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Review Article

Leveraging 3D Cell Culture and Artificial Intelligence Technologies for Regenerative Medicine

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Abstract

Background: The domain of regenerative medicine is perpetually evolving, aiming to repair, regenerate or replace damaged or unhealthy tissues and organs by utilizing advanced techniques such as stem cell therapies and tissue engineering. Tissue engineering and regenerative medicine hold great potential to enhance patient treatment and accelerate recovery. However, they face challenges like trial and error, inefficient production, lengthy processes and excessive human involvement that can lead to mistakes. Solutions to these issues may be found through the application of Artificial Intelligence (AI), automation and robotic technologies.

Objective: It is to fulfill our mission by implementing awareness and educational initiatives in the domain of regenerative medicine production, while also showcasing how AI and automation, combined with robotics, can transform conventional tissue engineering and regenerative medicine approaches, offering renewed hope to patients.

Methodology: With advancements in technology, contemporary medicine is starting to utilize AI to address intricate errors that may arise in regenerative medicine. The application of AI is transforming cell culture by automating incubators and cell counters, lessening the necessity for manual work and enabling healthcare professionals to cultivate a substantial number of stem cells for clinical use. AI now includes technologies such as Machine Learning (ML) and robotics, which empower machines to perform complex tasks that were traditionally handled by humans.

Results: AI is significantly influencing stem cell research with numerous advantages in areas such as drug development, regenerative medicine and the generation of induced Pluripotent Stem Cells (iPSCs). It can forecast stem cell behavior, enhance culture conditions and accelerate the development of new therapies. The transformative potential of AI in healthcare is immense, providing cutting-edge solutions for diagnosis, early detection, treatment planning and enhancing patient outcomes. AI-enabled robotic systems have transformed surgical procedures, increasing both precision and results. Furthermore, AI enhances administrative efficiency and workflow processes in healthcare, optimizing operations and cutting costs.

Conclusion: Through interdisciplinary collaborations and the responsible development and application of innovative technologies, we may eventually unlock the complete potential of AI to usher in a new era of personalized and effective regenerative treatments.

Keywords: Artificial Intelligence; Automation; Regenerative Medicine; Robotic; Stem Cell-Based Therapies; Tissue Engineering

Fig. 1 shows a schematic of potential future developments for the idea of robot-aided in situ 3D printing of tissues using stem cells in the context of robotically assisted, AI-driven minimally invasive surgery.

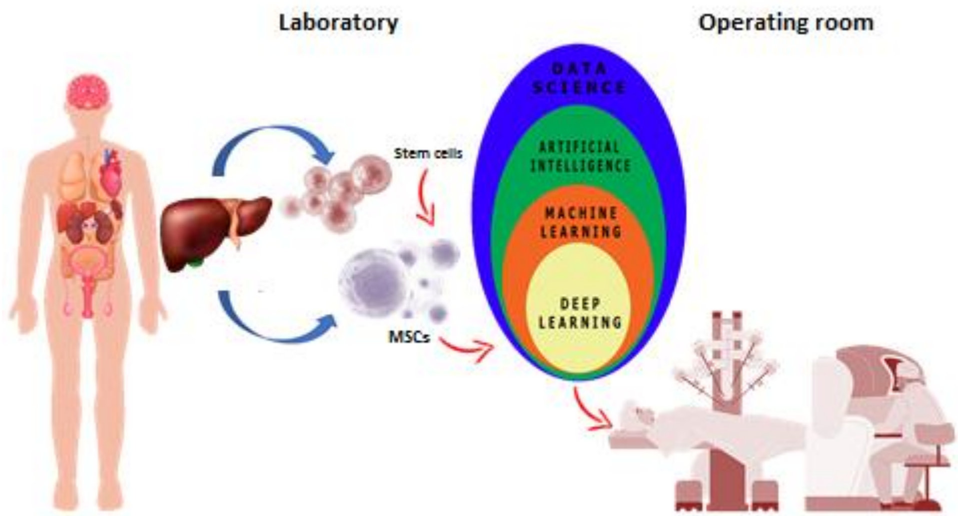

Figure 1: Diagram of future directions for the notion of robotically assisted 3D printing employed stem cells in the frame of AI-powered robotic surgery.

