

Application of regenerative medicine in the treatment of skin conditions: an overview

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Abstract. This study provides an overview of the applications of regenerative medicine in the treatment of various dermatological conditions, with a particular focus on recent advancements in gene editing, bioengineered skin grafts, and cellular therapies. Regenerative techniques could address the underlying causes of disease and show promise in curing disorders such as radiodermatitis, dystrophic epidermolysis bullosa (DEB), vitiligo, and chronic wounds, whereas standard therapy typically merely relieves symptoms. Furthermore, the article examines the challenges that regenerative medicine currently faces, including high costs, immunological rejection, and moral dilemmas, as well as how cutting-edge tissue engineering and intelligent biomaterials may transform skin regeneration.

Keywords: regenerative medicine, skin conditions, cell therapies, skin grafts, gene editing, chronic wound, dystrophic epidermolysis bullosa (DEB), vitiligo, radiodermatitis.

1. Introduction

Around the world, an estimated 1.8 billion people are suffering from skin conditions at any given time [1]. With 41.6 million disability-adjusted life years (DALYs) and 39.0 million years lost due to disability (YLDs), skin and subcutaneous diseases ranked 18th as the leading cause of global DALYs in 2013 [2]. From 1990 to 2017, DALYs from skin and subcutaneous conditions in the United States increased in all 50 states and the District of Columbia, and the age-standardized DALY rate for skin and subcutaneous conditions per 100,000 people in the U.S. ranked 12th among all conditions in 2017 [3].

Among many ways to address this worldwide issue, regenerative medicine offers a beacon of hope. Regenerative medicine is a growing field and clinical practice that aims to replace, repair, and regenerate damaged cells, tissues, or organs to restore their original functions [4]. More specifically, induced pluripotent stem cells (iPSC) have gained significant traction within the field, especially when it was discovered that iPSCs could be differentiated into keratinocytes, which proved their potential for dermatological applications [5]. Recent advances in the field have also demonstrated the ability to develop viable therapies from iPSCs to treat certain skin diseases, such as dystrophic epidermolysis bullosa (DEB) [6]. This article will explore the various skin conditions that could benefit from these groundbreaking methods, assess the state of regenerative medicine technology today, and highlight recent findings and success stories that show the promise and progress of the field.

2. Overview of Common Skin Conditions

Skin conditions present varying degrees of challenges in terms of treatment. Among them, chronic wounds and ulcers, DEB, vitiligo, and side effects from radiotherapy are some of the conditions that stand out as conditions where regenerative medicine holds substantial promise [7-9]. A chronic wound is one in which the healing process cannot return the original tissue to its anatomical and functional integrity after three months or if the repair process fails to proceed via a typical, timely, and predictable sequence [10]. The wound would remain in a state of chronic inflammation, which would impede the healing process [11]. It is crucial to recognize that every wound has the potential to become chronic; they are usually categorized as arterial, diabetic, pressure, or venous ulcers based on their location, depth, and appearance [12]. They can diminish physical, emotional, and social well-being, resulting in a major decline in quality of life [13].

EB, or epidermolysis bullosa, is a rare genetic and hereditary dermatosis that is characterized by the development of blisters and mucocutaneous fragility; the development of these blisters can be triggered by minimal damage, which distinguishes it from other dermatological conditions [14]. A specific type of EB, dystrophic epidermolysis bullosa (DEB), is believed to be caused by mutations in the COL7A1 gene, which causes severe skin fragility in the basement membrane zone (BMZ) as a result of collagen VII (C7) loss [6]. Collagen VII plays a crucial structural role in anchoring fibrils, which are essential for connecting the dermis to the basal lamina and, subsequently, the epidermis [15]. Patients with DEB specifically exhibit skin deformities such as milia development, nail alterations, and finger coalescence [16]. DEB has a prevalence of between 1 in 120,000 and 350,000 individuals in Europe [17].

