**A Zr-based Bulk Metallic Glass for Future Stent Applications: Materials Properties,
Finite Element Modeling, and *In Vitro* Human Vascular Cell Response**

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Abstract: Despite the prevalent use of crystalline alloys in current vascular stent technology, new biomaterials are being actively sought after to improve stent performance. In this study, we demonstrated the potential of a Zr-Al-Fe-Cu bulk metallic glass (BMG) to serve as a candidate stent material. The mechanical properties of the Zr-based BMG, determined under both static and cyclic loadings, were characterized by high strength, which would allow for the design of thinner stent struts to improve stent biocompatibility. Finite element analysis further complemented the experimental results and revealed that a stent made of the Zr-based BMG was more compliant with the beats of a blood vessel, compared with medical 316L stainless steel. The Zr-based BMG was found to be corrosion resistant in a simulated body environment, owing to the presence of a highly stable ZrO₂-rich surface passive film. Application-specific biocompatibility studies were conducted using human aortic endothelial cells and smooth muscle cells. The Zr-Al-Fe-Cu BMG was found to support stronger adhesion and faster coverage of endothelial cells and slower growth of smooth muscle cells than 316L stainless steel. These results suggest that the Zr-based BMG could promote re-endothelialization and potentially lower the risk of restenosis, which are critical to improve vascular stent implantation integration. In general, findings in this study raised the curtain for the potential application of BMGs as future candidates for stent applications.

Keywords: Bulk metallic glass; Stent; Mechanical properties; Corrosion; Biocompatibility

1. Introduction

Atherosclerosis is caused by plaque build-up in arteries, narrowing or clogging of the blood vessel, and leading to insufficient oxygen and nutrient delivery to the end organs [1]. Adverse events of atherosclerotic disease include heart attack and stroke, both of which can be lethal to patients. Stent technology is employed as a typical treatment for atherosclerosis. Vascular stents are typically used to restore the lumen of a narrowed or clogged blood vessel in order to diminish the pressure difference within the vessel and provide sufficient oxygen and nutrients to the end organs. Surgical interventions with stents have achieved great success to counteract atherosclerosis. Currently, materials used in US Food and Drug Administration (FDA) approved stents are mainly metallic materials including stainless steels, nitinol alloys, Co-alloys, Pt-Ir, etc. [2, 3] Despite the prevalent uses of these alloys in stent-assisted angioplasty, many issues persist during clinical practices. For example, mechanical failures to the stents can occur due to the pulsatile loading from the vessel wall [4]. The aggressive body environment can lead to corrosion and release of toxic metal ions of some constituent elements (i.e., Ni, Mo, etc.), raising questions regarding their long-term biocompatibility [5]. Moreover, the major difficulty that remains for current stent materials is the occurrence of thrombosis and restenosis. These post-surgical complications are caused by aggregation of platelets around the material and the dysfunctional proliferation of smooth muscle cells, both giving rise to re-narrowing of the lumen [6, 7]. The development of drug eluting stents to locally release anti-inflammatory therapeutics (e.g., heparin, paclitaxel, sirolimus, etc.) provides a short-term solution [8]; yet later-stage complications (i.e., late stent thrombosis or restenosis) have been reported [9, 10]. To intrinsically reduce stent failures

1 caused by material incompatibility, there has been continuous research from a material's
2 perspective to identify materials with higher performance and biocompatibility [8]. In
3 general, the desired properties of future stent materials were proposed as: 1) high
4 elasticity to facilitate *in vivo* stent expansion from its collapsed form, 2) high strength and
5 fatigue resistance to withstand the pulsatile pressure from the blood vessel wall, 3)
6 radiopacity or magnetic resonance imaging (MRI) compatibility for *in vivo* imaging, 4)
7 good biocompatibility to diminish thrombosis and restenosis, and 5) drug delivery
8 capacity to further treat the implantation site if necessary [2, 8].

9 The emergence of a novel group of metallic materials, named bulk metallic glasses
10 (BMGs), provides new opportunities for the development of biomedical materials. The
11 amorphous microstructure of BMGs, in contrast to the long-range atomic ordering of
12 conventional crystalline alloys, yields a unique combination of materials properties [11-
13 14]. The excellent mechanical properties, high corrosion resistance, and exceptional
14 thermal formability of BMGs are considered favorable for their potential biomedical
15 applications [15, 16]. There have been a rising number of studies reported to reveal the
16 biocompatibility of BMGs and their perspective as hard-tissue prostheses [15-20].
17 However, limited data are available regarding their potential as soft-tissue implants [16].
18 By comparing the material properties of BMGs with the aforementioned desired
19 properties of stent materials, it is recognized that BMGs satisfy the requirements for stent
20 applications to a great extent. BMGs exhibit high elasticity with elastic strains as high as
21 2% [21], almost twice the value for crystalline alloys. High strength is a characteristic
22 property of BMGs, which can reach up to 5 GPa [22-24]. Another feature of BMGs to
23 highlight for stent applications is their high MRI compatibility. An earlier study has

demonstrated that Zr-based BMGs exhibited a definitive shape as compared to the distorted configuration of a Cu-4Cr-2Nb (weight percent) crystalline alloy under MRI [25]. Moreover, BMGs are easily amenable for surface modification and functionalization [26, 27]. However, to the best of the authors' knowledge, the capability and biocompatibility of BMGs in the context of potential stent materials remain unexplored.

To bridge the gap of knowledge, a newly-developed $\text{Zr}_{62.5}\text{Al}_{10}\text{Fe}_5\text{Cu}_{22.5}$ (atomic percent, at.%) BMG [28] was identified as the model material, owing to the absence of potentially toxic elements (i.e., Ni, Be, etc.) that were used to facilitate BMG formation. Initial cytocompatibility of this Ni-free Zr-based BMG has been previously demonstrated with bone marrow mesenchymal stem cells [28]. In the present work, application-specific properties were characterized to study the Zr-based BMG as a candidate vascular stent material, including mechanical properties, corrosion resistance, and surface characteristics. Biocompatibility of the Zr-based BMG was examined through *in vitro* assays using human aortic endothelial cells (HAECs) and human aortic smooth muscle cells (HASMCs). The 316L stainless steel was employed as the reference material, due to the longest history and dominant market share of stainless steels as stent materials [2].

