Magnesium Biomaterials – Past, Present and Future

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Abstract:

Following a reinvigorated interest in the late 1990s, magnesium (Mg) and its alloys have experienced increasing research attention in the realm of biomaterials. From essentially no papers on the topic several years ago, there are presently 10-15 articles published in international journals each week dealing with different aspects of Mg bio performance. Given the dynamic nature of the topic, many works reproduce a great deal of information in a non-systematic manner, and unfortunately also repeat the same systematic errors – which leads to many articles providing information of limited value. This review seeks to provide a succinct overview of the area, highlighting some of the most important considerations for this field, and suggesting critical improvements and changes that are needed to ensure the continual and efficient development of Mg biomaterials.

Keywords: magnesium, biomaterial, *in vitro*, corrosion, *in vivo*, coating

1) Introduction

The potential advantages of magnesium (Mg) over other non-resorbable biomaterials, especially for orthopedic applications, are obvious. The details in Table 1 are an abridged summary of some key considerations that have been consolidated to provide a succinct overview. If fully realized, functional bioresorbable implants based upon Mg-alloys would be unique to the field, providing the mechanical benefits of a metal combined with the degradable and biological advantages displayed by polymers and synthetic biomaterials.[1] However, in spite of significant recent research, there remain challenges to the successful implementation of Mg-based materials in a variety of applications in the body. Many of these challenges are related to corrosion, be it rate, morphology, or products, as discussed below,

The key advantages that Mg possesses over current materials, such as its biodegradability[2-7] and low specific strength[8] (i.e. reduced chance of stress shielding), also pose some of the greatest challenges to its use in the wider context. The notion that implants made from Mg and its alloys from the bio perspective are designed to degrade also means that their shape and mechanical properties constantly change over the life of the implant, adding another layer of complexity to carrying out a full life-cycle design.[9-12] This is in addition to the potential harm of hydrogen evolution[13, 14] and soluble (or insoluble) corrosion products[15], which may contain elements of unknown toxicity. Such multiple and competing considerations require careful management and an interdisciplinary approach to research (involving metallurgists, corrosion scientists, toxicologists, mechanical modelers, and surgeons). As a consequence, whilst the benefits that Mg alloys offer over current materials are obvious; the potential pitfalls of working with Mg must be overcome through systematic research and careful planning. In the present study, which has been separated into topical areas below, some of the core issues presently related to the field are discussed.

2) The requirement to alloy Mg: Strength versus toxicity

Pure Mg is incapable of providing the necessary mechanical[16, 17] and corrosion[18] properties required for a wide variety of implant applications. Therefore potential alloying elements need to be carefully considered. Common alloying elements for Mg include aluminum (Al), zinc (Zn), calcium (Ca), rare earths (RE), lithium (Li), manganese (Mn) and zirconium (Zr). Of all the available elements, perhaps the most controversial is Al. Al is the most common alloying addition to structural Mg-alloys[19] allowing a gain in mechanical properties whilst not increasing the corrosion rate.[20] Several studies have found few if any negative side effects when testing Al-containing Mg alloys both *in vitro*[21-23] and *in vivo*[24, 25]. It must be

considered though, that such studies were typically short-term and may have been heavily influenced by the corrosion of the alloy itself, especially in *in vitro* tests where platelet adhesion[21] or similar methods are used. In such cases it is realistically impossible to isolate the effect an increased corrosion rate might have on the perceived toxicity of the investigated alloy.

Long-term effects of exposure to Al are unclear, and animal studies have found Al toxicity to result in a variety of potential problems, from affecting the reproductive facilities[26] to inducing dementia[27], and potentially leading to Alzheimer's disease[28, 29]. Similar biocompatibility concerns exist for alloys containing RE, which although studied *in vitro* [30-33] and *in vivo* [34, 35], also suffer from a similar lack of knowledge of their long term effects when implanted.[30, 36] This creates the potential that the significant amount of work that has been and will be performed using alloys containing Al/RE may, in the end, go unused if the materials cannot be proven to be non-toxic. One immediate knowledge gap in the literature that should be addressed with some urgency) is the recommended daily dosage limits for RE elements (i.e. Ce, La, Nd, Pr, Y, Gd). This is needed for the biomaterials field in general and not just for work related to Mg. Similarly, although Li has been used in medicine for almost 150 years[37, 38], it has not been employed widely in implanted materials – where continual exposure may occur on the mg/day level.[39]

The development of suitable biodegradable implant alloys is a multidisciplinary challenge, since freedom in alloy design must be confined to a range of alloying additions that are biologically nontoxic, whilst still providing the requisite mechanical properties. This leaves a small number of compatible elements that can provide mechanical or corrosion benefits when alloyed with Mg. The two which are perhaps the most biocompatible include Ca and Zn.[12] Although research using other alloying elements should continue, focus should be initially on the toxicity (especially over the long-term) of these two elements and their corrosion products before they can be developed more fully.

