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COMPRESSION BIOREACTOR AND APPLICATIONS IN TISSUE ENGINEERING

[1] Ipshita Basak, [2] Sannidhee Gupta, [3] Shuvam Bhowmick, [4*] Nandan Kumar Jana

[1]B.Tech Biotechnology Student, [2] B.Tech Biotechnology Student, [3] B.Tech Biotechnology Student, [4*] Associate Professor

[1,2,3,4*] Department of Biotechnology

[1,2,3,4*] Heritage Institute of Technology, Kolkata, India

[4*]Corresponding Author: nandankumar.jana@heritageit.edu

Abstract: Tissue engineering has been proposed in regenerative medicine to meet this requirement by producing tissues in vitro. Bioreactors are essential for turning cells and tissue-based structures into large-scale biological products that are clinically useful, safe, and cost-efficient. Bioreactors can be used in tissue engineering to help with the in vitro formation of new tissue by giving biochemical and physical regulatory signals to cells and stimulating differentiation and/or extracellular matrix production prior to in vivo implantation. In this review paper, we have talked about the compression bioreactor and its various applications in the field of tissue engineering. We believe that by combining the efforts of multiple discipline participants, an unique bioreactor system capable of quick, large-scale tissue cultivation will be developed in the near future.

Keywords: **Compression, Cartilage, Bioreactor, Perfusion**

I. INTRODUCTION

Any manufactured equipment or system that supports a biologically active environment is referred to as a bioreactor [1]. A bioreactor is a vessel in which a chemical process involving organisms or biochemically active compounds produced from such organisms is carried out. This process could be aerobic or anaerobic. These bioreactors are typically cylindrical in shape, with sizes ranging from litres to cubic metres, and are frequently composed of stainless steel. In the context of cell culture, it can also refer to a device or method for growing cells or tissues [2]. These devices are being developed for use in tissue engineering, biochemical/bioprocess engineering, and other applications.

Bioreactors have played an important role in TE because they can cultivate mammalian cells in a controlled environment on a large scale [3]. Several operational factors, including pH, temperature, oxygen tension, and cell perfusion, as well as external stimuli such as mechanical forces, can be adjusted and controlled [4]. Bioreactors can help with the formation of new tissues in vitro. They give cells the biochemical and physical signals they need to proliferate, differentiate, and generate ECM [5]. In vivo cells, for example, respond to mechanical stimulation, which bioreactors may give, allowing cells to make ECM in a shorter time span while maintaining the construct's optimal mechanical stiffness [6]. Mechanical stimulation has also been demonstrated to promote stem cells to descend into distinct lineages, allowing for the production of various cell types [5].

Bioreactors can be in a variety of shapes and sizes, depending on the tissue and application. When developing bioreactors, there are a few basic principles that can be used. First and foremost, they should be simple to assemble and efficient in tissue formation in a short period of time, while also maintaining sterility. Second, the materials employed to construct these bioreactors must be harmless to the majority of tissue types, if not all. Most metals have been ruled out because they have the ability to release ions into the medium, which can be highly harmful to cells. If the bioreactors are to be reused, they must be capable of being sterilized. Additionally, sensors must be integrated inside them in order to correctly monitor culturing conditions [7]. Most cells will respond to extremely small forces, therefore the pumps must be precise in creating mechanical stimuli to the smallest degree possible [8][9].

Compression bioreactors were designed to simulate the physiological environment of bone in vitro, with repeated mechanical stimulation required for successful bone regeneration. A motor, a linear motion system, and a compression chamber in which one or more pistons apply static or dynamic compressive loads directly to the cell/scaffold structures make up these culture systems [10].

II. COMPRESSION BIOREACTOR

Compression bioreactors were designed to mimic the physiological environment of bone in vitro, with repeated mechanical stimulation required for functional bone regeneration. It is a technological device that allows the application of mechanical parameters such as frequency, strain, duration, and loading on scaffolds while simulating the in vitro physicochemical environment of Articular Cartilage. These culture systems include a motor, a linear motion system, and a compression chamber in which one or more pistons apply static or dynamic compressive loads to the cell/scaffold constructs.

