International Journal of
Life Sciences
International Peer Reviewed Open Access Refereed Journal

Int. J. of Life Sciences, 2024; 12 (4): 419-428
ISSN:2320-7817(p) | 2320-964X(o)

Review Article Open Access

AI Integration in Lung Scaffolds for Biomaterial Selection and Properties

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Manuscript details:

Received: 22.12.2024
Accepted: 26.12.2024
Published: 31.12.2024

Cite this article as:
Tiffany Goh (2024) AI Integration in Lung Scaffolds for Biomaterial Selection and Properties, *Int. J. of Life Sciences*, 12 (4): 419-428.

Available online on http://www.ijlsci.in
ISSN: 2320-964X (Online)
ISSN: 2320-7817 (Print)

ABSTRACT

Chronic lung diseases, including emphysema, interstitial fibrosis, and pulmonary vascular diseases, are the third leading cause of death worldwide, affecting more than 500 million people. These diseases are currently treated with lung transplantation when other medical therapies fail; however, there are significant challenges including donor shortages and high mortality rates, with over 75% of implanted lungs failing within 10 years. To address these limitations, lung tissue engineering (LTE) has emerged as an alternative approach to treat chronic lung diseases by transplanting functional bioengineered lungs. This review article aims to highlight the importance of biomaterial selection and to analyze the chemical and mechanical properties that are ideal for lung scaffolds. In this paper, AI applications in various LTE technologies that support the optimization of biomaterial selection and scaffold design are explored. The discussion of these topics gives a comprehensive overview of the material properties and emerging AI technologies improving the designs of lung scaffolds and their functionality. The integration of AI in scaffold design will produce progress in LTE as it will lead to more effective lung scaffolds.

Keywords: lung tissue engineering, biomaterials, scaffold properties, artificial intelligence, tissue engineering.

INTRODUCTION

Chronic lung diseases are disorders of the airways and other structures of the lung that are the third leading cause of death worldwide, impacting more than 500 million people globally (Gould et al., 2023; Santis et al., 2018; Soriano et al., 2020). Lung diseases such as emphysema, interstitial fibrosis, and pulmonary vascular diseases are currently treated with lung transplantation when other medical therapies fail; however, this treatment is largely ineffective due to donor shortages and high mortality rates (Prakash et al., 2015). With more than 75% of implanted lungs failing in the first 10 years as well as the imbalance of supply and demand of donor lungs, the majority of patients are unable to fully recover from lung diseases (Prakash et al.,

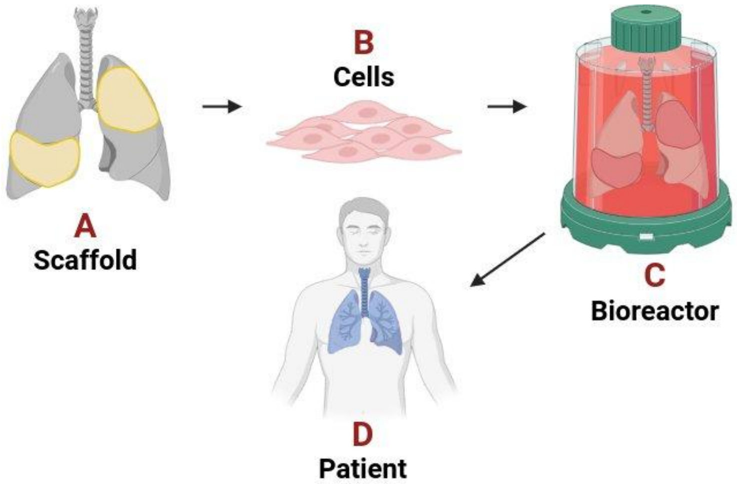

Figure 1. The process of LTE contains steps A, B, C, D (A) Ex: scaffold containing a combination of decellularized ECM and polymers (B) scaffold will be seeded with cells such as stem cells, epithelial cells, lung fibroblasts, etc. (C) cells are cultured in a bioreactor (D) resulting scaffold implanted into patient

2015). To address these limitations, lung tissue engineering (LTE) has emerged as an alternative approach to treat chronic lung diseases by transplanting functional bioengineered lungs.

