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Topic Insights

Medical Additive Manufacturing: From a Frontier Technology to the Research and Development of Products

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1. Research and development (R&D) and the challenges of raw materials for medical additive manufacturing

Raw materials for medical additive manufacturing have a wide range of commonalities that are also seen in many other fields, making them an important basis in the field of three-dimensional (3D) printing. Problems and challenges related to material types, powder properties, formability, viscoelasticity, and so forth also share common features. For example, many metal materials are used in the field of aviation, while metals, polymers, and inorganic materials are used in the field of biomedicine. The most widely used materials in biomedicine are biocompatible. Various homogeneous and non-homogeneous composites are also available for 3D printing, and impose an additional challenge in additive manufacturing; the use of heterogeneous composites in 3D printing is particularly challenging.

In Guangdong, Hong Kong, and the Macao Great Bay Area, 3D printing has become one of the most important branches of the industrial development. In the medical field, 3D printing was initially used for bio-prosthetics; however, it has now expanded to cell, tissue, and organ printing, as well as medical robots. Many devices with special components or special properties require specific materials that are suitable for 3D printing and sometimes also four-dimensional (4D) printing (in which products change with time as an additional dimension). In the gradient design of additive manufacturing products, the product should be constructed and printed first. Basic functions such as biodegradability and biocompatibility can be tested at very beginning of product development. Intelligent devices such as the shape memory alloys of 3D printed vascular stents are also in the research and development (R&D) phase. Attractive materials are thus emerging that will provide medical doctors with more options for clinical applications—especially for treating challenging medical disorders.

The super-nano duplex magnesium alloy that was first reported in *Nature* in 2017 is a kind of biodegradable metal with excellent particle-disintegration performance; its use has advanced 3D printing and even opened up opportunities for 4D printing. Although the human body is a complex mechanical system, 3D and 4D printing may surpass the limits of human mechanics and enhance the human body with new technological innovations. Conventional 3D technology is mainly developed overseas and is coupled with the R&D of raw materials; thus, such raw materials are usually monopolized by the companies that develop them. The question of how to independently develop raw materials in the form of powder or ink in order to meet the requirements of medical applications is of great importance for domestic applications. Therefore, attention must be paid to the innovation and development of raw materials, quality control, and the development of standards and regulations—especially for Class III implants that are developed for clinical applications.

Drug-resistant antibiotics are greatly needed in clinical settings and are becoming increasingly important. Extensive research on how to combine materials with antibacterial drugs has been carried out in recent years. Reports have been published on combining antibiotics with materials, including single-dimensional materials such as metals, sodium, silver ions, gold ions, and copper ions, and two-dimensional (2D) materials, such as molybdenum sulfide, graphene, and so forth. The combination of new materials with antibiotics and further integration with 3D printing will be the next step in material additives, and one that requires further investment toward clinical applications.

The relationship between 3D printing and material development requires synergy at the very beginning. From the perspective of material fabrication, the molding, preparation, and solidification processes of 3D printing are different from traditional machining processes. For example, titanium alloy has mature use in clinical applications but cannot be used directly for 3D printing. Materials must first be atomized into powder and the composition design must be optimized to fit the 3D printing process. Therefore, the R&D of raw materials that are suitable for 3D printing and the directional design of traditional medical metal materials are key research directions that require multidisciplinary collaboration.

In recent years, magnesium and its alloys have shown good application potential for bone defect repair, especially under conditions with poor tissue regeneration potential. Both animal experiments and clinical trials have shown that magnesium alloys have good osteogenic effects and treatment efficacy. However, since magnesium and its alloys are extremely easily oxidized, the issue of how to decrease the oxidation of pure magnesium powder or the powders of its alloys is a key problem in 3D printing manufacturing processes. During the 3D printing solidification process after oxidation, the powder easily forms a cold partition that will significantly reduce the fatigue properties of the material, leading to premature failure of the device. During the powder preparation of pure magnesium or its alloys, the control of oxygen content is critical; therefore, 3D printing equipment should be designed in conjunction with R&D and the selection of the relevant materials to be used. By solving these challenges in a synergistic manner, it will be possible to deal with the current problems of 3D printing and usher in great development of the application of 3D printing technology in the field of medical devices, especially in counties with huge medical needs, such as China.