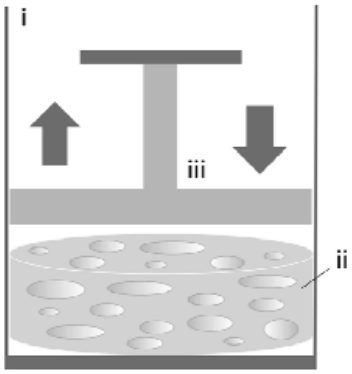

Fig 1:Schematic representation of a compression bioreactor showing the compression chamber (i), the cell/scaffold construct (ii), and the piston (iii), which applies static or dynamic compressive loads directly to the constructs. In these systems, the compression is controlled by a motor and a system that provides linear motion [10]

2.1 Working Principle

The compression bioreactor is depicted in its entirety. The piston is moved downward by a stepper motor and upward by a spring covered by white bellows. Parallel to the stepper motor, a digital gauge measures the vertical displacements of the piston independently. The cartridge serves as a container for cell cultivation and mechanical strain application in the scaffold. It can be disassembled or assembled and screwed to the bioreactor chassis. The cartridge cap contains an embedded piston and gas exchange vents protected from the outside environment by 0.22 m filters. The technical sketch depicts the bioreactor's inner structures [11].

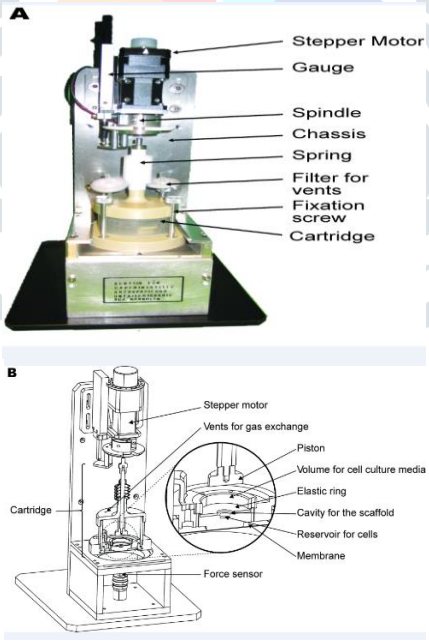

Fig 2: The Compression Bioreactor [11]

The piston compresses both the elastic ring and the scaffold that is located over the cell reservoir. The bottom of the cartridge is formed by a non-permeable membrane, which isolates the cell cultivation system and protects it from contamination. A force sensor is installed beneath the membrane, which is required for accurate measurements of the induced forces [11].

2.2 Description of Parts with Diagram

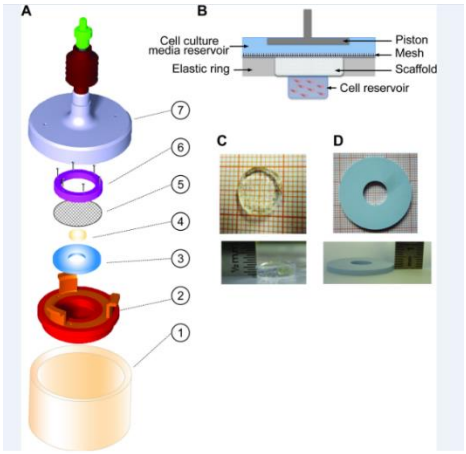

Fig 3: Assembling of the cartridge components [11].

A)The illustration depicts parts of a disassembled cartridge. The reservoir is located in the middle of the scaffold holder (2), where the cells are placed. Over them is a scaffold (4), which is held in place by an elastic ring (3) and a mesh above it (5). The mesh is held in place by a ring that is screwed to the structure (6). The scaffold holder is housed as an independent movable unit within the cylindrical container (1) and is protected by a cap (7) that houses the piston and spring. The cartridge is made of materials that can be sterilized. B) The schematic drawing depicts a cross-section of the components of a scaffold holder without the upper anchored ring. The mesh is intended to keep the scaffold from moving upward during the lift maneuvers. An alginate scaffold C) and an elastic ring D) are shown in detail from above and in a skew side view.

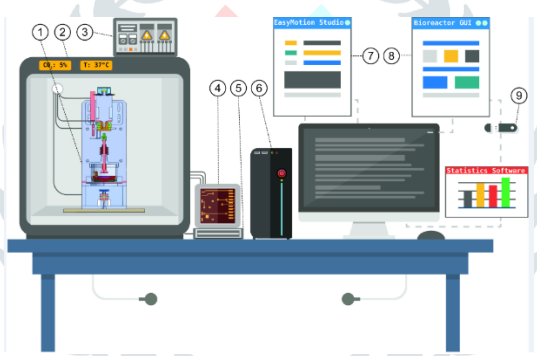

Fig 4: The system of the bioreactor is designed as a standalone unit [11].

