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Advanced biomaterials for regenerative medicine and their possible therapeutic significance in treating COVID-19: a critical overview

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Abstract

The potential of biomaterials in medical sciences has attracted much interest, especially in promoting tissue regeneration and controlling immune responses. As the COVID-19 pandemic broke out, there was an increased interest in understanding more about how biomaterials could be employed to fight this dreaded disease, especially in the context of regenerative medicine. Out of the numerous regenerative medicine possibilities, stem cells and scaffolding (grafting) technology are two major areas in modern medicine and surgery. Mesenchymal stem cells are useful in tissue repair, tailored therapy and the treatment of COVID-19. Using biomaterials in COVID-19 treatment is intricate and needs multidisciplinary and cross-disciplinary research. Cell-based therapy and organ transplants pose immunological rejection challenges. Immunomodulation enhanced, tumorigenicity decreased, inflammation addressed and tissue damage restricted; bioengineered stem cells need clinical insights and validation. Advanced stem cell-based therapies should ideally be effective, safe and scalable. Cost and scalability shall dictate the dawn of techno-economically feasible regenerative medicine. A globally standard and uniform approval process could accelerate translational regenerative medicine. Researchers, patient advocacy organisations, regulators and biopharmaceutical stakeholders need to join hands for easy navigation of regulatory measures and expeditious market entry of regenerative medicine. This article summarises advances in biomaterials for regenerative medicine and their possible therapeutic benefits in managing infectious diseases like COVID-19. It highlights the significant recent developments in biomaterial design, scaffold construction, and stem cell-based therapies to treat tissue damage and COVID-19-linked immunological dysregulation. It also highlights the potential contribution of biomaterials towards creating novel treatment strategies to manage COVID-19.

Keywords: biomaterial, COVID-19, regenerative medicine, stem cell, tissue engineering

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Introduction

The trade of human body parts has been known since ancient times and documented in historical medical literature. Charles Lindbergh (the first pilot to cross the Atlantic) teamed up with Alexis Carrel (a Nobel laureate from the medical field) to explore the possibility of ex-vivo preservation of organs for an extended duration[1]. The kidney was the first organ entirely replaced in 1955[2]. As identical twins were involved in this transplant, there was no risk of organ rejection, and hence, the immune system's reaction to the implanted organ did not need to be addressed. Murray, who subsequently won the Nobel Prize for the research, carried out a kidney transplant in a genetically non-identical patient in the early 1960s. With this, a new chapter in medical history was written. Here, the immunologic barrier was success fully crossed, which opened the doors to the prospects of employing transplantation in extended scenarios.

Inadequately addressed immune suppression, inability to monitor and control organ rejection, and an increasingly dire shortage of potential donors prompted medical professionals and researchers to explore alternate options. Thus, synthetic materials were developed to restore or replace a damaged human body tissue or organ. For instance, novel synthetic materials like silicone and tetrafluoroethylene (Teflon) in an array of gadgets with potential medical applications led to a new commercial sector thriving. However, although structural restoration could be possible with these implants, the original functional component of the tissue or the organ could not be attained. As a result, cell culture, multiply, and harvest methods were perfected. Research on the extracellular matrix and its interaction with the growth factors and legends alongside the cells paved the way to deeply comprehend cellular and tissue proliferation and differentiation.

Similarly, pacemakers and artificial hearts are other examples. Elderly people infrequently experience slower-than-normal heart beat due to heart blockage or electrical pulse issues. An artificial cardiac pacemaker, or simply a pacemaker, is implanted to generate electrical pulses to the heart chambers, delivered by electrodes. A pacemaker is implanted in the chest that supplies the required electrical pulse to the heart and maintains the heart rate. A pacemaker is too much mechanical, and a more life-like upgraded version of it is the artificial heart. Although the heart pumps blood, it has subtleties that are difficult to completely emulate with synthetic materials and power supplies. Historically though, artificial hearts have biomedical issues like clotting, foreign object rejection, longevity, and practicality regarding the device lifespan and the equipment to run it. William DeVries requested permission to implant Jarvik-7 artificial heart in human beings, in 1981. He did it on 1 December 1982 into Barney Clark having severe congestive heart failure.

The first human bone marrow cell transplant was done in the 1970s, which marked the acceptance of cell transplantation among the scientific community. Researchers started fusing the tools and materials from cell biology ideas around this time, and thus, tissue engineering as a new discipline emerged. Tissue engineering gained formal recognition as several associated scientific disciplines converged towards the shared objective of tissue replacement. Stem cell biology was also integrated with the fields of tissue engineering and cell transplantation over the last three decades. The common idea behind all of these fields was live tissue and organ regeneration. William Heseltine of the Human Genome Sciences coined the term regenerative medicine in 1999, collectively for all such fields combined into one[3].

HIGHLIGHTS

- Advancements in creating scaffolds, stem cell-based therapeutics, and biomaterial design have been notable.
- Biomaterials have a potential role in strategising the development of cutting-edge COVID-19 therapeutics.
- Biomaterials-based regenerative medicine could benefit as therapeutics to treat infectious illnesses like COVID-19 and others.

Organ transplant continues to be the cornerstone of patient care with severely malfunctioning organs, and the number of patients needing it greatly outweighs organ supply. This supply–demand imbalance is likely to worsen as the global population ages. Recent developments in regenerative medicine offer innovative donor organ substitutes. Researchers have developed native and stem cells, created new tissues and devised foolproof regenerative medicine treatment plans over the past two decades for almost all human body tissues and organs. It became a reality and a scientific milestone with the extension and transition of stem cell research from totipotency to pleuripotency. This article provides a summary of pathbreaking developments in the field of regenerative medicine and the associated growth factors and hormones. Biomaterials are crucial additions in regenerative medicine. Referred to as 'scaffolds', they could be made of both synthetic and natural matrices. Apart from facilitating the creation of new tissues and creating an ideal spatial condition for restoring tissue shape and function, biomaterials are capable of introducing bioactive substances[4,5] or drawing in cells and growth factors from the body after a tissue or an organ implanted[6,7]. The goal of implanting a biomaterial that is devoid of cells is to promote the inherent ability of a human body to self-heal.

Regenerative medicine has its roots in discovering that some lower order animals, especially amphibians, had a remarkable ability to regenerate an array of body parts like the jaw, retina, tail and limbs[8]. Invertebrates demonstrate it even better. The head fragment of an accidentally severed planarian worm regenerates a new tail structure and the tail a new head. Arguably the best-studied example of this phenomenon is the regeneration of Salamanders' limbs, wherein the lost appendage regrouped with all the differentiated tissues. Although the phenomenon is less prevalent in higher mammals, distal fingertip regeneration in infants and the seasonal shedding of antlers[9] are examples of complicated tissue regeneration[10]. A great deal of work has been done since then to compare operational mechanisms in humans with inferior species. The development of a growth zone, or blastula, at the injury site, is the process that most animals share as the ability to regenerate. Central epithelial cells migrate from the cut margins to the wound surface 12 h after amputation. The growth of limbs and the creation of blastula depend on this transitory epithelium[11]. Then, the differentiated cell at the site loses its mature phenotype and is driven to rejuvenate the cell cycle by a phenomenon that is less well understood yet.

Uterine tube culture research demonstrated that retinoblastoma (Rib) protein sequestration in the presence of elevated serum concentrations is largely responsible for cell cycle rejuvenation[12]. However, neither the dedifferentiation process nor the ability of the cells across species to respond similarly is precisely known. After the cell cycle is rejuvenated, the blastemal cells multiply and form a conical mound that gives rise to all the

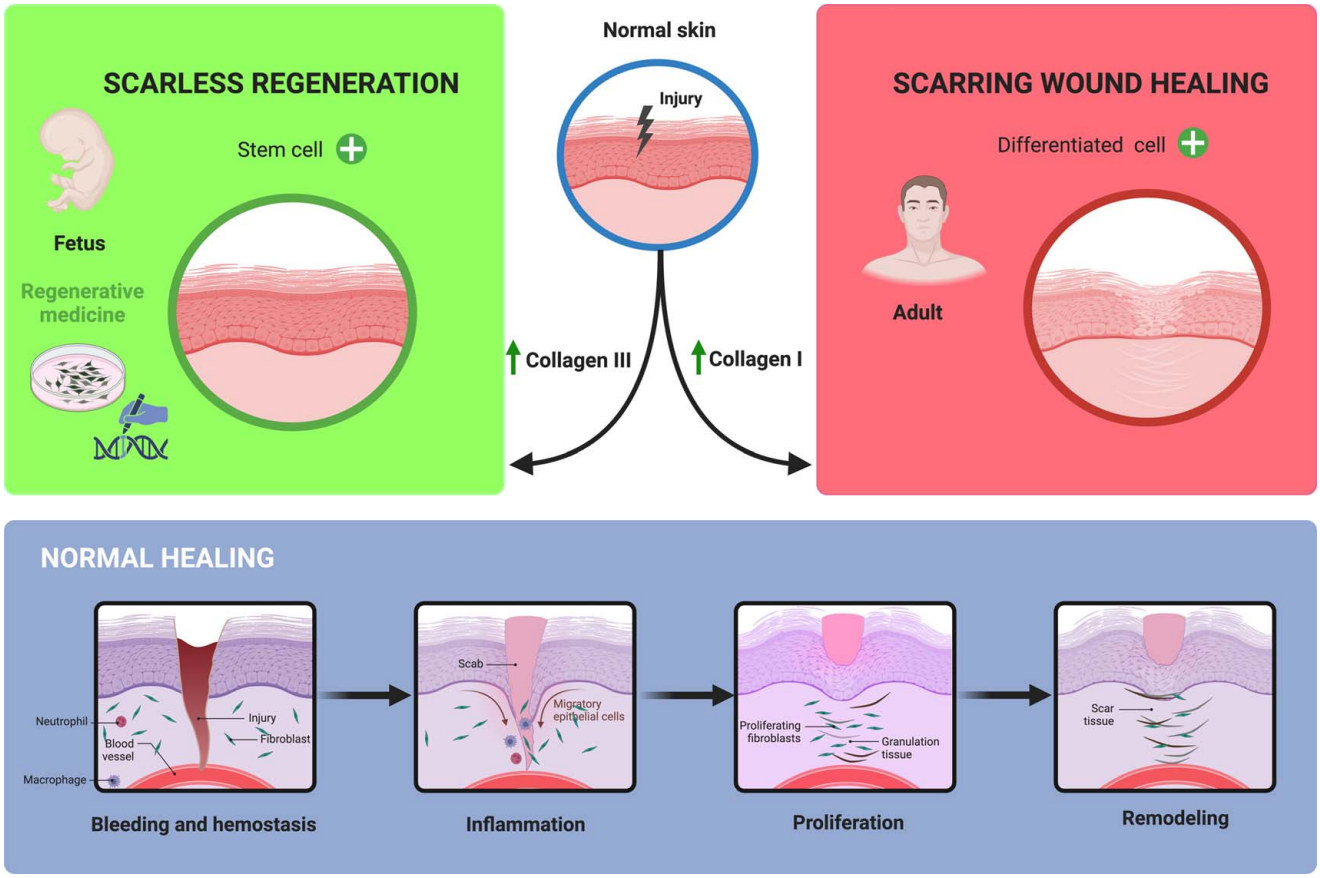

Figure 1. The architecture and full regeneration ability of human skin as the hallmark of repair in the early foetal stage (green box) that is lost in adults (red box), forming scars (grey box) (created with BioRender.com).