2. Materials and Methods

2.1 Materials

The $\text{Zr}_{62.5}\text{Al}_{10}\text{Fe}_5\text{Cu}_{22.5}$ BMG rods (abbreviated as ZrAlFeCu BMG) with a diameter of 6 mm were fabricated using arc melting and copper mold casting technique described previously [29]. The amorphous microstructure and thermal stability of the as-cast rods were examined using laboratory X-ray diffraction (XRD) and differential

1 scanning calorimetry (DSC), as shown in Figure S1 (see supporting information). The
2 reference 316L stainless steel (abbreviated as 316L SS) rod was purchased from
3 McMaster-Carr.

4 Test specimens were machined from the alloy rods using a diamond saw. For
5 mechanical testing, samples with an aspect ratio (length:diameter) of 2:1 were obtained
6 with two end surfaces ground to 1,200-grit surface finish. Sample fixture was used during
7 grinding to ensure that the end surfaces were parallel to each other and normal to the long
8 axis. For corrosion testing, samples (10 mm long) were mounted in epoxy resin, with
9 exposed surfaces ground to 600-grit surface finish. Substrates for surface
10 characterizations and cell culture studies were cut into a disc-shape (1.5 mm thick) with
11 600-grit surface finish. The geometry of samples for flow tests was $0.8 \times 3 \times 18 \text{ mm}^3$.
12 Samples were ultrasonically cleaned in acetone, ethanol, and deionized water (DI water)
13 before all types of testing.

14 2.2 *Quasi-Static and Cyclic Mechanical Properties*

15 Mechanical properties of the ZrAlFeCu BMG under quasi-static loadings were
16 tested. Vickers hardness of the alloys was measured under a 200-g load at room
17 temperature with a microhardness indenter (Buehler, USA). Uniaxial compression
18 experiments were conducted at room temperature, using a Materials Test System (MTS)
19 servohydraulic machine at a strain rate of 10^{-4} s^{-1} .

20 High-cycle compression-compression fatigue tests were conducted in air at room
21 temperature. An MTS machine was employed to apply the load to the specimens at a
22 frequency of 10 Hz (sinusoidal waveform) with an R ratio of 0.1 ($R = \sigma_{\min} / \sigma_{\max}$, $\sigma_{\min}$ and
23 $\sigma_{\max}$ are the applied minimum and maximum stresses, respectively).

Fractography after static and cyclic compression tests was observed, using scanning electron microscopy (SEM; Zeiss, USA) at acceleration energy of 20 keV. Secondary electron images were collected.

2.3 Finite Element Analysis of Stent Mechanics

The ABAQUS/Standard Finite Element Analysis (FEA) package was employed to calculate the stress and strain fields of a stent under physiological loadings with systolic and diastolic pressure loads of 50 mmHg and 150 mmHg, respectively, according to American Society for Testing and Materials (ASTM) F2477 [30]. A three-dimensional (3D) FEA model of stent-vessel system was constructed with the geometric parameters shown in Table 1. Considering stent sliding in the vessel was more disastrous, the outer diameter was set to be 0.1 mm larger than vessel inner diameter to ensure anchoring. Due to the symmetric condition in the axial direction and axisymmetry in tangential directions, a "30°" segment of half model was considered in our simulation. A 5-parameter third-order Mooney-Rivlin hyperelastic material was designated to simulate the arterial vessel wall using the constitutive model parameters that were reported in the literature [31]. The strain-energy density functions for hyperelastic model can be expressed as:

$$W = a_{10}(I_3 - 3) + a_{01}(I_2 - 3) + a_{20}(I_1 - 3)^2 + a_{11}(I_1 - 3)(I_2 - 3) + a_{30}(I_1 - 3)^3 \quad (\text{Eq. 1})$$

where W was the strain energy density function, a_{ij} were the constitutive model parameters, and I_1 , I_2 , and I_3 were the strain invariants.

The ZrAlFeCu BMG (elastic modulus, $E = 80$ GPa; Poisson's ratio, $\nu = 0.38$) and 316L SS ($E = 193$ GPa, $\nu = 0.28$) were treated as linear elastic materials. Based on

axisymmetric boundary condition, the tangential degree of freedom was constrained on the axial cross sections of stent and vessel segments to only allow radial expansion/compression. A general contact model with friction coefficient of 0.3 and non-penetrating normal condition was adopted to simulate the interfacial interactions between the two components.

2.4 Corrosion Resistance Characterizations

The corrosion test was performed, using a three-electrode cell consisting of a test specimen as the working electrode, a saturated calomel electrode (SCE, $E_{SCE} = 244$ mV) as the reference electrode, and a platinum foil as the counter electrode. Electrochemical experiments were performed at 37 °C in a phosphate buffered saline (PBS) solution aerated with a 4 volume percent (vol.%) O_2/N_2 gas mixture to mimic physiological conditions. Prior to each polarization scan, the corrosion cell was immersed in the solution for 1 h to allow the open-circuit potential (OCP) to achieve a steady-state value. Potential-controlled cyclic-anodic-polarization experiments were conducted using the EG&G Princeton Applied Research 2263 potentiostat with the start potential of 20 mV below OCP, and a scan rate of 0.167 mV/s towards positive direction. The scans were reversed at pitting when the corrosion current density reached 10^4 mA/m². The potential was then decreased at the same scan rate until a potential of 50 mV below OCP was obtained. The corrosion morphology after polarization was analyzed by SEM. The chemical distributions of the constituent elements within a corroded area were mapped, using the energy-dispersive X-ray spectroscopy (EDX, Oxford, UK).

2.5 *Surface Chemistry and Wettability*

The chemical compositions of the ZrAlFeCu BMG surface before and after 1 h immersion in PBS were studied by an X-ray photoelectron spectrometer (XPS) with an Al K α monochromated X-ray source. Survey spectra and narrow scan spectra for Zr3d, Al2p, Cu2p, Fe2p, O1s, and C1s were recorded. Results were analyzed with XPSPEAK 4.1 data processing software using Shirley background.

Wetting behaviors of both polar DI water and non-polar diiodomethane (DII) on the samples were determined by the sessile-drop contact-angle method using a CAM-Plus contact-angle goniometer (Cheminstruments, USA). The surface free energy (SFE) for the tested samples was calculated following Owens-Wendt's equation, as described in our previous work [19].