To allow conditions for cell cultivation, the bioreactor (1) is connected to a power supply (3) and placed inside a CO2 incubator. The bioreactor's connection wires are routed through an electronic box (4), which houses a motion controller, a force sensor amplifier, and an interpolator for the digital gauge. The motion controller receives information from the stepper motor, and the amplifier processes the force sensor signals generated by the loading. The electronic box (4) is connected to the connector block (5), which communicates with the computer's PC card (6). The PC card synchronizes the start of the experiment with the motion controller software "EasyMotion" (7), where the experiment settings are saved. The custom-made software "Bioreactor," written in LabView 2011, visualizes and records data such as force, piston displacement, and time at a rate of 50 Hz. Finally, the data can be exported (9), and statistical software such as Origin 9.0G, which was used in this study, can be used to analyze it [11].

III. APPLICATIONS OF COMPRESSION BIOREACTOR IN TISSUE ENGINEERING

3.1 Compression Bioreactor for Cartilage Synthesis [48]

Articular cartilage is responsible for bearing mechanical loads and resisting cyclic compressive and tensile stresses that occur in moving joints. The chemical and structural properties of cartilage extracellular matrix have a direct impact on cartilage's capacity to fulfill these activities (ECM). The strength and tensile stiffness of cartilage are influenced by the orientation and organization of type II collagen fibril networks [12].

Mechanical stimuli have a substantial impact on the development and functioning aspects of articular cartilage. Mechanical forces have an effect on cellular hyaluronan synthesis, cartilage matrix deposition, and joint formation in vivo [13]. Mechanical stimuli influence chondrogenic differentiation and cartilaginous tissue development in three-dimensional in vitro culture systems depending on the kind, amplitude, frequency, and duration of the pressures applied. Hydrodynamic shear, hydrostatic pressure, compression, and tensile forces are

only some of the mechanical stimuli that can be applied to developing tissue constructs. Uniaxial compression is the most often used mechanical treatment in cartilage tissue engineering. Collagen and/or GAG synthesis has been reported to be stimulated by dynamic compressive stresses applied to chondrocyte cells at a cyclical frequency [14, 15]. In scaffold-seeded mesenchymal stem cells subjected to dynamic compression, stimulatory effects on chondrogenesis have also been documented [16–19].

Transient shear or sliding forces, in addition to compressive loading, are necessary to better simulate the mechanical forces put on cartilage during the rolling and squeezing action of articular joints. Studies of the impact of these combined stresses on chondrocyte and stem cell cultures have shown that they improve expression of chondrocytic marker genes, cartilage matrix synthesis, matrix component distribution, and construct mechanical characteristics when compared to unstimulated controls [20–23]. Fluid perfusion has also been used with simultaneous compression and sliding or frictional forces to imitate the hydrodynamic effects of synovial fluid entering the tissue during joint activity [24].

When interpreting the outcomes of mechanostimulation tests, several things must be taken into account. The direct stimulatory effects of mechanical treatment must be distinguished from the consequences of improved transport of trophic factors to the cells in treated samples [23, 27], because dynamic loading of cartilage increases the rate of mass transfer of vital components such as oxygen, nutrients, and growth factors within the tissue [25, 26]. Physical manipulation of the tissue must also be taken into account to account for any increase in the amount of cartilage components escaping from the construct into the culture media [14, 23]. Because scaffold materials and accumulating ECM dissipate the energy exerted during mechanical loading, the degree to which the mechanical forces applied are modulated by the embedding matrix is also an important factor affecting the cellular response [17, 28].

3.2 Fracture Healing and the Perfused Compression Bioreactor

Secondary bone fracture repair is a physiological process that involves endochondral bone production and results in functional tissue regeneration. Early mobilization and the application of mechanical loads has been shown to improve the process of fracture healing in vivo investigations. The impact of certain mechanical stimuli and their effects during distinct periods of fracture healing, on the other hand, has yet to be determined.Based on a unique perfused compression bioreactor (PCB) system, the feasibility of an in vitro human organotypic model of physiological loading of a cartilage callus was demonstrated. The fracture callus model was then utilized to look into the regulatory role of dynamic mechanical loads.