necessary cell types when the right environment is present. The establishment of blastulas and subsequent growth of limbs are linked to surface markers, cytokine gradients, and positional effects. The proximal-distal (PD) position, in particular, plays a crucial role in limb regeneration[13]. Hyperactivity of the gene prod1 and its product glycosylphosphatidylinositol (GPI)-anchored surface protein and CD59 are linked to a more proximal identity[14]. The protein is detected on dedifferentiated blastula cells. The proximal fraction consumes the distal in proximal and distal blastula cell co-culture. Although additional mediators might exist, retinoic acid and its different precursors form a proximal-distal gradient necessary to induce prod1 and CD59 expression[15,16]. When exposed to a high quantity of reti noic acid, a wrist blastula regrouped to form a full arm[17].

The human foetal development and urodele limb regeneration mechanisms share tightly controlled gene expression, and molecular gradient-based growth and differentiation commonalities. Blastemal cells are highly proliferative and multipotent, similar to the multipotent stem cells in an embryo. However, the tissue and cell dedifferentiation and merging mechanisms to form regenerative blastula have little known link to either healing or human physiology, and is less known. The process may overlap in the first two trimesters of the damage response in the human foetus. It includes complete regeneration of human skin with no scar during this stage as a skin wound heals[18]. This regenerative ability disappears with the advancement of intrauterine development. Human foetal skin imbibes the 'adult' trait by the third trimester when it is incapable of restoring the original tissue architecture after an injury[19].

Scar formation is the outcome of late-term foetal trauma (Fig. 1). A focus of the investigation for nearly two decades is how the skin regenerates only at the intrauterine development stage. Although no single factor was found to govern scar-free repair in embryonic wound healing, variations in the inflammatory response, cytokine levels, tissue architecture and gene expression were observed[20]. The complicated innate cell components and environmental stimuli interactions appeared to be the cause of regenerative skin wound repair in early human foetuses. Stem cell biology research on resident stem cells in adult skin epithelium showed that the recovery was almost always non-regenerative and led to scarring in clinical settings despite the remarkable capability of these cells in model systems. Adult skin stem cells required induction signals from the surrounding mesenchymal dermis to activate; it was interesting to note[21], suggesting that understanding the behaviour of intrinsic resident stem cells and the environmental factors activated these cells. It could be the key to understanding human cutaneous regeneration.

Materials

A search for relevant literature and reports was carried out online on the databases Scopus, PubMed, Google Scholar and the Web of Science. Updated data were also sourced from the dedicated

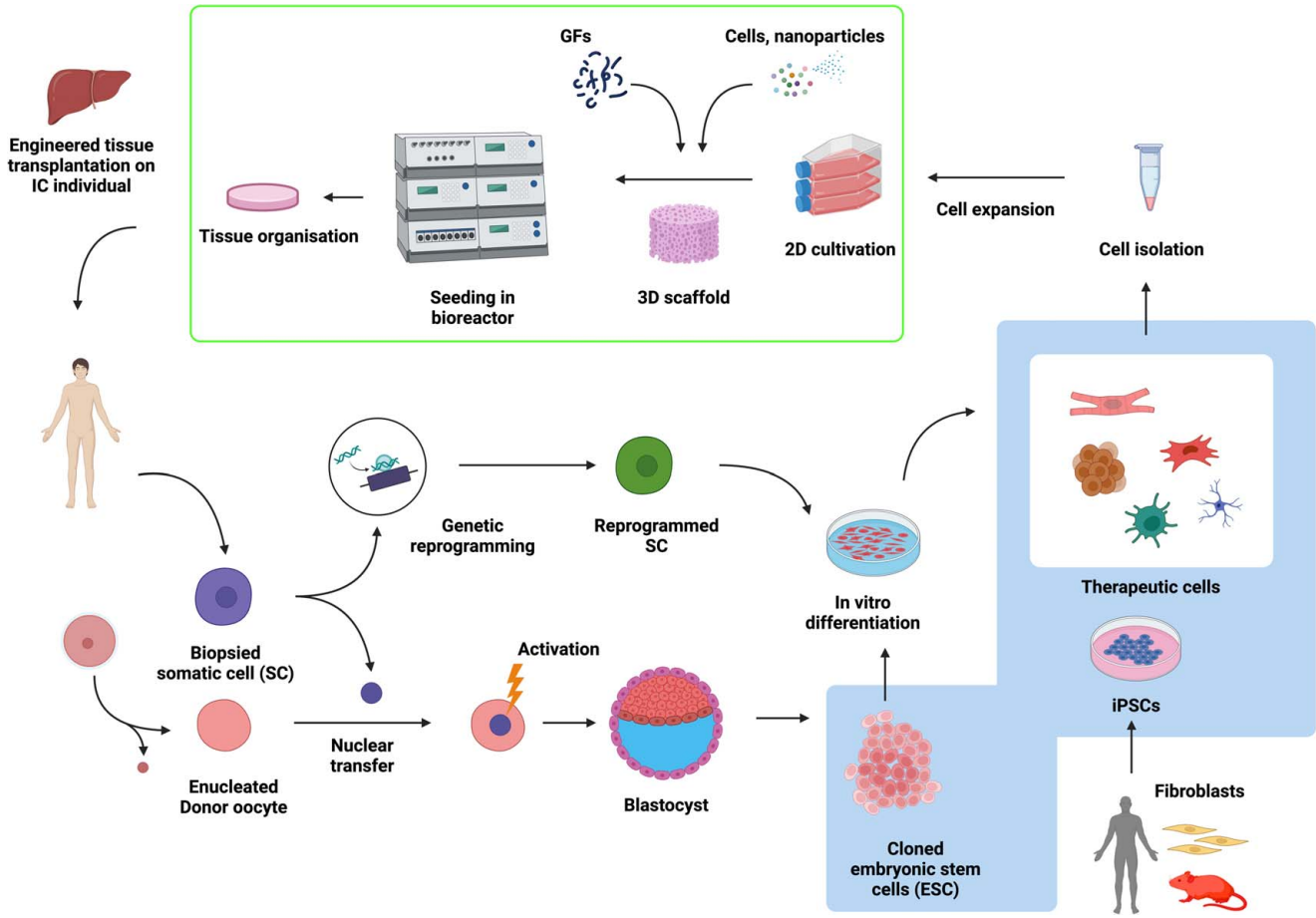

Figure 2. Combined tissue engineering and therapeutic cloning approach to generate tissue/organ (created with BioRender.com).

websites of global health agencies like the WHO, CDC and ECDC. The most recent and relevant reports were selected based on the search-string combinations and selection criteria. For the secondary data analyses, only the literature published in the English language were included and vernacular language literature were excluded. Duplicate articles and conference abstracts were also excluded from the finally selected set of literature under this investigation.

Pluripotent cells including stem cells

Despite the great advancements in primary animal cell culture techniques, all human cells cannot be grown in laboratory conditions. The techniques have not yet been standardised to a point where large-scale cultivation and expansion of human cells or organs related to the pancreas, liver and the nervous system outside of the body is attainable. Keeping this in view, it was assumed that native cells could be replaced with pluripotent cells, including the stem cells[22]. The two primary characteristics of human embryonic stem cells are their capacity to split into a range of specialised cell types and their ability to multiply in an undifferentiated but pluripotent (self-renewal) state. It was demonstrated *in vitro* that these were capable of differentiating into cells from all three embryonic germ layers. They could be obtained by aspirating the inner cell mass of the embryo in its blastocyst stage (5 days after being fertilised).

Formation of skin and neuronal cells indicate ectodermic differentiation[23–26]. Mesoderm differentiation is indicated by the formation of muscle, blood, endothelial cells, cartilage and the heart cells[27–29]. The formation of pancreatic cells indicated endodermis differentiation[30]. However, their clinical utility is limited as they might trigger an immune response. Reprogramming and cloning are two promising examples of novel stem cell technologies that can counter the rejection barrier. Early stage embryo is created using an acolyte with a somatic cell nucleus through somatic cell nuclear transfer (SCNT), another name for therapeutic cloning. This is explanted *in vitro* to create embryonic stem cell lines with source-identical genetic material. These antilogous stem cells could facilitate tissue and organ replacement application as they could develop into nearly any type of adult differentiated cell[31].

Figure 2 depicts the combination of therapeutic cloning and tissue engineering to generate tissues and organs. Stem cell differentiation is the ability of a cell to both self-renew and produce clonal progeny when it differentiates[32]. The embryonic development begins with a totipotent zygote that could grow into any kind of body cell, tissue or organ, including the placenta. The blastocyst is formed after up to 7–8 time fertilisation-induced cell divisions. The pluripotent cells are contained in the inner cell mass (trophoblast; usually of 15–30 cells) of the blastocyst, and the outside wall of the cyst adheres to the uterine wall, which

ultimately forms all the foetal tissues and organs. Called embryonic stem cells (ESCs), these were observed in mice in the 1980s and in humans in the late 1990s. These further differentiate to form multipotent or lineage-specific stem cells.

