

REVIEW

## Regenerative medicine and tissue engineering from an innovative approach

### Medicina regenerativa y la ingeniería de tejidos a partir de un enfoque innovador

Ana Maria Chaves Cano<sup>1</sup>  , Alfredo Javier Pérez Gamboa<sup>2</sup>  , William Castillo-González<sup>3</sup>  

<sup>1</sup>Fundación Universitaria Juan N. Corpas. Bogotá, Colombia.

<sup>2</sup>Centro de Investigación en Educación, Naturaleza, Cultura e Innovación para la Amazonia. Florencia, Colombia.

<sup>3</sup>Universidad de Ciencias Empresariales y Sociales. Buenos Aires, Argentina.

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Corresponding Author: William Castillo-González 

#### ABSTRACT

**Introduction:** regenerative medicine, as an area of scientific work and development within the medical sciences, opens new doors in the management and treatment of various pathologies (chronic or not).

**Objective:** to assess the implementation of regenerative medicine and tissue engineering based on an innovative approach.

**Method:** a comprehensive review of related bibliographic sources was conducted. The search strategy used the terms regenerative medicine and tissue engineering. The databases used were SciELO and PubMed. A multi-step screening process was used to select the articles.

**Development:** thirteen primary research projects were selected. Different areas within regenerative medicine and tissue engineering were addressed. The application of biocomponents such as hydrogels and blood products is gaining ground due to their limited antigenic effects. Furthermore, stem cells remain a promising alternative, with a growing trend toward preventive actions for chronic conditions. For their part, the development of research and clinical studies is key to the theoretical and practical contributions of these techniques and the new ones developed.

**Conclusions:** regenerative medicine and tissue engineering are presented as novel and revolutionary alternatives within medicine. Their applications are broad and at the same time specific to each specialty. Numerous studies and research (in vitro and in vivo) provide theoretical advances that may constitute novel treatments in the future.

**Keywords:** Stem Cells; Tissue Engineering; Regenerative Medicine; Regenerative Therapy; Innovation.

#### RESUMEN

**Introducción:** la medicina regenerativa, como área de trabajo y desarrollo científico dentro de las ciencias médicas, abren nuevas puertas en el manejo y tratamiento de diferentes patologías (crónicas o no).

**Objetivo:** valorar la implementación de la medicina regenerativa y la ingeniería de tejidos a partir de un enfoque innovador

**Método:** se desarrolló una revisión exhaustiva de fuentes bibliográficas relacionadas. Para la elaboración de la estrategia de búsqueda se implementaron los términos: medicina regenerativa e ingeniería de tejidos. Las bases de datos empleadas fueron: SciELO y PubMed. Para la selección de los artículos, realizo un proceso de cribado dividido en varios pasos.

**Desarrollo:** fueron seleccionadas 13 investigaciones principales. Se abordaron diferentes áreas dentro de la medicina regenerativa y la ingeniería de tejidos. La aplicación de biocomponentes como los hidrogeles y hemoderivados gana terreno por sus escasos efectos antigénicos. Por otra parte, las células madres se

mantienen como una alternativa prometedora; con una tendencia creciente hacia las acciones preventivas de afecciones cónicas. Por su parte, el desarrollo de investigaciones y estudios clínicos es clave para los aportes teóricos y prácticos de estas técnicas y las nuevas desarrollados.

**Conclusiones:** la medicina regenerativa y la ingeniería de tejidos se presentan como alternativas novedosas y revolucionarias dentro de la medicina. Sus aplicaciones son amplias y a la vez particulares para cada especialidad. Numerosos son los estudios e investigaciones (in vitro e in vivo) que aportan avances teóricos que pueden constituir novedosos tratamientos en un futuro.

**Palabras clave:** Células Madre; Ingeniería de tejidos; Medicina regenerativa; Terapia Regenerativa; Innovación.

## INTRODUCTION

In the current times where visual and physical details are an indissoluble part of our work, the treatment and management of any injury from the aesthetic point of view has become an aspect to be taken into account in different scenarios. On the other hand, new advances go beyond the limits of aesthetics and have focused on the resolution of chronic diseases whose therapeutic pillars are based on symptomatic management.