From a disciplinary development perspective, 3D printing has evolved from traditional material printing, such as the printing of protective functional devices, to cell-to-material printing for tissue repair and organ regeneration. It has also evolved from a single-repair function to disease treatment or tissue functional regeneration. For example, the application of 3D printing in bone tumor surgery combines a traditional bioceramic bone repair function with a phototherapy function in order to deal with early tumor recurrence after bone tumor surgery and enhance related bone defect repair. 3D printing has previously been used to produce porous scaffold materials for bone defect regeneration. Recently, it has also been transformed for application in soft tissues, such as for skin and muscle repair. Scientists are able to make 3D printed hearts with complicated structures and 3D printed alveoli with respiratory function.

The key scientific issues to be solved in the 3D printing process are: first, how to realize the integration of complex bionic structures and functions of the human body; second, how to enable the spatial and temporal distribution and arrangement of multiple organs; and third, whether traditional tissue regeneration and the repair of organ function can be effectively unified in order to target the nature of diseases. In the field of bionic structures, a 3D printed bioceramic lotus root structure can effectively guide cell growth and promote skull regeneration. An actual tissue or organ has a very fine and complex structure, which includes the different spatial distribution of different cells; if the spatial and temporal

arrangement of various cells can be established by means of 3D printing, then complex organ regeneration in the body will be resolved. When treating diseases such as bone tumors, surgery can remove most of the tumor mass but may not be able to kill residual tumor cells after resectioning and post-surgically restoring function; however, 3D printing may provide a solution.

Although many articles have been published in these fields in the past few years, there is still a long way to go before real bedside applications become routine. China has made great efforts to take advantage of 3D printing for bone tissue regeneration. The combination of biological 3D printing and tissue engineering might solve the challenges of internal structure and internal function in the material cell printing of complex tissues, although biosafety and ethical issues must also be taken into account.

There are four main aspects to be considered in the direction of future raw materials used in 3D printing: First, 3D printing places new demands on the R&D of materials by requiring materials in powder form; second, the combination of 3D printing medicine and materials places new requirements on the identification of relevant materials; third, material processing properties and their regulation should be considered in 3D printing for medical applications; and fourth, in biological 3D printing, higher demands are placed on the spatial distribution of different materials and cells.

2. R&D and applications of cutting-edge technologies for medical additive manufacturing

The influence of shape, structure, design, and facility on the performance of orthopedic implants depends on the printing mechanism and process. The repeatability of printing facilities is also a challenging issue that should be considered during the manufacturing process. In addition to raw materials and 3D printing facilities, the following processes are critical in additive manufacturing: processing multi-material composites with different processing features; and incorporating the heterogeneity of different materials that may require complex processing techniques. In multi-material processing, the interface characteristics of different materials lead to interface instability between materials, which makes the integrity of the final product vulnerable to damage. The precise formation of complex multi-layer structures and the permutation and combination of gradients are also important issues for consideration. In bioprinting, living cells are regarded as part of the biomaterial, and it is crucial to be able to maintain cell activity and function after printing.

Metal-based medical materials (such as titanium alloy) have insurmountable problems as orthopedic materials in clinical applications; for example, they have a high elastic modulus that may induce the stress occlusion effect, as well as insufficient toughness. Polyetheretherketone (PEEK) is a new-generation medical implant material. It has the advantages of a similar density and modulus in comparison with natural cortical bone, but possesses a low thermal conductivity. However, the use of 3D printing to produce PEEK instruments has encountered a challenge in the manufacturing process that needs to be solved as soon as possible. Chinese engineers invented the cold deposition process for 3D printing, which regulates the preparation process through nozzle cooling rates, cooling conditions, and other parameters. This process permits the regulation of crystallinity and control over the molecular level of the crystallinity of PEEK, in order to achieve control of its mechanical properties. Engineers have conducted more than 70 clinical cases to date using 3D printed PEEK instruments to examine a range of issues, from meeting shape requirements at very beginning of the process to meeting performance requirements. However, integration of an artificial prosthesis with the host tissue is a challenging task that needs to be solved in the material design and preparation process in the future. In principle, the material should be designed to fulfil its expected functions, while the manufacturing processes should be integrated to meet the functional requirements of the personalized prosthesis.

3D printing technology for biological tissues, also known as bioprinting, has been used to assemble embryonic stem cells into spheres, control the size of these spheres, and differentiate stem cells to form embryos. For example, bioprinting can deposit stem cells into spheres and induce them to become liver cells that can be used in a drug test. An *in vitro* 3D model constructed by means of bioprinting technology is closer to the human body than traditional models, and the results obtained from such a model can reflect the actual situation more realistically. As in the drug development process, experiments conducted using a 2D model are often inaccurate and have a low success rate, leading to the waste of significant resources. Bioprinting can be used to produce a model that is bionic and closer to the human body, thus providing an excellent tool for biological development, cancer research, and new drug development.

