Construction of Clinical-grade Stem Cell Banks and Post-prints

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Abstract

In recent years, stem cells have demonstrated tremendous development potential and broad clinical application prospects across multiple domains, including disease treatment, tissue repair, and anti-aging cosmetology, establishing themselves as a pivotal research direction in life sciences and garnering extensive global attention. High-quality clinical-grade stem cell banks constitute not only a prerequisite for stem cell products to enter clinical practice, but also a critical success factor for the stem cell industry, and will undoubtedly provide indispensable resources for stem cell clinical research. This article, integrating China' s national context with the practical experience and exploratory insights from the Affiliated Dongfang Hospital of Tongji University in the construction and management of clinical-grade stem cell banks, elaborates on the planning, establishment, and full-process chain management of such banks, encompassing collection, preparation, testing, cryopreservation, distribution, quality management system establishment, as well as stem cell lifecycle information tracking and data management, serving as a reference for peers in the field.

Full Text

Construction and Management of Clinical-Grade Stem Cell Banks

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Abstract

In recent years, stem cells have demonstrated tremendous development potential and broad clinical application prospects in disease treatment, anti-aging,

cosmetology, and other fields, becoming one of the most important research directions in life sciences and attracting widespread global attention. High-quality clinical-grade stem cell banks are not only prerequisites for stem cell products to enter clinical practice, but also key factors for the success of the stem cell industry, and will undoubtedly provide indispensable resources for stem cell clinical research. Based on China' s national conditions and the practical experience and exploratory efforts in the construction and management of clinical-grade stem cell banks at East Hospital Affiliated to Tongji University, this article focuses on the planning of clinical-grade stem cell banks, establishment of quality management systems, and full-process chain management including stem cell lifecycle information tracking and data management, providing a reference for peers in the field.

Keywords: clinical-grade stem cell bank; stem cell preparation; quality management system; information traceability

2. Construction and Requirements

2.1 Site Selection

Clinical-grade stem cell banks should be located in safe, independent, and enclosed areas free from interference, far from major sources of contamination such as pathogenic microorganisms and radioactive isotopes. Whenever possible, the facility should be adjacent to sample collection and clinical treatment sites to reduce sample transport time, facilitate timely processing, and achieve seamless workflow integration. Storage areas should preferably be situated on lower floors above ground level to prevent flooding, mold, and moisture, while maintaining stable temperature and humidity and avoiding rainwater intrusion.

2.2 Functional Area Planning and Management

The facility should be divided into core functional areas and auxiliary areas. Core functional areas encompass sample and cell reception rooms, preparation and processing rooms, quality control laboratories, and master control rooms, with reception consultation rooms and collection rooms established when necessary. The clean area for cell preparation should include buffer zones and meet requirements for cell separation, expansion, and culture, with clean corridors surrounding each preparation suite to increase workflow flexibility. The cell preparation operation area should establish clean zones that comply with Good Manufacturing Practices (GMP). According to the *Cleanroom Design Code* (GB50073), the clean area is generally planned at 2-4 m^2 per person. Environmental monitoring and other requirements refer to the Sterile Products Annex of GMP [13].

To minimize batch-to-batch variation in research, multiple cell banks should be established for the same batch of cells at specific passages. The storage

area should prevent confusion, errors, and cross-contamination. Auxiliary functional areas include offices, warehouses, and washing/disinfection rooms. Since stem cells from different research directions within the same institution may have different origins and culture conditions, standardized methods and quality criteria should be adopted for centralized collection, preparation, storage, and distribution to ensure biosafety and minimize potential risks and contamination from external factors. This approach offers clear advantages, as studies have shown that cell line identification errors or contamination rates reach 18-36% [5-7], and quality control testing companies report mycoplasma infection rates of approximately 7-11% of total tested samples.

The layout process and flow should be rational, orderly, and clearly labeled, with dedicated passages for medical waste to reduce contamination risk. To facilitate the transfer of samples, materials, and cell preparations according to specified processes and flows, pass-through windows should be reasonably installed at entrances and exits to improve work efficiency. Clinical-grade stem cell bank construction must comply with national laws and regulations and international ethical principles of stem cell research associations [9].

2.3 Staffing

An organizational structure appropriate to the business scope should be established, with clearly defined management pathways, authorities, and interrelationships. Qualified operators and managers with relevant training and practical experience should be assigned. Collection personnel must be trained and certified, holding physician or nurse practice certificates, with collection information verified by two individuals. Preparation personnel should receive training in aseptic gowning. The quality management responsible person and the quality authorized person should not hold concurrent positions. If delegation of duties is necessary, the delegate must meet the same qualification requirements, though the delegator still bears ultimate responsibility.

2.4 Facilities and Equipment

Essential safety facilities include eyewash stations and emergency showers, which should be regularly inspected. The HVAC purification system in clean rooms should be designed with adequate space for all facilities and equipment throughout the process. According to the area and function of each zone, heating, ventilation, and air conditioning should be planned to minimize the risk of pathogen transmission. The cleanroom' s air filtration system should be regularly cleaned, with primary and medium-efficiency filters replaced periodically. High-efficiency filters should be leak-tested regularly during operation. The Grade A/B zone should employ online airborne particle monitoring systems, with monitoring frequency and items including airborne particles in both static and dynamic states, surface microorganisms, etc.

