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REGENERATIVE MEDICINE IN BURN INJURY: A BIBLIOMETRIC ANALYSIS AND LITERATURE REVIEW

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ABSTRACT

Introduction: Burn injuries represent a significant global health concern, demanding effective management strategies to mitigate their impact. Regenerative medicine offers promising approaches to address burn injury management, utilizing innovative techniques to improve wound healing and tissue regeneration. This paper presents a comprehensive bibliometric analysis and literature review, highlighting trends, hotspots, and article profiles in the application of regenerative medicine for burn injury management, offering valuable insights for future research to enhance burn care.
Methods: A Scopus database search spanning from 2004 to 2024 was conducted using keywords related to regenerative medicine, burn injuries, and wound healing, yielding 602 relevant documents for analysis. Subsequent bibliometric analysis using VOSviewer and Biblioshiny identified key trends and contributors in the field.
Results: The results indicate an increase in research studies over the years, peaking in 2022, followed by a slight decline. Zhang Y emerged as the top researcher, with the United States leading in research output. Researchers primarily focused on four main areas: materials and techniques, injury management, cell-based therapies, and wound healing strategies. Emerging areas such as 3D printing, nanotechnology, and photothermal therapy are gaining interest for future research.
Conclusion: This study provides valuable insights into the evolving landscape of regenerative medicine for burn injury management. Zhang Y's significant contributions and the United States' leading role underscore the global effort in advancing research in this area. The exploration of new technologies like 3D printing and nanotechnology, alongside traditional approaches, signifies the dynamic nature of biomedical research in addressing burn injuries.

Highlights:
1. This research analyzes regenerative medicine trends for burn injuries, providing valuable insights into focal points and article characteristics, enhancing understanding of this critical healthcare issue.
2. This research analyzes trends in regenerative medicine for burn injuries, highlighting emerging areas like 3D printing, nanotechnology, and photothermal therapy as promising future research directions.

INTRODUCTION

Burn injuries pose a significant global health challenge and can be life-threatening.[1] It is caused by exposure to hot liquids, solids, flames, radiation, electricity, friction, or chemicals. Burns contribute significantly to injury, disability, and mortality, particularly in low-to-middle-income countries.[2] Extensive burn injuries have lasting physical effects, including persistent pain, scarring, inflammation, metabolic changes, contractures, amputations, and disfiguring scars.[3,4] These injuries are recognized not only as acute trauma but also as a chronic disease, impacting various body systems and leading to long-term consequences for mortality, metabolism, immune function, cardiovascular health, and susceptibility to infections and tumors.[5]

Regenerative medicine is a multidisciplinary field focused on repairing, replacing, or regenerating cells, tissues, or organs to restore impaired function caused by congenital defects, disease, trauma, or aging.[6] In the context of burn injuries, regenerative medicine plays a crucial role by offering innovative approaches for wound healing. Stem cells and their derivatives, such as exosomes and conditioned media, have shown promise in promoting burn wound repair through various signaling pathways.[7] The benefits of regenerative medicine for burn injuries include enhanced skin repair, reduced scar formation, improved immune response, and functional skin reconstruction. Overall, regenerative medicine aims to improve burn wound healing, minimize scarring, and restore functional skin.[8]

This study conducts a thorough bibliometric analysis and literature review on the application of regenerative medicine in burn injury management. We highlight the trends, hotspots, and article profiles. It aims provide insights for future research to enhance burn care management.

METHODS

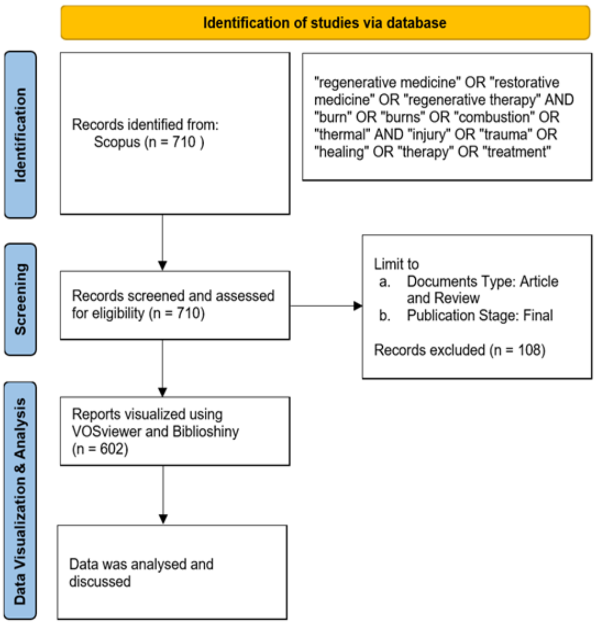

Figure 1. PRISMA 2020 flow diagram for bibliometric analysis

The data was acquired from the Scopus database through a search conducted with the keywords "regenerative medicine" OR "restorative medicine" OR "regenerative therapy" AND "burn" OR "burns" OR "combustion" OR "thermal" AND "injury" OR "trauma" OR "healing" OR "therapy" OR "treatment". The initial search obtained 710 documents. Subsequently, the search results were refined to include only documents classified as Article or Review document and in the Final publication stage, resulting in a finding 602 documents. The complete process is illustrated in Figure 1. The downloaded data were then analysed with VOSviewer (version 1.6.20) for mapping the cluster analysis and data visualization.[9] Additionally, study characteristics and thematic map analysis were examined using Biblioshiny software.

RESULTS

Study Characteristics

A total of 602 papers were gathered from 357 sources, covering the years 2004 to 2024. The annual growth rate stands at 10.96%, and the average document age is 6.07 years. The rise in collected papers is attributed to increased governmental interest in regenerative medicine, marked by a rise in federal funding and recognition of its pivotal role in healthcare. On average, each document receives 42.19 citations. The cumulative contributor count reaches 3,180 individuals, with 1,622 author-provided keywords. Notably, there are 42 single-authored documents, indicating a preference for individual contributions. However, with an average of 6.05 co-authors per document and an international co-authorship rate of 26.91%, collaboration among authors from various locations or institutions remains significant.

Annual Scientific Publications

The exported data provides a chronological overview of the annual publication trends from 2004 to 2024. Starting modestly with 2 articles in 2004, the number gradually increases over the years, showing occasional fluctuations. A noticeable uptick to 18 articles in 2012 is followed by a substantial rise to 82 articles in 2022, marking a significant peak. However, the trend reverses in subsequent years, with a notable decrease to 16 articles in 2024. This decline may be due to the fact that 2024 is only in its initial third period, allowing for additional articles to be added. This data highlights the dynamic nature of scholarly output over the analyzed period, capturing both periods of growth and decline in research productivity. The complete annual scientific productions were depicted in Figure 2.