2.6 *Cell Cultures*

HAECs were received from Cascade Biologics, USA and HASMCs were received from Lifeline Cell Technology, USA. Cells were maintained in basal culture medium supplemented with vasculife SMC lifefactors kit (0.1% recombinant human (rh) fibroblast growth factor basic (FGF), 1% rh insulin, 0.1% ascorbic acid, 5% L-glutamine, 0.1% rh epidermal growth factor (EGF), and 5% fetal bovine serum) and 1% antibiotics (Lifeline Cell Technology, USA) at 37 °C in 5% CO₂. At confluency, cells were harvested using 0.25% trypsin with ethylene diamine tetraacetic acid (Invitrogen, USA) and seeded to the substrates for cell behavior studies. Before cell seeding, the substrates were sterilized by 30-min ultraviolet light exposure.

1 2.7 *Cell Viability and Proliferation*

2 The viability of HAECs and HASMCs on the surfaces was examined using the
3 LIVE/DEAD[®] Viability/Cytotoxicity Kit (Life Technologies, USA). Cells were seeded to
4 the samples at a density of 1×10^4 cells/cm² and incubated for 24 h. After incubation,
5 cells were dyed in PBS solution containing 2 μ M calcein to label live cells and 4 μ M
6 ethidium homodimer-1 to label dead cells for 20 min at 37 °C. A Zeiss Axio Observer A1
7 inverted fluorescent microscope (Zeiss, Germany) was employed to record the
8 fluorescent images after staining.

9 Adhesion of HAECs and HASMCs onto the surfaces was investigated by
10 immunofluorescent staining. Cells were seeded on the substrates at a density of 5×10^3
11 cells/cm². After incubation, the cells were fixed with 4% paraformaldehyde,
12 permeabilized with 0.1% Triton X-100 (Sigma, USA) and blocked with 1% bovine serum
13 albumin (Sigma, USA) [19]. HAEC adhesion was investigated at 4 and 24 h. Vinculin of
14 HAECs was labeled to visualize cell adhesion with primary anti-vinculin monoclonal
15 antibody (Santa Cruz Biotechnology, USA) followed by secondary Alexa Fluor 488 goat
16 anti-mouse IgG1 (Invitrogen, USA) staining. F-actin was stained with Alexa fluor 594
17 conjugated phalloidin (Invitrogen, USA). Cell nuclei were dyed with 4,6-diamidino-2-
18 phenylindole (DAPI) (Chemicon, CA). HASMC adhesion was examined at 4 h post
19 seeding. F-actin and cell nuclei of HASMCs were stained following above protocol. The
20 fluorophore-labeled samples were subsequently mounted on glass coverslips with
21 antifading fluoromount G solution (Southern Biotech, USA). Fluorescent images were
22 collected using a Zeiss fluorescent microscope (Zeiss, Germany). Adherent cell

number/densities were then calculated based on the images recorded at 4 h using ImageJ (NIH, USA).

The proliferation of HAECs and HASMCs was monitored at days 1, 3, and 5, using a water-soluble tetrazolium salt (WST-1, Roche applied science, USA) assay. Cells were seeded to the substrates at a density of 5×10^3 cells/cm². At each time point, samples were placed in fresh culture medium containing 10% WST-1 reagent. The plate was incubated at 37 °C for 2 h to allow the reaction to proceed, followed by brief mixing on a plate shaker for 1 min at the end of the incubation. Subsequently, the supernatants were transferred to a 96-well plate. The absorbance was read against a blank control at 460 nm on a Synergy 2 Multi-Mode Microplate Reader (BioTek, USA).

The cell morphology after proliferation was observed using SEM. Cell layers were fixed with 3% glutaraldehyde at 4 °C for 24 h and immersed in ascending grades of ethanol (25%, 50%, 75%, and 100%) for 10 min each for dehydration. The drying with 100% ethanol was performed twice to ensure a complete removal of water. Subsequently, chemical dehydration with hexamethyldisilazane (HMDS) was performed by immersing samples in the mixtures of dry ethanol and HMDS at volume ratios of 2:1, 1:1, and 1:2, followed by 100% HMDS. Dried specimens were coated with gold using an SPI sputtering device for 20 s at 20 mA for SEM imaging.

2.8 Endothelial Cell Adhesion under Dynamic Settings

Adhesion of HAECs on the substrates was further examined under a dynamic setting. Substrates were mounted to a coverslip base using bees wax. Cells were seeded at a density of 1×10^5 cells/cm² and incubated statically at 37 °C for 20 h. Flow tests were then performed to the cell layers using the Biopetechs FSC3 system (Biopetechs, USA) as

schematically presented in Figure S2 [32]. Briefly, at the time of flow testing, coverslips carrying substrates with adherent cells were assembled into the flow system, and cells were maintained in the micro-environmental chamber at 37 °C throughout the experiment. The cells were subjected to shear stress of 4.05 dyns/cm² generated by the flow of the culture medium for 2 h. The flow direction was guided along the long axis of the specimen. In parallel, reference groups of cells were statically cultured on the substrates for the same duration. Both groups of samples were subjected to fixation and fluorescent staining of vinculin and cell nuclei using the technique described above. The fluorescent images collected with the Zeiss fluorescent microscope were analyzed with ImageJ to quantify cell parameters, including cell density, spread area, perimeter, circularity, and alignment.

2.9 Statistical Analysis

Data were reported in the form of mean ± standard deviation (STDEV). Statistical comparisons were made between each pair of data using Student's t-test (JMP Software, USA). The statistically significant differences were denoted by asterisks in the figures at $p < 0.05$.

3. Results

3.1 Mechanical Properties of the ZrAlFeCu BMG

The microhardness and compression behavior of the ZrAlFeCu BMG are plotted in Figure 1. The microhardness of the ZrAlFeCu BMG was measured to be 4.5 GPa, in comparison with the 2.4 GPa of 316L SS (Figure 1a). Under quasi-static compression, the ZrAlFeCu BMG showed the yield strength of 1.7 GPa, the elastic limit of 2%, and the

1 Young's modulus of 80 GPa, as revealed by the compressive stress-strain curve (Figure
2 1b). The fracture morphology of ZrAlFeCu BMG under compression was characterized
3 by shear banding visible on the lateral surface and vein pattern on the fracture surface of
4 the material, which are shown in Figure 1c.

