



Bio-Manufacturing Research Center at Tsinghua University

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Overview and research infrastructure

As one of the leading laboratories in the interdisciplinary field of additive manufacturing and bio-3D printing, the Bio-Manufacturing Center at Tsinghua University is highly dedicated to conducting cutting-edge research in the emerging field of bio-manufacturing. The latter is comprised of research involving biomaterials, living cells, proteins, and/or other biological compounds as basic building blocks to fabricate biomimetic structures, in vitro functional biological models and/or cellular systems with application to tissue engineering, regenerative medicine, disease pathogenesis, drug screening, and tissue/organ-on-a-chip.

The Bio-Manufacturing Center, which was originally the Laser Rapid Prototyping Center at Tsinghua University, was one of the first Chinese research institutions carrying out research on rapid prototyping technology since early 1990s. More importantly, it has been a pioneering institution

accumulating research on bio-manufacturing and bio-3D printing for more than 20 years.

During the past 10 years, the Center's aim has been to establish a state-of-the-art leading research center for interdisciplinary research, education, and technological innovation. Focus is given to exploring a new paradigm of modern engineering and manufacturing for applications in bioengineering, biomedicine and health sciences, as well as facilitating the development of the emerging field of Bio-manufacturing.

Research work of the Center has been sponsored by the Ministry of Science and Technology of China (MOST), the National Natural Science Foundation of China (NSFC), the National Health Commission of China (NHC), and the Beijing Municipal Science & Technology Commission with over 40 international-, national-, regional-, and corporate-funded projects. To this date, the Center has published over 100 original research papers and applied for over 50 patents in the area of bio-manufacturing and additive manufacturing.

In recent times, the Center has also been directly affiliated with the Bio-manufacturing and Rapid Forming Technology Key Laboratory of Beijing, the “Bio-manufacturing and Engineering Living Systems” Innovation International Talents Base (111 Base) of China, the Bio-3D Printing International Science and Technology Cooperation Base of Beijing, and the Bio-manufacturing and Medical Devices Frontier Innovation Center in the Department of Mechanical Engineering at Tsinghua University. Additionally, the Center is also affiliated with the Bio-Manufacturing Engineering Institution of the Chinese Mechanical Engineering Society as well as the Biomaterials Advanced Manufacturing Institution of the Chinese Society for Biomaterials. Furthermore, branch laboratories have also been established at the Graduate School at Shenzhen of Tsinghua University as well as in the Tsinghua-Berkeley Shenzhen Institute (Fig. 1).

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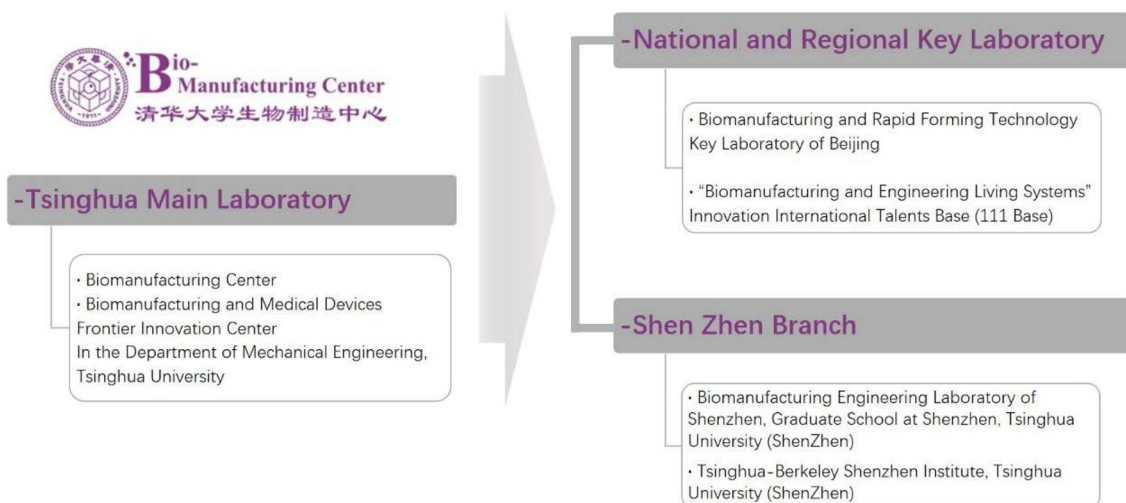


Fig. 1 Laboratory and Research Infrastructure of Tsinghua Bio-Manufacturing Center

Research personnel

Currently, the Center has nine full-time faculty members and over 50 postdoctoral researchers and graduate students. Since 2010, the Center has been led by Professor Wei Sun, who is a National “Thousand-Talent” Distinguished Professor at Tsinghua University (China) and the appointed Albert Soffa Chair Professor of Mechanical Engineering and Mechanics at Drexel University (USA). Moreover, Professor Wei Sun currently serves as the Editor-in-Chief of the highly esteemed international journal *Biofabrication* and is the Founding President of the International Society for Biofabrication (ISBF).