The process of LTE consists of three steps: scaffold construction, seeding cells, and cultivating cells in bioreactors, which forms a scaffold into tissue or an organ (Calle et al., 2014). Scaffold construction includes selecting biomaterials and designing a scaffold that can successfully mimic the extracellular matrices (ECM) of the lung (Fig. 1A). Then, the fabricated scaffold will be seeded with appropriate cell types (Fig. 1B) to be cultured in a bioreactor (Fig. 1C) for cell proliferation, growth, and differentiation to take place and ultimately result in functional lung tissues to be implanted into the patient (Fig. 1D).

Scaffolds hold great importance in the field of tissue engineering as cells are unable to form into organs on their own; cells need a structure to keep them in place. This is akin to the ECM, which are the non-cellular components primarily composed of a network of proteins and polysaccharides that already surround and exist in native tissues to support the cells in performing their functions (Frantz et al., 2010). Native ECM of any tissue shapes and provides structural support for cells to attach, grow, and migrate, and signal to encourage cells to carry out processes including cell proliferation and differentiation (Chan & Leong, 2008). The main objective of a scaffold is to closely mimic the ECM to lay out a stable, physiologically relevant, degradable, and biocompatible environment that leads to the regeneration of tissues. Since lung scaffolds are complex, additional functions of the alveoli structure such as large surface area, flexibility, and high gas permeability must be considered when designing this matrix (Lü et al., 2022). Therefore, scaffolds have many properties including hydrophilicity, isotropy, porosity, biocompatibility, biodegradability, tensile strength, and compression that must match the unique properties of native lung tissues.

These various requirements can be sorted into two main categories: chemical and mechanical. Generally, scaffolds must exhibit biological properties such as hydrophilicity, isotropy, and porosity. The hydrophilicity of the scaffold's surface influences adhesion and proliferation of cells attached, with cells preferring surfaces that are more hydrophilic (Suamte et al., 2023). Porosity of scaffolds is crucial to cell migration and the transportation of nutrients, oxygen, and waste materials. Variables including pore size and number of pores are adjustable, and they can affect the uniform distribution of cells (Suamte et al., 2023; Tonndorf et al., 2021). Biocompatibility and biodegradability are properties necessary to ensure the survival of cells and that the foreign material does not cause a negative immune response, with the scaffold eventually degrading while the cells make their own ECM (O'Brien, 2011). Other than this, mechanical properties including tensile strength and compression determines the scaffold's durability and ability to withstand strain (Suamte et al., 2023).

Many different biomaterials can be utilized to make these lung scaffolds, and they must be carefully selected for the type of tissue being made. Commonly, the biomaterials used in tissue engineering consist of synthetic polymers, natural polymers, and others (O'Brien, 2011). Synthetic polymers, which include polymers such as polylactide (PLA) and polyglycolide (PGA), are usually used due to their ability to be easily processed in a controlled way and high mechanical properties (Ashammakhi et al., 2022). Due to their biocompatibility, elasticity, and degradability, natural polymers are typically utilized; some examples of this material are collagen and gelatin (Ashammakhi et al., 2022). As the lung is a complex organ with many cell types and functions, hybrid scaffolds made from many materials are usually utilized to be best suited to match all the requirements (Nichols et al., 2009). Furthermore, properties can be tailored by adjusting the biochemical or biomaterial contents of the engineered scaffold (Cosson et al., 2015).