Vitiligo is an umbrella term that encompasses a group of chronic pigmentation disorders; these disorders are characterized by the symmetrical white patches that grow over time due to significant loss of melanocytes in the epidermis and, in some cases, hair follicles [18]. Despite the identification of over 50 distinct susceptibility genes for vitiligo, the low concordance rate of 23% observed in monozygotic twins suggests that genetic factors may not be the sole determinant of vitiligo development [18]. Current theories posit that vitiligo may result from a complex interplay of factors, including oxidative stress and immunological reactions [18]. Globally speaking, vitiligo affects around 1% of the population [19].

Radiotherapy, or radiation therapy, is the utilization of X-rays or subatomic particles for both therapeutic and palliative purposes, with a primary focus on the treatment of cancer [20]. While it is an effective method for cancer treatment, it can also cause various side effects affecting the skin in the treated area. Radiation-induced dermatitis (RID) affects around 95% of radiation patients and can significantly impact their quality of life and treatment outcomes [21]. Radiation-induced proinflammatory cytokine release and activated growth factors combine to generate a complex that drives the alteration of inflammatory processes and cell proliferation [22]. Acute exposures to radiation would result in erythema, pigmentation, or blisters, and long-term, low-dose exposure would result in skin atrophy, which is manifested as a decrease in the number of epidermal cells and the thinning of epidermal layers [23]. These symptoms are collectively known as radiodermatitis [24].

3. Current Available Treatments and Limitations

At the time of writing, there are a number of treatment options available for each of the aforementioned conditions. However, it should be noted that each of these options has its own set of limitations, most of which are limited to symptomatic treatments without addressing the underlying causes. For chronic wounds, a well-known and effective treatment is debridement, which refers to the removal of dead tissues and foreign materials from the wound site [25]. However, it may cause significant pain for the patient, and different individuals may respond differently to debridement [26]. Hydrogel dressing is a more modern method that uses three-dimensional networks of hydrophilic polymers to create a moist environment that promotes tissue regeneration; however, the type and severity of the wound might affect the success rate of hydrogel dressings [26]. With the exception of regenerative medicine, current treatments for DEB are limited and mostly symptomatic. One possible

treatment approach is to apply 1% diacerein cream to the wound site [27]. Once absorbed into the body, diacerein is metabolized to its active form (rhein), which has anti-inflammatory and analgesic properties by blocking specific cytokines and proteolytic enzymes and reducing collagen breakdown [27]. However, as previously discussed, this approach is mostly palliative, and the availability of diacerein can be quite restricted and is typically considered experimental [27].

There is currently no cure for vitiligo [28]. Due to the autoimmune nature of the disease, immunosuppressants such as glucocorticoids and calcineurin inhibitors are currently used as topical treatments [28]. Another possible treatment is phototherapy, which involves exposing the affected areas of the skin to ultraviolet B (UVB) radiation to stimulate repigmentation [29]. Another option for people with vitiligo is to wear make-up to conceal the depigmented area or to use specific medications to depigment the unaffected skin [18]. However, due to the nature of these therapies, they are only temporary and do not treat the underlying problem. Treatment options for RID are also limited to topical treatments. The choice of treatment depends on the severity of the dermatitis and may include topical corticosteroids, non-corticosteroid medications, or different dressings (Kiprian et al., 2022). In addition to the topical aspect of the treatment, present therapies are limited by a lack of consensus on the best management techniques and the possibility of side effects such as systemic absorption and medication combinations [30].

4. Advances in Regenerative Medicine

As the limitations of conventional therapies for these dermatological conditions become increasingly evident, there is a clear necessity for novel and more efficacious techniques. A pivotal challenge is that numerous established methodologies merely provide symptomatic alleviation but fail to address the fundamental causes that impede genuine healing, leading to recurrent issues and diminished quality of life. The field of regenerative medicine represents a significant paradigm shift in the management of these conditions. By prioritising the repair, replacement, and regeneration of damaged tissues [4], regenerative medicine offers promising prospects for not only enhancing outcomes but also providing curative solutions for these conditions.

