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LABORATORY REPORT

Research Center of 3D Bioprinting in Shanghai Ninth People's Hospital

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The center was first established in 2013 and affiliated to the Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. In 2015, the center was entitled as 3D Bioprinting Clinical Transformation Collaborative Innovation Center. In 2016, the center was renamed as Medical 3D Printing Innovation Research Center of Shanghai Jiao Tong University School of Medicine. Although the center was established in 2013, the clinical application of 3D printing in Shanghai Ninth People's Hospital can be traced back to the 1990s. As early as 30 years ago, Prof. Kerong Dai had tried to rebuild patients pelvic by manually cutting the foam boards and layering them together based on the theory of 3D printing for preoperative planning model of abnormal skeleton structures and development of personalized prosthesis. That was the first application of 3D printing in the area of medicine in China. Now, The Research Center of 3D Bioprinting in Shanghai Ninth People's Hospital comprised of subcenters including the outpatient department of 3D printing, medical 3D printing innovation research center and Shanghai key laboratory of orthopedic implant.

The Innovation Research Center is highly focused on the innovative research and clinical transformation through the combination of the preeminent engineering department of Shanghai Jiao Tong University and clinical advantages of School of Medicine. The purpose of the center is to accomplish the clinical needs-oriented transformation, proposed by Prof. Kerong Dai. He stressed that the mission of the center is to solve clinical problems and to promote clinical transformation. Besides, the conception of the center is focused on digitization, personalization, precision and networking. According to the digital design and processing technologies from computer-aided design (CAD), computer-aided manufacturing (CAM) and 3D printing, personalized products, such as medical models, surgical guides and implants, were expectantly developed to be used on the personalized surgery to realize the precise treatment. Additionally, the networking is to spread the new technique to benefit more patients. As for the functions of the center, they could be classified as the following four aspects:

(1) Development and transformation of 3D-printed medical application. It is to develop innovative medical devices and medical treatment modes using 3D printing technology.
(2) Demonstration base of 3D-printed medical application. The successful clinic case of 3D-printed medical application in Shanghai Ninth People's Hospital will be demonstrated.
(3) Talent training base of 3D-printed medical application. There are various education-training classes, salons and international conferences held every year.
(4) Service base of 3D-printed medical application. Scientific services were provided for other institutions (Fig. 1).

Up to now, the team led by Prof. Kerong Dai has won the second prize of National Invention Award for the development and first application of shape-memory alloy embracing device in clinical practice. Moreover, the team was nominated and acquired the second prize of National Science and Technology Progress Award for its innovative design and implantation of 3D-printed prosthesis for patients. In 2004, the group obtained the only registration license of personalized osteoarticular medical device in China.

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Fig. 1 Organizational structure and affiliations of 3D bioprinting center in Shanghai Ninth People's hospital

Research directions

1. 3D-printed medical models, rehabilitation devices and surgical guides.

In the field of orthopedics, 3D-printed medical models have obvious advantages in surgical planning, reducing the doctor's operation time and avoiding possible mistakes during the operation. Up to now, the group has fabricated various normal and diseased tissues or organ models, which could be used for medical teaching, surgical planning and so on (Fig. 2). Besides, these models made a great contribution to the design and preparation of customized prosthesis. Additionally, patients with fractures needed to be fixed with plaster or splint could also benefit from 3D printing. In this area, the group made a lot of progress in fabricating 3D-printed rehabilitation devices, which is light in texture, simple to process and fits perfectly with the skin to better secure joints and bones.

As for surgical guides, Prof. Kerong Dai and Jinwu Wang's team combined the technology of digital design and 3D printing to produce personalized guides, such as shoulder joint percutaneous guides, which could avoid the disadvantages including repeated punctures, poor accuracy, possibilities of tumor dissemination (Fig. 3). These personalized medical models, assistive devices and surgical guides could help orthopedic surgeons to be more accurate in diagnosing and treating of bone and joint diseases.