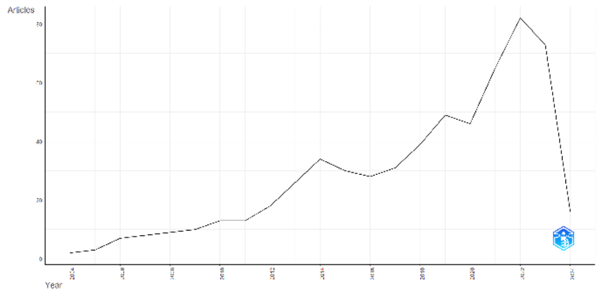

Figure 2. The annual publication of regenerative medicine in burn injury from 2004 to 2024

Authors, Institutions, and Country Data

The list of most relevant authors reveals individuals who have made substantial contributions to the research field, as evidenced by their publication counts. Leading the list are Zhang Y and Zhang Z, with a combined output of eight publications. Following closely are Applegate LA, Michetti M, Nilforoushzadeh MA, Raffoul W, Scaletta C, and Zhang X, each credited with seven publications, showcasing their steadfast dedication to scholarly inquiry and the dissemination of cutting-edge findings. Additionally, the inclusion of Amirkhani MA and Atala A, renowned for their scholarly prowess, with six publications each, underscores the depth and diversity of expertise within this esteemed group of authors. This data emphasizes the significant role these authors play in shaping discourse and advancing progress in their field of study, highlighting their valuable insights and unwavering commitment to scholarly inquiry.

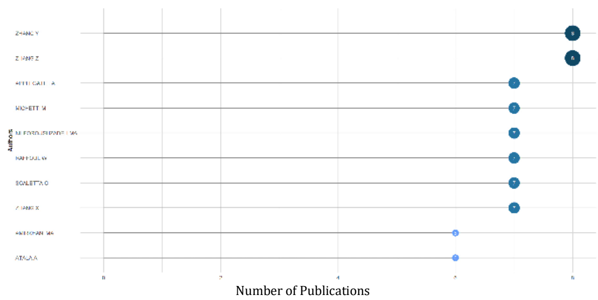

Figure 3. Top relevant authors for regenerative medicine in burn injury

The most significant affiliators represent a diverse array of institutions from around the globe. Leading the list is Lausanne University Hospital, with an impressive total of 72 articles, indicating its substantial contribution to scientific research. Close behind is the University of California, with 46 articles, demonstrating its prominence in academia and research endeavors. Tehran University of Medical Sciences also emerges as a notable affiliation, contributing 32 articles to the scientific literature. Furthermore, institutions such as University College London, China, and the University of Modena and Reggio Emilia have made substantial contributions, with 25, 24, and 22 articles respectively. The authors with the highest number of publications, ranking within the top ten in terms of productivity, were visualized in Figure 3. This data underscores the global collaboration and the pivotal role played by these institutions in shaping the landscape of scientific research.

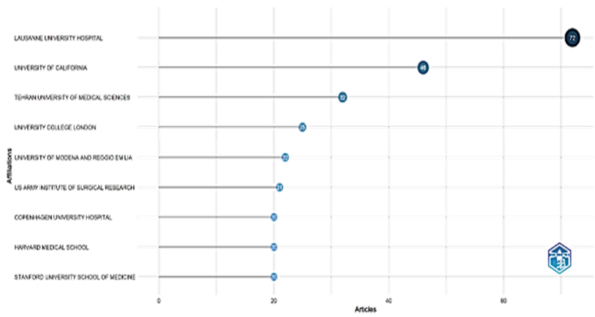

Figure 4. Top relevant affiliations for regenerative medicine in burn injury

The analysis of countries' scientific output reveals a diverse global landscape of research. Leading the list is the United States, with a formidable total of 527 scientific contributions, highlighting its enduring status as a powerhouse in scientific innovation and discovery. Following closely is China, with 426 publications, showcasing the country's rapid rise in the global scientific arena and increased investment in research and development. This data is unsurprising because the most relevant authors are Zhang Y and Zhang X, who both come from China. Italy and Iran also emerged as significant contributors, with 228 and 205 publications respectively, demonstrating their substantial contributions to advancing knowledge within their respective fields. Additionally, countries such as Japan, India, Brazil, Germany, South Korea, and France exhibit considerable scientific output, each contributing valuable insights to the collective pool of scientific knowledge.

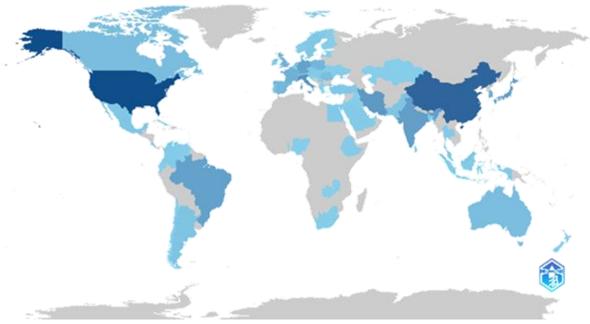

Figure 5. Top countries' scientific productions were visualized by contrasting shades on global map

Indonesia is positioned 34th in the ranking, indicating its scientific engagement with 13 publications, which could serve as catalysts for further research. Figure 5 visually represents this data on a global map using distinct shades. The darker shades on the Global Map indicate a greater publication rate ratio in comparison to the lighter shades. This examination offers valuable perspectives on the global distribution of scientific output, emphasizing the varied contributions of countries in fostering scientific advancement and innovation.

Research Hotspots and Frontier Trends in The Field of Regenerative Medicine

Figure 6 shows a network visualization map depicting keyword occurrences related to regenerative medicine in burn injury. It illustrates the connections between clusters and the assessed problem areas. Researchers established a minimum threshold of five occurrences for keyword inclusion. Out of the initial 6811 keywords considered, only 85 met this criterion across four clusters.

Cluster 1 (red) predominantly encompasses topics related to materials and techniques used in biomedical applications. Keywords such as 3D printing, alginate, collagen, nanofiber, nanoparticles, biocompatibility, biomedical applications, graphene, hydrogel, photothermal therapy, hydroxyapatite, silk fibroin, scaffold, and chitosan are included. These topics primarily focus on materials and methods utilized in biomedicine, including manufacturing techniques, drug delivery systems, and scaffold materials for tissue engineering.