2. Different Types of Biomaterials

TABLE 1. ***Natural and synthetic polymers for tissue engineering*****.**

Material	Type	Key Properties/ Function	References
Collagen	Natural Polymer	High tensile strength, self-assembles into fibrils, structural integrity, and basement membrane formation (Types I, III, and IV). Supports scaffold stability and cell adhesion.	(Ashammakhi et al., 2022; Frantz et al., 2010)
Gelatin	Natural Polymer	Biocompatible, elastic, biodegradable; hydrolyzed structure allows greater modification and functionalization.	(Revete et al., 2022; Sajkiewicz & Kołbuk, 2014)
Hyaluronic Acid (HA)	Natural Polymer	Hydrophilic, promotes cell migration, proliferation, and ECM regeneration. Improves hydration and structural support	(Revete et al., 2022)
Chitosan	Natural Polymer	Antibacterial, biocompatible, and biodegradable. Supports wound healing and cell proliferation.	(Revete et al., 2022)
Alginate	Natural Polymer	Hydrophilic, forms gels in the presence of divalent cations. Improves elasticity and supports nutrient transport.	(Lee & Mooney, 2012)
Polylactide (PLA)	Synthetic Polymer	High mechanical properties, biodegradable, easily processed. Provides structural integrity.	(Makadia & Siegel, 2011)
Polyglycolide (PGA)	Synthetic Polymer	Rapid degradation rate, high strength. Used for temporary scaffold structures.	(Makadia & Siegel, 2011)
Polylactide-co-Glycolide (PLGA)	Synthetic Polymer	Combines properties of PLA and PGA, tunable degradation rate. Balances mechanical strength and biodegradability.	(Makadia & Siegel, 2011)
Polycaprolactone (PCL)	Synthetic Polymer	Highly elastic, slow degradation rate, biocompatible. Mainly used for long-term structural scaffolds.	(Homaeigohar & Boccaccini, 2022)
Polyurethane	Synthetic Polymer	Highly elastic, gas permeable. Improves gas exchange in lung scaffolds.	(Lü et al., 2022)

Typically, the design of scaffolds is time-consuming and resource-extensive because bioactive molecules have to be individually evaluated (Guo et al., 2023). However, such issues can be tackled with recent approaches in tissue engineering, including the application of artificial intelligence (AI), with machine learning (ML) algorithms aiding in scaffold design (J. L. Guo et al., 2023). AI can predict cell behavior in different environments by analyzing their interactions with biological systems, leading to the optimization of the material properties (Nosrati & Nosrati, 2023). The fabrication process can be simulated by AI, which is immensely beneficial for the prediction of the scaffold's properties, such as mechanical strength and porosity (McDonald et al., 2023; Nosrati & Nosrati, 2023).

Lung tissues are complex and hard to engineer, which is why extensive research must be put into LTE for more discoveries to be made in this field. This review article aims to highlight the importance of biomaterial selection and to analyze the chemical and mechanical properties that are ideal for lung scaffolds. In this paper, AI applications in various LTE technologies that support the optimization of biomaterial selection and scaffold design are explored. The discussion of these topics gives a comprehensive overview of the material properties and emerging AI technologies improving the designs of lung scaffolds and their functionality. The integration of AI in scaffold design will produce progress in LTE as it will lead to more effective lung scaffolds.

2.1 Decellularized Scaffolds

An approach used by some scientists to make lung scaffolds is to decellularize native lung tissues, leaving only the ECM. This approach alleviates donor shortages because donor tissue does not have to come from humans; DNA is removed from these scaffolds which prevents immunogenicity, the ability to trigger an immune response, and, thus, porcine and non-human primate lungs can be used (Santis et al., 2018). After the native cells from the tissue are removed while preserving the micro- and macro- structure of the lungs, the cells derived from the patient can then be seeded into the scaffold (Gilpin & Wagner, 2018). The steps to make the scaffold will be simpler and the resulting scaffold would be more biocompatible as it reduces the risk of rejection from the immune system due to the presence of a natural ECM. However, physical methods such as freezing, heating, or using electricity to kill off the native cells can be less toxic, but it would sacrifice the mechanical properties of the ECM (McInnes et al., 2022). On top of this, lungs are typically decellularized with detergent-based solutions which are toxic to cells and harm the tissue's macrostructure. For example, sodium dodecyl sulfate (SDS) could leave harmful wastes even after the washing process, which can be disruptive to cellular function and kill the cells (Shakir et al., 2022).

2.2 Natural Polymers

Natural polymers are usually used for their biocompatible, elastic, and degradable properties that allow them to be easily integrated with biological systems. The most commonly used materials are collagen, gelatin, hyaluronic acid (HA), chitosan, and alginate, which not only offer structural support, but also possess moieties that promote cell adhesion, improving tissue integration (Ashammakhi et al., 2022). Each of these natural polymers possesses certain properties which make them more suitable for different purposes. For instance, collagen is known for its high tensile strength and can self-assemble into fibrils so the scaffold can withstand pulling force (Frantz et al., 2010). In lung tissues, collagens I, III, and IV are the main types, where collagens I and III provide structural integrity and collagen IV forms the basement membrane that separates tissues (Calle et al., 2014). Whereas gelatin is a derivative of collagen and similarly possesses many properties, it has substantially more freedom in its modification and functionalization because it is hydrolyzed and lacks a tertiary structure allowing for better reactivity (Revete et al., 2022; Sajkiewicz & Kołbuk, 2014).