2. Designing and 3D printing of individualized metal orthopedic implant
   Since 1990s, the team led by Prof. Kerong Dai has focused on using 3D printing technology to prepare individualized metal orthopedic implants (Fig. 4). Up to now, the team has successfully designed and fabricated the specialized implants for curing various tumor in pelvic, hip joint, shoulder, cervical and other parts of body. Besides, 3D-printed metal prosthesis manufactured by this team has also been used for complicated prosthesis replacement revision (such as the large area of osteolysis in acetabular wall after hip replacement), deformity of low limb and necrosis of lunate. Moreover, in addition to orthopedic, this technology has also been applied in other medical field, such as oral and maxillofacial, ophthalmology, otolaryngology. It is worth mentioning that under the instruction of Prof. Kerong Dai, the team first used memory titanium alloy to fabricate the bone fixation device worldwide and won the second prize of National Science and Technology Progress Award. Lately, the team has won the first prize of Shanghai Science and Technology Progress Award for its efforts in applying customized metal orthopedic implant in treating pelvic tumor patients.

3. 3D bioprinting technology used for fabrication of tissue-specific, biphasic scaffolds

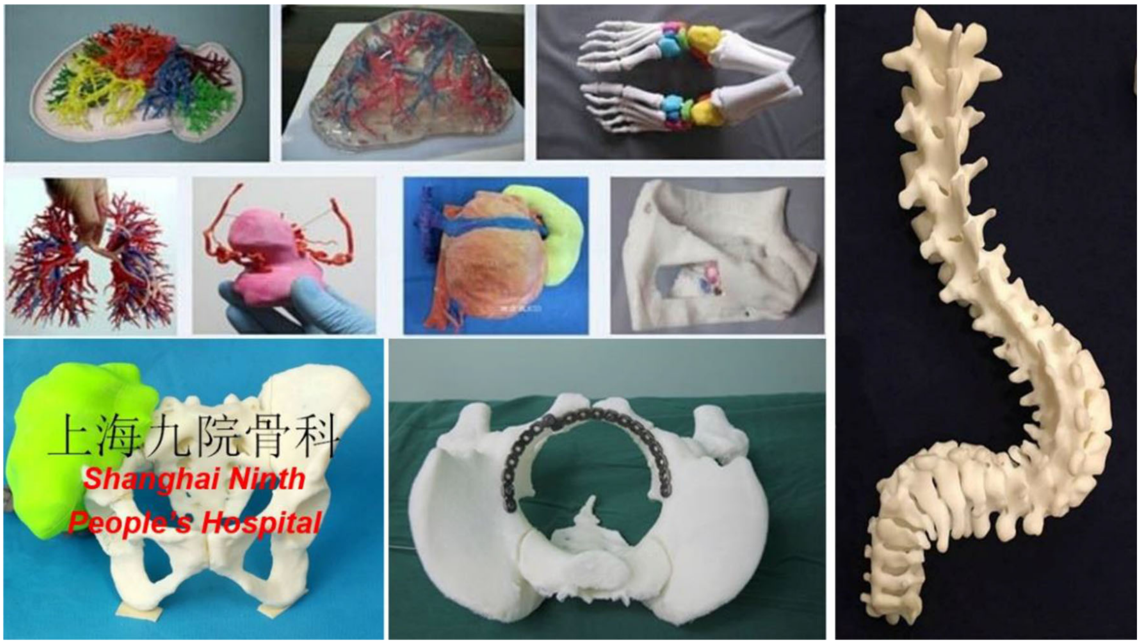
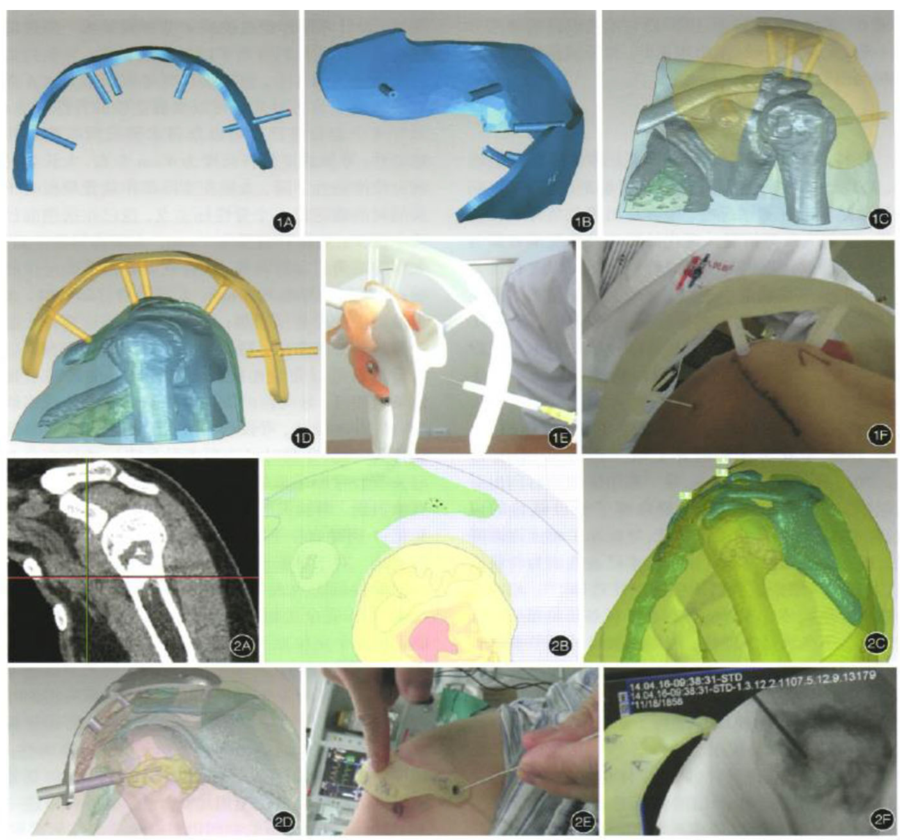


