercapnia in patients with acute respiratory distress syndrome (ARDS) or during acute exacerbations of chronic obstructive pulmonary disease (ae-COPD). ECCO₂R can be used in these patients to enable protective mechanical ventilation or even avoid intubation altogether. The low extracorporeal blood flows used during ECCO₂R, however, can result in suboptimal flow dynamics within most HFM gas exchangers intended for ECMO. Thus, multiple devices specifically designed for ECCO₂R have been developed over the past two decades. Initial work by Federspiel and colleagues at the University of Pittsburgh led to the development of the Hemolung (ALung, Pittsburgh, PA) [27]. The Hemolung integrates a centrifugal pump with an annular HFM bundle that surrounds a spinning core. The spinning core increases blood mixing at the HFM surface thereby enhancing gas exchange efficiency at low blood flow rates. In a small retrospective study of 15 patients, the Hemolung successfully achieved the intended goal of avoiding intubation or enabling protective ventilation in all but one patient. The Hemolung was able to achieve a CO₂ removal rate of 90–100 mL/min at blood flow rates of 450–550 mL/min over a median support duration of 5 days. Importantly, 93% of patients survived to weaning from ECCO₂R and 67% survived to discharge [28]. Multiple other small-scale studies have reported similarly positive findings for use of the Hemolung in patients with hypercapnic respiratory failure [29, 30]. Two ongoing randomized clinical trials are evaluating the use of the Hemolung in ae-COPD and ARDS patients. The Novalung iLA Activve is another venovenous ECCO₂R device featuring a centrifugal pump and HFM bundle. In a study of ten patients with hypercapnic respiratory failure, the iLA Activve was able to achieve a median CO₂ removal rate of approximately 70 mL/min at a blood flow rate of 1 L/min [31]. In a separate retrospective analysis of twelve patients, the iLA Activve enabled reduction in ventilation pressures and minute volumes with limited complications due to circuit thrombosis and bleeding [32]. Multiple other extracorporeal systems designed for ECCO₂R have now been developed and recently shown positive results in small-scale clinical studies [33–35]. ECCO₂R devices enable a less invasive respiratory support modality for the treatment of hypercapnic respiratory failure. Early clinical investigations show promise for this approach and larger scale, randomized clinical trials underway will further elucidate its utility.

A primary challenge to all artificial lungs intended for long-term use is intra-device thrombosis. The large blood-contacting surface area of these devices results in increased thrombogenicity relative to VADs. Current clinically available respiratory support systems have a typical lifetime of 1–2 weeks before a system exchange is required (most often due to thrombosis) [36]. Some degree of improved

thrombogenicity can be achieved via device design. Primary goals in this respect should be to maintain low blood shear stresses to minimize platelet activation, reduce stagnation and recirculation to prevent local accumulation of procoagulant molecules, and minimize overall blood-contacting surface area [37]. Most currently used gas exchangers utilize coatings (such as immobilized heparin) on blood-contacting surfaces to decrease thrombogenicity. Improved thromboresistant approaches, however, are still sorely needed. Accordingly, several groups are pursuing the development of novel thromboresistant coatings for implementation within artificial lungs. Novel approaches under investigation include the immobilization of zwitterionic molecules that mimic the exterior of cell membranes as well as the use of nitric oxide producing materials that inhibit platelet activation [38–44]. It should be noted that surface modification for improved hemocompatibility is a vast topic only briefly touched upon here but discussed more thoroughly elsewhere [45]. Thrombotic complications are likely the largest challenge to the long-term use of artificial lungs. Improved thromboresistance via surface coatings or new pharmacological agents will be necessary to ultimately realize the vision of artificial lungs capable of destination therapy.

Intracorporeal Devices

With the lack of donor organs available for transplantation, the need to develop alternatives for destination therapy continues to evolve. The “holy grail” of artificial lung development is a durable, fully intracorporeal device that allows long-term support with minimal inhibition of patient mobility or ambulation. Although a truly implantable gas exchanger has not yet been developed, multiple approaches have been pursued and may offer potential pathways.

