SCOPING REVIEW

The Landscape of Stem Cell Research in Pakistan

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Abstract

Objective: The present study is a scoping review of the progress of the field of stem cell research (SCR) in Pakistan in the last two decades.

Methods: Data was extracted from electronic search engines, international clinical trial registry platforms, and PubMed and presented in tabular and graphical form.

Results: China, India and Iran are investing heavily in SCR. In Pakistan, reasonable growth in terms of the number of publications is observed in this area, however, clinical translation of the field does not demonstrate any considerable progress. The Government of Pakistan has developed the regulatory framework and initiated preliminary policymaking, adopting rules from international regulatory agencies like World Health Organization (WHO) and Federal Drug Authority (FDA), however, further clarity and policymaking are needed to address the growing trend of stem cell tourism in the country.

Conclusion: The field of SCR is still in its infancy in Pakistan, and needs improvement; scientists, academia, policymakers, and funding agencies must come together to foster high-impact stem cell research in the country. This will aid in elevating the economic burden of many incurable diseases in the country. The outcomes of this study will be helpful for policymakers in their decision-making process.

Keywords: Stem Cell, Regenerative Medicine, Stress

DOI: 10.47391/JPMA.AKUS-04

Introduction

The recent past has witnessed a dizzying pace of progress in the field of SCR and regenerative medicine (RM), pushing the walls beyond scientific research to wider applicability and commercialisation[1]. The application of stem cells (SCs) in therapeutics is being touted as the future cure for all those disease conditions that have been historically labelled as "degenerative, incurable, and irreversible"[2]. These stem cell therapy innovations have also enriched hopes for more affordable treatments for many non-communicable diseases prevalent in low- and middle-income countries (LMICs), including Pakistan[3]. However, despite rapid progress, the debate around social, cultural, and ethical issues connected to SCs as therapy has led to new roadblocks. Besides the ethical and moral concerns that exist for all types of clinical research, the human embryo when used as a source of SCs has added new ethical dimensions to SCR[4]. Within this context, while international agencies such as UNESCO International Bioethics Committee (IBC), US Federal Drug Regulatory Authority (FDA), and the International Society for Stem Cell Research (ISSCR) have established guidelines and the developed world has responded with the "permissive approach" to these, many developing countries, including Pakistan still portray an abstruse picture[5].

Several other non-scientific factors impede the progress of the field in LMICs, especially in Pakistan that includes a lack of funding landscape and regularity clarity, a shortage of biomedical scientists, and a lack of SCR-focussed research centres. Unfortunately, the Government of Pakistan has placed a low priority on biomedical research in general, and SCR in particular. While the country is facing pressing priorities in delivering basic health services to its population, it is also battling an increasing burden of non-communicable diseases, where extended and costly care draws considerable resources. Currently, the funding support of Pakistan's government to SCR lags well behind other neighbouring LMICs such as Iran and India who have invested heavily in the field[6].

Despite these challenges, however, recent years have seen reasonable growth in this field in Pakistan. Several institutes have started projects with specialized stem cell labs. The major institutes carrying out SCR include Aga Khan University, Centre of Excellence in Molecular Biology (University of Punjab), Centre for Advanced Molecular Biology (University of Punjab), Dr. Punjwani Centre for Molecular Medicine, and Drug Research (University of Karachi), Armed Forces Institutes of Pathology, National

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Institute of Blood Disease and Bone Marrow Transplantation (NIBD)[3].

In the present article, we evaluate the progress of SCR from Pakistan's perspective during the span of the last two decades. We also aim to examine Pakistan's present regulatory framework that has emerged to govern this field in the country. This study will help the government and policymakers in their decision-making to encourage and enhance the development of stem cell interventions (SCIs) while ensuring safe, accessible and ethical development.

Methods

The descriptive research method has been used in this paper. Data was extracted from electronic search engines, international clinical trial registry platforms, and PubMed using the following keywords: "stem cell", "stem cell research", "stem cell research in Pakistan", "clinical trials", "research articles", "stem cell regulations in Pakistan". Key terms were also entered in the Google Scholar search engine and the title of the relevant article was again entered in the above databases.

