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Advancements within Molecular Engineering for Regenerative Medicine and Biomedical Applications an Investigation Analysis towards A Computing Retrospective

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ABSTRACT The field of molecular engineering in medicine has witnessed remarkable progress in recent years, revolutionizing healthcare, diagnostics, and therapy development. However, the pandemic showcased there is still more requirement for progress along with further detailed investigation which is paramount and also a necessity moving forward. This research investigation delves into the interdisciplinary realm of molecular engineering, exploring its impact on regenerative medicine, biomaterials, tissue engineering, and the innovation from various advanced biotechnologies which has accelerated health science. The main objective for this research aims at providing an in depth investigative exploration of biomaterial applications with their respective roles within regenerative medicine and its associated advancements along with, tissue engineering, organ-on-a-chip device peripheral mechanics functionality and how bioprinting is paving the way for the creation of functional tissues and organs with a case study analysis on drug discovery, immune engineering, to the field of precision medicine, gene editing with the insight towards drug discovery processing, design and screening pipelined for biologics and the how therapeutics and drugs will play out in future healthcare. This exploration also provides many meaningful and remarkable conclusions on the advanced technologies which are explored and investigated throughout the step-by-step systematic technical computing methods approached for the research.

INDEX TERMS Artificial Intelligence (AI), Biomedical Engineering (BME), Biomedical Instrumentations Measurement and Applications, Deep Learning, Machine Learning, Molecular Engineering, Regenerative Medicine.

I. INTRODUCTION

Molecular engineering represents an innovative and interdisciplinary field focused on the deliberate design and manipulation of molecular properties and interactions to create improved materials, systems, and processes tailored for specific functions. This approach, often referred to as "bottom-up" design, allows engineers and scientists to directly influence the behavior of macroscopic systems by altering their molecular structures. This field is inherently interdisciplinary, drawing knowledge from chemical engineering, materials science, bioengineering, electrical engineering, physics, mechanical engineering, and chemistry. It significantly overlaps with nanotechnology, as both fields examine material behaviors at the nanoscale or smaller. Molecular engineering's scope is vast, limited only by imagination and the laws of physics, with applications spanning healthcare, energy, electronics, and beyond. Molecular engineering offers a rational approach to problem-solving, in contrast to traditional trial-and-error methods. Rather than relying solely on empirical correlations, it seeks to understand the chemical and physical origins of system properties to manipulate them directly.

This approach often leads to the creation of entirely new materials and systems, addressing critical needs in diverse

domains, including energy production, healthcare, and electronics. Historically, molecular engineering emerged as a concept in the 1950s, with pioneers like Arthur R. von Hippel envisioning a new way of engineering materials from their atomic and molecular constituents. Richard Feynman's influential 1959 lecture on nanotechnology further solidified these ideas. However, it wasn't until the 1980s, with the publication of "Engines of Creation" by Drexler, that the modern concepts of molecular-scale science began gaining broader recognition.

Applications of molecular engineering are wide-ranging and include consumer products, such as antibacterial surfaces, OLED displays, and self-cleaning coatings. It also plays a pivotal role in energy harvesting and storage through innovations like flow batteries, lithium-ion batteries, and advanced solar cells. In environmental engineering, molecular engineering contributes to water desalination, soil remediation, and carbon sequestration. Furthermore, the field is instrumental in immunotherapy, synthetic biology, and gene editing techniques like CRISPR, offering promising avenues for medical advancements.

The tools and techniques employed by molecular engineers encompass computational approaches, microscopy, molecular characterization, spectroscopy, surface science, synthetic methods, and various specialized instruments. These enable the precise manipulation and analysis of molecules and materials at the molecular and nano-scale, facilitating the development of novel materials and technologies. Molecular engineering represents a dynamic and transformative field that harnesses the principles of molecular science to engineer materials and systems with unparalleled precision. Its applications are far-reaching, holding immense potential for addressing complex challenges across diverse sectors, ultimately reshaping the landscape of science and technology. In recent years, medical science has undergone a remarkable transformation with groundbreaking discoveries that have fundamentally changed healthcare.

These advances have significantly improved disease diagnosis, treatment, and patient care, offering new hope and improved quality of life. These innovations span various domains, from novel medications and therapies to cutting-edge technologies. One of the most promising areas is regenerative medicine, which aims to restore, replace, or regenerate damaged tissues and organs using approaches like cell therapy, tissue engineering, and gene therapy. Stem cell therapy, tissue engineering, and gene therapy hold the potential to revolutionize the treatment of previously incurable conditions.

The development of implantable artificial organs is another revolutionary stride in medical science. Researchers have created artificial organs, including hearts, kidneys, and skin grafts, using a combination of polymers and biological tissues. These advancements promise to extend lives and enhance the quality of life for patients in need of organ transplants. Nanotechnology plays a vital role in medicine by enabling targeted drug delivery, reducing side effects, and potentially treating previously incurable diseases. Recent developments include the use of nanoparticles for more effective and less harmful cancer therapies, and the creation of imaging agents that can specifically target and visualize disease cells.

Gene editing technology, particularly CRISPR-Cas9, is poised to transform medicine by allowing precise genetic modifications. This technique holds promise for curing genetic disorders and treating diseases like Alzheimer's, HIV, and cancer. However, ethical considerations and safety concerns must be addressed. Artificial intelligence (AI) and machine learning are revolutionizing healthcare by analyzing vast amounts of medical data for improved diagnosis, personalized treatment, and patient monitoring. These AI systems have shown impressive capabilities, such as diagnosing skin cancer, predicting patient mortality, and detecting the onset of psychosis. Chimeric Antigen Receptor (CAR) T-cell therapy is an exciting development in cancer treatment, using genetically modified T cells to target and destroy cancer cells. Research indicates its effectiveness in treating various lymphoma types and potential applications in other cancer treatments.

The development of mRNA vaccines, as exemplified by COVID-19 vaccines, has transformed vaccine technology. These vaccines offer rapid development, lower production costs, and adaptability to emerging viral variants. This breakthrough technology has implications for future disease prevention and treatment. Advances in 3D printing have enabled the creation of custom-made implants, anatomical models, and prostheses, reducing the need for invasive surgeries and improving patient care. Telemedicine has gained prominence, especially during the COVID-19 pandemic, offering remote access to medical services, improving healthcare accessibility, and potentially lowering costs.

Virtual reality (VR) is enhancing medical education, allowing students to practice medical procedures in a safe and controlled environment, thereby improving skills and patient safety. Wearable health monitoring devices, such as fitness trackers and smartwatches, have revolutionized personal health management, providing real-time data on physical activity, heart rate, sleep patterns, and more. These devices empower individuals to take control of their health and allow healthcare professionals to remotely monitor patients, leading to early disease identification and prevention.

These recent developments in medical science have the potential to transform healthcare delivery, improve patient outcomes, and open new avenues for treatment and prevention.

II. METHODOLOGY

The methodology employed concerning this research aimed to thoroughly investigate the impact of Molecular Engineering and Regenerative Medicine towards the technical computing functionality within Biomedical Application systems, situated within the landscape of Biomedical Engineering. The research process followed a systematic, step-by-step iterative approach.

Initially, an extensive review of existing available knowledge was conducted, delving into available literature to identify gaps in research and potential contexts. Subsequently, the gathering of required data and its processing were executed within the KNIME data analytics platform. A wide set of data mining techniques were applied using various methods and functionality tools, with a focus on ensuring the quality and relevance of the sampled datasets, data models, data tools through meticulous preprocessing and post-processing steps. Next, towards performance analytics, along with visualization representations of the functionality techniques, were then integrated into design illustration prototypes. These prototypes underwent evaluation using suitable metrics and were compared against a range of traditional and existing technical computing approaches in terms of datasets and available solutions and experimentational simulations associated with the process involved. To make sure the processing was a definitive output, the models and applications data were selected based from the commercially available biomaterials in terms of products availability from company resources and their usage and applicability in retrospect to organoids. The obtained results were meticulously analyzed and interpreted in the context of the research objectives, with discussions on implications for Biomedical Engineering Applications in conjunction with Regenerative Medicine, leading to potential future speculations.

FIGURE 1. A block diagram of the research methodology

In the final stages of exploration and results, the findings were summarized, acknowledging any limitations encountered during the research process. Suggestions for future research prospects within the domain were also outlined. It is very important to note that many applicable resources have limitations and lacked certain features of deployment due to a work in progress, but facilitated a comprehensive exploration of how the designed prototyping toolsets and computing peripheral features can enhance the perspective of Biomedical Engineering. It also shed light on the role of Regenerative Medicine, particularly in the realm of Molecular Engineering, within towards mainly the technological digital framework realm of computing, promising advancements and improved terminologies for the field. To better understand, FIGURE 1 provides a visualization concerning the approach.

III. BACKGROUND RESEARCH AND AVAILABLE KNOWLEDGE

The field of regenerative medicine holds immense promise within the realm of biomedical engineering, with a focus on enhancing cell activity for tissue regeneration. Damaged or injured tissues often exhibit limited natural healing potential, hindering cell migration, proliferation, and differentiation. Scientific technologies have been developed to enhance these natural healing abilities, potentially leading to patient-friendly tissue regeneration.