Multiple researchers pursued the development of intravascular HFM-based gas exchangers in the 1990s and 2000s. These devices were designed to be placed within the inferior vena cava and utilized a long array of HFMs that facilitate the same gas diffusion process described for extracorporeal devices. The absence of extracorporeal blood conduits and a device housing would be expected to mitigate blood activation via a decreased blood-contacting surface area. The limited space available within the vena cava, however, presents a major challenge for device design. Initial designs demonstrated limited amounts of gas exchange and also exhibited unacceptably high complication rates during clinical trials [46, 47]. Subsequent research has focused on increasing gas transfer efficiency via blood mixing induced by pulsating balloons or spinning impellers positioned within an annular HFM bundle [48, 49]. These efforts, however, have yet to result in a clinically useful intravascular device.

Schumer et al. used benchtop studies to explore the feasibility of implantation of a traditional extracorporeal gas exchanger positioned at the right upper lobe. Device blood flow would be driven by the native heart while the sweep gas pathway would be connected to the endobronchial system with the intent of gas flow being induced via the patient’s breathing. A simplified benchtop study demonstrated the feasibility of supporting up to 25% of the cardiac output based on hemodynamic and gas exchange requirements [50]. However, the typical device lifetime and size of current extracorporeal gas exchangers make their implantation unrealistic.

Microfluidic-based artificial lung technology may offer an attractive alternative to the traditional HFM approach in the pursuit of an implantable device. These devices typically consist of small blood conduits or microchannels (hydraulic diameter of ~ 10–300 μm) separated from a gas pathway via a thin (~ 15–50 μm) gas-permeable, polydimethylsiloxane (PDMS) membrane. Oxygen and CO_2 transfer occurs via diffusion across the PDMS membrane along the respective concentration gradients. In theory, these devices offer multiple potential benefits over the HFM-based approach. The small scale of the blood conduits drastically decreases gas diffusion distances and increases the ratio of gas-exchanging membrane surface area to blood volume relative to HFM devices. Both of these characteristics would be expected to improve gas exchange capabilities, potentially even enabling the use of room air as a sweep gas. Additionally, microchannel devices also enable a more biomimetic approach to artificial lungs. Blood-filled microchannel networks can be designed to mimic the geometry and branching of native vasculature thereby resulting in more physiologic levels of pressure and shear stress within the blood [51]. A major limitation, however, to clinical implementation of these devices is the need to incorporate large numbers of microchannel modules in parallel to achieve physiologic levels of gas transfer. Single modules have rated blood flow rates of approximately 15–60 mL/min and thus dozens if not hundreds of parallel devices would be needed to achieve clinically relevant support [52–54]. Hemocompatibility and concerns of thrombosis also remain a significant challenge to this approach with the small blood conduits being particularly susceptible to embolization. Accordingly, coatings for improved hemocompatibility or even surface endothelialization are being pursued [51, 55, 56]. In vivo evaluation of microchannel devices has been limited to a few acute studies in small animal models [51, 53]. Microchannel-based devices represent a promising approach that may enable a pathway to intracorporeal artificial lungs. Demonstration of extended device lifetimes and sufficient in vivo support in large animal models is needed in order to progress this technology closer to clinical implementation.

A summary of the discussed approaches to artificial lung devices is provided in Table 1.

Table 1 Summary of artificial lung technologies

Device	Primary advantages	Primary disadvantages
Extracorporeal pumping HFM gas exchangers	<ul style="list-style-type: none"> • High versatility – can be used during poor cardiac function and with less invasive dual lumen cannulas • High degree of control over blood flow rate (and thus gas exchange support) 	<ul style="list-style-type: none"> • Supraphysiological blood shear stress due to presence of rotary blood pump
Extracorporeal low-resistance (pumpless) HFM gas exchangers	<ul style="list-style-type: none"> • Avoidance of high blood shear stress associated with pumps • Simpler and more compact device relative to pumping devices 	<ul style="list-style-type: none"> • Pump can increase management complexity and complication rates • Requires sufficient cardiac function and invasive connection to vascular system
Intravascular HFM gas exchangers	<ul style="list-style-type: none"> • Decreased blood-contacting surface area due to absence of device housing and blood conduits 	<ul style="list-style-type: none"> • Less control over blood flow rate (and thus gas exchange support) • Limited gas transfer rates primarily due to size constrictions imposed by intravascular placement
Microchannel-based gas exchangers	<ul style="list-style-type: none"> • Potential for improved gas exchange efficiency due to small scale of blood conduits • Biomimetic network of blood conduits induces more physiologic blood flows, pressures, and shear stress 	<ul style="list-style-type: none"> • High complication rate due to complex intravascular placement • Concerns of scalability • High susceptibility to thrombosis—long-term use has yet to be demonstrated

