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# Nanofibers: An Effective Biomedical Tool for Burn Management

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***Abstract:*** ***The largest organ in the body and the organ that interacts most directly with the environment is the skin. As a result, the skin is susceptible to numerous injuries, including burns. Cell types, cytokines, mediators, the neurovascular system, and matrix remodelling work in concert to heal skin wounds. Through re-epidermalization, interactions between epidermal and stromal cells, angiogenesis, and habitation of hypertrophic scars and keloids, tissue regeneration technology significantly improves skin restoration. With the use of several skin substitutes, skin healing success rates for burn injuries have dramatically increased. For the reconstruction of skin tissue, we examine the use of cells, growth factors, scaffolds, or scaffolds seeded with cells in this review. We also compare the high efficacy and affordability of each therapy. We outline the key components, successes, and difficulties of cell-based therapy for minimising scar formation and enhancing the management of burn injuries.***

## I. INTRODUCTION

More than a million individuals experience burns every year in the USA alone, making it one of the most frequent injuries in the world [1]. The skin is harmed by heat, radiation, electricity, or chemicals, which results in a burn. Deep or extensive burns can have serious side effects, such as sepsis from a bacterial infection, shock from hypovolemia, or scarring tissue contraction from incorrect wound healing. Skin injury results in the death of skin cells, which causes a massive loss of body fluids, dehydration, electrolyte imbalance, renal failure, and circulatory failure to follow. An infection poses a major risk to the lives of burn sufferers. Due to the loss of protection provided by the skin's undamaged layers, burned skin is incredibly vulnerable to germs and other infections. Each of these side effects has the potential to kill or severely hurt the patient. In order to prevent burn injuries and save patients' lives, it is crucial to act quickly to treat them. This includes adopting the right treatment method and administering intravenous fluids and nutrients to counteract dehydration and replenish lost proteins. Due to the use of numerous skin grafts during the past few decades, the survival rates of burn patients have dramatically increased. Autologous skin grafts are frequently used, however they fall short in treating severe burns in individuals with small donor site areas [2, 3]. Skin substitutes, particularly those made of cells, are essential for solving this shortage. The combination of cell-sheets, scaffolds, cell-scaffolds, and hydrogels with substances that promote healing initiates, accelerates, and promotes wound healing and re-epithelialization, which reduces the formation of scar tissue and prevents complications from burn injuries. When compared to autologous skin replacement, skin replacements have demonstrated high efficacy and cost-effectiveness [12, 13]. We concentrate on examining the fundamentals, successes, and difficulties of cell-based therapy for skin tissue regeneration in the treatment of burn injury in this work. It is impossible to overstate how crucial a role the skin plays in maintaining homeostasis and shielding us from harmful environmental chemicals. It is continuously involved in a variety of functions, including signal perception, hormone, neuropeptide, and cytokine generation and activation [4]. It also regulates temperature and water balance. The epidermis, dermis, and hypodermis are the three primary layers that make up the skin, together with the appendages (hair, sweat and sebaceous glands, sensory neurons, blood and lymph vessels, etc.) that they form. [5]. Extracellular matrix (ECM) and different cells, including epidermal, stromal, endothelial, and neural cells, make up the total skin tissue. The fundamental components for usage in skin replacement and regeneration following an injury include cells, growth factors, and matrix. The epidermis, dermis, hypodermis, and skin appendages make up the complex tissue that makes up the skin [5]. The primary barrier separating the environment from internal organs and tissues is the first layer of skin, or epidermis. It is divided into five layers, or strata: the granular layer (stratum granulosum), the clear layer (stratum lucidum), the spinous layer (stratum spinosum), and the basal layer (stratum basale) [6, 7]. The keratinocytes, Merkel cells, melanocytes, and Langerhans cells are among the cell types that make up the epidermis, which is thin and stratified [8]. The majority of the epidermis's cells, or keratinocytes, are what give it its stratified structure and numerous, tight intercellular connections. Melanocytes are found in the basal layer (stratum basale) and create dendrites that can reach the spinous layer (stratum spinosum), where they produce melanin, a pigment that absorbs UV radiation and shields the skin from its harmful effects [7].