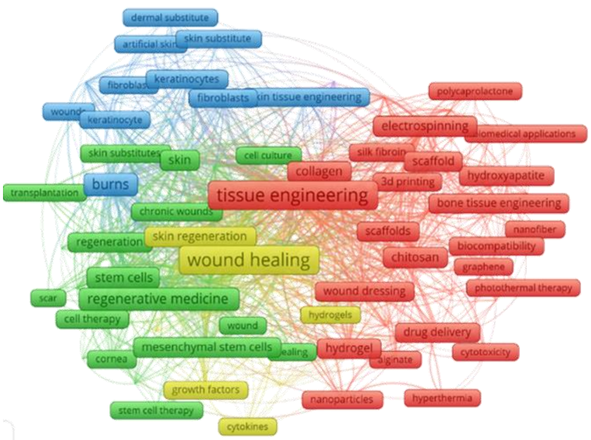

Figure 6. The visualization map of keyword occurrence

Cluster 2 (blue) encompasses topics related to burn treatment and skin substitutes such as skin tissue engineering, dermal substitute, artificial skin, keratinocytes, and fibroblast. These topics revolve around artificial or bioengineered products used to replace damaged skin in burn patients and the overall goal of promoting effective skin regeneration.

Cluster 3 (green) comprises topics associated with regenerative medicine focusing on cell-based therapies. Keywords such as regenerative medicine, stem cells, mesenchymal stem cells, stem cell therapy, cornea, transplantation, cell culture, chronic wounds, scar, and wound are included. This cluster focuses on regenerative medicine, including cell-based therapies, tissue regeneration, and engineering approaches to repair or replace damaged tissues.

Cluster 4 (yellow) focuses on topics related to wound healing and management, with a spotlight on the biological and therapeutic aspects of wound healing and regenerative medicine. Keywords such as wound healing, skin regeneration, growth factor, and cytokines are included. The integration of these biological components into advanced therapeutic strategies and biomaterials represents a significant frontier in improving patient outcomes in wound care and tissue regeneration.

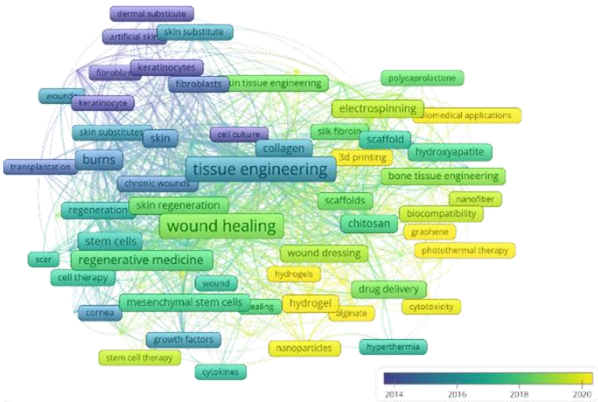

Figure 7. The visualization map of the keyword overlay by year. Yellow color indicates newer keyword distribution.

Figure 7 illustrates the evolution of research trends concerning regenerative medicine in burn injury. Prior to 2020, areas such as tissue engineering, wound healing, biomaterials, and stem cell therapy held significant importance in scientific research, with ongoing studies some time. Some topics, like stem cell therapy and tissue engineering, garnered substantial recognition among other scientists, evident from the frequency of citations their articles received. Research on topics like wound healing and tissue regeneration also made a significant impact relative to the number of articles published on these subjects.

After 2020, researchers continue to explore topics like 3D printing, hydrogel, alginate, graphene, and photothermal therapy. The studies published after 2020 are more recent, indicating researchers' exploration of newer ideas and technologies. Although newer topics such as 3D printing, nanotechnology, and photothermal therapy may not have garnered as many citations yet, they hold promise for the future as interest in them grows. The impact of these emerging topics may vary, but they have the potential to gain prominence as they become more widely recognized.

Overall, scientific research both before and after 2020 has focused tissue engineering and wound healing, while also venturing into newer fields like 3D printing and nanotechnology. This shift towards exploring new technologies underscores the continuous progress and dynamic nature of biomedical research.

Thematic Map Analysis

We conducted a thematic mapping analysis to provide valuable insights for researchers regarding potential avenues for future research in specific thematic areas.[9] The Thematic Map was created using author keywords and formulated based on a two-dimensional matrix that incorporates two distinct metrics: centrality (X-axis, indicating theme relevance) and density (Y-axis, representing theme development level).

In our thematic analysis of Figure 8, each quadrant of the thematic map conveys distinct characteristics of research themes within the field. Starting from the lower right quadrant, we come across the basic themes, which show a significant balance of low density and high centrality. This is highly important in the field of research. Clusters such as regenerative medicine, wound healing, and tissue engineering are fundamental areas that have been extensively studied and form the basis of our understanding. Interestingly, a cluster involving drug delivery, chitosan, and scaffolds, which are not core keywords, also appears in this quadrant.

Conversely, the lower left quadrant encompasses Emerging or Declining Themes, representing new or evolving topics that may either rise to prominence or diminish from the research arena over time. Here, clusters such as graphene and stem cell therapy illustrate themes currently under exploration that could potentially influence future research trajectories.

Moving to the upper left quadrant, we encounter Niche Themes, characterized by high density but lower centrality. These themes are highly developed yet somewhat isolated within the broader research discourse. Clusters such as nanomedicine, electrospinning, nanofibers, and silk fibroin represent specialized areas of research that have received significant attention and advancement despite their relatively limited integration into mainstream research agendas.

Finally, in the upper right quadrant lie the Motor Themes, distinguished by their high density and centrality, indicating their pivotal role and extensive exploration within the field. These themes serve as driving forces behind research endeavors, representing well-established and essential aspects of scientific inquiry. Clusters such as fibroblasts, keratinocytes, biotechnology, collagen, skin regeneration, and adipose-derived stem cells exemplify themes that are not only highly developed but also crucial to advancing our understanding and applications within the field of study.

