Bulk Metallic Glasses for Implantable Medical Devices and Surgical Tools

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With increasing knowledge of the materials science of bulk metallic glasses (BMGs) and improvements in their properties and processing, they have started to become candidate materials for biomedical devices. A dichotomy in the types of medical applications has also emerged, in which some families of BMGs are being developed for permanent devices whilst another family – of Mg-based alloys – is showing promise in bioabsorbable implants. The current status of these metallurgical and technological developments is summarized.

1. Introduction

Medical devices made from metallic alloys are in widespread use, and a process of continuous metallurgical improvement has led to enhanced biomechanical and biocompatible performance of these materials. The traditional alloy is a polycrystalline material, and a significant body of literature exists describing, for example, innovations in the formulation and processing of titanium- and cobalt-based alloys for orthopaedic applications.[1] Problems still being addressed include adverse corrosion, wear, and fatigue behavior, manufacturing difficulties, a lack of elasticity, and high modulus (which can cause stress shielding).

Bulk metallic glasses (BMGs) are a relatively new class of metallic materials developed over the past three decades. Whereas conventional alloys have a crystalline structure, BMGs exhibit no long-range atomic order, appearing instead as an atomically frozen liquid. In the last 20 years, many metallic alloys that can form glassy solids have been developed across a broad range of compositions, including Pd-, Pt-, Zr-, Fe-, Ti-, Mg-, Co-, and Au-based systems. The lack of atomic order yields some remarkable mechanical, chemical, and physical properties when compared with their conventional counterparts. The glass-forming ability (GFA) of any alloy refers to the ease with which it can be produced in amorphous form by cooling from the liquid. A high GFA indicates a relatively low required cooling rate and a resultant high maximum or critical diameter (d_c) when cast into a copper mould.

Their inherent lack of dislocations and hence slip planes leads to exceptionally high strength and elasticity, approaching the theoretical limit. While oxide glasses and ceramics exhibit low toughness and brittle failure, BMGs can display toughness comparable to crystalline metals.[2] The lack of grain structure means that BMGs are homogeneous and exhibit isotropic behavior, even at sub-micrometer length scales, and, without grain boundaries or precipitates as oxidation sites, corrosion rates are significantly reduced compared to conventional metals.

BMGs soften above an alloy-specific glass-transition temperature (T_g) before eventual, time-dependent, crystallization at a higher, crystallization temperature (T_x). In this supercooled liquid region (SCLR) between T_g and T_x, the viscous BMGs may be plastically shaped under low applied forces using polymer-processing techniques, such as hot embossing, extrusion, foaming, and injection and blow moulding, before again cooling to a solid metallic glass. With relatively low processing temperatures and no solidification shrinkage, parts can be formed to net-shape with excellent accuracy, and geometries, and surface patterns previously difficult in metals can be achieved with ease.[3–7]

Such remarkable properties and behavior have led to significant interest in BMGs as engineering materials over the past 20 years, but it is only recently that their potential for use as a biomaterial has been studied.[8]

To date, our understanding of material biocompatiblity has evolved mainly through empirical testing, observing the interaction of materials with cells and host tissue in vitro and in vivo. Materials can induce host responses varying from local and systemic inflammation, hypersensistivity, toxicity, and even tumorogenesis, meaning that thorough evidence of material safety is required before regulatory approval and clinical translation. We now largely recognise the material characteristics that generate both favorable and undesired host responses, as outlined by Williams,[9] offering the opportunity for informed material design, while being cognisant that biocompatibility is specific to the application and host environment.[10]

The original requirement of first generation "biocompatible" materials was bio-inertness.[11] This included a resistance to corrosion in the body, and here Ti- and Co-based alloys scored highly.[12] Less-inert metals, such as Mg, were therefore not deemed suitable, although the ions released on dissolution are generally not harmful to the human body. However, current design requirements for biomaterials, including most recently biometals, include eliciting an appropriate host response,[13] and this can include the need to biodegrade and resorb. There are potential advantages for BMGs that span applications of

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DOI: 10.1002/adma.201505347

first-generation bioinert biometals through to third-generation materials that seek a controlled degradation profile and interaction with the host.[14] We therefore divide this article on recent progress into applications of BMGs as: i) bioinert devices, including permanent implantable devices and surgical tools, and ii) bioresorbable implants. It can be seen that the alloy families are quite distinct in both cases.

2. Bioinert Systems

BMG alloys, which have potential for use as non-absorbable medical devices, are usually based on Zr, Ti, or Fe. Toxic or potentially harmful elements such as Be, Cu, and Al are generally to be avoided, if possible.

Certain BMG alloys have superior properties to current biometals for applications as surgical tools or load-bearing implants, such as high strength, low elastic modulus, and a high elastic strain limit. The modulus provides a better match to cortical bone, thus reducing stress shielding, which is useful for hard-tissue prostheses.[12] They also have very high hardness and wear resistance. Toughness for some compositions approaches values of crystalline metals, and is significantly better than oxide glass/ceramics. Composites (crystals in an amorphous matrix) rival crystalline counterparts for toughness while retaining benefits of glassy structure, although few corrosion studies have been completed. **Figure 1** shows the relative strength and elastic stiffness of a range of BMGs from the literature,[12] in comparison to Co–Cr, stainless steel, and Ti alloys. BMGs are typically more corrosion resistant than the crystalline equivalents due to their chemical homogeneity and lack of grain structure. The attributes of BMGs, which are particularly suited to medical devices – both inert and resorbable – are summarized in **Table 1**.

Table 1. Outlining the benefits, applications, and challenges associated with the use of BMGs in medical-device applications.

BMG attributes for medical devices	
High strength	
Formability in SCLR	
Relatively low E	
High elastic strain limit	
A. Bioinert devices	**B. Bioresorbable devices**
Corrosion resistant	Optimal rate of corrosion and H_2 evolution
Wear resistant	Strength decay inversely proportional to wound healing such as osteogenesis
Controllable surface topography	Non-toxic ion release
	Revision/removal surgery not needed
Potential Applications	
Orthopaedic prostheses	Bone screw or surgical plate
Surgical scalpels	Intramedullary nails
Flexible vascular stents	Temporary vascular stents
Research Challenges	
Unknown fatigue, stress corrosion, and wear debris behaviour	
Matching GFA with clinical needs and biocompatibility	

Specific BMG alloys have been under development/study for medical applications. Due to the fact that nickel is toxic and a possible carcinogen, the association of aluminium with Alzheimer's disease, and the biological toxicity of Be, Ni-free BMGs, and compositions that are Al- and Be-free are desirable. However, Be and Al both provide excellent glass-forming ability (GFA) and were instrumental in development of BMGs, so not many early BMG compositions exist without one of these elements.

