# Additive manufacturing innovation for musculoskeletal tissue repair and regeneration: from bench to bedside

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Additive manufacturing (AM) or three-dimensional (3D) printing is a technique that builds the 3D objects from a 3D digital model (either by a computer-aided design or by scanning the object) in a layer-by-layer fashion. There are seven categories of AM process as defined in the ISO/ASTM 52900:2021,[1] based on their working principles. These include vat photopolymerization, powder bed fusion, material extrusion, binder jetting, directed energy deposition, material jetting, and sheet lamination.[1] Over the past decades, AM technology has been exploited in many fields such as the medical, automotive, aerospace and industries.

The human musculoskeletal system, consisting of different types of bones, muscles, ligaments and tendons, is one of the key systems in the human body. Injuries and diseases to the musculoskeletal system will primarily affect the human body's movement.[2,3] The musculoskeletal disorders are characterized by pain and limitations in mobility, dexterity and overall level of functioning, reducing patients' ability to work and maintain a good quality of life. A recent analysis of Global Burden of Disease data showed that approximately 1.71 billion people globally have musculoskeletal conditions.[4] Diseases such as osteoarthritis, rheumatoid arthritis, psoriatic arthritis, gout, and ankylosing spondylitis affect joints; osteoporosis, osteopenia and associated fragility fractures, as well as traumatic fractures, affect bones; sarcopenia affects muscles, and back and neck pain affects the spine of the human body. Injuries to musculoskeletal tissues are prevalent, particularly in sports-active adults, and can be acute as a result of a traumatic event, or chronic as a result of overuse or cumulative trauma injuries.[3] For example, ruptures of the Achilles tendon and anterior cruciate ligament are among the most frequent and severe injuries sustained in a sports-active population. Cartilage can be damaged as a result of a trauma, and if not treated properly, can lead to degenerative diseases of the joints such as osteoarthritis,[5] and eventually, lead to a stage where a total joint replacement is required.

Treatment for musculoskeletal tissue injuries is broad and ranges from "wait-and-see" approaches to surgical operations. Surgical treatments will depend on the type of tissue and the injury sustained. Musculoskeletal tissues are complex units, with compositional, mechanical, structural and cellular heterogeneity. For example, ligaments and tendons are connective tissues comprised of a dense band of aligned collagen (mainly type I) with embedded resident cells (fibroblasts/tenocytes) that connect bone to bone and muscle to bone, respectively. The attachments between these interfacing tissues are unique and complex, with well-defined spatial changes in cell phenotype, matrix composition and mechanical properties.[6] Considering the intricacies of the musculoskeletal tissues and the inherent heterogeneity in cellular, structural and mechanical properties, it is clear that biomedical devices for the treatment of musculoskeletal disorders, including repair and regeneration of musculoskeletal tissues, should recapitulate the compositional, mechanical, structural and cellular heterogeneity. This is difficult to achieve using traditional manufacturing methods.

Advances in AM have opened new possibilities to fabricate biomedical devices or constructs with synergistic biological and mechanical properties that can mimic the natural tissue structures and physiological environment. In the past two decades, there are many AM systems have been developed. These provide engineering solutions in designing and producing structure-complex objects with unique material combinations and delicate multi-functional, topologically optimized geometries.[7,8] As a result, AM has been increasingly used as a revolutionary approach in the healthcare sector, since the 2020s there has been an explosion of publications on the application of AM in medical and life science research, as shown in **Figure 1**.

This has involved increasing consideration of AM technology for translation to clinical practice for medical applications. The trend in research output continues to increase exponentially with almost 2300 publications on AM applications for medical applications being recorded in the year 2021 (searched using Web of Science databases). Hence there is great urgency and adequate justification for the dedication of appreciable journal emphasis to AM technology translation.

In the past two decades, a wealth of information has emerged on AM applications in musculoskeletal tissue repairs and regeneration. Amount 10,798 publications selected from the Web of Science Core Collection AM applications in medical and life science, the number of original research articles exemplified by some of the most common research fields confirms that both biomedical engineering and biomaterials have topped the AM applications (over 4000 publications combined). It should be noted that surgery and tissue engineering (about 900 publications combined) are also key application fields of AM technology (**Figure 2**). As biomedical engineering, biomaterials, surgery and tissue engineering are key research topics that are relevant to musculoskeletal disorder treatments, tissue repairs and regeneration, the numbers of research publications in these key areas indicate that AM technology has tremendous translation potential in the treatment of musculoskeletal disorders.