The field of regenerative medicine is concerned with the use of stem cells, which possess the capacity for infinite division and differentiation into a multitude of cell types; this property has enabled researchers to repair tissue and organ anomalies due to a variety of causes [31]. Stem cells are classified according to their regenerative potential into the following categories: embryonic stem cells (ESCs), tissue-specific progenitor stem cells (TSPSCs), mesenchymal stem cells (MSCs), umbilical cord stem cells (UCSCs), bone marrow stem cells (BMSCs), and iPSCs; each type of stem cells have their distinct characteristics and potential applications [32]. Because the transplanted cells were produced from individuals, regenerative medicine can effectively avoid the immunological rejection concerns associated with heterologous transplants [31]. Another promising aspect of regenerative medicine is gene therapy. One notable feature of gene therapy is its capacity to transport therapeutic proteins and RNA directly to tissues, thereby enabling local synthesis and sustained release of the desired biomolecules, which is a crucial factor in successful regeneration [33]. In addition, gene editing methods such as CRISPR/Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats and CRISPR-associated protein 9) can be used for transforming somatic cells into iPSCs, activating or repressing the transcriptions of specific genes and the insertion of DNA segments into the human genome [34-36].

5. Application of Regenerative Medicine in Skin Conditions

The utilization of regenerative medicines in the management of dermatological disorders presents a multitude of distinctive benefits. The following exemplifications will elucidate these advantages in greater detail.

Cellular therapy is a promising aspect for the healing of chronic wounds. In particular, bone marrow mesenchymal stem cells (BMSCs) can be differentiated into fibroblasts, which in turn promote the production of collagen at the site of the wound. Furthermore, they produce the essential

growth factors required for the healing of the wound [37]. Another candidate for this purpose is adipose-derived stem cells (ADSCs), which are preferred for a number of reasons, including their ease of isolation, relative abundance, and rapid expansion [38]. Once developed, stem cells can be cultured onto natural or synthetic scaffolds, which can then lead to the regeneration of tissues at the wound site [39]. Furthermore, iPSCs have been used to create detailed, customized three-dimensional skin models for disease modeling and autologous grafting [40]. A number of cell therapies have already received approval from the U.S. Food and Drug Administration (FDA), including Apligraf®, which is a dermo-epidermal graft containing fibroblasts derived from human infant foreskin [41-42]. In the context of gene therapy, a common objective is to facilitate angiogenesis at the site of the wound. There have been clinical trials conducted with the aim of increasing the expression of specific growth factors by encoding them into DNA plasmids, resulting in a significant elevation in vascular endothelial growth factor (VEGF) levels for a period of days or even weeks [43]. There have also been therapies based on CRISPR/Cas9, which can activate gene repairs at specific sites by inducing non-homologous end-joinings (NHEJs) and consequently homology-directed repairs (HDR), providing a versatile tool to correct point mutations related to chronic wounds and healing [44].

The treatment of DEB is undergoing a notable enhancement as a consequence of advancements in regenerative medicine, including the deployment of skin grafts and topical gene therapies. As mentioned in the introduction, Neumayer et al. demonstrated viable skin graft products where iPSCs were cultured using biopsies from the patient [6]. Using CRISPR/Cas9, the genetic mutation responsible for the loss of collagen VII (COL7A1) was fixed concurrently with the cells' conversion to iPSCs. The resulting iPSCs were then cultivated to create viable skin grafts that underwent in vitro and in vivo safety testing, were properly stratified, and included every cell type required for normal skin development. In 2022, Gurevich et al. employed a herpes simplex virus type 1 (HSV-1) vector that had been genetically modified and rendered non-replicating for the delivery of COL7A1 vectors, designated "beremagene geperpavec" (B-VEC) [45]. The results of the phase 1 and 2 clinical trials demonstrated an increase in the expression of collagen VII and an increase in the rate of closure for wounds related to DEB. More recently, Guide et al. conducted phase 3 of B-VEC and demonstrated the significant effectiveness of this topical gene therapy [46].