3) The role of alloy coatings: Slowing the initial corrosion rate

An area that has recently received (in the past 2 years) the most attention in the bio-Mg field is the study of coatings or surface modification to slow the degradation rates of various Mg alloys. Coatings for biomaterials, especially biodegradable Mg, have the same requirements as the base materials themselves of being biocompatible and fully degradable. The latter point is particularly salient for understanding what occurs over the implant life cycle. In the case of Mg, coatings themselves cannot be perfect barriers to corrosion (which would be the goal of a

coating system on a structural material). To allow an Mg-implant to biodegrade, the coatings must at some stage cease to be a corrosion barrier, although they may be required to provide an effective method to reduce the initial corrosion rate of the bare metal so the surrounding bone tissue (in the case of orthopedics) may start to form. Ideally, the coating would itself degrade gradually, helping to control the overall corrosion process while leaving no harmful traces. This also presents certain, if not infinite, opportunities to functionalize coatings in order to assist in bio-acceptance, or minimize adverse surgical aspects.

There are a large number of possible coating technologies for Mg biomaterials, including; anodization, metal-metal coatings, plasma spray, chemical vapor deposition (CVD), pulsed laser deposition (PLD), ion beam assisted deposition (IBAD), solution coatings, calcium phosphate (CaP) deposition achieved by various means, and the well-known methods of electrodepostion and conversion coating. A succinct review of these systems has been recently published by Waterman *et al.*[40]. Of all the methods currently reported in the literature, CaP coatings have garnered the majority of the attention due to their intrinsic biocompatibility (CaP deposition is a precursor to bone growth)[41, 42], relative ease of deposition via various routes[43 44], and widespread use for other biomaterials.[43, 45, 46] Some coatings, such as PLD and IBAD, require a line of sight for deposition and consequently are limited in their use for more complex shapes. [47, 48] Ion implantation is also a low throughput method, albeit studied previously.[49, 50] It is conceivable that coating technology will also be adopted from structural Mg-alloys, meaning that the future is likely to see a greater number of studies adopting more routine coatings, such as conversion coatings and ionic liquid treatments[51, 52], and electrodeposited/electroless coatings[53].

4) Challenges and future focus for Mg biomaterial research

There are a number of issues that appear to be currently holding back or slowing the development of Mg alloys as biomaterials. A primary issue is related to the fact that a strong knowledge of material science, corrosion engineering, and biological interactions is required to fully understand, properly design, and carry out appropriate experiments. In this sense, developing Mg biomaterials may be considered more difficult than developing most current metallic biomaterials, as Mg corrodes much more rapidly and the degradation must be part of the design process (i.e. not the case for stainless steel or Ti implants).

This challenge demands a complicated solution that requires consideration of toxicity, corrosion and mechanical performance over the life of the material. Unfortunately, much of the current literature, although sometimes promising, adds little actual valuable knowledge

towards systematic development of the Mg alloys. One obvious aspect of *in vitro* tests is that the environment is not dynamic like the human body, meaning it is a closed environment (unless special attention is paid to make it a more realistic experimental setup). These closed conditions very rapidly alter as a result of the corrosion process, with rapid changes in the pH (within tens of minutes), metal ion concentration, presence of soluble corrosion products, and hydrogen gas evolution (not just into the bulk, but stagnant bubble formation on corroding surfaces). Consequently, there is a disconnect between short and long-term *in vitro* tests, with the latter type being almost entirely unreliable (given the environmental change). Thus, while short-term tests are the most reproducible, their long-term relevance is yet to be proven and is in need of future benchmarking via parallel *in vivo* studies. Short-term tests, by virtue of what the name implies, necessarily rely on electrochemical measurements to provide mechanistic insights and estimates of charge transfer (i.e. dissolution), which again mandates that work carried out adheres to best practices with regards to execution of such tests.[54]

It is not only unrealistic to expect a large number of studies to be carried out *in vivo* (i.e. via rats), but it may also be premature and unethical in any event given that basic aspects such as toxicity of alloying elements in the long term and reliability of long-term *in vitro* tests have not been adequately addressed to date. Nonetheless, in the coming years we will likely witness a greater transition from *in vitro* to *in vivo* tests. Extreme caution, however, must be taken to ensure that the value of *in vivo* tests is maximized by careful selection of alloy-coating combinations that are viable implant candidates.

What the author believes is needed at this stage is a systematic approach to alloy composition design, coating composition, and perhaps most importantly, *in vitro* test development. Some work has been done in this area, with novel media flow prototypes [55, 56] and development of new, more corrosion-relevant media [57]. Yet there has been little effort to collect this data for comparison and wider use. The establishment of a database of collected results would allow much greater comparison and a more comprehensive discussion of new data in light of what has already been published. This data could eventually lead to the development of a tool, such as a neural network (discussed previously [12]), which would allow understanding of implant performance without the need for it to be physically produced. Such a tool would be extremely valuable for the final patient-specific implant design, where each implant (material and coating) could be designed specifically to match the needs of the intended recipient.

While the publication and collection of Mg biomaterial experiments is important, the benefit is minimized if the experiments are not performed appropriately. The degradation of the Mg alloy

is perhaps the most important aspect with regard to its success as it is related not only to its mechanical properties but also its toxicity and the potential for hydrogen gas problems. As such there are numerous tests available to investigate the corrosion rate, both instantaneous and long term.[54] Each of these tests has its own unique parameters and concerns that must be taken into account, not only when setting up and running the experiment but also to correctly interpret the resultant data. An outline of many such factors has been published previously[54], but it is an area that must constantly be updated and improved. A standardized experiment design template, outlining the appropriate setup, operation, and interpretation of *in vitro* tests would be immensely useful for researchers in this field. Methods that can be directly compared across research labs will allow the community to efficiently collect good results and reduce the effort spent on irrelevant studies.