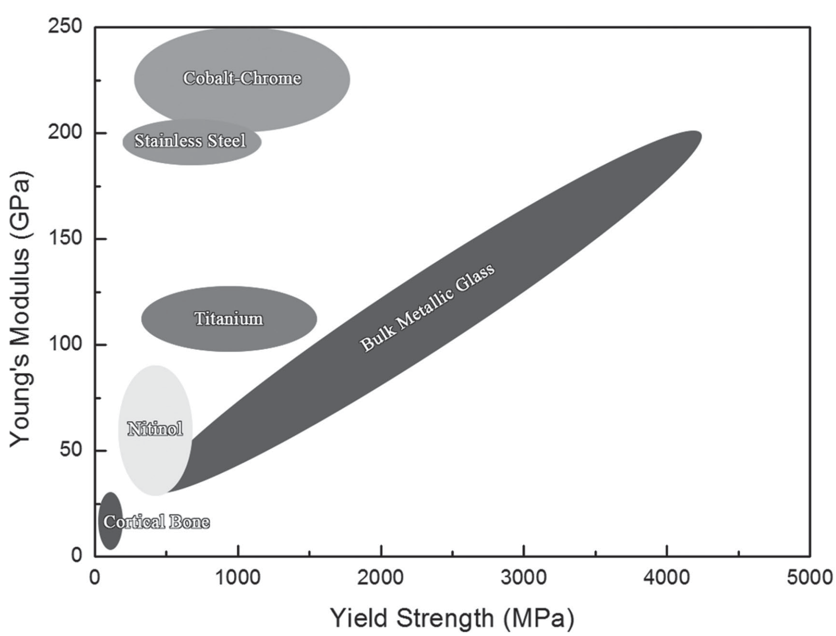

Figure 1. Range of mechanical properties of metallic biomaterials. Data for the information in the figure are taken from refs. [12], [13], and [15].

2.1. Fe Systems

Wang et al. recently investigated the corrosion resistance and biocompatibility of three compositions of Fe-based BMGs,[16] by electrochemical measurements and indirect contact cytotoxicity assays, respectively. In comparison with 316 L SS biomedical stainless steel, Fe-based BMGs showed better corrosion resistance in two simulated body fluids (Hank's solution and artificial saliva). They found that a passive film on an Fe-based BMG surface is quite stable, as with 316 L SS; whereas Zr-based BMGs typically show a weak repassivation ability in chloride environments.[12] The corrosion current densities obtained from the anodic polarization curves were lower for the BMGs than for the stainless steel. The analysis indicated that two of the Fe-based BMGs have a larger polarization resistance value than that of 316 L SS in artificial saliva. The pitting corrosion potentials of Fe-based BMGs were much higher than

Adv. Mater. 2016, DOI: 10.1002/adma.201505347

that of the 316 L SS, resulting in very few ions being released into the electrolytes, while a significant level of Ni- and Fe-ion release was found for 316 L SS under the same conditions. The indirect cytotoxicity results suggest that all three Fe-based BMG extracts have no cytotoxicity to L929 and NIH3T3 cells. Fe-based BMGs therefore show promise for biomedical applications, especially in dental implantology, due to high toughness and wear resistance, and where their limited GFA and higher elastic moduli would pose less of a problem.

2.2. Ti Systems

Recent work has focussed on development of BMG alloys with suitable properties, whilst avoiding toxic components. Attempts by Zhu et al. showed good GFA with d_{crit} up to 7 mm, and no Ni, Be, or Al, but did include significant amounts of Pd.[17] The corrosion behavior of the alloys in both lactic acid and PBS was excellent, offering significant resistance to pitting over both pure Ti and crystalline Ti-6Al-4V. The strength was reported to be 1970 MPa, with significant ductility in ribbon samples, although bulk ductility is not mentioned.[18] Cu-free alloys were produced by Oak and Inoue in the Ti–Pd–Zr–Si system – with good corrosion resistance, high hardness and strength, and good ductility, although the samples were in ribbon form only due to poor GFA.[19] More recently, alloys designed based on individual elemental toxicity, were produced in fully glassy form by Calin et al.,[20] in the TiNbZrSi system, although again only in ribbon form – bulk samples were not possible due to the low GFA – but the corrosion behavior was again superior to Ti-6Al-4V. Xie et al. reported that spark sintering of gas-atomized Ti-MG powders can produce high-density, large-volume parts[21] with good corrosion resistance (although no comparisons were made to as-cast BMGs or commercial alloys). Lin et al. very recently reported interesting results for a TiZrTaSi alloy, which contains no toxic elements, showing improved mechanical properties over the previously mentioned alloys, corrosion resistance much higher than that of Ti-6Al-4V and 316L SS, some ductility, and a very wide supercooled-liquid region, which suggests that the alloy could be formed in bulk.[22] Pang et al. continued in this vein to develop a TiCuZrFeSnSiAg system with a critical casting diameter up to 7 mm. The material exhibited strength of 2 GPa, significant compressive bulk plasticity, similar corrosion resistance to that of Ti-6Al-4V in PBS, and similar cell viabilities with MC3T3-E1 pre-osteoblast cells.[23]

2.3. Zr Systems

Liu et al.[24] and Sun et al.[25] performed in vitro corrosion and cytotoxicity testing on ZrCuAlAg alloy systems, all of which exhibit extremely good GFA (up to 20 mm d_{crit}). The Ag-bearing BMGs performed significantly better than Ti6Al4V in Hanks solution[25] and phosphate-buffered saline (PBS)[24] due to Al_2O_3 passivation (which appears to be increased by Ag content), and showed marginally improved cell viabilities with L929[25] cells, and marginally worse with MG63[24] cells over Ti6V4Al, falling into the same cytotoxicity Grade 0–1 (along with all current biomedical alloys). Ag-bearing BMGs also show antibiotic effects,[26] and could lead to a reduction in surgical revisions due to infection. In vivo implanted BMGs showed excellent host compatibility, with no gas formation nor immune response, and show similar osseointegration as Ti6Al4V.[25]