Introduction

According to Laila M Montaser, recent developments in regenerative medicine have confirmed the possibility of creating viable and workable 3D tissue engineering designs that incorporate living cells for tissue repair and improvement. In the fields of tissue engineering and regenerative medicine, 3D bioprinting has emerged as a promising new method for creating intricate biological frames. By precisely and carefully assembling biomaterials sheet by sheet in a desired 3D platform, it seeks to reduce the difficulties associated with standard tissue engineering processes. Stem cells activated from a person's own body can cleave after printing and differentiate in a way that formats and substitutes any sort of body tissue thanks to a versatile 3D tissue engineering skill [1].

One of the guiding concepts of the Lab of the Future is automation, which goes hand in hand with digitalization. If the unique technique of 3D bioprinting is supported by robotics, artificial intelligence and complete laboratory automation, it will be a remarkable achievement that could benefit patients and humanity. By using an AI-driven manufacturing approach, AI may help make individualized regenerative therapies commercially viable for the first time.

AI technology has significantly improved scientific research efficiency [2]. AI integration has the potential to completely transform a number of medical specialties. The application of AI to the development of stem cell-based treatments for regenerative medicine is covered in this paper on AI for Good. Stem cell-derived regenerative medications have the potential to treat some of the most difficult illnesses this decade, including diabetes, Parkinson's, liver, heart, kidney and lung problems. The safest and most efficient treatments for various illnesses are provided by patient-specific cells. However, because of their high unpredictability, substantial manual interventions and expensive operational overhead, the current autologous approaches are not scalable. Induced differentiation ranks among the most experience and skill-sensitive experimental processes in the field of regenerative medicine, with the establishment of optimal conditions often spanning several years. Regenerative medicine research frequently necessitates a multitude of experiments that are both labor-intensive and time-consuming. Specifically, generating distinct tissues from stem cells-a procedure known as induced cell differentiation can take several months and the success rate is influenced by a myriad of factors. Identifying the best type, dosage and timing of reagents, along with ideal physical conditions such as pipette strength, cell transfer duration and temperature, is challenging and demands significant trial and error. Laboratory automation is an emerging technology that aims to replicate human skills in machines [3].

Cell Culture

Research in cell culture and regenerative medicine often requires numerous experiments that are both time-consuming and labor-intensive. In particular, creating specific tissue from stem cells a process called induced cell differentiation involves months of work and the degree of success depends on a wide range of variables. Finding the optimal type, dose and timing of reagents, as well as optimal physical variables such as pipette strength, cell transfer time and temperature is difficult and requires an enormous amount of trial and error [4]. A joint research group led by Genki Kanda at the RIKEN Center for Biosystems Dynamics

Research (BDR) has developed a robotic Artificial Intelligence (AI) system for autonomously determining the optimal conditions for growing replacement retina layers necessary for vision. The AI controlled a trial and error process spanning 200 million possible conditions that succeeded in improving cell culture recipes used in regenerative medicine [3].

Given the heterogeneous and complex internal states of cells, it is essential to ascertain appropriate culture conditions tailored to each specific strain and/or lot [5]. In the field of regenerative medicine, stem cells possess the capability to facilitate the repair of damaged tissues and organs, thereby presenting prospective therapeutic interventions for degenerative conditions such as Parkinson's disease, diabetes, heart disease, Inflammatory Bowel Disease (IBD), spinal cord injuries and various dermatological disorders among others [6-11]. Adipose-Derived Stem Cells (ADSCs) represent a subset of Mesenchymal Stem Cells (MSCs) characterized by their remarkable potential for self-renewal and differentiation into various cell types [12]. Therapies based on MSCs have demonstrated advantageous outcomes across a diverse array of preclinical models and clinical trials pertaining to human ailments [13]. Research has indicated that MSCs exhibit immunomodulatory effects, which contribute to the attenuation of inflammation, frequently identified as a primary factor underlying degenerative conditions such as arthritis [14]. MSCs have exhibited considerable therapeutic efficacy in promoting tissue regeneration, specifically by stimulating epidermal cell migration and proliferation [15].

