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PERSPECTIVES

Clinical translation of autologous cell-based tissue engineering techniques as Class III therapeutics in China: Taking cartilage tissue engineering as an example

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Summary Autologous cell-based tissue engineering (TE) techniques have been clinically approved for approximately 4 years in China, since the first cartilage TE technique was approved for clinical use by the Zhejiang Health Bureau. TE techniques offer a promising alternative to traditional transplantation surgery, and are different from those for transplanted tissues (biologics or pharmaceutical), the clinical translational procedures are unique and multitasked, and the requirements may differ from those of the target tissues. Thus, the translational procedure is still unfamiliar to most researchers and needs further improvement. This perspectives paper describes the key guidelines and regulations involved in the current translational process, and shares our translational experiences in cartilage TE to provide an example of autologous cell-based TE translation in China. Finally, we discuss the scientific and social challenges and provide some suggestions for future improvements.

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Introduction

As physical injuries, chronic diseases, and degenerative disorders associated with elderly patients become more prevalent in China [1], transplantation is regarded as ideal treatment for traumatic injury or surgically created defects; however, the shortage of transplant tissue/organs greatly restricts its application [2]. Tissue engineering (TE)-based regenerative medicine strategies are emerging as promising therapeutic modalities, which apply a combination of cells, scaffolds, and bioactive factors to restore, maintain, or improve the tissue structure and function [3]. Studies on TE are growing quickly in China, and a large number of promising findings have been reported in the literature, especially in the highly translational orthopaedic and musculoskeletal research [4,5]. However, few results from these studies have been introduced into clinical application [5]. To fill the gap between the bench and bedside, multidisciplinary issues must be addressed. It is a cooperative work that should integrate participants with different disciplines and experiences [6].

The translational channel of TE technique applications is different from transplanted tissues, biologics or pharmaceuticals, but has some similarities. The general procedure includes technique/product design and development, quality management, clinical trials, application regulation and registration, and pricing and marketing [7]. Moreover, depending on the specificity of target tissue, each technique may have its own requirements. Researchers may be familiar with the good expertise at the science and product development stage, but often encounter problems upon reaching the later stages. With the uniting of the scientists, engineers, clinicians, regulatory experts, and business executives from different backgrounds, our group successfully translated an autologous cell-based TE technique into clinical therapy for the first time in China in 2010. Here we would like to discuss the systematic requirements, and share our experience and lessons, to give an example of the translation procedure of TE techniques in China for researchers who are interested in and wish to take further steps in their own research work.

TE techniques are categorised as Class III medical techniques and approved for clinical use

On April 21, 2009, TE techniques became the first batch of Class III medical techniques approved for clinical use in China [Document No. (2009-84)] [8]. The details are shown in Table 1.

This document officially admits TE techniques into clinical practice, and clearly specifies the responsible departments. Notably, the province-level, but not state-level health departments undertake the technical and clinical-use review procedure, indicating the lower risk and higher efficiency of TE techniques translation.

General procedure

For TE techniques, there are several steps to be accomplished prior to obtaining clinical approval (Fig. 1).

Table 1 [Document No. (2009)-84] General Office of the Ministry of Health of P.R. China: The first batch of Class III medical techniques approved for clinical use [7].

No.	Name	Technical review institutions	Clinical use review departments
19	TE techniques	Provincial health departments notified bodies	Provincial health departments

Technique provider

The technique provider (i.e., TE research centre, high-tech enterprise) should carry out comprehensive preclinical studies to fully demonstrate the safety and efficacy of their techniques, including physical, chemical, and biological testing. After internal self-examination, official test reports from external bodies are needed in accordance with the prevailing industrial standards. In China, we obtained test reports for cell biologics from the National Institute for Food and Drug Control (NIFDC), and for Class III medical devices from the provincial medical device supervising and inspection centre of the China Food and Drug Administration (CFDA).

Contract manufacturer

Contract manufacturer must ensure the manufacturing environment be certified by the provincial Food and Drug Administration (FDA) or higher supervisory body, and in accordance with the code of good manufacturing practice (cGMP) for sterile medical products. Standard Operating Procedures (SOPs) are needed for management and quality control. The SOPs directory will be provided in the following section.

