

# Stem Cells and Regenerative Medicine in the Treatment of Musculoskeletal Disorders

Pranay Mehta<sup>1</sup> and Jothsna Kethar<sup>#</sup>

<sup>1</sup>Gifted Gabber

<sup>#</sup>Advisor

## ABSTRACT

Regenerative medicine is a field of medicine focused on the repair or replacement of damaged or diseased cells, tissues, and organs through the use of various medical technologies. These technologies include stem cell therapy, tissue engineering, and gene therapy, among others. Millions across the globe are plagued with musculoskeletal disorders (MSD) with ranging debilitating effects that are detrimental to the functionality of one's life. The healing process of MSD can be arduous and sometimes worse than the injury itself. The various methods of treatment including stem-cell based therapy and the origin and composition of these stem cells has been reviewed in this paper, in order to present a way in which the natural healing process of MSD can be amplified and catalyzed.

## Introduction

Musculoskeletal Disorders are commonly known to be long-term, sustainable injuries that negatively impact the daily lives of everyone who endures them. This impact results in an arduous, long rehabilitation process. However, why does this treatment process have to be so extensive? Prior investigation shows that in order to optimize the treatment process there has to be a restructuring of biomechanical relations between the normal and injured tissues. This is achieved through means of therapeutic practices and exercise to prevent further inactivity and immobilization. The precision required to successfully carry out this rehabilitation process innately slows down the rate of recovery. This article discusses the use of stem cells and regenerative medicine to expedite the treatment and quality of rehabilitation of MSD. Stem cell treatment and regenerative medicine tie into each other as both pertain to tissue reengineering. This new field of tissue reengineering and regenerative medicine, differing from the current clinical method of using bio-compatible alloys to treat Musculoskeletal Disorders, looks to enhance the damaged tissues in a way that will amplify the natural healing process in several ways.

## What are Stem Cells?

In order to understand the potential role that stem cells could play in the treatment of musculoskeletal disorders, it is critical to understand the origin of these cells. Research conducted during the mid-20th century marked the beginnings of stem cell research in the modern world. This research budded from animal trials to human trials within the span of 20 years and revealed two main types of stem cells, embryonic and adult stem cells. Embryonic stem cells (ESCs), found in an early-stage embryo or a blastocyst, are pluripotent meaning they have the ability to divide indefinitely and develop into any cell in the body. This innate versatility enables these cells to aid in the regeneration of damaged tissues or organs. Similarly, adult stem cells, which were previously believed to be more limited in cellular capability, are now being investigated as there is new evidence supporting their extensive functionality. For instance, it was previously believed that adult stem cells most commonly found in bone marrow, could only aid in the production of blood cells. However, recent evidence suggests that adult stem cells may have the potential to create various types of

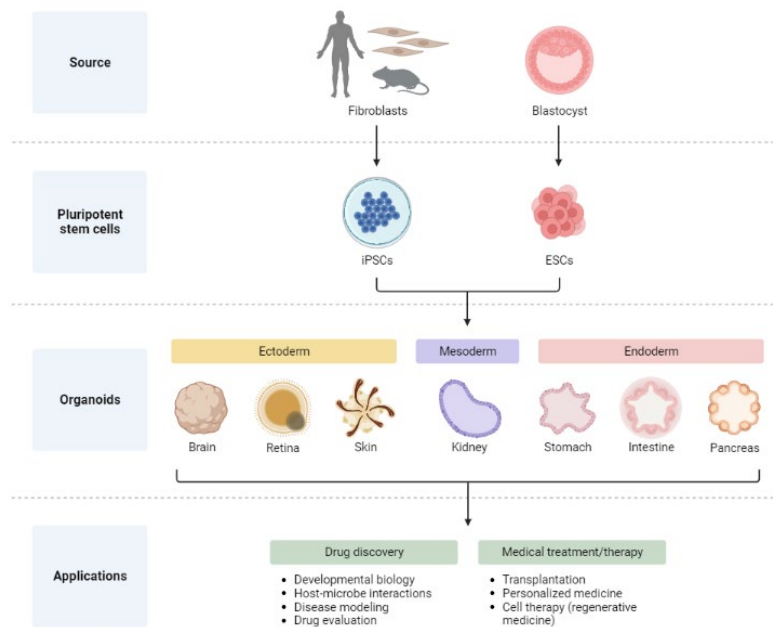
muscle cells. This development led to further testing of these stem cells in people who suffer from heart disease and neurological issues.