However, conventional cell culture conditions involve the use of polystyrene dishes, which do not mimic the complex cellular interactions found in native tissues. This difference in cell conditions results in lower cell activity in vitro compared to in vivo, affecting functions like differentiation, proliferation, metabolism, and cytokine secretion. Consequently, drug screening outcomes in vitro do not always align with preclinical or clinical studies due to variations in cell condition and activity. Therefore, to advance regenerative medicine, it is essential to enhance cell function and activity both in vitro and in vivo [1].

Biomaterials play a pivotal role in enhancing cell activity for regenerative medicine. These materials can augment cellular functions both in damaged tissues in vivo and in vitro cell culture conditions, aiding the realization of regenerative medicine's potential. Collagen, a natural biomaterial, is abundantly found in the body and is a critical component of the extracellular matrix (ECM).

Collagen-based materials have been extensively used to promote cell activity in various tissues, including bone, cartilage, muscle, and cancer. For example, collagen scaffolds combined with controlled drug release systems have facilitated bone regeneration, and collagen-fibrin hydrogels have supported osteogenic differentiation of cells. Furthermore, anisotropic collagen scaffolds have stimulated the assembly of muscle bundles and the migration of invasive cancer cells, showcasing collagen's versatility in tissue engineering and drug research [2,3].

Gelatin, derived from collagen, is another valuable biomaterial. Gelatin-based hydrogels offer advantages such as high biocompatibility and the ability to support cell sheets' viability, growth, and function. These hydrogels can release

growth factors like basic fibroblast growth factor (bFGF), which enhance cardiac contractile function and promote the expression of specific proteins like β-casein in epithelial cells. Gelatin sheets, when combined with ovarian tissues and bFGF, have significantly increased the proliferation of stromal and endothelial cells. In wound healing applications, gelatin sheets impregnated with platelet-rich plasma have accelerated capillary and tissue formation [4,5,6]. Moreover, gelatin-based hydrogel systems with drug release capabilities are employed to mimic cancer cell invasion, enabling the evaluation of cancer cell behavior in response to various stimuli, such as transforming growth factor-β1. Alginate, a natural polysaccharide derived from seaweed, is widely used in cell encapsulation systems for tissue engineering and drug research. Alginate-based hydrogels support the differentiation of embryonic stem cells into primordial germ cells and promote osteogenesis and mineralization when encapsulating mesenchymal stem cells. Injectable alginate-based hydrogels have been developed for cell delivery to damaged tissues, offering advantages such as oxygen permeability and biocompatibility. These injectable gels can eventually disappear after transplantation, avoiding long-term interference with tissue regeneration. Moreover, alginate-based hydrogels have been utilized to create cancer tissue models that mimic cancer invasion and metastasis, facilitating anti-cancer drug screening. Chitosan, a biopolymer derived from chitin, is known for its biocompatibility and versatility [7]. It has been applied in various regenerative medicine approaches, including blood vessel regeneration, cartilage formation, bone regeneration, intervertebral disc therapy, and skin tissue engineering. Chitosan-based scaffolds and membranes have demonstrated the ability to mimic the properties of native tissues, promoting cell adhesion, proliferation, and expression of tissue-specific markers. Chitosan nanohybrids and composites have shown enhanced bioactivity and osteoconductivity for bone regeneration. Additionally, chitosan hydrogels have been employed for nerve regeneration and as drug delivery systems, supporting the culture and migration of stem cells and neurons.

Silk fibroin, derived from silkworms, offers unique properties for tissue engineering applications. Silk fibroin scaffolds have been utilized for bone and cartilage regeneration, providing a microenvironment conducive to osteogenic and chondrogenic differentiation. These scaffolds can be optimized through the incorporation of other materials like gelatin to enhance cell growth and tissue-specific gene expression. Furthermore, silk fibroin membranes have been investigated for their effects on acoustic energy transfer and tensile strength in cartilage and tympanic membrane regeneration. Biomaterials play a crucial role in enhancing cell activity for regenerative medicine. Natural biomaterials like collagen, gelatin, alginate, chitosan, and silk fibroin offer diverse advantages, including biocompatibility, controlled drug release, and support for tissue-specific differentiation. These biomaterials have been instrumental in tissue engineering, drug research, and the development of in vitro models to advance regenerative medicine's potential for tissue regeneration and disease treatment [8,9].

Agarose is a biomaterial widely used in regenerative medicine due to its unique properties. Composed of D-galactose and 3.6-anhydro-L-galactopyranose units, agarose can absorb water and facilitate the permeation of oxygen and nutrients to encapsulated living cells. It forms gels through hydrogen bonding and electronic interactions, eliminating the need for harmful crosslinking agents. Importantly, agarose has shown low immunogenicity. Researchers have leveraged its tunable properties to create gels of varying stiffness for tissue engineering applications. For instance, combining agarose with polydopamine has been found to enhance water content, cell adhesion, collagen deposition, and angiogenesis, making it a valuable tool for regenerative medicine, including nerve and cornea regeneration. Matrigel, derived from a complex protein mixture found in mouse Engelbreth-Holm-Swarm tumor, serves as an alternative basement membrane for cell culture when replicating human basement membrane integrity is challenging. Matrigel is particularly valuable in cancer research, aiding in invasion assays, morphology evaluation, and gene expression studies. When combined with other biomaterials like alginate, Matrigel maintains the high malignancy, spreading, migration, and invasion activities of cancer cells. This makes it a crucial biomaterial for studying cancer cell behavior in a biomimetic matrix. Matrigel-assisted tissue engineering shows promise in cancer tissue engineering and anti-cancer drug validation, enhancing the accuracy of in vitro experiments [10].

Poly (lactic acid) (PLA) is a biomaterial with an elastic modulus similar to bone, making it suitable for bone tissue engineering. PLA can be combined with hydroxyapatite (HA), which plays a vital role in extracellular matrix (ECM) remodeling and homeostasis. Porous PLA-HA scaffolds have been developed, enabling efficient culture of osteoblast cells. The HA distribution on the scaffold's surface enhances cell adhesion and wettability. PLA-HA scaffolds have been supported by microanalysis and 3D printing technology, further advancing their utility in bone tissue engineering. Poly (lactic-co-glycolic acid) (PLGA) is a copolymer known for its biodegradability and biocompatibility.

Its properties, including degradability, can be tailored by adjusting the ratio of lactic acid and glycolic acid or molecular weight. PLGA formulations are easy to prepare through methods like solvent evaporation or spray drying. It is widely used in medical applications, such as drug delivery systems. PLGA has also found use in tissue engineering, especially in the brain and nervous system. It supports the culture of cells like nerve cells and Schwann cells, promoting axonal growth and nerve regeneration. Additionally, PLGA conduits, often combined with other substances like salidroside, have shown promise in facilitating peripheral nerve regeneration. These biomaterials, including agarose, Matrigel, PLA, and PLGA, play vital roles in various aspects of regenerative medicine, from supporting cell culture to aiding tissue engineering and drug delivery. Their unique properties and tunability make

TABLE 1

Selection of the commercially available biomaterials for regenerative medicine

Product	Tissues/ Organs	Description	Company
AlloDerm®	Skin	Acellular dermal matrix for soft-tissue augmentation and replacement	LifeCell Corp.
Apligraf®	Skin	Allogeneic fibroblasts on a bovine collagen I matrix with upper keratinocyte cell layer	Organogenesis
Dermagraf®	Skin	Allogeneic fibroblasts on a vicryl mesh scaffold	Shire Regenerative Medicine, Inc
GraftJacket®	Skin	Acellular dermal matrix for soft-tissue augmentation and chronic wound treatment	Wright Medical Technology Inc.
TransCyte®	Skin	Allogeneic fibroblasts on a nylon mesh with upper silicone layer	Shire Regenerative Medicine, Inc
Oasis® Wound Matrix	Skin	Decellularized porcine small intestinal submucosa	Cook Biotech
Integra® Bilayer Wound Matrix	Skin	Type I bovine collagen with chondroitin-6-sulfate and silicone	Integra Life Sciences
Epicel®	Skin	Autologous keratinocyte cell sheets	Genzyme
Carticel®	Cartilage	Autologous chondrocytes	Genzyme
NeoCart®	Cartilage	Autologous chondrocytes on type I bovine collagen	Histogenics
VeriCart™	Cartilage	Type I bovine collagen	Histogenics
AlloMatrix®	Bone	Demineralized bone matrix combined with calcium sulfate	Weight Medical Technology Inc.
Osteocel® Plus	Bone	Allogeneic bone with mesenchymal stem cells	NuVasive
Pura-Matrix™	Bone	Hydrogel composed of a self-assembling peptide	3DMatrix
Osteoscaf™	Bone	Poly(lactic-co-glycolic acid) and calcium phosphate scaffold	Tissue Regeneration Therapeutics
INFUSE® bone graft	Bone	Recombinant human bone morphogenetic proteins-2 in combination with bovine type I collagen	Medtronics
Lifeline™	Blood vessels	Autologous fibroblast tubular cell sheet integrated with endothelial cells	Cytograft Tissue Engineering
Omniflow®	Blood vessels	Polyester mesh with cross-linked ovine collagen	Binova
Anginera™	Heart	Allogeneic fibroblasts on vicryl mesh	Theregen
CardioValve® SynerGraft Pulmonary Heart Valve	Heart	Decellularized allogeneic pulmonary valve	Cryolife

application of regenerative medicine techniques.

