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The Research Grants Council of Hong Kong
NSFC/RGC Joint Research Scheme
Joint Completion Report

(Please attach a copy of the completion report submitted to the NSFC by the Mainland researcher)

Part A: The Project and Investigator(s)

1. Project Title

Study of the degradation behavior and osteogenic effects of Mg-Si based biodegradable materials

2. Investigator(s) and Academic Department/Units Involved

	Hong Kong Team	Mainland Team
Name of Principal Investigator *(with title)*	Prof. Kenneth M. C. Cheung	Prof. Yufeng Zheng
Post	Head & Clinical Prof	Professor
Unit / Department / Institution	Dept. of Ortho and Trauma HKU	Dept. of Materials Sci and Eng PKU
Contact Information	cheungmc@hku.hk	yfzheng@pku.edu.cn
Co-investigator(s) *(with title and institution)*	Prof. Kelvin W.K. Yeung, Dr. Karen H.M. Wong, HKU	Dr. Yan Cheng, Dr. Huafang Li, Ms. Wenting Li, PKU

3. Project Duration

	Original	Revised	Date of RGC/ Institution Approval *(must be quoted)*
Project Start date	1-1-2017	N/A	
Project Completion date	31-12-2020	N/A	
Duration *(in month)*	48	N/A	
Deadline for Submission of Completion Report		N/A	

Part B: The Completion Report

5. Project Objectives

5.1 Objectives as per original application

1. To fabricate and characterize the material and mechanical properties of magnesium-silicon (Mg-Si) based biomaterials e.g. micro-structure, hardness, corrosion behaviors and degradation rate etc. (by mainland team);
2. To systematically evaluate the toxicity, bioactivity and bio-functional properties e.g. osteoconductivity and osteoinductivity of the newly fabricated Mg-Si based biomaterials by using *in vitro* approaches (by HK team);

3. To comprehensively investigate the *in vivo* biological response (i.e. biomaterial degradation under *in vivo* condition, the ability of new bone formation under the influence of degradation products, tissue inflammatory etc.) of the new biomaterials by using established animal models (by HK Team).

5.2 Revised Objectives
Not applicable

6. Research Outcome

Major findings and research outcome
(maximum 1 page; please make reference to Part C where necessary)

The biomedical research reveals that the essential elements of human body, calcium (Ca), magnesium (Mg), silicon (Si), zinc (Zn) and strontium (Sr) play important roles during the mineralization, growth and vascularization of bone tissues. In the previous study on magnesium alloys, metallic elements Ca, Zn and Sr had been widely used as alloying elements for Mg, whereas non-metallic element, e.g., Si, was not the choice basically. Indeed, the osteogenic tendency of Si has been proven by a number of studies. Hence, our study aims to develop a series of biodegradable Mg-Si based biomaterials such as Mg-Si, Mg-Si-Ca, Mg-Si-Sr, Mg-Si-Zn, Mg-Si-Ca-Sr, Mg-Si-Ca-Zn, Mg-Si-Sr-Zn for bone surgery. In this study, we had investigated their microstructures, mechanical properties, *in vitro* and *in vivo* biodegradation behavior, biocompatibility and the ability to induce local bone formation. We discovered that the addition of Si in 0.2wt% and Ca in 1.0wt% in Mg matrix could significantly increase the mechanical strength and bio-adaptability of Mg-Si alloy. The addition of these two elements (Ca and Si) would accelerate the formation of a self-assembled, multilayered implant–tissue interface, which coordinated its biodegradation with the bone healing process. At the initial stage of implantation, a burst release of Mg^{2+} from Mg-Si-Ca alloy activated the monocyte-macrophage lineage, leading to an immune microenvironment favoring the recruitment of mesenchymal stem cells (MSCs) and initiation of osteogenic differentiation. With the formation of the biomimicking calcified matrix at the degrading bone–implant interface, the ion release kinetics of the Mg-Si-Ca alloy was turned down, leading to a new peri-implant microenvironment for osseointegration and osteogenesis by targeting the integrin signaling pathways in MSCs.
For the other Mg-Si based ternary alloys, Mg-0.2Si-1.0Sr could also significantly promote bone repair after implantation. Particularly, when its degradation completed, the cancellous bone adjacent to the implant in terms of bone mass and bone density had dramatically increased. We also observed that the degradation products from Mg-0.2Si-2.0Zn alloy might help thicken the cortical bone. We believed that the osteogenic mechanism could attribute to the release of magnesium ions, zinc ions and silicon ions in bone tissue microenvironment. The released cations altered the local bone