Regenerative medicine, as an area of work and scientific development within the medical sciences, opens new doors in the management and treatment of different pathologies (chronic or not) such as diabetes mellitus, organ transplantation (at different levels, especially renal, bone marrow and others). In addition to the management of degenerative diseases such as Alzheimer's disease. Greater life expectancy and perfection of therapeutic guidelines are achieved. These strategies include the use of stem cells, growth factors and the use of the extracellular matrix.<sup>(1)</sup>

Within regenerative medicine, tissue engineering is aimed at the healing and management of skin lesions through the gradual restoration and reestablishment of the functions of the skin as an organ. Products or forms of treatment through the use of synthetic or biological materials (autologous, allogenic or xenogenic) are just some of the examples of applications.<sup>(2,3)</sup>

One of the main contributions and areas of work where regenerative regeneration strategies or techniques can be found are based on the treatment of burns and aesthetic and reconstructive surgery.<sup>(4)</sup> Undoubtedly, tissue injury from burn injuries can generate feelings of frustration or depression in the patient, so the application of regenerative medicine techniques are key not only for tissue revitalization, but also help in the psychological care of the patient.

There are many studies that address the applications of regenerative medicine and the progress evidenced to date. A clear example is the research developed by Zurita Delgado et al.<sup>(5)</sup> referring to the treatment of epidermolysis bullosa through its systematic review of new regeneration techniques through stem cells and regenerative medicine itself.

On the other hand, the use of new technology opens up new opportunities for the treatment of patients and a host of therapeutic varieties. Among them is the use of 3D printers or bioprinters; an instrument based on the generation of new tissues and/or (artificial) organs<sup>(6)</sup> that would guarantee a greater contribution to the quality of life of patients who are part of the long waiting lists for treatment through organ transplants.

The advance of technologies has been evidenced in each of man's work scenarios. Medicine, with its different specialties, has not resisted the updating of each of its processes through the implementation of new digital and technological tools. Many chronic pathologies or injuries secondary to massive injuries have seen their resolution through the opportunities offered by regenerative medicine (with its different forms and methods), with the updating of therapeutic protocols (previously only with a symptomatic approach). On the basis of the above, the authors of the present article intend to assess the implementation of regenerative medicine and tissue engineering from an innovative approach.

## METHOD

An exhaustive review of bibliographic sources related to the subject was carried out in order to fulfill the objective set by the authors.

For the elaboration of the search strategy, the following terms were used: regenerative medicine and tissue engineering as well as their equivalents in English (*Regenerative medicine and tissue engineering*), keywords; in addition to the equivalent descriptors from the Descriptor in Health Sciences (DeCS) and its counterpart in English (MeSH). The words and descriptors were related using Boolean operators: (*Regenerative medicine*) AND (*tissue engineering*). The databases used were: SciELO and PubMed. Articles on revision, meta-analysis, original research and others considered of interest for the research were included.

For the selection of the articles, a screening process divided into several steps was carried out. In the first step, the filters provided by the databases (especially the temporal filter) were used. The resulting total

of articles (second step) was reviewed based on the analysis of the identifying elements of each document (title and abstract). In the third step, the articles were analyzed in depth to extract the main results and contributions of each study.

## DEVELOPMENT

The implementation of the search strategy yielded a total of 28 592 investigations (PubMed 28 568 and SCielo 24 articles). In the PubMed database, temporal filters were applied (articles with one year of publication); with 3250 investigations. The following filters were used: research available in full text (Free Full Text) and with results (Associated data) showing 25 researches. For the Scielo database, 24 researches were found. The 5-year filter was applied, showing 8 researches. After reviewing the titles and abstracts, 13 studies were selected (figure 1). The main results of each of the studies analyzed are shown in table 1.