IV. BIOMATERIAL APPLICATIONS IN REGENERATIVE MEDICINE

The role of biomaterials in regenerative medicine and biomedical applications is paramount, offering the potential to replace damaged tissues and organs and treat chronic diseases. Recent advances in biochemistry, molecular biology, engineering, and material sciences have expanded the opportunities for their clinical use. These biomaterials act as scaffolds, resembling the extracellular matrix (ECM), which naturally supports tissues and organs. They provide structural support, mimic the physiological microenvironment, and contribute to various molecular and signaling events that maintain cell morphology and function. The ability of biomaterials to mimic the native ECM is crucial for regenerating damaged tissues effectively. Natural hydrogels, such as chitosan, collagen, and decellularized tissues, have inherent biodegradability and biocompatibility, making them suitable for tissue engineering. Synthetic hydrogels like polyethylene glycol (PEG) offer advantages such as large-scale production and tunable properties, enhancing their utility in 3D cell culturing and tissue engineering. Tuning hydrogel properties facilitates a better understanding of cell-substrate interactions and the creation of tissue models, ultimately improving tissue regeneration efficiency.

While these biomaterials hold immense promise, challenges persist in translating them into practical applications. Many synthetic hydrogels are synthesized under harsh chemical conditions, necessitating careful removal of unreacted reagents to prevent cross-contamination. Achieving the dynamic and heterogeneous nature of the native cellular microenvironment remains a challenge. Manufacturing and processing techniques are being adapted to synthesize biomaterials with desirable features safely. Photochemical reactions offer spatiotemporal control over hydrogel properties, enabling precise three-dimensional adjustments. Understanding the molecular pathways between cells and biomaterials is crucial for developing biomaterials that elicit specific cellular responses, enhancing tissue regeneration control. The structural, mechanical, and biochemical properties of synthetic scaffolds still fall short of replicating complex human tissues. Achieving precise regulation of physiological processes within biomaterials is challenging. The integration of key biomolecules and signals for bioactivation is essential. Monitoring cellular behavior in synthetic microenvironments and tracking introduced signals are integral to developing effective and cost-efficient biomaterials for clinical use.

Microfabrication technologies provide a diverse range of sizes, shapes, and architectures to create complex functional engineered tissues and organs. Bridging the gap between scientific knowledge and biomaterial development, along with a deep understanding of their role in tissue regeneration, is crucial. Advances in synthetic technology are paving the way for new generations of multifunctional biomaterials, holding promise for the rapidly growing field of regenerative medicine. Biomaterials are at the forefront of regenerative medicine, offering a bridge between scientific innovation and practical clinical applications. Their ability to mimic the native cellular microenvironment and support tissue regeneration is driving advancements that have the potential to transform healthcare and improve patient outcomes. In the realm of products especially concerning organs (tissues) various companies have made numerous advancements with promising outcomes for health medication and a large number of research and development is still ongoing even to this day. To provide an idea concerning this matter the Table 1 illustration is given for a better understanding.

V. ADVANCEMENTS IN THE REALM OF REGENERATIVE MEDICINE

Regenerative medicine is a dynamic field focused on repairing and rejuvenating damaged or diseased cells, tissues, and organs. Its overarching goal is to restore proper function to these biological components, often disrupted by injury, illness, or natural aging processes. Regenerative medicine encompasses various strategies, including tissue engineering and therapeutic stem cell utilization, along with the production of artificial organs. These approaches typically involve a combination of scaffolds, cells, and bioactive molecules, traditionally emphasizing biomaterials, stem cells, and growth factors. However, recent developments have expanded the scope to include an immune-centric approach, making it a thriving area of exploration in regenerative medicine. Traditional regenerative methods have leaned on autografting, where a patient's own tissues are employed to facilitate healing. However, this approach is not without complications, particularly graft rejection. To address these challenges, there's a growing interest in harnessing the power of the immune system.

Active control of immune responses presents a promising avenue for regenerative therapies. A deeper understanding of the immune mechanisms involved in tissue regeneration could shed light on graft and biomaterial acceptance, offering alternative solutions to traditional autografting.

The immune system's response to tissue damage plays a pivotal role in assessing the integrity of the healing process, and it involves both innate and adaptive immunity. Key players include macrophages, neutrophils, and various molecules that trigger inflammatory responses, clear cellular debris, remodel the extracellular matrix, and synthesize cytokines. While innate and adaptive immunity have traditionally been viewed as separate processes, recent research development reveals significant overlap between them. Danger signals, such as damage-associated molecular patterns (DAMPs), neutrophils, and macrophages, are central actors in modulating tissue healing.

In the realm of immunomodulation in regenerative medicine, two prominent strategies have emerged: biomaterials and scaffolds. Biomaterials, encompassing metals, ceramics, polymers, and composites, are inherently

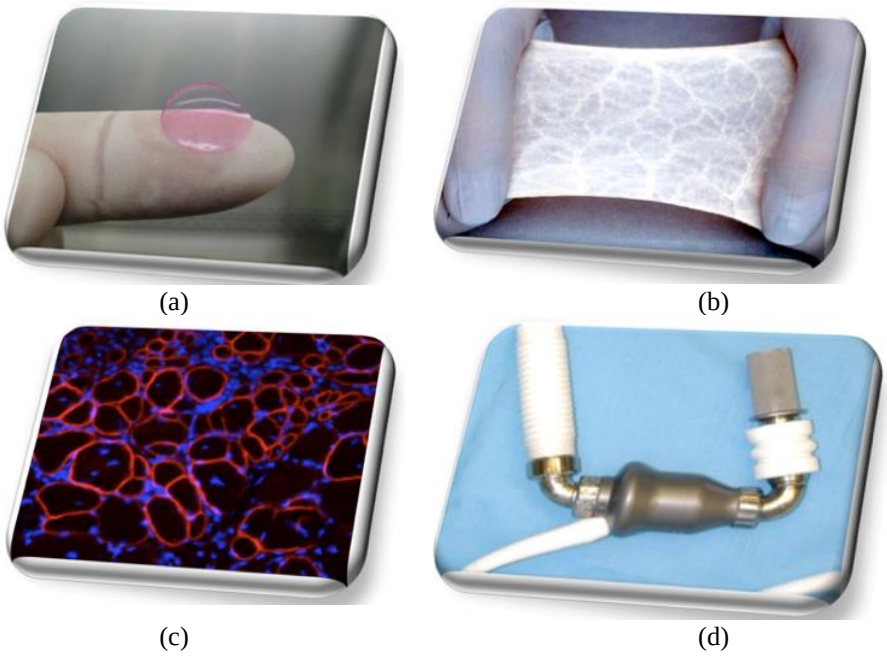


FIGURE 2. Some recent advancements in tissue engineering (a) A mini bioengineered human liver that can be implanted into mice [23], (b) A biomaterial made from pigs' intestines which can be used to heal wounds in humans. When moistened, the material, which is called SIS, is flexible and easy to handle [23], (c) Cellular Therapies, (d) Medical Devices and Artificial Organs.

foreign to the human body and thus carry the risk of rejection, akin to autografts. However, an innovative approach involves delivering biomaterials through immune components that act as immunomodulators, potentially triggering pro- or anti-inflammatory responses. The success of this approach depends on the physicochemical properties of the biomaterial, including its form, level of crosslinking, hydrophobicity, and nature.

Another promising avenue is the use of decellularized extracellular matrix (ECM) as a scaffold. This involves removing cells from excised tissues, leaving behind a scaffold structure that influences cellular processes and fosters pro-regenerative conditions. Researchers have explored this technique in bioengineering livers using decellularized scaffolds, enhancing their therapeutic potential through structural modifications. For instance, crosslinking with nano-graphene oxide has shown promise in improving liver function, offering a hopeful alternative to traditional organ transplantation. These advancements in immunomodulation, biomaterials, and scaffolds underscore the exciting potential of regenerative medicine to transform healthcare and offer new solutions for healing and tissue restoration.

VI. REGENERATIVE MEDICINE AND TISSUE ENGINEERING

Tissue engineering and regenerative medicine are fields at the forefront of medical research, dedicated to addressing the challenges of repairing or replacing damaged or diseased tissues and organs. Tissue engineering, an evolution of biomaterials development, involves the strategic combination of scaffolds, cells, and biologically active molecules to create functional tissues. The primary objective is to construct viable structures that can restore, maintain, or enhance the functionality of compromised tissues or entire organs.