The Ag-bearing Zr alloys exhibited[24] fatigue strength in excess of 400 MPa (10^7 cycles) and high fracture toughness, as well as some compressive plasticity up to 0.2%. With a strength of ca. 1800 MPa and hardness around 430 GPa, the BMGs compare favorably with current biomedical alloys.[24] In the same research group, Wang et al. carried out fatigue testing on a similar alloy composition in SBF, whereby the fatigue limit decreased only by about 10%, to 366 MPa.[27]

Lin et al.[28] tested 7 Zr- & Ti- based metallic glasses in Hanks solution and human serum. Excessive copper, above 17.5 at%, rapidly increased the electrochemical activity and sample corrosion. While bulk samples showed no cytotoxicity, the ionic corrosion products of the high-Cu alloys showed acute toxicity to D1 bone-marrow stem cells.[28]

Hua et al. compared a low-Cu $Zr_{65}Ti_{12.5}Fe_{7.5}Cu_{10}Ag_5$ BMG with Ti-6Al-4V biomedical alloy for biocompatibility using MC3TC-E1 mouse pre-osteoblast cells, with excellent cell attachment,[29] and improved corrosion performance in PBS over the alloys reported in ref.[24] They further optimized the BMG composition to increase the toughness and bulk compressive plasticity up to 12%, while maintaining impressive strength. The paper does not mention d_{crit}, but a high value is expected due to the large SCLR of 62 K.[29] When immersed in an osteogenetic medium, bone matrix deposition by attached osteoblasts occurred at a significantly higher rate on an Al-bearing Zr BMG over Ti6Al4V.[5] Other researchers achieved a strongly bonded, bioactive calcium titanate coating on the surface of a Zr BMG by laser cladding, suggesting this would lead to greatly enhance tissue adhesion and growth on the material.[30]

3. Specific Bioinert Device Applications

3.1. Surgical Tools (Scalpels)

Due to the lack of any grain-size limitations on feature size, very sharp edges are possible on BMGs. Sharpness improvement on surgical blades by using BMG and metallic glass coatings has been reported;[31] low values of blade sharpness index (b.s.i.) indicate sharper edges. The b.s.i. on a fabricated ZrCuAlAgSi BMG blade was 0.24, a value of 0.23 was achieved for a martensitic steel blade coated with a thin film of the same alloy, whereas the uncoated steel blade value was 0.34. A surgical blade coated with an Fe-based metallic glass thin film, demonstrated a b.s.i. value of 0.28, while also displaying a significant increase (65%) in blade durability, due to its extreme hardness (1200 Hv).[32] The local roughness of all coated blades was extremely low (<5 nm).

Chu et al. sputter-coated a single-crystal Si wafer blade with Zr- and Cu-based thin-film metallic glasses,[33] thereby achieving a 27% increase in blade sharpness. They also reported significantly increased durability of blades throughout testing with no blade edge defects developing, in comparison with an uncoated blade, and significantly improved surface roughness

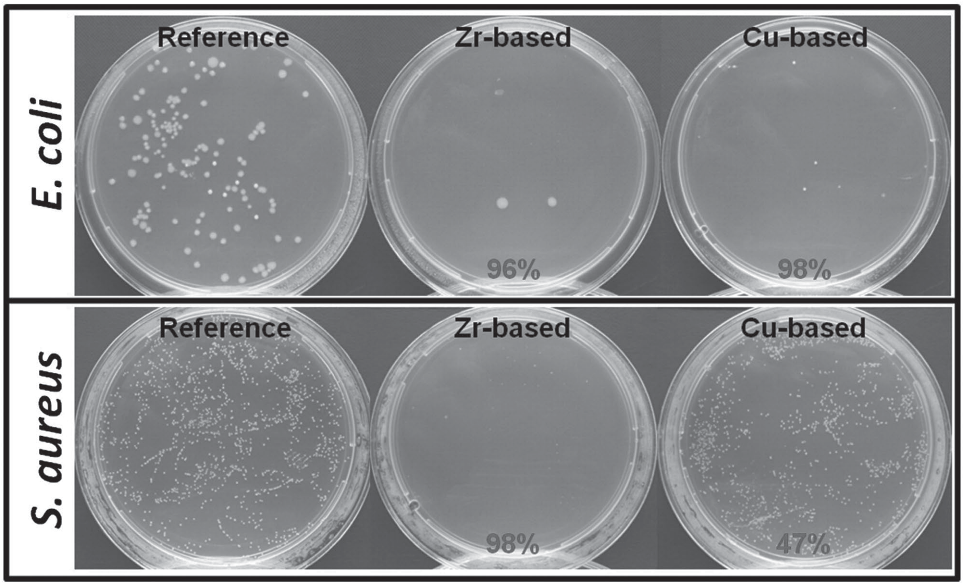

Figure 2. Gram-negative (*E. coli*) and Gram-positive (*S. aureus*) bacterial growth on ZrCuAgAl and Cu-based metallic glass films, in comparison to on a Si reference. The percentages shown represent the antibacterial rates of the materials, equal to $(N_0 - N_i)/N_0$, where N_0 and N_i are the numbers of viable bacteria on a reference bare sample and on a metallic-glass-coated sample after testing, respectively. Reproduced with permission.[33] Copyright 2014, Elseiver.

on coated blades. Good antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus* was achieved, as shown in **Figure 2**. Improved antimicrobial activity, against these and other common pathogens, on stainless steel sputter-coated with a thin film of Zr-based metallic glass, when compared with uncoated stainless steel, has also been reported.[34]

3.2. Stents

BMGs are also being evaluated as potential cardiovascular stent materials, and finite element modelling has been used to predict the relevant mechanical behavior of a ZrAlFeCu BMG in vivo.[35] The alloy, developed to avoid Ni and Be, has shown improved hardness and strength[35] over 316L SS (roughly twice, in both cases), which allows for stent struts to be markedly thinner – shown to significantly reduce restenosis[36] and improve the deliverability of the device. The FE results (see **Figure 3**) showed that the high elastic limit and low modulus allow a stent to flex more (facilitated by the thinner members) and deform during heart beats. Comparisons of the mechanical properties between stented and unstented arteries showed a better match over a 316L stent – compliance mismatch has been shown to be correlated with intimal hyperplasia, which also leads to restenosis.[37] Corrosion resistance in PBS was significantly improved over 316L SS in vitro, due to the formation of a ZrO_2-rich oxide film,[35] thus overcoming the relatively poor results that were summarized in an earlier report[12] for different compositions. Improved cell adhesion over that on 316L SS was observed, together with slower growth of smooth muscle cells, again reducing the potential incidence of restenosis. However, a corrosion fatigue study was not carried out.