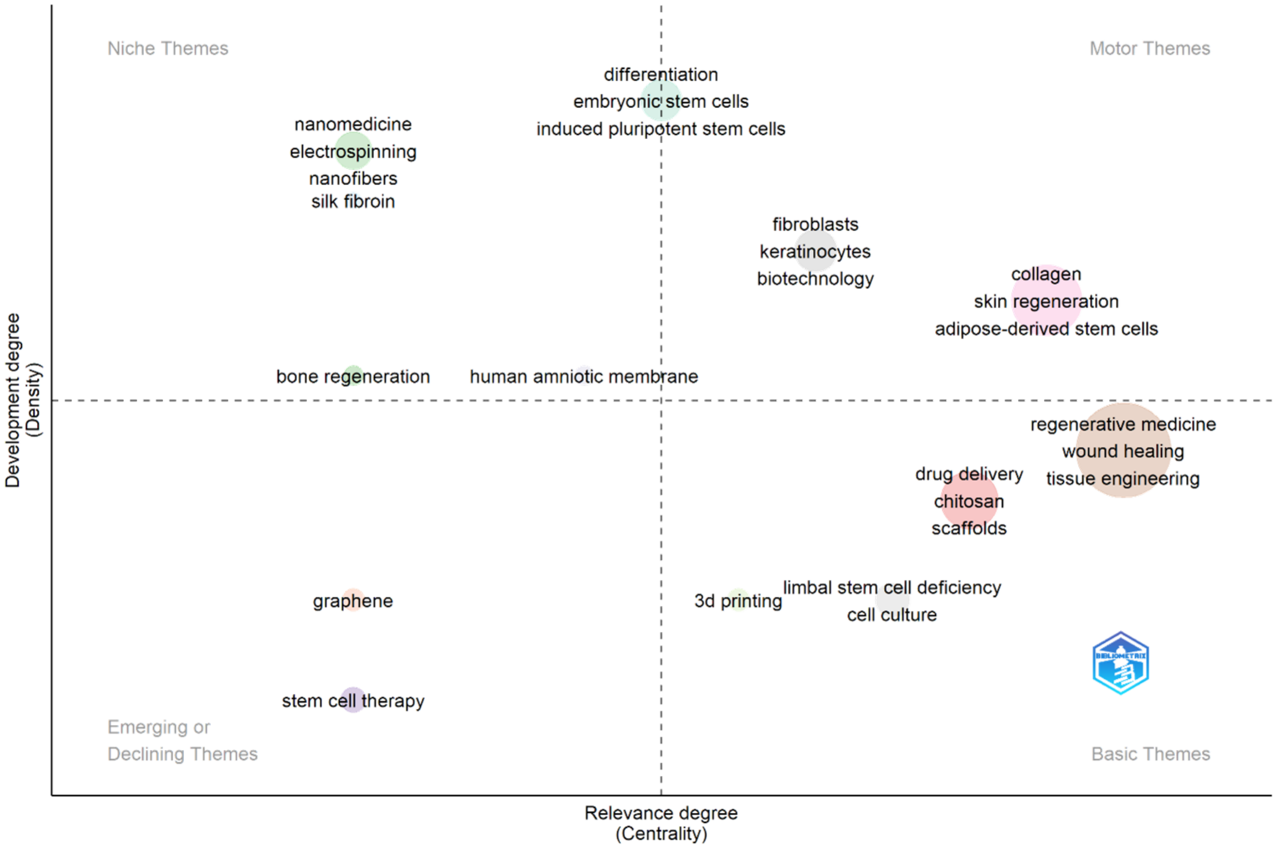

Figure 8. Thematic Map analysis

DISCUSSION

Burn injuries are defined as tissue damage caused by exposure to thermal, chemical, electrical, or radiation sources. According to the World Health Organization (WHO), burns can be classified based on their depth and extent of tissue involvement, ranging from superficial to deep and involving varying percentages of the total body surface area.[10] Epidemiological studies show a significant global burden of burn injuries, with around 180,000 deaths annually and millions living with lifelong disabilities.[11] Children and young adults are particularly at risk, often suffering burns from scalds and flames, while older adults are more likely to experience burns from hot liquids and fires.[12] Common causes of burn injuries include residential fires, occupational accidents, electrical malfunctions, and chemical exposures.[13]

Burn injury management usually requires a multidisciplinary approach involving wound care, infection prevention, fluid resuscitation, and rehabilitation. Conventional treatment methods include debridement, topical antimicrobial agents, skin grafting, and supportive care.[14] Although these interventions have improved survival rates and functional outcomes, they still have limitations. Challenges such as wound infections, scarring, contractures, and long-term disability persist, emphasizing the necessity for innovative therapeutic approaches to improve burn wound healing and tissue regeneration.[15]

Regenerative therapy for burn injuries presents several areas that require further research to advance treatment options and optimize patient outcomes. One critical area of investigation is the development of biomaterials specifically tailored for burn wound healing. Researchers are exploring innovative materials that mimic the native extracellular matrix (ECM) to promote cell adhesion, proliferation, and differentiation at the wound site. By optimizing the mechanical, structural, and biochemical properties of biomaterials, there is potential to enhance wound closure, prevent infection, and minimize scar formation in burn patients.[16,17]

Another crucial aspect of research is gaining a deeper understanding of the underlying regenerative mechanisms involved in wound healing. This includes elucidating the roles of stem cells, growth factors, and immune cells in tissue regeneration and inflammation modulation. By unraveling these mechanisms at a molecular and cellular level, researchers can develop targeted therapies that accelerate wound healing and promote more robust tissue regeneration in burn injuries.[18]

Furthermore, integrating different therapeutic approaches, such as stem cell therapy, growth factor delivery, and tissue engineering, requires comprehensive investigation. Researchers are exploring how to combine these strategies synergistically to maximize treatment efficacy, reduce healing time, and improve functional outcomes for burn patients. Clinical translation of these promising research findings into practice is essential, emphasizing the importance of conducting rigorous clinical trials to evaluate safety, efficacy, and feasibility in real-world settings.[19]

The sustainability of regenerative therapy technologies holds significant promise for improving outcomes in burn injury care, particularly in regions with limited resources. In the context of burn injuries, regenerative therapies offer innovative approaches to accelerate wound healing, reduce scarring, and improve functional outcomes.[20] However, the adoption and sustainability of these technologies in low-resource settings depend on addressing specific challenges related to cost, infrastructure, and capacity building.

For burn injury patients, optimizing the cost-effectiveness of regenerative therapies is paramount to ensure accessibility and affordability. Innovations aimed at reducing production costs and streamlining supply chain logistics can enhance the feasibility of incorporating regenerative treatments into burn care protocols.[21] Furthermore, investment in healthcare infrastructure, including facilities for cell culture and bioprocessing, is essential for scaling up regenerative therapies to meet the demand for burn injury treatment.

Capacity building initiatives that empower local healthcare providers and researchers to engage with regenerative medicine technologies are critical for sustainable implementation. By training professionals in burn care centers to utilize regenerative therapies effectively, countries can strengthen their healthcare systems and improve outcomes for burn patients. Integrating regenerative therapies into existing burn injury care protocols requires aligning regulatory frameworks and policies with local health systems to ensure equitable access and sustainable utilization.