*HFM hollow fiber membrane***Bioengineering/Regenerative Technology**

Regenerative medicine and stem cell technologies are now being pursued as a means to overcome the organ shortage by exploiting the lungs regenerative capacity with cell-based therapies. Cell-based therapies are being explored with the intent either to harness the endogenous regenerative capacity of the lung or to create de novo tissues which provide gas exchange.

Cell-based therapy is not a new paradigm in lung disease. Numerous reports published in the early 2000s using bone marrow-derived stem cells and endothelial progenitor cells demonstrated engraftment in animal models. A central requirement for successful therapy was pre-existing injury which was believed to be required for engraftment and differentiation. However, the fraction of cells engrafted was typically so low that a significant physiological effect could not be attributed to the stem cell mass. Nevertheless, there are ten recent or ongoing clinical trials using mesenchymal stem cell therapies and endothelial progenitor cells in a spectrum of pulmonary diseases (clinicaltrials.gov). These trials are listed in Table 2. As can be seen in Table 2, there is little established consensus regarding cell type, dosing strategies, disease etiology, and therapeutic metrics which will complicate clinical evaluation of this approach. Unfortunately, companies are marketing unproven and unvalidated stem cell-based therapies for a variety of pulmonary diseases.

On the horizon are newer cell-based technologies which make use of inducible pluripotent stem cell (iPSC) technology. The ability to successfully reprogram human somatic cells into pluripotent stem cells has laid the ground work for cell-based regenerative approaches to disease treatment and is based on several sentinel studies in the field of stem cell biology [57–59]. The advantage of this approach is that iPSCs can potentially give rise to any type of somatic cell. The pluripotent nature of these cells makes them ideal for lung regeneration wherein multiple cell types are involved in respiratory function. Recent work from the Harvard Stem Cell Institute has demonstrated a critical role for transforming growth factor beta and SMAD signaling pathways in the expansion of adult epithelial cells from various organs [60]. These approaches give rise to the ability to manipulate differentiation and dedifferentiation pathways and may allow artificial organogenesis. Although it may take years to materialize, the use of human iPSC-derived lung cells represents an attractive therapeutic platform for lung regeneration [57–60].

Taking these concepts further, efforts aimed at creating a bioengineered artificial lung are being explored. These pursuits follow the tissue engineering principle that cellularized 3-D matrices that facilitate gas exchange can be created in vitro and applied in vivo. This technology builds on past accomplishments in tissue engineering efforts which have