As natural polymers have poor mechanical properties due to their complex structure, they may not be able to support the tissue on their own (O'Brien, 2011). However, a recent study showed that natural polymers can be crosslinked, which is a chemical process where the polymer chains can be linked to form a network, improving their functionality as scaffolds due to becoming stronger and more stable (Moon et al., 2023). These natural polymers can be crosslinked using chemicals, heat, pH, or light, to improve mechanical properties and the durability of the scaffold (Moon et al., 2023).

2.3 Synthetic Polymers

Unlike natural polymers, which are composed of natural materials, synthetic polymers are artificially made and have different properties. Synthetic polymers have been used in LTE as they are widely available, have high mechanical properties, and are easily tunable due to their well-defined, stable chemical structures (Ashammakhi et al., 2022). Typical synthetic materials include PLA, PGA, polylactide-co-glycolide (PLGA), and polycaprolactone (PCL) (Ashammakhi et al., 2022). Similar to natural polymers, each of these polymers has properties that can be tailored to meet specific requirements in different tissues. For instance, recent studies demonstrated that some synthetic polymers have certain properties that are better than others. In one study, polyurethane had better gas permeability than poly(L-lactic acid), which is critical to LTE where gas exchange is significant (Lü et al., 2022). This indicates that polyurethane is a more suitable polymer to use in terms of gas exchange. It is important to note that using a single type of synthetic polymer is insufficient to fulfill all the requirements for lung tissue scaffolds, and, hence, different blends and combinations of these materials should be explored to match native lung tissues (Ashammakhi et al., 2022). The ratios of different synthetic polymers can be adjusted to combine desirable properties such as mechanical strength, biodegradability, and elasticity.

2.4 Hybrid Scaffolds

Hybrid scaffolds are being explored to provide all the requirements because lung tissues are complex with many unique functions. Natural polymers are not sufficient enough on their own as they do not have a strong enough structure to withstand tension and strain due to their limited mechanical properties and fast degradation rates (O'Brien, 2011). On the other hand, synthetic polymers have poor biocompatibility and no cell adhesion molecules, which may cause inflammation that prevent tissue formation and cell survival when the cells do not stick together (Ashammakhi et al., 2022). In a recent study, a hybrid bioactive scaffold was developed, consisting of a scaffold made of PCL and gelatin, along with ECM-derived cells to closely mimic the microenvironment of the alveolar-capillary barrier in lung tissues (Doryab & Schmid, 2022). PCL was used due to its strong structure and easily tunable properties, while gelatin was used as a sacrificial component due to its cell attachment abilities and left enough space after its degradation in order for the cells to deposit their own ECM (Doryab & Schmid, 2022). This resulted in a scaffold with more favorable characteristics, increasing the functionality of bioengineered lung tissues.

2.5 AI Application

ML algorithms can compile and be trained with existing datasets of material properties, biological responses, and performance of scaffolds to identify biomaterials best suited for LTE (J. L. Guo et al., 2023). In a study, AI had been used in biomaterial selection to analyze and predict antibacterial properties of biomaterials (Lata et al., 2007). The researchers using ML techniques such as neural networks, quantitative matrices (QM), and support vector machines (SVM) analyzed characteristics of over 400 known antimicrobial peptides to find new antimicrobial peptides by predicting antibacterial activity with high accuracy up to 92% (Fig. 3A) (Lata et al., 2007). Therefore, AI's ability to predict may eventually allow new functional biomaterials to be identified and accurately designed with applications in tissue engineering (Liu et al., 2023). AI models will have the ability to find characteristics and behaviors of certain materials through the use of AI to learn from existing patterns of biomaterials, increasing the efficiency of the biomaterial selection process.