The principal objective of regenerative medicine in the treatment of vitiligo is to address the loss of functional melanocytes. One such method involves the reintroduction of melanocytes into the patient's skin. This is frequently achieved through the formation of blisters on the patient's skin (suction blister epidermal grafting, SBEG), which are then subjected to selective concentration and culture of melanocytes [47-48]. This approach has been refined over many years and is often regarded as the most practical, secure, and successful method for the treatment of vitiligo [48]. An alternative approach is the utilization of multipotent mesenchymal stem cells (MSCs), which demonstrate high regeneration potential and can be isolated from a range of sources; in certain circumstances, these cells can undergo morphological changes to resemble melanocytes and express the key proteins involved in pigmentation [49]. Indeed, the co-cultivation of adipose tissue-derived MSCs and melanocytes has been demonstrated to be more effective than culturing either cell type alone [50]. Regenerative medicine has also emerged as a promising avenue for the treatment of radiodermatitis, offering methods that not only alleviate symptoms but also facilitate the healing of injured tissues. Similar to the treatment of vitiligo, MSCs are also a promising option for patients suffering from radiodermatitis; the treatment may be applied to chronic injuries through the reconstruction of tissues with adipose-derived stem cells (ADSCs) from non-irradiated regions, or it can be employed to address acute radiation injuries through the utilization of MSCs extracted from non-irradiated adipose tissue sites [51]. Intravenous MSC treatment has been demonstrated to be an efficacious method for reducing ulcer size and improving skin quality, two symptoms commonly associated with radiodermatitis; it has been postulated that MSC paracrine factors are indispensable for the suppression of inflammatory reactions [52].

An inventive method uses light-emitting diodes (LEDs) to promote skin regeneration. In one research, mice exposed to Strontium-90 (90Sr) radiation were given a 660 nm LED treatment for ten

minutes every other day. The researchers observed that the healing process was noticeably quicker and that there was an increase in angiogenesis, interleukin-10 (IL-10), and matrix metalloproteinase-9 (MMP-9). These results reflect a new direction in this field and show the promise of low-voltage LED technology in the context of tissue regeneration [53].

6. Current Challenges and Future Prospects

Despite the evident benefits of regenerative medicines in the management of diverse dermatological disorders, several substantial obstacles currently impede their widespread utilization. The intrinsic complexity and production costs of cell-based treatment represent one of the biggest barriers to its broader implementation. For the typical patient, the expenses of cell-based therapy are unaffordable due to the intricate manufacturing processes involved. According to one estimate, each batch yields 1 to 88 doses and costs between €23,033 and €190,799 in total [54]. The high cost of this promising therapy could render it unaffordable for many patients who would greatly benefit from it. Moreover, the scarcity of qualified professionals and the lack of adequate infrastructure in this field may contribute to the significant financial burden associated with regenerative medicine [55]. A further question is whether regenerative medicine is an effective treatment. Despite advances such as iPSCs, allogenic cells or tissues still carry the risk of immunological rejection. For example, it has been demonstrated that the incidence of immunological rejection is markedly elevated in teratomas derived from iPSCs generated from B6 mouse embryonic fibroblasts [56]. Furthermore, there has been considerable uncertainty in estimating the efficacy of regenerating medicines, as well as their long-term effectiveness [57]. There are also safety and ethical concerns related to regenerative medicine. Questions have been raised about the possibility that stem cells, like teratomas, might grow because of their similarities to cancer cells; furthermore, a significant portion of pluripotent stem cells are obtained from human embryos and fetal tissues, a procedure that could be offensive and unacceptable to some demographics [58]. Concerns about justice and fairness, information gaps between researchers and patients, and informed consent are further challenges surrounding regenerative medicine [59]. Nevertheless, the future outlook for regenerative medicine in the treatment of dermatological conditions remains optimistic. A number of technologies have the potential to transform the field of tissue engineering and regenerative medicine; these include solvent casting and particulate leaching (SCPL), gas foaming, electrospinning, soft lithography, and microfluidics [60]. These technologies could lead to the creation of better grafts that could better mimic the natural interactions found in the skin. In addition to conventional regeneration techniques, the development of intelligent biomaterials that may respond to environmental stimuli could markedly enhance the potential for healing skin disorders [61]. As the infrastructure and bioprocessing technologies continue to evolve, it is anticipated that regenerative treatments will become more cost-effective and accessible to a broader patient population in need [55].