A thorough analysis by the author of over 150 articles published specifically on biocorrosion experiments for Mg highlights the apparent lack of understanding of the importance of some of the most common variables for these tests.[54] Over 35% of the papers which included mass loss experiments performed their tests at room temperature rather than the physiological temperature of 37 °C, a change which can affect not only the corrosion rate [58] but also the adsorption of proteins onto a surface [59, 60]. The author has found in his own work that, depending on the alloys, a change of just 17 °C results in an increase of between 50% to over 800% in the measured corrosion rate (depending on alloy and test method). Similarly for pH, which is normally maintained between 7.4-7.6 in the body, over 60% of all published work either did not mention pH at all, or did not maintain it throughout the test. Like temperature, pH is crucial not only to corrosion, in which it primarily affects the formation of any layers (such as $Mg(OH)_2$ or calcium phosphate) on the surface, but is also vital to the binding of proteins to the surface. Unfortunately, this research trend continues for other variables as well, including a lack of the use of a buffer to control pH (75% of the papers)[61], and use of overly-simplistic solutions such as those containing just NaCl without any of the other inorganic minerals found in the body which are important to the formation of realistic corrosion layers (30%).

The cross-disciplinary nature of biocorrosion studies (which combine materials science, engineering, biochemistry, chemistry, medicine, etc) has the unfortunate consequence that important artifacts of experimental design and variable control can go overlooked when studies are performed by those who are experts in only some of these fields. As such, the errors that cause otherwise good science to be of limited or no real use, or at the very least, to be repeated, are commonplace in the literature. Currently, it seems this trend will likely continue if systematic improvements are not made. What is critically needed in this field is

the establishment of experiment standards. It has been shown that the ASTM standards for corrosion tests do not apply to Mg, especially for biocorrosion [62]. This leaves experimenters open to devise tests to the best of their ability based on their experience and any previous examples they may come across. While it is important not to impose constraints on the types of experiments that may be performed, the current approach all too often results in the kind of mistakes and errors mentioned above. The establishment of appropriate standards is necessary, at minimum setting out the variables that should be controlled (and their errors), typical experimental settings to be used (especially for electrochemical work), and what parameters are required to be reported in any published work to allow others to repeat and reproduce the work. Other core variables, such as the minimum purity level that may be referred to as "pure" Mg, should also be set and not be altered unless an experiment is specifically looking at the effect of this change.

The need and manner for establishing such a set of standards should be fully discussed and agreed to at an international level, possibly in a forum such as the yearly Biodegradable Metals Conference[63], since to be of greatest use they must be almost universally adhered to by biomaterial researchers These standards should not be proscriptive and in no way should inhibit or discourage researchers from developing new tests and improving those already established, but they should provide a common foundation on which most researchers could base their work. With set standards and thus an enhanced capability to compare research results on an international scale, it is expected that developments in the field would progress more rapidly and the amount of time wasted due to common experimental mistakes would be minimized. Once fully developed, these criteria should be submitted to the appropriate standards organizations (ASTM, NACE).

5) Conclusion

As the first decade of intense and modern research into bioresorbable Mg-alloys begins to draw to a close – a logical conclusion from a critical appraisal of the open literature suggests that it is now increasingly timely for researchers in this field to transition from 'appreciating the potential benefits' towards 'engineering systems into a final product'. This will require a more systematic approach that fully incorporates the interdisciplinary nature of the endeavor. It would also greatly benefit from the establishment of appropriate experimental standards in order to maximize the comparability of research on an international level. Three other key actions which could lead to even greater and more rapid research gains in the development of Mg's potential as a viable implant material are:

- Determining the toxicity of all potentially hazardous alloying elements. This needs to be further explored before these materials could be seriously considered as biomaterial candidates; in particular, elements such as the family of rare earths (Ce, La, Pr, Nd, Y, Gd), Li and Zr must receive greater attention, along with their long term exposure hazards.
- Developing coatings for Mg biomaterials. Appropriate coatings will likely be necessary for any successful Mg implant in order to provide initial protection by slowing hydrogen evolution and permitting more ready implant acceptance *in vivo*. Any such coating, however, must display a controlled biodegradation rate.
- Establishing a database of published results with their associated experimental parameters. Such a database could lead to the development of an alloy performance prediction method (such as a neural network). The database should be open access for greatest impact.

All of these actions could be undertaken either now or in the near future and that they would be of tremendous benefit for all future research in the field of Mg as a biomaterial.