## Origin of Stem Cell Research and Stem-Cell Therapy

In 1958, French oncologist Georges Mathe was able to successfully execute a stem cell transplantation and save the lives of six scientists who were severely exposed to radiation. Georges Mathe would further go on and expand on his bone marrow transplantations and apply it to the treatment of Leukemia. Furthermore in the 1960s, scientists Ernest McCulloch and James Till discovered hematopoietic stem cells (HSCs) and demonstrated their pivotal role in the formation of blood cells through a series of experiments conducted on mice. Later finding out the HSCs ability to self-heal and regenerate, a critical feature of stem cells.

## A Closer Look at the Applications of Stem Cells

Stem cells are derived from two main sources: fibroblasts and blastocysts. Fibroblasts are types of cells that make up a tissue, whether it be an adult tissue or the tissue in an animal, all connective tissue is built through fibroblasts. These cells are known for their production of extracellular matrix (ECM) proteins like collagen, glycosaminoglycans, and proteoglycans. This ability makes it easy for them to be grown and cultured. Skin-derived fibroblasts are used to produce induced pluripotent stem cells (iPSCs). iPSCs are known for their ability to develop into any type of cell in the body. Blastocysts are developing embryos, a rapidly dividing ball of cells. And from the 4th to 7th day of fertilization, ESCs can be found in the inner cell mass of the embryo. ESCs, by nature, are known for their capacity to continuously regenerate and self-renew. These cells are then used to derive organoids, three-dimensional human tissues generated by application of developmental biological principles *in vitro*. Through the uses of these technological developments there have been major breakthroughs in regard to drug discovery and medical treatment in the world of modern medicine. Cell therapy and regenerative medicine being one of the main focal points.