The following steps are essential for bioprinting. First, the properties of the 3D printed biomaterials are designed. Cells can also be used as biological materials, and cell functions should be considered after printing cell-containing biomaterials. These developments are also reflected in the R&D of machine hardware and materials for 3D printing. Second, it is necessary to determine how to make the bioprinted tissue functional. Usually, organs or tissues can be printed out directly, such as the heart and blood vessels, which only have similar morphologies at the beginning of the bioprinting process. However, in addition to printing these biological organs or tissues, the specific function needs to be generated, which poses a greater challenge to material design and manufacturing. Third, in cell printing, different cells need to be printed at specific locations in order to maintain a 3D structure to ensure that the printed cells are alive, have a specific spatial distribution, and perform the corresponding functions. The cell-to-cell interface is of particular importance when printing a variety of cells. However, it is currently difficult to achieve precision of cell placement in bioprinting while avoiding damage to living cells during the printing process, as such damage is common and particularly challenging for applications. Complex microchannels in microfluidic technology can be used as bioprinting heads for cell printing. Bioprinting is currently available for organ chips, which can be used to construct part of the functions of *in vitro* organs for new drug evaluation, drug screening, and so forth. To summarize, ① bioprinting should be used to construct advanced biomimetic organism modeling; ② from a technical perspective, printed organ chips must be able to achieve *in vivo* bionics; and ③ biological needs should be combined with artificial intelligence, big data, and deep learning, which requires early attention prior to future potential clinical applications. Biological scientists and clinicians should work together closely from very beginning of the process, which would include conducting targeted research on specific clinical indications or applications for later faster and effective translation into clinical applications.

Understanding how to transition 3D printing from morphology to function is extremely important for scholars and experts in biomanufacturing and clinical applications. The innovative concept of 4D printing involves changing the shape of 3D printed materials by modifying the temperature, electromagnetic field, and so forth over time. However, as 3D printed materials are applied to the human body, they can grow into the living body as the implantation time increases, which is also a kind of dimension. Human medical implants require a systematic manufacturing process that includes design, materials, 3D printing, post-processing (including heat processing and surface processing), quality testing, packaging, surgery, and rehabilitation. Every step must be done well in order

to ensure the success of clinical applications. In addition, National Medical Products Administration (NMPA) verification needs to be speeded up so that industrial breakthroughs can be achieved. Since medical implants are personalized, their verification is extremely difficult when following NMPA recommendations that focus on system validation. It is not enough for 3D printing to produce a similar shape when printing organs or tissues; it is also necessary for such products to have corresponding functions. This is the future development direction of medical 3D printing.

3. Establishment of standards or regulations for certification and an evaluation system for medical additive manufacturing products

Relevant institutional cooperation is necessary in R&D for later industrial applications, and the leading role of the superstructure is crucial. The first breakthroughs in medical additive manufacturing occurred in the fields of orthopedics and dentistry, and gradual maturity of this technology has also occurred in these fields. Therefore, the regulations that were proposed for 3D printed medical implants as early as 2010 were for orthopedic and dental products. At present, the NMPA has approved four 3D printed standard products for clinical application. The NMPA prioritizes mature or validated areas, such as the fields of orthopedics and dentistry, and decentralizes the manufacturing of customized product parts to various provinces. However, as additive manufacturing products include custom-designed products, the NMPA has planned to set up a complete evaluation system. At present, the NMPA has identified 40 guiding principles for medical device registration, among which are seven principles related to additive manufacturing. Relevant standard systems, regulatory systems, guiding principles, registered technical documents, and beacon systems will be established with the aim of focused development and breakthroughs toward clinical application. Additive manufacturing is easier to implement in some aspects of orthopedics than in others. The Chinese Academy of Engineering (CAE) should promote corresponding specialized research projects with the aim of combining the division of medicine and material, and establishing an efficient, scientific, and correct verification system.

The most important requirement in China's "Measures for the Supervision and Administration of Medical Device Production" is to ensure the safety and effectiveness of medical devices. At the moment, the US Food and Drug Administration (FDA) mainly promotes and protects public health by risk controlling and ensuring the safety and effectiveness of medical products in applications through reasonable conviction and with effective scientific evidence. Innovative medical devices in the field of additive manufacturing require regulatory science that verifies the registered products. Carrying out multi-center clinical trials and medical research and producing products that can be summarized and peer-reviewed for scientific publications are meaningful tasks to be completed before registration and provide important references for clinical practice. Such research and production would help with the R&D of innovative products and the monitoring of the entire process during clinical application. Sichuan University's Institute of Regulatory Science for Medical Devices is the world's first academic institution to handle regulatory issues related to medical devices. Its mission is to establish medical device regulatory science through pre-verification and risk control. Based on the background of users, product developers, and corporate risk control, this regulatory science should cover the full cycle of medical products.