tissue microenvironment that might stimulate the NF-κB signaling pathway of macrophages. The activated macrophages then released a various of inflammatory factors, especially IL-1ra, CCL5 and IL-8, that could promote the proliferation and differentiation of osteoblasts. At the same time, the combined cations including Mg^{2+}, Si^{2+}, Zn^{2+} would significantly inhibit the expression of pro-inflammatory cytokines (M-CSF, IL-1β and IL-6) that might reduce osteoclast differentiation. For the Mg-Si quaternary alloys, we also identified that Mg-0.2Si-0.5Ca-0.5Sr, Mg-0.2Si-1.0Ca-2.0Zn and Mg-0.2Si-1.0Sr-2.0Zn alloys presented comparable biocompatibility *in vitro* and *in vivo*. However, they were not as good as other Mg-Si based ternary alloys.

Further details of these experimental data can be found in the publication list in Part C.

Potential for further development of the research and the proposed course of action *(maximum half a page)*

With the current research outcomes, we are still unable to address the long-term safety issue of these new biogradable metals that may require by the medical device registration authority such as China FDA. Hence, the next stage of work will be studying the long-term in vivo study by using large animal models in order to fulfill the requirements of product registration. Once we finish all the *in vivo* studies, we plan to submit another proposal with potential industrial partners in order to carry out human clinical trial.

7. The Layman's Summary

(describe in layman's language the nature, significance and value of the research project, in no more than 200 words)

Patients with bone fracture or deformity are commonly treated by surgical intervention and fixation implants made of titanium alloys and 316L medical grade stainless steel. These implants are no longer useful to the patient following bone healing. If left inside the human body, the implant can potentially increase the stress-shielding effect at the bone-implant interface, eventually resulting in bone loss at the junction and failure of fixation. For this reason, the development of a biodegradable metal, e.g, magnesium (Mg), for bone fracture fixation is a desirable advance. Our works have demonstrated that some trace elements (e.g. calcium (Ca), zinc (Zn) and strontium (Sr), as well as silicon (Si) incorporated into Mg substrate) can enhance implant mechanical properties, while the these bioactive elements are able to induce the osteogenic differentiation and mineralization of bone cells, and to the growth and vascularization of bony tissue. The promising outcomes may help revolutionize the future development of orthopaedic implants, benefiting patients worldwide and eliminating the risks of a metallic implant left inside the body or the need to have further surgery to remove it.

Part C: Research Output

8. Peer-reviewed journal publication(s) arising directly from this research project

(Please attach a copy of each publication and/or the letter of acceptance if not yet submitted in the previous progress report(s). All listed publications must acknowledge RGC's funding support by quoting the specific grant reference.)

The Latest Status of Publications				Author(s) (*bold the authors belonging to the project teams and denote the corresponding author with an asterisk**)	Title and Journal/ Book (*with the volume, pages and other necessary publishing details specified*)	Submitted to RGC (*indicate the year ending of the relevant progress report*)	Attached to this report (*Yes or No*)	Acknowledged the support of this Joint Research Scheme (*Yes or No*)	Accessible from the institutional repository (*Yes or No*)
Year of publication	Year of Acceptance (*For paper accepted but not yet published*)	Under Review	Under Preparation (*optional*)						
2017				Wenhao WANG, **Kelvin W.K. YEUNG***	Bone Grafts and Biomaterials Substitutes for Bone Defect Repair: A review. ***Bioactive Materials***, 2(2017):	Yes, 2019	No	Yes	
2018				Zhengjie Lin, Jun Wu, Wei Qiao, Ying Zhao, **Karen H. M. Wong,** Paul K. Chu, Liming Bian, Shuilin Wu, **Yufeng Zheng, Kenneth M. C. Cheung,** Frankie Leung, **Kelvin W.K. Yeung***	Precisely controlled delivery of magnesium ions thru sponge-like monodisperse PLGA/nano-MgOalginate core-shell microsphere device to enable insitu bone regeneration. ***Biomaterials***, vol.174, pp.1-16, May 2018.	Yes, 2019	No	Yes	

