Tissue Engineering — A New Technology in China

Yilin Cao, MD, PhD and Wei Liu, MD, PhD

As proposed by the pioneers of tissue engineering research, Dr. Robert Langer and Dr. Joseph Vacanti from the Massachusetts Institute of Technology (MIT) and Harvard, in an article published in Science, tissue engineering is a multidisciplinary specialty which applies the principle of biology and engineering to generating biological tissues. Because of its significant role in regenerative medicine, the importance of tissue engineering has been well appreciated in the last ten years by many medical doctors and scientists. The development of tissue engineering will have an enormous impact on the principles of current medicine and may also change the conventional model of drug-based therapy. In addition, with the quick development of the bioreactor technology, in vitro generation of various types of engineered tissues such as skin and cartilage has became a reality. This in turn leads to the rise of a new biotechnology — tissue engineering.

During the past ten years, tissue engineering attracted the attention of many distinguished scientists and clinicians from China. These people have made great contributions to the rapid progress in tissue engineering research in China. In 1997, the Chinese tissue engineering society was formally established. A national scientific meeting is held every other year and the number of abstracts submitted is increasing quickly every year. Currently, most medical schools in China are involved in tissue engineering research and numerous tissue engineering research centers have also been established.

Under the financial support of the Chinese Ministry of Science and Technology, a national tissue engineering basic research project ("973" project) was launched in 1997. The project recruited basic scientists, clinicians and other experts from more than 20 universities from all over China. The project involves the research of bone marrow stem cells, embryonic stem cells, transplantation immunology, cell aging mechanism, synthetic biomaterial and biomaterial modification, biomechanics and tissue engineering, engineering of single cell type tissue and composite tissue. Another national tissue engineering research project ("863" project) was also initiated two years ago. The project covers the areas of development of tissue engineering products including bone, cartilage, tendon and skin, stem cell therapy and establishment of national criteria for clinical application of engineered tissue. This project is also sponsored by the Chinese Administration of Science and Technology in order to promote the advancement of tissue engineering and its clinical application.
One of the unique contributions from my colleagues to the international tissue engineering society is the generation of various types of tissues in large animals. In addition, the generated tissue can be used to repair many tissue defects that are created in large animals by mimicking clinical situations. As a national leading tissue engineering center, we have successfully generated bone, cartilage, tendon, skin, blood vessel, corneal stroma and peripheral nerve in our center using the general principle proposed by Dr. Robert Langer and Dr. Joseph Vacanti ten years ago.

For instance, by using calcium alginate and bone marrow stem cells, we have generated bone tissue and repaired cranial bone defect in a sheep model (Fig. 1a). To test whether engineered bone is strong enough, weight-bearing bone has also been generated and used to repair a femoral bone defect in a sheep model with full functional recovery (Fig. 1b).

Articular cartilage defect remains a challenge to the orthopedic surgeon because of the difficulty in its treatment. Tissue engineering technique, however, provides a promising approach to the defect repair. With isolated cartilage cells and biodegradable polymer, a full-thickness articular cartilage defect could be satisfactorily repaired, resulting in a smooth articular surface (Fig. 2a). Thus, it demonstrated great potential for clinical repair of articular defect. Recently, we have also employed bone marrow stem cells in the successful repair of articular defect (Fig. 2b). Because stem cells is easily grown in cultures dishes, a few milliliters of bone marrow will provide enough cell number to generate a functional cartilage tissue. Therefore, the approach becomes more practical for future clinical application.
Fig. 2 Tissue engineered repair of articular cartilage
Top: gross view; bottom: cross section

Fig. 3 Tissue engineered tendon (between arrows).
Top: gross view; bottom: histology
Tendon tissue has also been successfully generated using the same principle. In a study using hen model, tendon cells were first isolated, mixed with a degradable polymer of polyglycolic acid and then implanted to repair a hen tendon defect. Interestingly, the engineered tendons exhibited a gross view and histology similar to those of normal tendon (Fig. 3). More importantly, the generated tendon has gained 75 percent tensile strength of normal tendon, suggesting that the engineered tendon is fully functional. In addition to these tissues, full thickness skin (Fig. 4a), nearly transparent cornea (Fig. 4b) and blood vessels (Fig. 4c) have also been generated using the same principle. All these results indicate that tissue engineering is no longer a theory, but rather a practical approach to tissue regeneration and repair.
As an emerging biotechnology, availability for off-the shelf products of engineered tissues will be the ultimate goal. Fortunately, with the development of bioreactor technology, in vitro generation of engineered tissues has been proven to be feasible. As shown here, we have generated engineered tendon (Fig. 5a), skin (Fig. 5b), cartilage (Fig. 5c) and corneal epithelium (Fig. 5d) either in a bioreactor or in a culture dish. It is believed that high-quality engineered tissue products will become available in a few years with the advancement of bioreactor and organ culture technologies. An important issue that remains unsolved is the generation of universal cells than can be used for developing engineered tissue products, which are non-immunogenic or compatible to most of the recipients. Although relatively new now, tissue engineering is expected to become a mature biotechnology in next ten years, which will dramatically enhance medical treatment and become one of the most important biotechnologies of 21st century.

Professor Yilin Cao is from the Plastic Surgery department of Shanghai Second Medical University. He currently serves as the Vice Dean of Shanghai 9th People's Hospital, chairman of Plastic Surgery Department, and director of Shanghai Tissue Engineering Center. He is also the director of Shanghai Institute of Plastic and Reconstructive Surgery. In 1991, Professor Cao was funded by American Plastic Surgery Education Foundation to go to the US for clinical training as a visiting Professor. In 1992, he joined Dr. Jay Vacanti's Laboratory as a research fellow for tissue engineering research at Children Hospital, Harvard Medical School. His major contribution is the creation of cartilage in the shape of human ear in nude mouse, and thus he received James Barrett Brown Award in 1998 at the meeting of American Association of Plastic Surgeons. Professor Cao later became Assistant Professor at University of Massachusetts, School of Medicine (UAMMS) where he worked with Dr. Charles Vacanti and also served as laboratory director. There, he contributed to the tendon, cartilage and bone engineering. He was promoted as Associate Professor of UAMMS in 1996.

Professor Cao returned to China in 1997 and established the first tissue engineering center in Shanghai. This center has received total funding of US$10 million. Later, he launched two national tissue engineering research projects, which were supported, by The Administration of Science and Technology of China and serves as the national leader. His major contributions in this period are the tissue constructions of bone, cartilage, tendon and skin etc, in large animal models. Currently, his center has moved to clinical application of tissue-engineered bone with great success. Professor Cao has gained his international reputation in tissue engineering research and has been invited to give lectures in Korea, Japan, Singapore and Germany. He currently serves as the editorial board member of the journal Tissue Engineering and British Journal of Plastic Surgery.