5 Compression-compression fatigue behavior of ZrAlFeCu BMG is illustrated in
6 Figure 2. It is manifested in Figure 2a that, below the maximum applied stress of 1.054
7 GPa, the ZrAlFeCu samples were able to survive 10^7 cycles of loading. The 10^7 cycles
8 are commonly chosen to represent the fatigue life of a material at fatigue endurance limit
9 [33]. At maximum applied stresses higher than 1.054 GPa, samples failed within 10^6
10 cycles. The fractography of a representative sample failed at the maximum applied stress
11 of 1.360 GPa was analyzed, featuring the crack initiation site on the surface of the
12 sample, a small portion of crack propagation with relatively smooth morphology, and a
13 rough fast-fracture region with typical vein patterns.

14 3.2 Finite Element Analysis of a ZrAlFeCu BMG-based Model Stent

15 A truss-like stent configuration shown in Figure 3 was employed for FEA analysis.
16 The distributions of Von Mises stress and maximum principle strain were modeled over a
17 fully expanded stent under applied pressure loads ranging from 50 - 150 mmHg to
18 simulate the diastolic and systolic pressures from the vessel, according to ASTM F2477
19 [30]. The maximum Von Mises stress on the ZrAlFeCu BMG stent was found to be
20 approximately 65 MPa under 150 mmHg pressure loading (Figures 3a and b), which was
21 similar to the maximum stress of around 67 MPa for 316L SS (Figure 3c). The maximum
22 strain on the ZrAlFeCu BMG stent, as shown in Figure 3d, was predicted to be 7.1×10^{-4} .

1 In contrast, the maximum strain on a 316L SS stent was estimated to be near 3.0×10^{-4}
2 (Figure 3e).

3 3.3 Corrosion Behavior

4 The corrosion behavior of the ZrAlFeCu BMG was summarized in Figure 4. Prior
5 to polarization, the recorded open circuit potential of ZrAlFeCu BMG was shown to
6 increase with time (Figure 4a), indicating that the stability of the ZrAlFeCu BMG surface
7 was enhanced after immersion in the PBS solution. The polarization curves for both
8 alloys (Figure 4b) displayed spontaneous passivation, and the passive region observed for
9 the ZrAlFeCu BMG was much wider than that for the 316L SS. However, the passive
10 films were found susceptible to pitting at specific threshold potentials at which a steep
11 increase of current density in the polarization curves occurred. Such threshold potential,
12 commonly known as pitting potential (E_{pit}), along with other corrosion parameters,
13 including corrosion potential (E_{corr}) and pitting overpotential ($E_{\text{pit}} - E_{\text{corr}}$), were derived
14 from the polarization curves and presented in Figure 4c. The pitting overpotential is a
15 gauge of pitting resistance, the higher value of which indicates higher pitting resistance.
16 ZrAlFeCu BMG exhibited a pitting overpotential around 1500 mV, which was found
17 more than twice that of 316L SS (~ 600 mV), proving the high corrosion resistance of the
18 Zr-based BMG. It is worth noting that, during reversed scan (Figure 4b), the polarization
19 curves of ZrAlFeCu BMG and 316L SS crossed the curves of their respective forward
20 scans at E_{corr} , indicating that both materials possessed slight repassivation capability.

21 As shown in Figure 4d, SEM examination of the corroded ZrAlFeCu BMG sample
22 revealed the formation of corrosion pits on the surface and the typical honeycomb
23 structure within the pit, which was commonly observed in the corrosions of Cu-

1 containing Zr-based BMGs [34, 35]. EDX mapping in Figure 4e showed enrichment of
2 Cu in the pit and depletion of other alloying elements. The regional enrichment of O
3 implied the formation of corrosion products. The EDX measurements indicated that the
4 corrosion process of the ZrAlFeCu BMG was similar to the one proposed in our previous
5 studies, which involved the breakdown of passive film due to Cl^- attack, the preferential
6 dissolution of alloying elements and the formation of metastable CuCl and subsequent
7 CuO as a result of hydrolysis [34, 35].

8 *3.4 Surface Characterizations of the ZrAlFeCu BMG*

9 The XPS spectra (Figure 5), both survey and narrow scans, showed the presence of
10 O, Zr, Al and Cu, and the absence of Fe on the surfaces of as-cast and PBS-immersed
11 ZrAlFeCu BMG. C peaks were also detected due to the inevitable contamination.
12 Moreover, the chemical states of each element were analyzed by deconvolution of the
13 narrow scan spectrum (see Figure S3). O1s peaks were found composed of peaks for O^{2-}
14 and OH, which were responsible for metal oxides (M_xO_y) and the hydroxyl groups (-OH)
15 on the sample surface. Zr3d narrow scan spectrum was consisted of doublets of Zr 3d5/2
16 and 3d3/2, corresponding to the peaks of ZrO_2 (Zr^{4+}) and metal Zr (Zr^0). The peaks for
17 Zr^0 tended to disappear on immersed sample. Similarly, peaks for Al2p were analyzed,
18 showing the presence of Al_2O_3 . Cu existed mainly in the form of metal, with formation of
19 a small amount of oxides after immersion. The concentration of each element was
20 quantified in Figure 5b. The compositions of passive films formed on both as-cast and
21 immersed ZrAlFeCu BMG surfaces were mainly ZrO_2 with small amounts of Al_2O_3 and
22 Cu/CuO_x. After immersion, Zr content increased and Al content decreased in the passive

1 film. In addition, a higher amount of hydroxyl groups was found on the immersed surface
2 (Figure S3).

3 Contact angles of DI water and DII on ZrAlFeCu BMG and 316L SS were
4 presented in Figure 6a. The water contact angle on ZrAlFeCu BMG was measured to be
5 around 50°, which was slightly lower than the 56° of 316L SS, indicating good surface
6 hydrophilicity. Water contact angles on both substrates were lower than the Berg limit (θ
7 = 65°) [36]. The average contact angles for the nonpolar DII liquid were read as 37° and
8 35° for ZrAlFeCu BMG and 316L SS, respectively. SFEs and its polar and dispersive
9 components for both substrates were plotted in Figure 6b, as calculated using the contact-
10 angle data. Considering hydrophobic surfaces are characterized by low SFE (up to 50
11 mN/m) [37, 38], the calculated SFEs of ZrAlFeCu BMG and 316L SS being higher than
12 50 mN/m further imply that both surfaces are hydrophilic. No statistically significant
13 differences were found for the wettability and surface free energy between the two
14 groups of materials.