Notable examples include FDA-approved engineered tissues like artificial skin and cartilage, though their widespread clinical application remains limited. Regenerative medicine encompasses tissue engineering but extends beyond it, encompassing research on self-healing processes, where the body utilizes its mechanisms, often with the assistance of foreign biological materials, to regenerate cells and reconstruct tissues and organs. The terminology of "tissue engineering" and "regenerative medicine" has become increasingly interchangeable, reflecting the field's aspiration to shift from treating complex diseases to curing them. These domains are continually evolving, with applications not only in medical therapeutics but also in non-therapeutic areas, such as biosensors for detecting biological or chemical threats and tissue chips for assessing the toxicity of experimental drugs. The core concept revolves around manipulating the behavior of cells, their interactions with the environment, and their ability to form tissues and ultimately organs. The tissue engineering process typically begins with the creation of scaffolds from various materials, ranging from proteins to plastics. These scaffolds serve as the foundation for tissue development and facilitate the exchange of signaling

molecules. Cells, sometimes guided by a combination of growth factors, are then introduced into this environment. In favorable conditions, tissues form. In some cases, the cells, scaffolds, and growth factors are mixed together simultaneously, allowing for the tissue to self-assemble. Another approach involves utilizing pre-existing scaffolds derived from donor organs, with cells removed, leaving a collagen scaffold. This scaffold can be used as a template for growing new tissue. For instance, bioengineered liver tissue grown on decellularized scaffolds shows promise in metabolizing drugs similarly to human livers, offering a valuable tool for drug testing and reducing the reliance on animal models. Despite remarkable progress, tissue engineering and regenerative medicine still play relatively minor roles in clinical practice. Procedures like supplemental bladder implantation, skin grafts, and cartilage replacements have been performed, but more complex organs, such as the heart, lung, and liver, are not yet fully reproducible for transplantation. However, these engineered tissues serve as crucial research tools, particularly in drug development, where they can significantly accelerate the screening of potential medications and facilitate the advancement of personalized medicine while reducing costs and animal testing. Research funded by organizations like the National Institute of Biomedical Imaging and Bioengineering (NIBIB) is driving innovation in tissue engineering and regenerative medicine. Scientists are exploring diverse areas, from controlling stem cells through their environment to implanting human liver tissue in mice for drug testing.

Breakthroughs include engineering mature bone stem cells that can be transplanted successfully and creating lattices to help engineered tissues develop the essential vascular networks for survival. Moreover, novel solutions like a biological gel and adhesive combination have demonstrated promising results in regenerating cartilage tissue, offering hope for patients with joint-related issues. In parallel, groundbreaking efforts in kidney regeneration from a patient's own cells are promising steps toward addressing kidney disease and donor organ shortages. These advancements reflect the ongoing commitment to pushing the boundaries of what is possible in the fields of tissue engineering and regenerative medicine. Tissue engineering is also a field of immense promise, spanning various medical disciplines like orthopedics, cardiology, neurology, and dermatology. In orthopedics, it has offered solutions for repairing significant bone defects and non-healing fractures, while tissue-engineered cartilage constructs hold potential for addressing joint cartilage damage. In cardiology, engineered cardiac patches and blood vessels hold hope for individuals with heart diseases, and tissue-engineered nerve grafts are being investigated for restoring function in patients with spinal cord injuries and peripheral nerve damage.

These breakthroughs have the potential to revolutionize patient care across multiple specialties. Particularly remarkable are the developments in vascularized constructs, which are vital for ensuring adequate oxygen and nutrient supply to tissues. A critical frontier in tissue engineering lies in the realm of organ transplantation. The persistent shortage of donor organs presents a formidable challenge in medicine. Tissue-engineered organs, such as kidneys, livers, and lungs, have emerged as potential solutions, offering the prospect of alleviating the organ transplant demand and bypassing issues related to organ rejection. While challenges like achieving full functionality and long-term viability persist, progress in bioengineered organs augments the vision of a future where organ transplantation is no longer constrained by donor availability. However, tissue engineering confronts several pressing challenges. One of these challenges is the creation of adequate vascularization within large tissue constructs, as an efficient network of blood vessels is vital for supplying oxygen and nutrients to all cells.

Researchers are exploring various strategies, including the use of angiogenic factors, advanced bioprinting techniques to build vascular networks, and the development of perfusion systems that can provide nutrients and remove waste during tissue culture. Another critical concern is the immunological response and integration of engineered tissues within the host organism. The body's immune system can recognize these engineered tissues as foreign entities, potentially leading to rejection or inflammation. Scientists are actively investigating strategies to modulate the immune response, including the use of immunomodulatory biomaterials and cell-based therapies, to enhance host integration and reduce immune reactions. Tissue engineering, with its vast potential and ongoing research endeavors, offers a promising avenue for addressing critical medical challenges and enhancing patient outcomes across a spectrum of healthcare disciplines. Among the best of advancements in terms of tissue engineering the 4 mentioned within FIGURE 2 are the remarkable ones which has paved the way for future prospects within Tissue Engineering.

VII. AN INSIGHT TOWARDS ORGAN-ON-A-CHIP

Organ-on-a-chip (OOC) technology represents a cutting-edge approach in biomedical engineering research, particularly in the field of bio-MEMS (Micro-Electro-Mechanical Systems). These innovative devices are multi-channel 3-D microfluidic cell cultures integrated into a single chip, designed to replicate the activities, mechanics, and physiological responses of entire organs or organ systems. OOCs have emerged as a powerful tool that bridges the gap between traditional cell culture and in vivo studies, offering a more sophisticated in vitro approximation of complex tissues. This advancement holds great promise for drug development and toxin testing, potentially reducing the reliance on animal models.

While numerous publications claim to have successfully recreated organ functions on OOCs, it's important to note that this technology is still in its early stages of development. Researchers employ various designs and approaches, simulating organs ranging from the brain and lung to the heart, kidney, liver, and more. However, one limitation of early OOCs is their potential to oversimplify the complex network of physiological processes within the human body, potentially

missing significant biological phenomena. To address these limitations, ongoing efforts in microphysiometry aim to model more sophisticated physiological responses accurately through microfabrication, microelectronics, and microfluidics.

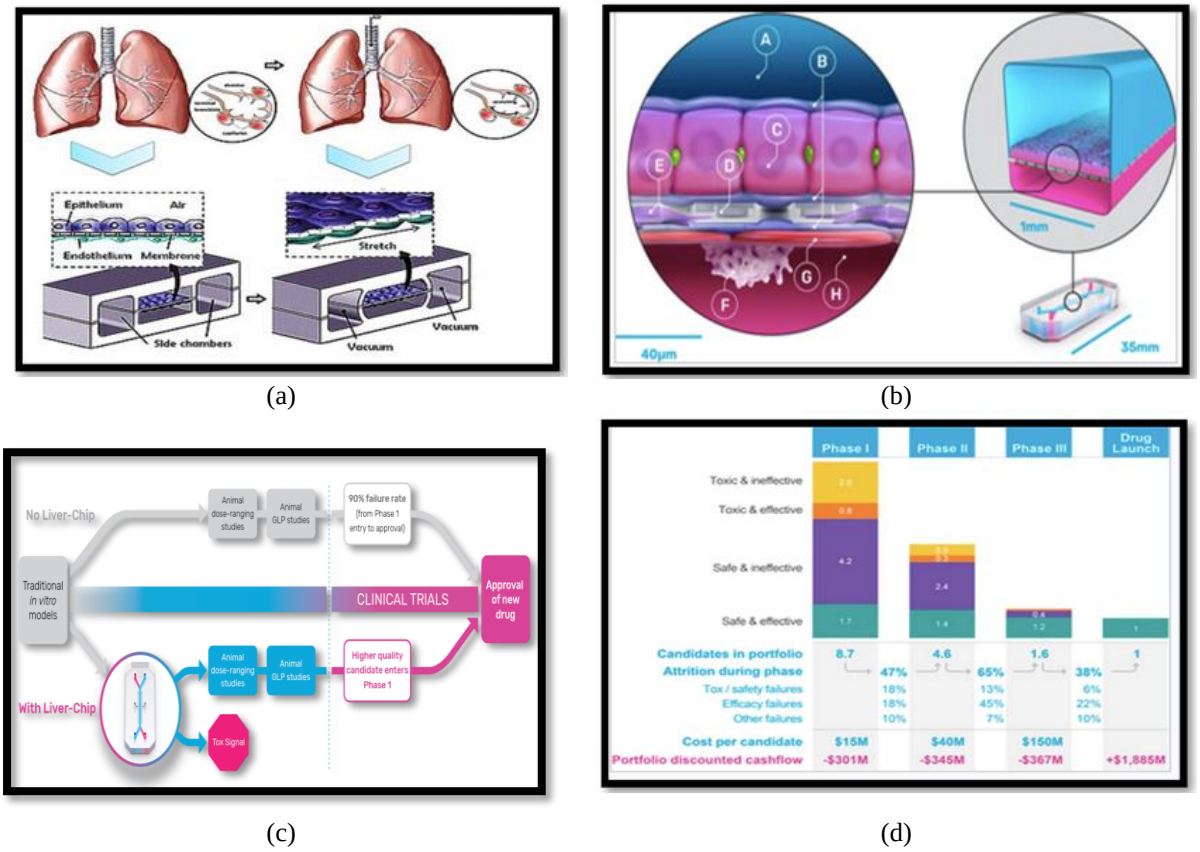
One significant achievement facilitated by organ chips is the study of the intricate pathophysiology of human viral infections. For instance, liver chips have enabled groundbreaking research into viral hepatitis. This technology allows researchers to delve into the effects of viruses on specific organs in a controlled and accurate manner. In parallel, lab-on-a-chip (LOC) devices have also made substantial progress in the last decade. These devices integrate various laboratory functions onto a single chip, primarily focusing on handling particles in microfluidic channels. This miniaturization of laboratory functions offers several advantages, including reduced reagent consumption, increased portability, better process control, and lower fabrication costs. The laminar flow properties of microfluidics have been harnessed for various cellular biology applications, such as studying cell motility, stem cell differentiation, biochemical signaling, and embryonic development. Transitioning from traditional 2D cell cultures to OOCs has been a significant step forward in cellular biology. While 3D cell culture models already improve cell differentiation and tissue organization compared to 2D cultures, they still fall short in mimicking many aspects of an organ's cellular properties. OOCs address these limitations by efficiently transporting nutrients and other soluble cues throughout 3D tissue constructs, replicating tissue-to-tissue interfaces, spatiotemporal gradients of chemicals, and notably the mechanically active microenvironments.