Artificial Intelligence

One of the numerous sectors where AI and ML are expanding quickly is healthcare [16]. With their ability to improve diagnostic accuracy, develop personalized treatment plans and support clinical decision-making, AI and ML have become essential components in the development of healthcare [17]. One kind of AI that works like neural circuits and gives computers the ability to do tasks just like human brains is called an Artificial Neural Network (ANN). An ANN-based subset of ML called Deep Learning (DL) enables numerous numerical leanings from various datasets [18].

Fig. 2 presents a diagram that illustrates the Artificial Intelligence (AI) vs Machine Learning (ML) vs Artificial Neural Network (ANN) vs Deep Learning (DL).

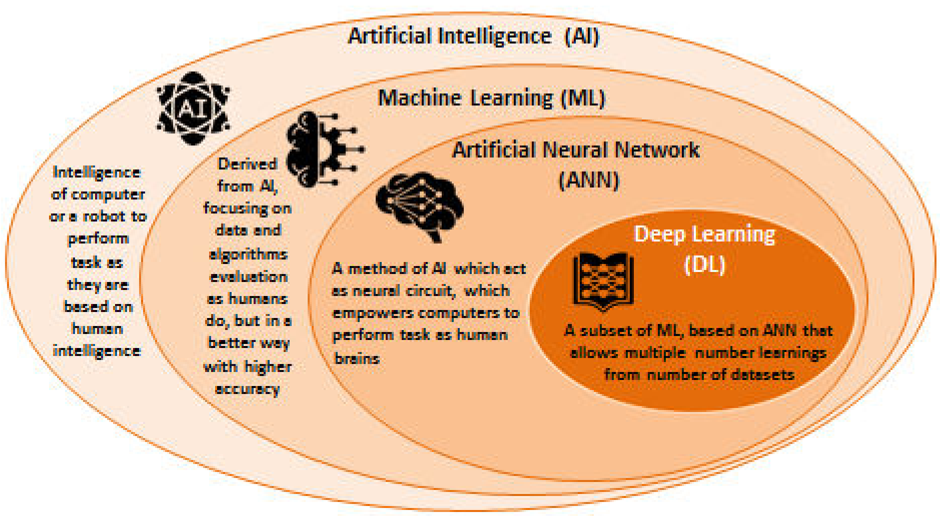

Figure 2: Schematic outlining the Artificial Intelligence (AI) vs Machine Learning (ML) vs Artificial Neural Network (ANN) vs Deep Learning (DL).

The use of AI in healthcare has improved surgical accuracy, predictive analytics and diagnostic tools. AI has shown significant advantages in a number of medical specialties. It supports automated picture interpretation, risk assessment and cardiovascular disease management in cardiology. AI improves tailored medication selection, treatment planning and cancer detection in oncology. While critical care sees improvements in patient triage and resource efficiency, radiology gains from enhanced image analysis and diagnostic precision. Similar notable advancements in diagnosis accuracy, individualized care and general patient care have been demonstrated by the application of AI in pediatrics, surgery, public health, neurology, pathology and mental health. AI has had a particularly significant impact when applied in low-resource environments, improving access to cutting-edge diagnostic and therapeutic tools [19].

AI has revolutionized healthcare, especially in the areas of robot-assisted surgery, rehabilitation, medical imaging and diagnostics, virtual patient care, medical research and drug discovery, patient engagement and adherence and administrative applications, according to a report by Mizna and colleagues [20].

AI has emerged as a transformational force in clinical medicine, altering patient diagnosis, treatment and care, according to Aravazhi and team [21]. In order to improve diagnosis accuracy, treatment personalization and patient care outcomes, tools for dealing with ML, DL and Natural Language Processing (NLP) algorithms have been developed. These tools allow for the unparalleled speed and accuracy of analyzing vast, complex medical datasets. For instance, NLP algorithms have significantly aided in the extraction of insights from unstructured data, such as electronic health records, while Convolutional Neural Networks (CNNs) have significantly increased the accuracy of medical imaging diagnosis.

This manuscript targets to explore AI in regenerative medicine, encompassing key technologies such as NLP, robots, ML and DL. A schematic representation of a few currently used branches of AI is shown in Fig. 3.