Hospital

Under a specific guideline for Class III TE techniques [Document No. (2009)-199], the hospitals (must be tertiary hospitals) who want to use the specific technique for human therapy should apply for clinical approval from the provincial health department and provide appropriate training for their clinicians in that specific technique platform.

Guideline for Class III TE techniques

Guideline for transplantation and treatment with TE techniques was issued by the Ministry of Health of P.R. China on Nov 13, 2009 [9]. The full text was translated into English as follows:

*"**Document No. (2009)-199***

Ministry of Health of P. R. China: Guideline for Transplantation and Treatment with TE Techniques (Trial Version)" [9]

"...This document is intended to provide criteria for technical review and clinical application, and to ensure the safety and effectiveness of TE techniques. Hospitals and affiliated doctors who seek permission to implement these techniques must comply with this document.

"...The TE techniques referred to here are therapeutic modalities utilizing artificially engineered tissues that contain autologous bioactive cells and are transplanted to repair, improve and restore the structure and/or function

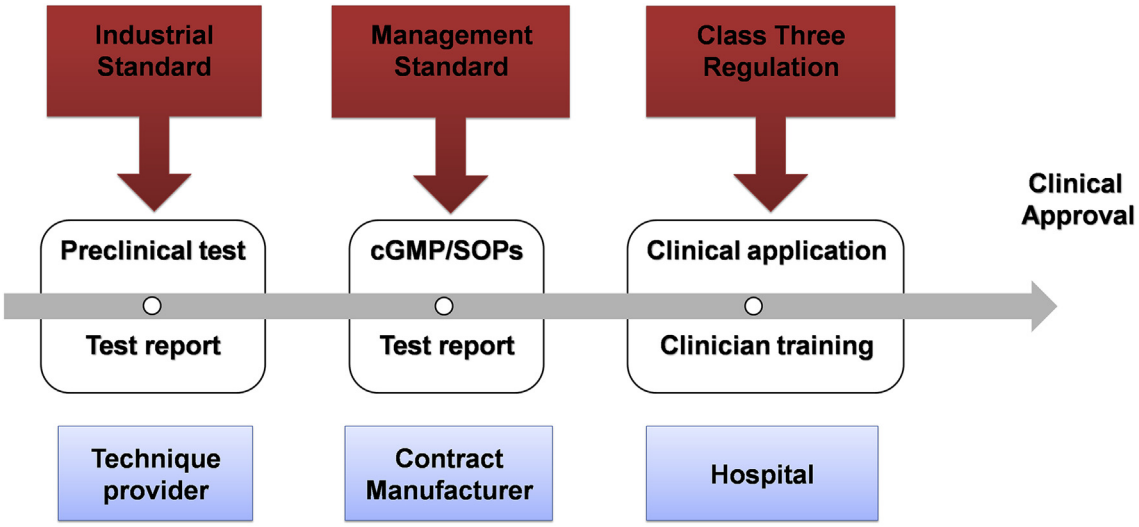

Figure 1 Translation procedures for tissue engineering products/techniques. cGMP/SOP = code of good manufacturing practice/Standard Operating Procedure.

of tissues or organs within the human body. It does not include the direct transplantation (i.e., autologous cartilage, dermatoplasty, etc.) of live or preserved cells, tissues and organs, as well as somatic cell therapy for other purposes. At present, tissue-engineered techniques are only applicable for clinical restoration of structural tissues (i.e., bone, cartilage, skin, etc.), but are prohibited for more complex tissues such as liver, kidney, brain that have higher metabolic rates.

Basic requirements for hospitals and processing environment"

*... **(1) Hospitals***

a. *Hospitals utilizing TE techniques should be qualified to perform their functions and tasks.*
b. *These should be tertiary hospitals established with authorized departments of orthopaedics, plastic surgery, burn, neurosurgery, ophthalmology, stomatology, and other departments that have the demand for TE therapies, as well as clinical laboratory, x-ray room, pathology department and other supporting departments and facilities for follow-up visit and examination.*
c. *Standardized and operational ethics committee for TE techniques should be set up with medical, legal, and ethical experts.*

"...**(2) *Processing environment***

a. The environment should be a cleanroom certified for human cell processing by the provincial FDA or above, and in accordance with cGMP for sterile medical products (YY0033-2000).
b. cGMP human cell processing cleanroom

a) The cleanliness class should be more than 10,000 for the whole environment, and 100 for the cell culture and tissue fabrication area.
b) The cleanroom should be well-organized and suitable for cell culture and tissue fabrication. Personnel and material flow should be isolated and well-controlled.
c) The cleanroom should be well-equipped for tissue/cell collection, isolation, culture, identification, processing and preservation. Cross-contamination should be prevented by strict rules and measures.
d) SOPs should be set up for each step of cell processing. Key procedures, quality control standards and test indexes should be determined. A regulated and complete quality management system (QMS) should be established.