All types of publications on "stem cell research" with at least one author affiliated with Pakistan and other selected countries were retrieved from the PubMed database on October 31, 2022. All articles published between 2000 and 2022 were selected. We compared our results from Pakistan to other countries in particular concerning the Muslim world and South Asia. The data was distributed by years, selected Muslim countries, and South Asian countries. The data was examined and presented in a tabular and graphical manner.

The data was also verified using various sources, including institutes' websites, funding agencies' websites (Higher Education Commission, Pakistan Science Foundation and Pakistan Academy of Sciences), as well as personal communication with field experts.

To evaluate the registries of clinical trials taking place in Pakistan focussing on stem cell therapies, a comprehensive search was conducted across international electronic databases during the period 2000-2022. The primary data was first retrieved from the information database of clinical research studies of the United States National Institute of Health: Clinicaltrial.Gov (https://clinicaltrials.gov/). All registries were then searched in World Health Organization (WHO) Clinical Trials Registry Platform (ICTRP) (https://www.who.int/clinical-trials-registry-platform). An electronic screening was done through search engines and PubMed to evaluate the outcomes and status of all clinical trials, and retrieved studies were evaluated for originality after a thorough evaluation of the abstracts.

The current status of stem cell regulations in Pakistan was evaluated by entering keywords in the Google Scholar search engine and information was verified by the websites of the regulatory authorities.

Results

Chronological Growth: Research Output from Pakistan in comparison to other countries

Over the past decade, several projects were approved by the Higher Education Commission of Pakistan (HEC) and the Pakistan Science Foundation (PSF) on stem cells[3]. To date, 489 articles have been published from Pakistan in the area of "stem cells" as per PubMed search results. Figure 1 shows the quantitative data in terms of the number of publications from Pakistan in the last two decades. Until 2010, only 10 articles were published,

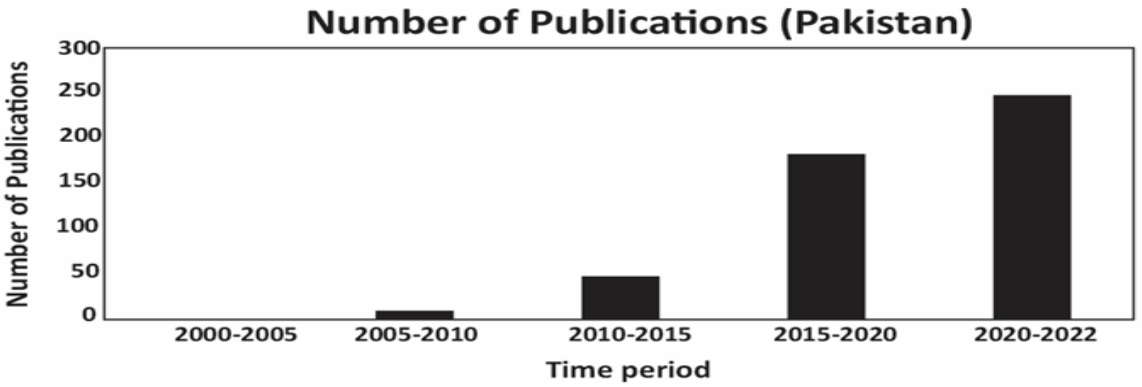

Figure-1: Graphical representation of publications from Pakistan in the area of stem cell research since 2000. The number of publications has increased in the last five years.