More research is needed to establish definitive superiority across all clinical scenarios, existing evidence suggests that regenerative therapies hold promise for enhancing wound healing, reducing pain, and improving quality of life for patients with burns and chronic wounds. a randomized controlled trial by Hendry S et al. (2024)[22] compared the use of autologous skin cell suspension (ASCS) therapy with standard wound care in patients with severe burns. The study demonstrated faster wound closure, reduced pain levels, and improved scar quality in the ASCS therapy group compared to the control group. Similarly, a study by Ramaswamy RSH et al. (2018)[23] reviewed several clinical trials and concluded that regenerative therapies, such as platelet-rich plasma (PRP) and stem cell-based treatments, significantly improved wound healing outcomes compared to conventional treatments. In terms of patient-reported outcomes and quality of life, studies have shown positive results with regenerative therapies. For instance, a study by Malekzadeh H et al. (2023)[24] evaluated the impact of adipose-derived stem cell therapy on chronic wounds and found significant improvements in pain relief, wound healing rates, and overall patient satisfaction compared to standard wound care approaches.

Regenerative therapy offers a promising shift in burn injury management, leveraging the body's natural healing mechanisms to facilitate tissue repair and regeneration. Essentially, it involves utilizing biological agents like stem cells, growth factors, and biomaterials to stimulate tissue regeneration and restore functional integrity.[25] These approaches target the underlying pathophysiology of burn injuries, such as inflammation, impaired angiogenesis, and fibrosis, to promote healthy tissue regeneration and minimize scar formation.[26] In simpler terms, regenerative therapy for burn injuries can be classified into four main areas: Tissue Engineering, Biomaterials, Cell-based therapies, and Bioactive Factors.

Tissue Engineering

Tissue engineering presents innovative solutions for addressing the structural and functional deficits associated with burn injuries. Engineered skin substitutes, consisting of cells, scaffolds, and bioactive factors, demonstrate significant potential in promoting wound healing and tissue regeneration.[27] Recent advancements in tissue engineering techniques, including 3D bioprinting and decellularized matrices, enable the fabrication of complex tissue constructs resembling native skin, offering a promising alternative to traditional skin grafts in burn injury management.[28]

Cell-Based Therapies

Cell-based therapies show promise in enhancing wound healing and tissue regeneration for burn injuries. Mesenchymal stem cells (MSCs) and adipose-derived stem cells (ASCs) exhibit therapeutic potential due to their immunomodulatory and regenerative properties.[29] Clinical studies demonstrate the effectiveness of MSC and ASC-based therapies in promoting wound closure and reducing scar formation in burn injury patients.[30] Advances in cell culture techniques, such as microcarrier-based systems and bioreactor culture, facilitate large-scale expansion and delivery of therapeutic cells for clinical applications.[31]

Adipose-based cell therapy has emerged as a promising approach in the treatment of burn injuries. Adipose-derived stem cells (ADSCs) obtained from fat tissue have shown potential for promoting wound healing and tissue regeneration in burn patients. These stem cells can differentiate into various cell types and release growth factors that stimulate angiogenesis and modulate inflammation, contributing to accelerated wound closure and reduced scar formation. Clinical studies have demonstrated the safety and efficacy of

ADSC-based therapies in improving burn wound healing and functional outcomes.[32]

Biomaterials

In addition to cell-based therapies, biomaterials play a crucial role in burn wound care, particularly in intensive care units (ICUs). Biomaterials such as hydrogels, films, and nanofibers are used as wound dressings to create a favorable environment for healing, protect the wound from infection, and promote tissue regeneration. These materials can provide moisture balance, control inflammation, and deliver therapeutic agents to enhance wound healing. In ICU settings, advanced biomaterials are essential for managing complex burn injuries and preventing complications.[33]

Biomaterials play a crucial role in facilitating tissue regeneration and providing structural support for burn wound management. Hydrogels, scaffolds, and nanomaterials are utilized to create an optimal wound healing environment.[34] Recent developments in biomaterial design focus on improving biocompatibility, mechanical properties, and bioactivity to enhance tissue regeneration.[35] Additionally, biomaterial-based dressings and coatings are engineered with antimicrobial properties to reduce infection risk and promote wound healing.[36]

Bioactive Factors

The controlled release of bioactive factors, including growth factors and cytokines, offers a promising approach to stimulate tissue regeneration in burn injuries. Delivery systems based on biomaterials allow for the gradual release of bioactive factors at the injury site, promoting cell proliferation, angiogenesis, and remodeling of the extracellular matrix.[17] Recent research has focused on refining the timing and distribution of bioactive factor release to maximize therapeutic benefits while minimizing adverse effects.[33] Additionally, innovative methods such as gene therapy and exosome-based therapies hold potential for delivering bioactive factors to the wound site with precision.[37]

Recent advancements in regenerative approaches, including tissue engineering, biomaterials, cell-based therapies, and bioactive factors, hold great promise for improving outcomes in burn injury management. By harnessing the synergistic effects of these innovative strategies, researchers and clinicians are poised to revolutionize the treatment landscape for burn injury patients in the coming years.

3D Printing and Nanotechnology

The convergence of 3D printing and nanotechnology presents exciting opportunities to advance burn injury care. By harnessing these technologies, researchers are exploring innovative approaches to wound healing, tissue regeneration, and personalized treatments that could significantly improve outcomes and quality of life for burn patient. Advancements in 3D printing and nanotechnology hold promising implications for burn injury treatment and recovery. One notable application is the development of customized skin grafts using 3D bioprinting technology. Researchers are exploring the use of patient-specific cells and biomaterials to create bioengineered skin substitutes that closely mimic natural skin properties. These advanced grafts could improve wound healing and reduce scarring in burn patients, offering personalized solutions tailored to individual injury characteristics.[38]

The integration of 3D printing with microfluidics also offers potential benefits for burn injury management. Microfluidic devices can be used to create precise delivery systems for administering therapeutic agents or growth factors directly to burn wounds, optimizing treatment efficacy and minimizing adverse effects.[39-41]

Additionally, nanotechnology plays a crucial role in enhancing wound dressings and topical treatments for burn injuries. Nanomaterials, such as nanoparticles and nanofibers, can be incorporated into dressings to enhance antibacterial properties, promote wound healing, and prevent infection. The controlled release of therapeutic agents from nanocomposite materials can provide targeted and sustained treatment at the wound site, improving outcomes for burn patients.[42]

Photothermal Therapy

Photothermal therapy in burn injury involves using light energy, typically in the near-infrared range, to generate heat within tissues. This heat can selectively target damaged tissue, promoting wound healing and tissue regeneration while minimizing damage to surrounding healthy tissue. In the context of burn injuries, photothermal therapy can enhance drug delivery by increasing the permeability of the skin barrier, allowing therapeutic agents to penetrate deep into the wound site. Additionally, photothermal therapy can induce hyperthermia, which stimulates cellular responses such as the expression of heat shock proteins, further aiding in tissue repair. Overall, photothermal therapy offers a promising approach to improve the treatment outcomes of burn injuries by combining targeted drug delivery with localized heating effects to promote healing and reduce scarring.