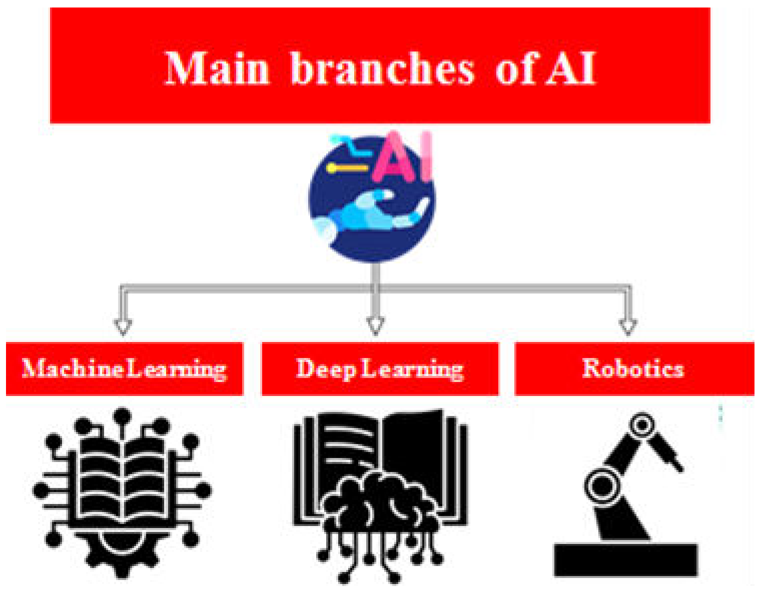

Figure 3: Schematic of the main branches of Artificial Intelligence (AI).

According to Marques, et al., the use of AI and its self-learning processes (also known as ML) in medicine has completely changed the state of health around the world by enabling quicker and more precise diagnosis, individualized treatment plans and effective clinical data management [22]. AI and medicine interact in a wide range of domains, including data management, diagnosis, intervention, patient-doctor contact, health education and decision-making procedures. Medical imaging analysis, diagnosis, medication research and discovery, predictive analytics for patient outcomes, virtual health assistants and remote patient monitoring are just a few of the many uses of AI in medicine. Additionally, it is utilized in clinical decision support systems and robotic surgery driven by AI for therapeutic recommendations, administrative workflow automation and triage.

According to Lu and colleagues, the growing use of AI in the medical field portends a revolutionary period in healthcare, with promises of better patient outcomes, diagnosis and treatment. However, as a result of this quick advancement in technology, medical education is facing an increasing number of ethical dilemmas [23].

Artificial Intelligence and Stem Cell Medicine

Two of the most revolutionary developments in contemporary science, AI and stem cell biology, have the potential to have a big influence on healthcare.Together, they hold the potential to expedite advances in tailored therapies, regenerative medicine and the comprehension of complicated illnesses. A new age of medical innovation that has the potential to completely transform healthcare is being ushered in by the convergence of AI and stem cell research [24].

AI systems can reduce trial and error in lab settings by analyzing clinical data to determine the best conditions for differentiation. AI can speed up the production of specialized cells for study and medical applications by forecasting how stem cells would act in specific scenarios [25]. In a similar vein, AI can advise a physician on the kind and quantity of stem cells to employ for any given indication, such as diabetes, heart disease or arthritis. Additionally, AI can assist physicians in choosing the best method and route for administering the cells.

Role of AI in 3d Cell Culturing

AI is revolutionizing 3D cell culture and has improved several facets of this cutting-edge biotechnology technique. The possible uses range from enhancing data analysis and improving cultural conditions to automating processes and promoting innovative research techniques. Big dataset analysis, pattern recognition and outcome prediction are all made possible by AI algorithms, especially ML models [26].

By automating image processing, analysis and acquisition, it visualizes 3D cell cultures while taking into account sophisticated microscopy and imaging. When AI is used instead of manual methods, imaging processes are improved. AI-powered solutions can enhance image quality, eliminate artifacts and more efficiently handle enormous amounts of data.

DL techniques, particularly CNNs, have enabled high throughput and objective image analysis. CNNs are essential for automated image segmentation, feature extraction and cellular structure classification. For instance, this improves the contrast and resolution of 3D pictures, which facilitates the analysis and assessment of cellular structures and activities [27].