Fig. 2 Medical models fabricated by 3D printing

Fig. 3 Customized percutaneous guide plate manufactured by 3D printing and CAD



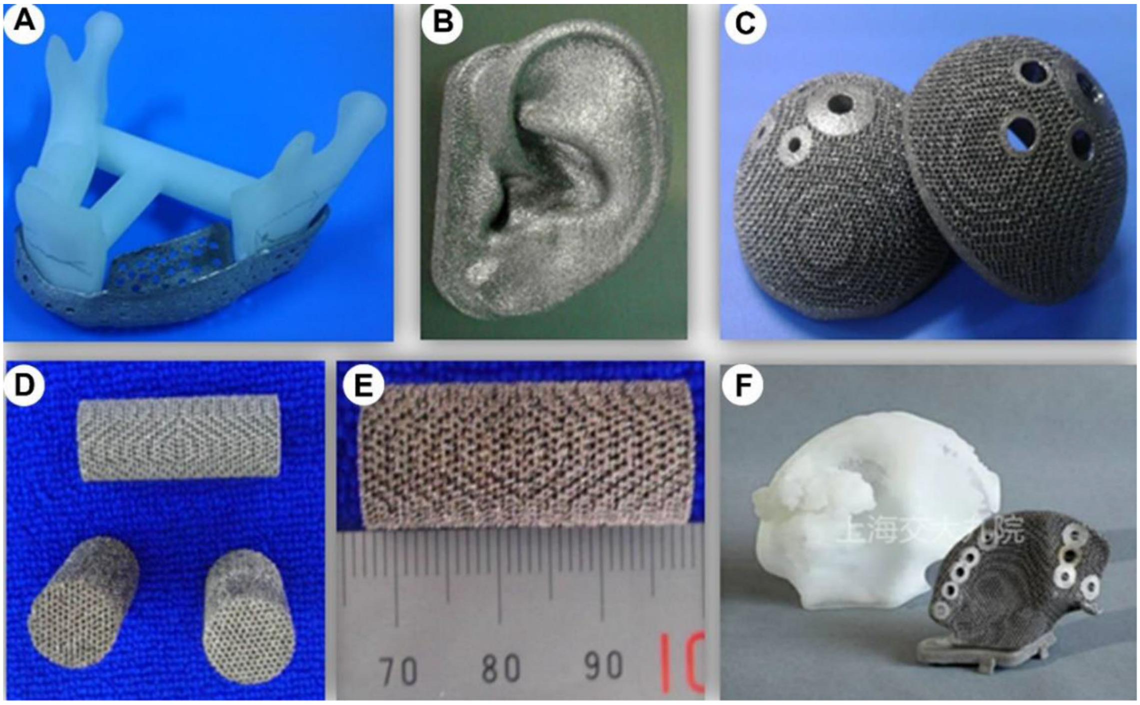


Fig. 4 Customized metal implants

CAD/CAM technology and autologous bioreactor technique were used to process and culture a biphasic scaffold with desired shape and structure for repairing of impaired hip joint. Specifically, the biphasic scaffold consisted of chondral layer of polylactic acid/polyglycolic acid (PGA/PLA) and subchondral layer of polycaprolactone/hydroxyapatite (PCL/HA), was designed and used for regeneration of goat femoral head. The content of HA in PCL/HA was optimized to a proper ratio so that the scaffold could achieve appropriate stiffness which was more conducive to articular cartilage and bone regeneration, respectively. Later, chondrocytes and bone marrow stromal cells (BMSCs) were seeded into each phase of the scaffolds (Fig. 5). After 10 weeks of implantation in nude mice subcutaneously, the cell–scaffold constructs successfully regenerated goat femoral heads.

The regenerated femoral heads presented a precise appearance in shape and size similar to that of native goat femoral heads with a smooth, continuous, avascular and homogeneous cartilage layer on the surface and stiff bone-like tissue in the microchannels of PCL/HA scaffold. Additionally, histological examination of the regenerated cartilage and bone showed typical histological structures and biophysical properties similar to that of native ones with specific matrix deposition and a well-integrated osteochondral interface. The strategy established in the team provides a promising approach for regenerating a biological joint which could be used to reconstruct the impaired joint. Recently, the team has used 3D bioprinting techniques for integrated fabrication of femoral head with bio-ink and PCL.

4. Multi-nozzle 3D bioprinting of bio-ink technology

In 2018, a project entitled "Development and Application of 3D Printing Technology and Equipment for Multi-cell Precision Manufacturing of Vascularized Biomimetic Joint" was supported by National Key R&D Program of China (No. 2018YFB1105600), which was initiated by Prof. Jinwu Wang and undertook by 25 institutions. The research contents of this project contain bio-ink system preparation, 3D printing technology software development, 3D printing equipment development, high-throughput drug screening and 3D-printed biomimetic joint construction. As for the bio-ink for construction of 3D-printed artificial joints, the team has cooperated with many institutions including Sichuan University, Donghua University and Shanghai Institute of Ceramics, Chinese Academy of Sciences. Lately, various bio-inks that could meet the printing needs of biosafety standards, as well as the distinct physical/biological demands of tissues such as bone, cartilage and blood vessels have been developed. The 3D-printed bio-ink systems are capable of integrating cells, bioactive factors and matrix materials together and can facilitate the proliferation and differentiation of seed cells. Under the support of the project, the team has started a solid cooperation with Prof. Qingmao Hu