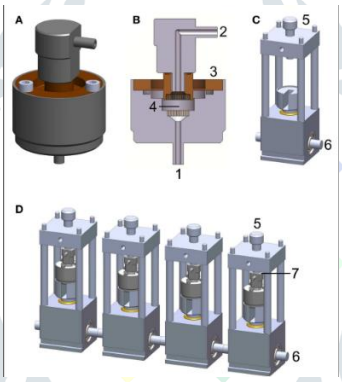

Fig 5: Perfused Compression bioreactor (PCB). (A) Bioreactor chamber holding the scaffold in place and ensuring hermetic sealing as well as force transmission toward the cell loaded construct. (B) Cross section of bioreactor chamber indicating medium inlets/outlets (1 and 2), flexible force transmitting disk (3), and intended space for scaffold/construct placement (4). (C) Power transmission rack including cam-shaft (6), which moves the plunger in order to apply a sinusoidal compression pattern onto the bioreactor chamber. The chamber is held in place with a preload screw (5) allowing for defined loading regimes. (D) A complete PCB system comprises four bioreactor chambers, four force transmission devices, and four force sensors (placed at position 7, not shown)[40]

Bone fracture healing is described as a natural, physiological process that leads to functional tissue regeneration via a carefully choreographed sequence[29,30]. When there is direct contact between the fracture ends, primary fracture healing begins, re-establishing the anatomically correct and biomechanically competent lamellar bone structure [31].In the vast majority of cases, however, a gap exists at the fracture site, resulting in indirect or secondary fracture healing.

Hemorrhage and inflammation, soft callus development, hard callus creation, and callus remodeling are the four key phases of secondary fracture healing, which mimics the process of endochondral bone formation [32,33].In vitro model systems, on the other hand, provide for a methodical approach to studying the impact of mechanical stimuli during different phases of secondary fracture healing in a controlled environment.

In vitro models have previously been limited to applying mechanical loads to cartilaginous tissues in order to develop more functional tissues or to investigate the impact of different loading regimes on chondrogenesis [34,35,36,37], but the effect of mechanical loading during the process of hypertrophic cartilage formation and remodelling, which is critical in fracture healing.

An in vitro model based on a perfused compression bioreactor (PCB) system is prepared to: (i) apply physiological strain/loads, (ii) perfuse a construct for mass transfer and vascularization simulation, and (iii) compress stiff load-bearing scaffolds in a physiological manner.
Both collagen-based and nickel–titanium (NiTi)-based tissue constructions were validated using dynamic mechanical stress, demonstrating the versatility of the technique.Bone compressive strength (100–200 MPa) is part of the system [38,39]. A hypothesis is made in a proof-of-concept study that physiological compressive loading during hypertrophy improves extracellular matrix mineralization of cartilaginous constructions and stimulates MSC maturation into late hypertrophic chondrocytes.

To examine the process of fracture healing, a PCB system was made to apply physiological dynamic mechanical loads and strains to designed structures. A proof-of-concept investigation was carried out using dynamic mechanical loads on cell seeded collagen and NiTi-based constructions, demonstrating the new system's broad operational range.The PCB was thoroughly tested and found to be safe and reliable in terms of ensuring defined dynamic mechanical loading of live designed tissues. The PCB has a wider operational range than previously documented systems [41,35,42,43,44,45,46].Compression Bioreactor is displacement-driven, a wide range of scaffolds and tissues can be examined with dynamic mechanical stress without requiring further system adaption. Furthermore, by altering the eccentric cam-shaft, this range can be expanded even further, allowing the displacement to be adapted to the necessary range. Study shows that in an in vitro model of the transition from a soft to a hard callus ,the effect of physiological compressive stresses during hypertrophic differentiation is investigated. The formation of a soft cartilaginous callus is an important stage in secondary fracture healing [33], MSC were seeded on OPTIMAIX scaffolds and primed for chondrogenesis in the first phase of the study. The designed structures that resulted revealed cartilaginous properties such as I ECM containing GAGs and collagen type-II, (ii) cells embedded in lacunae, and (iii) chondrocytic gene expression. Furthermore, the cartilaginous structures were stable in size and shape, allowing for dynamic loading within the PCB.