Safety management should follow dual-circuit power supply or emergency power

facilities and backup storage space. Liquid nitrogen and dry ice areas should be equipped with gas monitors. The storage area should fully consider floor load-bearing capacity, with tile flooring prohibited in liquid nitrogen zones to reduce nitrogen consumption and shorten the distance from liquid nitrogen tanks to the storage area. The refrigerator area should fully consider heat dissipation, with dedicated heat dissipation channels installed when necessary. Operators should be equipped with thick insulated gloves and protective outerwear to ensure safety, with low-temperature-resistant epoxy flooring preferred. Fencing and safety warning signs should be installed with regular safety inspections.

All equipment including centrifuges should undergo regular metrological verification or mandatory inspection to ensure continuous and stable system operation. Liquid nitrogen equipment operators and maintenance personnel should have safety qualifications for special gas operations, or maintenance can be outsourced to professional companies. All equipment should be filed, controlled, and managed by designated personnel with unique identification.

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3. Collection, Preparation and Testing

Prior to collection, donors must undergo enrollment screening and testing for infectious disease markers, including HIV, HBV, HCV, CMV, and Treponema pallidum [15]. Qualified donors must sign informed consent forms before sample collection following standard operating procedures. Clinical-grade stem cell preparation should be rigorous and prudent, with independent review to ensure safety and efficacy. Even minimal in vitro manipulation of cells may introduce additional risks, such as pathogen contamination, and genotypic and phenotypic instability due to increased passage number. Cells may become aneuploid or undergo deletions and other genetic or epigenetic abnormalities under stress, potentially causing severe pathological changes such as cancer [16]. Therefore, clinical-grade stem cell preparation must follow GMP principles to prevent contamination of raw materials and products during production.

All reagents and processes in preparation must comply with the quality control system and regulations to ensure reagent quality and consistency with established protocols, forming standards for cell identification, purity, and potency analysis. Preparation of stem cells from infectious disease-positive donors must be conducted in independently designed positive-pressure rooms. All materials contacting original samples and stem cell preparations must be sterile, non-toxic, and meet required grades, with pharmaceutical-grade materials preferred whenever possible. Non-sterile and non-single-use materials must be cleaned and sterilized, with batch numbers qualified and monitored to enable complete and accurate tracking of detailed material information at each step. Key materials used, including reagent and equipment lists, manufacturers, and analysis certificates (COA) for critical reagents such as serum, enzymes, and growth factors, must be documented. Antibiotics should be avoided when possible during cell

culture or preservation, and animal-derived or undefined components should be avoided. Animal serum should be replaced with defined chemical components whenever possible, with allogeneic human serum or plasma prohibited.

Testing of clinical-grade stem cell preparations includes comprehensive quality testing, batch release testing, and release-for-distribution testing. To ensure safety and efficacy of stem cell therapy, each batch must meet comprehensive quality requirements based on current stem cell knowledge and technology, as well as guidelines for quality control and preclinical research [17]. Release criteria generally derive from regulations, clinical trial applications, and literature. Test results must be reviewed and approved by testing supervisors and quality authorized persons before release with the cells. Procedures for post-release testing and review of all related records should be established.

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4. Labeling, Storage and Distribution

4.1 Labeling

Each stem cell preparation should be assigned a unique code with a rule ensuring uniqueness and uniformity, enabling traceability to the donor and preparation information through the code [19]. Labels should be cryogenic and moisture-resistant, containing all information regarding identity, storage location, and handling. Clinical-grade stem cell banks should specify storage conditions, duration, and destruction protocols for non-compliant products. The International Society of Blood Transfusion (ISBT) 128 code recommended by the International Council for Commonality in Blood Banking Automation can be used. With the adoption of automated equipment, container-encoded and RFID electronic tags are emerging, gradually replacing traditional label printing and manual attachment.

4.2 Storage

During cryopreservation, ice crystal and solute damage should be avoided by controlling cooling rates using programmed freezers or alternative methods, with dimethyl sulfoxide or glycerol as cryoprotectants [20]. The internationally recognized storage temperature is -150°C to -196°C using vapor-phase liquid nitrogen tanks. For long-term storage, cells from the same source should be divided into multiple portions stored in different containers at different locations (mirror image storage) to prevent damage or loss from force majeure events [21]. As automated liquid nitrogen storage equipment emerges and develops, cell retrieval is moving toward automation and intelligence.

Containers must have a sterility assurance level of 10 (99.9999% probability of being sterile), be single-use, leak-proof, and free from interfering substances. To avoid cross-contamination from container leakage, outer containers made of

materials resistant to temperature changes should be used for transport, such as dry liquid nitrogen tanks.