2018				Pan Xiong; Zhaojun Jia; Ming Li; Wenhao Zhou; Jianglong Yan; Yuanhao Wu; **Yan Cheng***; **Yufeng Zheng***	Biomimetic Ca SrP-Doped Silk Fibroin Films on Mg-1Ca Alloy with Dramatic Corrosion Resistance and Osteogenic Activities. ***ACS Biomaterials Science & Engineering***, 2018.8.13, 4(9)	Yes, 2019	No	Yes	
2018				Bian, Dong ; Deng, Jiuxu; Li, Nan; Chu, Xiao; Liu, Yang; **Li, Wenting**; Cai, Hong; Xiu, Peng; Zhang, Yu; Guan, Zhen peng; **Zheng, Yufeng***	In Vitro and in Vivo Studies on Biomedical Magnesium Low-Alloying with Elements Gadolinium and Zinc for Orthopedic Implant Applications, ***ACS Applied Materials & Interfaces***, 2018.02.07, 10(5)	Yes, 2019	No	Yes	

2017				Bian D., Zhou W., Deng J., Liu Y., **Li W.,** Chu X., Xiu P., Cai H., Kou Y., Jiang B.*, **Zheng Y.***	Development of magnesium-based biodegradable metals with dietary trace element germanium as orthopaedic implant applications, ***Acta Biomaterialia***,2017. 12,64	Yes, 2019	No	Yes	
2018				Jinhua Li, Jin Wen, Bin Li, Wan Li, Wei Qiao, Jie Shen, Weihong Jin, Xinquan Jiang, **Kelvin W K Yeung**, Paul K Chu	Valence State Manipulation of Cerium Oxide Nanoparticles on a Titanium Surface for Modulating Cell Fate and Bone Formation, ***Advanced Science***, 2018, 5(2), 1700678	Not yet	Yes	Yes	

2018				Wei Liu, Jinhua Li, Mengqi Cheng, Qiaojie Wang, **Kelvin W. K. Yeung**, Paul K. Chu, Xianlong Zhang	Zinc-Modified Sulfonated Polyetheretherketone Surface with Immunomodulatory Function for Guiding Cell Fate and Bone Regeneration, ***Advanced Science***, 2018, 5(10), 1800749	Not yet	Yes	Yes	
2019				Zhengjie Lin, Shuilin Wu, Xuanyong Liu, Shi Qian, Paul K. Chu, **Yufeng Zheng**, **Kenneth M.C. Cheung**, Ying Zhao, **Kelvin W.K. Yeung**	A surface-engineered multifunctional TiO2 based nano-layer simultaneously elevates the corrosion resistance, osteoconductivity and antimicrobial property of a magnesium alloy, ***Acta Biomaterialia***, 2019, 99, 495	Not yet	Yes	Yes	

2019				Yizhou Zhu, Xiangmei Liu, Jun Wu, Tak Man Wong, Xiaobo Feng, Cao Yang, Shuilin Wu, **Yufeng Zheng**, Xuanyong Liu, **Kenneth M C Cheung, Kelvin W K Yeung**	Micro- and Nanohemispherical 3D Imprints Modulate the Osteogenic Differentiation and Mineralization Tendency of Bone Cells, ***ACS Applied Materials and Interfaces***, 2019, 11, 35513	Not yet	Yes	Yes	
2019				Wei Liu, Jinhua Li, Mengqi Cheng, Qiaojie Wang, Yebin Qian, **Kelvin W K Yeung**, Paul K Chu, Xianlong Zhang	A surface-engineered polyetheretherketone biomaterial implant with direct and immunoregulatory antibacterial activity against methicillin-resistant Staphylococcus aureus, ***Biomaterials***, 2019, 208, 8	Not yet	Yes	Yes	

2019				Zhengjie Lin, Ying Zhao, Paul K Chu, Luning Wang, Haobo Pan, **Yufeng Zheng**, Shuilin Wu, Xuanyong Liu, **Kenneth M C Cheung**, Takman Wong, **Kelvin W K Yeung**	A functionalized TiO2/Mg2TiO4 nano-layer on biodegradable magnesium implant enables superior bone-implant integration and bacterial disinfection, ***Biomaterials***, 2019, 219, 119372	Not yet	Yes	Yes	
2020				Yiming Xianga, Qilin Zhou, Zhaoyang Li, Zhenduo Cui, Xiangmei Liu, Yanqin Liang, Shengli Zhu, **Yufeng Zheng**, **Kelvin Wai Kwok** Yeung, Shuilin Wu	A Z-scheme heterojunction of ZnO/CDots/C3N4 for strengthened photoresponsive bacteria-killing and acceleration of wound healing, ***Journal of Materials Science and Technology***, 2020, 57, 1	Not yet	Yes	Yes	