7. Conclusions

This paper presents an overview of the potential applications of regenerative medicine in the treatment of skin conditions. The paper then proceeds to examine four common types of skin conditions, delineating the limitations of traditional therapeutic modalities. It subsequently discusses how regenerative medicines can address these shortcomings. The advancement of cell therapies, bioengineered skin grafts, and gene editing has facilitated the development of regenerative approaches to enhance patient outcomes, thereby paving the way for future developments in conjunction with other approaches. Nevertheless, obstacles such as high costs, immune rejection, and ethical concerns must be overcome in order to realize the full potential of regenerative medicine. As technology progresses, interdisciplinary research between regenerative medicine and other emerging fields could revolutionize dermatology and offer new hope to patients suffering from these conditions.

References

- [1] Asiedu, K. B. (2023, March 31). WHO's first global meeting on skin NTDs calls for greater efforts to address their burden. World Health Organization. <https://www.who.int/news/item/31-03-2023-who-first-global-meeting-on-skin-ntds-calls-for-greater-efforts-to-address-their-burden>
- [2] Mengist Dessie, A., et al. (2022). Prevalence of skin disease and its associated factors among primary schoolchildren: A cross-sectional study from a northern Ethiopian town. *Clinical, Cosmetic and Investigational Dermatology*, 15, 791–801. <https://doi.org/10.2147/ccid.s361051>
- [3] Laughter, M. R., et al. (2020). The burden of skin and subcutaneous diseases in the United States from 1990 to 2017. *JAMA Dermatology*, 156(8), 874. <https://doi.org/10.1001/jamadermatol.2020.1573>
- [4] Mason, C., & Dunnill, P. (2007). A brief definition of Regenerative Medicine. *Regenerative Medicine*, 3(1), 1–5.
- [5] Bilousova, G., Chen, J., & Roop, D. R. (2011). Differentiation of mouse induced pluripotent stem cells into a multipotent keratinocyte lineage. *Journal of Investigative Dermatology*, 131(4), 857–864.
- [6] Neumayer, G., et al. (2024). A scalable and cGMP-compatible autologous organotypic cell therapy for Dystrophic Epidermolysis Bullosa. *Nature Communications*, 15(1). <https://doi.org/10.1038/s41467-024-49400-z>
- [7] Khandpur, S., Gupta, S., & Gunaabalaji, D. R. (2021). Stem cell therapy in dermatology. *Indian Journal of Dermatology Venereology and Leprology*, 87, 753–767. https://doi.org/10.25259/ijdv19_20
- [8] Bellei, B., Papaccio, F., & Picardo, M. (2022). Regenerative Medicine-Based Treatment for Vitiligo: An Overview. *Biomedicines*, 10(11), 2744. <https://doi.org/10.3390/biomedicines10112744>
- [9] Vickers, E. R., et al. (2021). Regenerative Medicine to Reduce the Side Effects from Radiotherapy Causing Skin Cancer, Fibrosis, Neuropathic Pain and Hair Loss. *Journal of Cancer Therapy*, 12(8), 461–477.
- [10] Bowers, S., & Franco, E. (2020, February 1). Chronic Wounds: Evaluation and Management. AAFP. Retrieved August 14, 2024, from <https://www.aafp.org/pubs/afp/issues/2020/0201/p159.html>
- [11] Taylor, J. E., et al. (2005). Extent of iron pick-up in deferoxamine-coupled polyurethane materials for therapy of chronic wounds. *Biomaterials*, 26(30), 6024–6033. <https://doi.org/10.1016/j.biomaterials.2005.03.015>
- [12] Werdin, F., et al. (2009). Evidence-based management strategies for treatment of chronic wounds. *Eplasty*, 9, e19.
- [13] Augustin, M., & Maier, K. (2003). Psychosomatic Aspects of Chronic Wounds. *Dermatology and Psychosomatics / Dermatologie Und Psychosomatik*, 4(1), 5–13. <https://doi.org/10.1159/000070529>
- [14] Bardhan, A., et al. (2020). Epidermolysis bullosa. *Nature Reviews Disease Primers*, 6(1).
- [15] Shinkuma, S., McMillan, J. R., & Shimizu, H. (2011). Ultrastructure and molecular pathogenesis of epidermolysis bullosa. *Clinics in Dermatology*, 29(4), 412–419. <https://doi.org/10.1016/j.clindermatol.2011.01.010>
- [16] Oliveira, T. M., et al. (2008). Clinical management for epidermolysis bullosa dystrophica [In Russian]. *Journal of Applied Oral Science*, 16(1), 81–85. <https://doi.org/10.1590/s1678-77572008000100016>
- [17] Laimer, M. (Ed.). (2021, May). Dystrophic epidermolysis bullosa. Orphanet. Retrieved August 15, 2024, from <https://www.orpha.net/en/disease/detail/303?name=Epidermolysis%20bullosa%20dystrophica&mode=name>