The stratum basale (above the basement membrane), which is home to Merkel cells, which are in charge of mechanic perception, is also where these cells are located. The stratum spinosum is home to Langerhans cells, which function as antigen-presenting cells and engulf infections and other foreign objects to aid in immune defence [5]. Keratinocytes, which make up the majority of cells in all epidermal layers and begin to differentiate in the basal layer, assure keratinization [9]. Keratinocytes become anucleated and have clustered keratin in the stratum granulosum while developing and migrating to a skin surface. Then, in the stratum corneum, they flatten and perish. The strong intercellular connections of corneocytes (differentiated keratinocytes), which are expelled due to desmosome loss, inhibit water evaporation and skin dryness [10]. Desquamation, or the peeling of the skin, involves this process. However, because the epidermis lacks a direct blood supply, nutrients are delivered and leftovers are eliminated through the epidermal basement membrane by diffusion from the dermis underneath [8, 11]. ECM elements include collagen type IV, nidogen, laminin, and perlecan combine to produce the semipermeable basement membrane [12, 13]. The dermis, a thick layer underneath the epidermis, is mostly made up of connective tissue and ECM [7, 8]. It is more diverse than the epidermis and contains a variety of structures, including blood and lymphatic arteries, sweat and sebaceous glands, and hair follicles. Papillary and reticular are the two layers that can be distinguished. The first one is thin and superficial and is displayed by the flowing connective tissue, which is made up primarily of capillaries and reticular, elastic, and unorganised collagen fibres of type III. The latter is thick and deep and is represented by compact connective tissue, which has collagen (type I and III) fibres that are crosslinked elastic and well-organized, as well as big blood vessels [7]. The connective tissue mostly consists of collagen, which gives the skin its strength, but it also contains elastin (which gives the skin its elasticity and flexibility) and proteoglycans (which provide the tissue its moisture and viscosity) [12]. Proteolytic enzymes (matrix metalloproteinases), which are produced by fibroblasts, neutrophils, keratinocytes, and other skin cells and are involved in a variety of skin activities, constantly remodel it [14, 15]. The primary cell type of the dermis is called fibroblasts, which also secrete numerous growth factors (such as TGF-), cytokines (such as TNF), and matrix metalloproteinases. Fibroblasts also create components of the ECM, including as collagen, elastin, and proteoglycans. This "cocktail" ensures keratinocyte proliferation and differentiation as well as the creation of the ECM [16]. Fibroblasts are therefore crucial for wound healing and skin remodelling [17]. Additionally, the dermis is home to numerous immune cells, including leukocytes and dendritic cells, which can migrate through it [4]. The hypodermis (subcutaneous tissue) is situated between the dermis and muscles [7]. Energy is provided, the interior tissues and organs are protected from injury and the cold, and it takes part in the creation of hormones such estrone and leptin [4]. Adipocytes arranged in lobules create the hypodermis. These lobules include nerves and a lymphatic and microvascular network that assures the transport of nutrients and oxygen, and they are divided from the connective tissue by septa [7]. The skin appendages [6, 18], such as nails, hair follicles, sweat glands, and sebaceous glands, are also a part of the skin structure. Basal cells in the basement membrane generate the hair follicles, which are found all over the body (except from the palms and soles) and are in charge of regulating body temperature and physical perception [6]. Nails are made up of keratinized and dead cells [7]. Sebaceous glands, which generate sebum (oily substance), near the base of hair follicles, guarantee that the skin and hair are lubricated and waterproof [19]. Ceruminous and mammary glands are modified sweat glands that are in charge of producing cerumen and milk, respectively [7, 21]. Sweat glands discharge sweat onto the skin's surface [20]. Recent research has demonstrated that the skin has its own stem cells. These cells are fairly varied and may be further classified into subgroups including epidermal, follicular, hematopoietic, melanocyte and sebaceous gland stem, mesenchymal stem-like, and neural progenitor cells [6, 22].

## II. METHODS FOR REGENERATING SKIN TISSUE

Skin wound healing is a methodical process that typically consists of four overlapping classic phases [23, 24]: hemostasis (coagulation), inflammation (mononuclear cell infiltration), proliferation (epithelialization, fibroplasia, angiogenesis, and formation of granulation tissue), and maturation (formation of collagen deposits or scar tissue). The origins, the severity and size of the burn, the patient's general health, and the types of graft or materials used to cover burn wounds are just a few of the variables that affect how the skin heals following burn injuries. The effects of the healing process may vary depending on how severe the burns were. Burns that are superficial heal in two weeks with little scarring. Within a few hours of the injury, keratinocyte migration from skin dermal appendages ensures the re-epithelization of partial thickness burns. Due to the need for quick wound closure, healing in severe burns begins at the borders rather than the centre [25,26,27]. Due to dendritic cells secreting a number of substances, the early cell proliferation is accelerated, ensuring quick burn healing. Therefore, substances that promote dendritic cells are viewed as medicines for bettering burn wound care [28]. Hypoxia-inducible factor 1 [29] and angiogenic cytokines like VEGF and CXCL12 [30] are responsible for inducing angiogenesis during burn healing, and it is also ensured by an increase in endothelial progenitor cell blood levels that correspond with the burned skin area [30, 31].

The TGF- pathway, which promotes remodelling and scar formation, is activated, ensuring greater contraction [26]. Burns may have systemic consequences in contrast to other wound types [32, 33], affecting nearly all bodily systems and altering the function of the lungs, kidneys, heart, liver, gastrointestinal tract, bone marrow, and lymphoid organs as well as multiple organ dysfunction syndrome [32]. Tumour necrosis factor alpha (TNF-) and interleukins 6, 8, and 1-beta, which have systemic effects, are inflammatory mediators that are secreted at the burn site. Their serum concentration and burn surface area are correlated. The risk of infections, multiple organ dysfunction syndrome, and death is thought to increase as their concentrations grow [34,35,36].

## III. KINDS OF CELLS EMPLOYED IN SKIN REGROWTH

The tissue-engineered in the skin utilised for burn therapy is primarily made up of cells. They can be broken down into three primary categories: autologous, allogeneic, and xenogeneic, and contain both stem and somatic cells. The use of autologous cells is one of the key trends in selecting a cell type for patient therapy since they do not result in immune rejection and have a low tumorigenicity due to the absence of epigenetic alterations. Animal cells are no longer frequently used to regenerate skin tissue; instead, ECM or its components, which they produce, are. Plant stem cells, which are frequently used in cosmetics, are intriguing since they offer a much wider range of applications than animal and human cells. The tissue-engineered skin utilised for burn therapy is primarily made up of cells. They can be broken down into three primary categories: autologous, allogeneic, and xenogeneic, and contain both stem and somatic cells. The use of autologous cells is one of the key trends in selecting a cell type for patient therapy since they do not result in immune rejection and have a low tumorigenicity due to the absence of epigenetic alterations. Animal cells are no longer frequently used to regenerate skin tissue; instead, ECM or its components, which they produce, are. Plant stem cells, which are frequently used in cosmetics, are intriguing since they offer a much wider range of applications than animal and human cells.