Multipotent cells include haematopoietic stem cells (HSCs) that could differentiate to produce blood cells, but not in others[33]. Damaged mature tissue could promote tissue regeneration in some instances. Notable homoeostatic renewal level is exhibited by numerous differentiated tissues like the liver, small intestine, bone marrow and epidermis. Each of these adult tissues has a tiny progenitor stem cell fraction with the capacity to self-renew and differentiate into mature adult cells of multiple lineages. The native adult stem cell could also induce differentiation in the nearby committed cells for a more basic kind of regeneration. Once activated, the resident stem cells may function by fusing with differentiated adult cells[34], producing progenitor or tran sient amplifying cells, or inducing nuclear reprogramming in the committed cells. Although stem cells have been extracted from adult muscle, the central nervous system, the gut and the heart; however, the two best-described derived adult stem cells are bone marrow and the epidermis[35]. These two are detailed below.

Bone marrow-derived stem cells

As of now, the hematopoietic system is the most thoroughly studied adult stem cell model that allows only rare and unique HSCs to demonstrate long-term self-renewal. Found in the bone marrow, these cells self-renew and produce every variety of blood cells. HSC was discovered in the 1960s when it was demonstrated to rebuild a lethally irradiated blood-forming system in mice[7,36–38]. With the advent of reliable rodent models and advanced fluorescent cell sorting technology, identifying and classifying HSCs and their more committed progeny downstream have progressed significantly. However, only HSCs have been studied in detail thus far, not the committed or more ephemeral progenitor cells. HSCs have been effectively employed in both preclinical and clinical transplantation research. Notch and Wnt signalling pathways are believed to be needed for HSC for sequestering and activating bone marrow. However, a study on genetic ablation showed that one or both of these pathways might not be necessary[39].

It was proposed that the HSC progenitor downstream was stimulated, differentiated and then released from bone marrow by extrinsic signalling (external stimuli) from the neighbouring stoma cells[40]. Apart from haematopoietic progenitors, human bone marrow possesses characterised stem cells, the MSCs and multipotent adult progenitor cells (MAPCs)[41]. Apart from the bone marrow, MSCs were later also extracted from various other (like neural, adipose, pancreatic tissues and skeletal muscle) sources[42]. These matured and committed cells moved from the bone marrow niche to differentiate at injury sites, as demon strated in animal studies *in vitro*. Cardiac, neuronal and endo thelial tissue progenitors are among the well-documented ones[43–45]. Although yet to be understood well, MAPC is con sidered to have developed from MSC cultures after a considerable number of cell doublings. MAPC has a much higher potency than MSCs, differentiating into a wide variety of adult tissue types and remaining pluripotent for long[46].

However, whether MAPC is solely generated through in-vitro culture or it exists in enough quantity *in vivo* is still unknown[47]. The therapeutic potential of non-haematopoietic cells on tissues has been studied. Animal bone marrow transplant models with tie2-labelled grafts showed that bone marrow-derived cells integrated into expanding ischaemic tissue vasculature after an ischaemia injury[48]. Apart from local satellite cells, gynogenic precursors arising from bone marrow were also involved in muscle regeneration, undergoing differentiation and participat ing in regenerating the damaged fibres[49]. The possibility to inte grate the capacity of progenitor cells to develop into cardiac endothelium and muscle tissue was seen in human transplanta tion trials. It made the heart the most researched target for bone marrow-derived regenerative cell therapy. Yet, the spread of these cells and their actual phenotype are unclear[50,51].

Epidermal stem cells

While epidermal renewal caused by cell division at the basal layer of the epidermis is usually known, a plethora of recent research highlighted the significance of distinct stem cell types resident in the bulge region of the outer follicle, termed as HFSC (hair follicle stem cell)[52]. It was initially believed that HFSCs were only involved in regenerating the sebaceous glands and hair follicles. It was revealed later that they might also be critical in intermolecular long-term epidermis replenishment and repopulation of the epidermis after damage, possibly through the transitory (short lifespan) amplifying cell progeny. Using cutting-edge tagging technique, studies demonstrated that stem cells make up 6% of the cells in the adult epidermis[53]. Dermal papilla cells, a separate subset of the adjacent cells, induced and orga nised the activating and directing of HFSC proliferation and differentiation[54]. HFSCs are capable of reconstructing skin cells when incorporated into a wound alongside the organiser cells from the dermal papilla. To label and purify the stem cells, many useful markers (like K15, α6-integrin, CD34 and teasing C) were developed through their expression profiling[55,56]. It was pro posed that, similar to HSC activation signalling, Notch and Wnt regulated the nuclear β-catenin[57].

Stem cell niches

The term introduced in 1991 by Caplan states that stem cells are unspecialised cells in the body that have the ability to self-renew and differentiate into distinct cell types with distinct roles. These exhibit their ability to clone in both in-vitro and in-vivo settings. Stem cells undergo self-renewal from their niche-like milieu through signals-regulated genetic pathways, providing an optimal transplantation platform to treat terminal illnesses. Cell therapy has attracted a lot of interest in treating numerous illnesses in both humans and animals. Cells are cultured under strict control in laboratories for stem cell treatments. Stem cells fall into categories like embryonic, foetal and adult, and also as adult, foetal or embryonic as per origin[58]. Primordial cells need a different milieu to grow and nourish than adult tissues, to sustain the resident stem cell population. Stem cell niche could protect against apoptotic stimuli and/or differentiation, and restrict excessive cell doubling. Some adult stem cells receive activation signals, which might be in response to damage, signalling to emerge from their niche and multiply or develop into fully grown replacement tissue. Due to matrix architecture, mechanical stressors, cytokine release, inflammation and varying oxygen tension, adult tissue can have variable microenvironment requirements. Considering biocompatibility as a case instance, Figure 3 depicts the factors behind creating a more favourable environment for stem cells to encourage them to regenerate to mature tissues.

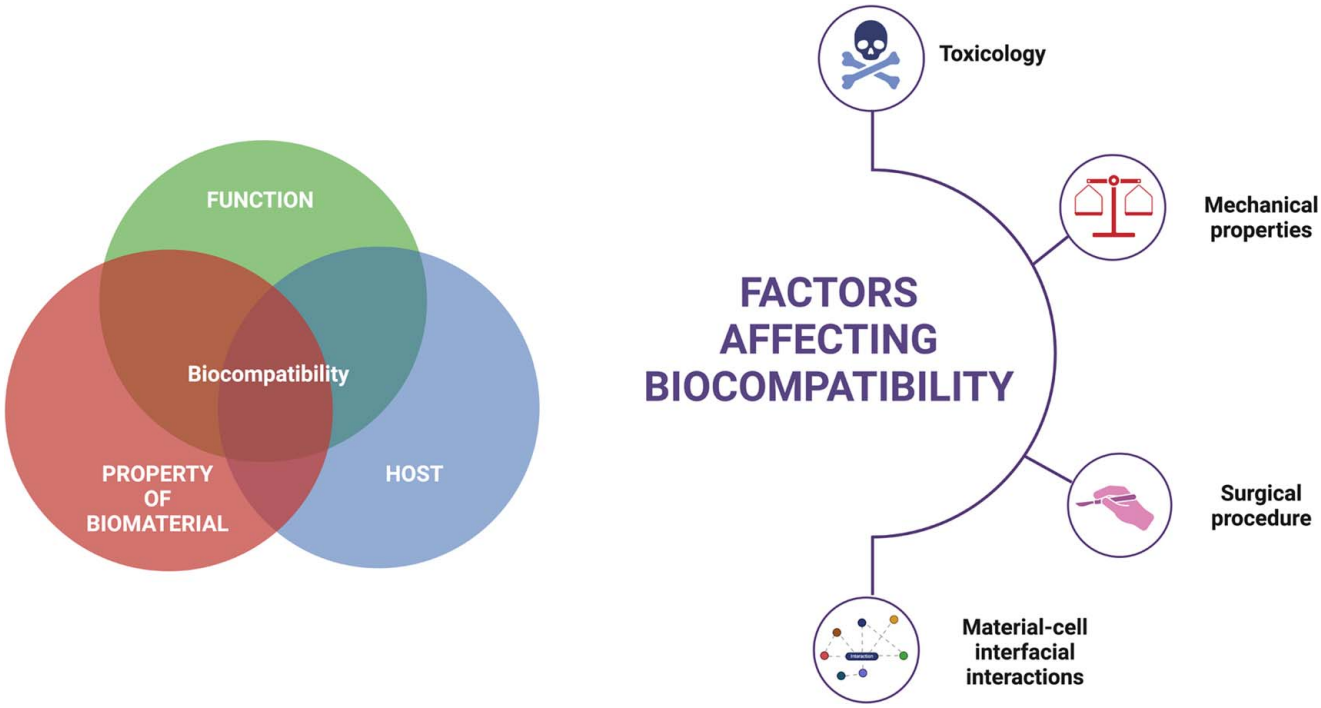

Figure 3. Biocompatibility as a popular technique in fabricating replacement tissues (created with BioRender.com).

The ratio of scar formation to regeneration may vary depending on the local oxygen tension[59,60]. A growing embryo in the uterus flourishing in a somewhat hypoxic environment is a regenerative wound-healing model. While continuously exposed to a hypoxic environment, skin wound exhibits low HIF-1α expression levels in the regeneration phase[61,62]. HIF-1α regulates several genes participating in inflammation and angio genesis downstream. A third-trimester wound exhibits elevated HIF-1α levels as compared to an adult wound. It clearly links to decreased hypoxia response and HIF-1α levels observed in foetal regenerative phenotype. Varying oxygen tension was con nected to embryogenesis and adult stem cell trafficking of numerous organ systems, occurring naturally or in response to damage. Hypoxia is necessary to preserve stem cell niche and facilitate differentiation[63–66] and is a significant regulator of haematopoietic progenitor cells recruitment to the wound region[67].