15 3.5 Endothelial and Smooth Muscle Cell Viability and Proliferation on ZrAlFeCu BMG

16 Live/Dead staining revealed that adherent HAECs and HASMCs on both
17 ZrAlFeCu BMG and 316L SS substrates are highly viable (Figure 7). It indicated that
18 both substrates exhibited no cytotoxicity and supported the attachment of HAECs and
19 HASMCs within a relatively short timeframe of 24 h. For both cell types, the number of
20 adherent cells was qualitatively higher on the ZrAlFeCu BMG substrate than on the 316L
21 SS substrate.

22 Cell adhesion of HAECs and HASMCs at 4 h after seeding was evaluated through
23 the quantitative image analyses. As shown in Figure S4, no statistically significant

1 differences were observed in regards to the densities of adherent cells on both substrates.
2 This indicated comparable populations of HAECs and HASMCs on ZrAlFeCu BMG and
3 316L SS at an early time point.

4 The proliferation behavior and metabolic activities of the HAECs and HASMCs on
5 both substrates were monitored from day 1 to 5 using WST-1 assay and SEM
6 observation, as shown in Figure 8. The histograms for WST-1 results for HAECs in
7 Figure 8a presented significantly higher cells metabolic activities on the ZrAlFeCu BMG,
8 which was correlated to a higher number of cells, than on 316L SS at all three time points
9 (Figure 8a). From day 3 to 5, it was noticed that the metabolic activities of HAECs
10 reached plateau on the ZrAlFeCu BMG, whereas continuous growth was observed on
11 316L SS. Nevertheless, the cell metabolic activities on 316L SS were still significantly
12 lower than on the ZrAlFeCu BMG at day 5.

13 The SEM images in Figures 8c and S5 illustrated the growth of HAECs into larger
14 populations as a function of incubation time, however, with different proliferation
15 behaviors on the two different substrates. HAECs on ZrAlFeCu BMG started with a
16 larger population at day 1, with cell-cell interactions readily observed. Cell interactions to
17 a larger extent can be observed and cells tended to merge into a confluent layer on the
18 ZrAlFeCu BMG at days 3 and 5. On 316L SS, a lower number of adherent cells were
19 observed with individual cells extending short filopodia. The cell-cell interactions can be
20 observed on 316L SS at day 3, as they interacted through long and thin filopodia. This
21 interaction was enhanced on day 5 and cells were approaching confluency. The SEM
22 observations were in agreement with the WST-1 assay results.

Similarly, HASMC proliferation was examined and manifested in Figures 8b, 8d and S5. HASMCs proliferated on both substrates during the investigated timeframe. At days 1 and 3, the numbers of cells were significantly higher on the ZrAlFeCu BMG than on the 316L SS. Cells reached near-confluency at day 5, with comparable metabolic activities of HASMCs on both substrates as demonstrated by WST-1 assay and direct visualization of the cultures under SEM. SEM images in Figure 8d also presented HASMC interactions with each other at each time points.

3.6 Endothelial Cell Adhesion under Static and Dynamic Settings

Adhesion of HAECs on the test substrates under a dynamic flow setting was presented in Figure 9. Representative fluorescent images (Figure 9a) elucidated the cell adhesion with and without the effect of shear stress generated by the flow of culture medium. Semi-quantifications on cell parameters, including cell numbers, alignments, spread areas, perimeters, and circularities, were performed based on the fluorescent images. Denudation of endothelial cells from each substrate after the flow test was evidenced in Figure 9b. The remaining fractions of cells adherent on ZrAlFeCu BMG and 316L SS were found to be 87% and 75%, respectively. As shown in Figure 9c, the angle between the long axis of cell nuclei and flow direction was shifted to smaller angle ranges on both substrates, indicating that cells were realigned under the shear stress of the flow towards flow direction. The tendency of realignment is more prominent on 316L SS. The average angle between the long axis of cell and flow direction was reduced from 44° to 31° on ZrAlFeCu BMG and 25° on 316L SS, respectively (Figure S6a). The average spread area was also reduced on both substrates due to the effect of flow (Figure S6b). Cells subjected to flow were found more polarized after flow with a decrease in average

circularity from 0.5 to 0.4 on ZrAlFeCu BMG, but more rounded up on 316L SS with an increase in average circularity from 0.4 to 0.6.

4. Discussion

Current efforts to minimize biological complications associated with metallic vascular stents, such as in-stent restenosis, are mainly based on strategies featuring new designs, textured surfaces, coatings, and/or the inclusion of drug-releasing function [2, 8]. Another proposed solution is to radically substitute existing stent materials with ones exhibiting improved properties. The latter can be leveraged with recent advances in the field of materials science. One such example is the development of a family of amorphous metals, also known as BMGs, which has garnered great interests as potential orthopedic biomaterials, but less explored for other biomedical applications. In this study, we rationalize that a Ni-free Zr-based Zr-Al-Fe-Cu BMG showing a set of appealing materials characteristics is a worthy candidate for vascular stent applications. Through both experimental investigations and computational modeling benchmarked against a common stent material 316L SS, we demonstrated that the Zr-Al-Fe-Cu BMG is a legit contender to replace 316L SS for making better performing vascular stents.

4.1 Mechanical Properties of the Zr-based BMG

During service, vascular stents experience loadings from blood vessel walls, which pose requirements on their mechanical properties. The ZrAlFeCu BMG was featured with a high hardness that was about twice of that for 316L SS, and high yield strength that was considerably higher than that of 316L SS. The high strength of the Zr-based BMG greatly enables the production of stents with thinner struts, which benefits its deliverability. In addition, it has been demonstrated that the use of thinner struts can reduce the rate of

1 restenosis [8, 39, 40]. It is also worth mentioning that high elastic limit of about 2% and
2 low Young's modulus indicated that the elastic deformation with external loading was
3 facilitated.