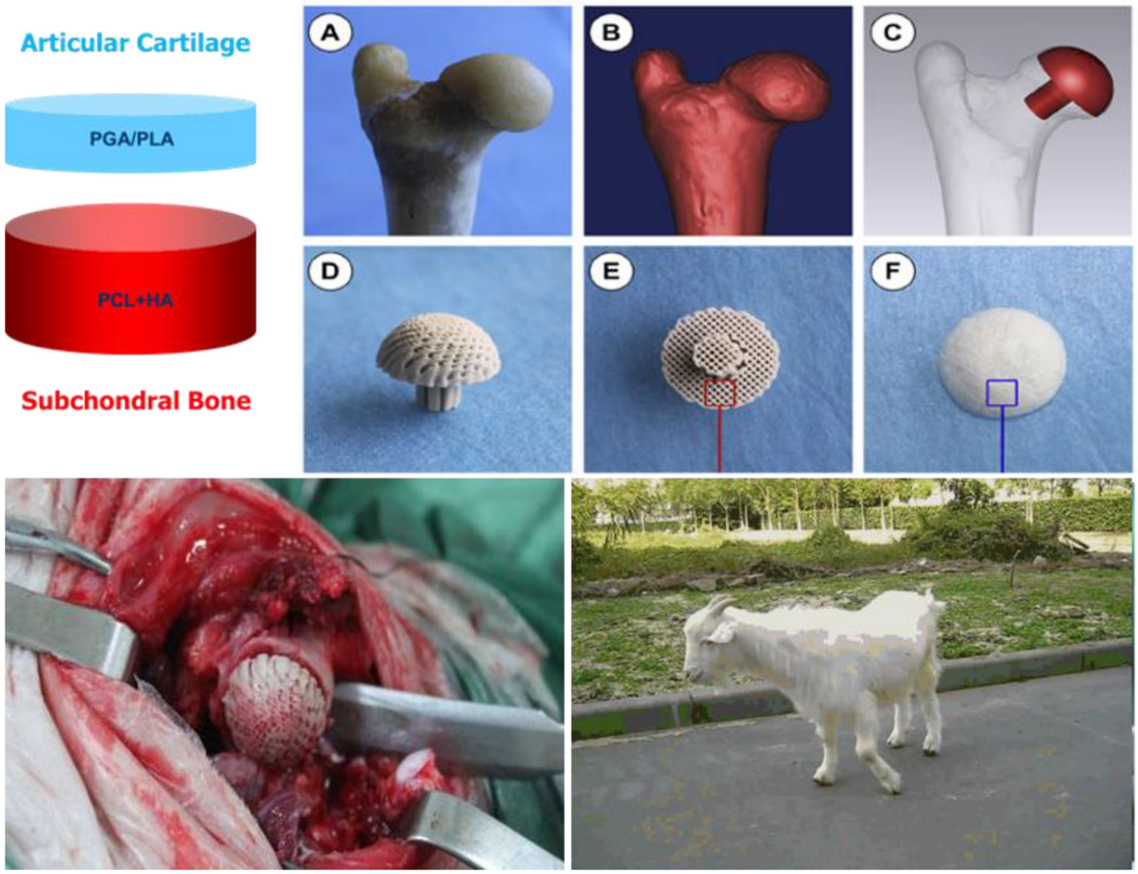


Fig. 5 Fabrication of tissue-specific, biphasic scaffolds using CAD/CAM technology and surgical replacement of the goat femoral head with a 3D bio-printed scaffold in vivo

from Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences in developing digital simulation models and exploiting 3D printing precision modeling methods and software for reconstruction of tissues, such as bone, cartilage and joints. Additionally, the center has been engaged in applying 3D bioprinting of tissue and organ-on-a-chip for Chinese traditional medicine screening. The team led by Prof. Kerong Dai and Jinwu Wang has collaborated with the team led by Prof. Yongjun Wang from Shanghai University of Traditional Chinese Medicine on the high-throughput drug screening of Chinese herbal monomers for a long time. Up to now, the center has accumulated a lot of experience and some key technologies in high-throughput drug screening on joint disease model. In addition to what mentioned above, the team is trying to explore the optimal suture location and the suture method of the artificial joints in animals, which could promote the nutrition/oxygen exchange and cell survival before further transplantation (Fig. 6). Moreover, cell survival maintenance system and bioreactor are also the key researches of the team. Collectively, the center attempts to develop customized 3D bioprinting technologies and fabricate personalized implanted scaffolds/tissue substitutes for further clinical applications.

Facilities

In the center, many types of 3D printing equipment are equipped (Fig. 7), including metal-based printer, polymers-based printer and bioprinter, in which they can process medical models, rehabilitation devices, surgical guides and implants. As for the 3D bioprinters, they are equipped with different kinds of nozzles and the tissues-printed types cover bone, cartilage, vessels, ligament, meniscus, ear and nose. Besides, the center still focusses on designing and developing innovative 3D printers itself with other teams. For example, an engineer named Wenbo Jiang has developed a two-nozzle bioprinter as early as in 2014. Also, the center is equipped with other facilities for cell culture, biological testing and evaluation, such as cell culture incubators, fluorescence microscope, microplate readers, quantitative PCR systems, flow cytometry, laser confocal microscopes and micro-CT.

