Research Assessment Exercise 2020
Impact Case Study

University: The Chinese University of Hong Kong
Unit of Assessment (UoA): 3 (Clinical Medicine)

Title of case study: Seeking Biodegradable Metals for Clinical Use

(1) Summary of the impact (indicative maximum 100 words)

Our patented biodegradable orthopaedic implants made of pure magnesium (Mg) have facilitated skeletal regeneration in problematic orthopaedic conditions, including osteoporotic fracture and osteonecrosis. Our Mg screws have been designed to fix vascularised bone grafts to treat osteonecrosis of femoral head (ONFH). Compared to the conventional approach, these screws enhanced stabilisation of bone grafts and improved fusion over 200 ONFH patients. Our collaboration with surgeons and industrial partners has helped establish testing guidelines for biodegradable metallic implants. On July 1st, 2019, our product-registration, multicentre clinical trial in China for application of our innovative Mg screws in OFH patients has been approved.

(2) Underpinning research (indicative maximum 500 words)

Approximately one third of elderly individuals older than 60 years have osteoporosis worldwide, with over 8.9 million osteoporotic fracture cases annually due to population ageing. In Hong Kong, a city with a population of over seven million residents and the world's longest life-span, there are approximately 15,000 new osteoporotic fracture cases annually, including 5,500 cases of hip fractures that occupy 17% of the orthopaedic in-patient beds. Due to the increase in ageing population both globally and in Hong Kong, these numbers will continue to increase exponentially. This has led to a high demand for innovative medical devices that improve the prognosis of osteoporotic fractures and their associated clinical problems. These devices are particularly important for treatment of tissues with poor regenerative capabilities due to diseases such as osteoporosis, osteonecrosis, and damage to the tendon/ligament-bone insertion (TBI). The conventional orthopaedic implants developed for bone fracture and TBI fixation are made of permanent metals, which are rigid and do not promote tissue regeneration and remodelling. Magnesium (Mg) implants have not been widely used in clinical applications due to its impurity, weak corrosion resistance, and limited mechanical strength. However, advancements in material development have helped to overcome these disadvantages, allowing Mg-based implants to be compete with conventional implants with their novel property in terms of biodegradability that prevents the necessity of a second surgery for implant removal and the osteopromotive properties of Mg ions that are released during degradation.

Committed to this revolutionary, highly promising, and clinically relevant research and development (R&D), Professor Ling QIN formed and led a multi-disciplinary team composed of material scientists, engineers, and clinicians to develop pure Mg implants, Mg-alloy implants, and hybrid systems to translate the devices "from bedside-to-bench-to-bedside" with following milestones and breakthroughs:

1) Several challenging orthopaedic disorders have been identified and a clear mission has been set for each one to develop innovative Mg-based biodegradable implants for future applications. These disorders include fracture fixation and healing enhancement of osteoporotic fractures, osteonecrosis, and TBI repair, of which impaired skeletal tissue regeneration defines the key pathophysiology of the primary and secondary causes.

2) High purity Mg (99.99%) was designed and tested as part of an innovative intramedullary nail for long bone fracture fixation and also an interference screw for anterior cruciate ligament (ACL) reconstruction, using previously established preclinical rabbit and rat disease models, respectively. A Mg-based hybrid system was also developed for broader applications in order to establish a system that could support the mechanical properties required for bone fixation, as well as facilitate and enhance bone regeneration.
3) Unique biological mechanisms have been identified, involving neuronal regulation in periosteum-dependant healing enhancement of osteogenesis and angiogenesis.

This science-based translational approach to developing clinical applications has been recognised by the academic community and the relevant novel findings were published in ***Nature Medicine*** [R1] and ***Biomaterials*** [R2]. Patents have been filed in China and the USA.