Increased oxygen sensitivity during stem cells and scaffold integration is compelling to promote stem cell activation and improve healing. Homoeostasis in the functioning of stem cells of the skin and other tissues and organs is dependent on the mechanotransduction mechanism that governs cellular activity through mechanical forces[68,69]. Differentiation and apoptosis of adult stem cells are regulated by matrix-sensing elements like α6β4 and β1-integrins via MAPK[70]. Modifying or eliminating these structural components would result in significant stem cell differentiation and death. Genes that favour scar formation dur ing wound healing in adults are mechanotransduction activated[71,72]. Mechanical injury triggers stem cells in the epi dermal stem cell niche to migrate upward into epithelium[73,74]. Skin, haematological system, intestinal crypts and testes are mechanically distinct stem cell niches[75]. Providing optimal mechanical conditions for tissue reaction and regenerative repair during healing using a mechanics-based management and mon itoring strategy could be advantageous.

Tissue engineering

Conventionally, tissue engineering is the process of restoring injured tissues through biological replacements[76,77]. Cell-based therapeusis involves a systematic supply of stem cells to a target region irrespective of the capacity for direct tissue replacement or regenerative activation in the native tissue. However, delivering effective regenerative treatment involves more than just obtaining the 'seeds'; it also involves overcoming isolation and expansion obstacles. Signalling profile elicitation that could activate the stem cells (creating a 'conducive environment') from the native environment as a therapeutic element is an important consideration. Tissue engineering, a rapidly growing science, is a technique that addresses both 'soil' conditioning and 'seed' transport.

Advancements in cell seeding, the creation of biocompatible and biodegradable scaffolds and implantation schedules have significantly progressed. A scaffold serving as a support structure for several cells and tissues (like vascular, fibrous and organ-specific cells) and also as a blueprint to create three-dimensional tissue is often considered as non-cytotoxic therapeusis. An ideal scaffold expectedly deteriorates and eventually disintegrates as the transplanted cells multiply and integrate into a recipient tissue bed, leaving a mature construct indistinguishable from the surrounding tissue. An array of synthetic (polyglycolide, polylactide, polylactide-coglycolide) and natural (collagen, hydroxyapatite, alginate) materials are used to serve as the basis for designing the state-of-art scaffold for cell differentiation and adhesion[78]. Incorporating peptides like RGD (Arg-Gly-Asp) in biomaterials and manipulating the surface at the nanoscale level supposedly improved cell migration and adhesion[79–81]. The inclusion of

growth-stimulating substances further enhanced the outcome by expanding the specific cell types[82].

A scaffold eventually becomes a part of the host and provides the planted and native cells with the same level of support as before. The construct needs nutritional exchange *ex vivo* to seed and expand the scaffold before implanting. Microfabrication and innovative bioreactor procedures in the integrated circuit industry have increased the survival rates of the seeded cells *ex vivo*[83,84]. A key obstacle in such designs is creating a functional circulatory system[85]. A novel method to stimulate the formation of vascular networks outside living systems involves the etching of silicon wafers and the perfusion of endothelial cells through it[86]. Designed biomaterials use targeted gene delivery and growth factors to enhance local wound-healing response[87]. Using implanted materials to modify the environment around a reci pient with designed and integrated advanced biomaterial could support adult tissue to regenerate.

Potential of MSCs as a therapeutic tool to manage and treat COVID-19

One way of extended application of stem cells is asynchronous replicators. The mesenteric cells could produce fat, muscle, cartilage, bone, tendon, dermis and marrow stoma tissues[88,89]. Human mesenchymal stem cells (hMSC) could be identified by employing markers like CD29, CD44, CD73, CD90 and CD105. They do not express a few other markers like CD14, CD34 or CD45 as in the case of human leucocyte antigen (HLA)[90]. Found practically in pockets in every organ in an adult, these cells pro tect from normal aging. MSCs are found in pockets and niches like brain[91], intestine[92], kidney[93], liver[94], pancreas[95], synovial[96], skin[97], hair follicle[98], adipose tissue[99], lungs[100], muscle[101], cord blood[102], peripheral blood and trabecular bone[103], throughout the human body. These regions (niches) provide the perfect environment for the specialised cells to thrive.

These stem cells are categorised as embryonic stem cells (ESCs) or adult stem cells (ASCs), depending on where the origin of the tissue. Induced pluripotent stem cells (iPSCs) are adult stem cells exhibiting pluripotency even after having undergone differentiation[104–106]. While MSCs can be generated from embryonic stem cells, the therapeutic potential of the undifferentiated embryonic stem cells to produce MSCs is often limited, such as malignant tumours affecting all three germ layers in nude mice[107].

The SARS-CoV-2 virus

The COVID-19 pandemic struck so abruptly and instantaneously that it put community health science and technology to the test and affected the global economy badly[108]. This novel virus assumedly already contracted humans, remaining latent and unidentified for an unaccounted duration till December 2019[109]. The virus is a single-stranded 26–32 kb genome positive-sense RNA virus as also in the MERS virus[110,111]. With 79.6% identical sequence and length to MERS, SARS-CoV-2 was the biggest RNA virus ever discovered. Of the four coronavirus genera (α, β, γ and δ), human coronaviruses (HCoVs) are in two genera: α (SARS-CoV, HCoV-HKU1, MERS-CoV and HCoV-OC43) and β (NL63 and HCoV-229E)[112]. Bat-derived SARS-like coronaviruses (bat-SL-CoVZXC21 and bat-SL-CoVZC45) and MERS-CoV, respectively, share around 50% and 88% of their sequences within β coronavirus[113].

The International Virus Classification Commission (IVCC) designated the new β-CoV as SARS-CoV-2, which has 10 open reading frames (ORFs) in its genome. About two-thirds of the viral RNA is made up of the first open reading frame (ORF1a/b) incorporated into two bigger polyproteins. Viral replicase transcriptase complexes in SARS-CoV and MERS-CoV are produced by processing two polyproteins, pp1a and pp1ab, into 16 non-structured proteins (nsp1–nsp16)[114]. These non-structural proteins transport the rough endoplasmic reticulum (RER) membranes to double-membrane vesicles, the sites of transcription and viral replication[115]. Four structural proteins are enco ded by a different set of SARS-CoV-2 ORFs on three genome segments of membrane (M), envelope (E), spike (S) and nucleo capsid (N). It also encodes numerous auxiliary proteins with no involvement in viral replication or any other known role.

Pathophysiology of SARS-CoV-2

Based on radiographic data, the clinical signs of SARS-CoV-2 patients are fatigue, malign, fever, dry cough, dyspnoea and pneumonia. A significant proportion of COVID-19 patients harbour neurological abnormalities[116]. The symptoms of MERS-CoV and SARS-CoV are similar. The mechanisms of SARS-CoV and MERS-CoV enhanced our knowledge of SARS-CoV-2 pathogenesis, although the critical SARS-CoV-2 pathophysiology is yet not fully understood. Vaccines are at the forefront in countering infectious diseases as preventive measures as they direct and boost the immune system to fight against viruses and bacteria. Vaccines inject a tiny, benign fraction of a specific microbe into the body to trigger an immune response. A vaccinated individual is less likely to develop serious pathogen-based illness as the antibodies respond swiftly to exposure to such pathogen[117]. Vaccination can induce herd immunity too. The caution is that a recovered patient must rigorously follow miti gation measures like the population at risk, which has not yet been exposed[118].

Interaction of viral protein with cell surface receptors

Coronavirus S protein is a host cell entry pass by locating angiotensin I converting enzyme 2 (ACE2) receptor[119–121]. ACE2 is a critical interacting enzyme in SARS-CoV and SARS-CoV-2 (C-type lectin CD209L), MERS-CoV and SARS-CoV[44,122–124]. The encased spike glycol protein interacts with the cellular receptor[125]. The human cell surface has a large distribution of ACE2 receptors, particularly on the type 2 lung alveolar cells[126,127]. The heart, liver, kidney and digestive systems also have it in abundance. Endothelial cells and smooth muscle cells express ACE2 allowing the virus to swiftly enter the body into the circulating blood. Thus, all these ACE2-expressing organs and tissues are involved in battling COVID-19. It helps to explain why multiorgan dys functions with arrhythmia, acute cardiac injury, shock and acute renal shock are common in respiratory distress syndrome (RDS) subjects. The entry of coronavirus into the host cells needs cellular serine protease TMRRSS2[128]. Human cells like alveolar type 2 and capillary endothelium have widely distributed ACE2 recep tors on the surface, and a significant portion of the alveolar type 2 cells express TMPRSS2[129–132]. It is to be noted that coronavirus enters the body by direct membrane fusion of viral and the plasma membrane[133].

SARS-CoV controlled the viral infectivity and membrane fusion through a crucial proteolytic cleavage at the S2' location of

S protein[134]. Apart from membrane fusion, SARS-CoV entry is also intriguing due to its clattering-independent and dependent endocytosis[135]. The viral RNA escapes into the cytoplasm after entering the cell, where it decodes into two polyproteins and a structural protein. The viral genome then begins replicating and duplicates itself as the freshly designed envelope glycoprotein crosses the Golgi body or the endoplasmic reticulum membrane. The combined nucleocapsid protein and genomic RNA shape the nucleocapsid. The virus particle then explodes in the intermediate compartment of the endoplasmic reticulum and Golgi apparatus (ERGIC). The virus eventually liberates with the fusion of the plasma membrane and the viral particles trapped in vesicles[136].

The coronavirus antigen architecture

As the virus penetrates the cell, the antigen is presented to the cells (APCs). The antigen is essential for the defence system of the body against the virus. Human cytotoxic T lymphocytes (CTLs) that are virus-specific identify the peptides accessed through human leucocyte antigen (HLA) or major histocompatibility complex (MHC). Familiarising with SARS-CoV-2 antigen presentation is necessary to comprehend COVID-19 pathogenesis. MHC I has a significant impact on SARS-CoV antigen presentation, while MHC II has a secondary role. Individuals with genetic markers like HLA-B*4601, HLA-B*0703, HLA-DR B1*1202[137] and HLA-CW*0801[138] were at a greater risk of contracting SARS-CoV. Conversely, the HLA-DR0301, HLA-A*0201 and HLA-CW1502 alleles conferred resistance against SARS[139]. The two Major Histocompatibility Complex II (MHC II) markers that are linked to infection risk during MERS-CoV infection are HLA-DQB1*02:0 and HLA-DRB1*11:01[140]. The risk of con tracting SARS-CoV infection is also linked to polymorphism in the antigen presentation-associated MBL (mannose-binding lec tin) gene[141]. Such information would provide useful evidence regarding the mechanism of COVID-19 infection and the sug gested management measures.