"...There should be at least two in-service doctors with expertise in clinical translation of TE techniques, as well as some other professionals who have received appropriate training and are proficient in TE techniques.

Basic requirements for personnel

"... ***(1) Doctors***

a. *Acquire the certification as medical doctor and practice in TE related fields.*
b. *In-service doctors with minimal qualification as associate chief clinician and are qualified for clinical application of TE techniques.*

"... ***(2) Other professionals***

a. *At least one director with a minimal qualification of associate professor with TE expertise.*
b. *Cell processing personnel must acquire at least a college education in a relevant expertise, have the theoretical knowledge and practical skills of cell biology and TE, and be qualified through appropriate training and assessment.*
c. *Quality control personnel must acquire at least a college education of a relevant expertise, and be qualified through appropriate training and assessment.*

Basic requirements for technique management

"... ***(1)*** *Establish the QMS for TE techniques. Establish the test methods and evaluation criteria for the key*

factors that influence the clinical application of TE techniques, including the seed cells, scaffold materials, bioactive factors, and microenvironment.

a. *Set the quality control specifications for human-derived cells*

The QMS referred here is only applicable to autologous cells for engineered tissues. Allogeneic cells are not allowed for clinical use.

According to the Pharmacopoeia of the People's Republic of China, Guideline for the Research and Quality Control of Human-derived Cells and General Principle for Cell Culture issued by CFDA, the quality control specifications for human-derived cells are established. The basic requirements include the donor source, cell culture SOPs, specifications for cell processing and evaluation to ensure traceability and stability. The testing parameters should include cell collection, isolation and identification, cell culture medium, cell purity, cell viability, homogeneity, biological effect, exogenous factor, and presence of pathogenic microorganisms (i.e., endotoxin, bacteria, fungi and mycoplasma).

b. *Setting the quality control specifications for scaffold materials*

The materials that are utilized in TE techniques must be certified with a test report from the medical device supervising and testing center of CFDA, which includes physical, chemical and biological properties.

c. *Setting the quality control specifications for engineered tissue*

According to the pharmaceutical industry standard of the People's Republic of China Tissue Engineered Medical Product (YY/T0606-2007), the fabrication processes including cell seeding, tissue culture and engineered tissue fabrication should be under stringent quality control. Quality control specifications and relevant SOPs should be set up to ensure the safety and effectiveness of clinical translation of TE techniques.

*"... **(2)** The appropriate treatment plan should be based on the patient's condition, available treatment modalities, patient preference and financial capacity. The indications and contraindications should be emphatically considered.*

*"... **(3)** A specialized TE treatment procedure should be co-determined by technicians and clinicians with at least associate professor qualifications. Rational treatment and management plan including precautions for failures and complications should be made.*