Bolouki N et al. (2021)[43] studied the potential of photothermal therapy via cold atmospheric plasma (CAP) for improving drug delivery effectiveness in treating large and irregular burn wounds. They utilized CAP-induced crosslinking with methylcellulose (MC) to enable sustained delivery of therapeutic substances like platelets (SP) and polyethyleneimine-polypyrrole nanoparticles (PEI-PPy NP). The CAP-treated SP-PEI-PPy NP-MC polymer complex demonstrated enhanced mechanical properties, biocompatibility, sustained drug release, and near-infrared (NIR)-induced hyperthermia effects. This innovation highlights the potential of photothermal therapy in engineering carrier designs for burn treatment, offering improved drug delivery effectiveness and targeted heat delivery. This method holds promise as an innovative solution for future bioengineered carrier designs, facilitating enhanced mechanical properties, biocompatibility, sustained drug release, and NIR-induced hyperthermia effects to promote heat shock protein expression and drug permeation into deep lesions.

The use of stem cells or genetic manipulation in treating burn injuries raises important considerations related to safety, efficacy, and ethical implications. One significant concern is the risk of tumorigenicity associated with stem cell therapies, where the uncontrolled growth of stem cells or genetically modified cells may lead to tumor formation or other adverse effects. Additionally, genetic manipulation techniques like gene editing carry the risk of unintended genetic changes or off-target effects, which could pose long-term safety concerns for patients.[44]

Ethical considerations are paramount in the use of these advanced therapies. Obtaining informed consent from patients or research participants is crucial, ensuring they understand the experimental nature of the treatments and potential uncertainties involved. There are also ethical implications regarding resource allocation, ensuring equitable access to experimental therapies without exacerbating healthcare disparities.[45]

To address these concerns, robust regulatory and oversight processes are in place. Regulatory approval from government agencies, such as the FDA or equivalent bodies, is required before clinical trials can proceed. Institutional review boards (IRBs) or ethics committees evaluate study protocols, informed consent procedures, and participant protections to ensure compliance with ethical standards. Continuous monitoring and reporting of clinical trials are essential to track safety and efficacy outcomes and promptly address any adverse events.[46-48]

Guidelines and standards established by regulatory agencies and professional organizations further ensure that research adheres to ethical principles and patient safety standards. Collaboration among researchers, regulatory bodies, and ethics committees is critical to advancing innovative therapies while safeguarding patient welfare and upholding ethical standards in stem cell and genetic therapies for burn injury treatment.

Efforts to ensure the accessibility and inclusivity of regenerative therapies for all patients are crucial for advancing equitable healthcare practices. One key strategy involves research and development focused on creating cost-effective regenerative therapies that can be produced at scale. Innovations in manufacturing techniques, such as 3D bioprinting and automated cell processing, aim to reduce production costs and increase the availability of regenerative products, making them more accessible to diverse patient populations.

Another important aspect is the promotion of diversity in clinical trials and evidence generation. Inclusive clinical studies that represent a broad range of patient demographics, including diverse ethnic and socioeconomic backgrounds, are essential. By ensuring diverse representation in research, clinicians and researchers can better understand how regenerative therapies perform across different patient groups and tailor treatments accordingly.

Regulatory policies and reimbursement strategies also play a pivotal role in enhancing accessibility. Governments and regulatory agencies can streamline approval processes for innovative therapies, provide incentives for research and development in regenerative medicine, and ensure adequate reimbursement mechanisms. These policies facilitate patient access to cutting-edge treatments and promote health equity.[49,50]

Collaborative efforts across research, regulatory, and healthcare sectors are essential for ensuring the accessibility and inclusivity of regenerative therapies. By addressing barriers and implementing inclusive practices, healthcare systems can improve patient access to innovative treatments and advance health equity on a global scale.

Strength and Limitations

Bibliometric analysis tools like VOSViewer and Biblioshiny provide valuable insights into scholarly communication networks. VOSViewer excels at visualizing key patterns in network literature, such as topic clusters and keyword relationships. Biblioshiny, with its user-friendly interface, enhances accessibility by presenting literature data like the distribution of publication years, publication types, and the frequency of specific authors. However, the manual input required to determine cluster sizes in VOSViewer can influence how networks are colored, and Biblioshiny's reliance on predefined metrics may not fully capture the complexity of scholarly impact, potentially missing important aspects of academic influence beyond citation counts. Therefore, researchers should use these tools judiciously, supplementing their insights with contextual understanding. These tools offer a novel approach to bibliometric analysis by combining powerful visualization (VOSViewer) and user-friendly data presentation (Biblioshiny), significantly enhancing the ability to identify and understand complex scholarly communication networks. Their innovative features allow for more nuanced and accessible analyses compared to traditional bibliometric methods, fostering deeper insights and broader usage across various research disciplines.

CONCLUSION

The field of regenerative medicine in burn injury management is poised at the cusp of transformative advancements. By leveraging the synergistic potential of tissue engineering, cell-based therapies, biomaterials, and bioactive factors, this innovative approach offers a multi-faceted strategy to enhance wound healing, reduce scarring, and improve functional outcomes. As research continues to evolve, integrating these therapies into clinical practice will require rigorous clinical trials to ensure safety, efficacy, and feasibility. The future of burn care lies in the sustainable adoption of these cutting-edge technologies, promising a significant leap forward in patient care and recovery.

Through bibliometric and visualization methods, we concluded the following: (1) The number of publications in the field of regenerative medicine for burn injuries has significantly increased over the past two decades. (2) Our analysis underscores the critical role of 3D printing and nanotechnology. Future research should prioritize these areas, foster international collaboration, and increase funding to stimulate innovation in burn care. (3) Given that this study relied solely on the Scopus database, we recommend that future research incorporate a variety of databases (e.g., PubMed, Web of Science, and Springer) to capture a broader spectrum of high-quality scientific contributions.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

The authors declare no conflicts of interest regarding the publication of this article.