4 In addition to the quasi-static mechanical testing, the ZrAlFeCu BMG was
5 examined with cyclic loading in our study, as vascular stents endure cyclic pulsatile
6 loading from the blood vessel wall after deployment. It is known that fatigue fracture can
7 occur to materials after a certain number of cycles even when the imposed stresses are
8 much lower than the yield strength. The applied stresses concentrate at defects,
9 introducing accumulation of fatigue damage to the material and eventually resulting in
10 catastrophic failure. For vascular stents, the typical requirement for their fatigue life is 10
11 years of equivalent use at 72 beats per minute or at least 380 million cycles [30]. To
12 experimentally characterize the fatigue endurance of the ZrAlFeCu BMG, the fatigue
13 process was accelerated by increasing the frequency of the cyclic loadings in practical
14 measurements. In comparison with the fatigue strengths of 316L stainless steel typically
15 lower than 500 MPa under different loading conditions [41, 42], the high endurance limit
16 of ZrAlFeCu BMG (> 1 GPa) under cyclic loadings, further qualified this material as a
17 stent material in terms of its mechanical properties.

18 To gain insights into the mechanical behaviors of future stents made from Zr-based
19 BMG under physiologically relevant loadings, FEA was employed to model the
20 distributions of Von Mises stress and maximum principle strain over a fully expanded
21 stent. The maximum Von Mises stress on the ZrAlFeCu BMG-based stent was
22 comparable to that on the 316L SS stent, and was significantly lower than the yield stress
23 and fatigue endurance limit of the ZrAlFeCu BMG. The results indicate that such BMG-

1 stent can sustain the physiological loadings, and it is possible to further reduce the strut
2 thickness of the stent. The maximum strains on stents made of both materials were much
3 smaller than their elastic limits, implying that the deformation of stent with the blood
4 vessel would be constrained within elastic region. However, the strain for ZrAlFeCu
5 BMG was found twice as large as that for 316L SS, which suggested that the stent made
6 of ZrAlFeCu BMG could be more flexible and deformed more easily with the blood
7 vessel during beats. This was owing to the lower Young's modulus of the ZrAlFeCu
8 BMG, which made it a more compliant material for stent applications. The "compliance
9 mismatch" between the native artery and the stent was reported to be correlated with
10 intimal hyperplasia, particularly at the distal end of the stent [43]. The use of a more
11 compliant material as the base material for stent fabrication, in addition to the design of
12 different geometries for compliance matching stents, would be beneficial to improve stent
13 biocompatibility [43, 44]. It should be noted that the present FEA study was based on one
14 type of stent configuration in its deployed form to showcase the potential mechanical
15 advantages of BMG-based stent over 316L SS-based stent. The fabrication of BMG
16 stents with different configurations could be realized using established stent-making
17 techniques, amongst which laser cutting is considered as a viable and convenient
18 approach [45, 46]. Braiding/knitting metallic glass wires may also be applicable to
19 achieve additional designs and geometries [45]. Future FEA studies should be carried out
20 to aid the selection of stent design variables most suitable for BMG materials and guide
21 the development of BMG-based prototype stents with improved mechanical performance.
22 Examples of such simulation studies include modeling Zr-based BMG stents using
23 different configurations relevant to clinically used stents [47], their complex strain

conditions in crimped forms, during expansion, and after deployment [48], and the mechanical impact of stenting to a pathogenic blood vessel [31].

4.2 Corrosion and Surface Properties of the Zr-based BMG

In order to maintain the mechanical integrity of the stent and hinder the production of metal ions and corrosion products that can be toxic to cells or tissues, requirements on the corrosion resistance have been imposed to indwelling stent materials. The corrosion behavior of the ZrAlFeCu BMG was characterized in comparison with 316L SS in PBS solution, which contained the major ions present in blood plasma [49]. Higher corrosion resistance of ZrAlFeCu BMG compared to that of 316L SS was demonstrated by polarization test, suggesting the improved stability and inertness of the alloy in the aggressive physiological environment. In addition, the large passive region of the ZrAlFeCu BMG indicated high stability of the passive film of this material. The enhanced corrosion resistance of the ZrAlFeCu BMG coupled with its high fatigue strength in air found in this study served as indications to its potential resistance to the deleterious corrosion fatigue effect imposed by the aggressive body environment. It has been previously demonstrated that the fatigue lives of Zr-based BMGs have been greatly reduced when immersing in corrosive solutions [50-52]. In our previous research, the fatigue endurance limit of a Zr-Al-Ni-Cu BMG under four-point-bend fatigue was found to be reduced from 450 MPa in air to 270 MPa in PBS solution at 37 °C [50]. The underlying degradation mechanism was related to the anodic dissolution induced corrosion pits, which acted as crack initiation sites at low stress levels [50, 51]. In the present study, the higher pitting resistance of the Zr-Al-Fe-Cu than that of the Zr-Al-Ni-Cu BMG is expected to defer pit formation and benefit corrosion fatigue strength. In

parallel, 316L SS was also found susceptible to pitting, which could undermine its mechanical integrity and lead to fracture at low stresses. It was exemplified in previous research that the fatigue strength of 316L SS under cyclic tension was demoted from 220 MPa in air to approximately 200 MPa in PBS solution [53]. It is worth mentioning that the slightly higher repassivation ability of 316L SS may be effective in combating corrosion pit propagation and recovering readily formed pits, which would contribute to the corrosion fatigue resistance. Further investigations on the corrosion fatigue of Zr-Al-Fe-Cu BMG and 316L SS under the same experimental settings with physiologically relevant loadings and environments will offer additional gauge of the applicability of the BMG materials for in vivo usage.

The high corrosion resistance of the ZrAlFeCu BMGs can be attributed to the formation of the passive films, mainly composed of ZrO_2 , on the surface of the alloy, which is akin to the corrosion-resistant mechanism of other Zr-based BMGs [35]. The tendency of pitting, although at very high anodic potential, was also rooted from the susceptibility of ZrO_2 and Al_2O_3 to the attack of Cl^- in the solution. When comparing the surface chemistry of the Zr-based BMG before and after immersion in PBS, an increased Zr:Al ratio ($\text{ZrO}_2:\text{Al}_2\text{O}_3$) was observed in the passive film formed in PBS. It has been reported that ZrO_2 formed on pure Zr is nobler and more resistant to Cl^- induced pitting than Al_2O_3 on pure Al [54]. Therefore, this increase in Zr content suggested that the passive film formed in PBS solution is more stable than that formed in air, further proved by the experimental observation of increased OCP with time during immersion (Figure 4a). Overall, the corrosion resistance of ZrAlFeCu was considered sufficient to provide a

1 stable substrate for the stent material to survive in and induce minimal chemical
2 interruptions to its surrounding *in vivo* environment.