Table 1: Review of Mg Biomaterial Benefits and Drawbacks

Benefit/Drawback	Details
	Benefits
Low Density / High Specific Strength	Mg is the lightest of all structural metals (1.738 g/cm^3)[8] with values close to those typical for cortical bone (1.75-2.1 g/cm^3).[64] Pure Mg has a strength to weight ratio of approximately 130 kN•m/kg, however rapidly cooled alloys can reach 490 kN•m/kg.[65] This is 2 x greater than one of the most commonly used titanium alloys (Ti6Al4V, 260 kN•m/kg) and as a result less material may be used to provide a similar mechanical function in the body.
High Damping Capacity	Mg is unique due to its extremely high damping capacity (ability to absorb energy), the highest of any metal.[66] In the biomedical field this can be very important in heavy load-bearing applications, where the shock and vibration absorbing properties of Mg could provide significant benefit over other materials.
Machinability and Dimensional Stability	Mg is recognized as the easiest structural metal to machine, and stable final dimensions are easy to achieve.[67] Consequently complex shapes are easily producible, which is crucial for the often intricate shapes that are required for medical applications, which frequently have to be tailored individually to fit each patient.
Reduction in likelihood of stress shielding	Stress shielding is the process by which bone mass and density will decrease in the vicinity of an implant with a mismatched (usually higher) stiffness value, as it transfers the load away from the adjacent bone. This can cause serious problems and implant failure if it continues,[68-71] and is known to be a problem with current orthopedic devices based on stainless steel or titanium, which have a density, elastic modulus, and yield strength an order of magnitude higher than that of bone.[72] Pure Mg has an elastic modulus of ~45 GPa, which is much closer to that of human cortical bone (~20 GPa) than most common Ti alloys (110-120 GPa).[1] Combined with a density very close to that of bone, stress shielding related problems can be greatly reduced for many orthopedic implants, most critically in high load bearing areas.
Biocompatibility and osteogenesis	Current biomaterials such as pure Ti are relatively inert in the body, meaning they exhibit little host response, positive or negative.[73, 74] In contrast, Mg is considered biocompatible and non-toxic [2-7], and has been shown to increase the rate of bone formation [5, 75]. Mg is also an important ion in the formation of the biological apatites that make up the bulk of bone mineral, a key part to

	new bone formation.[76, 77] Mg is known to have a positive influence on bone fragility and strength. [5, 78, 79]
Safe degradation	Titanium, stainless steel, and Co-Cr implants are not designed to degrade safely in the body. However, all surgically implanted metal alloys undergo some electrochemical degradation due to the complex and corrosive environment of the body.[80] Combined with significant wear that can occur in load-bearing applications, particles of the implant can be released into the surrounding tissues, causing discomfort and potential health risks. [81, 82] In addition this wear and corrosion can lead to the need for a second implant during the patient's lifetime. Although the bulk material may be considered bio-inert, the way in which the particles are metabolized within the body can lead to acute inflammation and eventually implant failure.[83] Mg has the unique position of being able to minimize all these issues. The gradual release of Mg ions in the body is dealt with effectively[2-7]. The corrosion of Mg in the body would result in an eventual complete degradation. This means the implant would not remain in the body for longer than is needed to perform its task and/or be replaced by bone. This also means that patients would benefit from only temporary exposure to a "foreign" object in their body. This is extremely crucial, as over time complications can and do occur for many implants, with more issues likely to arise the longer an implant remains *in vivo*.[84]
	Drawbacks
Low Elastic Modulus	Although the lower elastic modulus of Mg may be beneficial with respect to stress shielding, it also means that there may be a greater chance of failure in high-load applications, such as the spine where compressive loads during certain activities may exceed 3500 N.[85] It is vital to ensure that any implant is designed to sustain its load without deformation. However this aspect is even more crucial when considering degradable materials, as an appropriate mechanical support is required throughout the entire bioresorption and bone remodeling process.
Rapid degradation	Mg implants are intended to completely degrade but at a rate that reduces H_2 gas formation and that is similar to bone remodeling. The rapid degradation of Mg implants observed early in the last century [86, 87] has been greatly reduced by recent advances in controlling the purity of Mg and alloying elements, however they remain an issue.[19, 88, 89]
Resorption problems	The rapid degradation of Mg alloys may cause an adverse biological response

as Mg and other element ions are released too quickly into the surrounding tissues. All of the alloying elements will eventually enter the patient and must be selected with non-toxicity as a primary factor. However, elements normally present in the body (*e.g.* Zn, Ca, Mn) can also be toxic if the release rate is too high as the levels cannot be dealt with appropriately (*e.g.* excess Mg *via* kidneys, hydrogen gas *via* soft tissues). Thus, a truly biocompatible Mg alloy is required to avoid the use of toxic alloying elements and ensure an appropriate release rate for other elements, even those which are naturally occurring.

Hydrogen evolution

The release of H_2 and subsequent cyst formation following implantation of Mg can cause various problems. Gas pockets may form next to the implant that cause separation of tissue and/or tissue layers.[13, 14] H_2 bubbles may delay healing at the surgical site, leading to necrosis of surrounding tissue.[90] In the worst case scenario, gas bubbles could block the blood stream, causing death.[91] If the degradation is too rapid, the amount of H_2 produced will accumulate where it cannot diffuse through the surrounding soft tissues at a sufficient rate.[92]

The *in vitro* hydrogen evolution rate for various Mg alloys containing Zn, Al, and Mn are reported to be within tolerable rates (*i.e.* < 0.01 ml/cm2/day).[66] However it should be noted that these rates may depend strongly on the location of the implant, with certain applications (such as stents) allowing increased rates of H_2 evolution due to blood flow. There does not appear to be an absolute rate, and each alloy must be investigated in relation to its intended function. Consequently, it is reasonable to expect that hydrogen evolution during Mg degradation will not present a problem, provided that the corrosion rate of the Mg-based device is controlled.