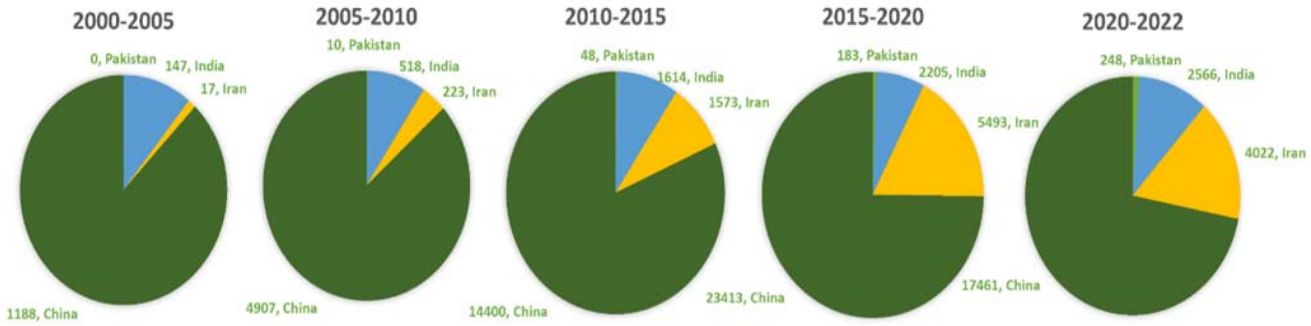

Figure-2: Comparative analysis of stem cell research publications from Pakistan with other neighboring countries (2000-2022). Maximum publications are produced by China.

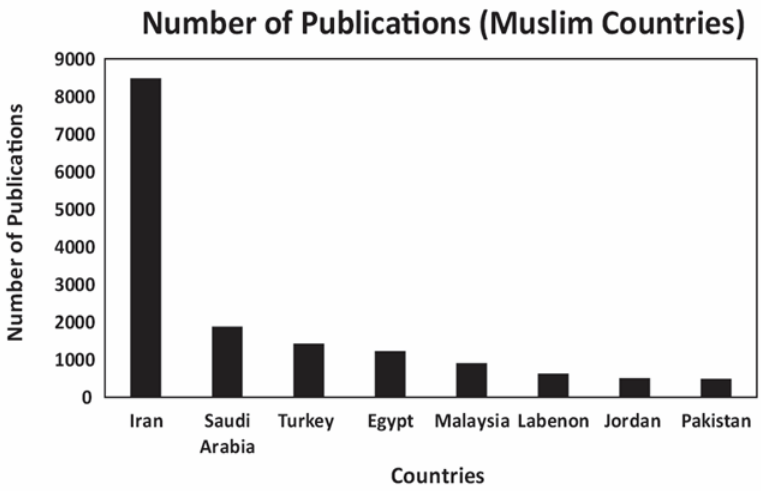

Figure-3: Comparative analysis of stem cell research publications among selected Muslim countries. Maximum publications are produced by Iran.

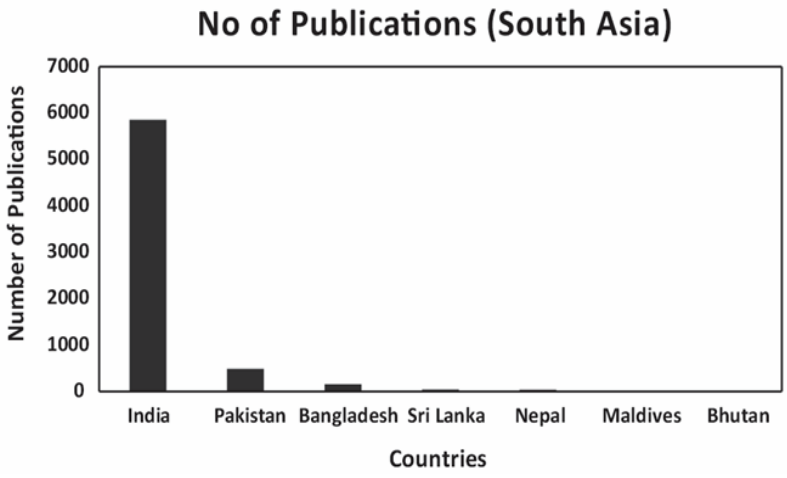

Figure-4: Comparative analysis of stem cell research publications from Pakistan with other South Asian countries (2000-2022). Maximum publications are produced by India.

however as research on stem cells accelerated in Pakistan the number of publications increased to 48 (2010-2015), and 183 (2015-2020).