- [18] Picardo, M., & Taieb, A. (2019). Vitiligo. In Springer eBooks (2nd ed.). Springer Nature Switzerland AG.
- [19] Whitton, M., et al. (2016). Evidence-based management of vitiligo: summary of a Cochrane systematic review. *British Journal of Dermatology*, 174(5), 962–969. <https://doi.org/10.1111/bjd.14356>
- [20] Maani, E. V., & Maani, C. V. (2022, October 24). Radiation therapy. In StatPearls [Internet]. StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK537036/>
- [21] Iacovelli, N. A., et al. (2020). Topical treatment of radiation-induced dermatitis: current issues and potential solutions. *Drugs in Context*, 9, 1–13. <https://doi.org/10.7573/dic.2020-4-7>
- [22] Gottlöber, P., Krähn, G., & Peter, R. (2000). Das kutane Strahlensyndrom [The Cutaneous Radiation Syndrome]. *Hautarzt*, 51(8), 567–574. <https://doi.org/10.1007/s001050051173>
- [23] Wang, Y., et al. (2020). Prevention and treatment for radiation-induced skin injury during radiotherapy. *Radiation Medicine and Protection*, 1(2), 60–68. <https://doi.org/10.1016/j.radmp.2020.02.004>
- [24] Kondziolka, J., & Wilczyński, S. (2021). Overview of the Active Ingredients in Cosmetic Products for the Care of Skin That Has Been Exposed to Ionizing Radiation – Analysis of Their Effectiveness in Breast Cancer Radiotherapy. *Clinical Cosmetic and Investigational Dermatology*, 14, 1065–1076.
- [25] Frykberg, R. G., & Banks, J. (2015). Challenges in the Treatment of Chronic Wounds. *Advances in Wound Care*, 4(9), 560–582. <https://doi.org/10.1089/wound.2015.0635>
- [26] Firlar, I., et al. (2022). Functional Hydrogels for Treatment of Chronic Wounds. *Gels*, 8(2), 127.
- [27] Will, L. M., Reichrath, J., & Vogt, T. (2021). Epidermolysis bullosa dystrophica pretibialis – Clinical snapshot and management of a rare orphan disease. *JDDG Journal Der Deutschen Dermatologischen Gesellschaft*, 19(7), 983–986. <https://doi.org/10.1111/ddg.14446>
- [28] Ezzedine, K., et al. (2015). Vitiligo. *The Lancet*, 386(9988), 74–84. [https://doi.org/10.1016/s0140-6736\(14\)60763-7](https://doi.org/10.1016/s0140-6736(14)60763-7)
- [29] Scherschun, L., Kim, J. J., & Lim, H. W. (2001). Narrow-band ultraviolet B is a useful and well-tolerated treatment for vitiligo. *Journal of the American Academy of Dermatology*, 44(6), 999–1003.
- [30] Kiprian, D., et al. (2022). How to manage radiation-induced dermatitis? *Nowotwory Journal of Oncology*, 72(2), 86–95. <https://doi.org/10.5603/njo.2022.0017>
- [31] Mason, C., & Dunnill, P. (2008). A brief definition of regenerative medicine. *Regenerative Medicine*, 3(1), 1–5. <https://doi.org/10.2217/17460751.3.1.1>
- [32] Mahla, R. S. (2016). Stem Cells Applications in Regenerative Medicine and Disease Therapeutics. *International Journal of Cell Biology*, 2016, 1–24. <https://doi.org/10.1155/2016/6940283>
- [33] Balmayor, E. R. (2023). Bringing gene therapy to regenerative medicine. *Molecular Therapy — Methods & Clinical Development*, 30, 81–82. <https://doi.org/10.1016/j.omtm.2023.05.021>
- [34] Choudhury, S., Surendran, N., & Das, A. (2021). Recent advances in the induced pluripotent stem cell-based skin regeneration. *Wound Repair and Regeneration*, 29(5), 697–710. <https://doi.org/10.1111/wrr.12925>
- [35] Hsu, M. N., et al. (2019). CRISPR technologies for stem cell engineering and regenerative medicine. *Biotechnology Advances*, 37(8), 107447. <https://doi.org/10.1016/j.biotechadv.2019.107447>
- [36] Grath, A., & Dai, G. (2019). Direct cell reprogramming for tissue engineering and regenerative medicine. *Journal of Biological Engineering*, 13(1). <https://doi.org/10.1186/s13036-019-0144-9>
- [37] Fathke, C., et al. (2004). Contribution of bone marrow–derived cells to skin: collagen deposition and wound repair. *Stem cells*, 22(5), 812–822. <https://doi.org/10.1634/stemcells.22-5-812>

