PERSPECTIVES

The RAPIDOS project—European and Chinese collaborative research on biomaterials

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Summary  The research project entitled “rapid prototyping of custom-made bone-forming tissue engineering constructs” (RAPIDOS) is one of the three unique projects that are the result of the first coordinated call for research proposals in biomaterials launched by the European Union Commission and the National Natural Science Foundation of China in 2013 for facilitating bilateral translational research. We formed the RAPIDOS European and Chinese consortium with the aim of applying technologies creating custom-made tissue engineered constructs made of resorbable polymer and calcium phosphate ceramic composites specifically designed by integrating the following: (1) imaging and information technologies, (2) biomaterials and process engineering, and (3) biological and biomedical engineering for novel and truly translational bone repair solutions. Advanced solid free form fabrication technologies, precise stereolithography, and low-temperature rapid prototyping provide the necessary control to create innovative high-resolution medical implants. The use of Chinese medicine extracts, such as the bone anabolic factor icaritin, which has been shown to promote osteogenic differentiation of stem cells and enhance bone healing in vivo, is a safe and technologically relevant alternative to the intensely debated growth factors delivery strategies. This unique initiative driven by a global consortium is expected to accelerate scientific progress in the important field of biomaterials and to foster strong scientific cooperation between China and Europe.

Background on the European Union—China joint project

The genesis

The launching of the biomaterials coordinated research call by the European Commission and the National Natural Science Foundation of China (NSFC) originated from the undertakings of European and Chinese scientists represented by the European Society for Biomaterials (2007–2013 president: Professor Luigi Ambrosio) and the Chinese Committee for Biomaterials (president: Professor Xingdong Zhang) together with the representatives of the respective funding agencies. Following initiatives such as the China—Europe Symposia on Biomaterials in Regenerative Medicine started in 2006, and held alternatively in Europe and China promoting collaboration between European and Chinese researchers and fostering the exchange of talent, trends in biomaterials research and applications were identified [1,2]. This collective endeavour targeted the enhancement of international collaboration in translational research and development where the needs to develop innovative biomaterial products for clinical applications in a truly international effort are desirable in order to reach the markets in a short to medium term [3,4].

Among the research directions that were expected to lead to consolidation and extension of the knowledge and competitiveness of Europe and China in biomaterials in regenerative medicine, rapid prototyping (RP) technology for custom-made scaffolds was recognised for its strong potential. This led to the first coordinated call for research proposals in biomaterials by the European Commission and the NSFC, launched in 2013 [5,6].

The call

The proposed call from the European Union (EU) commission was entitled "Biomaterials: imaging and rapid precise prototyping technology for custom made scaffolds" [7].

The expected impacts were targeting the development of technologies for the production of custom-made structures for the repair or regeneration of human tissues, and the improved manufacturing and performance of custom-made scaffolds for tissue repair or regeneration in the medium to long term. Additionally, a more robust European–Chinese research cooperation as well as successful joint research activities, publications, contributions to scientific events, and more intensive exchange and training of researchers were anticipated.

Formation of the RAPIDOS consortium

History of a successful application

The 9th World Biomaterials Congress organised in Chengdu, China, during the summer of 2012, which attracted biomaterial scientists from around the globe, was a catalyst for the project genesis on biomaterials—imaging and rapid precise prototyping technology for custom-made scaffolds—as most of the partners to be united in this single location. Back from the world congregation, e-mail exchanges and discussion between the initial groups were started for the definition of an exciting research project and integration of partners with complementary expertise (Fig. 1). The proposals were submitted in October 2012 to the European Commission and the NSFC. The project was positively evaluated in February 2013 and effectively started on 1 July 2013 for both Chinese and
Bone is a biological tissue with a robust capacity to heal and regenerate. Indeed, most bone fractures will, when appropriately treated, heal without any complication. However, there are still numbers of cases when the current surgical techniques together with bone grafts such as the autologous bone gold standard graft are insufficient. Examples of such impaired bone regeneration are large trauma with infections (e.g., road accidents) and bone metabolic disorders including avascular necrosis [9,10]. In March 2010, the United Nations General Assembly proclaimed the period 2011–2020 as the Decade of Action for Road Safety [11]. Road traffic injuries kill nearly 1.3 million people annually. If current trends continue, road crashes are predicted to rise from ninth leading cause of death to fifth by 2030. About 50 million individuals sustain nonfatal injuries that represent an important cause of disability worldwide. Road traffic injuries are the leading cause of death among young people, aged between 15 and 29. Until recently, the extent of the road safety situation around the world was unclear. In 2009, the World Health Organization published the global status report on road safety as the first assessment of the road safety situation at the global level.