2021				Zhengjie Lin, Danni Shen, Weixiao Zhuo, **Yufeng Zheng**, Tiantian Kong, Xuanyong Liu, Shuilin Wu, Paul K. Chu, Ying Zhao, Jun Wu, **Kenneth M.C. Cheung, Kelvin W.K. Yeung**	Regulation of extracellular bioactive cations in bone tissue microenvironment induces favorable osteoimmune conditions to accelerate in situ bone regeneration, ***Bioactive Materials***, 2021, 6(8), 2315	Not yet	Yes	Yes	
2021				Wei Qiao, **Karen H.M. Wong**, Jie Shen, Wenhao Wang, Jun Wu, Jinhua Li, Zhengjie Lin, Zetao Chen, Jukka P. Matinlinna, **Yufeng Zheng**, Shuilin Wu, Xuanyong Liu, Keng Po Lai, Zhuofan Chen, Yun Wah Lam, **Kenneth M.C. Cheung, Kelvin W.K. Yeung**	TRPM7 kinase-mediated immunomodulation in macrophage plays a central role in magnesium ion-induced bone regeneration, ***Nature Communications***, Accepted, 2021	Not yet	Yes	Yes	

9. Recognized international conference(s) in which paper(s) related to this research project was/were delivered *(Please attach a copy of each delivered paper. All listed papers must acknowledge RGC's funding support by quoting the specific grant reference.)*

Month/Year/ Place	Title	Conference Name	Submitted to RGC *(indicate the year ending of the relevant progress report)*	Attached to this report *(Yes or No)*	Acknowledged the support of this Joint Research Scheme *(Yes or No)*	Accessible from the institutional repository *(Yes or No)*
November, 2018, Cairns, Australia	The role of magnesium ion on osteogenesis and its clinical applications	Australia-China Conference of Tissue Engineering and Regenerative Medicine (ACCTERM 2018)	Yes, 2019	No	Yes	
March, 2018, New Orleans, Louisiana, USA	Precise Control Delivery of Magnesium Ions thru Sponge-like Monodispersed PLGA/nano-MgO-alginate Core-shell Microsphere Device to Enable In-situ Bone Regeneration	ORS 2018 Annual Meeting	Yes, 2019	No	Yes	

10. Student(s) trained *(Please attach a copy of the title page of the thesis.)*

Name	Degree registered for	Date of registration	Date of thesis submission/ graduation
Zhengjie, Lin	PhD	September 1, 2014	Aug 31, 2018

11. Other impact *(e.g. award of patents or prizes, collaboration with other research institutions, technology transfer, etc.)*

Award

- ***COA Orthopaedic Young Researcher Award 2nd Prize*** selected by The 13th Annual Congress of Chinese Orthopaedic Association, Xiamen, PR of China, 21st-24th Nov, 2018.

Patent

(1) 中国专利, 郑玉峰(#); 杨宏韬; 张泽川; 沈丹妮, 一种Zn-Li-Mg系锌合金及其制备方法与应用，申请, 2018.3.23，CN201810244009
(2) 中国专利, 郑玉峰(#); 杨宏韬; 张泽川, 一种Zn-Li-Mn系锌合金及其制备方法与应用，申请, 2018.3.23，CN201810243999
(3) 中国专利, 郑玉峰(#); 李文婷(#); 成艳(#); 夏丹丹; 刘晓, Mg-Si-Ca-Zn系镁合金及其制备方法与应用，申请, 2019.4.18，CN201910312727.6
(4) 中国专利, 郑玉峰(#); 李文婷(#); 成艳(#); 夏丹丹; 刘晓, 一种含Sr的镁合金，申请, 2019.4.18，CN201910312395.1
(5) 中国专利, 郑玉峰(#); 边东; 刘嘉宁; 成艳(#); 夏丹丹, 一种含Mg-RE系镁合金及其制备方法与应用，申请, 2019.2.19，CN201910121354.4
(6) 中国专利, 鄢江龙; 夏丹丹; 郑玉峰(#); 成艳(#), 一种骨科植入器械表面涂层的制备方法，申请, 2020.8.14，CN202010582000.2

Scholarly books, monographs and chapters

- Zheng yufeng(#); Xu Xiaoxue; Xu Zhigang; Wang Junqiang; Cai Hong; Metallic Biomaterials: New Directions and Technologies, Wiley-VCH Verlag GmbH & Co. KGaA, 2017.

12. Statistics on Research Outputs *(Please ensure the summary statistics below are consistent with the information presented in other parts of this report.)*

	Peer-reviewed journal publications	Conference papers	Scholarly books, monographs and chapters	Patents awarded	Other research outputs (Please specify)
No. of outputs arising directly from this research project [or conference]	13	2	1	0	COA Orthopaedic Young Researcher Award