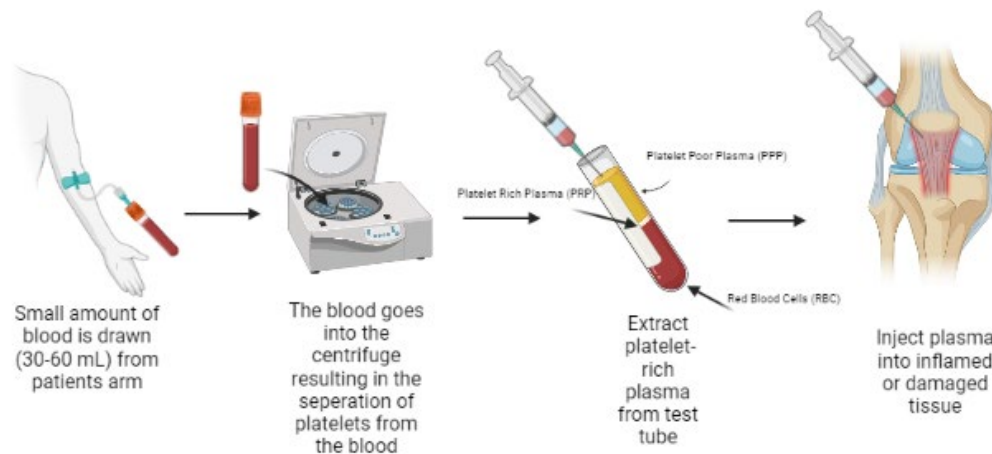


**Figure 1.** Sources of Pluripotent Stem Cells and their various applications in modern medicine

## What is Regenerative Medicine?

Regenerative medicine is the process by which stem cells are used in order to promote a self-healing process in the body, by means of repairing damaged tissues or organs. It is a process by which stem cells are cultured into different types of cells, such as blood cells, nerve cells, or muscular tissue cells and are implanted into patients with their respective problems. Once implanted, this new wave of healthy cells can assist in the regeneration of that organ or tissue. Typically, cells secrete their own support-structures, known as extracellular matrices. These matrices or scaffolds act as communication centers for the cells, where, depending on the surrounding stimuli, the cell will receive messages from signaling molecules that can start a chain reaction of responses from the cell. With the understanding of these natural processes, scientists and researchers have manipulated and artificially replicated this process for the treatment of diseased or inflamed tissues. Platelet rich plasma therapy (PRP) is a form of regenerative medicine in which a small amount of blood is drawn from the patient and then centrifuged multiple times. The first centrifugation is used to separate the red blood cells from the platelets and plasma and is spun at a maximum rate of 3400 RPM for approximately 4 minutes. The rate of centrifugation can vary depending on gender ,3000 RPM for 3 minutes for women in comparison to the previously stated rate and time for men. If the results are not as desired the blood can then be respun at around 2500-3500 RPM for 1-2 minutes in order to obtain the desired results. After being fully centrifuged, the platelet-rich plasma can then be extracted from the test tube and be used to inject into the damaged tissue. The increased concentration of growth factors in this platelet rich plasma is what expedites the healing process of the target area.

### Platelet Rich Plasma Therapy Process



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**Figure 2.** Platelet cells collection and Regenerative of Musculoskeletal Treatment how they play a role in Platelet-Rich Plasma Therapy.

## Regenerative Medicine’s impact on the Treatment of Other Diseases

Cardiovascular diseases (CVD) remain the lead cause of death globally, in a broad sense CVD is a disease of the heart or blood vessels in which blood flow to the brain, body, or heart can be reduced due to a clot, or the buildup of fatty deposits in the arteries thus narrowing the path of blood flow. Relying on the pluripotency of stem cells and stem-cell therapy along with the potential of adult and embryonic cells to develop into any sort of cell, scientists Claire Packer, Beth Boddice, and Sue Simpson conducted a search in the regenerative medicine field. Identifying products known to be used in the developmental treatment of CVD. And only products that were entering Phase II or III trials were identified as they were closer to licensing. The scientists had found that in the market there were 49 products in Phase II/III clinical trials, 13 were Phase III trials and 36 were Phase II. Now upon conducting a deeper look on the Phase III trials of refractory angina they found that Baxter Healthcare Corporation, IL, USA was implementing CD34 autologous bone marrow-derived stem cell therapy in order to treat refractory angina. CD34 stem cells are a type of mesenchymal stem cell involved in the formation of blood vessels. A similar Phase II trial had 167 patients with refractory angina, and in this trial those who received a low dose of CD34 cells endured significantly less episodes of refractory angina per week for the next 6 months than those in the control group (6.8 vs 10.9 episodes;  $p = 0.02$ ). However, there was little difference in the episodes of angina per week between those who received high doses of CD34 cells versus low doses. Additionally, the improvement in exercise tolerance was far greater in the low-dose group than in the control group and greater but not by a huge margin in the high-dose group (mean  $\pm$  standard deviation (SD):  $139 \pm 151$  vs  $69 \pm 122$  s;  $p = 0.014$ ).

**Table 1.** Table of companies/research units who conducted Phase III clinical trials using stem cells in order to treat other diseases through various therapy methods.

