INTRODUCTION

The use of stones, shells, wood, bone, ivory and iron and copper for surgical implants (especially teeth) dates back more than 4000 years (Hildebrand, 2013; Howland, 2018). The use of metal and alloy surgical implants for various bone repair and replacement was introduced around the end of the 19th century following the development of x-radiology and the discovery of anaesthetics and antiseptics to reduce infection. Stainless steel plates and screws to repair bone fractures were among the first biocompatible materials (circa 1926) followed by titanium and cobalt-based alloys introduced between 1935 to 1950 (Gomez & Morcuende, 2005; Knight et al., 2011; Navarro et al., 2008). In addition to permanent metal and alloy bone replacement appliances and devices, bone screw and plate devices made of magnesium and its alloys and zinc and its alloys have been, and continue to be, used as biodegradable surgical implants and bone scaffolds which chemically dissolve in the body as the bone section is repaired, eventually leaving only the repaired bone (Witte, 2010; Zheng et al., 2014). Similar strategies have been used for millions of soft vessel stent inserts over the past decades where the insert dissolves in time along with the repair of the diseased or damaged vessel tissue (Moravej & Mantovani, 2011; Purnama et al., 2014).

Some of the more popular surgical implant devices over the past three decades have included reconstruction plates and complex devices, spinal rods and inserts, and especially partial and total knee and hip replacement devices along with a variety of other orthopaedic and skeletal application devices (Gomez & Morcuende, 2005; Knight et al., 2011; Navarro et al., 2008); dominated by Ti and Ti alloys, especially Ti-6Al-4 V (Kang & Feng, 2018; Wang et al., 2013; Zhang & Chen, 2019). Indeed, tens of millions of knee and hip arthroscopies have been performed in the two decades ending the 20th century and the two decades beginning the 21st century worldwide; mostly using commercial surgical devices manufactured from...
cast or wrought Ti-6Al-4 V and other alloys which have been observed to have good biocompatibility, especially involving minimal elemental toxicity (Kim et al., 2019). However, a major drawback for solid Ti-6Al-4 V and other metal and alloy implant devices involves the fact that the elastic modulus or Young’s modulus for solid, fully dense bone implant devices is much higher than that for bone. For example, the Ti-6Al-4 V alloy implant modulus is ~110 GPa, while that for bone can vary from <1 GPa for soft or trabecular bone to ~20 GPa for hard, outer cortical bone. This difference, which can vary from a factor of ~5 to ~100, creates a condition referred to as bone stress shielding. In this condition, bone is induced by signalling molecules to remodel at the bone/implant interface as it attempts to alter the composition of matrix collagen and hydroxyapatite crystals to match the metal implant modulus. This can cause bone loss and aseptic loosening of the implant, requiring revision surgery (Dress et al., 2007). A similar loosening can occur for failure of cemented implants, especially femoral and tibial implant stems, also requiring revision surgery (Dress et al., 2007).

2 | BRIEF OVERVIEW OF ADDITIVE MANUFACTURING/3D PRINTING

While numerous strategies to produce porous, biomedical metal implants have been pursued over the past several decades, no successful applications were achieved for Ti and Ti alloys until the emergence of metal 3D printing around 2004. Such porous, open-cellular device structures could not only allow for tailoring of the stiffness or Young’s modulus since the Young modulus is related to the relative density \( \rho_s/\rho_e \): E = E_s(\rho_s/\rho_e)^2; where \( E_s \) is the solid (fully dense) elastic(Young’s) modulus and \( \rho_e \) is the fully solid density (4.43 g/cm³ for Ti-6Al-4 V alloy), and porosity is given by \((1 - \rho_s/\rho_e) \times 100 \text{ (in per cent)}\) but also an open-cellular implant structure could allow for bone cell ingrowth and the elimination of cement to bond the device to the bone.