In essence, organs-on-chips represent the next wave of 3D cell-culture models, offering a more accurate portrayal of the biological activities, dynamic mechanical properties, and biochemical functionalities of living organs. This breakthrough technology holds immense potential for advancing our understanding of human physiology and disease, drug development, and toxicity testing. Organ-on-a-chip (OOC) technology is revolutionizing our approach to studying various organs and their functions, offering a sophisticated bridge between traditional cell culture and in vivo research. One of the remarkable developments in this field is the brain-on-a-chip, which combines neuroscience with microfluidics. These devices allow for improved cell culture viability, high-throughput screening, and the modeling of organ-level physiology and diseases in vitro. Brain-on-a-chip platforms utilize organotypic brain slices, preserving tissue architecture and enabling the study of multicellular interactions. Microfluidic systems enhance culture viability and have even allowed for thicker brain slices, offering more in vivo-like characteristics. These devices support drug screening, modeling the blood-brain barrier, and simulating neurological diseases such as Alzheimer's and Parkinson's, providing valuable insights into treatment and diagnostics.

In the realm of gut research, the gut-on-a-chip technology has emerged as a powerful tool to mimic the complex environment of the human intestine. These chips use microchannels separated by flexible, porous membranes to culture gut epithelial cells. By inducing peristalsis-like fluid flow and co-culturing with gut microbiota, researchers can study drug absorption, toxicity, and the effects of inflammatory bowel diseases. This technology significantly reduces research costs and time, making it a valuable tool for drug development and understanding the gut's role in drug absorption and metabolism.

Lung-on-a-chip devices are designed to replicate the physiological aspects of the alveolar-capillary interface in the human lung. These chips utilize microfluidic channels and a porous membrane to mimic the stretching of lung tissue during respiration. Researchers can study responses to inflammation and infections, making them valuable for toxicology studies and understanding environmental health risks. While lung-on-a-chip technology offers promise, it still faces challenges in fully replicating native alveolar epithelial cell responses. In the realm of cardiac research, heart-on-a-chip devices are tackling the challenge of replicating in vivo cardiac tissue environments. Microfluidics have allowed for the creation of platforms to monitor cardiomyocyte metabolism and extracellular potentials. These chips can study the relationship between tissue structure, gene expression, and cardiac contractility. They also provide a means to investigate cardiac diseases, drug responses, and tissue-level interactions. Additionally, 3D microfluidic heart-on-a-chips have been instrumental in studying heart diseases, such as cardiac hypertrophy and fibrosis, offering insights into biomarker levels and responses to treatment.

Organ-on-a-chip technology is transforming our ability to model and study various organs and diseases in a controlled, in vitro environment. These devices offer great promise in drug development, disease modeling, and understanding complex physiological processes. However, they also face challenges and limitations, which researchers continue to address in their pursuit of more accurate and sophisticated organ-on-a-chip systems. Researchers have been making significant strides in the development of organ-on-a-chip devices, which are microfluidic platforms designed to simulate the functions of various organs in the human body. These devices hold immense potential for advancing medical research and drug testing by providing a more accurate representation of human physiology compared to traditional laboratory techniques. Kidney-on-a-chip devices aim to replicate the functions of nephrons, the fundamental units of the kidney. These microfluidic devices simulate glomerular filtration, tubular reabsorption, and secretion, mimicking the intricate processes of the renal system. By closely mimicking the nephron's function, these chips can offer insights into kidney function and be used for drug screening. Moreover, the development of a kidney-on-a-chip has the potential to make renal replacement therapies more portable and efficient, benefiting patients who require frequent dialysis.



(a) (b)

(c) (d)

FIGURE 3. A visual representation of organ-on-a-chip retrospective (a) Schematic drawing of a lung-on-a-chip. The membrane in the middle can be stretched by vacuum in the two side chambers [23], (b) Schematic of a liver-chip [23], (c) Proposed positioning of the Liver-Chip within a typical pharma preclinical workflow [23], (d) Potential financial impact of improved preclinical testing with liver-chips according to recent studies [23]

The liver-on-a-chip is a microfluidic device that replicates the hepatic system's complex functions. It utilizes primary hepatocytes and other non-parenchymal cells to create a liver model that is cost-effective and beneficial for drug testing. While some liver-on-a-chip systems use poly (dimethylsiloxane) (PDMS), others opt for more inert materials like polysulfone or polycarbonate. These devices have the potential to revolutionize drug development by predicting drug-induced liver injury, reducing costs, and improving efficiency in the pharmaceutical industry. Prostate-on-a-chip systems aim to recreate the prostate epithelium, providing valuable insights into cancer metastasis and the effects of microenvironmental changes. These microfluidic platforms offer adjustable topography and enable researchers to study cellular reactions to changes in the microenvironment. They can also be used to facilitate the collection of prostatic fluid and assess drug candidates for metastasis scenarios. Cardiovascular diseases often result from changes in the structure and function of small blood vessels.

Blood vessel-on-a-chip devices simulate the biological response of arteries, enabling organ-based screens during drug development and enhancing our understanding of pathologic changes in small arteries. These microfluidic platforms can accommodate fragile blood vessels, making them scalable, cost-effective, and potentially automated in manufacturing. Human skin is the body's first line of defense against pathogens and various diseases. Skin-on-a-chip applications include testing topical pharmaceuticals, studying skin diseases, and creating noninvasive cellular assays. While the development of skin-on-a-chip has faced challenges like collagen scaffolding detachment and incomplete differentiation, dynamic perfusion in microfluidic cultures has shown promise in improving cell viability and differentiation. The endometrium, a crucial tissue in pregnancy, has been modeled on microfluidic platforms to study implantation and other stages of pregnancy. These models help researchers gain insights into the complex processes involved in female reproduction.

Organ-on-a-chip technology represents a groundbreaking approach to mimicking human organ functions in the laboratory. These devices hold the potential to revolutionize drug testing, disease research, and personalized medicine by

providing more physiologically relevant systems for experimentation. As research in this field continues to advance, organ-on-a-chip devices may become indispensable tools in the fields of medicine and pharmaceutical development. Researchers are making significant progress in the development of human-on-a-chip technology, which involves creating multi-channel 3D microfluidic cell culture systems that mimic multiple organs in the human body. Unlike traditional organ-on-a-chip models that often focus on a single cell type, human-on-a-chip devices aim to replicate the complexity of multiple organs working together. One notable example is the integrated cell culture analog (μCCA), which includes lung cells, drug-metabolizing liver cells, and fat cells interconnected in a 2D fluidic network. This system mimics the circulation of a blood surrogate, providing essential nutrients and removing waste from the cells. The goal is to create a more realistic in vitro pharmacokinetic model, enhancing drug testing and research.

A microfluidic human-on-a-chip has also been developed, featuring four different cell types to mimic the liver, lung, kidney, and fat. To ensure the validity of these devices, researchers have worked on optimizing a standard serum-free culture medium that can support all cell types simultaneously. This common medium helps maintain the functional levels of cells, ensuring that drug testing on the microfluidic platform yields results consistent with the physiological and metabolic reactions of whole human organs. Furthermore, human-on-a-chip designs are becoming increasingly sophisticated. Some allow for the precise tuning of microfluidic transport to multiple tissues using a single fluidic actuator, making them valuable for modeling various physiological conditions. As these devices evolve, pharmaceutical companies may be able to measure the direct effects of drugs on multiple organs simultaneously. This capability can help ensure that a drug's beneficial effects on one organ do not compromise the functions of others, improving drug safety and efficacy. One of the primary motivations for developing human-on-a-chip technology is to replace animal testing in drug development. Animal experiments are expensive, time-consuming, and ethically controversial. Moreover, the translation of results from animal models to humans can be challenging due to species differences.

By creating biomimetic microfluidic systems that reproduce complex organ-level responses, researchers aim to revolutionize fields like toxicology and pharmaceutical development. These microfabricated cell culture systems offer more affordable and controlled alternatives to traditional animal testing, providing a closer representation of human physiology. Additionally, physiologically based perfusion in vitro systems have emerged as a promising approach to replicating in vivo cell environments. Multi-compartmental perfused systems have gained interest in pharmacology and toxicology, as they aim to reproduce in vivo mechanisms related to drug absorption, distribution, metabolism, and elimination (ADME).