No.	Company/Research Unit	Therapy	Therapy Type	Delivery	Indications	Additional Phase III trial information
1	Baxter Healthcare Corporation, IL, USA	CD34 Stem Cells	Autologous CD34 endothelial progenitor cell G-CSF mobilization and apheresis	Targeted intramyocardial injection	Refractory angina	Interventional study, randomized, parallel assignment, 291 enrolled patients [14]
2	Cardium Therapeutics, CA, USA	Generx™ adenovirus serotype 5-mediated human <i>FGF-4</i> gene transfer	Factor-based therapy	Single intracoronary infusion	Stable angina, not suitable for revascularization	Interventional study, 11 participants, randomized, parallel assignment, study completed in May 2016 [15]
3	Barts Health NHS Trust, UK	Bone marrow-derived mononuclear cells	Autologous bone marrow mononuclear cells	Single intracoronary reinfusion during PCI	Acute myocardial infarction	Interventional study, 375 participants, parallel assignment, study completed in November 2019 [16]

No.	Company/Research Unit	Therapy	Therapy Type	Delivery	Indications	Additional Phase III trial information
4	University of Rostock, Germany	CD133 cells	Autologous CD133 bone marrow cells with CABG	Intramyocardial injection	Previous myocardial infarction	Interventional study, 81 participants, randomized, parallel assignment, quadruple masking (Participant, Care Provider, Investigator, Outcomes Assessor), study completed in September 2017 [17]
5	Meshalkin Research Institute of Pathology of Circulation, Russia	Bone marrow-derived mesenchymal stem cells	Autologous bone marrow mesenchymal stem cells with CABG	Intramyocardial injection	Acute myocardial infarction	Interventional study, 50 participants, randomized, parallel assignment, double masking (participant, outcomes assessor), study completed November 2016 [18]
6	American Association for Cancer Research	EGF	EGF concentrated serum, immunotherapy	Vaccine administered at four injection sites, two deltoid regions and two gluteus regions	Non-small cell lung cancer (NSCLC)	405 patients with stage IIIB/IV NSCLC were randomly assigned to a vaccine group, which received CIMAvax-EGF or a control group, treated with best supportive care, four to six weeks after first-line chemotherapy [19]

## What are Musculoskeletal Disorders?

Musculoskeletal Disorders (MSD) are injuries or disorders of the muscles, nerves, tendons, joints, cartilage, and spinal discs. They affect the functionality and ability of a person's body and the means by which they live their lives. Some symptoms include pain, swelling, inflammation, limited flexibility, reduced or complete loss of function, and inability to put weight on the injured area. MSD are caused due to long-term exposure to a variety of risk factors. There are two categories of risk factors: ergonomic (work-related) and individual risk factors. Ergonomic risk factors include severe force, repetition, and poor posture endured in one's work space. Individual risk factors include poor work practices, poor fitness, and poor health habits. Overtime, this exposure to risk factors will fatigue the body and cause MSD.

The rehabilitation process for MSDs is long. It is critical to understand the effects and symptoms that come with MSD and how they can impair one's everyday life. One of the most common types of musculoskeletal disorders, especially seen in athletes, is the torn Anterior Cruciate Ligament (ACL). This injury arises due to a sudden shift in direction or cutting motion, that exerts a large amount of force on one concentrated area resulting in a tear. Now