From 2020 onwards, Pakistan has produced 284 publications However, compared to neighbouring countries China, Iran and India, Pakistan still had a very low output. Extensive work in basic and translational stem cell research is taking place in other countries of the region. Figure 2 shows a comparative analysis of publications as per PubMed data. Starting from 2020 onwards, China, Iran and India have published 17461, 4022, and 2566 publications, respectively.

In the Muslim world, the maximum number of publications produced so far is from Iran. Figure 3 shows a comparison of research output from selected Muslim countries between 2000-2022. In comparison the total number of publications from Pakistan is low.

From South Asia, India has taken lead in SCR; in the period between 2000-2022, it produced 5855 publications Figure 4.

Clinical Trials

In Pakistan, like the rest of the world, the new potential treatments and promise of cure have spurred hopes for millions of people suffering from life-threatening forms of diseases.

Table-1: List of clinical trials involving stem cell therapies in Pakistan as per ClinicalTrial.Gov data.

List of Clinical Trials Registered in Clinicaltrial.Gov Registry Platform from Pakistan

No.	Clinical Trial	Institute	Phase	Status
1	Comparison Between Skin Graft Versus Skin Graft and Stem Cell Application [14]	King Edward Medical University, Lahore, Punjab, Pakistan	Phase 1	Completed
2	Adipose Tissue Derived Stem Cell Based Hair Restoration Therapy for Androgenetic Alopecia [15]	King Edward Medical University, Lahore, Punjab, Pakistan	Phase 2	Completed
3	Autologous Mesenchymal Stem Cells Transplantation for Spinal Cord Injury- A Phase I Clinical Study [16]	Armed Forces Bone Marrow Transplant Centre, Rawalpindi, Punjab, Pakistan	Phase 1	Completed
4	Allogenic Bone Marrow Mesenchymal Stem Cells Infusion in Patients With Steroid-refractory GVHD (Graft vs host Disease)[17]	Armed Forces Bone Marrow Transplant Centre, Rawalpindi, Punjab, Pakistan	NA	Completed
5	Induced Pluripotent Stem Cells for Niemann Pick Disease [18]	Children's Hospital and Institute of Child Health, Ferozepur Road, Lahore, Pakistan	NA	Completed
6	Establishment of Human Cellular Disease Models for Morquio Disease [19]	Children's Hospital and Institute of Child Health, Ferozepur Road, Lahore, Pakistan	NA	Completed
7	Establishment of Human Cellular Disease Models for Wilson Disease [20]	Children's Hospital and Institute of Child Health, Ferozepur Road, Lahore, Pakistan	NA	Completed
8	Investigational Treatments for COVID-19 in Tertiary Care Hospital of Pakistan [21]	Pak Emirates Military Hospital, Rawalpindi, Punjab, Pakistan	NA	Completed
9	A Novel TBI Free Conditioning Protocol for Haploidentical Transplant in Acquired Aplastic Anemia (FluCAB-Prime) [22]	National Institute of Blood and Marrow Transplant (NIBMT), Rawalpindi, Punjab, Pakistan	Phase 2	Completed
10	Long Term Effects on Skin Hyper Pigmentation with and Without Mesenchymal Stem Cell Enriched Adipose Tissue Grafting for "Contour Deformities with Pigmentary Changes on Face [23]	Plastic Surgery Department King Edward Medical University Lahore, Punjab, Pakistan	Phase 2	Completed
11	Investigation of Therapeutic Efficacy and Safety of UMSCs for the Management of Retinitis Pigmentosa (RP) [9]	Stem Cell laboratory, Jinnah Burn & Reconstructive Surgery Centre, Lahore, Punjab, Pakistan	Phase 2	Ongoing
12	Effects of Muscle Energy Technique in Knee Osteoarthritis Patients	Riphah International University	NA	Ongoing
13	Induced Pluripotent Stem Cells for the Development of Novel Drug Therapies for Inborn Errors of Metabolism (iPSC-IEM) [10]	Children's Hospital and Institute of Child Health, Ferozepur Road, Lahore, Pakistan	NA	Ongoing
14	Efficacy of Intravenous Infusions of Stem Cells in the Treatment of COVID-19 Patients [24]	Jinnah Hospital, Lahore, Punjab, Pakistan	Phase 2	Unknown Status
15	Mesenchymal Stem Cell Infusion for COVID-19 Infection [25]	National Institute of Blood and Marrow Transplant (NIBMT), Rawalpindi, Punjab, Pakistan	Phase 2	Unknown Status