References

1. M. P. Staiger, A. M. Pietak, J. Huadmai, and G. Dias: 'Magnesium and Its Alloys as Orthopedic Biomaterials: A Review', *Biomaterials*, 2006, **27**(9), 1728-1734.
2. N.-E. L. Saris, E. Mervaala, H. Karppanen, J. A. Khawaja, and A. Lewenstam: 'Magnesium: An update on physiological, clinical and analytical aspects', *Clinica Chimica Acta*, 2000, **294**(1-2), 1-26.
3. J. Vormann: 'Magnesium: Nutrition and Metabolism', *Molecular Aspects of Medicine*, 2003, **24**, 27-37.
4. Merck International: 'Water, Electrolyte Mineral, and Acid/Base Metabolism', in 'Merck Manual of Diagnosis and Therapy', (eds. R. S. Porter, et al.), 2006, Merck & Co., Inc.
5. T. Okuma: 'Magnesium and Bone Strength', *Nutrition*, 2001, **17**, 679-680.
6. F. I. Wolf and A. Cittadini: 'Chemistry and Biochemistry of Magnesium', *Molecular Aspects of Medicine*, 2003, **24**, 3-9.
7. A. Hartwig: 'Role of Magnesium in Genomic Stability', *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, 2001, **475**, 113-121.
8. The American Foundry Society Technical Department, *Magnesium Alloys*. 2006, The American Foundry Society Technical Department,: Schaumburg, Illiniois.
9. M. Schinhammer, A. C. Hänzi, J. F. Löffler, and P. J. Uggowitzer: 'Design strategy for biodegradable Fe-based alloys for medical applications', *Acta Biomaterialia*, 2010, **6**(5), 1705-1713.
10. T. Adachi, Y. Osako, M. Tanaka, M. Hojo, and S. J. Hollister: 'Framework for optimal design of porous scaffold microstructure by computational simulation of bone regeneration', *Biomaterials*, 2006, **27**(21), 3964-3972.
11. S. J. Hollister, R. D. Maddox, and J. M. Taboas: 'Optimal design and fabrication of scaffolds to mimic tissue properties and satisfy biological constraints', *Biomaterials*, 2002, **23**(20), 4095-4103.
12. N. T. Kirkland, M. P. Staiger, D. Nisbet, C. H. J. Davies, and N. Birbilis: 'Performance-Driven Design of Biocompatible Mg-Alloys', *JOM Journal of the Minerals, Metals and Materials Society*, 2011, **63**(6), 28-34.
13. G. Song: 'Control of biodegradation of biocompatable magnesium alloys', *Corrosion Science*, 2007, **49**(4), 1696-1701.
14. C. K. Seal, K. Vince, and M. A. Hodgson: 'Biodegradable surgical implants based on magnesium alloys: A review of current research', *IOP Conference Series: Materials*

Science and Engineering, 2009, 012011.

15. F. Witte, H. Ulrich, M. Rudert, and E. Willbold: 'Biodegradable magnesium scaffolds: Part 1: Appropriate inflammatory response', *Journal of Biomedical Materials Research Part A*, 2007, 748-756.
16. D. Vojtěch, H. Čížová, and K. Volenec: 'Investigation of magnesium-based alloys for biomedical applications', *Kovove Mater*, 2006(44), 211–223.
17. S. Ganeshan, S. L. Shang, Y. Wang, and Z. K. Liu: 'Effect of alloying elements on the elastic properties of Mg from first-principles calculations', *Acta Materialia*, 2009, **57**(13), 3876-3884.
18. N. T. Kirkland, J. Lespagnol, N. Birbilis, and M. P. Staiger: 'A Survey of Bio-Corrosion Rates of Magnesium Alloys', *Corrosion Science*, 2010, **52**(2), 287-291.
19. I. J. Polmear: 'Magnesium and Magnesium Alloys', in 'ASM Specialty Handbook', (ed. A. International), 3-84; 1999, USA, The Materials Information Society.
20. E. Ghali, W. Dietzel, and K.-U. Kainer: 'Testing of general and localized corrosion of magnesium alloys: A critical review', *Journal of Materials Engineering and Performance*, 2004, **13**(5), 517-529.
21. X. Gu, Y. Zheng, Y. Cheng, S. Zhong, and T. Xi: '*In vitro* corrosion and biocompatibility of binary magnesium alloys', *Biomaterials*, 2009, **30**(4), 484-498.
22. F. Witte, F. Feyerabend, M. Kammal, and R. Willumeit: 'Unphysiologically high magnesium concentrations support chondrocyte proliferation and redifferentiation', *Tissue Engineering*, 2006, **12**(12), 3545-3556.
23. F. Witte, F. Feyerabend, P. Maier, J. Fischer, M. Stormer, C. Blawert, W. Dietzel, and N. Hort: 'Biodegradable magnesium-hydroxyapatite metal matrix composites', *Biomaterials*, 2007, **28**(13), 2163-2174.
24. F. Witte, I. Abeln, E. Switzer, V. Kaese, A. Meyer-Lindenberg, and H. Windhagen: 'Evaluation of the skin sensitizing potential of biodegradable magnesium alloys', *Journal of Biomedical Materials Research Part A*, 2008, **86A**(4), 1041-1047.
25. O. Duygulu, R. A. Kaya, G. Oktay, and A. A. Kaya: 'Investigation on the potential of magnesium alloy AZ31 as a bone implant', *Materials Science Forum*, 2007, **546-549**, 421-424.
26. J. L. Domingo: 'Reproductive and developmental toxicity of aluminum: A review', *Neurotoxicology and Teratology*, 1995, **17**(4), 515-521.
27. T. D. Lucey and B. Venugopal: 'Metal toxicity in mammals'; 1977, New York, Plenum Press.
28. S. S. A. El-Rahman: 'Neuropathology of aluminum toxicity in rats (glutamate and GABA impairment)', *Pharmacological Research*, 2003, **47**(3), 189-194.