3.3. Other Applications

Researchers showed[38] that ZrAlCuNi BMG offers similar performance to Ti6Al4V, when used as stabilizing intramedullary nails in bone fixation in vivo in rat femurs, although with reduced bone-nail bonding, leading to easier removal when healing is completed.

The Ni-free Zr BMG used by Liu et al.[24] exhibited a 20-fold decrease in wear rate of ultrahigh-molecular-weight polyethylene (UHMWPE) acetabular cup material when compared against the performance of a CoCrMo biomedical alloy in both Hank's solution and calf bovine serum, due to its highly hydrophilic surfaces increasing fluid lubrication. The wear results are reportedly superior to any current conventional metal-on-polymer joints.[39] Wear on the alloy itself shows significant improvement over Ti6Al4V in dry conditions, and in both PBS[40] and foetal bovine serum.[41]

Foam of BMGs match the moduli and yield strength/elasticity of human bones very well. These BMG foams (BMGFs) are promising for bioimplant application without a significant stress-shielding effect, and the porosity allows for bone ingrowth and vascularization.

Schroers et al.[42] first reported BMG foams in a Pd system, created via high-pressure alloying with B_2O_3 and then heating the BMG into the SCLR in a low-pressure environment. The created foam showed 88% porosity, and exhibited excellent matching with the properties of cancellous bone, in terms of stiffness and compressive strength. Due to the size-dependent nature of the mechanical properties in BMGs,[43] the foam's thin struts demonstrate excellent plasticity.[42] Li et al. also demonstrated BMG foams fabricated via hot-pressing of BMG powders with NaCl, and subsequent dissolution of the NaCl to reveal an open porous foam. A Young's modulus as low

DOI: 10.1002/adma.201505347

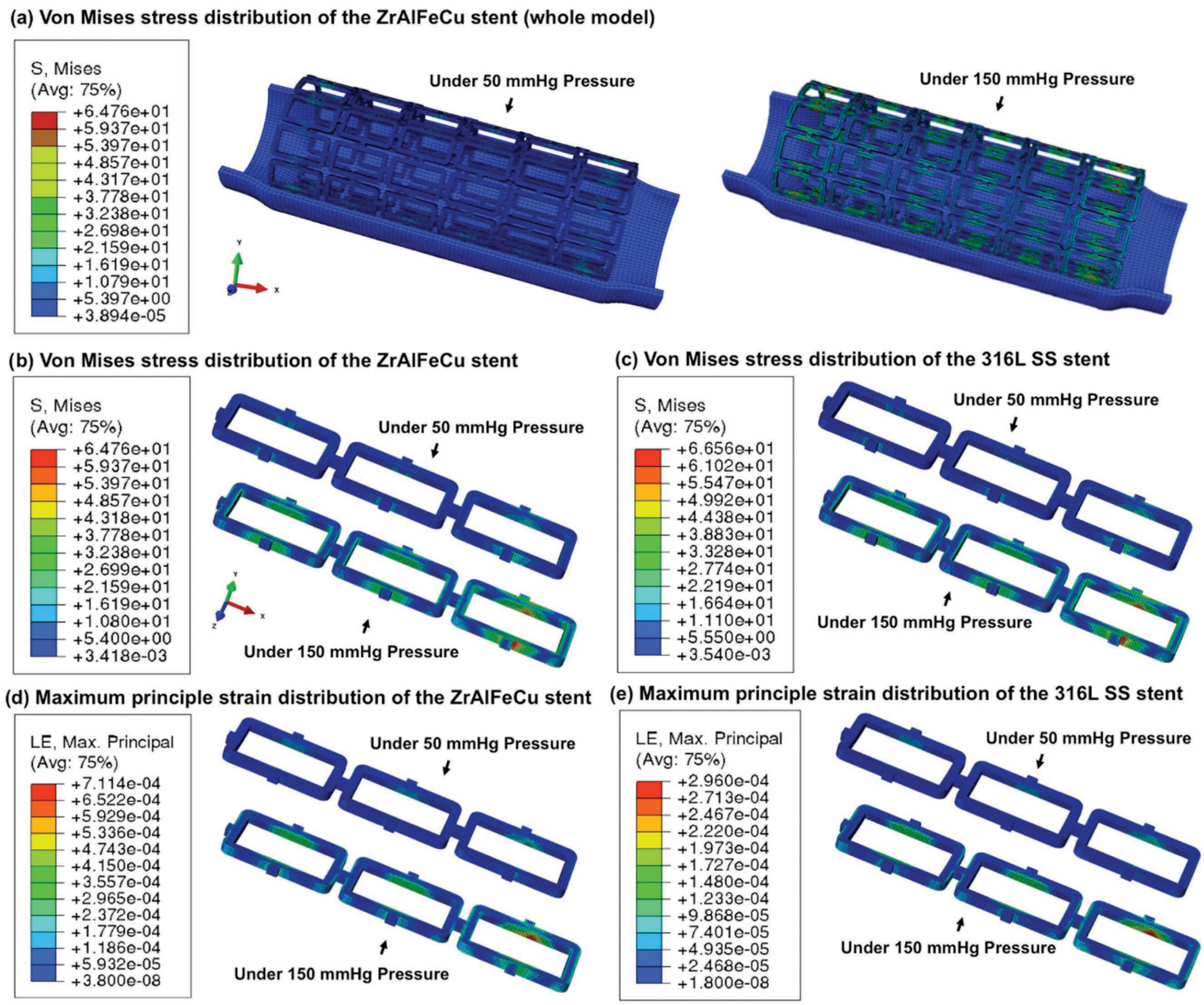

Figure 3. FE stress analysis of a Zr-based BMG (a,b,d) and stainless-steel (c,e) stent under pressure. Note significantly increased strain values in BMG members, when compared with stainless-steel members at the same applied stresses (d) vs (e). Reproduced with permission.[35] Copyright 2015, Elsevier.

as 10 GPa was reported for a non-biomedical Zr-based BMG system (ZrCuNiAl).[44]

4. Bioresorbable Systems

4.1. Magnesium as a Biomaterial

There are clinical advantages for certain metallic medical implants to dissolve in a controlled fashion in vivo following surgery, provided the corrosion products are not harmful, thus obviating the need for further surgery to extract the implant after it has served its function, reducing both the burden on the health system, and the associated risks toward the patient.[15]