Bone is the most often transplanted tissue after blood, and the need for bone graft substitute materials is enormous. Worldwide, the number of bone grafts used in surgical procedures has been estimated at more than 24 million in 2010. About one-third represents the European market, whereas the total Asian markets (China and India) for bone graft substitutes and other biomaterials increased by 53.2% from 2009 to 2010. The bone graft sales are forecasted to reach a total of $3.3 billion worldwide in 2017 [12]. Therefore, the global increase of needs for bone graft substitutes and emergence of large healthcare providers in Asia support the necessities for better bone repair solutions based on biomaterial scaffolds.

Among the pertinent nonhealing bone fractures, the region of the head is a major target for development of precise custom-made bone constructs. In craniomaxillofacial surgery, large blow-out orbital floor fractures have still mitigated outcomes, and improved scaffold solutions are needed [13]. The reconstruction of large bone defects in proximal femur or proximal tibia in orthopaedic trauma surgery is also an enormous challenge for biomaterial devices owing to the requirements for both complex shape and partial load-bearing ability, but also because of the risk of incidence of steroid-associated osteonecrosis or infection, which may exceed 30% for large open fractures [14].

Biomaterials and bone Tissue Engineering (TE) have failed until now in facilitating reliable bone repair [15]. The technical issues for the engineering of a scaffold for bone TE are as follows: (1) fabrication of biomaterial scaffolds with anatomical fit of complex three-dimensional (3D) large bone defects; (2) fabrication of biomaterials with adequate mechanical and structural stability/degradation kinetics; (3) controlling the behaviour (adhesion, proliferation, differentiation, and matrix remodelling) of cells and tissues at the interface with biomaterials; and (4) fabrication of biomaterials with optimised macroarchitecture for improved mass transport and perfusion for delivery of biological effectors. These effectors could be antibacterial agents [e.g., magnesium (Mg)] compounded with the biomaterials to decrease infection in large trauma due to road traffic accidents, growth factors, nutrients, or other cells.
However, the main desirable biological capacities of a biomaterial scaffold for bone are osteoconductivity, osteoinductivity, and osteogenicity. Calcium phosphate (CaP) ceramics and incorporated growth factors can provide these properties [16,17]. The use and efficacy of growth factor containing bone graft substitutes (e.g., Infuse; recombinant human bone morphogenetic protein-2 or rhBMP-2) is intensely debated nowadays [18], and use of Chinese medicine extracts such as the bone anabolic compound icaritin, which has been shown to promote osteogenic differentiation of stem cells and enhance bone healing in vivo, is a promising alternative [19,20].

For bone repair, patient-specific tissue engineered biomaterials can address several drawbacks of the current orthopaedic devices: optimised shape for best cosmetic, mechanical and anatomical stability, no thermosensitivity associated with the use of metallic implants, optimised internal architecture in accordance to the delivered biological effectors (e.g., cells, antibacterial agent, Chinese medicine extract, magnesium), and mass transport for vascularisation and bone ingrowth. However, there are also other clinical considerations to be taken into account. Definitely, a macroscopic precision above 0.5 mm for the considered biomaterial scaffolds is unnecessary for bone repair as surgeons would not be able to achieve construct positioning with a better accuracy in challenging surgical situations [21]. Additionally, clinical available 3D imaging instruments [e.g., computed tomography (CT)] have a precision not lower than 0.2 mm, and sometimes precision less than 0.4 mm can be achieved, like in the orbit. Hence, the clinical focus is necessary to achieve real and relevant progresses toward fitting custom-made biomaterial products.