Worldwide more than 7000 clinical trials employing adult SCs have been registered on the National Institute of Health (NIH), ClinicalTrials.gov portal site to date. Table 1 shows a list of clinical trials that were enrolled in ClinicalTrials.Gov. In Pakistan, only 15 clinical research studies have been registered on ClinicalTrials.gov so far and out of these, 11 are enrolled with World Health Organization Clinical Trials Registry Platform (ICTRP).

A pilot study involving autologous mesenchymal stem cell transplantation for Spinal Cord Injury in Phase 1 clinical trial was carried out by Armed Forced Bone Marrow Transplant Centre, Rawalpindi. The study concluded with positive results for the safety of the administration of MSCs, however, further investigation through randomized placebo trials was suggested[7]. Another phase 2 study involving 100 participants with contour deformities was concluded in 2020 and was undertaken by the Plastic Surgery Department at King Edward Medical University, Lahore. The study demonstrates major improvements in hyperpigmentation of skin when autologous adipose tissue was injected into the affected areas of the face[8].

There are two noteworthy clinical trials currently ongoing. The Stem Cell Laboratory of Jinnah Burn & Reconstructive Surgery Centre (Lahore) is carrying out a phase 2 open-label trial, for studying therapeutic efficacy and safety for umbilical cord-derived mesenchymal stem cells (UMSCs) for the management of Rhinitis Pigmentosa. This study is in collaboration with The Layton Rehmatullah Benevolent Trust Free Eye Hospital (Lahore) and the Centre of Excellence in Molecular Biology (Lahore)[9]. Another phase 2 clinical trial is being carried out at Children's Hospital and Institute of Child Health (Lahore) with an estimated enrollment of 1000 participants. The study is sponsored by CENTOGENE GmbH, Germany and aims at the development of novel treatments through new cellular models involving IPSCs for "inborn Errors of Metabolism"[10].

Regulatory Affairs in Pakistan

In Pakistan, clinical trials are conducted through a regulatory approach following guidelines laid down by World Health Organization (WHO) and International Conference for Harmonization (ICH). After approval from the Federal Government, the 2017 Bio-Study Rules were published by the Drug Regulatory Authority of Pakistan (DRAP) (https://www.dra.gov.pk/) to implement internationally accepted standards as adopted by WHO and ICH. All clinical trials are subject to approval from a clinical studies committee. To strengthen the governance of clinical trials and regulate the execution of clinical trials of therapeutic goods in Pakistan, DRAP also maintains the Clinical Trial Registry of Pakistan (CTRP) (https://ctr.dra.gov.pk/).

The main regulatory authority for stem cell or related medical research in Pakistan is the Pakistan Medical Research Council (PMRC). The National Bioethics Committee (NBC) published the ethical guidelines for stem cell-related research following the implementation of proactive measures for SCR in Pakistan which can be accessed at http://nbcpakistan.org.pk/guidelines.html. Rule 9 of the 2017 DRAP Bio-Study Rules states that NBC approval is mandatory for all clinical trials in the country.

The NBC guidelines further make it mandatory for all centres performing SCR to be registered with Human Organ Transplant Authority (HOTA) (http://nbcpakistan.org.pk/guidelines.html). The scope of HOTA includes the evaluation of scientific, technical ethical and legal issues concerning cell-based research and therapies.

The NBC guidelines about human embryonic stem cell research address several key issues. As per guidelines, the use of adult SCs for particular haematological disorders is permissible, although, the commercial sale of adult SCs is restricted[6]. The guidelines explicitly prohibit obtaining SCs from a foetus by terminating a pregnancy. It is critical to guarantee that foetus is not harmed during the harvest of cord blood stem cells and that the precise time for the umbilical cord clamping is determined. Parents should provide informed consent that includes the risks and advantages of the surgery. In the event of any conflict, maternal wishes take precedence.