3 Surface properties are not only directly related to the corrosion resistance of
4 metallic materials, but also affect thrombosis and neointimal hyperplasia [2]. It has been
5 reported that the stability of the oxide film determines the release of metal ions, which
6 can induce activation of platelets and leukocytes [2]. Therefore, higher stability of the
7 passive film would account for the biocompatibility of the material, which rationalizes
8 the benefit of the highly stable ZrAlFeCu BMG surface. In addition, surface wettability
9 and SFE play a critical role in regulating biological response on biomaterial surfaces [55].
10 In the context of stent materials, SFEs directly influence hemocompatibility of
11 biomaterials. For example, Kwok and co-workers reported that by doping diamond-like
12 carbon (DLC) films with phosphorus, the SFE of DLC film increased from 42.9 to 72.4
13 nJ/cm² and an improvement in hemocompatibility of the DLC film was observed [56].
14 Recently, Shabalovskaya et al. evaluated wettability and surface energy of native Nitinol
15 surfaces and their results suggest a positive correlation between the polar component of
16 SFE and the hemocompatibility of Nitinol [57]. In fact, the significance of surface
17 properties is evident from many of the surface modification-based strategies striving to
18 improve vascular stent performances [2, 8, 58].

19 4.3 Cell Responses to the Zr-based BMG

20 Vascular stents are in direct contact with the inner walls of blood vessels that are
21 naturally lined with endothelium formed by endothelial cells. Research has shown that
22 stent coverage with an endothelial cell layer can greatly reduce the risk of restenosis and
23 thrombosis [59, 60]. However, in the event of excessive proliferation of smooth muscle

cells triggered by the acute inflammatory response to stent placement, restenosis could occur and lead to implant failure [61, 62]. Therefore, appropriate behaviors of vascular endothelial and smooth muscle cells to promote endothelial cell coverage and reduce restenosis are essential to stent integration, which justified our choices of HAECs and HASMCs for the cell culture studies. From the *in vitro* viability assays, the cytocompatibility of the ZrAlFeCu BMG was shown to be as good as that of 316L SS.

Comparing the proliferation behaviors of different types of cells on the ZrAlFeCu BMG and 316L SS, the benefits of using the Zr-based BMG as a potential stent material were disclosed. As the initially adherent cell density was comparable on both substrated (Figure S4), fast rate to reach confluency of HAECs was found on the ZrAlFeCu BMG, as concluded from the WST-1 assay (Figure 8). At day 5, the plateau in metabolic activities on ZrAlFeCu BMG can be explained by the contact inhibition of HAECs [63]. It has been established that sparse ECs are in active growth mode, while confluent cells switch themselves to survive mode that requiring lower energy [63] and, hence, lower metabolic activities. In fact, the SEM observations revealed an increase in the number of HAECs on ZrAlFeCu BMG from days 3 to 5. Although the proliferation rate (slope of the dashed line in Figure 8a) of HAECs on ZrAlFeCu BMG was slightly higher than that on 316L, the greater number of initially adherent cells led to an earlier formation of confluent HAEC layer on the Zr-based BMG surface than on 316L SS. This suggested faster re-endothelialization on the Zr-based BMG and can be beneficial for successful implant integration. Research has shown that re-endothelialization of the stent can greatly reduce the risk of restenosis and thrombosis, whereas lack of endothelialization is usually an indicator of stent failure [59]. Conversely, the proliferation rate (slope of the dashed

1 line in Figure 8b) of HASMCs was found lower on ZrAlFeCu BMG than on 316L SS.
2 Despite the higher number of adherent cells on the BMG surface at day 1, HASMCs
3 reached near-confluency at day 5 on both substrates. Combining the results of the two
4 experiment sets, it was established that the ZrAlFeCu BMG supports faster HAEC
5 coverage but slower HASMC growth, as compared to 316L SS, which suggested a lower
6 risk of restenosis on the Zr-based BMG.

7 A number of factors were postulated to be responsible for the different cell
8 behaviors on ZrAlFeCu BMG and 316L SS, including but not limited to surface
9 chemistry, corrosion resistance, microstructure, and mechanical properties. The major
10 constituents of the ZrAlFeCu BMG surface were ZrO_2 and Al_2O_3 , which are also known
11 as the biomedical ceramics, zirconia and alumina. In fact, zirconia and alumina have been
12 successfully applied as coating materials to improve the corrosion resistance and
13 biocompatibility of biomedical stainless steels [64-67]. This can be related to the higher
14 biocompatibility of the ZrAlFeCu BMG over 316L SS in our study. Moreover, the
15 apparent differences in microstructure and mechanical properties between the two
16 materials could also contribute to the different cell responses, which need further
17 investigation to fill the knowledge gap. The underlying mechanism governing the initial
18 cell attachment and proliferation on the Zr-based BMGs in comparison with those on
19 316L SS would also be an interesting subject for future research.

20 Besides proliferation, the strength of HAEC adhesion on the two different
21 substrates was studied. The cells or cell layer adherent on the stent will naturally
22 experience the flow of blood during service, which creates shear force to potentially
23 affect cell adhesion and proliferation after stent deployment [68, 69]. In the present work,

1 the quality of cell adhesion to the substrate was indirectly evaluated by forcing a shear
2 stress to the cell layer under flow of culture medium. The adhesion of HAECs was found
3 stronger on the ZrAlFeCu BMG, as the fraction of remaining cells was higher than on
4 316L SS after flow test. Alignment of cells along the flow direction was observed, in
5 agreement with the findings in previous studies [69, 70]. A stronger tendency of cell
6 realignment under the flow observed for the 316L SS substrate suggested that HAECs on
7 316L SS were more susceptible to the effect of flow than on ZrAlFeCu BMG, likely
8 resulting from a weaker interaction between HAECs and 316L SS. Furthermore, the
9 fluidic flow induced morphological changes to the adherent HAECs. The HAECs
10 exhibited a well-spread morphology on ZrAlFeCu BMG under static incubation as shown
11 in Figure 9a (also see Figure S7). Under the effect of the shear stress, these adherent
12 HAECs became more polarized and reduced cell size, possibly owing to the loss of focal
13 adhesion sites to a certain degree. The initially large spread area of HAECs on ZrAlFeCu
14 BMG may contribute to the higher quality of adhesion. In contrast, the more polarized
15 HAECs on 316L SS during static incubation (Figures 9a and S7) were found to be
16 smaller but more circular after flow. It is important to note that HAECs cultured on both
17 substrates were capable of re-aligning with the flow direction (Figure 9c). The ability of
18 endothelial cells to sense and align with flow is considered critical to the atheroprotection
19 [71]. This process affects the production of vasomediators (i.e., nitric oxide, prostacyclin,
20 endothelin-1, etc.) and regulates subsequent inflammation [71-73]. Failure of cell
21 realignment could result in inflammatory activation [71]. The flow induced cell
22 realignment, morphological changes of HAECs may be associated with changes in other
23 cell behaviors such as adhesion, division, metabolism, ion channel activation, protein

1 expression, phenotypic modulations, et al. [70, 71, 73], which require further examination
2 on ZrAlFeCu BMG over longer time frames.