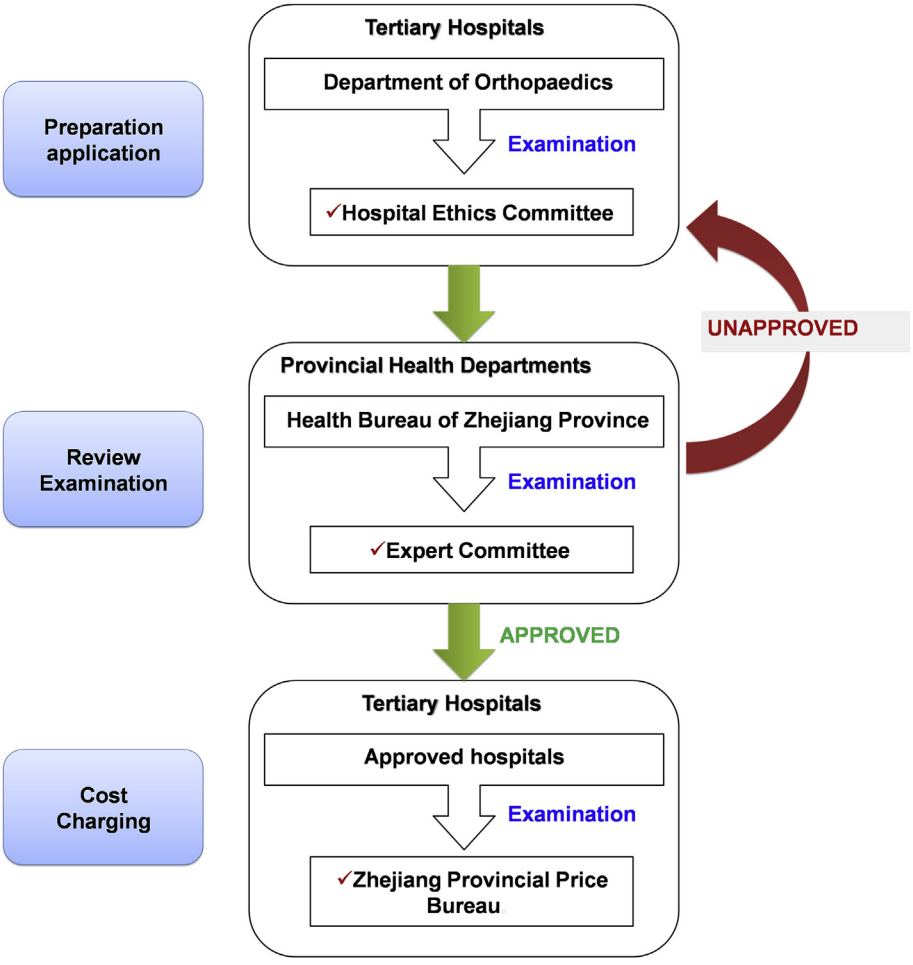

Figure 2 Clinical approval procedures for Class III cartilage TE technique.

"... ***(4)*** *Before commencement of the medical procedure, doctors should inform the patients and their family members of the purpose, risk, postoperative care, possible complications, appropriate precautions and alternative treatment options. The patients should sign the informed consent form.*

"... ***(5)*** *Hospitals should set up a complete clinical database with strict postoperative follow-up system.*

"... ***(6)*** *Hospitals and doctors should receive regular inspection for clinical application of TE techniques. The inspection includes case selection criteria, treatment efficacy, severe complications, morbidity, medical accidents, postoperative patient management, patients' life quality, follow-up visit, and patient records.*

"... ***(7)*** *Other management requirements*

a. *Utilize the CFDA or state-level FDA-approved medical device. Set the registration system to ensure traceability. In the isolation and culture procedure, single-use devices should only be used once and cannot be reused for tissues and cells derived from different sources.*
b. *Strictly regulate the price and fiscal policies Fees should be charged according to the provision of relevant medical procedures."*

This guidance document was developed as a special control guidance to support the technical review and clinical application of TE techniques, and provides specific requirements regarding the hospitals, processing environment, personnel, and technique management. It not only directs the applicant hospitals for data preparation, establishment equipment, personnel education, and program management, but also guides the regulatory bodies for standard and efficient review and surveillance. The hospitals that seek permission for TE techniques implementation must address all issues identified in this guidance by meeting the minimum requirements.

Clinical translation of cartilage TE technique—A Zhejiang province model

According to the guidelines, by coordinating the technique provider, contract manufacturer, and hospitals, our research group launched the autologous chondrocyte-based cartilage TE technique in Zhejiang province since 2010, and this is now implemented in the five largest tertiary hospitals in Zhejiang Province. Notably, it is the first batch of authorised clinically approved TE techniques in China.

Cartilage tissue is a physiologically non-self-renewing, avascular tissue with a singular cell type, the chondrocytes, which functions as the load-bearing joint surface. Trauma or diseases that cause cartilage degradation often lead to osteoarthritis. The therapeutic function of autologous chondrocyte transplantation for cartilage defect repair was established in the 1980s, and the clinical report was published in 1994 [10], The overall zero to 5-year therapeutic efficacy is 70—90% in general, as evidenced by relief of symptoms and improvement of joint function [11]. A recent report has shown that after up to 20 years of follow up, good results are maintained [12]. The TE technique for cartilage repair was developed to reduce the open injury site and shorten the surgical time; biomaterials were introduced as the second generation of autologous chondrocyte implantation/transplantation (ACI/ACT); and an "all in one" graft that combined the seed cells and

Table 2 Checklist of the application documents for Class III cartilage TE technique [13].