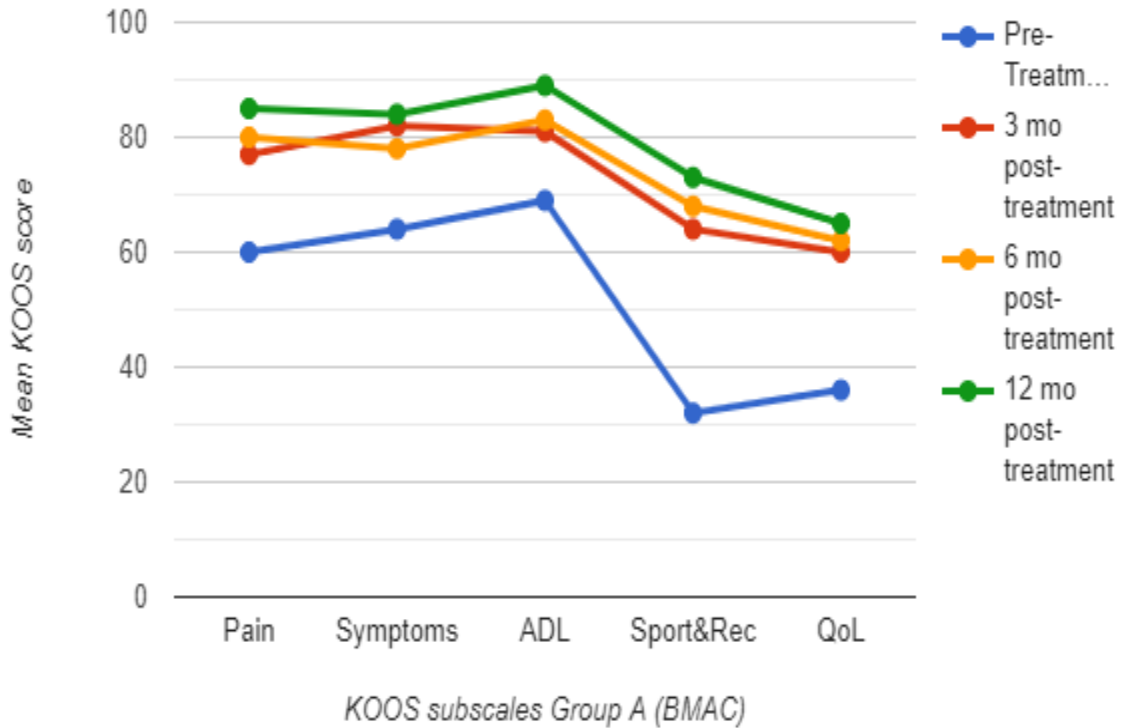
mechanically, this tear drastically hinders any sort of movement, the ACL is responsible for stabilizing the knee joint, prohibiting any sort of forward shift in the leg. So naturally, when torn, it is impossible to perform any sort of daily activities. Some instantaneous symptoms of the torn ACL include rapid swelling, severe pain, a feeling of instability in the knee joint, and loss of range of motion. The standard rehabilitation process for this MSD has undergone many changes in recent years due to developing research in the biomechanical relations of the injured knee, shifting away from methods used in the 1980s that relied on operative casting, along with delayed weight bearing exercise and a limitation in range of motion (ROM), to the current early rehabilitation program with early ROM training and weight bearing exercises.