3D cell-culture investigations are more dependable and repeatable when AI is used for quality assurance. AI is revolutionizing drug research and accelerating drug screening by accelerating the 3D cell culture screening procedure. Conventional drug testing methods can be resource and time-intensive [28].

Due to the fact that AI-driven methods can quickly evaluate how large chemical libraries affect 3D cell cultures; they have greater success finding promising medication prospects.

By employing ML models that can forecast the toxicity and effectiveness of medications, researchers can focus on the most promising options. This acceleration of the drug development process could lead to new therapies hitting the market sooner. Incubators and bioreactors are examples of 3D cell-culturing equipment that requires routine maintenance to ensure peak performance. AI can predict maintenance needs by analyzing data from machinery sensors and identifying patterns that point to potential faults. Predictive maintenance reduces maintenance costs and helps avoid unscheduled equipment downtime, so experiments will not be disrupted. By predicting and fixing maintenance-related problems, AI improves the overall efficacy and dependability of 3D cell-culture systems. The quality and homogeneity of the 3D cell cultures being maintained determine the appropriate experimental outcomes. AI- driven quality control systems have the ability to continuously observe cell cultures and spot environmental changes or unusual development patterns [29].

These technologies can automatically adjust parameters or alert researchers to potential issues in order to preserve the ideal conditions of cultures and guarantee that tests proceed smoothly.

By facilitating automated data processing, predictive modeling and real-time cellular behavior monitoring, AI has had a substantial impact on the field of 3D cell culture research. ML algorithms improve the efficiency and reproducibility of biological research by optimizing the culture conditions. Researchers can evaluate massive datasets produced by imaging and drug-screening tests by utilizing AI, which will enable them to anticipate therapeutic outcomes more quickly and accurately.

Artificial Intelligence and Robotics

One of the biggest problems of the twenty-first century is automating scientific discovery [30,31]. Combining AI and robotics to create a closed loop of computation and experimentation is a promising strategy [32]. Finding the best experimental protocols and parameter combinations through repeated experimentation and result validation in accordance with a predetermined validation method is a very straightforward type of autonomous knowledge discovery. The creation of a robotic search system that can independently identify the ideal circumstances for cell culture was documented by Kanda, et al., [3].

By improving accuracy, productivity and patient outcomes, AI and robotics are transforming surgical procedures. The use of robotics in surgery tackles important issues including surgical precision, minimally invasive procedures and healthcare accessibility as global healthcare systems embrace AI-driven technologies more and more [33]. The use of robots in surgery tackles important issues including surgical precision, minimally invasive procedures and healthcare accessibility as international healthcare systems embrace AI-driven technology more and more [34].

AI has transformed healthcare in a number of fields, including medical research and drug discovery, virtual patient care, medical imaging and diagnostics, rehabilitation, patient engagement and adherence, administrative applications and robot assisted surgery. Robotic physical treatment, personalized programming and real-time monitoring and feedback systems are all made possible by AI in rehabilitation. Combining AI with cutting-edge technologies like virtual reality, augmented reality and the Internet of Things could lead to broader healthcare applications. Future prospects include the potential for wider applications in healthcare and rehabilitation, integration with new technologies and improvements in robotics and AI algorithms [35]. AI-driven technologies including ML, DL, computer vision and robotic-assisted surgery have the potential to improve clinical processes and patient outcomes [36].

International Researches of Montaser and Group on the Application of New Technologies in Stem Cell Medicine

A 2023 study by Montaser LM, asserted that bioprinting holds great promise for tissue regeneration [37]. In the lab, the concept of in situ 3D Bioprinting (3DBP) was utilized to simply implant cells *in-vivo*, avoiding the intermediate stage of *in-vitro* cell growth. With the speed at which science is developing, the remaining issues will be resolved soon, bringing in a new age in healthcare and an improvement in people's quality of life. With 3D printing (3DP), the middleman is eliminated. This advantage extends to *in-vitro* bioprinting, which avoids the middle step of *in-vitro* cell development in the lab and enables stem cells to be put into the body for growth (in situ). Because onsite bioprinting with robots is less invasive, less painful, takes less recovery time, lowers the risk of infection and requires fewer hospital stays, it can be advantageous for certain surgical procedures. Mobile emergency printers will probably be utilized in remote areas and underdeveloped countries. Through the use of 3DP technology science education, the goal is to inspire a new generation of researchers both domestically and abroad, showcase state-of-the-art advancements in robotic-assisted 3DBP for tissue engineering and regenerative medicine and improve 3DP scientific literacy for students and society.