A nanovaccine combination could simultaneously target multiple antigens, providing more comprehensive protection against an array of infectious agents. Another potential benefit of the nanovaccine combination is the ability to tailor the immune response to specific diseased populations. A nanovaccine combination could be designed to induce a robust Th1 immune response that is associated with the protection against intracellular pathogens, while others may induce a Th2 immune response that protects against an extracellular pathogen[142].

Avoiding immunosurveillance

Both MERS-CoV and SARS-CoV employ numerous strategies to dupe the immune system and sustain inside the host cell. Pattern recognition receptors (PRRs) recognise pathogen-associated molecular patterns (PAMPs), a conserved microbial structure. MERS-CoV and SARS-CoV would bring in double-membrane vesicles. The host was unable to identify the dsRNA in the vesicles as they multiply without PRRs later[143]. IFN-I pathway reduced to IFN-β (IFN-I) and IFN-α by SARS-CoV and MERS-CoV in infected mice[144,145]. Interferon could be inhibited by MERS-CoV accessory protein 4a by interacting with the double-stranded RNA at the MDA5 activation level[146]. MERS-CoV prevented ORF5, ORF4a and ORF4b membrane proteins and interferon regulatory factor 3 (IRF3) from nucleus transportation and sti mulated interferon β (IFN β) promoter[147]. Similar to MERS-CoV infection-related downregulation of gene expression related to antigen presentation, coronavirus also impacted antigen presentation[148]. Thus, preventing the immunity evasion ability of SARS-CoV-2 was an essential and effective strategy to tackle viral infections.

The cytokine storm phenomenon

The thymus, spleen, bone marrow and macrophages do not possess ACE2, as also the immune cells like B and T lymphocytes[149]. It implies that immunological treatment could benefit a COVID-19 patient. However, the overactive immune system in a patient generates more inflammatory chemicals while getting rid of the virus that triggered cytokine storm[150]. The immune effectors cells initiate a lethal and uncontrollable inflammatory response owing to SARS-CoV infection, flooding the lungs with pro-inflammatory chemokines (CXCL10, CXCL9, CXCL8, CCL5, CCL3, CCL2, etc.) and pro-inflammatory cytokines (IFN-α, IFN-γ, TNF-α, TGF-β, IL-33, IL-18, IL-12, IL-6, IL-1β, etc.). Similarly, elevated levels of IL-6, IFN-α, IL-6, CCL5, CXCL8 and CXCL10 were observed in MERS-CoV infection. So, steering the cytokine storm clear while treating COVID-19 patients is essential as it triggers self-attack by the immune system of the body, resulting in ARDS, cardiac arrest, air exchange dysfunction and MOD. Comparing the SARS-CoV and MERS-CoV infections, SARS-CoV infection had higher death rates[151]. Reduced pro-inflammatory cytokine release reduces the risk of cytokine storm, increased anti-inflammatory cytokine levels and greater secretion of natural antimicrobial peptides, which are all linked to appropriate vitamin D levels in the host. These might contribute to stimulating the Th2 immune response and the activation of macrophages and other defense cells. However, the correlation between low vitamin D levels and a bad prognosis for the illness is yet to be established. There have been efforts to interpret the immunoregulatory char acteristics and potential role of vitamin D in countering COVID-19[152].

Reaction of cellular and humoral immunity

The body develops cellular and humeral immunity after antigen presentation, fuelled by T and B cells that are virus-specific. Typical IgM and IgG pattern is formed by the antibody profiles against SARS-CoV, just like other acute viral infections. As the SARS-specific IgG antibody persisted longer beyond 12 weeks, it could be claimed that the IgG antibody served as a protection against the virus[153]. Numerous studies have focused on cellular immunity against coronaviruses than the humoral response. There is significantly less $CD8^+$ in the peripheral blood of SARS-CoV-2-infected patients[154]. While there are more $CD4^+$ T cells, there are also more HLA-DR (CD4, 3.47%) and CD38 (CD8, 39.4%) T cells, which indicate the activation of these cells[155]. Reduced $CD4^+$ and $CD8^+$ T cells in COVID-19 patients suggested an acute phase response. Some SARS-CoV subjects maintained $CD4^+$ and $CD8^+$ memory T cells beyond recovery, even in the absence of the antigen. Further, T cell proliferation, IFN-γ pro duction, and DTH response remained for about 4 years. There were observable T cell memory responses against the SARS-CoV S peptide in 14 out of 23 SARS-CoV patients 6 years after recovery[156]. The designated $CD8^+$ T cells appeared to exhibit similar events in mice in the case of MERS-CoV too[157]. It could help revamp the therapeutic interventions.

Controlling nCOVID-19

Research organisations and universities globally developed about 90 vaccines to combat COVID-19[158,159]. A plethora of techniques and technologies, some being never used in any approved medicine or vaccine, were tested and validated. Many therapeutics and preventives were either combined, repurposed or reformulated, and the safety was assessed through animal trials. Several proteins, viruses, and nucleic acids, as well as acids-based vaccines, were tried intraperitoneally in volunteers. Similarly, transplanted mesenchymal stem cells (MSCs) have also been demonstrated to improve the outcomes in COVID-19 patients. The Italian college of intensive care, resuscitation, analgesia and anaesthesia released guidelines highlighting the significant potential of stem cells to provide prompt relief in COVID-19. Although immunotherapy is a potential treatment option, its ability minimises and cannot be relied on alone where only one or two immune factors are involved. This is because viruses can trigger cytokine storms in the lungs, which can lead to fatal outcomes like cardiac arrest, acute respiratory distress syndrome (ARDS), multiple organ failure and coinfections.

Thus, immunotherapy is not enough while treating COVID-19, and it is advisable to avoid or evade cytokine storms. Stem cells like MSCs possess innately strong immunomodulatory ability and are advantageous without cytokine storm. Cell therapies drive biomedical research in tissue engineering and regenerative medicine. They are used to treat renal[160–162], pulmonary[163] and cardiovascular[164–166] illnesses. Despite research studies validating the immunomodulatory or regen erative effects of such treatments, the Federal Trade Commission (FTC) filed a lawsuit opposing the use of stem cell-based therapy[167]. The Food and Drug Administration (FDA), US, evaluated the contentions on stem cell-based therapy through clinical trials and released new guidelines about clinical trial clearances prior to adopting the therapy[168–174]. Researchers and medical professionals joined hands to counter the fatal viral (COVID-19) infection, find solutions to cure this worst pandemic of the 21st century and end it.

As per the statement issued by the International Society for Stem Cell Research (ISSCR), no stem cell-based medication was currently licensed to treat or prevent COVID-19. While other therapeutic options were investigated, MSCs were proposed as therapeutic options to manage and cope with treatments associated with the deadly COVID-19. Stem cell infusion to counter COVID-19 morbidity and mortality are being investigated. MSC infusion involving a 65-year-old COVID-19-infected Chinese woman was investigated, after which many stem cell clinical trials have been initiated. Recent Chinese research found positive results in seven COVID-19 patients who received stem cell treatment. The WHO has also established a central database listing all the countries where stem cell clinical trials were being actively conducted.

Citing results of the initial trials conducted in China, Mr Zhang Xining, the Director of Biological Technology of Beijing's Ministry of Science and Technology, announced in a press conference in February 2020 that stem cell-based therapy was safe and effective[175]. However, extensive research and clinical trials were needed to validate the claim further. If confirmed, it could possibly help produce siRNA from ncRNAs against the genomic RNA of the virus. The mRNA-based antiviral treatments developed recently include gene therapy and vaccine vectors. As this approach could help develop and fine-tune the COVID-19 treatment plans, insightful investigations to fully understand the role of mRNA in regulating ACE2 receptors are needed[176].

Potentials of MSCs in countering COVID-19

Basic regenerative medicine research, translational investigations and human clinical trials are important in developing a roadmap for clinical applications of MSCs[177,178]. Clinical trials involving GVHD[179] and SLE[180] have amply demonstrated the safety and efficacy of MSCs. The body expedites immune overreaction after COVID-19 infection and initiates a cytokine storm (a phenom enon of excess production of immune cells and cytokines) that generates a large number of inflammatory substances[181]. This is how MSC treatment stands out as a useful 'Corona warrior' to treat COVID-19 patients. MSCs play a pivotal role in two distinct ways: the ability to differentiate and through immunomodulatory effects. Due to their potent immunomodulatory capabilities, MSCs have an inherent ability to protect against the coronavirus at the cellular level. MSCs can effectively mitigate the phenom enon of cytokine storm through peregrine secretions that release anti-inflammatory substances.

Possessing the peregrine secretion ability, MSCs release a wide range of cytokines or engage in direct communication with killer cells, dendrite cells and immune cells (macrophages and T and B cells). The TLR receptor in MSCs is activated by pathogen-associated chemicals like the RNA or LPS of coronavirus that initiate immunomodulation of MSCs[182,183]. MSC therapy reduces the overreaction of the immune system and encourages endogenous repair by enhancing the chemical environment in the body. After intravenous injection of MSC, a portion of it is entrapped in the lungs, enhances the pulmonary environment by countering lung dysfunction, avoiding pulmonary fibrosis and protecting alveolar epithelial cells and COVID-19-associated pneumonia.