Ever since the first reported use as wire ligature in 1878,[45] magnesium has been suggested for biomedical applications. Found in natural abundance in vivo, it plays an important biological role in many metabolic functions, and, as a result, is extremely biocompatible, with the average 70 kg adult carrying approximately 25 g, primarily in bone tissue.[46]

One of its conventional engineering weaknesses, namely its poor corrosion resistance in electrolytic environments, suddenly becomes a potentially attractive strength – as it degrades in vivo to a harmless oxide that is efficiently excreted by the body.[46] Interestingly, the corrosion products of magnesium metal exhibit a remarkable antibiotic effect against a number of common aerobic bacterial organisms. Measured in vitro, Mg^{2+} ions offer an equivalent antibacterial effect to fluoroquinolone by increasing local pH values, and, if effective in vivo, could greatly reduce the need for revision surgeries due to infection.[47]

As an absorbable stent, magnesium would greatly reduce the risk of restenosis, chronic vessel inflammation, and patient injuries associated with permanent stents, with improved mechanical behavior and cost over current absorbable polymer materials.[48,49] As a potential bone-fixturing material,

Table 2. Selected mechanical properties of potential biomedical materials.[15,54–56]

Properties	Cortical bone	MgZnCa BMGs	Crystalline Mg alloys	Ti-6Al-4V	Stainless steel	Synthetic hydroxyapatite
Density [g cm^{-3}]	1.8–2.1	2.0–2.8	1.74–2.2	4.4–4.5	7.9–8.1	3.1
Elastic modulus [GPa]	3–30	22–50	41–45	110–117	189–205	73–117
Compressive yield strength [MPa]	130–180	400–1190	100–560	758–1117	170–310	600
Fracture toughness [MPa$^{1/2}$]	3–6	NA	NA	55–115	50–200	0.7

magnesium alloys exhibit exceptionally low densities of 1.7–2 g cm^{-3}; significantly lower elastic moduli than current titanium and cobalt–chrome biomedical metals, and strength and toughness exceeding polymer and ceramic biomaterials respectively, as outlined in **Table 2**. Furthermore, implanted magnesium has been shown to provide a stimulatory effect on the rate of bone regrowth in the surrounding tissue.[50,51] Indeed, a drug-eluting, absorbable magnesium stent, and absorbable bone screws are now commercially available, and have both been the recent subjects of positive clinical human trials.[52,53]

4.2. Glassy Magnesium Alloys

Despite the recent resurgence in interest and limited commercial success, conventional crystalline magnesium alloys still exhibit significant issues. Strength and fatigue values have been reported to decrease by an order of magnitude under an applied strain in vitro.[54] Despite continuing research, too-rapid corrosion can lead to implant failure before healing can complete, and the same corrosion often leads to catastrophic H_2 evolution in patient areas with poor transport mechanisms.[50,54] Magnesium-based BMGs exhibit remarkably improved mechanical properties when compared with crystalline equivalents, as per Table 2. Indeed, a number of Mg-based BMG families exhibit high strengths, often exceeding 1000 MPa, greater than stainless-steel biomedical alloys,[57] and, in some cases, even titanium and cobalt–chrome alloys.[58]

Without initiation sites for intergranular attack, glassy Mg alloys have significantly enhanced corrosion resistance over their crystalline forms.[59] Corrosion resistance of magnesium is also heavily influenced by alloying elements in solid solution,[60] but the solubility of most alloying elements is relatively low. With no solid solubility limits, metallic glasses offer the potential to greatly improve corrosion rates.

While studies into magnesium BMGs for engineering applications have gathered momentum over the past 30 years due to their light weight and excellent mechanical properties, the majority of Mg-based compositions studied contain significant copper, nickel, and/or gadolinium, and hence are unsuitable for use in absorbable applications. It is only since 2008 that research has focused specifically on the Mg–Zn–Ca family, as a biologically compatible system with potential for medical devices.[61]

Glassy, Mg-rich alloys with a Zn content above 29 at%, show a marked increase in corrosion resistance over any current crystalline Mg alloys.[62] The composition develops a dense, amorphous $ZnO/ZnCO_3$ layer on the surface, preventing the rapid dissolution of the bulk magnesium. H_2 gas evolution is effectively suppressed in vivo, without any effect on the biocompatibility, and the ionic degradation products remain well within the recommended daily allowances for humans.[63] Such behavior in not possible with crystalline Mg, as the Zn content would form secondary intermetallic phases rather than a homogeneous structure, and the internal galvanic couple would accelerate corrosion.[64]

$Mg_{66}Zn_{30}Ca_4$, for example, corrodes in vivo at less than half the rate of WE43, a particularly corrosion resistant crystalline alloy, and at less than 20% the rate of other common magnesium alloys, outlined in **Figure 4**. Exhibiting a strength of roughly 800 MPa in both tension and compression, a high elastic strain up to 2%, and high facture toughness, the alloy shows significantly improved mechanical properties over conventional Mg alloys. An elastic modulus of 45 GPa also reveals a stiffness close to that of cortical bone.[55,56,65–68] Microalloying with 2 at% silver or strontium in place of calcium further enhances the corrosion properties and strength of the alloy, as well as improving the antibacterial effect (Ag) and osteogenesis (Sr).[69,70] Cytotoxicity testing revealed that alloy samples were able to support significant cellular activity to a high degree against a control, with increased cell viabilities up to 90%, (compared to 60% for crystalline Mg alloys), while a stimulatory effect on the rate of bone growth is also reported.[66,67,71,72]

Despite such promising characteristics, the alloys must overcome some critical stumbling blocks to be seriously considered for clinical purposes. Critical casting diameters of the initial MgZnCa alloys were capped at 3 mm, potentially restricting use to small pins and screws. As-cast ingots of higher diameters are only partially amorphous.[74] More recently, small alloying additions of Sr have been shown to enable an amorphous structure up to 6 mm.[69] Further exploration of the composition space revealed Ca-rich alloys with significantly increased casting diameters, and improved thermoplastic processing properties, excellent cell proliferation, and increased bone hyperplasia.[72,75,76] While the Young's modulus of the ternary systems is almost identical to that of dense cortical bone (20–35 GPa), the strengths are not as impressive as the Mg-rich systems, exhibiting failure in compression at around 400 MPa. Despite very limited H_2 evolution, the corrosion of the ternary alloys is very rapid, with some of the Ca-rich alloy pins dissolving completely within just 3 h.[75] Recently however, it has been demonstrated that additional alloying elements such a Yb and Sr can significantly reduce the corrosion rate of the Ca-rich systems (Figure 4), bringing it significantly below crystalline Mg-alloys, and suggesting a viable alternative to the smaller-diameter Mg-rich systems.[73,77]