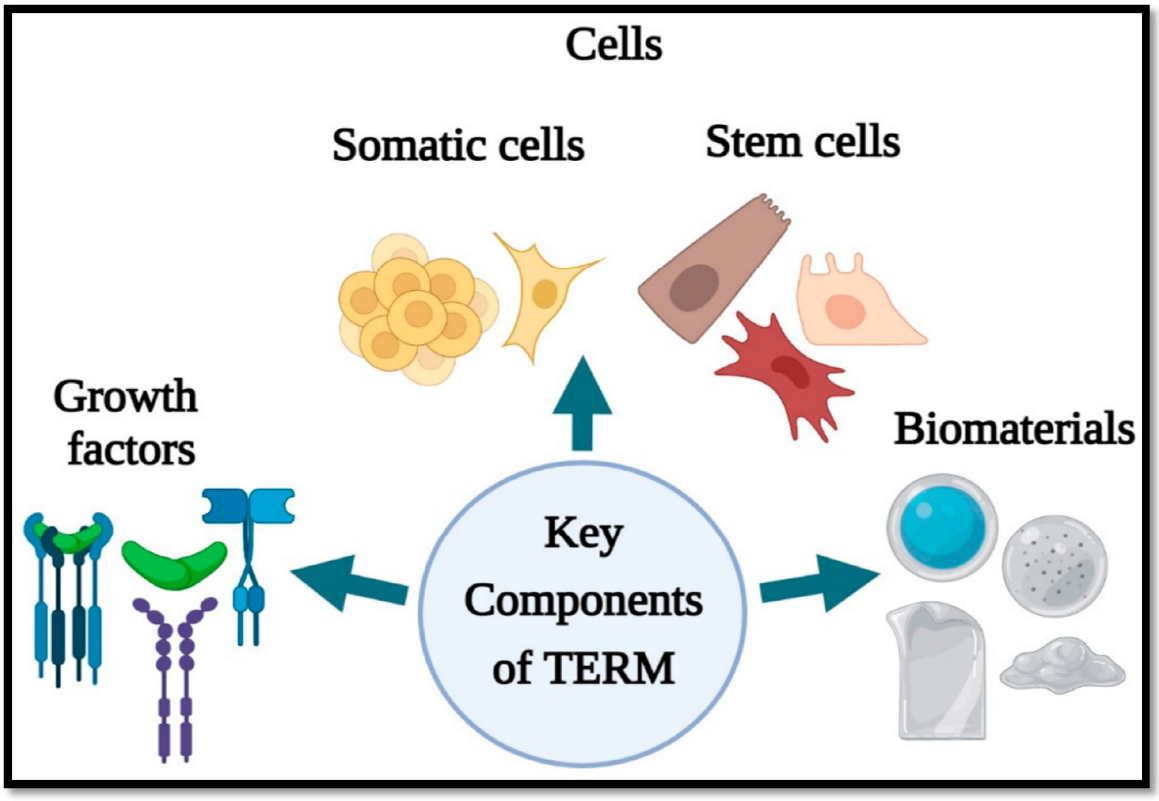



Fig No. 1 shows Use of stem and somatic cells to regenerate skin tissue

Common cells utilised in burn and wound healing products include keratinocytes and fibroblasts [41]. The majority of the epidermis' cells, or keratinocytes, are what give it its stratified structure and many, tightly-bound intercellular connections. The primary cell type of the dermis, fibroblasts, secrete a variety of growth factors (TGF-), cytokines (TNF), and matrix metalloproteinases that ensure the creation of the ECM and the proliferation and differentiation of keratinocytes [16].

Keratinocytes are found in commercial goods including Epicel, Cryoskin, and BioSeed-S; fibroblasts are found in Dermagraft, TransCyte, and Hyalograft 3D; and a mixture is found in Apligraf, Theraskin, and OrCell. The utilisation of these cells makes it possible to produce standardised product batches on a big scale. However, the majority of these materials are non-permanent bioactive dressings that include growth factors, ECM, and cytokines for successful skin restoration [41, 42, 43]. Allogeneic fibroblasts and keratinocytes frequently exhibit immune rejection, however this is primarily seen in allogeneic keratinocytes, which can be accounted for by variations in HLA expression and cytokine production [45]. Due to their high expansion capacity, low immunogenicity, and intense secretion of bioactive molecules like basic fibroblast growth factor, vascular endothelial growth factor, and keratinocyte growth factor, foetal fibroblasts are of particular interest because they can significantly improve skin repair. However, their use is constrained by moral dilemmas [46,47,48,49]. Because they have beneficial characteristics including a fast rate of proliferation, are accessible, and retain their potency and differentiation potential for a long time, epidermal stem cells (ESC) are of special interest for the regeneration of skin tissue [65, 82]. They belong to the heterogeneous or autogenous origins group of skin stem cells. ESC are primarily related to the regeneration of skin [17]. They are uncommon, seldom divide, and produce cells with short lifespans and quick division rates that are essential to the regeneration process [65]. They can be found in the base of sebaceous glands and the bulge region of hair follicles, but their main population, which is in charge of skin repair, is found in the basal layer of the epidermis [6, 65]. However, after a number of passages, we may encounter progressive aneuploidy or polyploidy as well as mutation accumulation when working with ESC culture. Furthermore, ESC are not constrained by ethical concerns because they can be readily extracted from the patient's epidermis and transplanted to the same patient. Epidermolysis, cutaneous and ocular injuries, etc., can all be successfully treated with grafts containing autologous holoclones ESC [83, 84]. Mesenchymal stromal cells (MSC), which can come from a variety of tissues, including the skin as previously indicated, exhibit characteristics that are comparable to but not identical to those of ESC.