3 **5. Conclusions**

4 In the present study, the potential of a Ni-free Zr-Al-Fe-Cu BMG to serve as
5 vascular stent material was exploited for the first time. The following conclusions were
6 reached based on our experimental findings:

7 1) The mechanical property of the Zr-based BMG was featured by high strengths under
8 both quasi-static and cyclic loadings, facilitating the design of stents with thinner struts to
9 feasibly reduce the risk of restenosis. Complementary FEA analysis on a specific stent
10 configuration further verified the mechanical advantages of the high-strength Zr-based
11 BMG, and additionally revealed its compliance with the beat of the blood vessel wall, as
12 compared with 316L stainless steel.

13 2) Corrosion resistance of the Zr-based BMG was found significantly higher than that of
14 medical 316L stainless steel, indicating its high stability in the *in vivo* environment,
15 which was attributed to the formation of ZrO₂-rich surface oxide film.

16 3) *In vitro* cell culture studies revealed the general cytocompatibility of the Zr-based
17 BMG. More importantly, faster coverage of endothelial cells and slower growth of
18 smooth muscle cells were observed on the Zr-based BMG than on 316L stainless steel,
19 which suggests promoted re-endothelialization and lower risk of restenosis. In addition,
20 the Zr-based supported stronger endothelial cell adhesion.

21 While these promising findings unveil additional exciting biomedical prospect for
22 the Zr-based BMG, further investigations, both *in vitro* and *in vivo*, are needed before

1 BMG vascular stent becomes a reality. From the material perspective, corrosion fatigue
2 study in simulated physiological environment is essential to estimate and qualify the
3 service life of Zr-based BMG stents. From the biocompatibility aspect, one such study
4 that deserves immediate attention is the evaluation of hemocompatibility of the Zr-based
5 BMG, which is vital for any blood-contacting device.

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1 **Table and Figure Captions**

2 Table 1 Geometric parameters of the stent-vessel system for FEA

3 Figure 1 Quasi-static mechanical properties of the ZrAlFeCu BMG: a) Vickers
4 hardness in comparison with 316L stainless steel; b) engineering stress-strain curve; and
5 c) SEM observations of fractured sample

6 Figure 2 Fatigue behavior of ZrAlFeCu BMG: a) stress-fatigue life (S-N) curve under
7 cyclic compression-compression loading; and b) fractography of specimen failed at a
8 maximum applied stress of 1.36 GPa

9 Figure 3 Finite element analyses on the Von Mises stress (a-c) and maximum principle
10 strain (d, e) distributions of ZrAlFeCu BMG (a, b, d) or 316L SS (c, e) stent under 50 or
11 150 mmHg pressure load

12 Figure 4 Corrosion characteristics of the ZrAlFeCu BMG: a) open circuit potential
13 (OCP) with time; b) corrosion polarization curve and c) corrosion parameters in
14 comparison with 316L stainless steel; d) SEM images showing corrosion morphology;
15 and e) EDX maps of Zr, Cu, Fe, Al and O

16 Figure 5 XPS surface chemical analyses of the ZrAlFeCu BMG before and after PBS
17 immersion: a) representative XPS survey spectra and narrow scans (top: as-cast; bottom:
18 immersed) for O1s, Zr3d, Al2p, Cu2p and Fe2p; and b) quantifications on the
19 concentrations of different elements

20 Figure 6 Surface wettability of ZrAlFeCu BMG and 316L stainless steel: a) deionized
21 (DI) water and diiodomethane (DII) wetting behavior (insets: shadow images of
22 droplets); and b) surface free energy (SFE) with its polar and dispersive components

1 Figure 7 Live/Dead staining (green/red) showing high viability of HAECs and
2 HASMCs on indicated substrates after 24 h of culture (Scale bar: 100 μ m)
3 Figure 8 Proliferation studies of vascular cells HAECs (a, c) and HASMCs (b, d) on
4 indicated substrates over a period of 5 days: a-b) Cell metabolic activity measured by the
5 WST-1 assay (data presented as Mean $\pm$ STDEV; *denotes statistically significant
6 differences at $p < 0.05$; $n = 3$); c-d) SEM images showing cell morphology (scale bars:
7 500 μ m in large images and 5 μ m in insets)
8 Figure 9 HAEC adhesion after 2 h flow test: a) immunostained focal adhesions of
9 HAECs on indicated substrates (scale bars: 200 μ m; white arrows indicate flow
10 directions); b) number of adherent cells before and after flow test (results were
11 normalized to those obtained on non-flowed control sample within each group); and c)
12 histograms of the absolute cell orientation angle relative to the long axis of the specimen
13 or the flow direction obtained from analysis of over 80 cells per group (inset: schematic
14 presentation of the cell nuclei orientation angle measurement)

15

1 **Table**

2 Table 1 Geometric parameters of the stent-vessel system for FEA

Part	Inner diameter (mm)	Outer diameter (mm)	Length (mm)
Stent	2.90	3.10	3.85
Vessel	3.00	3.40	5.00

3
4
5

Fig. 1

Fig. 2

a) Von Mises stress distribution of the ZrAlFeCu stent (whole model)

b) Von Mises stress distribution of the ZrAlFeCu stent

c) Von Mises stress distribution of the 316L SS stent

d) Maximum principle strain distribution of the ZrAlFeCu stent

e) Maximum principle strain distribution of the 316L SS stent

Fig. 3

Fig. 4

Fig. 5

Fig. 6

Fig. 7

Fig. 8

Fig. 9

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Graphical abstract