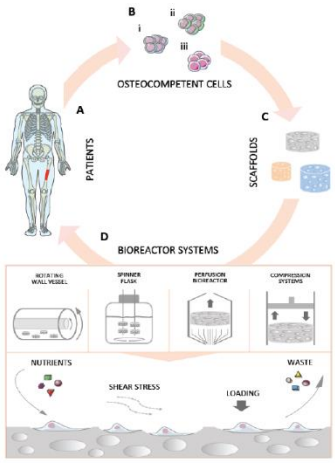

Fig 6 :Engineering bone tissue grafts using bioreactor systems. (A) Patients affected by skeletal defects (in red) resulting from congenital malformations, disease or trauma are examined for bone reconstructions. (B) Patient-specific osteo competent cells derived from:(i) adult tissues; (ii) induced pluripotent stem cells; or (iii) blastocysts generated via somatic cell nuclear transfer are interfaced to (C) three-dimensional porous biomaterial scaffolds of different nature and architecture, and cultured under dynamic conditions in (D) bioreactors systems, which nurture the development of bone tissue by supporting efficient nutrition of cultured cells and applying mechanical stimuli that are critical for functional regeneration [47].

The PCB system has shown to be a versatile instrument for the in vitro application of dynamic physiological mechanical loads onto scaffolding materials with a wide variety of mechanical properties in this work. Mechanical loading, by the decrease in GAG and collagen type-II, the thickened mineralized border, increased amounts of type-X collagen, and positive BSP staining, enhances ECM mineralization during hypertrophy of cartilaginous constructs and triggers the maturation process of MSC toward late hypertrophic chondrocytes. Furthermore, scaffold-based structures mature when they are subjected to cyclic mechanical loading. Research findings show that dynamic mechanical loading applied by the PCB can accelerate the development of mesenchymal stromal cells into late hypertrophic chondrocytes and the mineralization of the extracellular matrix deposited. The PCB is a promising technique for studying fracture healing and evaluating alternative fracture treatments based on engineered tissue grafts or pharmacological substances in vitro, reducing the need for animal testing.

3.3 Tissue Constructs for Implantation [55]

Ghaedi [49] created bioengineered lung tissue from induced pluripotent stem cell (iPSC)-derived epithelial cells on decellularized lung tissues from rat and human lungs, emphasizing the importance of good gas exchange across the lung, which necessitates the integrity of the physical barrier expressed in vivo from both epithelial and mature endothelial cells with appropriate tight junctions and adhesive molecules. Only epithelial cells were employed in this investigation. Nonetheless, this example shows that decellularized scaffolds enable the survival, proliferation, and function of airway epithelial cells within and across species.

Tissue engineering initiatives to develop small diameter vascular grafts of less than 6 mm diameter have resulted from the desire to provide a shorter and more effective path for patients seeking a coronary artery bypass. This is a time-consuming procedure. Tondreau [50] devised a simple method that cut the duration from more than 4 months to 4 weeks by starting with "offline" cultivated fibroblast sheets that were then rolled into mandrels, decellularized, and recellularized using patients' own endothelium cells in a perfusion bioreactor. The graft was extensively mechanically tested for burst pressure compliance, thickness, and suture strength retention, resulting in a graft made entirely of human dermal fibroblasts and reseeded with endothelial cells, which could dramatically reduce the time it takes to treat patients.

An endothelial layer on biological graft matrices is thought to be significant for antithrombotic action [51] and graft failure prevention. However, in artificial grafts, the pulsatile flow of a bioreactor can disrupt the endothelial cell surface under high flow conditions, similar to what cusps may experience during valve opening in native valves, so while one may try to mimic the natural environment, some compromise in bioreactor designs may be required to allow adaptation of the recellularized grafts [52]. Hussein defined a heparin-gelatin mixture as an antithrombotic agent prior to cell seeding in a different organ system, the liver, again using decellularized tissue as the bioreactor scaffold,

which positively impacted attachment and migration of endothelial cells, as well as leading to enhanced function from the parenchymal fraction of subsequently seeded HepG2 epithelial cells [53].

There is potential in this area due to a lack of organs for transplant, the scientific effort to "grow" organs for transplantation, and improvements in decellularization/recellularization procedures. The bioreactors needed to apply this strategy must be tailored to the physiology of that organ [54].