MSCs have been shown to considerably improve the treatment of numerous illnesses of hepatic, cardiovascular, renal and acute respiratory syndrome-related conditions[184]. It can be inferred that the potential of MSC-based therapy to treat COVID-19 infection that might play a critical and substantial role when used in conjunction with traditional treatment needs to be investigated through clinical trials[185]. As of now, there are no FDA-approved MSC-based therapies to treat COVID-19. However, the medical infrastructure faces high pressure during pandemic-like situa tions, such as during COVID-19, to prescribe treatment measures even with little available data on their efficacy or safety. Such pressure situation results in an even greater dilemma of the importance of practicing evidence-based medicine and the need to provide access to otherwise promising medications whose safety and efficacy were yet to be established. With this in consideration, convalescent plasma therapy (CPT) is one of the several immu nomodulatory treatment modalities demonstrated to be promis ing in managing COVID-19[186]. Table 1 lists a few other such promising modalities.

Biomaterials in regenerative medicine

The objective of biomimetics of extracellular matrices is to direct the function of engineered biomaterials at the molecular level in regenerative medicine. Cells are encircled by solid or fluid matrix,

Table 1

A list of some MSCs with potential role to counter COVID-19 pandemic.

Function	Description	Reference
Immunomodulation	MSC can modulate immune response and reduce the COVID-19-associated inflammation and cytokine storm	[187]
Tissue repair and regeneration	MSCs can promote tissue repair and regeneration of the damaged lung tissues due to COVID-19	[188]
Antiviral effects	MSCs secrete factors that have potential antiviral effects and help combat SARS-CoV-2 directly	[189]
Reduction of fibrosis	MSCs may help reduce pulmonary fibrosis, a common complication in severe COVID-19 cases	[190]
Enhanced recovery	Patients receiving MSC therapy had improved recovery time and reduced severity	[191]

especially in higher vertebrates including mammals that provide mechanical support and facilitate chemical signalling[192,193]. Extracellular matrix structure possesses extraordinary spatial and temporal sophistication, making way for cellular signalling as a bioengineering wonder. Examples of such materials for signalling are proteins and polysaccharides, macromolecules and cofactors as tiny molecules. Thus, molecular dynamics and molecular recognition processes need to be strictly controlled in the matrix environment as molecules approach the cell surface. For instance, a specific signalling protein (like a ligand) binds to a dimer or complex proteins or signal proteins on the cell surface (receptor), producing entirely different biological effects. An artificial matrix must be 'bioactive' in interacting with the biological milieu to advance the field of regenerative medicine. It may perform numerous tasks during the interaction, like controlling stem cell differentiation, preventing apoptosis, regulating cell proliferation, attracting or directing appropriate cells towards the targeted regeneration site, angiogenesis initiation (development of new blood vessels), and nourishing the growing cell mass.

Hydrogels, polymers and other soft materials that are potential bioactive matrices have been investigated a lot in recent times[194–197]. Among these argentine-lysine-aspartate (RGD) is by far the most widely studied[198–201]. It is a component of fibronectin, an extracellular protein, with a peptide sequence as the epitope to bind receptor proteins on the cell surface. The transmembrane proteins (integrins) serve as receptors that bind to the epitope of the extracellular protein, forming dimers. The binding of ligands to receptors initiates cellular adhesion to the matrix. It is a highly intricate phenomenon involving many cytoskeletal and cellular proteins. Cell survival and signal trans duction that leads to cell proliferation and division depend on biological adhesion. Cellular adhesion to the matrix is vital in regeneration, which phenomenon has led to the popularity of bioactive materials in regenerative medicine.

Self-assembling monolayers as a model system to understand the relationships involved in cell adhesion have been researched. Although the exact impact of integrating RGD in biomaterials for regenerative medicine is unknown, biological cell adhesion definitely plays a significant role in the migration and proliferation of cells, as revealed through studies on RGD-containing surfaces *in vitro*. Incorporating growth factors into polymers is another suggested approach to create biomatrices that shall be useful in encouraging angiogenesis and regenerating specific tissues. With the goal to eventually substitute regenerated tissue for the space to fill as the material degrades, numerous biodegradable polymers have been investigated[202–205]. Invasive surgery is necessary to implant prefabricated polymer in the desired tissue area. Creating an injectable bioactive substance in liquefied form and then allowing it to self-assemble and solidify in the desired location is an alternative approach (Fig. 4).

As the artificial matrix is intended to decompose or dissolve and readily remove harmlessly, biodegradation is a desirable trait of the molecular architecture of biomatrix. Cells may be involved in regenerative therapy strategies wherein they could be considered in biomaterial designing on two counts: one, as specially textured and molecularly designed materials for extracorporeal

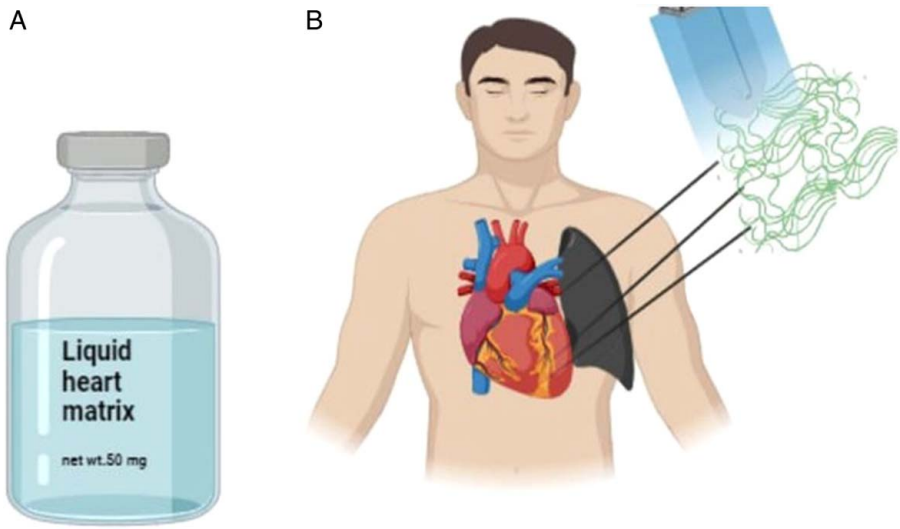

Figure 4. Injectable liquefied biosubstance that allows self-assembly and solidification. (A) The liquid that creates a bioactive matrix to aid in heart muscle regeneration; (B) liquid solidifies into a nanostructure matrix with all necessary bioactive components after entering the tissue.

devices to help guide stem (progenitor) cells into the desired lineage before patient delivery, and two, in a self-assembling matrix to deliver the matrix inside the body. Tissue-engineered scaffold offers cellular architecture, mechanical support and shape for in-vivo or in-vitro development of new tissue in its most basic form as the implanted cells spread and organise. Synthesised polyester candidates like alginate, chatoyant, collagen, fibrin, poly-L-lactic acid (PLLA) and poly-L-glycolic acid (PLGA) make up the majority of degradable biomaterials employed often[206].

Numerous fabrication techniques that provide an array of possible architecture, porosity, size and form are developed[207–210]. Synthetic and natural composite polymers to particularly create hard tissues offering materials with varying strengths and porosities, either alone or combined with bioactive ceramics like hydroxyapatite or specialised glasses, are standardised[211]. Biomaterial scaffolds offer to develop tis sue-engineered constructs more than just a transient architectural framework. Interactive biomaterials facilitating the coordination of cell attachment, development and tissue morphogenesis are advantageous in novel regenerative medicine applications with joint efforts of materials science, biomedical engineering, and cell and molecular biology. Bioinstruments and biotechniques are being used to investigate and assess the biocompatibility of bio degradable polymers as a fundamental connection between novel biomaterials and the host tissue[212–216]. Quantitative methods can be applied while assessing host tissue response to extra cellular matrix (ECM) biomaterials[217]. Apart from its contribu tion to mechanical integrity, ECM plays a crucial role in signal ling and regulating growth, upkeep and tissue regeneration. ECM works in concert with solubilised signals from growth factors and hormones to regulate gene expression in a tissue-specific manner through many transduction mechanisms[218–220]. The use of tis sue-engineered scaffold as ECM substitute could also be considered[221].

ECM is a dynamic structure that actively remodels the cells that it interacts with[222]. Creating scaffolds that more closely mimic the biological characteristics of natural ECM is a key tissue engineering aspect[223]. Deconstructing mature ECM and com prehending its intricate roles in mature or renewing tissues is challenging. Being dynamic, ECM undergoes continuous com positional and structural changes as tissues grow, change, mend and mature. Biomaterials researchers have tried to simulate its functionalities in numerous manners. Decellularised tissues or organs can provide tissue-engineered biological ECM if techni ques to create a ECM mimicked from purified components are not available *de novo*[224]. The use of xenogeneic materials as ECM components is possible due to the relatively high evolu tionary conservation level. Various tissue engineering cellular matrices are successfully employed in animal models, and reg ulators have approved a few xenogeneic products for clinical trials. The bladder, small intestine submucosa and decellularised heart valve are few such examples[225]. As decellularised matrix preserves the 3-D microarchitecture of the original ECM and a complex collection of molecules, the use is expected to grow. Numerous xenogeneic and decellularised medical items are cur rently commercially available. However, their use has issues that need to be addressed despite the benefits. These include the immunogenicity potential of the material, the likely presence of infectious agents, variation in preparations, and the difficulty in fully identifying and characterising the bioactive ingredients in the material.

A naturally found biomaterial is acknowledged in regenerative medicine due to its inductive properties and is widely used as a surgical mesh device in clinical applications. Substances from secreted structural and functional elements of resident cells are often used to make ECM material, and the source tissue deter mines its precise makeup and ultrastructure. The intricate mix ture of molecules making up the ECM scaffold is structured in a special customised 3D design from which ECM is sourced. ECM signals trigger cell migration, proliferation and differentiation[226–229]. The original ultrastructure and composi tion of ECM need to be preserved for biological scaffolds for the best result during tissue/organ decellularisation[230–235]. The tis sues and organs from which ECM scaffold materials are obtained include blood vessels[236–238], ligaments[239], heart valve[158,240–243], skin[244], neuron[245–249], skeletal muscle, tendon[250–252], small intestinal submucosa[253,254], heart[255,256], urine bladder[257–259] and liver[260]. The most extensive research on the links between structure and function was documented for the small intestinal submucosa and urine bladder. Unless treated with cross-linking agents, the breakdown products of ECM scaffold materials are significant bioactive contributors to constructive remodelling[261,262]. An unfavourable host remodelling response occurs when the cellular material from the source tissue does not remove completely[263–266].