No.	Category	Content	Preparation
1	Introduction	General information of applicant medical institution	
2	Personnel	Technical personnel Program personnel Program leader Primary personnel	
3	Facility	Specialised equipment, facilities, and the work experience of relevant departments Supporting facilities	
4	Program	Introduction Purpose and significance Embodiments Specific operating standards	
5	Treatment	General information about the technique Domestic and worldwide application Indications Contraindications Adverse reactions	
6	Technique	Technical routes Quality control measures Clinical criteria and assessment methods Comparison with other alternative treatments (risk, effect, charge, time, etc.)	
7	Ethics	Comments from ethics committee	
Attachment			
1	Institution	The Practice License of Medical Institution (copy) General information about medical institution (including number of beds, personnel, equipment, facilities, techniques, etc.)	
2	Ethics	Examination report from the ethics committee Ethics committee member list (including name, workplace, major, position, title etc.)	
3	Management	Management system and quality control measures	
4	Treatment	Informed consent Risk evaluation and emergency plan	
5	Pre-clinical	Clinical trial report	

biomaterials, was directly delivered to the defects without either periosteal cover or fixing sutures, which was defined as matrix-associated autologous chondrocyte implantation/transplantation (MACI or MACT) [11]. We obtained the preclinical data, retrieved the test report for autologous chondrocyte from NIFDC, and obtained the cGMP report for processing in a clean-room from Zhejiang FDA. After the technological and production procedures were performed, we helped the prospective hospitals apply for clinical approval. Here we elaborate on the clinical application process [13] (Fig. 2).

Overview of the application procedure

Preparation and application

The orthopaedic department of the applicant tertiary hospitals prepares all the required materials, equipment, and personnel according to the Guideline for Transplantation and Treatment with TE Techniques [Document No. (2009)-199]. After obtaining approval from the hospital ethics committee, the orthopaedic department submits the application to provincial regulatory bodies for clinical use qualifications of cartilage TE technique.

Review and examination

The application is examined by the expert committee of the Health Bureau of Zhejiang Province according to the Guideline for Transplantation and Treatment with TE Techniques [Document No. (2009)-199]. If the application is not approved, the applicant hospital should improve the programme based on the rejection notification and resubmit the application.

Cost and charging

If the hospital is qualified and passes the acceptance review, the approved hospital performs appropriate cost accounting and is examined and approved by both the Zhejiang Provincial Price Bureau and the Health Bureau of Zhejiang Province. Then the orthopaedic department of the applicant hospital can implement the cartilage TE technique with officially charging.

Checklist of the application documents

Here we summarise the checklist of the application documents. The applicant hospitals should check every detail before submitting the application (Table 2).

Document management system

To ensure consistent quality control of cartilage TE technique, a complete document management system should be established. In our case, we adopted the experience shared by Mayhew et al [14]. Under the GMP documentation management principle, we designed and established our document management system (Fig. 3). Here we also share our main documents list as a reference for future TE technique contributors (Table 3).

The challenges for clinical translation of TE techniques

The cultured autologous chondrocytes for ACI was approved by the FDA as biological products in 1997 [15], and the general cell-based therapies development pathway was well established [16]. However, in China, regulations were lacking for a couple of years. Thus, we tried to unite the scientists, engineers, clinicians, regulatory experts, business executives; connected and communicated with the research centres, the university hospitals, the industry companies and the government administrations; proposed, established, and finally carved a translational path—the Class III autologous cell-based TE techniques.

Our successful bench-to-bedside (B2B) translation experience of autologous chondrocyte-based cartilage TE technique is a milestone in China, which proved the feasibility and implicates the possibilities for the future application of more TE techniques. This is a start of industrialisation, and we need to realise that there will be more hurdles along the way, in the quest for more innovative researchers, entrepreneurs, supervisors, administrators, and translational experts to turn them into