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AUTHOR CONTRIBUTION

Data collection, analysis and interpretation of the results was primarily undertaken by NAR and MYBP, under the supervision of SD. GEO, LPD, PS were critical revision of the article and proofreading. All authors contributed to the drafting of the manuscript and approved the final version for submission.

REFERENCES

1. Kuznetsova TA, Andryukov BG, Polovov SF, and Gazha AK. Modern aspects of burn injury immunopathogenesis and immuno-biochemical markers of wound healing (review of literature). *Klinicheskaia Laboratornaia Diagnostika.* 2022. 67(8):451-457. DOI: 10.51620/0869- 2084-2022-67-8-451-457

2. van Niekerk A. Burn-related injuries. In *Oxford Research Encyclopedia of Global Public Health.* 2022. DOI:10.1093/acrefore/9780190632366.013.305
3. Spiwak R, Sareen S, and Logsetty S. Techniques to assess long-term outcomes after burn injuries. *European burn journal.* 2022. 3(2): 328-339. DOI: 10.3390/ebj3020028
4. Wiechman SA. Long-Term Outcomes Following Burn Injuries. *Handbook of Burns Volume 2: Reconstruction and Rehabilitation.* 2020. 2:15-23. DOI: 10.1007/978-3- 030-34511-2_2
5. Popp D, Branski LK, and Kamolz P. Long-Term Sequelae of Burn Injury: Current Understanding of Pathophysiology, Therapeutic, and Rehabilitative Options with an Emphasis on Hypertrophic Scarring and Laser Therapy. *Burn Care and Treatment: A Practical Guide.* 2021. 181-197. DOI:10.1007/978-3-030-39 193-5_14
6. Mason C and Dunnill P. A brief definition of regenerative medicine. *Regenerative Medicine*. 2008.3(1):1–5. DOI: 10.2217/17460751.3.1.1
7. Abdul Kareem,N, Aijaz A, and Jeschke MG. Stem cell therapy for burns: story so far. *Biologics: Targets and Therapy*. 2021: 379-397. DOI:10.2147/BTT.S259 124
8. Shpichka A, Butnaru D, Bezrukov EA, Sukhanov RB, Atala A, Burdukovskii, V, et al. Skin tissue regeneration for burn injury. *Stem cell research & therapy*. 2019. 10:1-16. DOI: 10.1186/s13287-019-1203-3
9. Agbo FJ, Oyelere SS, Suhonen J, and Tukiainen, M. Scientific production and thematic breakthroughs in smart learning environments: a bibliometric analysis. *Smart Learning Environments*. 2021.8:1-25. DOI:10.1186/s40561-020 -00145-4
10. World Health Organization (WHO). Burns. Available from: https://www.who.int/news-room/fact-sheets/detail /burns
11. Peck MD, Kruger GE, Van Der Merwe A. E, Godakumbura W, and Ahuja RB. Burns and fires from non-electric domestic appliances in low and middle income countries: Part I. The scope of the problem. *Burns.* 2008. 34(3):303-311. DOI:10.1016/j.burns.2007.08.014
12. Aslan Baradaran, Edward W Buchel, and Joshua Vorstenbosch. Thermal Burns. (Accessed 23 October 2003). Available from:https://emedicine.medscape.com/article/1278244-overview?form=fpf
13. Haagsma JA, Graetz N, Bolliger I, Naghavi M, Higashi H, Mullany EC, et al. The global burden of injury: incidence, mortality, disability-adjusted life years and time trends from the Global Burden of Disease study 2013. *Injury Prevention.* 2016.22(1):3-18. DOI:10.11 36/injuryprev-2015-041616
14. Church D, Elsayed S, Reid O, Winston B, Lindsay R. Burn wound infections. *Clinical microbiology reviews.* 2006. 19(2): 403-434. DOI:10.1128/cmr.19.2. 403-434.2006
15. Colton BN, Nicholas CD, James MH, Michael M, and John GW. Burns: Pathophysiology of Systemic Complications and Current Management*. Journal of Burn Care & Research.*2017.38(1): e469–e481. DOI: 10.1097/BCR.0000000000000355
16. Oryan A, Alemzadeh E, and Moshiri A. Burn wound healing: present concepts, treatment strategies and future directions. *Journal of wound care.*2017. 26(1):5-19. DOI:10.12968/jowc.2017.2 6.1.5.
17. Hama R, Reinhardt JW, Ulziibayar A, Watanabe T, Kelly J, Shinoka T. Recent Tissue Engineering Approaches to Mimicking the Extracellular Matrix

Structure for Skin Regeneration. *Biomimetics*. 2023. 8(1):130. DOI:10.3390/biomimetics8010130
18. Eming SA, Martin P, and Tomic-Canic M. Wound repair and regeneration: mechanisms, signaling, and translation. *Science translational medicine.* 2014. 6(265): 265sr6-265sr6. DOI:10.1126/scitranslmed.3009337
19. Eming SA, Martin P, and Tomic-Canic M.Wound repair and regeneration: mechanisms, signaling, and translation. *Science translational medicine.* 2024. 6 (265): 265sr6-265sr6. DOI: 10.1126/scitranslmed.3009337
20. Stone II R, Natesan S, Kowalczewski CJ, Mangum LH, Clay NE, Clohessy RM, et al. Advancements in regenerative strategies through the continuum of burn care. *Frontiers in pharmacology.* 2018.9:672. DOI: 10.3389/fphar.2018.00672
21. Kowal S, Kruger E, Bilir P. et al. Cost-Effectiveness of the Use of Autologous Cell Harvesting Device Compared to Standard of Care for Treatment of Severe Burns in the United States. *Adv Ther.* 2019. 36:1715–1729. DOI:10.1007/s12325-019-00961-2
22. Henry S, Mapula S, Grevious M, Foster KN, Phelan H, Shupp J, et al. Maximizing wound coverage in full-thickness skin defects: a randomized-controlled trial of autologous skin cell suspension and widely meshed autograft versus standard autografting. *Journal of Trauma and Acute Care Surgery.*2024. 96(1):85-93. DOI: 10.1097/TA.0000000000004120
23. Ramaswamy RSH, Reddy R, Babu NC, and Ashok GN. Stem-cell therapy and platelet-rich plasma in regenerative medicines: A review on pros and cons of the technologies. *Journal Oral Maxillofac Pathol.*2018. 22(3): 367-374. DOI:10.4103/jomfp.JOMFP_93_18.
24. Malekzadeh H, Tirmizi Z, Arellano JA, Egro FM, Ejaz A. Application of Adipose-Tissue Derived Products for Burn Wound Healing. *Pharmaceuticals.* 2023. 16(9):1302. DOI:10.3390/ph16091302
25. Mao AS and Mooney DJ. Regenerative medicine: Current therapies and future directions. *Proceedings of the National Academy of Sciences*. 2015. 112(47): 14452-14459. DOI:10.1073/pnas.1508520112
26. Gurtner GC, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. Nature. 2008; 453 (7193):314-321.DOI: 10.1038/nature07039
27. Shevchenko RV, James SL, James SE. A review of tissue-engineered skin bioconstructs available for skin reconstruction. *Journal of the royal Society Interface.* 2010. 7(43):229-258. DOI:10.1098/rsif.2009.0403
28. Murphy SV and Atala A. 3D bioprinting of tissues and organs. Nature Biotechnology. 2014. 32(8): 773-785. DOI: 10.1038/nbt.2958
29. Nuschke A. Activity of mesenchymal stem cells in therapies for chronic skin wound healing. *Organogenesis.* 2014. 10(1):29-37.DOI: 10.4161/org.27405
30. Kadam S, Muthyala S, Nair PD, and Bhonde R. Human placenta-derived mesenchymal stem cells and islet-like cell clusters generated from these cells as a novel source for stem cell therapy in diabetes. *The review of diabetic studies: RDS*.2010. 7(2):168-182. DOI: 10.1900/RDS.2010.7.168
31. Nguyen MK and Alsberg E. Bioactive factor delivery strategies from engineered polymer hydrogels for therapeutic medicine. *Progress in polymer science.* 2014. 39(7): 1235-1265.DOI:10.1016/j.progpolymsci.2013.12.001
32. Kohlhauser M, Tuca A, and Kamolz LP. The efficacy of adipose-derived stem cells in burn injuries: a systematic