Moreover, while ductility and reasonable flaw tolerance are reported in sub-millimeter Mg-BMG samples,[56] bulk samples

Adv. Mater. 2016, DOI: 10.1002/adma.201505347

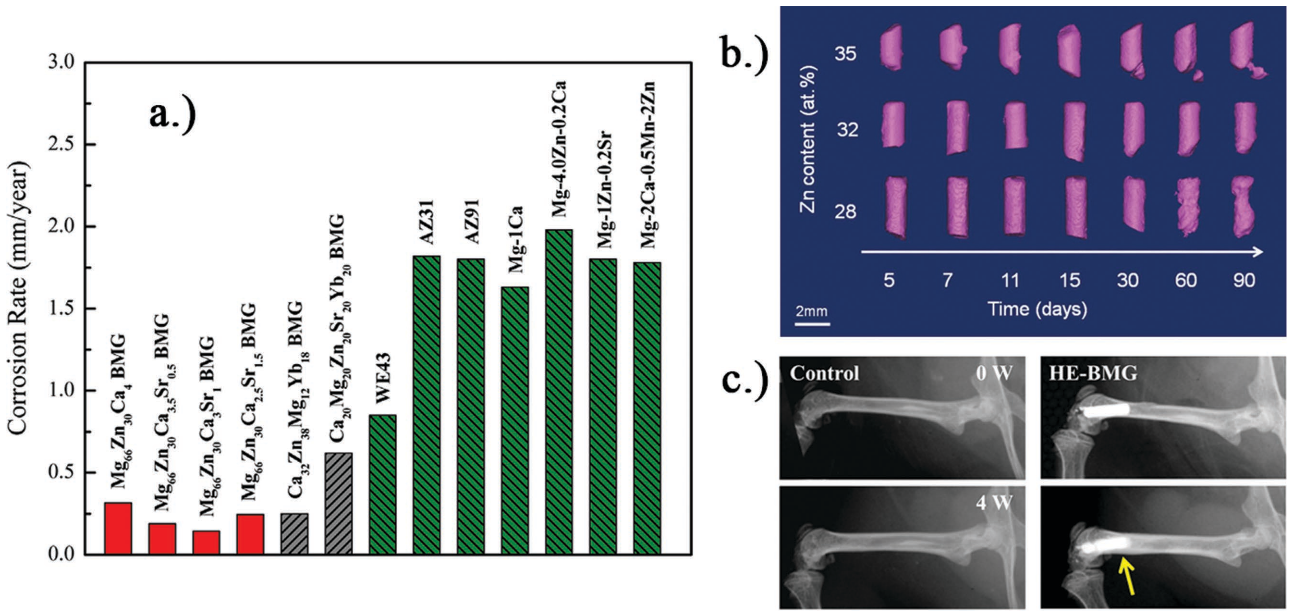

Figure 4. a) corrosion rates of Mg-based alloys in physiologically relevant solutions. Reproduced with permission.[69] Copyright 2015, Elsevier. b) Images of $Mg_{95-x}Zn_xCa_5$ (at%) implanted in rat femurs, reconstructed from in vivo μ-CT scans. Note visible degradation after 30 days for the $x = 28$ sample, while minimal and no degradation are visible on the $x = 32$ and $x = 35$ samples, respectively. Reproduced with permission.[62] c) Radiographs of mice distal femora with and without implanted high-entropy CaMgZnSrYb alloy, immediately after implantation, and 4 weeks postoperatively. The sample shows no gas formation, no inflammation, and enhanced circumferential osteogenesis in the implanted bone (yellow arrow), indicating new bone formation. Reproduced with permission.[73] Copyright 2013, Elsevier.

of the ternary alloy still exhibit the lack of plasticity characteristic of many metallic glasses. Initial surface corrosion offers plentiful crack initiation sites, which can propagate rapidly through the bulk of the material, causing brittle failure.[78] Interestingly, due to rapid bone ingrowth into the samples, the cracking does not appear to cause catastrophic failure of the implants in vivo, and a recent comparative study reports that despite the failures, the implanted glassy alloys performed better than both PHB polymer and crystalline MGWZ21 implants.[79]

In an attempt to address the typically brittle nature of Mg BMGs, Yb addition at 2 at% was found to introduce significant bending ductility, while excellent corrosion and biocompatibility properties were retained.[68] In a different approach, alloying with Y at 10 at% is shown to produce a composite material, with crystallites of roughly 10 µm embedded in a glassy matrix. The material exhibits 19% plasticity and ductile failure, while retaining the strength and elasticity of a BMG, and corrosion rates only marginally higher than a fully glassy component.[80] However, there remains a dearth of research on the mechanical behavior of all the Mg BMG systems in a corrosive biological environment, and further work to understand their performance in both in vitro and in vivo is required before serious clinical consideration will take place.

5. Conclusions

Progress in development of medical devices is often materials-limited, and new bulk metallic glasses are enabling new types of implant and surgical tools. Bioinert alloys, based on Ti, Zr, or Fe, are being developed for potential use as cardiovascular stents, permanent orthopaedic prostheses, and surgical devices such as scalpels. Research on bioabsorbable BMGs based on Mg is also yielding promising results, with the ultimate goal being implants that do not need a follow-up surgical intervention for their removal. In all cases the applications will rely on the unique properties of amorphous metals, but significant scientific and engineering challenges need to be overcome before the successful clinical applications of most of the relevant medical devices.

Received: October 30, 2015
Revised: December 18, 2015
Published online:

[1] R. Kaiser, K. Williamson, C. O'Brien, S. Ramirez-Garcia, D. J. Browne, *Mater. Sci. Technol.* **2014**, *31*, 1298.
[2] D. C. Hofmann, J.-Y. Suh, A. Wiest, G. Duan, M.-L. Lind, M. D. Demetriou, W. L. Johnson, *Nature* **2008**, *451*, 1085.
[3] J. Schroers, *Adv. Mater.* **2010**, *22*, 1566.
[4] N. Zhang, J. S. Chu, C. J. Byrne, D. J. Browne, M. D. Gilchrist, *J. Micromech. Microeng.* **2012**, *22*, 065019.
[5] W. He, A. Chuang, Z. Cao, P. K. Liaw, *Metall. Mater. Trans. A* **2010**, *41*, 1726.
[6] J. Padmanabhan, E. R. Kinser, M. A. Stalter, C. Duncan-Lewis, J. L. Balestrini, A. J. Sawyer, J. Schroers, T. R. Kyriakides, *ACS Nano* **2014**, *8*, 4366.
[7] N. Zhang, A. Srivastava, B. Kirwan, R. Byrne, F. Fang, D. J. Browne, M. D. Gilchrist, *J. Micromech. Microeng.* **2015**, *25*, 095005.
[8] J. Schroers, G. Kumar, T. M. Hodges, S. Chan, T. R. Kyriakides, *JOM* **2009**, *61*, 21.