4.3 Review, Release and Distribution

Stem cells must undergo review and release control before distribution. The cell bank performs strict quality control testing, with release processing implemented through selection of practical and controllable release testing or after obtaining release test reports. This includes sample inventory receipt, stem cell isolation, quality testing, and other information. The release standard should specify whether the product can achieve expected functions, application dosage in clinical settings, and provide detailed introduction of release standards and each test result, including test methods, sensitivity, or acceptable result ranges.

Distribution of cell therapy products should clearly specify expiration dates and times for both fresh and cryopreserved products. Transport and transfer procedures must ensure product integrity and personnel health/hygiene. Validation should demonstrate maintenance of cell viability and functional integrity during transport to infusion sites. Stem cell transport should be supervised by trained logistics personnel or commercial carriers, with evidence of appropriate temperature maintenance. Temperature data loggers are most widely used currently, with transport temperatures required to comply with standard operating procedures of the receiving institution [23].

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5. Information Management System

The information management system for clinical-grade stem cell banks must be constructed according to its purpose and functions, focusing on lifecycle data tracking to achieve bidirectional traceability. The system should enable closed-loop management from clinical application back to clinical research, meeting the needs of multicenter studies. The global database must interface with site systems, drawing on experience from AstraZeneca's cell bank information system for pharmaceutical research at its Alderley Park R&D facility in the UK [8]. This Global Cell Bank comprehensively manages cell banking from acquisition of various cell sources to generation of working cell banks, with a single global database storing all relevant unit data, allowing users to search for and request cells from branch banks worldwide (such as in Sweden, Boston, and Shanghai).

Clinical-grade stem cell bank information management encompasses extensive data, including: (1) donor and recipient demographic information associated with pre- and post-application stem cells, such as clinical research project initiation; (2) stem cell isolation, growth conditions, culture media, methodology and validation information, and related quality testing and data during the process; (3) information management of original samples, stem cell preparations, and derivatives. The storage module enables tracking of cryopreserved cell locations, usage, and quality control data generation. The system can associate

stem cell preparation information with clinical data, enabling rapid retrieval of target samples through combined queries. The system also constructs a clinical research data center module interfacing with hospital information systems, pathology information systems, and communication systems, with backup templates established.

Tongji University Affiliated East Hospital has adopted a Browser/Server model and modular design to build a stem cell clinical research information management system compliant with management pathways and workflows. The system enables full-process data tracking and traceability for stem cell clinical research, with each module interfacing through ports to track donors, key equipment, critical materials, operational processes, and more.

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6. Comprehensive Quality Management System

Medical institutions conducting stem cell clinical research are responsible for quality management of stem cell preparations and clinical studies, conducting project review, registration, and process supervision. They should implement comprehensive quality management system requirements and perform quality management and risk control throughout the entire process of stem cell preparation and clinical research. Using Tongji University Affiliated East Hospital as an example, the clinical-grade stem cell bank has established ISO 9001 quality management system certification and complete quality system documentation including risk control procedures. The system achieves traceability from source sample quality testing through stem cell preparation infusion or implantation into recipients to disposal of remaining preparations. The hospital has established a stem cell clinical research review system with complete quality control, conducting regular audits of inventory systems, establishing nonconforming product release regulations, and implementing corrective and preventive actions to achieve continuous quality improvement.

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7. Summary and Outlook

To meet the industrial development needs of stem cell banks in China and satisfy long-term strategic storage and clinical translation requirements, rational planning and construction of clinical-grade stem cell banks are essential. Industry consensus and national standards are urgently needed regarding policy frameworks, evaluation indicators, translation models, and ethical guidelines for cell bank resource application. With increasing national emphasis on stem cell medicine and continuous maturation of key stem cell technologies, relevant issues in future stem cell industry development will be continuously updated and improved.

References

[1] The world' s first bone marrow transplantation for severe combined immunodeficiency opened the door to medical application of stem cells.
[2] Global stem cell industry market size exceeds 100 billion USD, with stem cell products approved for market and more expected in 2018. China' s stem cell and translational research has made significant progress, with related products entering Phase I/II clinical trials.
[3-4] Scientists in Israel and other countries are using induced pluripotent stem cell reprogramming technology to establish clinical-grade stem cell banks for different populations.
[5-7] Studies show cell line identification error or contamination rates of 18%-36%, with mycoplasma infection rates reported by quality control testing companies at 7%-11%.
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[10] Interim Measures for the Management of Human Genetic Resources.
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[13] Sterile Products Annex, Good Manufacturing Practice.
[15] Donor screening should include HIV, HBV, HCV, CMV, and Treponema pallidum.
[16] Minimal in vitro manipulation may introduce risks including pathogen contamination, aneuploidy, and malignant transformation.
[17] Quality control and preclinical research guidelines for stem cell preparations.
[19] ISBT 128 coding standard for blood transfusion.
[20] Cryoprotectants such as dimethyl sulfoxide or glycerol should be used.
[21] Mirror image storage in different containers and locations prevents loss from force majeure events.
[23] Transport temperatures must comply with standard operating procedures.
[24] The information system enables advanced search, screening, and combined queries.

Note: Figure translations are in progress. See original paper for figures.