With the advent of additive manufacturing and metal 3D printing using commercially available laser and electron beam powder bed fusion systems (popularly referred to as selective laser melting (SLM) or electron beam melting (EBM) systems), complex, biomedical implant devices began to be fabricated, including Ti alloys and Co-Cr-Mo alloys. In these systems, shown typically in Figure 1 for EBM, a computer-aided design (CAD) model directs the electron beam to selectively scan and melt specific powder layer regions which solidify prior to the creation of the next powder layer, which is similarly scanned and selectively melted, creating a 3D structure layer-by-layer. Figure 1a shows a schematic view of the electron beam melting (EBM) system where the powder (Figure 1b) in cassettes is gravity fed to a raking system (r) which forms succeeding layers on the selectively melted and solidified prior layers as the forming 3D product drops down as each layer is formed and scanned. Typical Ti-6Al-4 V product microstructure is shown in Figure 1 (c); consisting of lenticular (lamellar) alpha-phase grains surrounded by thin (dark) regions of beta phase. The CAD models which drive this layer-building process can either be created mathematically or by utilizing layer data from micro-CT scans which are embedded layer-by-layer in software models (Diegel et al., 2019; Gibson et al., 2015; Leary, 2020; Murr, 2020). Commercially available software such as Materialise/Magics NV (Louvain, Belgium) can provide suites of CAD models utilizing geometric or polyhedral unit cell constructs to build complex, open-cellular metal or alloy mesh and foam structures which can emulate porous, open-cellular bone structure with pre-determined porosities (or densities) and corresponding Young’s modulus (E) as discussed above.

Figure 2 shows some examples of these CAD models along with electron beam powder bed fusion (EBM) fabricated mesh and foam samples (Figure 2a, b) and a mathematically based foam model in Figure 2b lower left (Bakke, 1992). The models shown in Figure 2c, d emulate soft-core bone foam structure surrounded by a less porous and more dense hard bone foam structure; illustrating an ideal trabecular/cortical bone stem design. In this context, the design porosities in Figure 2c, d are 83% and 56%, respectively, corresponding to relative densities \( \rho_s/\rho_e \) of 0.17 and 0.44, respectively. These relative densities correspond to Ti-6Al-4 V Young’s moduli (E) of 3.2 GPa and 21.3 GPa, respectively. Densities in mesh and foam structures can be manipulated by altering the strut and ligament thicknesses as well as their spacing, (Figure 2), which determines the average pore diameter. The strength (particularly compressive strength) is also dependent on these parameters as they influence the relative density (Murr, 2020). It might be noted that excess powder filling the cellular pores is ultrasonically removed through the open structure.

3 | ADVANTAGES AND APPLICATIONS OF 3D FABRICATED, OPEN-CELLULAR BIOMEDICAL IMPLANT DEVICES

While as noted for Figure 2, mesh and foam biomedical implant device Young’s moduli (E) can be tailored to eliminate bone stress shielding, there are other important biocompatibility issues which are addressed by porous device designs. One of the more apparent issues involves osseointegration or bone cell (osteoblast) ingrowth into porous structures which at the least can be created on specific regions of implant device surfaces or interiors. This can eliminate cement for bonding and assure no loosening of the device as noted previously. Indeed, this strategy has been utilized even in commercial appliance manufacture for roughly the past several decades (Boyan et al., 2001; DiPrima et al., 2016). In addition, while traditional (commercial) implants, especially orthopaedic implants, have involved rather standard ranges of appliance/device sizes, laser and electron beam powder bed fusion fabrication (SLM and EBM) allows custom or personalized, patient-specific fabrication using micro-CT scan data for affected, potential arthroplasties and other skeletal augmentations or replacements (Murr, 2017, 2020).