3. Chemical and Mechanical Properties

3.1 Hydrophilicity

Hydrophilicity refers to the ability of the surface of a material to absorb and retain water, modulating cell adhesion for better cell proliferation and function (Suamte et al., 2023). Hydrophilicity is crucial in maintaining hydration of the alveolar surface to allow for clear airways and efficient gas exchange. The study of PEGDA, a derivative of polyethylene glycol (PEG), a synthetic polymer known for its hydrophilic and biocompatible properties, demonstrated that using PEGDA in scaffolds increases their hydrophilicity by producing a moist environment (Hakim Khalili et al., 2023). PEGDA not only supports cell growth and transportation of nutrients that makes cells more likely to grow on these hydrophilic surfaces, but it is also a synthetic polymer, resulting in mechanical properties that are easily tunable which is vital for soft tissues like lungs (Hakim Khalili et al., 2023).

3.2 Isotropy

Isotropy is the uniformity in response in all directions when a force is applied (Tonndorf et al., 2021). This is important for lungs such that it ensures that cells can grow evenly in all directions in order to form a uniform structure that promotes consistent gas exchange to occur. In a study, the distribution and size of pores were tuned by adjusting parameters of the shape and structure of the Triply Periodic Minimal Surface (TPMS), which are structures commonly used in tissue engineering due to their interconnected pores that can mimic lung microstructures (Feng et al., 2021; Hesselmann et al., 2022). This helps create lung scaffolds that possess a uniform structure, which is directly connected to the consistent mechanical properties throughout the lung needed when breathing.

3.3 Porosity

In tissue engineering, porosity is the measure of void spaces in the scaffold or tissue. This is critical for any scaffolds because it impacts cell migration, diffusion of nutrients and oxygen, and the removal of waste products (Suamte et al., 2023). In lungs, this also affects the ratio of air flow in the alveoli and the blood flow through the capillaries (ventilation-perfusion ratio) vital to the gas exchange process (Sarabia-Vallejos et al., 2021). In a study, murine lungs were altered by mimicking pulmonary diseases including emphysema, which involved enlarging the airspace volume, essentially increasing the overall porosity of lungs (Sarabia-Vallejos et al., 2021). The study showed that this had reduced the surface area available for gas exchange, impacting the ventilation-perfusion ratio, where lungs have sufficient ventilation but cannot efficiently transfer oxygen and wastes via the bloodstream (Sarabia-Vallejos et al., 2021). Furthermore, the porosity of healthy lungs were also compared, highlighting the importance of consistent porosity to ensure uniform and efficient gas exchange as well as reducing stress if certain areas were overinflated or underinflated (Sarabia-Vallejos et al., 2021).

3.4 Biochemical content

It is important to understand the components of the lung ECM because they are significant in the tissue development and mechanical support and elasticity. The biochemical content of the ECM mainly includes collagen, elastin, fibronectin, and glycosaminoglycans (GAGS). Collagen is the most abundant protein, providing tensile strength and structural integrity; elastin makes allows tissues to stretch and recoil, which is important for the inflation of air sacs; fibronectin can bind with other components and contributes to cell adhesion; GAGs are attracted to water, providing a structure to withstand compression (Hackett & Osei, 2021; Kular et al., 2014). Studies indicate an increase in collagen 1 and the loss of elastin leads to stiffer tissues, causing lung diseases like COPD and asthma due to reduced airflow and elasticity (Hackett & Osei, 2021). On the other hand, a deficiency in collagen weakens structural support, impairing lung function by reducing the ability to recoil (Hackett & Osei, 2021).

3.5 Biodegradability

Biodegradability is the ability of a scaffold to gradually break down and be replaced by new regenerated tissue (Egorikhina et al., 2021). It is an important aspect of LTE because biodegradable scaffolds act as a non-toxic template to encourage cell migration, differentiation, proliferation, and reduce immunogenicity (Shakir et al., 2022; Suamte et al., 2023).