These systems, combined with mathematical pharmacokinetic (PK) models, allow researchers to estimate concentration-time profiles within each organ, making it possible to predict drug behavior with high accuracy. Human-on-a-chip technology represents a significant advancement in the field of biomedical research. These microfluidic platforms have the potential to transform drug development, toxicology studies, and disease modeling by providing a more accurate representation of the human body's complex interactions between organs. As these devices continue to evolve and become more accessible, they hold great promise for improving drug safety and efficacy while reducing the reliance on animal testing in pharmaceutical research. To better understand the complexity and functionality involved for this technology the FIGURE 3 provides a visual representation towards the retrospective of the matter.

VIII. BIOPRINTING, CREATING FUNCTIONAL TISSUES AND ORGANS

The field of 3D printing, also known as additive manufacturing, has been instrumental in various industries, and it's increasingly making its mark in healthcare. Within healthcare, 3D bioprinting stands out, where living cells are incorporated into the 3D printing process. This technology is gaining traction, with the global 3D bioprinting market projected to reach over $4.7 billion by 2025 in per accordance to recent announcements.

A key aspiration of 3D bioprinting is to address the organ shortage crisis by enabling the creation of complex tissues and organs. While functional human organs are still in the experimental phase, simpler tissues like skin and cardiac patches have already been successfully 3D bioprinted. These bioprinted tissues find applications in drug testing, toxicity assessment, tissue engineering, and more. The advantages of 3D bioprinting are numerous. It allows for the creation of anatomically accurate structures, porous designs, incorporation of multiple cell types, and precise delivery of growth factors and genes. However, one major challenge remains: achieving vascularization within bioprinted tissues, which is essential for the survival of larger, complex organs.

In the realm of 3D bioprinting ink, Boston-based company Cellink has taken a unique approach by focusing on the development of standardized bioinks. These bioinks are composed of various materials, such as gelatin, collagen, or alginate, infused with human cells. They are designed for specific tissue types and are compatible with most 3D bioprinters available today. Cellink also manufactures its own cost-effective, mobile 3D bioprinters, offering complete bioprinting solutions for academic institutions and pharmaceutical companies. While these bioinks are primarily used for research purposes, they hold the potential for future applications in human tissue replacement, with cartilage and skin being potential early candidates for FDA approval. In the realm of bioprinting techniques, laser direct-write (LDW) printing has shown promise for achieving single-cell spatial resolution. Researchers at Tulane University have been

pioneering LDW printing to deposit various cell types with exceptional precision, aiming to mimic the cellular heterogeneity found in native tissues for the last few years. This technology relies on laser bursts to propel cells through a biopolymer film onto a receiving substrate, ultimately forming 3D tissues. LDW printing has already been used to create complex tissues like collagen fibers, muscle fibers, and neural circuits. It also offers opportunities to investigate disease mechanisms, tissue functionality, and even cancer cell behavior.

Moreover, 3D bioprinting is not limited to creating tissues but is also playing a pivotal role in designing cost-effective lab tools for biologists. Researchers at the University of Southern California are utilizing 3D bioprinting to build modular microfluidic systems, which simplify fluid mixing for diagnostic tests and microbioreactor processes. These systems facilitate precise fluid mixing and can generate uniform microdroplets for various applications. By incorporating off-the-shelf components like photodiodes and sensors into their devices, they aim to drive down costs and enhance device functionality. Looking forward, the field of 3D bioprinting is expanding into 4D, where printed structures can respond dynamically to their environment. GE Healthcare, among others, is interested in technologies that improve and streamline the bioprinting process. This includes high-power microscopes for detailed tracking of cellular responses and digital modeling and data management tools to control the printing process more effectively. Such developments are poised to enhance the versatility and applications of 3D and 4D bioprinting in healthcare and beyond. In a noteworthy application, Organovo has leveraged 3D bioprinting to create therapeutic liver tissues, termed NovoTissues, for treating rare liver diseases like α-1 antitrypsin deficiency (AATD) and hereditary tyrosinemia type 1 (HT-1). These bioprinted liver tissues have demonstrated promising results in preclinical studies, modulating disease progression and improving survival rates in animal models. While challenges remain on the path to FDA approval, the potential for bioprinted tissues to address unmet medical needs is evident.

In terms of materials, a recent study published in 3D Printing and Additive Manufacturing introduced a novel additive manufacturing system that combines 3D printing with plasma treatment. This system enables the creation of complex scaffolds with varying physical, chemical, and biological properties. By manipulating the distance between the plasma head and the printed material, researchers were able to modify the scaffolds effectively, improving their mechanical properties and biocompatibility. This innovation holds promise for tissue engineering applications, offering greater control over scaffold characteristics. 3D bioprinting is revolutionizing healthcare by pushing the boundaries of tissue engineering, drug testing, and medical device fabrication. The field is advancing rapidly, with bioinks, printing techniques, and materials playing crucial roles in its evolution. As more research continues, the potential to create functional human organs and personalized medical treatments using 3D bioprinting becomes increasingly feasible, promising a brighter future for healthcare innovation and patient care.
Bioprinting is a cutting-edge additive manufacturing process akin to 3D printing, but with a remarkable twist – it employs cells and biomaterials to construct intricate structures layer by layer.

Unlike traditional 3D printing, bioprinting has the potential to revolutionize various industries, particularly in regenerative medicine, drug discovery, and cosmetics. Understanding the core steps of bioprinting is essential to appreciate its significance.

Pre-bioprinting: This initial phase involves the creation of a digital file that serves as the blueprint for the bioprinter. These digital files often originate from CT and MRI scans. Researchers also prepare cells and combine them with a bioink, ensuring that there are sufficient cells for successful bioprinting of a tissue model. Advanced imaging systems are employed to monitor and confirm cell viability.

Bioprinting: In this pivotal stage, researchers load the bioink, enriched with living cells, into a specialized cartridge. They select one or more printheads, depending on the desired structure they aim to fabricate. Different types of tissues require varying cell types, bioinks, and equipment, showcasing the adaptability of bioprinting technology.

Post-Bioprinting: To ensure the stability and integrity of the printed structures, most constructs undergo a crosslinking process. This is typically achieved through treatment with an ionic solution or exposure to UV light. The specific composition of the construct guides researchers in determining the appropriate crosslinking method. Following crosslinking, the cell-laden constructs are placed within an incubator for cultivation and maturation. The applications of bioprinting are vast and hold immense promise across diverse domains.

Drug Development: Bioprinted tissues offer a more ethical and cost-effective alternative to animal testing and clinical trials. Researchers can use these tissues during the early stages of drug development to assess drug candidates' efficacy swiftly, ultimately saving time and resources.

Artificial Organs: Bioprinting has the potential to address the long-standing organ shortage crisis by enabling the creation of functional artificial organs. While this application is still evolving, it holds the promise of reducing transplant waiting lists and providing timely medical interventions.

Wound Healing: Bioprinting has led to the development of specialized bioinks tailored to specific tissue types, including skin cells, neurons, and hepatocytes. These bioinks pave the way for potential therapeutic procedures such as skin grafts, bone bandages for combat injuries, and even applications in plastic surgery.

While bioprinting is a relatively recent innovation, it has made remarkable progress in a short span. The field of biocompatible 3D printing emerged in the early 1980s, with cell-embedded bioprinting introduced in 2003 by Thomas Boland. As more researchers gain access to the latest bioprinting technologies, the pace of innovation is poised to accelerate. The future holds great promise, and collaborations in the field, such as those with CELLINK, are expected to yield exciting discoveries and advancements in the upcoming years to come.

IX. DRUG DELIVERY AND IMMUNE ENGINEERING A CASE STUDY ANALYSIS

The case study analysis explores the challenges and opportunities associated with the oral delivery of immunotherapeutics, emphasizing the critical role of biomaterials and drug delivery systems (DDS). Oral drug administration is a convenient and noninvasive method but faces various obstacles, including enzymatic degradation, pH variations in the gastrointestinal tract, first-pass metabolism, and mucosal and epithelial barriers. These challenges are particularly complex when delivering fragile immunotherapeutics like antibodies, mRNA, and DNA. The human intestine, with its dense population of immune cells, offers a promising target for modulating immune-related diseases. One significant advantage of oral delivery is the potential to generate tolerance to intravenously delivered therapeutics, reducing the production of antidrug antibodies that can diminish efficacy. Immunotherapeutics such as interleukins, growth factors, and small molecules like rapamycin hold great potential for oral delivery. DDS can be tailored to deliver these agents to specific sites in the gut, offering targeted immune modulation. Despite the promise of DDS, natural barriers in the GI tract must be overcome for successful oral immune engineering.

This analysis provides insights into the major immunotherapeutics that can be delivered orally and strategies for improving oral drug targeting, highlighting the significant potential for systemic immune response modulation through oral delivery. This comprehensive analysis also delves into the challenges and strategies associated with the oral delivery of immunotherapeutics, highlighting the crucial role of biomaterials and drug delivery systems (DDS). While oral drug administration is a convenient method, it faces multiple obstacles such as enzymatic degradation, pH variations in the gastrointestinal tract, and mucosal barriers. Biomaterials, particularly those with mucoadhesive properties, offer a promising solution to increase drug residence time in the gastrointestinal tract. Mucoadhesion involves the formation of chemical bonds, often hydrogen or ionic bonds, between mucosa and mucoadhesive materials. Thiolated polymers, which form strong covalent disulfide bonds with the mucosal layer, significantly enhance mucoadhesion, thus increasing the drug absorption. This approach holds potential for delivering immunotherapeutics locally in the mucosa for diseases like ulcerative colitis and inflammatory bowel diseases, where precise immune modulation is crucial. In addition to mucoadhesion, nanoparticle systems with specialized mucolytic agents show promise in cleaving mucus substructures, allowing drug carriers to bypass the mucosal layer. Combining multiple targeting mechanisms, such as self-nanoemulsifying drug delivery systems (SNEDDS) paired with mucoadhesives, enhances drug solubility and adhesion to the mucosal layer, improving bioavailability. These strategies provide valuable tools for delivering anti-inflammatory cytokines, growth factors, and other immunotherapeutics to specific sites in the gut, ultimately offering targeted immune modulation.