The first key application of AM technology in the musculoskeletal system is patient-specific medical products such as orthopaedic implants which makes it possible to offer more individual treatments.[9] This implant can recreate the patient's natural contoured anatomy, thus improving implant fit to the patient leading to an improved *in vivo* performance. The second is to fabricate scaffolds, both biodegradable

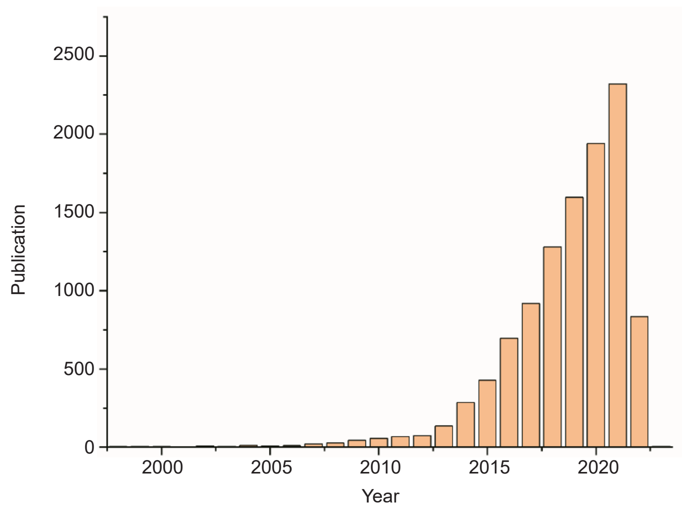


**Figure 1.** Publication trend of additive manufacturing application in medical science (from 2000 – 2022) (last checked on June 17, 2022).

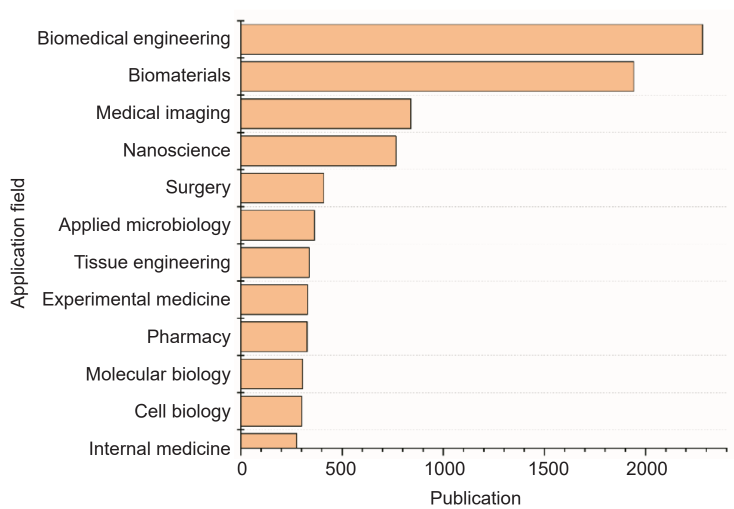


**Figure 2.** A topic search using Web of Science databases for publications of additive manufacturing applications in medical and life science. Search term: All=(((additive manufacturing) OR (3D printing) OR (Biofabrication)) AND ((tissue repair) OR (regeneration) OR (medical))).

and non-degradable, with or without cell integration, for musculoskeletal tissue repairs and regeneration. Researchers have developed different AM systems to produce tissue engineering scaffolds from a range of biomaterials; some of which have been successfully translated into clinical practice.[10, 11] The third area is the development of surgical instruments and supporting devices such as surgical guides, orthoses and prostheses, and tissue phantom and educational models.[12] In these applications, the customization potential of products, combined with cost-efficiency, makes it possible to manufacture better and more economically viable surgical products.

In this special issue of ***Biomaterials Translational***, we collected a series of papers that embrace a wide variety of subjects relevant to the potential uses of AM technology for applications in musculoskeletal disorder treatment and surgical therapeutic procedures. Donate et al.[13] introduce the collaborative activities in the Biomaterials and Additive Manufacturing: Osteochondral Scaffold (BAMOS) project under the Horizon 2020 Research and Innovation Staff Exchanges (RISE) program. Sahranavard et al.[14] present a systemic review in the 3D bio-printing of decellularized extracellular matrix-based bio-inks for cartilage regeneration and repairing). Sun et al.[15] reviewed the orthopaedic applications of polyether-ether-ketone using AM technology. Shao and co-workers report their recent research using 3D printed titanium prostheses with bone trabeculae to promote mechanical-biological reconstruction after resection of bone tumours.[16] And finally, Liu and co-workers report their systematic investigations on the mechanical properties of polyether-ether-ketone for the repair of large bone defects, a key aspect of AM technology.[17]

This collection of papers demonstrated that with AM, the design of the development of medical products is no longer driven by manufacturability, but by functionality which was required for the treatment of musculoskeletal disorders. However, there are still challenges facing the clinical translation of AM to musculoskeletal disorder treatment. The future of additive manufactured tissues for musculoskeletal repair and regeneration will depend on the advancement of tissue maturation with increased mechanical strength, and improved methods for vascularization for nutrient supply upon implantation. Much progress has been made in scaffold design but fully functional human anatomic additive manufactured tissues are still perhaps many years away from being realized. Nonetheless, the emergence of AM is an inspiring and exciting advance in the field of musculoskeletal disorder treatment.



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