(3) References to the research (indicative maximum of six references) ***(*: Corresponding author)***

Research and Development

R1. Zhang Y, Xu J, Ruan YC, Yu MK, O'Laughlin M, Wise H, Chen D, Tian L, Shi D, Wang J, Chen S, Feng JQ, Chow DHK, Xie X, Zheng L, Huang L, Huang S, Leung K, Lu N, Zhao L, Li H, Zhao D, Guo X, Chan K, Witte F, Chan HC, Zheng Y, **Qin L***. Implant-derived magnesium induces local neuronal production of CGRP to improve bone-fracture healing in rats. ***Nat Med.*** 2016 Oct;22(10):1160–9. ***(IF: 30.641; Citation: 127)***

R2. Wang J, Wu Y, Li H, Liu Y, Bai X, Chau W, Zheng Y, **Qin L***. Magnesium alloy based interference screw developed for ACL reconstruction attenuates peri-tunnel bone loss in rabbits. ***Biomaterials***. 2018 Mar;157:86–97. ***(IF: 10.273; Citation: 8)***

R3. Wang J, Xu J, Song B, Chow DHK, Shu-Hang Yung P, **Qin L***. Magnesium (Mg) based interference screws developed for promoting tendon graft incorporation in bone tunnel in rabbits. ***Acta Biomater***. 2017 Nov;63:393–410. ***(IF: 6.638; Citation: 4)***

Clinical Investigations

R4. Zhao D*, Huang S, Lu F, Wang B, Yang L, **Qin L***, Yang K, Li Y, Li W, Wang W, Tian S, Zhang X, Gao W, Wang Z, Zhang Y, Xie X, Wang J, Li J. Vascularized bone grafting fixed by biodegradable magnesium screw for treating osteonecrosis of the femoral head. ***Biomaterials***. 2015 Dec 15;81:84–92. ***(IF: 10.273; Citation: 55)***

R5. Zhao D*, Witte F, Lu F, Wang J, Li J, **Qin L***. Current status on clinical applications of magnesium-based orthopaedic implants: A review from clinical translational perspective. ***Biomaterials***. 2016 Oct 11;112:287–302. ***(IF: 10.273; Citation: 148)***

Guideline and Regulations on Innovative Biodegradable Metals: Mg-based Implants

R6. Wang J, Witte F, Xi T, Zheng Y, Yang K, Yang Y, Zhao D, Meng J, Li Y, Li W, Chan K, **Qin L***. Recommendation for modifying current cytotoxicity testing standards for biodegradable magnesium-based materials. ***Acta Biomater***. 2015 Jul;21:237–49. ***(IF: 6.638; Citation: 78)***

(4) Details of the impact (indicative maximum 750 words)

Industrial Collaboration and Clinical Application of Biodegradable Mg Screws

Since 2014 and 2017, we have been collaborating with two companies, Eontec Company in Dongguan, China, and Chung Nam (CN) Innovations in Hong Kong [S1], respectively, in order to manufacture Mg-based implants and facilitate their translation from basic science to industry manufacturing and finally to clinical applications. These collaborations have led to successful patent applications in China and patent applications are currently under final review in the USA [S2], establishing a solid foundation for establishing collaborations between academic and industrial institutions.

In 2015, Eontec Co., Ltd manufactured our clinically tested, pure Mg screws that have since been implanted in human patients by our clinical collaborator, Professor Dewei ZHAO (Department of Orthopedics, Affiliated Zhongshan Hospital of Dalian University, PR China) during hip-preserving surgeries using vascularised bone graft implantation to treat ONFH with successful clinical outcomes. Our clinical studies were published in Biomaterials (SCIE Impact Factor = 10.273) demonstrating promising efficacy in stabilisation and healing enhancement of the bone flap in ONFH patients, using pure Mg screw fixation [R4]. In the pure Mg screw group, two patients (out of 23) suffered from femoral head collapse, while six patients (out of 25) in the control group suffered from femoral head collapsed. The Harris hip score of the Mg group patients was significantly higher than the patients in the control group at six months and twelve months' post-operation follow-up. The Mg screw degraded 25.2% in screw diameter after twelve months [R4] and fully degraded approximately three years after implantation. The use of biodegradable Mg screws provides a promising bone graft-screw fixation method in treating ONFH and preventing femoral head collapse. Currently, our Mg screws have been applied in over 200 patients with ONFH. Furthermore, on July 1st 2019, the National Medical Products Administration (formerly known as the Chinese Food and Drug Association (CFDA)) approved a multi-centre clinical trial on the application of our high purity Mg screws on the fixation of the bone flap to treat ONFH [S3].