They are capable of producing cells from the mesodermal, ectodermal, and endodermal lineages and have a high differentiation potential and some degree of flexibility. MSCs can also be used in medicine thanks to their paracrine, trophic, and immunomodulatory capabilities. By producing growth factors, cytokines, and chemokines, MSC can travel to the wounded tissues, differentiate, and control tissue regeneration. Their anti-inflammatory cytokine production and inhibition of the proliferation of T cells, B cells, and CD4+ and CD8+ natural killer cells serve as the foundation for their immunomodulatory function. Because they lack the co-stimulatory proteins CD40, CD80, or CD86 as well as class I and class II MHC molecules, MSC are thought to be hypoimmunogenic. As a result, there is a low chance of immunological rejection after allogenic MSC implantation. Adipose-derived stromal cells that have been isolated from the stromal vascular fraction are frequently employed in burn therapy because they are easy to obtain and promote improved healing processes.

They are widely used because it has been shown that they retain their therapeutic properties even after being frozen. It is important to note that even freshly extracted stromal vascular fraction has been shown to be useful in burn therapy, however it can produce higher levels of inflammatory mediators than stromal cells obtained from adipose. However, there are still not enough randomised controlled preclinical and clinical trials. The MSC derived from bone marrow (BMSC) needs special consideration among the MSC obtained from other tissues (adipose tissue, umbilical cord, etc.). They can also differentiate into tissues with mesodermal, ectodermal, and endodermal origins thanks to their plasticity. BMSC are regarded as having a role in skin formation. According to studies, bone marrow can produce fibroblast-like cells, which are found in the dermis and actively proliferate in the skin throughout the regeneration processes, in addition to hematopoietic and mesenchymal cells [69]. The tumour microenvironment may modify the angiogenesis capacity and anti-tumor response, which could be detrimental to BMSC. Additionally, they could produce tumor-associated fibroblasts and change the phenotype of healthy immune cells into one that promotes tumour growth and immunosuppression. But these days, induced pluripotent stem cells (iPSC) are the focus of attention when it comes to tissue regeneration. By employing somatic cell reprogramming as a magic wand, we can create patient-specific cells with a customised phenotype and use them in clinical settings.

Dermal fibroblasts, melanocytes, and keratinocytes are the most often employed cells for cell reprogramming because they are simple to obtain and separate from punch biopsies. Dermatology applications for iPSC technology are now possible thanks to research demonstrating that both murine and human iPSC can be developed into dermal fibroblasts, keratinocytes, and melanocytes. It's interesting to note that fibroblasts produced using this method sometimes exhibit improved qualities as compared to their parental fibroblasts, such as greater ECM production. This could be a result of the altered epigenetic signature that happens during iPSC differentiation and is essential for their application in skin tissue regeneration.

## IV. GROWTH FACTOR TREATMENT

Pro-epidermal growth factors are administered as part of growth factor therapy to speed up the healing of wounds. These growth factors are bioactive chemicals the body secretes, and their purpose is to promote the expansion of cells involved in inflammation and skin wound healing. They include substances that promote angiogenesis (platelet-derived growth factor [PDGF]; vascular endothelial growth factor [VEFG]; epidermal growth factor [EGF]; hepatocyte growth factor [HGF]); anti-scarring [TGF-ß3]; epidermal tissue regrowth; and stromal cell growth [FGF]).