[9] D. F. Williams, *Biomaterials* **2008**, *29*, 2941.
[10] D. F. Williams, *Biomaterials* **2014**, *35*, 10009.
[11] L. L. Hench, *Science* **1980**, *23*, 826.
[12] M. D. Demetriou, A. Wiest, D. C. Hofmann, W. L. Johnson, B. Han, N. Wolfson, G. Wang, P. K. Liaw, *JOM* **2010**, *62*, 83.
[13] N. B. Morgan, *Mater. Sci. Eng. A* **2004**, *378*, 16.
[14] L. L. Hench, J. M. Polak, *Science* **2002**, *295*, 1014.
[15] H. Waizy, J.-M. Seitz, J. Reifenrath, A. Weizbauer, F.-W. Bach, A. Meyer-Lindenberg, B. Denkena, H. Windhagen, *J. Mater. Sci.* **2012**, *48*, 39.
[16] Y. B. Wang, H. F. Li, Y. F. Zheng, M. Li, *Mater. Sci. Eng. C* **2012**, *32*, 599.
[17] S. L. Zhu, X. M. Wang, F. X. Qin, A. Inoue, *Mater. Sci. Eng. A* **2007**, *459*, 233.
[18] J.-J. Oak, D. V. Louzguine-Luzgin, A. Inoue, *J. Mater. Res.* **2007**, *22*, 1346.
[19] J.-J. Oak, A. Inoue, *J. Non-Cryst. Solids* **2008**, *354*, 1828.
[20] M. Calin, A. Gebert, A. C. Ghinea, P. F. Gostin, S. Abdi, C. Mickel, J. Eckert, *Mater. Sci. Eng. C* **2013**, *33*, 875.
[21] G. Xie, F. Qin, S. Zhu, A. Inoue, *Intermetallics* **2012**, *29*, 99.
[22] H. C. Lin, P. H. Tsai, J. H. Ke, J. B. Li, J. S. C. Jang, C. H. Huang, J. C. Haung, *Intermetallics* **2014**, *55*, 22.
[23] S. Pang, Y. Liu, H. Li, L. Sun, Y. Li, T. Zhang, *J. Alloys Compd.* **2015**, *625*, 323.
[24] Y. Liu, Y.-M. Wang, H.-F. Pang, Q. Zhao, L. Liu, *Acta Biomater.* **2013**, *9*, 7043.
[25] Y. Sun, Y. Huang, H. Fan, Y. Wang, Z. Ning, F. Liu, D. Feng, X. Jin, J. Shen, J. Sun, J. J. J. Chen, *J. Non-Cryst. Solids* **2015**, *419*, 82.
[26] H.-W. Chen, K.-C. Hsu, Y.-C. Chan, J.-G. Duh, J.-W. Lee, J. S.-C. Jang, G.-J. Chen, *Thin Solid Films* **2014**, *561*, 98.
[27] Y. Wang, Y. Liu, L. Liu, *J. Mater. Sci. Technol.* **2014**, *30*, 622.
[28] C. H. Lin, C. H. Huang, J. F. Chuang, J. C. Huang, J. S. C. Jang, C. H. Chen, *Mater. Sci. Eng. C* **2013**, *33*, 4520.
[29] N. Hua, L. Huang, W. Chen, W. He, T. Zhang, *Mater. Sci. Eng. C* **2014**, *44*, 400.
[30] Z. Liu, K. C. Chan, L. Liu, S. F. Guo, *Mater. Lett.* **2012**, *82*, 67.
[31] P. H. Tsai, Y. Z. Lin, J. B. Li, S. R. Jian, J. S. C. Jang, C. Li, J. P. Chu, J. C. Huang, *Intermetallics* **2012**, *31*, 127.
[32] J. S.-C. Jang, P.-H. Tsai, A.-Z. Shiao, T.-H. Li, C.-Y. Chen, J. P. Chu, J.-G. Duh, M.-J. Chen, S.-H. Chang, W.-C. Huang, *Intermetallics* **2015**, *65*, 56.
[33] J. P. Chu, T.-Y. Liu, C.-L. Li, C.-H. Wang, J. S. C. Jang, M.-J. Chen, S.-H. Chang, W.-C. Huang, *Thin Solid Films* **2014**, *561*, 102.
[34] P.-T. Chiang, G.-J. Chen, S.-R. Jian, Y.-H. Shih, J. S.-C. Jang, C.-H. Lai, *Fooyin J. Health Sci.* **2010**, *2*, 12.
[35] L. Huang, C. Pu, R. K. Fisher, D. J. H. Mountain, Y. Gao, P. K. Liaw, W. Zhang, W. He, *Acta Biomater.* **2015**, *25*, 356.
[36] B. O'Brien, W. Carroll, *Acta Biomater.* **2009**, *5*, 945.
[37] J. L. Berry, E. Manoach, C. Mekkaoui, P. H. Rolland, J. E. Moore Jr., A. Rachev, *J. Vasc. Interv. Radiol.* **2002**, *13*, 97.
[38] K. Imai, S. Hiromoto, *J. Mater. Sci., Mater. Med.* **2013**, *25*, 759.
[39] Q. Chen, K. c. Chan, L. Liu, *Philos. Mag.* **2011**, *91*, 3705.
[40] N. Hua, Z. Zheng, H. Fang, X. Ye, C. Lin, G. Li, W. Wang, W. Chen, T. Zhang, *J. Non-Cryst. Solids* **2015**, *426*, 63.
[41] Y. Wang, L. Shi, D. Duan, S. Li, J. Xu, *Mater. Sci. Eng. C* **2014**, *37*, 292.
[42] J. Schroers, C. Veazey, W. L. Johnson, *Appl. Phys. Lett.* **2003**, *82*, 370.
[43] M. F. Ashby, A. L. Greer, *Scr. Mater.* **2006**, *54*, 321.
[44] J. B. Li, H. C. Lin, J. S. C. Jang, C. N. Kuo, J. C. Huang, *Mater. Lett.* **2013**, *105*, 140.
[45] E. C. Huse, *Chic. Med. J. Exam.* **1878**, *172*, 2.
[46] J. Lewis III, *The Merck Manual of Diagnosis and Therapy*, (Eds: M.H. Beer, R. Berkow), Merck & Co., Whitehouse Station, NJ, USA **1999**, p. 984.