In 2017, Zoltrix Material International Limited, a daughter company of CN Innovations in Hong Kong, agreed to collaborating with our team to establish large-scale manufacturing of Mg-based implants (Class III orthopaedic implants) for fixation and regeneration of skeletal injuries and challenging musculoskeletal disorders [S4].

Regulation of Biodegradable Metallic Implants

Biodegradable metallic implants are innovative with promising clinical applications. The current testing conditions outlined by regulatory bodies are designed either for pharmaceuticals or non-degradable implants. Our research and published articles are making an impact on how biodegradable implants are tested and regulated. We have provided valuable and important recommendations to regulatory bodies or organizations, such as International Standard Organization (ISO) as stated by Professor Frank Witte, a world authority on biometals and leader of ISO standards for biodegradable metals for clinical applications [S4]. Professor Qin's group published a milestone paper on establishing a new ISO standard to test Mg-based biodegradable metals by modifying current cytotoxicity testing standards [R6]. This paper has been referenced by the US Food and Drug Administration (US FDA) as mandatory reading material and necessary material to update the ISO standard for testing biodegradable metallic implants. Furthermore, to assist the development of regulations for biodegradable metallic implants in China, the result of our preclinical study on Mg implants was presented to the Chinese FDA in 2017 [S6].

Our Mg-based screws and hybrid implant systems have received respectable invention awards, including a Gold Medal with Congratulations from the Jury of the International Exhibition of Invention, Geneva [S7]. Our studies have also been reported in local, regional and international media, newspapers, and websites (Chinese and English) [S8].

Professor QIN and his team's endeavour to seek innovative biometals for orthopaedic applications has recently been featured in ***Nature*** [S9]. All above achievements have formed a solid foundation required for planning and conducting clinical trials [R4, R5, S8] and proposing recommendations to establish, or modify standard practices and guidelines by relevant regulatory bodies that approve Class III orthopaedic implants for clinical applications [R6].

(5) Sources to corroborate the impact (indicative maximum of 10 references)

S1. Non-disclosure Agreement with Chung Nam (CN) Innovations on licensing and spin-off (through the Chinese University of Hong Kong (CUHK) Office of Research and Knowledge Transfer Services (ORKTS)).
S2. US Patent Application (Application no. US2018/0207327A1, publication date July 26, 2018).
S3. Clinical trial, in collaboration with Eontec Co Ltd, was approved by the National Medical Products Administration (formerly known as Chinese Food and Drug Administration) (Dated July 1 2019.)
S4. Collaboration letter from Zoltrix Material International Limited (Dated September 10, 2018.)
S5. Internal email communication with Prof. Frank Witte, Professor of Orthopaedics in Charite Medical University, Berlin, Germany, a leading member of establishing biodegradable metals for clinical applications.
S6. Invitation for Prof. Qin to present his studies on biodegradable Mg implants at the Chinese FDA.
S7. Gold medal and Certificate for our innovative Mg-based orthopaedic implants from the International Exhibition of Invention Geneva (April 15, 2016).
S8. Hong Kong local newspapers clipping on the CUHK press conference for magnesium-based biodegradable orthopaedic implants.
S9. Professor Ling QIN: Seeking biodegradable metals for clinical use (Special Feature). ***Nature***, May 23, 2018 *(https://www.nature.com/articles/d42473-018-00028-w)*.