29. T. P. Flatten: 'Aluminium as a risk factor in Alzheimer's disease, with emphasis on drinking water', *Brain Research Bulletin*, 2001, **55**(2), 187-196.
30. F. Feyerabend, J. Fischer, J. Holtz, F. Witte, R. Willumeit, H. Drücker, C. Vogt, and N. Hort: 'Evaluation of short-term effects of rare earth and other elements used in magnesium alloys on primary cells and cell lines', *Acta Biomaterialia*, 2010, **6**(5), 1834-1842.
31. S. Gruhl, F. Witte, J. Vogt, and C. Vogt: 'Determination of concentration gradients in bone tissue generated by a biologically degradable magnesium implant', *J. Anal. At. Spectrom.*, 2009, **24**(2), 181-188.
32. L. Bondemark, J. Kurol, and A. Wennberg: 'Orthodontic rare earth magnets—*in vitro* cytotoxicity assessment', *British Journal of Orthodontics*, 1994, **21**, 335-341.
33. V. E. Donohue, F. McDonald, and R. Evans: '*In vitro* cytotoxicity testing of neodymium-iron-boron magnets', *Journal of Applied Biomaterials*, 1995, **6**(1), 69-74.
34. H. Zhang, W. F. Zhu, and J. Feng: 'Subchronic toxicity of rare earth elements and estimated daily intake allowance', Ninth Annual V.M. Goldschmidt Conference, Cambridge, MA, USA, 1999.
35. D. W. Bruce, B. E. Hietbrink, and K. P. DuBois: 'The acute mammalian toxicity of rare earth nitrates and oxides', *Toxicology and Applied Pharmacology*, 1963, **5**(6), 750-759.
36. A. Drynda, N. Deinet, N. Braun, and M. Peuster: 'Rare earth metals used in biodegradable magnesium-based stents do not interfere with proliferation of smooth muscle cells but do induce the upregulation of inflammatory genes', *Journal of Biomedical Materials Research Part A*, 2009, **91A**(2), 360-369.
37. R. T. Timmer and J. M. Sands: 'Lithium Intoxication', *J Am Soc Nephrol*, 1999, **10**(3), 666-674.
38. Z. Bhagwagar and G. M. Goodwin: 'The role of lithium in the treatment of bipolar depression', *Clinical Neuroscience Research*, 2002, **2**(3-4), 222-227.
39. C. D. Yfantis, D. K. Yfantis, J. Anastassopoulou, T. Theophanides, and M. P. Staiger: 'New magnesium alloys for bone tissue engineering: *in vitro* corrosion testing', *WSEAS transactions on Environment and Development*, 2006, **2**(8), 1110-1115.
40. J. Waterman and M. P. Staiger: 'Coating Systems for Magnesium-Based Biomaterials - State of the Art', in 'Magnesium Technology 2011', 403-408; 2011, John Wiley & Sons, Inc.
41. F. Barrère: 'Biomimetic Calcium Phosphate Coatings: Physiochemistry and Biological Activity', PhD thesis, University of Twente, 2002.
42. B. León and J. A. Jansen: 'Thin Calcium Phosphate Coatings for Medical Implants';

2008, Springer.