Overcoming the epithelial barrier, drugs can employ mechanisms like passive diffusion, carrier-mediated diffusion, active transport, or transcytosis to reach systemic circulation. Strategies for enhancing these mechanisms include transient permeabilizing agents, prodrugs, and cell-penetrating peptides (CPPs). Prodrugs chemically modify drugs to enhance passive transport, while CPPs facilitate cell penetration and antigen delivery. Active transport systems, like molecular motors, enable the uniform distribution of vaccines in the gut, enhancing immune responses against mucosa-related infections. Furthermore, the case study analysis explored the current strategies for oral-to-systemic immunotherapeutic delivery, emphasizing the development of biomaterials to increase drug bioavailability. Natural and synthetic biomaterials, including chitosan-based nanoparticles and innovative devices like the MucoJet, aim to improve the absorption of immunotherapeutics through the gastrointestinal tract. These advancements represent significant progress in making oral drug delivery a viable option for immunotherapeutics, although challenges related to safety, cost, and clinical translation remain. This investigation analysis also underscores the critical role of biomaterials and drug delivery systems in addressing the challenges of oral immunotherapeutic delivery, potentially revolutionizing the treatment of various immune-related diseases through targeted and efficient drug administration.

X. GENE EDITING AND PRECISION MEDICINE

The field of precision medicine is rapidly advancing, bringing us closer to the development of personalized treatments for patients. Despite the immense potential, several challenges stand in the way of widespread adoption. This investigation will provide some key takeaways that shed light on solutions to these challenges and the diverse array of methods and technologies required to make precision medicine a reality. One of the groundbreaking aspects of precision medicine is the use of advanced therapies like genome editing technologies, such as CRISPR-Cas9. These technologies enable tailored modifications to correct genetic mutations, offering new avenues for treating previously intractable diseases. This represents a significant advancement in the field. With precision medicine, there is a need for alternative benefit-risk assessment calculations, particularly due to the

often-small sample sizes in treatment development. New and alternative statistical methods, like pairwise comparison of patient outcomes, are becoming essential for accurately assessing individual benefit-risk profiles.

Genomics at a population scale can help identify individual disease risks and the suitability of medicines even before the onset of diseases, shifting the standard of care from reactive to proactive. Initiatives like Estonia's 100,000 Genomes Project, which collects citizens' genomic data, demonstrate the potential of outreach, accessibility, and adaptability in achieving these goals. As genetic information accumulates, it can be harnessed to develop patient-tailored therapies and preventive treatments. Cutting-edge tools like genome editing hold the promise of directly altering genetic code to treat various conditions. Clinical trials for genome editing-based therapies are already underway, addressing diseases such as sickle cell anemia and cancer. However, implementing advanced therapies like genome editing presents new challenges, including how to calculate benefit-risk effectively, given the smaller sample sizes typically associated with individualized treatments. The proper suggestion would be using generalized pairwise comparisons as an alternative method, which takes into account individual patient priorities and outcomes.

Despite these exciting advancements, challenges remain, such as addressing data privacy and ownership in genome-based studies, regional regulatory differences, and the implications of acquired information, particularly concerning insurance rates and payer policies. Additionally, safety, quality, and ethical concerns surrounding new technologies must be addressed. Precision medicine holds immense potential, leveraging genomic data, advanced therapies, and innovative tools. Collaboration between industry and regulators, adaptability to new technology, and public trust are crucial for advancing personalized care. The future of healthcare holds the promise of tailored treatments that can revolutionize patient care.

The recent DIAmond session announcement on "Precision Medicine, Gene Editing, and Gene Therapy" provided valuable insights into the rapidly advancing field of precision medicine. The discussion involved a diverse panel of representing scientists, clinicians, government regulators, industry experts, and patient advocates, highlighting the progress, challenges, and opportunities in this dynamic area of healthcare. As per their discussion and point outs it was evident that, Precision medicine, encompassing gene therapy and gene editing technologies, is making significant strides in healthcare. The field is witnessing increased research activity, a growing market, and rising public awareness and acceptance of gene editing technologies like CRISPR-Cas9. These developments are driving innovation and expanding the potential for groundbreaking therapies. Technological advancements, such as more affordable genome sequencing and evolving gene editing tools, are paving the way for the collection of diverse genomic data. This wealth of information is crucial for developing improved gene therapies and advancing our understanding of genetic diseases. One notable observation is the increasing societal acceptance of gene therapy and gene editing technologies. Patients and physicians are eager to embrace innovative therapies that hold promise for treating genetic diseases previously considered untreatable.

However, several challenges must be addressed. Access to precision medicine and gene therapy is a concern due to high costs, particularly for rare diseases. Experts suggest that affordability can be achieved by streamlining manufacturing processes and scaling up production of gene therapy products. Regulators face the delicate task of balancing safety, quality, and efficacy assessments with the need to expedite innovative therapies for patients. Ethical concerns regarding heritable genetic modifications and variations in regulatory oversight in different countries also need attention. Managing the vast amount of genomic data collected presents challenges related to storage, analysis, privacy, security, and data sharing. Additionally, addressing off-target effects in gene editing remains a scientific challenge, necessitating ongoing research. Despite these challenges, numerous opportunities exist. Increasing data accessibility can accelerate research by sharing data among the scientific community. Patient engagement, particularly involving minority groups, is vital to improving perceptions of genetic testing and making a broader societal impact. Education and awareness initiatives can raise public understanding of precision medicine and genomics.

Looking ahead, there is potential for a shift toward preventive medicine as precision medicine deepens our understanding of disease causation and treatment. Preventive medicine can offer substantial benefits for population health and reduce overall healthcare costs. To maintain momentum, stakeholders must stay engaged and collaborate closely.
International cooperation is essential to address ethical concerns and align regulatory requirements. As the field advances, stakeholders must work collectively and take measured steps to ensure the safety and effectiveness of precision medicine while striving to bring innovative therapies to patients in a responsible manner. Ultimately, the primary responsibility of all stakeholders is to prioritize patient safety in their pursuit of progress in precision medicine and gene therapy.

XI. DRUG DISCOVERY, DESIGN AND SCREENING

The process of drug discovery, which involves identifying potential new therapeutic compounds, remains a challenging and resource-intensive endeavor despite advancements in biotechnology and computational tools. Drug design, a critical component of this process, entails creating molecules that interact effectively with specific biological targets. It often relies on computational modeling and bioinformatics, especially in the era of big data. In addition to traditional small molecules, therapeutic antibodies and biopharmaceuticals have gained prominence, necessitating advanced computational techniques to enhance their properties. The drug development journey includes preclinical research,

clinical trials, and regulatory approval, with a focus on optimizing drug properties like affinity, selectivity, efficacy, stability, and bioavailability.

The Special Issue published on IEEE "Drug Design and Discovery: Principles and Applications" highlights various research articles and communication pieces contributed by experts from around the world. One notable article discusses the use of a computational platform called CANDO for repurposing existing drugs to combat the Ebola virus. By integrating computational predictions and in vitro screening results, this platform helps identify potential treatments more efficiently, reducing time, cost, and resources required for future outbreaks. Another study explores the synthesis of novel compounds with potential antitumor properties, combining nitric oxide (NO) release with diterpenoids. This innovative approach showcases the potential of hybrid compounds as a strategy for discovering new anticancer agents.

Understanding protein-protein interactions is crucial in unraveling cellular networks. A recent study introduces a machine learning method called iPPBS-Opt, which utilizes pseudo amino acid composition and stationary wavelet transform to predict protein-protein binding sites. This method simplifies the prediction process and can aid in drug discovery and biomedical research. In the context of drug safety, an investigation into the nephrotoxicity of the widely used antibiotic vancomycin sheds light on its molecular targets in human kidney cells. This knowledge can lead to improved therapeutic strategies and reduced side effects in clinical applications. Additionally, the Special Issue also covers research on antimalarial agents, antiviral compounds, antimicrobial agents, antiepileptic drugs, and anti-inflammatory agents. These studies explore novel compounds, their synthesis, and their biological activities, contributing to the ongoing efforts to discover effective treatments for various diseases. The articles in that Special Issue collectively demonstrate the importance of computational methods, innovative compound design, and comprehensive pharmacological evaluations in drug discovery and development. These multidisciplinary approaches aim to accelerate the identification of promising drug candidates with enhanced safety and efficacy profiles, ultimately benefiting patients worldwide.