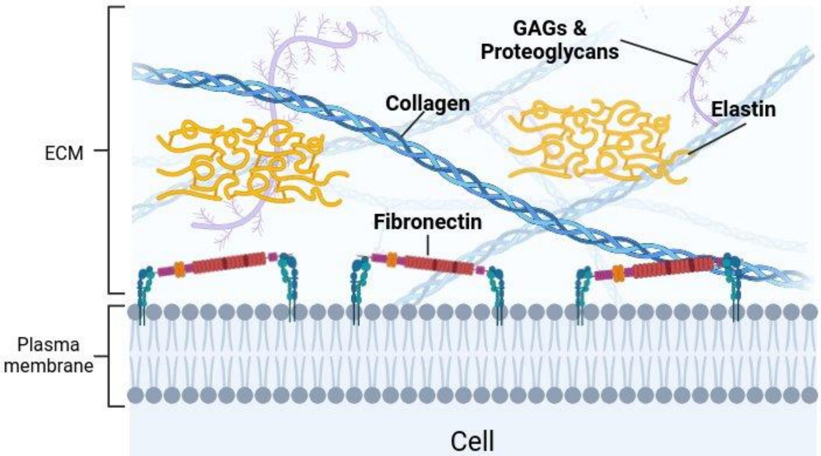

FIGURE 2. ***The ECM contains components such as collagen, GAGs, elastin, and fibronectin.***

Studies show that factors such as different ratios of materials can impact the rate and extent of biodegradation. For example, scaffolds derived from fish collagen degrade faster than those derived from bovine collagen because bovine collagen had a denser structure (Egorikhina et al., 2021). Lung scaffolds must have a moderate and controlled degradation rate such that it is long enough to support the soft tissue without being too long to trigger immune responses.

3.6 Biocompatibility

Biocompatibility refers to the ability for scaffolds to function without triggering severe inflammatory responses that may cause rejection from the immune system or interfere with the healing process (Huzum et al., 2021; O'Brien, 2011). Cytotoxicity, the ability of a biomaterial to kill cells, is also an important aspect to allow for cells to be unharmed and integrate into the surrounding tissue (Shakir et al., 2022). Researchers are currently implementing many approaches to adjust scaffolds to overcome foreign body response including the coating of biocompatible materials such as collagen and PLGA for better interaction with the native tissues (Morais et al., 2010). Additionally, the surface property and surface chemistry of the scaffold can also be adjusted, such as smoother surfaces can reduce macrophage adhesion which decreases immune responses (Morais et al., 2010).

3.7 Tensile strength

Tensile strength allows scaffolds to resist the stress of being stretched or pulled (Griffin et al., 2016). This is critical for soft lung tissues to withstand stress such as alveolar tension that balances the inflation and deflation forces to prevent the alveoli to collapse (Edwards & Annamaraju, 2023; Seadler et al., 2024). In a recent study, the tensile strength of lung scaffolds was adjusted using two types of methods using different crosslinking agents: EDC/NHS and tannic acid (Shirani et al., 2021). The tannic acid method was able to increase tensile strength, but it had thickened the alveolar walls (less efficient gas exchange) and had low numbers of mesenchymal cells, suggesting that it was cytotoxic. Meanwhile, EDC/NHS crosslinking was preferred as it was able to display tensile strength similar to native lungs without causing lower cell proliferation (Shirani et al., 2021). Therefore, it is important for researchers to increase the tensile strength to support lung structures without negatively affecting other properties.

3.8 Compression

Compression refers to the ability of a material to withstand pressing or squeezing stresses without breaking (Onal et al., 2022). Compression enables the lungs to function properly by allowing it to inflate and deflate (Naumann et al., 2022). A study involved testing the compression of rat and rabbit lungs, focusing on the composition of collagen and elastin fibers (Andrikakou et al., 2016). Rabbit lungs had a greater amount of collagen and elastin, and, therefore, displayed a greater compression and were stiffer compared to rat lungs (Andrikakou et al., 2016). Moreover, samples that were at the central regions closer to the bronchus had more consistent mechanical behavior compared to the outer edge of the lungs, likely due to the region being less porous (with less alveoli) and more connective tissues (Andrikakou et al., 2016).