There are differences in the domestic and international regulations that have been established for customized products. In the United Kingdom, the core management idea for customized devices is is as follows: Apart from issues regarding materials, the whole production process of additive manufacturing is viewed as the responsibility of surgical doctors, including clinical patient computed tomography (CT) or magnetic resonance imaging (MRI) image data acquisition, manufacturing, clinician confirmation, and subsequent clinical application. From the perspective of Chinese enterprises, the most important issue is to obtain a registration certificate from the NMPA before marketing. The situation in UK suggests that China should issue clear registration guidelines for custom-designed medical devices as soon as possible and promote clinical translation. Relevant registration guidelines should take into account both technical feasibility and the generation of practical benefits for all parties involved—especially the patients. The repeatability of medical additive manufacturing and the features of the final manufactured product, whether used in humans, animal models, or cell models, must be implemented in a standardized manner. This topic is worth thinking about and discussing further in future R&D and clinical applications.

All new technologies and new materials for clinical application—and especially 3D printed Class III medical products—require systemic evaluation and the approval of a regulatory body. Medical additive manufacturing technology is still in the early stage of exploration. At present, several problems in the clinical use of 3D printing technology in orthopedics and dentistry still need breakthroughs: The risk-bearing responsibility is not clearly defined and the path toward clinical registration and verification is long because it is difficult to assess the clinically expected effect of such products, especially in 3D printing manufacturing. The product quality-control system is also imperfect. Clinical research initiated by preclinical scientists is not aimed at clinical registration; however, the relevant management processes and quality-control systems must meet the corresponding surgical requirements.

4. Clinical applications of medical additive manufacturing products

3D printing is an important technology in the field of hip reconstruction in orthopedics. In addition to the 3D printed titanium alloy that is currently used in reconstructive surgery for bone tumors and hip joints, 3D printed porous tantalum, which has good biocompatibility, has been developed and studied. At this stage, 3D printed porous medical tantalum has been evaluated by scholars in the materials field and by orthopedic surgeons; in fact, there are already a few clinical applications of this material. Clinical applications of 3D printed porous tantalum have been carried out in spine, hip joint, and limb varicose surgery, with good clinical outcomes. 3D printed porous tantalum can realize the design and manufacturing of the bionic bone trabecular structure, and has good cell adhesion and biocompatibility. At the same time, the elasticity modulus and strength of the material are adapted to the local environment. The clinical results show that 3D printed porous tantalum can be effectively fused with the bone, and that function can be satisfactorily restored after surgery. Both experimental and clinical results confirm that 3D printing provides precise dimensions and has good treatment effects. 3D printing can also be used in telemedicine. In the Yunnan Military Region General Hospital in China, medical image information of patients with bone tumors is transmitted remotely to the 3D medical laboratory in the hospital for simulation design and print manufacturing; the products are then sent to the hospital in Yunnan, where the surgery is completed after the products are sterilized.

As the population of China gradually ages, there will be nearly 450 million elderly people over the age of 60 in 2020. Based on the currently reported rate of spinal fracture, at 30%, more than 100 million spine fractures are estimated to occur after 2020. From

the perspective of orthopedics, it is extremely demanding to treat such challenging conditions using 3D printing technology. As metallic material printing is now more mature in orthopedic applications, 3D printing can be used to realize individualized simulated and bionic structures. However, all existing printing technology is currently realized *in vitro* or *ex vivo* and cannot be achieved directly *in vivo*—or the so-called "*in vivo* printing." 3D printing technology may be able to solve the problem of bone defect filling for bedside repair. If *in vivo* printing can be achieved, more collaborative medical and industrial research on the potential application of 3D printing in orthopedics is expected to further benefit patients.

As discussed above, the prospect of 3D printing in clinical applications is broad, as it provides accurate and effective treatment methods for orthopedic surgeons. Collaboration between medical and industrial sectors in additive manufacturing and clinical application is very important, but should be well regulated by designated bodies so that experienced doctors and engineers can effectively cooperate and complete this challenging task. We hope that more standards and standardized treatment methods can be created through research in order to optimize the entire process, and that systematic evaluation of these materials can be successfully completed.