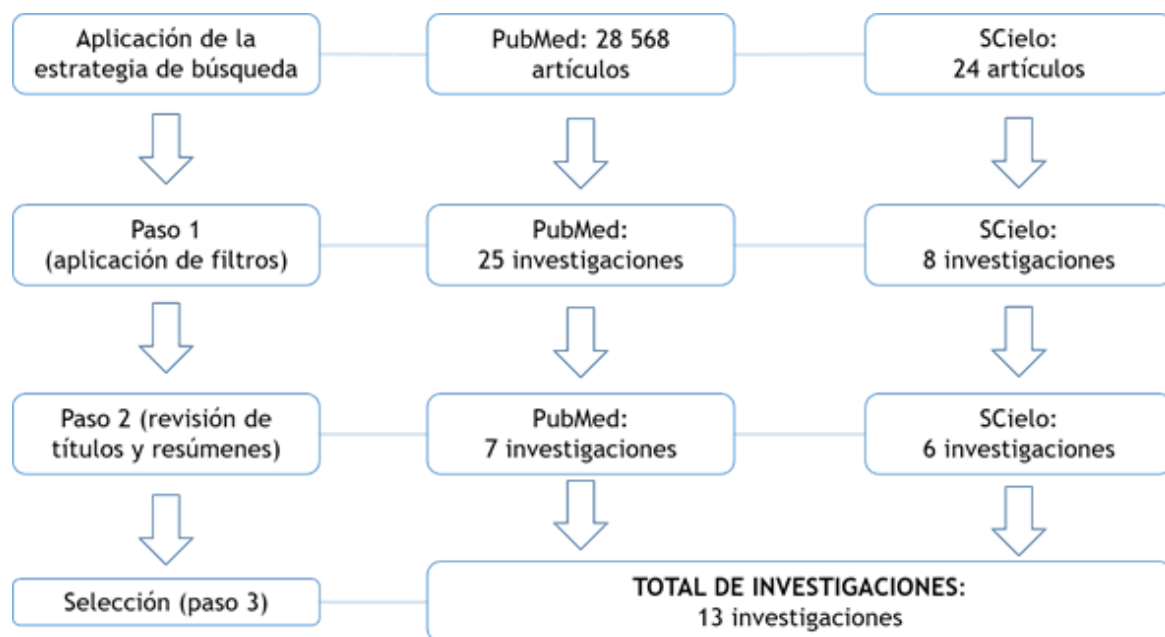


Figure 1. Distribution of the articles according to stages

Table 1. Presentation of the main contributions and results of the analyzed articles

Title	Author	Relevance of the study
The application of growth factors in the development of Bone Tissue Engineering	Orozco Muñoz et al. <sup>(7)</sup>	Study that frames the use of growth stimulating factors as part of the strategies of tissue engineering applied to traumatic injuries in Orthopedics and traumatology. Emphasizes the importance of knowledge of molecular biology.
Analysis of the Chemical Composition, Morphological Characterization, and Porosimetry of Allograft and Comparison with Xenograft for Dental Applications	Alarcón-Apablaza et al. <sup>(8)</sup>	Analyzes the physicochemical differences of two grafts and their possible applications in dental regeneration.
Cytotoxic and anti-inflammatory effects of chitosan and hemostatic gelatin in oral cell culture.	Narvaez-Flores et al. <sup>(9)</sup>	An experimental study is performed to evaluate the cell viability of chitosan and hemostatic gelatin in cell culture for dental therapeutics in tissue regeneration.
Novel Studies in the Designs of Natural, Synthetic, and Compound Hydrogels with Biomedical Applications	Cuellar Gaona et al. <sup>(10)</sup>	Systematic review on the application of regenerative substances and testing the efficacy of hydrogel composites.
A Review on the Advances of Biocompatible Materials and Their Processing Via Additive Manufacturing for Tissue Engineering Applications.	Jassen Morales et al. <sup>(11)</sup>	Research focused on the review of advances in regenerative medicine through the use of ad hoc biomaterials and additive manufacturing.
Cell culture: a promising environment for research on cardiology	Yuliet Montoya et al. <sup>(12)</sup>	Application of stem cell culture media for experimental research in various specialties, especially cardiology.
Engineered autologous nasal cartilage for repair of nasal septal perforations: a case series	Benedict Kaiser et al. <sup>(13)</sup>	Case series study on the use of tissue engineering for nasal cartilage regeneration.

Delivery of a Jagged1-PEG-MAL hydrogel with pediatric human bone cells regenerates critically sized craniofacial bone defects.	Archana Kamalakar et al. <sup>(14)</sup>	Study based on the application of hydrogel in the regeneration and healing of injuries and defects in pediatric patient's flesh-facial bones.
A genetic and microscopy toolkit for manipulating and monitoring regeneration in <i>Macrostomum lignano</i> .	Nelson Hall et al. <sup>(15)</sup>	Research showing advances in the exploration and investigation of tools for the study of tissue regeneration.
ALB-PRF facilitates chondrogenesis by promoting chondrocytes migration, proliferation and differentiation.	Lijuan Zeng et al. <sup>(16)</sup>	Based on the demonstration of ALB-PRF compound as a strategy for cartilage regeneration.
A single-cell 3D dynamic volume control system for chondrocytes	Qiang Zhang et al. <sup>(17)</sup>	Research showing advances in the application of the 3D cellular system for chondrocyte volume study.
Vasculogenic skin reprogramming requires TET-mediated gene demethylation in fibroblasts for rescuing impaired perfusion in diabetes.	Mohanty et al. <sup>(18)</sup>	Research based on vascular reprogramming techniques for blood reperfusion therapy in patients with diabetes.
Epicardial transplantation of antioxidant polyurethane scaffold based human amniotic epithelial stem cell patch for myocardial infarction treatment.	Jinying et al. <sup>(19)</sup>	They report the results of the use of amniotic epithelial cell transplantation in the treatment of acute myocardial infarction, as an alternative for cell regeneration.