43. B. Leon and J. A. Jansen, eds. *Thin Calcium Phosphate Coatings for Medical Implants*, (ed.B. Leon), 2009, New York, Springer.
44. J. Waterman, A. Pietak, N. Birbilis, T. Woodfield, G. Dias, and M. P. Staiger: 'Corrosion resistance of biomimetic calcium phosphate coatings on magnesium due to varying pretreatment time', *Materials Science and Engineering: B*, 2011, **176**(20), 1756-1760.
45. F. Z. Cui, J. X. Yang, Y. P. Jiao, Q. S. Yin, and Y. Zhang: 'Calcium Phosphate Coating on Magnesium Alloy for Modification of Degradation Behavior', *Frontiers of Material Science in China*, 2008, **2**(2), 143-148.
46. J. Waterman, M. P. Staiger, A. Pietak, T. Mahoney, G. J. Dias, and T. Woodfield: 'Biomimetic Calcium Phosphate Coatings for Improved Mg Metal Based Orthopaedic Implants', 3rd Indo-Australian Conference in conjunction with the 19th Annual Conference of the Australasian Society for Biomaterial and Tissue Engineering (ASBTE), Sydney, Australia, 2009, 77.
47. C. F. Koch, S. Johnson, D. Kumar, M. Jelinek, D. B. Chrisey, A. Doraiswamy, C. Jin, R. J. Narayan, and I. N. Mihailescu: 'Pulsed laser deposition of hydroxyapatite thin films', *Materials Science and Engineering: C*, 2007, **27**(3), 484-494.
48. J. X. Yang, Y. P. Jiao, F. Z. Cui, I.-S. Lee, Q. S. Yin, and Y. Zhang: 'Modification of degradation behavior of magnesium alloy by IBAD coating of calcium phosphate', *Surface and Coatings Technology*, 2008, **202**(22-23), 5733-5736.
49. Y. Z. Wan, G. Y. Xiong, H. L. Luo, F. He, Y. Huang, and Y. L. Wang: 'Influence of zinc ion implantation on surface nanomechanical performance and corrosion resistance of biomedical magnesium-calcium alloys', *Applied Surface Science*, 2008, **254**(17), 5514-5516.
50. X. B. Tian, C. B. Wei, S. Q. Yang, R. K. Y. Fu, and P. K. Chu: 'Corrosion resistance improvement of magnesium alloy using nitrogen plasma ion implantation', *Surface & Coatings Technology*, 2005, **198**(1-3), 454-458.
51. X. B. Chen, N. Birbilis, and T. B. Abbott: 'A review of corrosion resistant conversion coatings for magnesium and its alloys', *Corrosion*, 2011, **67**(3), 1-16.
52. Y. Zhang, M. Forsyth, B. Hinton, and G. Wallace: 'Control of Biodegradation of a Mg Alloy in Simulated Body Fluid', ICC 2011 : 18th International Corrosion Congress : Corrosion Control, Contributing to a Sustainable Future for All, Perth, W. A., 20-24 Nov. 2011, 2011, 1-8.
53. X.-B. Chen, H.-Y. Yang, M. A. Easton, T. A. Abbott, and N. Birbilis: 'Corrosion resistant electrochemical platings on magnesium alloys: A state-of-the-art review',

Corrosion, 2012, **In Press**.

54. N. T. Kirkland, N. Birbilis, and M. P. Staiger: 'Assessing the corrosion of biodegradable magnesium implants: A critical review of current methodologies and their limitations', *Acta Biomaterialia*, 2012, **8**(3), 925-936.
55. Y. Chen, S. Zhang, J. Li, Y. Song, C. Zhao, and X. Zhang: 'Dynamic degradation behavior of MgZn alloy in circulating m-SBF', *Materials Letters*, 2010, **64**.
56. J. Levesque, H. Hermawan, D. Dube, and D. Mantovani: 'Design of a pseudo-physiological test bench specific to the development of biodegradable metallic biomaterials', *Acta Biomaterialia*, 2008, **4**(2), 284-295.
57. L. Yang and E. Zhang: 'Biocorrosion behavior of magnesium alloy in different simulated fluids for biomedical application', *Materials Science and Engineering: C*, 2009, **29**(5), 1691-1696.
58. V. V. Gerasimov and I. L. Rozenfeld: 'Effect of temperature on the rate of corrosion of metals ', *Russian Chemical Bulletin*, 1957, **6**(10).
59. D. R. Jackson, S. Omanovic, and S. G. Roscoe: 'Electrochemical Studies of the Adsorption Behavior of Serum Proteins on Titanium', *Langmuir*, 2000, **16**(12), 5449-5457.
60. S. Omanovic and S. G. Roscoe: 'Electrochemical Studies of the Adsorption Behavior of Bovine Serum Albumin on Stainless Steel', *Langmuir*, 1999, **15**(23), 8315-8321.
61. N. Kirkland, J. Waterman, N. Birbilis, G. Dias, T. Woodfield, R. Hartshorn, and M. Staiger: 'Buffer-regulated biocorrosion of pure magnesium', *Journal of Materials Science: Materials in Medicine*, 2012, **23**(2), 283-291.
62. F. Witte, J. Nellesen, H.-A. Crostack, V. Kaese, A. Pisch, F. Beckmann, and H. Windhagen: '*In vitro* and *in vivo* corrosion measurements of magnesium alloys', *Biomaterials*, 2006, **27**(7), 1013-1018.
63. Anon. 'Biodegradable Metals Conference, http://www.biometal2011.org/', 2012 [viewed 2012 31st March].
64. A. M. Richards, N. W. Coleman, T. A. Knight, S. M. Belkoff, and S. C. Mears: 'Bone Density and Cortical Thickness in Normal, Osteopenic, and Osteoporotic Sacra', *Journal of Osteoporosis*, 2010, **2010**.
65. S. G. Kim, A. Inoue, and T. Masumoto: 'Increase of mechanical strength of a Mg85Zn12Ce3 amorphous alloy by dispersion of ultrafine hcp-Mg particles', *Materials Transactions, JIM*, 1991, **32**(9), 875-878.
66. M. M. Avedesian and H. Baker: 'Magnesium and magnesium alloys', ix, 314p.; 1999, Materials Park, Ohio, ASM International.
67. E. F. Emley: 'Principle of Magnesium Technology'; 1966, Pergammon Press.

68. E. Wintermantel and H. Suk-Woo: 'Biokompatible Werkstoffe und Bauweisen (Biocompatible Material and Design)', *Springer Verlag*, 1998, **2**.

69. W. S. Pietrzak, D. Sarver, and M. Verstynen: 'Bioresorbable Implants - Practical Considerations', *Bone*, 1996, **19**(1, Supplement 1), S109-S119.