A high resolution for scaffold TE is needed to create biomaterial scaffolds with correct external shape, adequate mechanical and resorption properties, and optimised internal architecture and biofunctionalities in combination with a clinically relevant cell source: human mesenchymal stromal cells (hMSCs) in the case of this consortium. Advanced solid free form fabrication, also called rapid prototyping, could provide the necessary control to create such innovative medical devices. Stereolithography (SLA) offers the high resolution necessary to create controlled architecture and anatomically well-fitting devices. The low-temperature rapid prototyping (LT-RP) is a unique technique in its ability to incorporate temperature-sensitive active compounds into the scaffolds [19,22,23].

Thus, the goal of this European and Chinese consortium is to apply RP technologies to create custom-made tissue engineered biomaterial constructs by integrating (1) imaging and information technologies, (2) biomaterials and process engineering, and (3) biological and biomedical engineering for novel and truly translational bone repair solutions [24].

There are major challenges to our approaches [25]. First, we need to integrate patient-specific clinical images together with relevant architecture design for optimal mass transport and delivery of biological stimuli (hMSCs and icaritin) and develop a valid surgical procedure. Second, we need to develop adequate biomaterial composites with controlled nanostructure and precise scaffold fabrication techniques. Third, it is necessary to create adaptive and biologically active TE constructs through the addition of osteogenic biological stimuli such as hMSCs isolated from the patient bone marrow (endogenous growth factor) and/or small anabolic molecule extract from Chinese medicine (e.g., icaritin). Finally, we need to combine all of the above advanced stages for the delivery and possibly product registration of the custom-made biomaterial tissue-engineered construct.

Concept and objectives of the RAPIDOS project

Imaging custom-made scaffold design

Image processing software and computer graphic technologies can now be semiautomated to provide radiologists and surgeons with tools to analyse clinical imaging data such as CT images and exploit this original dataset to create, for example, a 3D stereolithographic model of an implant that can be transferred as a set of coordinates for the printing system to create a custom-made scaffold implant (Fig. 2). In this consortium, we will develop a computer workflow based on clinical CT data in which it is envisioned that the surgeons will have an interactive tool to decide which scaffold implant design is suitable for the reconstruction of the bony defect with taking into account boundaries such as the biomaterials’ mechanical properties and fabrication parameters.

Biomaterials

A poly(trimethylene carbonate) (PTMC)-based resin will be used in combination with osteoinductive CaP [i.e., biphasic calcium phosphate (BCP)] particles for the preparation of the SLA scaffold. PTMC resins can be prepared and photocrosslinked to form a solid material [26,27]. PTMC is an amorphous polymer with a relatively low elastic modulus of 5–7 MPa at room temperature. PTMC degrades enzymatically in vivo via a surface erosion process without the formation of acidic degradation products [28,29]. The polymer has not been shown to calcify or lead to the formation of new bone upon implantation. However, its combination with BCP provides osteoinductive properties to the scaffold as the blended BCP becomes exposed upon in vivo degradation of the PTMC matrix. Moreover, the combination of bone anabolic icaritin loaded polymeric microspheres or nanofibres prepared from poly(lactic acid) (PLA) or poly(lactic-co-glycolic acid) (PLGA) within the PTMC resin will provide additional biofunctionality to the scaffold through the sustained release of the Chinese medicine extract provided by the Chinese partners [30,31]. In addition, such polyester fibres will strengthen the mechanical properties of the resulting polymer–polymer composites, owing to the high modulus of PLA and derivatives. The nanofibres will also provide a simple mean to texture the interface of the composites, which is a well-established factor impacting on cell adhesion and bone engineering [32,33]. PLGA/PLA composites will be the alternative biomaterial compositions for the direct comparison of several RP technologies. PLGA and CaP [i.e., tricalcium phosphate (TCP)] particles will be combined to form osteoinductive scaffolds. PLGA is
Furthermore, Chinese partners have synthesised a new biodegradable and bioactive ceramics has been shown to overcome: cell support structures with predetermined architectures can be prepared that not only precisely fit a (bone) defect, but also create accurate macrostructures down to a cell size (~20 \( \mu \text{m} \)) [49]. It has already been shown that scaffolds prepared via SLA fabrication can have adaptable mechanical stiffness and permeability that, in turn, can stimulate mesenchymal stromal cell (MSC) responses and potentially promote faster bone tissue regeneration [50]. LT-RP technology will be used and developed to yield biological effectors (e.g., cells, antibacterial agent, Chinese medicine extract, magnesium) incorporated into PLGA/TCP scaffolds by the Chinese partners (Fig. 2) [51]. PTMC/CaP composites prepared by LT-RP with a different degradation profile compared to PLGA/CaP will be prepared for direct comparison to the planned European study using SLA fabrication [52].