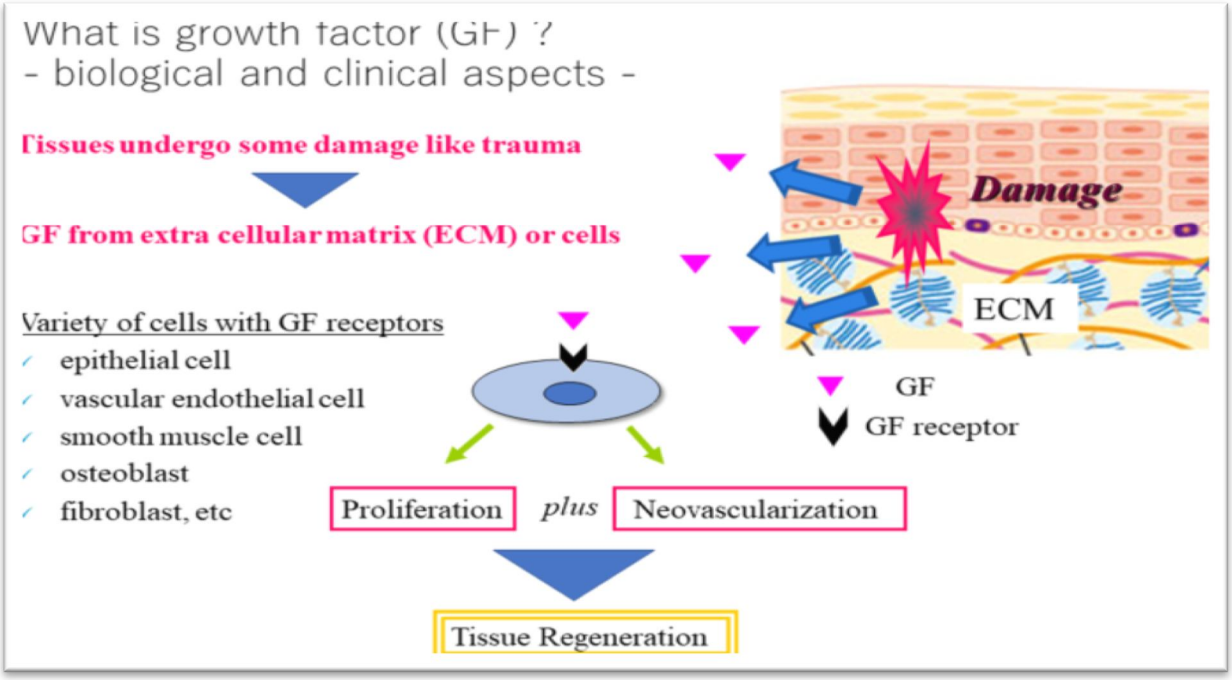



Fig No. 2 Shows Treatment using growth factors to restore skin tissue

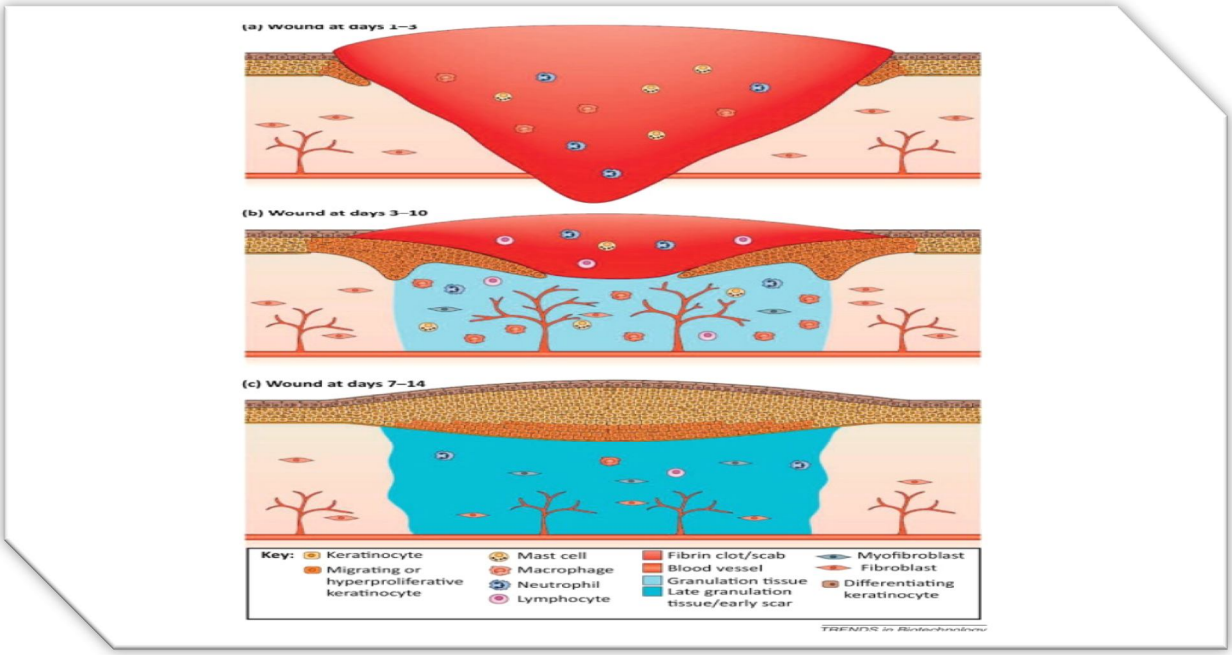
After a burn damage, growth factors like EGF and HGF are used to enhance re-epithelialization. It has been demonstrated that EGF and HGF promote epithelial cell motility, growth, and proliferation. Investigations into different delivery methods and their potential for skin tissue regeneration are ongoing. PDGF and VEGF can encourage angiogenesis at a defect site. Although PDGF-BB is FDA-approved for the treatment of diabetic ulcers, it has a poor track record in clinical trials, perhaps as a result of proteolytic enzyme damage or inadequate PDGF-receptor expression. A phase I trial demonstrating the safety and effectiveness of VEGF in the treatment of chronic wounds demonstrated high efficacy in in vivo studies. Both PDGF and VEGF must be continuously administered over a therapy time to encourage vascular formation, which has prompted research to create delivery methods with sustained release. For instance, Tan et al. found that collagen scaffolds loaded with VEGF dramatically accelerated the healing of diabetic rats' wounds, increased the tissue level of VEGF, and stimulated angiogenesis. Additionally, Gorkun et al. demonstrated the ability of VEGF-induced spheroids from adipose-derived stromal cells enclosed within modified fibrin gel to create a tubule-like network, suggesting a potential novel strategy for promoting angiogenesis in a wound and enhancing skin tissue regeneration. In the foetal and adult wound healing processes, TGF- isoform concentrations differ; in the former, TGF- 3 concentration is high, but TGF-1 and TGF-2 isoforms are absent or present in very small amounts, whereas in the latter, the situation is reversed, and the high TGF-1 and TGF-2 concentrations are brought on by platelet degranulation and synthesis in monocytes during inflammation. When TGF-1 and TGF-2 isoforms were suppressed and externally introduced TGF-3 isoform, the wound healing took place with less notable scar formation than that in the control. The complex nature of molecular pathways prevents scarring, however inhibiting all three isoforms did not guarantee this. Avotermin (TGF-3) was well tolerated and guaranteed scar reduction, according to clinical trials. Growth factors are frequently given locally (topically) to skin wounds. Growth factor therapy has the benefit of promoting healing by utilising the body's own cells. Its use may also hasten the healing of wounds, reducing the patient's incapacity or discomfort to a larger extent. Particulate systems, scaffolds, hydrogels, and their mixtures are just a few of the delivery methods available to guarantee growth factor stability and controlled release in wounds. In addition, although no studies have been found that have used microneedles or jet injectors to treat burns, they are potentially interesting.