The prevailing regenerative medicine and tissue-engineering techniques aim at repairing the damaged tissues[267]. Auto-graft ing using the tissue of a patient to promote recovery is the gold standard. However, due to numerous constraints the harvest limit of specific tissues, the duration and extent of surgery, and donor-site morbidity, finding alternatives is necessitated[268]. As the number of biomaterials being produced and researched grows, using them for the purpose seems appealing. Biomaterials form a significant part of the $400 billion global medical device market, but being foreign substances unfavourable immunological responses due to these could pose serious threats that can sig nificantly reduce patient outcomes and thus the current lower clinical use rate[269,270]. The negative responses often prevent the body from bending, leaving the patient suffering from unbearable pain, excessive inflammation, tissue damage and even medical device rejection. A significant obstacle to developing successful tissue-engineered and biomaterial-based medical interventions is a lack of thorough knowledge of the interactions between the immune system and biomaterials. Detailed characterisation to understand the immune response to biomaterials is necessary before clinical translation.

Tissue-engineered heart valves have not succeeded in human trials because of unfavourable foreign body responses and immunological rejection[271]. A key factor influencing effective clinical outcomes is the host immunological response to biomaterials[272]. Mechanical and physical characteristics of bio materials like porosity, degradability and mechanical strength largely determined their design. Immunoevasive (inert) bioma terial has been used for decades to stop unintended inflammation. More attention is being recently paid to the characteristics of biomaterials to control host immune response, thanks to the steady and notable rise in research articles over the last 5 years with the information on immunomodulatory biomaterials for tissue engineering and/or regenerative medicine flooding in the Web of Science and PubMed. Cross-disciplinary researchers have become more interested in controlling immune responses to bio materials to achieve tissue engineering or regeneration goals.

Biomaterials can be tried to induce immunological tolerance as a possible therapy for autoimmune illness or to prevent implanted graft rejection. The fewer dedicated articles in scientific databases indicate that the biomaterial sector needs a thorough investiga tion of toxicity levels before applying. The host immunomodula tion response to an implanted biomaterial could alter from one producing fibrous encapsulation or scar tissues to one promoting tissue integration and functional remodelling[273–275].

A thorough comprehension of long-term interactions between biomaterials and the immune system will enable the development of immunomodulatory biomaterials that can aid patients with immuno-mediated rejection of biologics, autoimmune illnesses, chronic inflammatory disorders and organ/graft rejection. Thus, a tried-and-tested method to assess the immune response of biomaterials is necessary for tissue engineering and repair. The International Organisation of Standardisation (ISO) guidelines is currently meant for in-vitro assessment of biomaterials[276]. The need to develop in-vitro assays for accurate prediction of biomaterial acceptance and to improve in-vitro protocols for biomaterial evaluation was highlighted by a multicenter investigation. It concluded that in-vitro evaluations of biomaterials used today are inadequate to forecast in-vivo acceptance[277]. The duration and cost of the study could be significantly reduced, and the quantity of inappropriate biomaterials entering a clinical setting ensures enhanced safety of the volunteer by employing the 3Rs, reduction, refinement and (animal) replacement. Ideally, the process to assess the immunological response of a biomaterial could be standardised to facilitate cross-material comparisons. It would include the evaluation of biological pathways in the case of medical devices, as per ISO standards (ISO-10993). That a biomaterial meets the standards for use in clinical settings is also the regulatory criteria of the USFDA. As immune responses to biomaterials are critical to determining the clinical outcomes, immuno-testing needs to be accounted for while evaluating. Assessing immunological responses to biomaterials could help determine the likelihood of in-vivo acceptance and reduce the risk of unfavourable clinical outcomes.

The chance of a biomaterial being accepted *in vivo* is predicted through its immune response *in vitro*. Examining the immune system and biomaterial interactions while developing a biomaterial is critical, so also its preclinical trial emphasising residual toxicity assessment. A complicated series of interconnected actions are triggered when a biomaterial is inserted into a living host. The initial phase is a foreign body response when the biomaterial is accepted as foreign by the host immune system. If the initial inflammatory response is not controlled, unintended biomaterial degradation by immune cells by releasing enzymes and other reactive materials and fibrous encapsulation of the biomaterial might occur. Tissue regeneration and remodelled microenvironment is the best-case scenario[278]. The biomaterial surface is coated with host plasma proteins before recruiting immune cells to set off the inflammatory response, thus providing a chemoattractant gradient. Complement family members are among such proteins which opsonise the implanted biomaterial and initiate an innate immune response. After being activated upon interaction with the biomaterial, these proteins effectively recruit immune cells (especially C3a and C5a). The human immune response is needed to regenerate and repair tissues after implantation, but the excess response may result in biomaterial failure. A viable approach to reduce the rejection of a biomaterial is to minimise excess adsorption of the complement protein formed due to the body's response to the implanted biomaterials[279].

The circulating polymorph nuclear leucocytes (primarily neutrophils) are the first recruited (in hours) cells during acute inflammation to an implanted biomaterial. These leucocytes eliminate detritus and initiate host responses by piercing the adjacent tissue. Neutrophils are often removed within a few days in a fresh wound. However, they remain in proximity to the implanted biomaterial for several weeks, exhibiting unknown effects. It was suggested that neutrophils participated in the immunoresponse of the host to an implanted biomaterial. Neutrophil extracellular traps and excessive neutrophil recruitment and persistence might cause the biomaterial to become fibrous. It may hinder tissue-biomaterial integration, leading to tissue rejection and biomaterial failure. The exact role of neutrophils needs clarification as research has yielded inconsistent findings. Neutrophils release various cytokines and chemokines to control immune response. These include the factors that attract and activate monocytes, macrophages, dendritic cells and lymphocytes. Neutrophils, monocyte chemoattractant protein (MCP-1) and macrophage inflammatory protein (MIP-1β) are increased by interleukin (IL-8)[280]. The monocytes circulating in the blood activate as acute inflammation turns chronic, move to the injury site (due to chemoattractant molecules) and differentiate into macrophages after extravasating the tissue. As macrophages release vital angiogenesis and tissue reorganisation enzymes, they are essential during the initial wound-healing stage. Macrophages exhibit a pro-inflammatory (M1-like) phenotype in acute inflammation. They secrete cytokines like IL-6, IL-8, TNF-α, IL-1α and IL-1β. The anti-inflammatory M2-like macrophages (more specifically, the M2 subtype M2c) are essential in tissue remodelling in long-term inflammation. They achieve it by secreting cytokines like IL-4, IL-10 and TGF-β as wound-healing and tissue regeneration factors. TGF-β not only has antifibrotic properties but also has a pivotal role in the progression of fibrosis. It is possible that this dual function of TGF-β was contingent upon its cell source and immunological environment. Further, the binary M1/M2 nomenclature for macrophages is thought to be oversimplified, as the local microenvironment could likely induce and modify a range of phenotypes while polarising macrophages.

A deeper insight into immune cell heterogeneity (macrophages and the function in immune response) may make it feasible to develop treatments targeting particular cell subtypes[281]. M1 macrophage contributes to the early vascularisation phase, but its persistence may injure the tissue as they secrete pro-inflammatory chemicals later. M2 macrophage could predominate as tissue regenerates, yet its overabundance could lead to encapsulation of the implanted biomaterial with fibrous matter, thereby hindering the healing process. A M1–M2 macrophage shift indicates the effect of the implanted biomaterial on the host. In chronic inflammation, macrophage polarisation into M1 and M2 phenotypes is mediated by T-helper (Th1 and Th2) cells. 'Frustrated phagocytosis' leads to the macrophage membranes fusing and consequently produce foreign body giant cells (FBGCs), as the macrophages try to boost their phagocytic ability to degrade the bigger implant. FBGCs production is also stimulated by the secreted IL-4 and IL-13 by the mast cells and Th2 cells. FBGCs stay at the implantation site for the duration of biomaterial implant and generate derivative species that eventually break down the implanted biomaterial. As inflammation continues to

worsen, collagen is overproduced by the fibroblasts, which cover the biomaterial surface and form a fibrotic collagenous capsule. It isolates the implanted biomaterial, leading to a failed attempt owing to the absorption of host tissue. If inflammation remains unresolved and persistent, and the cells are continuously and excessively drawn to an implanted biomaterial, FBGCs generation and ultimate rejection of biomaterial shall result due to this prolonged chronic pro-inflammatory milieu.

Excessively tainted biomaterial with endotoxins may generate pro-inflammation[282]. If the acute inflammatory phase is resolved and the inflammation is not excessive or persistent, immunomodulatory molecules and biochemical signals released by immune cells (especially macrophages) could lead to the microenvironment remodelling as modulated by host progenitor (stem) cells, fibroblasts and endothelial cells. Collagen and other macromolecules (like proteoglycans) are produced by fibroblasts to help create new ECM. Endothelial cells assemble to form new blood vessels that enable the exchange of nutrients with the growing tissue. Thus, accomplishing the intended shift from host vasculature development to the creation and integration of new tissue and effective wound healing and tissue repair was possible, which shall ultimately result in the successful regeneration of a functional implanted tissue[283].

Challenges and prospects

Regenerative medicine has come a long way, although numerous obstacles are standing in the way of its successful application in clinical settings. These challenges include issues related to science, technology, law, ethics and the economy. The biggest obstacle in organ transplantation and cell-based therapies is immunological rejection. Donor-derived allergenic cells could potentially elicit an immunological response that could reject the transplant and require a long-term immunosuppressant. The creation of universal donor cell lines, induced immunological tolerance, and genetic engineering of cells to elude immune detection are few strategies that could help reduce immune rejection. A functional vasculature needs to emerge at the implant site for the designed tissue/organ to receive enough oxygen and nutrients. The viability and health of a constructed tissue are limited by poor vascularisation that could lead to necrosis and reduced utility. To increase vascularisation, co-culture approaches, biomaterial-based solutions and biofabrication techniques incorporating endothelial cells and antigenic agents are some strategies.