**RP technologies**

In our consortium, high-resolution SLA will be used and developed by the EU partners (Fig. 2). It is a precise RP manufacturing method, in which objects are constructed in a layer-by-layer fashion by photopolymerisation [48]. By using SLA to directly prepare the TE scaffolds, the drawbacks of conventional scaffold preparation methods can be overcome: cell support structures with predetermined architectures can be prepared that not only precisely fit a (bone) defect, but also create accurate macrostructures down to a cell size (~20 \( \mu \text{m} \)) [49]. It has already been shown that scaffolds prepared via SLA fabrication can have adaptable mechanical stiffness and permeability that, in turn, can stimulate mesenchymal stromal cell (MSC) responses and potentially promote faster bone tissue regeneration [50]. LT-RP technology will be used and developed to yield biological effectors (e.g., cells, antibacterial agent, Chinese medicine extract, magnesium) incorporated into PLGA/TCP scaffolds by the Chinese partners (Fig. 2) [51]. PTMC/CaP composites prepared by LT-RP with a different degradation profile compared to PLGA/CaP will be prepared for direct comparison to the planned European study using SLA fabrication [52].

**Tissue engineering for bone repair**

This consortium aims to modulate and control the biological response of hMSCs seeded into scaffolds via (1) the optimisation of the scaffold architecture and (2) biofunctionality (icarin and Mg-loaded microspheres and particles). The anti-infection and antibacterial effects of PLGA/TCP/Mg and HACC incorporated into PLGA/TCP scaffolds will also be investigated. This specific objective will be coordinated with the Chinese partners to develop common experimental protocols in order to standardise the evaluation of the biological performance of the prepared TE constructs. Typically, MSC seeding efficiency, proliferation, alkaline phosphatase activity, osteogenic differentiation, calcium deposition in several scaffold architectures, PTMC/CaP (and PLGA/TCP) compositions and in the presence of icarin and Mg-loaded microcarbons at different concentrations will be assessed. The final goal will be the selection of scaffold characteristics (e.g., porosity, pore size and design, mechanics) that allow for improved cell response. Then, the *in vivo* assessment of the selected candidate custom-made bone TE construct(s) will be performed in a relevant preclinical model in parallel by the European and Chinese partners.
In vivo efficacy investigation will be designed to evaluate osteogenesis, for example, in a bilateral ulna bone segmental defect model implanted with composite scaffold in rabbits, with radiography and in vivo micro-CT for studying new bone regeneration and histology for host tissue and scaffold material interactions. Finally, a large animal pilot study has been performed to assess the whole chain of concepts from imaging to bone TE in order to demonstrate clinical feasibility of the custom-made biomaterial scaffold-based therapy prior to clinical testing.

Impact and perspectives on the RAPIDOS project

To date, a clinical CT imaging process technology workflow for the development of anatomically relevant and precise custom-made macrostructured designed scaffolds has been created. The goal of this workflow is to allow the surgeons to design and self-assess patient-specific implants taking into account the constraints of the biomaterial and fabrication process. The optimisation of composite formulations—poly(trimethylcarbonate)/CaP and PLGA/TCP/Mg for SLA and low-temperature rapid manufacturing, respectively—is well advanced, and already composite scaffolds can be fabricated via both SLA and LT-RP. PLA nanofibres loaded with icaritin have been prepared for incorporation into the photopolymerisable resin formulation for SLA. In vitro and in vivo studies have shown the osteopromotive effect of icaritin loaded into scaffolds, and magnesium was shown to influence biofilm formation onto the surface of PLGA/TCP/Mg scaffolds. We expect the combined approach of the project to give rise to additional and multiple innovations to be exploited by the networks of partners.