- [38] Acharya, G. (2018). A Glimpse into the Future of Chronic Wound Healing and Regenerative Medicine Using Self-Assembling Peptides. *Medicinal & Analytical Chemistry International*, 2(3).
- [39] Fani, N., et al. (2024). Current Advances in Wound Healing and Regenerative Medicine. *Current Stem Cell Research & Therapy*, 19(3), 277–291. <https://doi.org/10.2174/1574888x18666230301140659>
- [40] Dash, B. C., et al.(2022). Unlocking the Potential of Induced Pluripotent Stem Cells for Wound Healing: The Next Frontier of Regenerative Medicine. *Advances in Wound Care*, 11(11), 622–638.
- [41] U.S. Food and Drug Administration. (2024). Apligraf. Retrieved from <https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pma&id=319700>
- [42] U.S. Food and Drug Administration. (1998). Summary of Safety And Effectiveness Data (PMA No. P950032). Retrieved from https://www.accessdata.fda.gov/cdrh_docs/pdf/P950032B.pdf
- [43] Berthiaume, F., & Hsia, H. C. (2022). Regenerative Approaches for Chronic Wounds. *Annual Review of Biomedical Engineering*, 24(1), 61–83. <https://doi.org/10.1146/annurevbioeng-010220-113008>
- [44] Shaabani, E., et al. (2022). Gene therapy to enhance angiogenesis in chronic wounds. *Molecular Therapy — Nucleic Acids*, 29, 871–899. <https://doi.org/10.1016/j.omtn.2022.08.020>
- [45] Gurevich, I., et al. (2022). In vivo topical gene therapy for recessive dystrophic epidermolysis bullosa: A phase 1 and 2 trial. *Nature Medicine*, 28(5), 780–788. <https://doi.org/10.1038/s41591-022-01737-y>
- [46] Guide, S. V., et al. (2022). Trial of Beremagene Geperpavec (B-VEC) for Dystrophic Epidermolysis Bullosa. *New England Journal of Medicine*, 387(24), 2211–2219. <https://doi.org/10.1056/NEJMoa2206663>
- [47] Frączek, A., et al. (2022). Surgical Treatment of Vitiligo. *International Journal of Environmental Research and Public Health*, 19(8), 4812. <https://doi.org/10.3390/ijerph19084812>
- [48] Zokaie, S., et al. (2019). Cultured epidermal melanocyte transplantation in vitiligo: a review article. *Iranian journal of public health*, 48(3), 388. Retrieved from <https://pubmed.ncbi.nlm.nih.gov/31223565>
- [49] Olisova, O. Y., et al. (2023). New trends in the regenerative therapy of vitiligo. Literature review. *Russian Journal of Skin and Venereal Diseases*, 26(3), 263–271. <https://doi.org/10.17816/dv295040>