Cost efficacy and scalability are important factors in determining the feasibility of regenerative medicine, as well as its wide acceptance and medical applications. Producing complicated tissue constructs in large quantities while preserving quality and uniformity has logistical and technical barriers. Scalable manufacturing platforms, cost-effective processing strategies and automation are required to increase productivity and reduce manufacturing costs. Use of human–animal chimeras, genome editing and embryonic stem cells has given rise to ethical concerns regarding the moral implications of regenerative medicine research and therapeutic applications. Adherence to ethical rules and legislation, stakeholder engagement and open communication are necessary to strike a balance between advanced science and ethical values. Approval procedures for treatments based on regenerative medicine are complicated and lack uniformity. This makes it difficult to ensure safety, efficacy and quality to accelerate the transition of promising regenerative medicines from the bench to the bedside on a global scale.

To successfully negotiate the regulatory environment and provide prompt market access for novel therapies, cooperation among researchers, regulators, industry stakeholders and patient advocacy organisations is crucial. Numerous novel approaches and evolving technology hold promise to tackle the aforementioned bottlenecks to fully realise the potential of regenerative medicine. Advanced tissue engineering techniques aim to replicate the complexities of biological tissues and organs. Examples of such approaches are organoids, organ-on-a-chip platforms, and vascularised constructs. It will soon be possible to create functional tissues and organs for transplantation and disease modelling by employing cutting-edge manufacturing techniques in conjunction with biomaterials, stem cells and bioactive substances. Compared to traditional approaches, next-generation stem cell therapies like tissue-specific progenitor cells, exosome-based therapies, and modified stem cells offer improved safety, efficacy and scalability.

Therapeutic applications of engineered stem cells with enhanced immunomodulation ability and decreased tumorigenicity in autoimmune diseases, inflammatory conditions and tissue damage is an early possibility. Precision medicine could customise regenerative medicine as per the patient profiles uniquely by using proteomic, transcriptomic and genomic data. Customised outcomes are possible through patient-specific gene editing technologies and tailored biomaterials. Specialised MSCs are critical tools in the advancement of regenerative medicine and illness management. Osteocytes, chondrocytes, neurons, and other cell types could be used for human wellness. These cells could regulate immunity in addition to being easily separated and safely transplanted at the wound site. The efficacy of MSCs is proven through several in-vivo and in-vitro studies in animal models for various disorders, although the results of the clinical trials have not been that promising. MSCs are widely employed in treating numerous illnesses like heart failure, wound healing, tooth regeneration, etc. Stem cells could play a major role in treating neurodegenerative (like Parkinson's and Alzheimer's) diseases. Stem cells and their possible use in regenerative medicine are a hot topic and one of the most contentious areas of modern biology and medicine.

While many stem cells have been suggested in regenerative medicine; however, investigations on the safety and efficacy of pluripotent stem cells for use in clinical settings are far and few. Further, patent disputes and the lack of financial incentives for the biotechnology sector have been detrimental to collaborations and drag competitive stem cell research and development. The apathy and inability of public media to provide more false and misleading information has also been damaging. Nonetheless, the initial comments of the recent clinical trials of cardiac stem cells seem overly optimistic. Yet, the growing interest in stem cells with the early signs of clinical trials shall lead to a deeper understanding of their traits and potential that would lead to exciting new vistas in regenerative medicine.

The conceptual and technological difficulties while adopting advanced laboratory and sound clinical practices need to be overcome. Efforts to promote endogenous repair as a substitute for grafting may be ensured in addition to investigating the critical characteristics of various stem cells. MSCs hold great promises as standalone cell-based therapeutic agents owing to their remarkable self-renewal, tissue differentiation, immunomodulation and

regenerative traits. They recruit injured tissues, disperse therapeutic gene or agent(s), and exhibit peregrine effects to draw effectors cells needed to advance the benefits of regenerative medicine and illness management. Recent research has focussed on improving the therapeutic potential of MSCs through genetic engineering by expressing foreign genes, carrying therapeutic cargo or exhibiting targeting moieties to increase their survival and therapeutic efficacy. These strategies would ensure the dosaging of therapeutic MSCs for active medications at the target site and eliminate the need for repeated systemic delivery.

Further extensive research is needed to maintain or improve the affinity of modified MSCs towards inflammatory and malignant tissues for healing and regeneration and also to fully understand the behaviour of natural MSCs in healing and differentiation. To make MSCs clinically transferable, their quality and safety profile must be met as per standards and optimal ex-vivo treatment and preservation techniques need to be established. The two areas where MSCs have demonstrated great potential are tissue repair and tailored therapy. As is the scenario in the past decade, MSC-based therapy is anticipated to become even more popular as novel and undiscovered traits of MSCs are revealed. This review has attempted to delve into techniques to alter MSCs that could improve functionality and efficacy further. Overcoming technical obstacles related to altering MSCs is by no means simple, but it is a work worth embarking on considering the possible benefits. Interest in the field still grows with the advent of cutting-edge technology platforms and unique stem cell sources, especially using nanomaterials in research and medical applications. Given the diversity of the various tissue types in the human body (like electroactive, contractile, stiff, soft, 2D layered and 3D architecture), regenerative medicine research and development faces severe and complex challenges. Nanomaterials could be used to develop novel scaffolds, surfaces for medical devices, and/or particles with the capacity to affect the fate of stem cells in multiple demonstrated manners.

ECM-mimicking technique shall help in the cellular proliferation of pluripotent stem cells for self-renewal. Creating a nanoscaffold that mimics the embryonic process *in vivo* or transferring genetic materials by nanoparticles based on the understanding of embryonic stem cell biology through scientific rationale and collaborative approaches could be a directed differentiation strategy. Assessing the durability and long-term therapeutic effects of biomaterial-based therapies in COVID-19 patients needs long-term safety and efficacy evaluation. Longitudinal studies are necessary to track possible sustained side effects (like fibrosis, carcinogenesis and chronic inflammation) over time. Complex issues associated with treating COVID-19 using biomaterials necessitate multidisciplinary (materials science, immunology, virology and clinical medicine) research. The involvement of an array of experts with expertise shall expedite translational research and help discover innovative solutions. Regenerative medicine will eventually advance as safe, efficient and widely applicable biomaterial-based therapeutics to treat COVID-19 and other such infectious diseases in the future by addressing these issues.

Conclusion

Regenerative medicine is a special and relatively new field of medical sciences that holds high promises for the future. Of the various facets under it, stem cells and scaffolding (grafting) technology are the two major research and development areas in modern medicine and surgery. Their encouraging outcome, along with a deeper understanding of traits and potentials in early clinical trials, has led to numerous exciting regenerative medicine applications. Despite the many obstacles to the successful application in clinical settings, regenerative medicine has come a long way. The mesenchymal stem cells have high utility in tissue repair and tailored therapy including treating infectious diseases like COVID-19. Techniques to alter MSCs for improved efficacy and functionality are discussed in this article. Immunological rejection is a big challenge in cell-based therapies and organ transplants. Nanotechnology has paved the way for the development of novel scaffolds, medical device platforms and a multitude of applications of stem cells. Biomimicking nanoscaffolds seem a reality with advancements in scientific rationale, nanodevice technology, process automation, microfluidics, material engineering and directed collaborative strategies.

The use of biomaterials to treat COVID-19 and other such infectious diseases is an intricate biomedical issue that necessitates truly multidisciplinary and cross-disciplinary research, especially involving material science, immunology, virology and clinical medicine. Further, long-term safety and efficacy assessments are needed to ensure the durable, long-term therapeutic effects of biomaterial-based therapeusis of COVID-19 and other infectious diseases cases. Regenerative medicine is poised to advance as a safe, efficient and widely applicable biomaterial-based therapeusis to treat COVID-19 and other such infectious diseases in the future after addressing certain pertinent issues. Similarly, longitudinal studies over time are necessary to track the possible sustained side effects of clinical relevance like carcinogenesis, chronic inflammation and fibrosis. A matter of early medical investigation and validation is the therapeutic applications of the technically acceptable bioengineered stem cells for their role in enhanced immunomodulation, decreased tumorigenicity (as in autoimmune diseases), inflammation and tissue damage. Features like improved safety, enhanced efficacy and easy scalability are in the offing by advanced stem cell-based therapies like exosome-based therapies, tissue-specific progenitor cells and modified stem cells.

The cost efficacy of the product and scalability of the process are the determining factors in developing regenerative medicine that is techno-economically feasible. A scalable production platform, cost-effective processing strategy and optimal automation could increase productivity and reduce costs. There is a need to overcome the fundamental and technical challenges in the adoption of advanced laboratory techniques and internationally standardised (or accepted) clinical practices. Further, the ethical and medicolegal concerns, patent disputes and the lack of financial incentives by the governments for the biopharmaceuticals sector have dampened collaborative and competitive global stem cell research and development. Also, translational research and the discovery of innovative regenerative medicine solutions, even for ailments that are hitherto considered untreatable, could be expedited by involving the expertise from numerous quarters.

For wider medical applications and public acceptance of regenerative medicine, the approval procedures for treatments need streamlining, which are currently complicated and also lack global uniformity. A standard and uniform approval and application process at the global scale could ease the efforts in accelerating the translation of a promising regenerative therapeusis from the bench to the bedside and to ensure safety, efficacy and quality. Further, the cooperation among researchers, patient

advocacy organisations, regulators and industry stakeholders shall be crucial in successfully navigating the regulatory procedure and expediting the market access for such novel therapeutic interventions. Adhering to the ethical rules, medicolegal considerations and legislation, engaging the various stakeholders, and having open and seamless communication shall be necessary in balancing between the advanced medical sciences and the associated moral and ethical values.

Ethical approval

Not required.

Consent

Not required.

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Author contribution

A.K.S., M.A.S., A.M., and L.T.: methodology and writing – original draft; H.E.-H., M.D.Y., R.M., F.A.A., M.N.K., D.D., P.B., B.S.T., and Z.M.E.-B.: data curation and writing – original draft; M.S., G.B., S.R., S.B., K.B., P.S., and M.A.: validation and writing – original draft; R.K.M.: conceptualization, supervision, writing – review and editing; S.M.: writing – review and editing.

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