Finally, we hope that through our (EU–China) collaboration, we can advance therapeutic solutions to ease suffering from nonhealing bone fractures/defects in the future and help achieve faster patient recovery through the development of custom-made implant and patient-specific therapy.

Conflicts of interest

The authors have no conflicts of interest to declare.

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References

[1] European Society for Biomaterials. Available at: http://www.esbiomaterials.eu [accessed 11.12.14].

[2] Chinese Society for Biomaterials. Available at: http://www.csbm.org.cn [accessed 11.12.14].

[3] Qin L. Translation medicine in orthopedics (Editorial). J Orthop Transl 2013;1:1–5.

[4] Bian L, Mak AFT, Wu C, Cheng C, Gu Z, Zhang X, et al. A Model for facilitating translational research and development in China: call for establishing Hong Kong Branch of Chinese National Engineering Research Centre for Biomaterials. J Orthop Transl 2014;2:170–6.

[5] European Research Commission. Available at: http://cordis.europa.eu [accessed 11.12.14].

[6] National Natural Science Foundation of China. Available at: http://www.nsfc.gov.cn [accessed 11.12.14].

[7] RAPIDOS project description (European Commission web site). Available at: http://cordis.europa.eu/project/rcn/108972_en.html [accessed 11.12.14].

[8] RAPIDOS. Available at: http://www.rapidos-project.eu [accessed 11.12.14].

[9] Darouiche RO. Treatment of infections associated with surgical implants. New Engl J Med 2004;350:1422–9.

[10] Steinberg ME. Core decompression of the femoral head for avascular necrosis: indications and results. Can J Surg 1995;38:518–24.

[11] Ki-moon B. United Nations Decade of Action for Road Safety 2011–2020. Available at: http://www.un.org/en/roadsafety/2011 [accessed 11.12.14]. p. http://www.un.org/en/roadsafety/.

[12] Medipoint Bone Grafts and Substitutes — EU Analysis and Market Forecasts. Medipoint; 2014. p. 1–185. Available at: http://www.reportlinker.com/p02027473-summary/Medi-Point-Bone-Grafts-and-Substitutes-EU-Analysis-and-Market-Forecasts.html.

[13] Giannoudis PV, Dinopoulos H, Tsiridis E. Bone substitutes: an update. Injury 2005;36:520–7.

[14] Trampuz A, Widmer AF. Infections associated with orthopedic implants. Curr Opin Infect Dis 2006;19:349–56.

[15] Hollister SJ, Murphy WL. Scaffold translation: barriers between concept and clinic. Tissue Eng B Rev 2011;17:459–74.

[16] Xiao C, Zhou H, Ge S, Tang T, Hou H, Luo M, et al. Repair of orbital wall defects using biocoral scaffolds combined with bone marrow stem cells enhanced by human bone morphogenetic protein-2 in a canine model. Int J Mol Med 2010;26:157–25.

[17] Yuan H, Fernandes H, Habibovic P, de Boer J, Barradas AM, de Ruiter A, et al. Ostoeinductive ceramics as a synthetic alternative to autologous bone grafting. Proc Natl Acad Sci U S A 2010;107:13614–9.

[18] Carragee EJ,Hurwitz EL,Weiner BK. A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned. Spine J 2011;11:471–91.

[19] Wang XL, Xie XH, Zhang G, Chen SH, Yao D, He K, et al. Exogenous phytoestrogenic molecule icaritin incorporated into a porous scaffold for enhancing bone defect repair. J Orthop Res 2013;31:164–72.