It is rarely associated with systemic negative effects because it is frequently used topically. While VEGF is generally thought to assist burn healing, for instance, high VEGF serum levels can result in anasacra, edoema, and edema-related burn sequelae. The hypertrophic scarring can be caused by EGF and PDGF.

## V. SCAFFOLD TO HELP CURE SKIN WOUNDS

The various dressings and tissue-engineered constructions (Table 4) used in burn therapy depend heavily on biomaterials. They are primarily used to mimic the skin's ECM, which is composed of collagen, elastin, proteoglycans, nidogen, laminin, and perlecan [20, 21]. Collagen gives the skin strength, elastin ensures its elasticity and flexibility, and proteoglycans give it hydration and viscosity [20]. Biomaterials of different origins (natural, synthetic, or semi-synthetic) are used in skin grafts and substitutes; the choice of these materials during the scaffold fabrication process is crucial as it can affect in situ regeneration due to their properties that control cell behaviour and facilitate the formation of new tissue.




Scaffolds are used in Fig. No. 3 to promote wound healing and skin tissue regeneration.

The majority of goods on the market now either include collagen or decellularized tissues. Collagen types I and III are a key component of skin, so it is not surprising that the product design will resemble original tissue more closely than other designs. The majority of researchers and producers attempt to enhance collagen's weak mechanical qualities by cross-linking it or reinforcing it with synthetic substances like polylactide, polycaprolactone, and its copolymers. For example, the collagen gel in TranCyte is reinforced with nylon mesh and covered with a silicone film, the latter of which allows the preservation of a moist environment. Because they need particular raw materials (especially allogeneic) and can trigger a severe immune response and calcification (especially xenogeneic), products made from decellularized materials have more clinical constraints than collagen-based scaffolds. The first FDA-approved skin substitute, Apligraf, comprises bovine collagen, which is noteworthy [87]. It is important to note that hydrogel, which is frequently used in tissue engineering, has demonstrated to offer the most beneficial circumstances for the healing of burns. Aside from collagen, other gels utilised in the creation of bio-ink and skin substitutes include fibrin, hyaluronic acid, chitosan, and alginate. The aforementioned collagen is also a gel. Hydrogels' 3D network structure and other characteristics, which are similar to those of the natural ECM and are easily modifiable, promote not only cell proliferation and differentiation but also in situ cell recruitment. Gels offer a sufficient moist environment that is beneficial for the healing of burns. Additionally, they have the capacity to deposit and distribute bioactive substances, which facilitate the healing process.

## VI. DELIVERY IS IMMINENT

The most popular type of cell-based product utilised in burn therapy right now is dressings [41]. However, due to their shape, treating large, complicated wounds with a heterogeneous surface profile is not an option. For these purposes, technologies like cell spraying and three-dimensional (3D) bioprinting were created. A versatile platform known as 3D bioprinting permits in situ cell deposition in accordance with the pattern of the wound. Cells are dispersed across gels in 3D bioprinting, and these mixes are employed as bio-inks. In order to provide better support for cells, the process frequently entails printing hydrogel layers that are then cross-linked using UV, enzymes, ions, etc. For an inkjet bioprinter, Campbell and Weiss originally proposed in situ 3D bioprinting. This delivery method is particularly intriguing since it can guarantee full-thickness tissue regeneration followed by vasculogenesis due to progenitor cell migration and angiogenesis. However, despite encouraging results, there aren't many research using this technology. The complexity of the machinery and commercial unavailability could be to blame for this. Campbell and Weiss first suggested in situ 3D bioprinting for an inkjet bioprinter. The ability of this delivery strategy to ensure full-thickness tissue regeneration followed by vasculogenesis due to progenitor cell migration and angiogenesis makes it particularly noteworthy. Nevertheless, there aren't many studies employing this technology despite good results. This could be due to the machinery's complexity and commercial unavailability. Only a tiny donor site can provide the necessary amount [61]. Spraying a homogeneous cell suspension onto a wound encourages cell growth and enhances re-epithelialization. Although cell spraying cannot completely replace conventional autografting, extensive partial thickness burns can be treated quickly and easily. Due to the early re-epithelialization following a cell spray, several problems (bad aesthetic outcome, hypertrophic scarring, contracture, etc.) may be avoided or reduced. As with 3D bioprinting, this technology is pricy and necessitates specialised tools, aseptic facilities, and highly skilled workers.