## **Methods of Treatment**

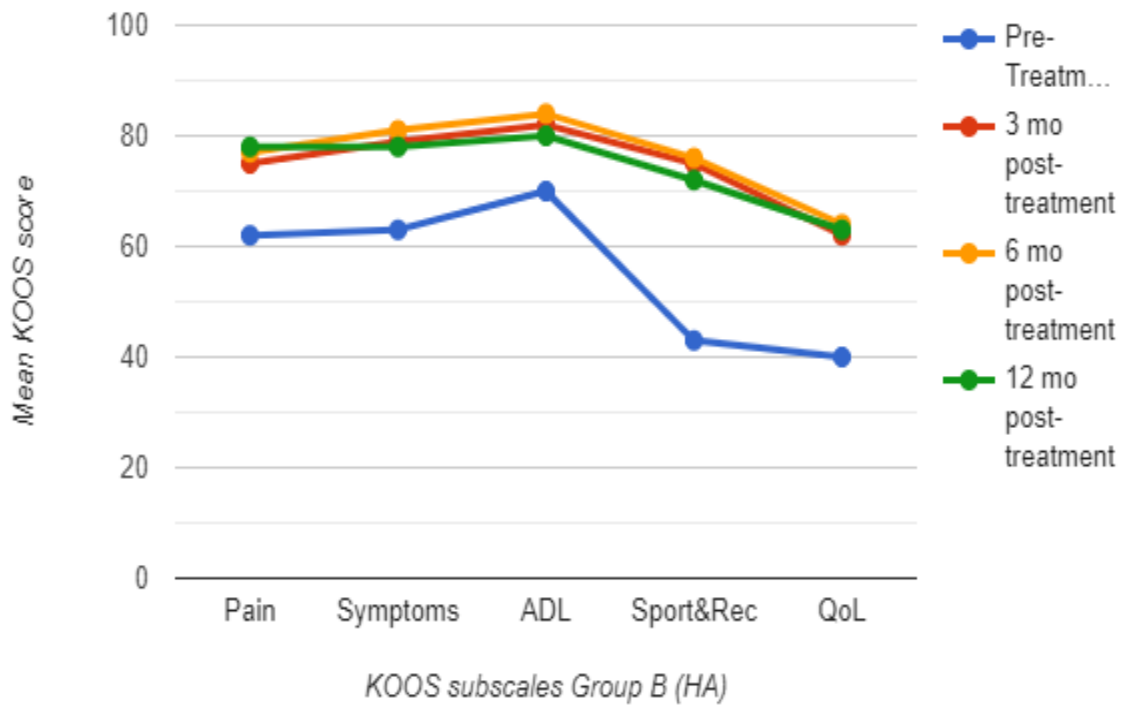
There are two methods of treatment, conservative and surgical. Conservative treatment is ideal for those with a sedentary lifestyle, where the body heals itself naturally, along with a slight involvement of physiotherapy. However, if after this treatment there are still issues in the knee-joint then ACL reconstruction surgery is recommended. In which, the damaged ligament will be removed and replaced with a piece of tendon, this piece is called a graft, and it can either be from your own knee or the knee of a deceased donor. After surgery is complete, the patient is put on crutches, prescribed pain medicines, and encouraged to rest and ice the injured area. Ideally, the surgery should restore ROM and stability to your knee. The average recovery period from the surgery is nine months.

## **Effects of Regenerative Medicines and Stem Cells on the Treatment of Musculoskeletal Disorders?**

Regenerative medicines rely on the body's own raw materials in order to enhance the treatment process of a wounded tissue or organ. Studies have shown that there are positive outcomes if introduced into the treatment plan of MSD. Additionally, other factors including, pain, expense, rehabilitation, and other complications, along with regeneration time has shown to be greatly reduced. Relying on the pluripotency of stem cells, an investigation into the effects that mesenchymal stem cell therapy would have on the treatment of osteoarthritis in the knee by Judy M. Opalek, PhD, Tamara McMath, MPH, and OhioHealth (the responsible party). This study was designed as a prospective, single blind, randomized, controlled pilot study, and a total of 32 participants were enrolled. The premise of this study was to discover and determine the response that knee osteoarthritis would have to autologous bone marrow aspirate concentrate (BMAC) injection immediately followed by either a PRP injection or a single injection of Gel-One® cross linked hyaluronate (HA), depending on which treatment group one was assigned to, with respect to pain, function, and quality of life for the 1 year following the trials. The results had shown significant improvements in both groups in regards to all Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales. The only exception being that at 6 months the HA KOOS scores had peaked, whereas the BMAC KOOS scores had peaked at 12 months. Additionally, it is important to note that in the BMAC group there was a greater reduction in pain at 12 months compared to the HA group.



**Figure 3.** BMAC treatment resulted in improvements in KOOS profiles. Mean KOOS Scores (n=17) at the pre-treatment, 3 months, 6 months and 12 month assessments after treatment with BMAC.



**Figure 4.** HA treatment resulted in improvements in KOOS profiles. Mean KOOS Scores (n=15) at the pre-treatment, 3 months, 6 months and 12-month assessments after treatment with HA.