[20] Huang J, Yuan L, Wang X, Zhang TL, Wang K. Icaritin and its glycosides enhance osteoblastic, but suppress osteoclastic, differentiation and activity in vitro. Life Sci 2007;81:832–40.

[21] D’Haese J, Van De Velde T, Komiyama A, Hultin M, De Bruyn H. Accuracy and complications using computer-designed stereolithographic surgical guides for oral rehabilitation by means of dental implants: a review of the literature. Clin Implant Dent Rel Res 2012;14:321–35.

[22] Xie XH, Wang XL, Zhang G, He YX, Wang XH, Liu Z, et al. Structural and degradation characteristics of an innovative porous PLGA/TCP scaffold incorporated with bioactive molecular icaritin. Biomed Mater 2010;5:054109.
[23] Chen S-H, Zheng L-Z, Xie X-H, Wang X-L, Lai Y-X, Chen S-K, et al. Comparative study of PLGA/TCP scaffolds incorporated or coated with osteogenic growth factors for enhancement of bone regeneration. J Orthop Transl 2014;2:91–104.

[24] Sun W, Darling A, Starly B, Nam J. Computer-aided tissue engineering: overview, scope and challenges. Biotechnol Appl Biochem 2004;39:29–47.

[25] Kim K, Yeatts A, Dean D, Fisher JP. Stereolithographic bone scaffold design parameters: osteogenic differentiation and signal expression. Tissue Eng B Rev 2010;16:523–39.

[26] Jin QM, Takita H, Kohgo T, Atsumi K, Itoh H, Kuboki Y. Effects of geometry of hydroxyapatite as a cell substratum in BMP-induced ectopic bone formation. J Biomed Mater Res 2000;52:491–9.

[27] van Leeuwen AC, Bos RR, Grijpma DW. Composite materials based on poly(trimethylene carbonate) and beta-tricalcium phosphate for orbital floor and wall reconstruction. J Biomed Mater Res B Appl Biomater 2012;100:1610–20.

[28] Schuller-Ravoo S, Feijen J, Grijpma DW. Preparation of flexible and elastic poly(trimethylene carbonate) structures by stereolithography. Macromol Biosci 2011;11:1662–71.

[29] Pego AP, Van Luyn MJ, Brouwer LA, van Wachem PB, Poot AA, Grijpma DW, et al. In vivo behavior of poly(1,3-trimethylene carbonate) and copolymers of 1,3-trimethylene carbonate with d,l-lactide or epsilon-caprolactone: degradation and tissue response. J Biomed Mater Res A 2003;67:1044–54.

[30] Zhang Z, Grijpma DW, Feijen J. Trimethylene carbonate-based polymers for controlled drug delivery applications. J Control Rel 2006;116:e28–9.

[31] Zhang Z, Grijpma DW, Feijen J. Poly(trimethylene carbonate) and monomethoxy poly(ethylene glycol)-block-poly(trimethylene carbonate) nanoparticles for the controlled release of dexamethasone. J Control Rel 2006;111:263–70.

[32] Gautrot JE, Malmstrom J, Sundh M, Margadant C, Sonnenberg A, Sutherland DS. The nanoscale geometrical maturation of focal adhesions controls stem cell differentiation and mechanotransduction. Nano Lett 2014;14:3945–52.

[33] Biggs M, Jonathan P, Richards RG, Dalby MJ. Nanotopographical modification: a regulator of cellular function through focal adhesions. Nanomed Nanotechnol Biol Med 2010;6:619–33.

[34] Kai H, Wang X, Madhukar KS, Qin L, Yan Y, Zhang R, et al. Fabrication of a two-level tumor bone repair biomaterial based on a rapid prototyping technique. Biofabrication 2009;1:025003.

[35] Pan Z, Ding J. Polylactide-co-glycolide) porous scaffolds for tissue engineering and regenerative medicine. Interface Focus 2012;2:366–77.

[36] Ge Z, Tian X, Heng BC, Fan V, Yeo JF, Cao T. Histological evaluation of osteogenesis of 3D-printed polylactide-co-glycolic acid (PLGA) scaffolds in a rabbit model. Biomed Mater 2009;4:025001.