Other research faculties in the center included:

Professors: Dr. Feng Lin (Tenured Professor, New Century Excellent Talents Award by Ministry of Education of China), Dr. Tao Xu (Tenured Professor, National “Thousand-Talent” Distinguished Experts).

Associate Professors: Dr. Lei Zhang, Dr. Ting Zhang, Dr. Rui Yao, Dr. Shengli Mi (Shenzhen lab)

Assistant Professor: Dr. Yuan Pang and Dr. Shaohua Ma (Shenzhen lab) (Fig. 2).

Major research directions

In the interdisciplinary field of bio-manufacturing, the main research directions in the Center are as follows:



Fig. 2 Group photographs of the Bio-Manufacturing Center at Tsinghua University: **a** Group photograph in front of the Department building. First row from left to right: Associate Prof. Rui Yao, Associate Prof. Ting Zhang, Associate Prof. Lei Zhang, Prof. Feng Lin, Prof. Wei Sun, Prof. Tao Xu, Associate Prof. Shengli Mi, Assistant Prof.

Yuan Pang, Lab manager Jia Wang; **b** Group photograph during the International Conference on Biofabrication (2017), which is organized by the Bio-Manufacturing Center at Tsinghua University (Beijing)

- Cell/organ 3D printing and in vitro functional complex tissue constructs manufacturing
- Biomimetic design manufacturing and regenerative medical model manufacturing
- Reconstruction of tissue-engineered blood vessels, myocardium tissue, and corneal
- Manufacture of 3D biological-/pathological-/pharmacological models and drug screening models
- 3D Cell printing for cell/tissue/organ-on-a-chip studies
- Engineering of bio-bots, living systems, and micro-physiological systems
- Development and manufacturing of advanced bio-manufacturing equipment
- Electron beam/laser additive manufacturing and equipment

Some recent highlighted work includes, but not limited to, the following:

1. Development and commercialization of original bio-3D printing and additive manufacturing equipment

The center has developed a number of original bio-manufacturing and additive manufacturing equipment suitable for different types of materials and applications. This includes low-temperature deposition manufacturing (LDM) equipment for the fabrication of 3D tissue engineering scaffolds with gradient structures, multi-nozzle micro-extrusion-based 3D Cell Printing equipment for the controlled assembly of 3D heterogeneous tissue constructs, drop-on-demand single cell printing equipment based on alternating viscous and inertial force for precise printing of single cell or cell aggregates, electron beam selective melting manufacturing (EBSM) equipment for additive manufacturing of metallic materials or tissue substitutes, as well as different types of bioreactors for in vitro culture and training on 3D tissue constructs. Some equipment has already been commercialized by two innovative technology companies: SunP Biotech.(Beijing) Co., Ltd. and QuickBeam Tech. Co., LTD (Tianjin).

2. Bio-printing of 3D tumor models for 3D cancer study

In recent years, researchers in the Center have attempted to construct 3D cancer models that show a greater resemblance to natural tumor tissue, trying to understand both cell–cell and cell–substrate interactions and the immune responses for the printed tumor-like models.

In 2014, the team built a 3D cervical tumor model with micro-extrusion-based 3D cell printing techniques. The results demonstrated that Hela cells in 3D printed models showed a higher proliferation rate and tended to form cellular spheroids. They showed higher MMP protein expression

and higher chemoresistance than those in 2D culture. These new biological characteristics from the printed 3D tumor models in vitro as well as novel 3D cell printing technology may together help the evolution of 3D cancer study. This work was quickly featured by BBC World News and reported by more than 50 international and national media outlets with the title “the world’s first 3D printed tumor model.”

In 2018, the group published another paper that implemented a 3D printed cervical tumor model to study the epithelial–mesenchymal transition (EMT) process. Their findings provided a better understanding of the regulation mechanism(s) of EMT, for use in future therapeutic programs. Moreover, this work was reported by Physics World online.

3. Bio-printing cell “blocks” and tissue models with stem cells and primary cells

With the development of cellular biology, the team spearheads 3D bio-printing of cell “blocks” with embryonic stem cells (ESCs) and human-induced pluripotent stem cells (hiPSCs). They systematically studied the influence of bioink properties and printing parameters on bioink printability, stem cell viability in the process of extrusion-based cell printing, and also studied how those parameters and micro-environments impacted stem cell behaviors.

In 2016, the team’s 3D printing of embryonic stem cells technology was honored by SOHU news as one of the five progresses in 3D printing technology. In 2018, Physics World online reported the work, saying that the discovery offers a novel and powerful tool for expansion of hiPSCs for applications such as Biofabrication and tissue engineering.”

Stem cell models aside, the team also worked on constructing 3D functional complex tissue/organ models with primary cells (e.g., myocardium tissue model with primary cardiac myocytes, 3D cerebral cortex model with primary brain neuron cells), for future studies on tissue engineering and regenerative medicine, 3D biology, pathology, and pharmacology.