## VII. PROBLEMS AND DIRECTIONS FOR THE FUTURE

Despite flaws, tissue-engineered skin substitutes and current dressings have, to far, greatly advanced clinical knowledge of burn treatment, enabling physicians to treat severe instances that enhance patients' survival rates and quality of life [42, 43]. Most of them merely work to supply cytokines and growth factors to speed up wound healing while temporarily shielding the denuded tissue from the hostile environment. Without a doubt, commercial goods made from autologous cells (fibroblasts and keratinocytes) are similar to the skin's natural structure and can successfully treat skin damage, but they are unable to completely replace the damaged tissue. The introduction and quick development of new products for cell-based therapies are constrained by a number of factors. First of all, the equipment needed for their creation is complicated and specialised, and it takes a lot of time and labour. A large quantity of cells are required to cover the wide burn regions, and if they are not autologous or hypoimmunogenic, a substitute may not be accepted. These goods have a limited shelf life and must be transported and stored under specific, difficult-to-maintain conditions. The activity of cell culture facilities and surgeons should be closely coordinated when autologous cells are used. The expense of using skin substitutes is also significant, but they can only replace the protective function of the skin [209]; none of these tissue-engineered structures can replace functions like thermoregulation, sensation, UV protection, excretion, perspiration, etc. There are currently three primary methods used in the construction of skin substitutes: cell-based, biomaterial-based, and delivery-based. In the first, in an effort to mimic native tissue form, scientists strive to create skin analogues utilising not just fibroblasts and keratinocytes, but also melanocytes and endothelial cells. The features of stem cells, such as hypo-immunogenicity and high differentiation potential, are frequently exploited in investigations. There is considerable controversy about the use of both autologous and allogeneic cells. A bank of allogeneic cells can offer a chance to treat patients with extensive and deep second-degree burns quickly, and in this situation, the most preferable cells are stem cells (e.g., adipose-derived or bone-marrow derived stem cells) possessing hypo-immunogenicity. However, some studies have shown that only autologous cells can promote rapid wound healing. Additionally, attempts are attempted to in vitro replicate skin appendages (such as hair follicles and sebaceous glands) and incorporate them into skin substitutes. The second strategy makes various attempts to functionalize scaffolds. For instance, the immobilisation of signalling molecules on their surface can encourage cell division and proliferation while regulating the adherence of cells to the matrix. The third strategy involves researchers attempting to create fresh delivery systems or enhance current ones. Cells can be administered intravenously to assure burn healing, but more frequently, they are immobilised on different materials and placed topically as dressings. Although dressings are the most popular method, they cannot be accurately adapted to the profile of the wound surface. Because they can address this problem, technologies like cell spray and bio-printing are of considerable interest.

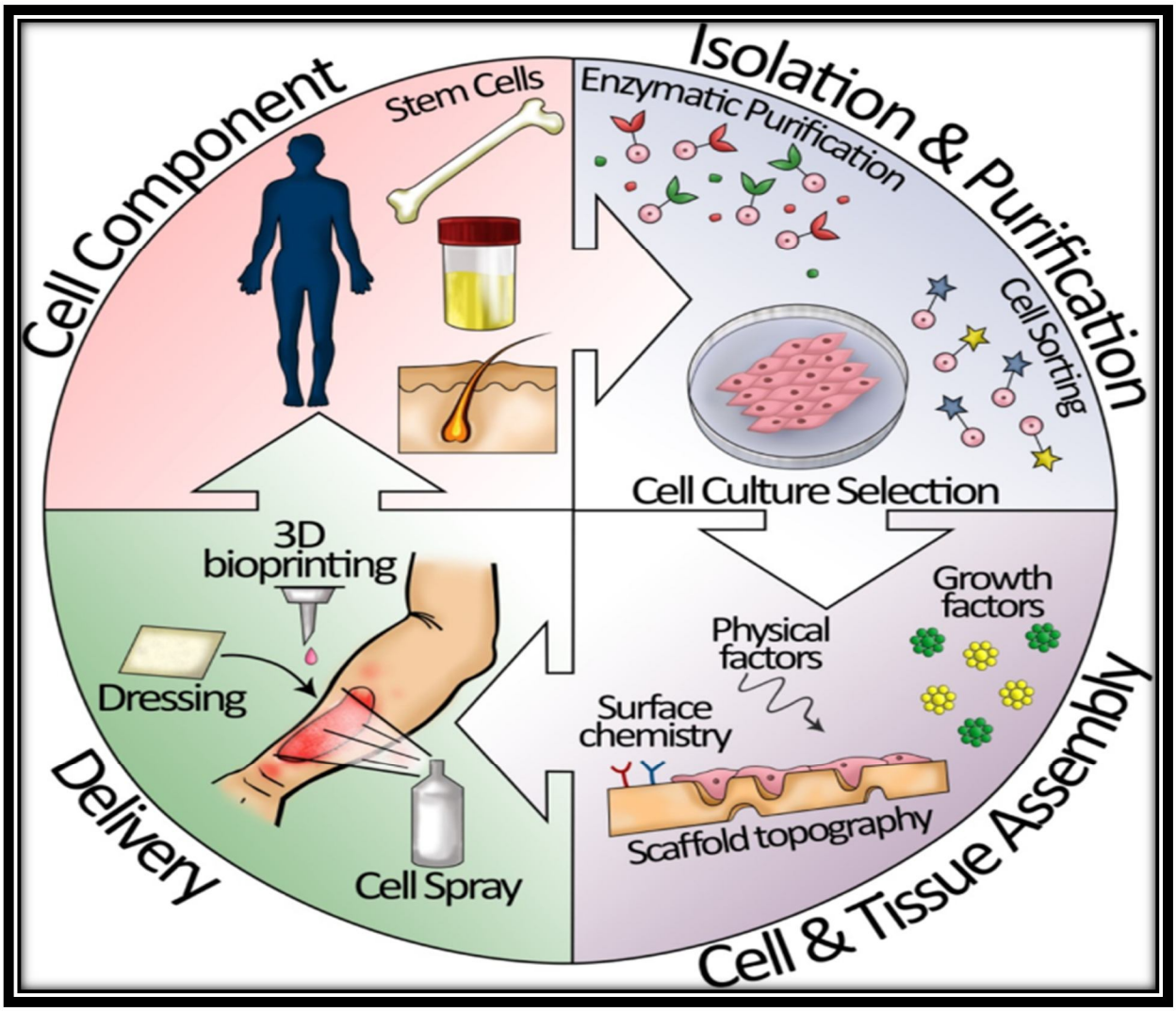



Fig. No. 4 Shows Autologous stem cell treatment in action

However, there are still several crucial issues that must be clarified before standardising all relevant procedures and creating guidelines for practitioners. In the majority of trials, cells and cell-based products are administered topically only once. However, in cases of severe burns that result in systemic inflammation and hypohydration, these treatments may not be sufficient, and only intravenous injections of cells will help the patient's condition. Although using autologous cells in big burns is impossible because to the shortage of donor sites and available time, they are thought to be preferable. The effectiveness of cell-based therapy also depends on the timing of interventions, which is determined by collaboration between clinicians and cell facility employees, especially in cases of serious burns. In order to fully utilise the promise of cell-based therapy, the challenges highlighted above should be resolved despite the excellent results of cell applications in burn care.