70. S. Vadapalli, K. Sairyo, V. K. Goel, M. Robon, A. Biyani, A. Khandha, and N. A. Ebraheim: 'Biomechanical rationale for using polyetheretherketone (PEEK) spacers for lumbar interbody fusion-A finite element study', *SPINE*, 2006, **31**(26), E992-998.

71. A. Tsantrizos, H. G. Baramki, S. Zeidman, and T. Steffen: 'Segmental stability and compressive strength of posterior lumbar interbody fusion implants', *Spine*, 2000, **25**(15), 1899-1907.

72. A. M. Rashmir-Raven, D. C. Richardson, H. M. Aberman, and D. J. D. Young: 'The response of cancellous and cortical canine bone to hydroxylapatite-coated and uncoated titanium rods', *Journal of Applied Biomaterials*, 1995, **6**(4), 237-242.

73. T. J. Blokhuis, M. Termaat, and H. J. Haarman: 'Properties of Calcium Phosphate Ceramics in Relation fo Their *In vivo* Behaviour', *The Journal of Trauma, Injury, Infection and Critical Care*, 2007, **48**.

74. B. Allan: 'Closer To Nature : New Biomaterials and Tissue Engineering', *British Journal of Opthamology*, 1999, **83**, 1235-1240.

75. C. R. Howlett, H. Zreiqat, R. O. Dell, J. Noorman, P. Evans, and B. A. Dalton: 'The effect of magnesium ion implantation into alumina upon the adhesion of human bone derived cells', *Journal of Material Science: Materials in Medicine*, 1994, **9**, 715.

76. L. Li, J. Gao, and Y. Wang: 'Evaluation of cyto-toxicity and corrosion behavior of alkali-heat-treated magnesium in simulated body fluid', *Surface and Coatings Technology*, 2004, **185**(1), 92-98.

77. H. Kuwahara, Y. Al-Abdullat, N. Mazaki, S. Tsutsumi, and T. Aizawa: 'Precipitation of Magnesium Apatite on Pure Magnesium Surface during Immersing in Hank's Solution', *Materials Transactions*, 2001, **42**(7), 1317-1321.

78. H. Y. Lopez, D. A. Cortes, S. Escobedo, and D. Mantovani: '*In vitro* Bioactivity Assessment of Metallic Magnesium', *Key Engineering Materials*, 2006, **309-311**, 453-456.

79. S. R. Kim, J. H. Lee, Y. T. Kim, D. H. Riu, S. J. Jung, Y. J. Lee, S. C. Chung, and Y. H. Kim: 'Synthesis of Si, Mg substituted hydroxyapatites and their sintering behaviors', *Biomaterials*, 2003, **24**(8), 1389-1398.

80. U. K. Mudali, B. Raj, and T. M. Sridhar: 'Corrosion of bio implants', *Sadhana - Academy Proceedings in Engineering Sciences*, 2003, **28**(3-4), 601-637.

81. D. A. Puleo and W. W. Huh: 'Acute toxicity of metal ions in cultures of osteogenic

cells derived from bone marrow stromal cells', *Journal of Applied Biomaterials*, 1995, **6**(2), 109-116.

82. D. Granchi, G. Ciapetti, S. Stea, L. Savarino, F. Filippini, A. Sudanese, G. Zinghi, and L. Montanaro: 'Cytokine release in mononuclear cells of patients with Co-Cr hip prosthesis', *Biomaterials*, 1999, **20**(12), 1079-1086.
83. O. E. M. Pholer: 'Failure of Orthopaedic Metallic Implants', in 'ASM Handbook on Failure Analysis and Prevention', 9 edn, 670; 1986, Metals Park, OH, ASM International.
84. F. W. Bach: 'Development of Biocompatible Magnesium Alloys and Investigation of the Degradation Behaviour', Sustainable Bioresorbable and Permanent Implants of Metallic and Ceramic Materials, Medical University of Hanover, 2006.
85. K. G. Davis, W. S. Marras, and T. R. Waters: 'Evaluation of spinal loading during lowering and lifting', *Clinical Biomechanics*, 1998, **13**(3), 141-152.
86. A. Lambotte: 'L'utilisation du magnesium comme materiel perdu dans l'osteosynthese', *Bull Mem Soc Nat Chir*, 1932, **28**, 1325-1334.
87. J. Verbrugge: 'Le Matériel Métallique Résorbable En Chirurgie Osseuse', *La Press Medicale*, 1934, **23**, 460-465.
88. H. Inoue, K. Sugahara, A. Yamamoto, and H. Tsubakino: 'Corrosion rate of magnesium and its alloys in buffered chloride solutions', *Corrosion Science*, 2002, **44**(3), 603-610.
89. F. Witte, N. Hort, C. Vogt, S. Cohen, K. U. Kainer, R. Willumeit, and F. Feyerabend: 'Degradable biomaterials based on magnesium corrosion', *Current Opinion in Solid State and Materials Science*, 2008, **12**(5-6), 63-72.
90. A. Meyer-Lindenberg, H. Windhugen, and F. Witte: 'US 200410241036.'.
91. R. Zeng, W. Dietzel, F. Witte, N. Hort, and C. Blawert: 'Progress and Challenge for Magnesium Alloys as Biomaterials', *Advanced Engineering Materials*, 2008, **10**(8), B3-B14.
92. D. Willliams: 'New Interests in Magnesium', *Medical Device Technology*, 2006, **17**(3), 9-10.