Although solid metal and alloy implants such as spinal, femoral or other bone support rods or stems, impose notable stress shielding and no bone cell ingrowth, they also eliminate vascularization (blood flow)
in the replaced bone volume. Open-cellular biomedical devices, on the other hand, pose the prospect for inducing bone structure (osteoinduction) and vascularization within the porous structures, rendering the implant ‘living’; and eventually serving as a bone scaffold (Correa et al., 2018; Murr, 2019; Nune et al., 2018). However, this requires infusing the implant with properly rejuvenated or processed intramedullary material extracted from the bone core prior to implant insertion, or infusion of the implant with a hydrogel matrix containing osseous tissue, primary endothelial cells and fibroblasts in connective tissue, along with the appropriate signalling molecules and other molecular structures to create bone tissue and vascular capillaries within the 3D, open-cellular device regime (Correa et al., 2018; Kumar et al., 2016; Li et al., 2018; Murr, 2019; Novosel et al., 2011; Unger et al., 2015). Open-cellular structures also afford an opportunity to seed the implant with effective antibiotics for the prevention of infection (Murr, 2017).

**FIGURE 1** EBM system schematic (a) SEM view of Ti-6Al-4 V precursor powder (b) Optical micrograph showing solid fabricated Ti-6Al-4 V microstructure composed of lenticular (elongated) alpha-phase grains (c). In (a) the electron gun, focusing lenses and scanning system are denoted ’1’. 2 denotes the focused electron beam. 3 denotes the powder cassettes which gravity feed powder to be raked ‘r’ across the bed into layers. 4 denotes the layer-building product Murr (2020)

### PERSONALIZED, PATIENT-SPECIFIC SURGICAL IMPLANT DEVICE FABRICATION USING 3D PRINTING/ADDITIVE MANUFACTURING

Even before the advent of metal and alloy 3D printing of biomedical implant devices, rapid prototyping systems using laser scanning were utilized in the fabrication of patient-specific, polymer surgical models which included a variety of vessels using soft polymer structures along with hard polymer structures to emulate bone; allowing for a wide range of surgical planning strategies. (D’Urso et al., 2000; Hoang et al., 2016; Rubio-Perez & Lantada, 2020). With the advent of metal implant device fabrication, such polymer surgical models were often combined with the 3D printed metal implant device to assure a perfect fit prior to surgery; optimal surgical planning. Figure 3 illustrates this concept for a cranial Ti-6Al-4 V mesh implant.
for a damaged skull bone section replacement. Such porous implant devices facilitate rapid and efficient bone cell (osteoblast) ingrowth, allowing the implant to eventually serve primarily as a bone tissue scaffold.

5 | IN-HOSPITAL, PATIENT-SPECIFIC, CUSTOM DESIGN INVOLVING SURGICAL MODELLING AND COMPLEX OPEN-CELLULAR IMPLANT DEVICE FABRICATION

While Figure 3 illustrates a simple, but effective example of cranioplasty involving polymer skull modelling and open-cellular metal skull bone replacement designed for a Young modulus around 6 GPa; both involving 3D printing/additive manufacturing, this model-fabrication strategy allows custom 3D fabrication where complex bone replacement surgeries are required. Figures 4 and 5 provide progressively complex examples of these surgical planning strategies and custom implant fabrication. Figure 4 shows a polymer pelvic model with an open-cellular Ti-6Al-4 V replacement device fabricated by EBM as shown in Figure 1a. In contrast, Figure 5 shows a pelvic section similar to Figure 4 for a patient-specific clinical trial which required more complex metal implant components to replace a cancerous pelvic section as well as the attachment of a total hip replacement device. The sequence of images in Figure 5 begins with the patient pelvic model in Figure 5a followed by the hip-acetabular prosthesis model with fastening screws in Figure 5b. Figure 5c, d shows views of the EBM-fabricated Ti-6Al-4 V, selectively open-cellular acetabular prosthesis, which was surgically implanted as implicit in Figure 5e. The complete, complex hip arthroplasty is shown in the X-ray image in Figure 5f 18 months after surgery.
It is clear from the examples provided in Figures 3-5 that such complex, customized surgical requirements are impossible to accomplish with commercially manufactured biomedical implant devices and require personalized, custom fabrication only available through 3D printing/additive manufacturing. This is especially true for the selective placement of porosity within the fabricated device. In addition, the most expedient means to accomplish this custom fabrication is to establish surgical, in-house (or in-hospital) 3D printing service centres having both polymer stereolithography/rapid prototyping 3D printers for patient-specific, polymer model production and laser or electron beam powder bed fusion systems (SLM or EBM systems) for metal or alloy biomedical device production. These model and device production systems are supplemented by necessary micro-CT scanning systems, X-ray imaging and appropriate software suites for embedding CT-layer scan data into CAD models and processing software for laser beam scanning and polymer activation and laser/electron beam selective powder layer scanning and melting to create the 3D layer-by-layer, biomedical device structures (Figures 2-5).