At present, the application and development of the preoperative planning model is relatively mature; however, in terms of manufacturing, 3D printed instruments are too rough to and do not have fine and smooth surfaces. Further improvement in this aspect would be very helpful to orthopedic surgeons for current bedside applications. Navigation robot technology, which is at a mature level of application, is now being applied in medical 3D printing; however, the future development potential of 3D printing surgical guide plates and accessories in orthopedics and dentistry remains to be verified in orthopaedics. Although the price of printed guide plates and accessories is relatively low, there are unavoidable drawbacks when such devices are used during surgery. For example, the plate can only be actually buckled onto the surface of the bone if a wide incision is used to cut to the bone and all the soft tissues are removed, which is very difficult to achieve in clinical practice. In addition, 3D printing has limited application prospects for bone surfaces that lack distinctive structural features, such as a smooth curved surface, for which it is difficult to achieve the resection, replacement, and fitting of preoperative simulated positions during surgery. In the process of developing a personalized prosthesis and internal support, 3D printing cannot solve problems related to long-term implantation, such as the prosthesis breaking, loosening, or falling off. In the future, when focusing on personalized design, it is necessary to pay attention to the safety of 3D printed individualized implants. When replacing mass-standardized products with personalized implants, the cost of 3D printed products is much higher than the cost of those made by traditional manufacturing processes; this presents a huge challenge in the reform of clinical medicine. Therefore, research on 3D printing should focus on solving the problems that could not be solved in the past using conventional approaches such as traditional subtractive manufacturing. One such problem is how to print out exactly the same structure as a trabecular bone structure, with a special coating on its surface, in a way that will favor bone growth. For the replacement of large bone defects, a suitable size of the printed structure is a prerequisite. This is also an issue to consider in 3D printing.

Optimization of a functional structure to induce soft tissue regeneration in joints surgery is of great importance. Soft tissue research has become a major national strategy with significant clinical significance in China, and perhaps in industrialized countries as well. Tissues of the locomotor system, such as cartilage, ligaments, and tendons, are important parts of the joints. Applications for soft tissue repair are included in the research on many materials, such as conventional metallic materials, tantalum, titanium, and other absorbable metals. However, such materials cannot be directly applied as biological materials, which imposes a huge demand and a significant challenge for the replacement of the entire soft tissue. Many natural biological materials, such as collagen, optimized silk fibroin, collagen gel, and extracellular matrix, which has a fine structure and a suitable biological microenvironment, have been suggested for current clinical practice in soft tissue application in terms of repair or replacement, and have achieved good results in *in vivo* experiments. The extracellular matrix has been confirmed for use as a printing material in 3D printing, and has been used for important achievements in cartilage regeneration. 3D bioprinting shows potential for the repair of soft tissue damage. In tissue repair, the microenvironment formed by 3D bioprinting is important for the migration of stem cells toward the sites of tissue lesions. Structurally and functionally optimized biomaterials for 3D printing are essential for regulating cells in tissue regeneration and repair. The degradation of extracellular matrix materials during *in vivo* repair interacts and balances well with tissue regeneration, in comparison with a non-degradable metal material. Additive manufacturing has realized the structural design and refined manufacturing of biomaterials, and a breakthrough has been achieved in the preparation of multi-stage microporous structures in complex shapes using amphoteric biomaterials that induce stem cell differentiation in order to achieve overall tissue repair.

In summary, the field of medical additive manufacturing has developed rapidly and has solved many challenging clinical problems to date. The demand for orthopedic surgery using 3D technology is high because many orthopedic products are becoming more acceptable in terms of morphology and functions. However, many unsolved and challenging situations still remain in clinical settings, including the selection of raw materials. 3D printing is undergoing a modern industrial revolution in which 3D printing technology is a promising area with a wide spectrum of R&D and applications. However, the development of 3D printing technology is centralized in a few leading industrial countries, and the corresponding materials are monopolized by these foreign countries. It is still necessary to consider how to develop raw materials with independent intellectual property rights, and how to break the technological bottleneck.

Furthermore, many 3D printing technologies, including selective laser sintering (SLS) and selective laser melting (SLM), have both advantages and disadvantages in comparison with traditional or conventional machining processes. In addition, adequate clinical applications are necessary. Besides the adaptation of a material to its function, a breakthrough is needed in the biological functions of 3D bioprinting at the organ level. In terms of the locomotor system, breakthroughs in achieving desired mechanical properties are relatively easy; however, this does not provide a real substitute for the lost skeletal parts. It might be better if lost parts could be replaced by implants with biological functions. As we look forward to joint research, innovation, and development-related platforms, it is clear that cooperation between doctors and industry is highly desirable. However, in 3D printing companies, a large part of additive manufacturing products still require processing by traditional processing methods. Clinical applications should be conducted with caution, and basic research should be innovative yet clinically rigorous.