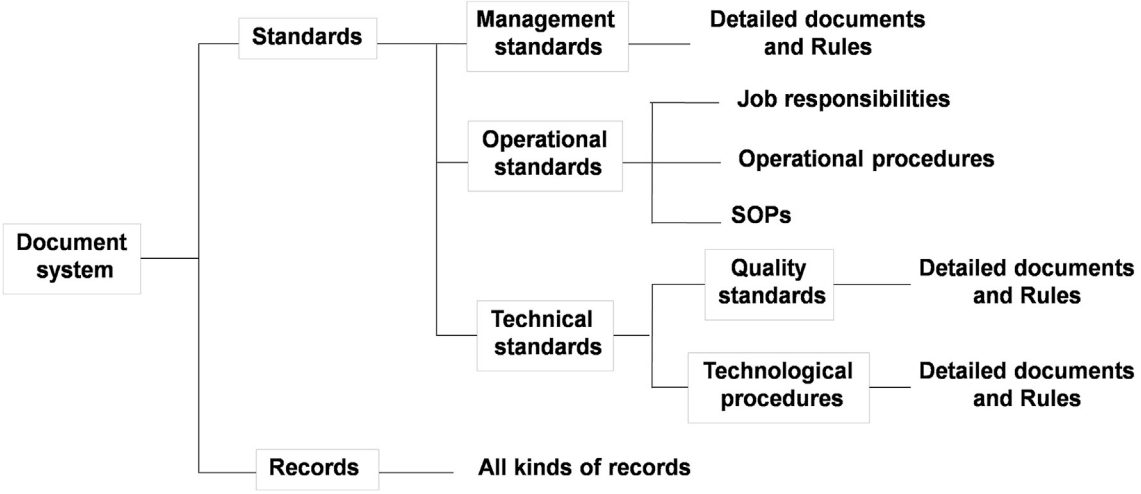

Figure 3 Document management directories. SOPs = standard operating procedures.

Table 3 Document management list [13].

1. Standards

1.1 Management standards (M — Management; C — Center; H — Human resource)

MS-M-001 Organisational chart
MS-M-002 Sterilisation management
MS-M-003 Production area maintenance
MS-M-004 Equipment maintenance
MS-M-005 Reagent testing
MS-M-006 Cell quality monitoring
MS-M-007 GMP change room management
MS-M-008 Material entry and exit management
MS-M-009Personnel and material flow management
MS-M-010 Reagent and consumable material management
MS-M-011 SOPs and records management
MS-M-012 Cleanroom environment monitoring
MS-M-013 Cleanroom examination (safety, sanitation, environment)
MS-M-014 Cleanroom state brand management
MS-C-001 Hospital matchmaking
MS-C-002 Document security
MS-H-001 Personnel training management
MS-H-002 Personnel training record
MS-H-003 Visitors' reception standard

1.2 Operational standards (O — Operation, Q — Quality control, CL — Cleaning, E — Equipment)

1.2.1 Job responsibilities

SMP-H-001 Director of clinical cell culture room
SMP-H-002 Technical personnel of clinical cell culture room
SMP-H-003 Cleaning personnel of clinical cell culture room
SMP-H-004 Transport personnel of clinical-use cells

1.2.2 Operational procedures

OS-O-001 Standard operational procedure for cartilage tissue-engineered technique
SOP—O-003 Standard operational procedure for clinical-use cells/tissues transportation

1.2.3 SOPs (E — Equipment)

SOP-Q-001 Reagent and consumable material maintenance
SOP-Q-002 Reagent standards and tests
SOP-Q-003 Sterility test
SOP-Q-004 Mycoplasma tests
SOP-Q-005 Endotoxin tests
SOP-Q-006 PCR tests
SOP-O-001 Consumable material preparation
SOP-O-002 Cleanroom entry and exit
SOP-O-003 Sanitiser preparation and utilisation in cleanroom
SOP-O-004 Filter utilisation and tests
SOP-O-005 Unqualified products disposal
SOP-O-006 Waste disposal
SOP-CL-001 Protective clothing cleaning
SOP-CL-002 Cleaning tools utilisation
SOP-CL-003 GMP cleaning
SOP-CL-004 Water sink, floor drain and sterilisation
SOP-CL-005 Cleanroom sterilisation
SOP-CL-006 Pass box cleaning and sterilisation
SOP-CL-007 Pipeline cleaning
SOP-E-001 Refrigerator utilisation and maintenance
SOP-E-003 Water bath cleaning
SOP-E-004 High pressure steam steriliser utilisation and cleaning
SOP-E-005Water processing system utilisation and maintenance
SOP-E-006 Microscope utilisation
SOP-E-007 Pipette cleaning
SOP-E-008 Biological safety cabinet utilisation and cleaning
SOP-E-009 Centrifuge utilisation and cleaning
SOP-E-010 Cell incubator utilisation and cleaning
SOP-E-011 Laminar airflow system utilisation
SOP-E-012Air-conditioning system operation and maintenance
SOP-E-013 Washing machine operation and maintenance