Laila M. Montaser declared that her extensive knowledge of liver tissue engineering may bea potential solution to the scalability of liver transplantation in the future. This could help with issues related to organ failure, liver cancer and the production of a skillfully functional organ that could be implanted or used as an instrument outside the body, as a practical way tocheck medications and for the study of pathological conditions like cirrhosis and liver cancer. This article displayed a potential biographical sketch of Montaser future approaches for in situ 3DBP using nanomaterial scaffolds made using the two most popular methods, electrospinning and 3DP. The author's research aimed to draw attention to the scientist's focus on insitu 3DP technological literacy of stem cells as a novel, inventive and ground-breaking technique [38].

In order to represent stem cell habitats and pathological tissue morphologies for drug testingor to replicate human tissue mix jobbing as physiologically appropriate substitutes, cell printing aims to move spirited cells in a three-dimensional manner. Stem cells extracted from a person's body can cleave after printing thanks to a controlled 3D tissue engineering technique, which can then be used to arrange and modify any tissue group in the body.

Montaser in her plenary talk entitled "Artificial Intelligence Manages Stem Cell Research" presented at 7th Ann Conf. of Clinical Pathology Department, Menoufia Faculty of Medicine 2024, Feb 22-23, Ismailia, Egypt under the theme of "Artificial Intelligence Laboratory Medicine"; awarded a certificate of appreciation as a speaker and chairperson (Fig. 4) and in appreciation of her significant contributions to the department and the advancement of research and knowledge, she was also given a Crystal Scientific Excellence Shield (Fig. 5); where she stated that the domain of regenerative medicine is always progressing and pursues to reform, rejuvenate or replace damaged or unwell tissues and organs utilizing most advanced ways like stem cell-based remedies and tissue engineering. Nonetheless, AI technologies have conquered novel gates for exploration inside that scope. There are only restricted digits of investigators with the expertise required to make stem cells with a top suitable modality to be harnessed in the human body. Endeavors are at present being initiated to employ AI to collect practices of researchers who address stem cells and calibrate them. AI has the chance to upgrade and speed several sides of regenerative medicine study and evolution, especially, though not exclusively, while multiplex designs are demanded. On the move fore, furthermore renovations in zones like ML, NLP, computer vision and robotics have the prospective to reveal modern prudence that could revolt how regenerative treatments are advanced and relocated joining AI with other emerging technologies such as nanotechnology and 3DBP may guide to unmatched improvements in inspiring personalized regenerative settlements. Advance shall be based on preserving a human-focal procedure that uses AI abilities to do the better benefits of patients and society [39].

Figure 4: Certificate of thanks and appreciation on the occasion of Laila Montaser valuable contribution as a speaker and chairperson at the 7th Conference of Department of clinical Pathology, Faculty of Medicine, Menoufia University, Ismailia, Egypt.

Figure 5: A crystal scientific excellence shield awarded to Prof Laila Montaser in recognition of her valuable efforts in serving the department and spreading knowledge and science.

Montaser asserted that the proceedings of SPIE Optics and Photonics in San Diego, California, in the United States, published three consecutive studies she orally delivered.

The first one was published in 2015 and claims that recent advances in materials science and engineering, as well as in cell and organ transplantation, have led to a rapid evolution of tissue engineering and regenerative medicine [40]. Although stem cells hold great potential for the treatment of a variety of wounds and degenerative diseases, several obstacles must be overcome before their therapeutic application can be realized. These include the creation of cutting-edge strategies to comprehend and regulate the actions of microenvironmental cues as well as innovative approaches to monitor and direct transplanted stem cells. The inability of implanted cells to engraft into target tissues has been a significant side effect of stem cell treatments. These issues could be resolved by integrating nanotechnology into stem cell biology. Significant progress has been made in tissue engineering and regenerative medicine through the combination of stem cell treatment and nanotechnology. These pairings enable nanotechnology to design scaffolds with different characteristics to regulate the fate of stem cells. Creation of nanofiber cell scaffolds that allow stem cells to adhere and proliferate, creating a microenvironment akin to a niche that can direct stem cells to continue healing injured tissues.