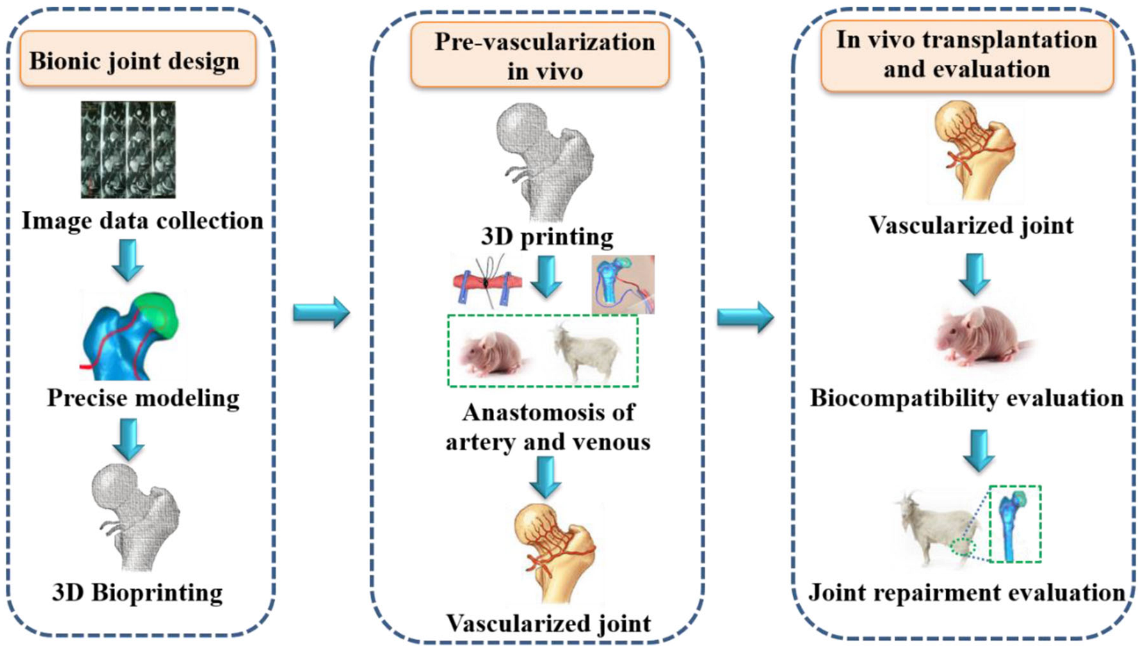


Fig. 6 Process for fabrication of 3D-printed joint with vascular network

Fig. 7 Different types of 3D printing equipment

International collaborations

The center is keeping in touch with many international research centers and research groups, including student exchange, visiting scholars and international program. They are affiliated to world famous hospitals, universities or foundations, such as Mayo Clinic, AO foundation from Switzerland, American Society for Bone and Mineral Research (ASBMR), Wyss biomedical center from Harvard Medical School, Chiba University of Japan, Georgia Institute of Technology. Other groups from international companies which focused on biomedicine, such as Johnson&Johnson Medical Ltd., Stryker Corporation, have deep communications with the center. Many of these institutions have built solid cooperation and long-term collaborations with the center.

Annually, the center will hold two international conferences. During these conferences, there are special sub-conference for the theme of 3D bioprinting and medical transformation. A latest conference named "The 8^{th} International Conference Rehabilitation Medicine & Engineering" was held in Shanghai, and many experts in 3D bioprinting field were invited to show their achievements in 3D bioprinting.

Perspectives

Since 1990s, a flourishing development has been witnessed in 3D printing technology and its medical application, which was from the fabrication of in vitro medical models and surgical guides to the construction of in vivo personalized implants. In the future, 3D printing is expected to fabricate bioactive artificial organs or tissues which could be used for the regeneration and replacement of human injured tissues. Of particular note is that the successful application of 3D printing in the field of medicine relies on the multidisciplinary cooperation, involving the collaboration of experts in medicine, materials science, engineering and other fields. 3D printing has great and far-reaching significance for the development of regenerative medicine, and it is possible to fundamentally change the situation of regenerative medicine in the coming decades.

Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflict of interest

Human or animal rights This article does not contain any studies with human or animal subjects performed by any of the author.

Selected Publications

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