1.3 Technological standards

1.3.1 Quality standards

TS-Q-001 Processing environmental standards
TS-Q-002 Cell standards

1.3.2 Technological procedures

STP-O-001 Cartilage tissue-engineered technique
STP-O-002 Postoperative rehabilitation

2. Records

2.1 Batch records

RSOP-O-001 Cover of batch production
RSOP-O-002 Cover of batch packaging
RSOP-O-003 Chondrocytes culture
RSOP-O-003 Cleanroom environment monitoring
RSOP-O-004 Material counting
RSOP-O-005 Water processing
RSOP-O-006 Laminar airflow system operation
RSOP-Q-001 Bacterium examination
RSOP-Q-002 Mycoplasma examination
RSOP-Q-003 Endotoxin examination
RSOP-Q-004 Cell quality examination
RSOP-C-001 Patients documentation
RSOP-CL-001 GMP cleaning and sterilisation

Table 3 (*continued*)

2.2 Production records
R SOP-O-002-1 Sanitiser preparation
R SOP-O-002-2 Sanitiser utilisation
RSOP-O-003 Filter changing
RSOP-O-004 Unqualified products disposal
RSOP-O-005 Waste disposal
RSOP-CL-001-1 Protective clothing cleaning and sterilisation
RSOP-CL-001-2 Protective shoes cleaning and sterilisation
RSOP-CL-002 Cleaning tools cleaning and sterilisation
R SOP-CL-004-1 Water sink cleaning and sterilisation
R SOP-CL-004-2 Floor drain cleaning and sterilisation
RSOP-CL-005 Cleanroom sterilisation
RSOP-CL-006 Pass box cleaning and sterilisation
RSOP-CL-007 Pipeline cleaning and sterilisation
RSOP-E-002 CO_2 utilisation and changing
RSOP-E-003-1 Water bath cleaning
RSOP-E-004-1 High pressure steam steriliser operation
RSOP-E-007 Pipette cleaning
RSOP-E-009 Cell incubator operation
RSOP-E-011-1 Cleanroom temperature and humidity
RSOP-E-011-2 Cleanroom pressure difference
RSOP-E-1 Equipment repair
RSOP-E-2 Equipment maintenance
RSOP-E-3 Equipment calibration

milestones. Here we list some predictable near future challenges:

Technical challenge—Diversity

The seed cell issue

Recent regulation was limited to the terminal differentiated adult tissue cells, but stem cells were still under strict regulation. What if the adult stem cells were involved in the new technique, e.g., bone marrow-derived mesenchymal stromal/stem cells used as the seed cells of the cartilage [17—20]/bone/other TE technique? Another example is, what if the seed cells are allogeneic cells, but with the biomaterials we could avoid the systemic exposure [21]? These different situations should be studied and discussed on a case-by-case basis [22].

The scaffolds/cell carriers

A lot of natural and artificial biomaterials have been developed and are continuously upgraded for the TE technique,