While, the second one in 2016 Montaser, et al., clarified that the Holy Grail of musculoskeletal medicine is the capacity to repair soft tissue damage and regenerate cartilage [41]. Because of its weak regenerative qualities, articular cartilage repair and regeneration are thought to be essentially unachievable. Cartilage deficiencies resulting from osteoarthritis, aging or joint damage are the most common cause of chronic disability and joint pain because of their poor capacity for self-healing. Current techniques, however, may result in the development of fibro or continuing hypertrophic cartilage and may not completely repair hyaline cartilage. Research into tissue engineering that combines stem cells, scaffold materials and environmental factors has been spurred by the absence of effective treatment modalities. With the goal of repairing, regenerating, and/or enhancing the functionality of damaged or diseased cartilage, the topic of articular cartilage tissue engineering has attracted a lot of attention and has enormous potential to advance cartilage therapy. Stem cells and/or Plasma Rich in Growth Factors (PRGF) may be useful for cartilage regeneration and tissue repair. Current cartilage therapies hold significant potential for improving cartilage diseases in a way that is consistently effective. Through the utilization of stem cells, innovative scaffolds inspired by biology and cutting-edge nanotechnology, tissue engineering may be the most effective means of achieving this goal.

The third one in 2020 Montaser and Fawzy demonstrated that organ failure is thought to be one of the most significant health issues globally [42]. An alternative to organ transplantation that would circumvent the issues of donor rejection and scarcity is the use of stem cells in human regenerative medicine. New procedures should be developed because the damaged liver can only be successfully repaired by a few number of present therapy approaches. Cell-based therapy is the newest method of liver regeneration. Because stem cells have a strong capacity for multi-lineage differentiation and proliferation, there is growing interest in using stem cell technology for hepatic tissue engineering. Because stem cells can repopulate and differentiate at the engrafted site, stem cell-based therapy has drawn interest as a potential substitute for organ transplantation. Strategies to support and increase stem cell adhesion, proliferation and differentiation *in-vitro* were developed by combining advances in stem cell biology with biomaterials science and engineering. Cells were often seeded on novel nano scaffolds made by electrospinning techniques prior to transplantation. These scaffolds replicate the extracellular matrix and give cells information crucial for tissue growth. The problems with injected cells' inability to engraft into target tissues could be resolved by applying nanotechnology to stem cell biology.

The Future of AI and Stem Cell Research

Although the collaboration between stem cell research and AI is still in its infancy, it has immense potential. AI will probably provide new information about the biology of stem cells as it develops further, allowing for more accurate and efficient treatments for a variety of illnesses. AI-guided stem cell therapies may become commonplace in healthcare in the future, providing individualized, regenerative treatments that might increase lifespans and enhance the quality of life for millions of people [24].

Conclusion

AI and stem cell therapy have the potential to completely transform healthcare by providing innovative treatments for diseases that were previously incurable. Their combined strength promises to usher in a new era of customized and regenerative medicine in addition to accelerating scientific discoveries. AI may help with outcome prediction and the identification of the best stem cell treatments. One of the guiding concepts of the Lab of the Future is automation, which goes hand in hand with digitalization. Cell culture procedures can be either completely autonomous or co-piloted by researchers using AI-driven automation and decision-making. 3D cell models are poised to transform personalized medicine as these developments progress, opening the door for more potent and focused therapeutic approaches. 3D cell cultures have improved our comprehension of medication interactions and disease causes by offering more precise physiological models. Even though there are still obstacles to overcome, continued advancements in AI, bioengineering and microfluidics should propel 3D cell models forward and guarantee their broad use in both clinical and research settings. Even though there are still obstacles to overcome, continued advancements in AI, bioengineering and microfluidics should propel 3D cell models forward and guarantee their broad use in both clinical and research settings. Future workplaces with innovative AI applications present significant challenges for occupational safety and health.

Conflict of Interest

The authors declare no conflicts of interest.

Ethics Approval and Consent to Participate

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