3.4 Designed for Disease Modelling, a Compression Bioreactor [55]

Tumor cell modelling for drug testing in human cells, comparable to tumour biopsies, would be a big step forward. A decellularized jejunal scaffold and colon cancer cells were used with fibroblasts to create a bioreactor with tissues at the interface of two separate fluid circulations that met apical and basolateral-specific culture conditions: concurrently modelling optimized fluid circulations in terms of ambient pressures, inlet and outlet velocities, and defining shear stress conditions present in compression bioreactor[56]. The tumor-like tissue that resulted featured beta catenin at cell boundaries and a stroma that was positive for vimentin and cytokeratins, as seen in colon adenocarcinomas.The 5FU (5-fluorouracil) response clearly distinguished this model from monolayer cultures and demonstrated the treatment response in humans.

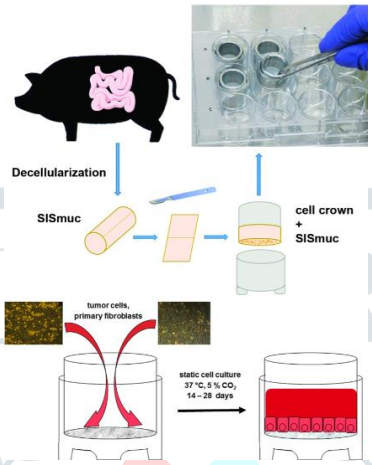

Fig 7 : 3D cell culture in a static system. The SISmuc scaffold derived from a porcine jejunum is fixed between two metal rings, the cell crown. Cells are seeded onto the scaffold and cultured in 12-well plates. For coculturing of tumor cell lines with primary fibroblasts, fibroblasts are isolated from the dermis of human skin biopsies and seeded onto the scaffold together with the tumor cells. 3D, three-dimensional; SISmuc, small intestinal submucosa with preserved mucosa [56].

3.5 Small Compression Bioreactors Often Mimic Larger Production Bioreactors as Bioartificial Organs [55]

Bioartificial organs for temporary replacement of function, rather than transplantation, have been created [56,57,55,58], particularly for the liver system, because the liver is highly regenerative and may heal itself given enough time after an assault of acute liver failure. While organ transplants are curative, the scarcity of donor organs means that many people die before receiving one. There are several experimental models available, and a few are now being tested in clinical studies. However, culturing on a human scale does not allow for rapid prototyping or optimization of production conditions in a bioreactor. A human-scale bioartificial liver machine (BAL) based on a fluidized bed bioreactor design that maximizes mass transfer (UCLBAL) was developed and evaluated in a pig model of acute liver failure [56,55,58]. There was a need to develop a small scale mimic on the small (not micro) scale to enable metabolic, gene expression, and protein studies, and since this small fluidized bed (sFBB) bioreactor enables flow studies that can be mathematically modelled, it is more easily scalable to clinical size and allows a comparison of dynamic versus static conditions suitable for drug biotransformation. Multiple units can be run at the same time, enhancing research capacity.

IV. CONCLUSION [9]

Bioreactors have been used in all aspects of TE, and research in this area has gotten us closer to developing a huge number of tissues in vitro for wide-scale medicinal applications. Mechanical stimulation is critical in cartilage tissue engineering to build tissue with a similar elastic modulus to biological tissue and for cells to produce an efficient ECM .The use of rotating bioreactors to upregulate gene expression in osteoblasts has been proven to be beneficial for bone tissue engineering. Because of their ability to stimulate bone cells and raise levels of bone formation markers and scaffold mineralisation, perfusion bioreactors have proved useful in bone engineering. Despite these promising findings, more research is needed to identify the specific biochemical and biomechanical components that are required for successful bone and cartilage engineering in vitro.

Bioreactor technology for vascular tissue engineering is yet 11 under-explored, although bioreactors with proper perfusion and fluid flow have been proven to provide an ideal environment for adequate tissue creation. Future research will be required to determine the best cell source for creating a tissue engineered vascular architecture. Multiple bioreactors have been used for in vitro skin creation due to the rapid growth of skin tissue engineering. The kerator has been developed as a way to reduce labour costs and material needs, but more research is needed to fully comprehend its capabilities for large-scale clinical manufacturing. Bioreactors for nerve engineering are still in their infancy, with only a few research indicating that they have the capacity to create functional tissue in vitro.

V. ACKNOWLEDGEMENT

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