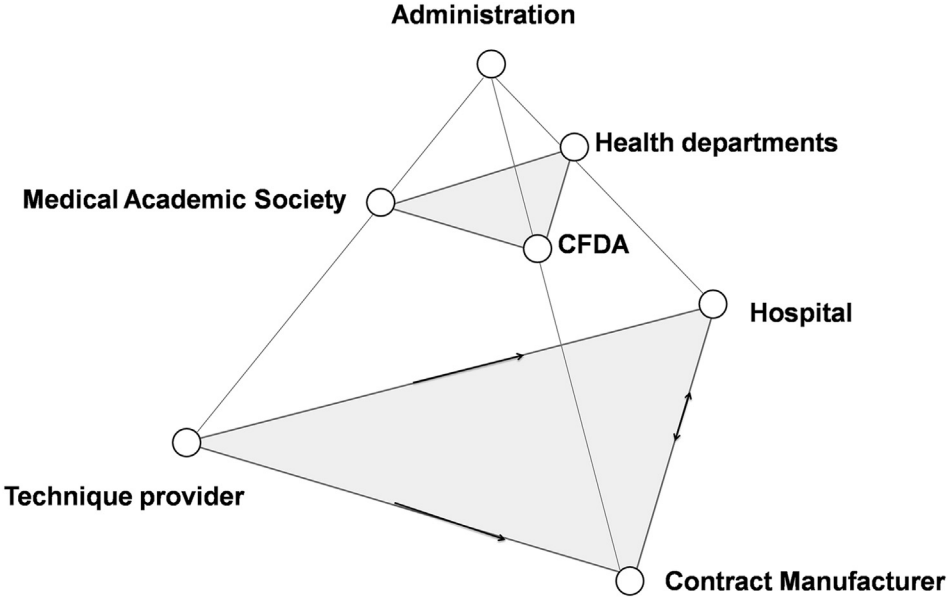

Figure 4 Organisation chart of all participants involved in the application and execution of the Class III TE techniques. CFDA = China Food and Drug Administration.

e.g., there is a branch of scaffolds or cell carrier choices for ACI/MACI [23], and more biomaterials were designed to improve the user experience and therapeutic efficacy [24]. The diversity of scaffold/cell carriers is also an issue that required attention. The scaffolds were usually in a product form, and meet different technique requirements.

Thus, the diversity of TE techniques continue to present challenges to the management, and feedback to the translation procedures, e.g., different cells have their own characters; different target tissue maintains their own complexity; and more importantly, the biggest challenge is to clearly identify the maturity of different techniques—the safety and efficacy is always paramount. However, the translational path is not completely blocked if we know where to go, and whom to talk with regarding a novel technique.

Challenges for each participant—roles and responsibilities

All participants involved in the translational procedure have their roles and responsibilities. We here list the organisational chart in our case to illustrate the relationships of all participants involved in the application and execution of the class three TE techniques (Fig. 4).

Before clinical approval

In the initial application phase, the technique or product should be evaluated for the safety and effectiveness. This incubating phase is usually support by abundant funds, and a group of people with specific expertise must be deployed to the research & development (R&D), quality management, clinical trials, regulation, and marketing position. The technique provider, the contract manufacturer, and the hospitals are involved in the application procedure, as the application pathway shown in Fig. 4. Also, the medical academic society, CFDA, and the health departments, are the administration end of each unit, separately. The technique provider here plays a role of intelligent/technical supporter and incubator, as well as a coordinator of the application.

After clinical approval

The technique provider and contract manufacturer implement this medical technique together. The engineered tissue is transferred between the hospital and contract manufacturer; the cell manufacturer is responsible for the cell quality assurance. The technique provider supervises the quality of the therapeutics as well as the implementation. The hospital conducts the therapeutics and is responsible for the entire procedure of bedside-laboratory-bedside. The governmental health department tracks the hospital quality monitoring. However, several challenges will be encountered when launching the new technique to the public. Will clinicians and patients recognise and accept the new technique? How should both clinicians and technicians be trained? The technique provider and universities take the responsibility to educate. We addressed these problems using the following two approaches. We held regular training classes and academic seminars for clinicians and technicians to introduce the basic science and clinical operational techniques of cartilage TE technique, to help them obtain full understanding and preparation of the novel technique. In addition, we set up translational bases such as training centres and cell culture laboratories at several tertiary hospitals. In this manner, TE knowledge can be disseminated directly (not only to clinicians, but also patients), further train the clinicians and technicians, and make carrying out clinical trials easier.

Conclusion

In this perspective paper, we provide a general outline of the clinical translation of autologous cell-based TE techniques and present efficient regulations in China. Our own cartilage TE translational research is used as an example to illustrate the practical details. For technique providers, the technique's safety and effectiveness should have been extensively investigated and verified. For hospitals using the specific technique, the qualification of hospitals and medical professionals should fulfil the required criteria. The contract manufacturing procedures should be performed under complete management systems. The culture cells should be extensively evaluated and verified by self-examination and CFDA certified testing. During the clinical translation process, multifactorial challenges from scientific and social aspects will interrupt the process, so multidisciplinary collaboration is needed from researchers, hospitals, and regulatory bodies to enable more promising results in the laboratory to translate into clinical use, ultimately benefiting patients.

Conflicts of interest

All authors have no conflicts of interest to declare.

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