### Use of biocomponents

Authors such as Orozco Muñoz et al.<sup>(7)</sup> in their research highlight the techniques of regenerative medicine, including tissue engineering. This technique involves the use of molecular and genetic therapy, as well as advanced cell therapy such as stem cells. It refers to the use of hemoderivatives such as platelet-rich plasmas and the existing evidence (through in vitro studies) of the application and platelet growth factors and their stimulation on trophoblastic proliferation that help the regeneration of damaged bone; with wide practical applications.

Platelet derivatives including fibrin-rich compounds are obtained from the centrifugation process of autologous uncoagulated blood. It emerged as an alternative treatment for the complications generated by platelet-rich plasma. Subsequently, its usefulness in tissue regeneration was demonstrated. Its continuous development has made it possible to obtain fibrin compounds with greater potential as fibrins rich in leukocytes. Their application guarantees a decrease in healing time, in addition to their anti-inflammatory effects.<sup>(20)</sup>

The application of biocomposites has undoubtedly revolutionized the treatment of regenerative medicine. Their low antigenicity makes them feasible alternatives that contribute to rapid healing and reduction of possible complications of major surgical interventions.

In turn, there are numerous compounds that can be applied as regenerative therapy due to their proven antiflamatopria efficacy in preventing bacterial growth (or cellularity) and promoting tissue regeneration. Narvaez-Flores et al.<sup>(9)</sup> analyzes and explores the application of dental compounds such as quintonasa or combined with hemostatic gelatin demonstrating its effect and anti-inflammatory application in a significant way; by decreasing between 5 and 11 % the viability of cellularity in their in vitro research. It also recognizes its application as part of the therapeutic strategies in dental regeneration.

Similar results have been obtained with the application of incomposites such as hydrogels. These can be classified according to their origin as natural, synthetic or composite. Greater repercussion and application of those composite materials has been achieved by including several components and/or physicochemical properties of their counterparts. They have gained popularity in the treatment of wounds by offering an ideal space for tissue regeneration, control of bacteria, among others.<sup>(10)</sup>

Another study offers satisfactory results on the use of hydrogel for the treatment of congenital lesions. According to the results presented by Archana Kamalakar et al.<sup>(14)</sup>, there are satisfactory results regarding the application of JAGGED1 in the solution of congenital bone lesions or defects in pediatric patients. The results, obtained in in vitro experiments, show a proliferation of osteosynthesis modeling cells through the activation of p70 S6K. These results have been presented as encouraging.

The ALB-PRF compound is presented as an opportunity for post-trauma cartilage proliferation. Its application is based on the results obtained from in vivo and in vitro investigations. They show that the compound favors regeneration from migration and proliferation of chondrocytes.<sup>(16)</sup>

Undoubtedly, the application of components that promote tissue growth has revolutionized regenerative medicine in the treatment of different tissue continuity solutions. It is projected as an area of work for the development of tissue engineering especially through the application of novel molecular biology and other techniques.

### Use of grafts and tissue regeneration

Tekines used in tissue revitalization have been revolutionized since their emergence. Jassen Morales et al.<sup>(11)</sup> discusses the advances achieved through additive manufacturing techniques and the use of ad hoc biomaterials as part of the tools of regenerative medicine. Additive manufacturing techniques focus on the production of cells and/or tissues in a biologically created environment with all the conditions for their growth. One of the main achievements has been experimented and applied in the regeneration of tissues and organs for transplantation.

Grafts are presented as alternatives with wide applications in the reconstruction of injuries or damaged areas. The knowledge of their components or characteristics helps to impose an adequate therapeutic conduct. The research of Alarcón-Apablaza et al.<sup>(8)</sup> focuses on the comparison from the physical-chemical and morphological point of view of allograft and bone xenograft (coil) for dental bone regeneration. In the study significant differences were found in relation to the chemical components of each composite. In addition the morphological structures differed in relation to porosity and spatial geometric structure.