[47] D. A. Robinson, R. W. Griffith, D. Shechtman, R. B. Evans, M. G. Conzemius, *Acta Biomater.* **2010**, *6*, 1869.
[48] B. Heublein, R. Rohde, V. Kaese, M. Niemeyer, W. Hartung, A. Haverich, *Heart* **2003**, *89*, 651.
[49] R. Waksman, *Catheterization Cardiovasc. Interventions* **2007**, *70*, 407.
[50] F. Witte, V. Kaese, H. Haferkamp, E. Switzer, A. Meyer-Lindenberg, C. J. Wirth, H. Windhagen, *Biomaterials* **2005**, *26*, 3557.
[51] H. Zreiqat, C. R. Howlett, A. Zannettino, P. Evans, G. Schulze-Tanzil, C. Knabe, M. Shakibaei, *J. Biomed. Mater. Res.* **2002**, *62*, 175.
[52] M. Haude, R. Erbel, P. Erne, S. Verheye, H. Degen, D. Böse, P. Vermeersch, I. Wijnbergen, N. Weissman, F. Prati, R. Waksman, J. Koolen, *Lancet* **2013**, *381*, 836.
[53] H. Windhagen, K. Radtke, A. Weizbauer, J. Diekmann, Y. Noll, U. Kreimeyer, R. Schavan, C. Stukenborg-Colsman, H. Waizy, *Biomed. Eng. OnLine* **2013**, *12*, 1.
[54] M. P. Staiger, A. M. Pietak, J. Huadmai, G. Dias, *Biomaterials* **2006**, *27*, 1728.
[55] Y.-Y. Zhao, E. Ma, J. Xu, *Scr. Mater.* **2008**, *58*, 496.
[56] B. Zberg, E. R. Arata, P. J. Uggowitzer, J. F. Löffler, *Acta Mater.* **2009**, *57*, 3223.
[57] A. Inoue, Z. Bian, *Mater. Sci. Eng. A* **2007**, *449–451*, 114.
[58] Q. Zheng, S. Cheng, J. H. Strader, E. Ma, J. Xu, *Scr. Mater.* **2007**, *56*, 161.
[59] A. Gebert, R. V. Subba Rao, U. Wolff, S. Baunack, J. Eckert, L. Schultz, *Mater. Sci. Eng. A* **2004**, *375–377*, 280.
[60] J. R. Scully, A. Gebert, J. H. Payer, *J. Mater. Res.* **2007**, *22*, 302.
[61] M. S. Dambatta, S. Izman, B. Yahaya, J. Y. Lim, D. Kurniawan, *J. Non-Cryst. Solids* **2015**, *426*, 110.
[62] V. Wessels, G. Le Mené, S. F. Fischerauer, T. Kraus, A.-M. Weinberg, P. J. Uggowitzer, J. F. Löffler, *Adv. Eng. Mater.* **2012**, *14*, B357.
[63] B. Zberg, P. J. Uggowitzer, J. F. Löffler, *Nat. Mater.* **2009**, *8*, 887.
[64] E. Ma, J. Xu, *Nat. Mater.* **2009**, *8*, 855.
[65] J. Byrne, E. D. O'Cearbhaill, D. J. Browne, *Eur. Cell. Mater.* **2015**, *30(Suppl. 3)*, 75.
[66] J. D. Cao, P. Martens, K. J. Laws, P. Boughton, M. Ferry, *J. Biomed. Mater. Res. B: Appl. Biomater.* **2013**, *101B*, 43.
[67] X. Gu, Y. Zheng, S. Zhong, T. Xi, J. Wang, W. Wang, *Biomaterials* **2010**, *31*, 1093.
[68] H.-J. Yu, J.-Q. Wang, X.-T. Shi, D. V. Louzguine-Luzgin, H.-K. Wu, J. H. Perepezko, *Adv. Funct. Mater.* **2013**, *23*, 4793.
[69] H. Li, S. Pang, Y. Liu, L. Sun, P. K. Liaw, T. Zhang, *Mater. Des.* **2015**, *67*, 9.
[70] H. Li, S. Pang, Y. Liu, P. K. Liaw, T. Zhang, *J. Non-Cryst. Solids* **2013**, *427*, 134.
[71] Z. Li, X. Gu, S. Lou, Y. Zheng, *Biomaterials* **2008**, *29*, 1329.
[72] Y. B. Wang, X. H. Xie, H. F. Li, X. L. Wang, M. Z. Zhao, E. W. Zhang, Y. J. Bai, Y. F. Zheng, L. Qin, *Acta Biomater.* **2011**, *7*, 3196.
[73] H. F. Li, X. H. Xie, K. Zhao, Y. B. Wang, Y. F. Zheng, W. H. Wang, L. Qin, *Acta Biomater.* **2013**, *9*, 8561.
[74] M. Ramya, S. G. Sarwat, V. Udhayabanu, S. Subramanian, B. Raj, K. R. Ravi, *Mater. Des.* **2015**, *86*, 829.
[75] J. D. Cao, N. T. Kirkland, K. J. Laws, N. Birbilis, M. Ferry, *Acta Biomater.* **2012**, *8*, 2375.
[76] J. D. Cao, K. J. Laws, C. Liu, M. Ferry, *Int. J. Mater. Prod. Technol.* **2013**, *47*, 233.
[77] W. Jiao, H. F. Li, K. Zhao, H. Y. Bai, Y. B. Wang, Y. F. Zheng, W. H. Wang, *J. Non-Cryst. Solids* **2011**, *357*, 3830.
[78] F. Qin, G. Xie, Z. Dan, S. Zhu, I. Seki, *Intermetallics* **2013**, *42*, 9.
[79] A. Celarek, T. Kraus, E. K. Tschegg, S. F. Fischerauer, S. Stanzl-Tschegg, P. J. Uggowitzer, A. M. Weinberg, *Mater. Sci. Eng. C* **2012**, *32*, 1503.
[80] X. L. Zhang, G. Chen, T. Bauer, *Intermetallics* **2012**, *29*, 56.

Adv. Mater. **2016**,
DOI: 10.1002/adma.201505347