As noted above, one of the more successful software packages available commercially is the Materialise-Mimics (Trademark) suite of medical software which allows a variety of mesh and foam structures to be modelled and fabricated as shown in Figure 2. In 2019, hospital point-of-care surgical planning and 3D printing centres utilizing Materialise medical software worldwide totalled 271: US/Canada 113; European Union 48; Japan 34; UK 31; China 24; Australia and South America 9 each (www.materialise.com/en/medical/mimics-innovation-suite/mimics.).

6 | FUTURE PROSPECTS AND BIOMEDICAL IMPLANT DEVICE INNOVATIONS

Figures 4 and 5 provide especially compelling examples of the utility and efficacy of custom, patient-specific, complex implant device fabrication in point-of-care, in-hospital surgeries. Although there are limited, timely data for the global establishment of such point-of-care surgical service centres, the proliferation has been significant over the past few years. For countries such as China and India, price controls and related cost measures assure a wider patient participation in custom-fabricated implant device surgeries. In addition, commercial manufacturers of implant devices have also become directly involved in the in-hospital surgical service centres as well as the fabrication of custom, patient-specific biomedical devices at remote company manufacturing sites using micro-CT scan data of individual patients, which is transmitted electronically.

For the most part, Ti-6Al-4 V biomedical device fabrication has become the standard using widely available prealloyed powders in commercial SLM and EBM systems (Figure 1). However, specialized alloy implant devices can be fabricated using Co-Cr-Mo alloys where hard materials are required, along with pure metals such as tantalum. The Young modulus for these metals is roughly twice that for T-6Al-4 V, and this becomes an issue where biomechanical compatibility involving stress shielding is important. Hard metals and alloys have reduced
wear and generally higher strength, and these may be over-riding issues for certain circumstances or specific device applications. In addition, there are Ti alloy compositions where the fully dense Young’s modulus is around 50 GPa, and it is possible to manufacture prealloyed powders having these compositions (Murr, 2018).

The examples shown in Figures 4 and 5 represent extent of clinical trials which began in China nearly a decade ago. While the US has performed similar trials nationwide, China has become a world leader in innovative and complex bone replacement surgeries as illustrated for example in Figure 5 (Cai, 2015; Xia et al., 2019). China has also embarked on programmes to manufacture SLM and EBM systems and deploy them in hospital point-of-care service centres at reduced costs, although as noted above, the US and Canada had five times the number of in-hospital, custom surgical centres fabricating patient-specific biomedical devices in 2019. The health approval system for devices and device components also differs around the world as well. In the US, the FDA has implant device approval authority and has approved numerous 3D printed, open-cellular or variously porous components, including acetabular cups, spinal inserts, cranial-maxillofacial implants, stents and dental implants (DiPrima et al., 2016).

While COVID-19 has variously dominated hospital functionalities worldwide in the first half of 2020, the passing of this global pandemic will likely see a rapid return to the proliferation of patient-specific, complex, open-cellular biomedical implant device development, clinical trials and the establishment of bone-related surgical service centres producing a wide range of custom bone replacement devices; based in part on contemporary applications and market analyses (Ahangar et al., 2019; Dall’Ava L et al., 2019; Gadia et al., 2018; Huang et al., 2019; Kalaskun, 2017; Lee et al., 2020; Murr, 2019, 2020; Tofail et al., 2018; Wohlers Report, 2019, 2019; Woo et al., 2020; Zhang & Chen, 2019). This trend in global customizing of biomedical devices might be popularly referred to as mass-personalization which is made possible by 3D printing in point-of-care surgical service centres, along with other emerging technologies (Marr, 2020).

REFERENCES
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