- [50] Lim, W. S., et al.(2014). Adipose-Derived Stem Cells Improve Efficacy of Melanocyte Transplantation in Animal Skin. *Biomolecules & Therapeutics*, 22(4), 328–333. <https://doi.org/10.4062/biomolther.2014.065>
- [51] Akita, S., et al.(2010). Mesenchymal stem cell therapy for cutaneous radiation syndrome. *Health Physics*, 98(6), 858–862. <https://doi.org/10.1097/hp.0b013e3181d3d52c>
- [52] Wang, K. X., et al. (2021). Mesenchymal Stem Cells for Mitigating Radiotherapy Side Effects. *Cells*, 10(2), 294. <https://doi.org/10.3390/cells10020294>
- [53] Camargo, C. P., et al.(2021). Light-emitting diode stimulates radiodermatitis recovery. *Acta Cirúrgica Brasileira*, 36(3). <https://doi.org/10.1590/acb360301>
- [54] Ham, R. M. T., et al. (2020). What does cell therapy manufacturing cost? A framework and methodology to facilitate academic and other small-scale cell therapy manufacturing costings. *Cytotherapy*, 22(7), 388–397.
- [55] United States Government Accountability Office. (2023). Regenerative Medicine: Therapeutic Applications, Challenges, and Policy Options (GAO-23-105430). <https://www.gao.gov/assets/gao-23-105430.pdf>
- [56] Zhao, T., Zhang, Z. N., Rong, Z., & Xu, Y. (2011). Immunogenicity of induced pluripotent stem cells. *Nature*, 474(7350), 212–215.

- [57] Hettle, R., et al. (2017). The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. *Health Technology Assessment*, 21(7), 1–204.
- [58] Zamborsky, R., et al. (2018). Regenerative Medicine in Orthopaedics and Trauma: Challenges, Regulation and Ethical Issues. *Ortopedia Traumatologia Rehabilitacja*, 20(3), 173–180.
- [59] Hermerén, G. (2021). The ethics of regenerative medicine. *Biologia Futura*, 72(2), 113–118.
- [60] Berthiaume, F., Maguire, T. J., & Yarmush, M. L. (2011). Tissue Engineering and Regenerative Medicine: History, Progress, and Challenges. *Annual Review of Chemical and Biomolecular Engineering*, 2(1), 403–430.
- [61] Amukarimi, S., Ramakrishna, S., & Mozafari, M. (2021). Smart biomaterials—A proposed definition and overview of the field. *Current Opinion in Biomedical Engineering*, 19, 100311. <https://doi.org/10.1016/j.cobme.2021.100311>