XII. BIOLOGICS THE FUTURE OF THERAPEUTICS AND DRUGS

A recent report published by GlobalData suggests that the rise of biologics in the pharmaceutical industry is set to continue, with these biologically derived drugs projected to surpass small molecules in terms of sales revenue. The report, titled 'Future of Pharma—Looking Ahead to 2022,' anticipates a significant increase in the sales of biologics over the next five years, with a staggering $120 billion more in sales predicted by 2027 compared to innovative small molecules. Quentin Horgan, Managing Analyst for the Drugs Database at GlobalData, describes biologics as "primary engines of value creation" and expects this trend to persist. Biologics are expected to dominate the sales of both large-cap and mega-cap bio/pharma companies. Horgan emphasizes the industry's shift towards biologics, not only in terms of drug approvals but also manufacturing processes. It is projected that nearly all subtypes of biologics tracked by GlobalData will experience significant growth in sales revenue, collectively accounting for 55% of all innovative drug sales by 2027. The current driving force behind biologics sales is monoclonal antibodies, exemplified by drugs like Opdivo (Ono Pharmaceuticals), Dupixent (Regeneron Pharmaceuticals), and Keytruda (Merck). These monoclonal antibodies are forecasted to contribute to 46% of biologics sales in 2027. Keytruda, which is primarily used for oncology indications, is expected to constitute 4% of all biologics sales in 2027. While monoclonal antibodies will maintain their dominance, the report highlights that gene therapies and gene-modified cell therapies will experience the most substantial growth. Between 2022 and 2027, both molecule types are forecasted to witness a remarkable increase of over 1,000 percent in sales. Notably, gene therapy sales are driven by pipeline therapies that are currently unapproved, such as RPA-501 by Rocket Pharmaceuticals, which is presently in Phase I of clinical trials. This underscores the dynamic evolution of the pharmaceutical industry towards biologics and the potential for groundbreaking advancements in treatment modalities.

The question of whether small molecules or biologics will shape the future of pharmaceuticals is explored in an opinion article. Drawing a parallel with technological advancements, the article asks whether biologics will replace small molecules much like Blu-ray Discs superseded videotapes. It delves into the characteristics and roles of these drug classes to provide insights into their future in healthcare. Small-molecule drugs, characterized by low molecular weight, have been foundational in traditional medicine. Icons like aspirin and penicillin have revolutionized healthcare, with penicillin reducing bacterial-related pneumonia deaths to less than 1% during World War II. Their predictable pharmacokinetics, simpler dosing, and cost-effectiveness make them attractive to healthcare providers and patients alike. However, their simplicity exposes them to fierce generic competition, impacting profits post-patent expiration.

In contrast, the pharmaceutical industry is experiencing a shift towards biologics, with eight of the top ten global best-selling drugs in 2016 falling into this category. Monoclonal antibodies, gene-based therapies, cellular products, and more constitute biologics. These complex drugs are vital in fields like oncology, where they address unmet clinical needs. Challenges for biologics include their high cost, complexity in manufacturing, fragility, and patient immune responses, which can affect long-term effectiveness. Ultimately, the analytics prediction suggests that while small molecules remain essential and cost-effective, biologics are poised to dominate the pharmaceutical landscape due to their efficacy in addressing complex diseases. As technology advances and

TABLE 2
Selection of biomaterials within research and development for regenerative medicine applications

Tissues/Organs	Cell types	Types of hydrogels	Applications	References
Bone	Osteoblasts	Poly(ethylene glycol) (PEG), poly(ethylene glycol) poly (lactic acid) (PEG-PLA)	Drug delivery, cell encapsulation, scaffold for bone regeneration	[11] [12]
Heart	Bone marrow cells, embryonic stem cells, cardiomyocytes	Fibrin, PEG, alginate, hyaluronic acid (HA), superabsorbent polymer (SAP)	Scaffold for heart tissue engineering	[13] [14]
Cartilage	Chondrocytes	Fibrin, PEG, SAP	Drug delivery, cell encapsulation, scaffold for cartilage regeneration	[15] [16] [17]
Eye	-	HA	Corneal transplantation	[18]
Skin	Fibroblast	Collagen, fibrin, HA	Abdominal wall, ear, nose and throat reconstruction, grafting	[19] [20]
Blood vessels	Stem cells, endothelial cells	PEG, alginate, HA	Vascular grafting	[21] [22]

production costs decrease, biologics are expected to become more accessible, potentially reshaping the future of medicine.

XIII. RESULTS AND DISCUSSION

Within the realm of regenerative medicine, the four distinct fields comprising cell transplantation, tissue engineering, drug research, and gene therapy rely extensively on the activity of highly dynamic cells. Scientific methodologies geared towards enhancing the cell activity are pivotal for the advancement of regenerative medicine. However, beyond the essential interaction between biomaterials and targeted cells, the interplay with immune cells in close proximity holds equal significance due to its potential to trigger immune responses. Notably, the response of immune cells such as neutrophils and macrophages, with their M1 (pro-inflammatory) and M2 (anti-inflammatory) phenotypes, is mainly influenced by local environmental conditions. Modifications induced by biomaterials, especially in M1 macrophages, can impede tissue regeneration.

Recent research delves into the intricate relationship between nanomaterials and immune cells, uncovering processes like bio-corona formation, immune sensing, immune evasion, and degradation. This emphasizes towards the direction that, the need for a holistic approach within the development of biomaterials-based regenerative medicine, considering both the enhancement of cell activity and the modulation of immune responses for overall success. Over time with technical computing framework developments this can be improved and upgraded further. Tissue engineering, a beacon of hope in regenerative medicine, blends biology, engineering, and medicine to craft functional, living tissues capable of restoring or enhancing damaged bodily tissues. Despite persistent hurdles and complexities, numerous ongoing research and technological advancements are progressing towards the creation of sophisticated and clinically relevant tissue-engineered products. While tissue engineering holds promise for revolutionizing healthcare, ethical considerations regarding the use of human cells or embryos necessitate stringent adherence to ethical guidelines. Organ-on-a-chip (OoC) technology has advanced in biomedical research, offering insights into disease modeling and drug testing.

While single-organ-on-a-chip models exist, the field is moving towards interconnected multiple OoC devices, promising groundbreaking discoveries. Integrating sensors into these chips facilitates monitoring critical physiological parameters. The ultimate goal is a human-body-on-a-chip, potentially replacing animal testing and accelerating pharmaceutical research. Innovations in biomaterials and fabrication techniques, including 3D printing and bioprinting, make OoC technology more cost-effective and efficient. These developments may lead to automated medical procedures, marking a significant step forward in biomedical research and healthcare. True that this technology and device integration is costly but in the near future that might change based on available materials for research and types of applications that can generate significant better results in terms of cell types and patterns. With AI, Machine Learning, Deep

Learning integration and deployment this technological computing processing can be developed and progressed further. But in each rotation a wide number of experimentation and research needs to be conducted for selection and final deployment in relation to the selected and chosen organs. For a comprehensive understanding, TABLE 2 offers a graphical representation of the contextual aspects. The results and findings highlight the intricate relationship between biomaterials, immune cells, and cell activity in regenerative medicine. The discussion underscores the need for a holistic approach, ethical considerations in tissue engineering, and the promising advancements in OoC technology with potential implications for future research and healthcare practices.

XIV. CONCLUSIONS

The future of tissue engineering and regenerative medicine holds considerable promise, as advancements in additive manufacturing, medical imaging, biomaterials, and cellular engineering converge to enable the fabrication of patient-specific vascular tissue constructs. Despite significant progress, there are substantial challenges involved, including precise cell and material requirements, achieving tissue maturation with its associative functionality, and ensuring proper vascularization and innervation. Ongoing multidisciplinary research and development efforts are anticipated to drive transformative innovations in these fields, potentially revolutionizing personalized medicine and regenerative therapies. The advantages of oral routes for drug administration in terms of patient compliance and convenience make them very attractive for immunotherapeutic delivery. However, challenges such as drug degradation and biological barriers persist.

Innovative particulate systems utilizing mucoadhesive and permeabilizing technologies show promise in improving drug bioavailability and are gradually progressing toward clinical translation. Nevertheless, their application in immune engineering requires careful consideration to ensure they do not disrupt the natural immune function of the gastrointestinal tract and are transient yet efficient in design. Sublingual and buccal routes, offering rapid onset of effects, are worth exploring for immunotherapeutic delivery, despite limited FDA approvals. Overall, the focus of research in these systems is expected to shift towards immunoengineering, constructing biomaterials targeting various immune cells and organs while preserving gastrointestinal tract integrity. The convenience of sustained administration and high patient compliance positions oral routes as a promising avenue for future developments in immunotherapy delivery. The exploration underscores the pivotal role of biologics in the future pharmaceutical landscape, particularly in addressing challenging diseases like cancer, autoimmune disorders, and genetic conditions.

The advent of gene-editing tools such as RNA interference and CRISPR-Cas9 is poised to revolutionize medical research, enhancing the role of biologics. However, the investigation also highlights the enduring significance of small molecules in the pharmaceutical industry. Recent discoveries renew interest in small molecules, especially those modulating protein-protein interactions, offering versatile treatment options. The ability of small molecules to penetrate cell membranes and their cost-effective production ensures their enduring significance in treating chronic conditions. In essence, the future of medicine envisions a harmonious coexistence of both small molecules and biologics, ensuring a diverse and complementary therapeutic arsenal.

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