[37] Bostman O, Hirvensalo E, Vainionpaa S, Makela A, Vihtonen K, Tormala P, et al. Ankle fractures treated using biodegradable internal fixation. Clin Orthop Rel Res 1989:195–203.

[38] Wang D-X, He Y, Bi L, Qu Z-H, Zou J-W, Pan Z, et al. Enhancing the bioactivity of polylactide-co-glycolic acid scaffold with a nano-hydroxyapatite coating for the treatment of segmental bone defect in a rabbit model. Int J Nanomed 2013;8:1855–65.

[39] Ehrenfried LM, Patel MH, Cameron RE. The effect of tricalcium phosphate (TCP) addition on the degradation of polylactide-co-glycolide (PLGA). J Mater Sci Mater Med 2008;19:459–66.

[40] Liu G, Zhao L, Cui L, Liu W, Cao Y. Tissue-engineered bone formation using human bone marrow stem cells and novel beta-tricalcium phosphate. Biomed Mater 2007;2:78–86.

[41] Chen SH, Wang XL, Xie XH, Zheng LZ, Yao D, Wang DP, et al. Comparative study of osteogenic potential of a composite scaffold incorporating either endogenous bone morphogenetic protein-2 or exogenous phytomolecule icaritin: an in vitro efficacy study. Acta Biomater 2012;8:3128–37.

[42] Li J, Song Y, Zhang S, Zhao C, Zhang F, Zhang X, et al. In vitro responses of human bone marrow stromal cells to a fluoridated hydroxyapatite coated biodegradable Mg–Zn alloy. Biomaterials 2010;31:5782–8.

[43] Janning C, Willbold E, Vogt C, Nellesen J, Meyer-Lindenberg A, Windhagen H, et al. Magnesium hydroxide temporarily enhancing osteoblast activity and decreasing the osteoclast number in peri-implant bone remodelling. Acta Biomater 2010;6:1861–8.

[44] Yang C, Yuan G, Zhang J, Tang Z, Zhang X, Dai K. Effects of magnesium alloys extracts on adult human bone marrow-derived stromal cell viability and osteogenic differentiation. Biomater 2010;5:045005.

[45] Witte F, Kaese V, Haferkamp H, Switzer E, Meyer-Lindenberg A, Wirth CJ, et al. In vivo corrosion of four magnesium alloys and the associated bone response. Biomaterials 2010;26:3557–63.

[46] Wu F, Wei J, Guo H, Chen F, Hong H, Liu C. Self-setting bioactive calcium-magnesium-phosphate cement with high strength and degradability for bone regeneration. Acta Biomater 2008;4:1873–84.

[47] Tan HL, Lin WT, Tang TT. The use of antimicrobial-impregnated PMMA to manage periprosthetic infections: controversial issues and the latest developments. Int J Artif Organs 2012;35:832–9.

[48] Peitola SM, Melchels FP, Grijpma DW, Kellomaki M. A review of rapid prototyping techniques for tissue engineering purposes. Ann Med 2008;40:268–80.

[49] Melchels FP, Feijen J, Grijpma DW. A review on stereolithography and its applications in biomedical engineering. Biomaterials 2010;31:6121–30.

[50] Kim K, Dean D, Wallace J, Breithaupt R, Mikos AG, Fisher JP. The influence of stereolithographic scaffold architecture and composition on osteogenic signal expression with rat bone marrow stromal cells. Biomaterials 2011;32:3750–3.

[51] Liao H, Walboomers XF, Habraken WJ, Zhang Z, Li Y, Grijpma DW, et al. Injectable calcium phosphate cement with PLGA, gelatin and PTMC microspheres in a rabbit femoral defect. Acta Biomater 2011;7:1752–9.

[52] Zeng N, van Leeuwen A, Yuan H, Bos RR, Grijpma DW, Kuiper R. Evaluation of novel resorbable membranes for bone augmentation in a rat model. Clin Oral Implants Res 2014;7. http://dx.doi.org/10.1111/cior.12519.