review. *Cellular & Molecular Biology Letters.*2024.29(1):10. DOI:10.1186/s11658-023-00526-w
33. Deng X, Gould M, and Ali MA. A review of current advancements for wound healing: Biomaterial applications and medical devices. *Journal of Biomedical Materials Research Part B: Applied Biomaterials*. 2022. 110(11): 2542-2573. DOI:10.1002/jbm.b.35086
34. Annabi N, Tamayol A, Uquillas JA, Akbari M, Bertassoni L E, Cha C, et al. 25th anniversary article: Rational design and applications of hydrogels in regenerative medicine. *Advanced materials.* 2024. 26(1): 85-124. DOI:10.10 02/adma.201303233
35. Lee K, Silva EA, and Mooney DJ. Growth factor delivery-based tissue engineering: general approaches and a review of recent developments. *Journal of the Royal Society Interface*. 2011. 8(55): 153-170.DOI:10.1098/rsif.2010.0223
36. Boateng JS, Matthews KH, Stevens HN, Eccleston GM. Wound healing dressings and drug delivery systems: A review. *Journal Pharmacy Science*. 2008.97(8): 2892-2923. DOI: 10.1002/jps.21210
37. Vader P, Mol EA, Pasterkamp G, and Schiffelers RM. Extracellular vesicles for drug delivery. *Advanced drug delivery reviews.* 2016. 106: 148-156. DOI: 10.1016/j.addr.2016.02.006
38. Mathew V, Dafydd O. Visscher, Paul P. M. van Zuijlen, Anthony A, and James JY, Skin bioprinting: the future of burn wound reconstruction?, *Burns & Trauma.*2019.7:s41038–019–0142–7. DOI:10.1186/s41038-019-0142-7
39. Brown C, et al. (2023). Microfluidic devices for targeted drug delivery in burn wound care: current trends and future perspectives. *Expert Review of Medical Devices*. 20(3):243-259.
40. Manita PG, Garcia-Orue I, Santos-Vizcaino E, Hernandez RM, and Igartua M. 3D Bioprinting of Functional Skin Substitutes: From Current Achievements to Future Goals. Pharmaceuticals. 2021. 14(4):362. DOI:10.3390/ph140403 62
41. Alapan Y, Hasan MN. Shen R. and Gurkan UA. Three-Dimensional Printing Based Hybrid Manufacturing of Microfluidic Devices. J. Nanotechnol. Eng. Med. 2015. 6:021007.
42. Na R. and Wei T. Recent perspectives of nanotechnology in burn wounds management: a review. *Journal of Wound Care.* 2021. 30(5): 350-370. DOI:10.12968/jowc.2021.30.5.350
43. Bolouki N, Hsu YN, Hsiao YC, Jheng PR, Hsieh JH, Chen HL, et al. Cold atmospheric plasma physically reinforced substances of platelets-laden photothermal-responsive methylcellulose complex restores burn wounds. *International Journal of Biological Macromolecules.* 2021. 192: 506-515. DOI:10.1016/j.ijbiomac.2021.09.168
44. Knoepfler PS. Deconstructing stem cell tumorigenicity: a roadmap to safe regenerative medicine. *Stem cells*. 2009. 27(5):1050-1056. DOI:10.1002/stem.37
45. King NM and Perrin J.Ethical issues in stem cell research and therapy. *Stem Cell Research & Therapy.* 2014. 5:1-6. DOI:10.1186/scrt474
46. Michèle C, Alexis L, Corinne S, Laurent W, Jeanne-PS, Murielle M, et al. Burn Center Organization and Cellular Therapy Integration: Managing Risks and Costs, *Journal of Burn Care & Research.*2021. 42(5): 911–924. DOI:10.1093/jbcr/irab080
47. Wong RSY, Maran S, and Goh BH. Current Guidelines, Challenges, and Future Recommendations for Regulation of Stem Cell Research and Therapy: A Commentary. Cytotherapy. 2024. DOI:10.1016/j.jcyt.2024.04.076

48. Bauer SR.Stem cell-based products in medicine: FDA Regulatory Considerations. Handbook of stem cells. 2004. 805. DOI:10.1016/B978-012436 643-5/50163-2
49. Tingting Q. Regenerative medicine with substantial promises but challenges in market access: strategies to accommodate such innovative products within the current healthcare system. 2021. *PhD Thesis. Aix-Marseille.*
50. Bubela T, McCabe C, Archibald P, Atkins H, Bradshaw SE, Kefalas P,et al. Bringing regenerative medicines to the clinic: the future for regulation and reimbursement. Regenerative medicine. 2015. 10(7): 897-911. DOI: 10.2217/rme.15.51