3.9 AI integration

AI is helpful in LTE because it can adjust and refine scaffold properties. The optimization of the size and shape of scaffolds are extremely important in determining the ideal properties of the scaffold. Because stiffness and porosity are properties that oppose each other (where improving one typically compromises the other), topology optimization (Fig. 3C), a computer based technique that removes unnecessary materials, is used to optimize the distribution of material in a given area (Gharibshahian et al., 2024). Researchers Hollister and Lin were the first to use topology optimization, designing scaffold unit cells to maximize permeability while maintaining a balance between flexibility and minimum porosity (Gharibshahian et al., 2024). This would be able to ensure enough structural support while not being too stiff to impair lung function. Furthermore, another recent study focused on the optimization of unit cell architectures for tissue engineering scaffolds to reach a given bulk modulus (measures material's resistance to uniform compression) and diffusivity (Gharibshahian et al., 2024). They utilized a topology optimization technique with the objective of minimizing the error between target and effective mechanical properties by limiting porosity (Gharibshahian et al., 2024). Hence, AI algorithms are able to optimize scaffold properties that lead to scaffolds with the ideal proportions of different and opposing properties to better integrate with native tissues with maximum functionality.

4. DISCUSSION

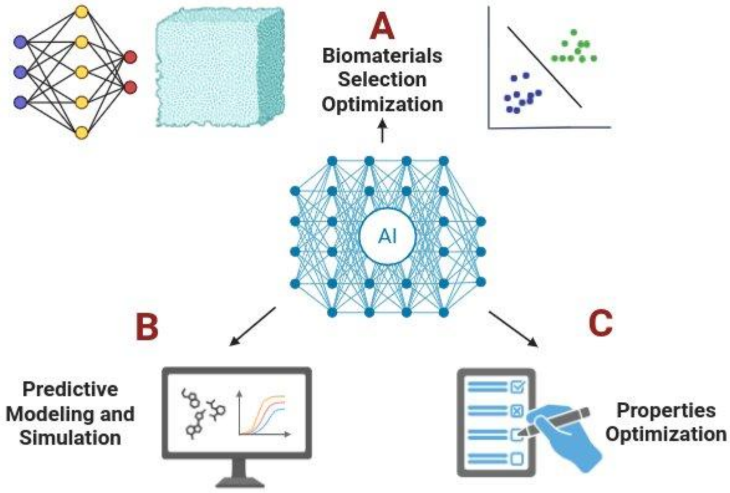

Figure 3. AI models can improve biomaterial selection, predictive modeling, and properties optimization (A) Ex: Neural Networks, QM, SVM to predict antibacterial activity with high accuracy and identify new biomaterials with optimal antibacterial and functional properties. (B) Ex: ANN simulates virtual tests under various conditions and predicts results with high accuracy. (C) Ex: Topology optimization to balance conflicting properties in scaffold design

A critical application of AI tools is the use of predictive modeling and simulations, where AI models can be used to simulate complex biological environments to test scaffold integration and immune responses virtually. This directly connects to AI models being able to test biocompatible properties of scaffolds in various environments, allowing researchers or other AI models to fine-tune the property before any physical tests. On the other hand, Xu et al. demonstrated how artificial neural networks (ANN) could accurately predict results in vascular tissue engineering up to 94% (Fig. 3B) (Gharibshahian et al., 2024). This application can be used in lung scaffolds that must accommodate complex vascular systems and structural needs for efficient gas exchange. Furthermore, many ML techniques can be utilized to find the best trade offs between different variables by evaluating how factors such as biocompatibility, degradation rates, diffusivity, and stiffness would impact the environment of bioengineered lung tissues. Decisions can also be made from data broken down into branch points, aiding in choices such as if a material's properties fit a certain threshold. For instance, techniques such as topology optimization have been implemented to design ideal scaffolds by balancing conflicting properties such as porosity and mechanical strength (Fig. 3C) (Gharibshahian et al., 2024). This can ensure lung scaffolds meet permeability and stiffness requirements.

However, it is also essential to consider transparency of AI algorithms when integrating AI in LTE in order to ensure that researchers are able to understand how these models make decisions for their predictions. With clearer understanding of AI in the decision-making process, researchers can validate the reliability of the predictions of these AI models reflective of only accurate and relevant data, leading to increased trust and applications of AI.

CONCLUSION

AI can help LTE with biomaterial selection and refinement scaffold properties. Researchers can create more effective scaffolds tailored to specific requirements of lung tissues through the use of predictive models and algorithms, which increases the efficiency and accuracy in scaffold design.

Conflict of Interest: The authors declare no conflict of interest in relation to this research.

Data Availability Statement: Not applicable.

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Peer review information
IJLSCI thanks the anonymous reviewers for their contribution to the peer review of this work. A peer review file is available.

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