4. Biomimetic design and fabrication of tissue scaffolds or tissue substitutes by customized bio-3D printing process and equipment

Based on customized 3D bio-printing technologies that were originally developed at the Center, the team also attempts to fabricate different kinds of implanted scaffolds/tissue substitutes for further clinical applications.

In order to keep the biological properties of materials during printing, the team developed an innovative bio-3D printing technique and equipment named low-temperature deposition manufacturing (LDM). The printing technique involves extruding scaffold materials into a low-temperature

forming chamber with an induced phase separation during freezing. Scaffolds fabricated by this process can better preserve the bioactivities of scaffold materials, and have been successfully used to repair various damaged hard tissues such as large segmental bone, articular cartilage, meniscus bone.

For the cartilage-defect repair, the team mimics the component and function of osteochondral tissue, and developed a biomimetic osteochondral scaffold with hierarchical organization and heterogeneous composition using LDM and other related technologies. After seeding and in vitro culture with goat autologous bone mesenchymal stem cells (BMSCs), the BMSC-scaffold constructs were implanted into a goat articular defect model. Forty-eight weeks post-implantation, superior hyaline-like cartilage and sound subchondral bone was observed and the implanted tissue constructs significantly enhanced the biomechanical and biochemical properties of the neo-osteochondral tissue. The research showed significance and potential use in clinical treatment of osteochondral diseases.

Furthermore, the group also developed innovative technologies for the fabrication of metal tissue substitutes using electron beam selective melting additive manufacturing. In 2017, a computational simulation of the fast and complex process of electron beam melting powder deposition was achieved for the first time. In January 2018, QuickBeam Tech. Co., LTD., the world's first electron beam selective melting additive manufacturing company

using equipment with bimetallic gradient structure forming capability was launched. Initial machine orders were made by regional Orthopedic Hospitals. Moreover in October 2018, the EBSM equipment passed the European CE certification.

Other ongoing works include development of personalized and fully degradable coronary stents, fabrication of 3D cervical drug-sustained release model and engineering of bio-bots, living systems, and micro-physiological systems with different biofabrication technologies.

Facilities

The Center in Beijing has world-class bio-3D printing and cell assembly equipment, dedicated control software, and three-dimensional data reconstruction software, as well as standard 1000-class and 10,000-class clean room required for cell culture and printing experiments. In addition, the Center is also equipped with facilities for cell culture, biological testing and evaluation, and scaffold and bioink characterization and evaluation. This includes several cell culture incubators, centrifuges, fluorescent microscopes, laser confocal microscopes, microplate readers, flow cytometry systems, biomaterials mechanical property testing machines, rheometers, quantitative PCR systems, and much more (Fig. 3).



Fig. 3 Photographs of laboratory space and facilities

International collaborations

Due to its international influence and impact, the Center is affiliated as the Bio-manufacturing and Rapid Forming Technology Key Laboratory of Beijing from the year 2014, and “Bio-manufacturing and Engineering Living Systems” Innovation International Talents Base (111 Base) by the Ministry of Education and the State Administration of Foreign Experts of China from the year 2017. Professor Gordana Vunjak-Novakovic from Columbia University (USA) and Professor Roger Kamm from the Massachusetts Institute of Technology (USA) served as the joint directors of the “111 Base.” Through this, the Center also maintains international collaborations and exchanges with more than 20 universities and research institutions worldwide in the field of bio-manufacturing. These include Harvard Medical School, MIT, Columbia University, University of Pennsylvania, Pohang University of Science and Technology, Singapore National University, University of Tokyo, Julius-Maximilians University at Würzburg, University of Manchester, and many more.

Additionally, as one of the leading institutions in the field, the Center has hosted several international conferences on additive manufacturing and bio-manufacturing. The most recent one (ICAM-BM, Beijing) took place in

December 2018 and before that the 2017 International Conference on Biofabrication (Beijing, October 2017) (Fig. 4).

Perspectives

The vision of the Bio-manufacturing Center at Tsinghua University is aimed toward establishing a leading research center for the conducting cutting-edge research, education, and innovation within the emerging and interdisciplinary field of Bio-manufacturing. As mentioned previously, the group’s focus will be highly directed toward research on engineering living system and human-like micro-physiological systems, exploring a new paradigm of modern engineering and manufacturing for innovative applications in bioengineering and health sciences, biology and biomedicine, and promoting the development of the field of advanced bio-manufacturing. With excellent faculty members, postdocs, graduate students, facilities, and international collaborations to our disposal, our group is eager to further help progress innovative and future developments within the field.



Fig. 4 The most recent international conferences organized by the Center: **a** 2017 International Conference on Biofabrication, October 15–18, 2017, Beijing, China; **b** The 5th International Conference on

Additive Manufacturing and Bio-Manufacturing (ICAM-BM 2018), Dec. 2–5, 2018, Beijing, China

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