The importance of a thorough analysis of each of the techniques and materials used in tissue regeneration is understood. These are two key elements, in the authors' opinion, that should be taken into account for the selection of materials; with the aim of obtaining encouraging results.

The research process based on these biocomponents is a key process; it is understood that the utilities of regenerative medicine include not only the area of medical assistance, but also the research process itself.

The use of 3D technology has positioned itself in the treatment of tissue regeneration. An example is the case study developed by Benedict Kaiser et al.<sup>(13)</sup> Other applications of 3D bioprinting technology have been evidenced in the management and treatment of chronic renal failure where it could solve the clinical situation of millions of people, by combining living cells and growth factors as well as biomaterials. Suitable environments are created for cell growth and development to obtain new tissues.<sup>(21)</sup>

The research is based on a series of cases that underwent treatment using 3D technology for the generation of nasal cartilage. The therapeutic system was found to be safe and easy to apply, and the results were feasible. Post-treatment studies were satisfactory in most of the patients, so it was considered a validated treatment.

### Application of stem cells as transplantation alternatives

Jinying et al.<sup>(19)</sup> in their experimental animal study, by transplantation of immunologically modified human amniotic cells has shown a significant reduction of cardiac injury by promoting myocardial cell reconstruction.

The application of stem cells as an alternative treatment for injuries or diseases has revolutionized the precepts and modalities of action of regenerative medicine. Hematopoietic and mesenchymal stem cells (from bone marrow, umbilical cord, placenta, blood and other filaments or components) have been studied and used in their application.<sup>(22)</sup>

Their applications go beyond the previously defined therapeutic horizons (treatment of chronic diseases); they can be used as a preventive alternative for multiple processes. In experimental studies, tissue engineering using stem cells was able to revitalize esophageal lesions caused by caustic, reflux or metaplastic lesions.<sup>(22)</sup> Other specialties (such as dentistry) benefit from stem cell therapy. In this scenario, advances have been made in the management of traumatic injuries, regeneration of dental tissues and other pathologies.<sup>(23)</sup>

These theoretical contributions: still under experimentation may open new possibilities in cancer prevention, especially in the digestive system, thus decreasing the incidence and prevalence of these diseases. It also highlights one of the basic functions within health care: prevention.

### Development of research in relation to regenerative medicine.

The progress of the research process guarantees the application of validated results; as well as the implementation of protocols and novel research methods. Models have been developed for the study of cell regeneration; models that are not only based on the observation of cell growth and division. They involve the study of the genetic component of the cell.<sup>(15)</sup>

For its part, the use of the 3D cellular system opens new opportunities for the understanding of physiological processes. Among them, its application has been seen in the study of the chondrocyte system within the joint mass. Results related to their proliferation, spatial distribution and matrix components are provided.<sup>(17)</sup> Undoubtedly, results that can contribute to the understanding and application of new therapeutic alternatives based on physiological processes.

Tissue nanotransfection (TNT) topically delivers Etv2, Foxc2, and Flt1 (EFF) plasmids are components that promote vascularization from proliferating fibroblasts. Their applications have been analyzed in the treatment of dermal lesions in patients with diabetes by means of natural regeneration from fibroblast proliferation and tissue revitalization. This alternative has been termed dermal vasculogenic reprogramming.<sup>(18)</sup> It is presented as a promising alternative for the management of superficial lesions or infections due to microvascular damage in patients with diabetes.



According to results developed by Marcial Becerril et al.<sup>(24)</sup> the incorporation of gold nanoparticles in tissue culture and scaffolding using tissue engineering techniques offers greater resistance capacity and physical and chemical properties.

Among them the diffusion of and absorption of water which favors a greater nutrition of the receptor tissue. In addition to having a degenerative capacity in a prudential time that allows the regeneration of the damaged tissue and the elimination of the allograft once its function is completed.

## CONCLUSIONS

Regenerative medicine and tissue engineering are presented as novel and revolutionary alternatives in medicine. Their applications are broad and at the same time specific to each specialty. Numerous studies and investigations (in vitro and in vivo) provide theoretical advances that may constitute novel treatments in the future.

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## CONFLICT OF INTEREST

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## AUTHOR CONTRIBUTION

*Conceptualization:* Ana María Chaves Cano, Alfredo Javier Pérez Gamboa, William Castillo-González.

*Writing - original draft:* Ana María Chaves Cano, Alfredo Javier Pérez Gamboa, William Castillo-González.

*Writing - proofreading and editing:* Ana María Chaves Cano, Alfredo Javier Pérez Gamboa, William Castillo-González.