Table 2 Clinical trials evaluating use of stem cell therapy in pulmonary disease

Study title	Status	Conditions	Interventions
Allogeneic Bone Marrow Mesenchymal Stem Cells for Patients with ILD and Connective Tissue Disorders	Recruiting	ILD, connective tissue diseases	Biological: allogeneic bone marrow–derived mesenchymal stem cells
Safety, Tolerability and Preliminary Efficacy of ADSCs for Patients with COPD	Active, not recruiting	COPD	Biological: ADSCs
Adipose Derived Cells for COPD	Withdrawn	COPD	Other: ADSCs
Safety and Efficacy of ADSCs for COPD	Completed	COPD	Drug: ADSCs
Safety and Efficacy of ADSCs for COPD	Withdrawn	COPD	Procedure: lipos aspiration with local anesthesia
Autologous Stem Cell Transplantation in Patients with Systemic Sclerosis	Recruiting	Systemic sclerosis, diffuse sclerosis, ILD, pulmonary hypertension	Drug: cyclophosphamide, mesna, rituximab, alemtuzumab, thiolepa, GM-CSF, intravenous immunoglobulin
PROCHYMAL (Human Adult Stem Cells) for the Treatment of Moderate to Severe COPD	Completed	COPD, pulmonary emphysema, chronic bronchitis	Radiation: total body irradiation Drug: Prochymal, placebo
Allogeneic Human Cells in Patients with Idiopathic Pulmonary Fibrosis via Intravenous Delivery (AETHER)	Completed	Idiopathic pulmonary fibrosis	Biological: allogeneic adult human mesenchymal stem cells, placebo
AZD9668, an Oral Neutrophil Elastase Inhibitor, in Bronchiolitis Obliterans Syndrome	Recruiting	Chronic graft vs host disease, bronchiolitis obliterans syndrome	Drug: AZD9668
Allogeneic Hematopoietic Stem Cell Transplantation	Recruiting	Histiocytosis, Langerhans cell	Biological: alemtuzumab
Reduced Intensity Hematopoietic Cell Transplantation for Patients with Resistant Langerhans Cell Histiocytosis	Terminated		Drug: fludarabine phosphate, melphalan Procedure: stem cell transplantation

ILD interstitial lung disease, COPD chronic obstructive pulmonary disease, ADSC adipose-derived stem cells

recapitulated various steps in lung development and have thus created milestones for developing a bioartificial lung. Decellularized scaffolds have been constructed from cadaveric lung and shown to provide an extracellular matrix which retains anatomic integrity and 3-D architecture ideal for lung tissue engineering [61, 62]. In support of this approach, Douglas and colleagues used fetal lung cells to generate alveolar-like structures on monolayer when cultured with an appropriate substrate [62, 63]. These types of 2-D tissue engineering approaches have laid the foundation for formation of more complex 3-D structures and identified substrate–cell interactions and crosstalk as critical components of tissue regeneration [64]. Researchers from the Harvard Stem Cell Institute have reported on the creation of functional bioartificial lungs based on acellular lung scaffolds. In this study, the authors used cadaveric rat lungs to create decellularized scaffolds which were then mounted on bioreactors and seeded with endothelial and fetal lung cells. The resulting bioartificial lungs were then orthotopically transplanted into rats for 14 days. The bioengineered lungs provided comparable gas exchange as that seen with cadaveric transplanted lungs, thus providing in vivo proof of concept for this technology [62]. In order to better facilitate mass production of bioartificial lungs, researchers have also explored the possibility of 3-D printing scaffolding material rather than using cadaveric lungs. The scaffolding would ideally be composed of native structural extracellular matrix components, prolong cell attachment, and be porous enough for efficient nutrient and gas transfer [65]. Despite promising results with stem cells, it must be recognized that in vitro systems have limitations and that gradual changes in genotype associated with culture conditions will likely affect their phenotypic behavior in an unpredictable manner. Nevertheless, one can envision that future efforts combining iPSC technology with 3-D bioactive scaffolds could provide the ideal platform on which to build a total artificial lung.

Conclusion

Although lung transplantation remains the definitive therapy for end-stage lung failure, clinical success with extracorporeal devices has shown this technology to be a critical lifesaving tool in the clinical arsenal. ECMO and associated extracorporeal devices have demonstrated their benefit and versatility in the management of chronic and acute lung failure with successful bridging to either recovery or transplantation. Engineering improvements to device design and efficiency are enabling longer term support that more easily facilitates patient ambulation and rehabilitation. Advancements enabling improved device longevity (i.e., improved thrombogenicity) and compactness will be needed to realize the goal of a fully implantable artificial lung. Our understanding of how best to

utilize cell-based therapies in the treatment of lung failure has vastly increased in recent years. This new knowledge along with breakthroughs in tissue engineering has enabled proof of concept work in fabricating materials and structures with attributes similar to those of the native lung.

Artificial lung development has been limited by both engineering problems, including durability, portability, and efficiency, as well as biological aspects including thrombosis and hemocompatibility. Engineering problems are generally considered surmountable, whereas biology is more difficult to control. Future efforts are expected to leverage discoveries in the bioengineering arena with better understanding of lung disease and regenerative capacity to bring a fully implantable artificial lung capable of destination therapy into clinical practice.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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