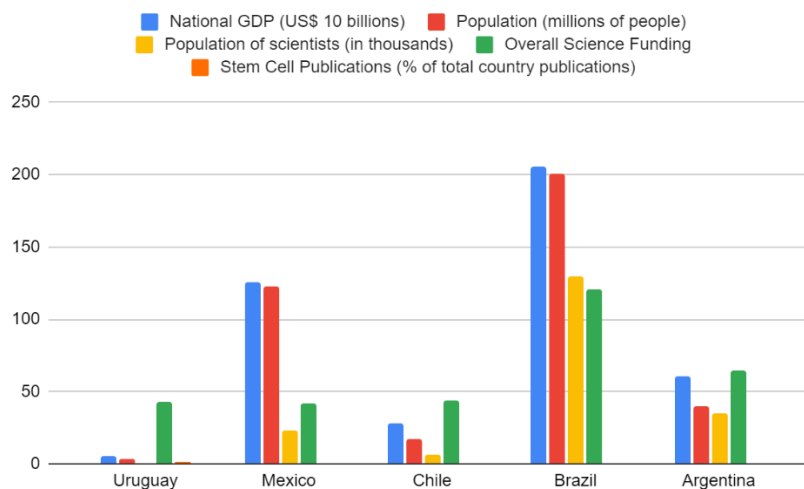
Results show that both treatment groups underwent statistically and clinically significant growth in regards to the KOOS subscales. BMAC has shown serious promise in the treatment process of knee OA, however in order to deliver concrete evidence, further trials will be needed with larger sample sizes, an extended follow-up, and placebo-based control.

## What are Some Challenges with Regenerative Medicines?

Regenerative medicine has the potential to revolutionize the way we treat a wide range of medical conditions, but it also faces a number of challenges. One of the biggest challenges with regenerative medicine is that it is still in the early stages of development and is not yet widely available. Despite significant progress in recent years, there are still many challenges that need to be overcome in order to make regenerative medicine treatments more widely available and accessible. This includes developing new technologies and techniques for growing and manipulating cells and tissues, as well as improving the safety and effectiveness of these treatments. Another challenge with regenerative medicine is that it can be expensive and time-consuming to produce the cells and tissues needed for these treatments. In order for regenerative medicine to become more widely available, it will be necessary to develop cost-effective and efficient methods for producing the cells and tissues needed for these treatments. This will require significant investments in research and development, as well as ongoing efforts to improve the efficiency of these processes. However, at a global level, stem cell research is already very low and increasing that initiative in research is a challenge of its own.

Ethical concerns are also a significant challenge for the field of regenerative medicine. Some people believe that the destruction of human embryos to obtain stem cells for these treatments is unethical, and there are ongoing debates about the ethics of using certain types of cells and tissues in regenerative medicine. Additionally, there are concerns about the potential risks and unintended consequences of using regenerative medicine treatments, and how these risks should be managed and minimized. Finally, there is still a lot of research that needs to be done in order to fully understand how regenerative treatments work and to develop safe and effective treatments for a wide range of medical conditions. This will require significant investments in research and development, as well as ongoing collaboration and coordination among researchers, clinicians, and regulatory agencies.

Overall, the challenges facing the field of regenerative medicine are significant, but with continued efforts and investments in research and development, it is possible to overcome these challenges and make these treatments more widely available and effective.



**Graph 2.** Graph representing the lack of stem cell research globally thus introducing challenges in the field of regenerative medicine.



## Conclusion

This research paper aimed to identify how stem cells and regenerative medicines could affect the treatment time of musculoskeletal disorders. An increase in activity is great for the body, however over exertion on one concentrated area will lead to the development of musculoskeletal disorders that take long periods of time to treat. Musculoskeletal Disorders plague approximately one-fifth of the global population. The self-healing properties of regenerative medicines, that rely on the innate versatility of stem cells and their capabilities in the body, can accelerate the healing process of these musculoskeletal injuries. Tissue reengineering and regenerative medicines are part of a relatively new field of medicine and treatment, future studies are needed that will concentrate and to optimize the effectiveness of stem cells and regenerative medicines on musculoskeletal treatment as a whole.

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