The NBC guidelines further maintain that an embryo cannot be created for the sole purpose of collecting stem cells. Only additional embryos can be utilized in in-vitro fertilization (IVF) clinics after approval from the couple. Human embryonic stem cells and foetal/adult cells can be used for in-vitro research. In-vitro cultivation of any embryo for more than 14 days or when primitive streaks develop is not permitted. In-vivo research on non-primate animals is permissible, nevertheless, the reproduction of animals resulting from these experiments is not permitted. Furthermore, human cloning and the implantation of human embryos in the uterus after modification at any stage are strictly prohibited[11].

Discussion

SCR has sparked tremendous scientific and public excitement. However, a range of ethical and moral concerns, legal challenges, and public controversies have emerged. As demonstrated in the data, the therapeutic

and scientific potential of SCs is beginning to be appreciated in Pakistan. However, in comparison to other countries in the region, the development of research in the area of stem cells and regenerative medicine in Pakistan is still a slow road.

The establishment of national guidelines for the conduct of biomedical research including SCR in Pakistan is commendable and reflects the national effort for bioethics empowerment, some issues, however, need further clarity and a more comprehensive approach. In particular, although participants' rights have been mentioned, there is further a need to develop informed consent regarding SCR which should be available on the NBC website. The NBC guidelines further need to expand to transparency and accessibility of the data on preclinical as well as clinical studies. The research outcomes need to be publicly available through publications in referred scientific journals[12].

Pakistan further needs to amend its regulatory framework and policies to address the need of, as highlighted in the 2021 ISSCR updates, establishing stem cell research oversight (SCRO) committees by "all institutions undertaking research in particular on human embryos, stem cell-based embryo models, organoids, chimeras, and genetic modification of gametes"[13].

Importantly, like most LMICs, there is a rising trend of "stem cell tourism" and earlier commercialization of stem cell interventions (SCIs) in Pakistan. The therapeutic misconception is an issue. Stem cell clinics that provide such unproven SCIs frequently operate in a regulatory vacuum and are in contravention of the established regulatory standards[12]. Urgent measures are needed for the re-examination of regulatory frameworks and articulation of public health policy to approve only those SCIs for which biosafety and bio-efficacy risks have been established. The approval from NBC and CTRP must be made mandatory for all clinical trials. Nonetheless, an independent body of data safety monitoring must be assigned to monitor the potentially harmful results of the trial.

Finally, there is also a need of expanding the funding landscape for this field in Pakistan. More funding is needed for providing financial incentives as well as developing institutional ground for SCR. The government's support should be formalized through defined laws that will allow researchers to design and carry out their often technically demanding and uncertain research proposals. Given that this field holds enormous potential to address distinctive health risks in Pakistan, investment in this area of science could be returned in the form of sustainable development of the country.

Conclusion

The field of SCR is still in its infancy in Pakistan in comparison to other neighbouring LMICs eg Iran and India and needs further development. It is encouraging that output in the field has gathered pace in the country over the past few years. The enormous potential of SCs to cure many prevalent health concerns in Pakistan necessitates the government to increase its investment in the field, and the scientists, and academia must come together with policymakers, and funding agencies to foster high-impact research in this field. There is also a dire need for strict oversight as well as legalization and policymaking to address the marketing of unproven stem cell therapies and the growing trend of stem cell tourism in the country.

Limitations: The number of publications presented in this paper is limited to the PubMed database. The articles published in other than PubMed-indexed sources have not been included in this paper. This review is purely quantitative and does not include quality indicators such as citation analysis and the impact factor of journals was not examined. Other databases such as Web of Science, Scopus, and Google Scholar may have more records, but this study is limited to the search results of the PubMed database.

Disclaimer: None to declare.

Conflict of Interest: None to declare.

Funding Disclosure: None to declare.

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