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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