## VIII. ABBREVIATIONS

1) *3D:* Three-dimensional
2) *BD:* Biodegradability
3) *bFGF:* Basic fibroblast growth factor
4) *BMSC:* Bone marrow stem cells
5) *CA:* Commercial availability
6) *CT:* Clinical trials
7) *ECM:* Extracellular matrix

8) *EGF:* Epidermal growth factor
9) *EPS:* Endothelial progenitor cells
10) *ESC:* Epidermal stem cells
11) *FDA:* Food and Drug Administration
12) *FGF:* Fibroblast growth factor
13) *GFs:* Growth factors
14) *HA:* Hyaluronic acid
15) *HGF:* Hepatocyte growth factor
16) *HLA:* Human leukocyte antigen
17) *iPSC:* Induced pluripotent stem cells
18) *KGF:* Keratinocyte growth factor
19) *MHC:* Major histocompatibility complex
20) *MMSC:* Multipotent mesenchymal stromal cells
21) *MSC:* Mesenchymal stromal cells
22) *ND:* No data available
23) *PDGF:* Platelet-derived growth factor
24) *Refs:* References
25) *TGF:* Transforming growth factor
26) *TNF-α:* Tumor necrosis factor alpha
27) *USC:* Urine-derived stem cells
**28)** *VEGF:* Vascular endothelial growth factor

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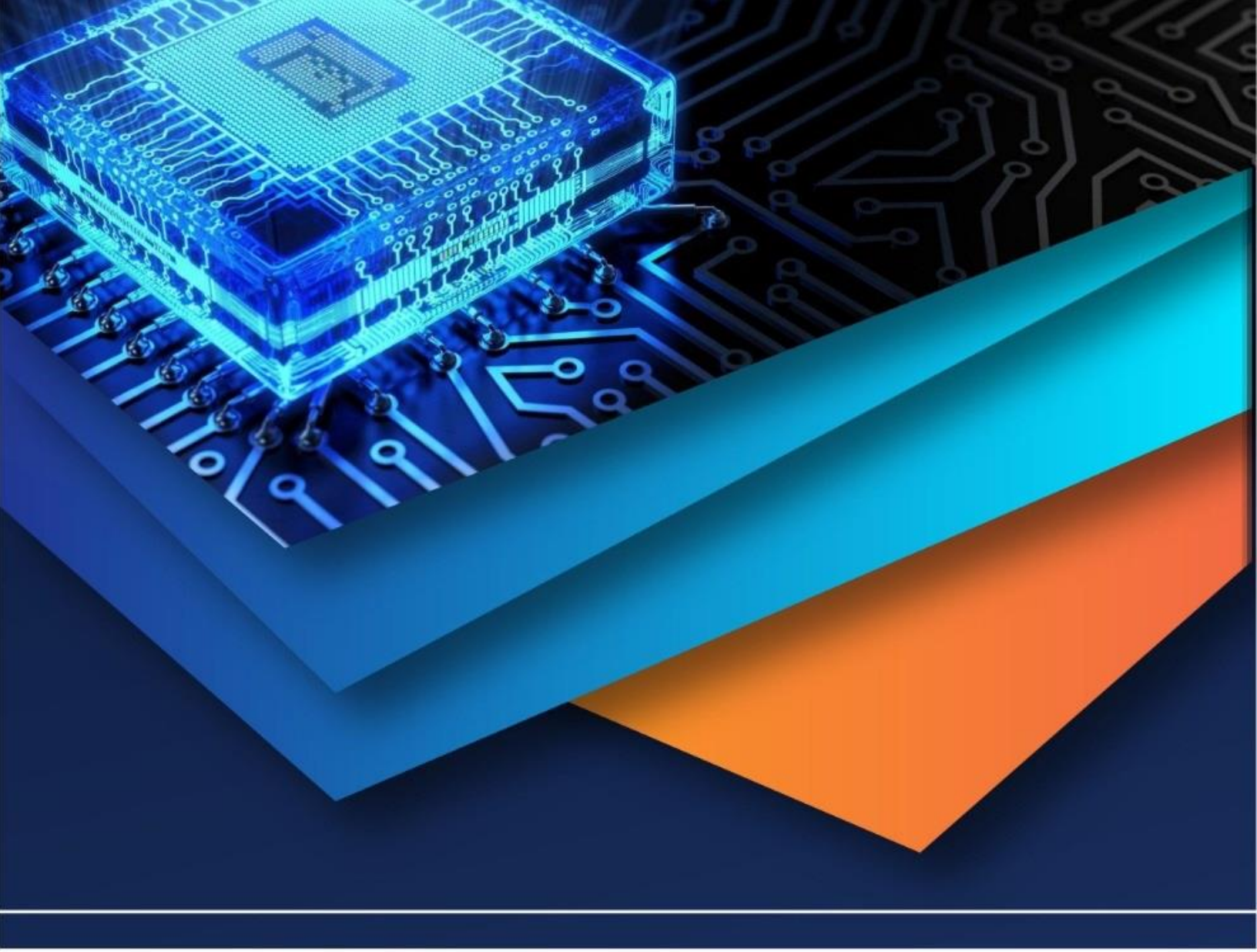

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