5th CUHK International Symposium on Stem Cell Biology & Regenerative Medicine

Musculo-Skeletal Regeneration: From Technology to Therapy

12 November 2015

The Jockey Club School of Public Health & Primary Care Building
Prince of Wales Hospital
Shatin, Hong Kong

Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong
SMART Programme, Lui Che Woo Institute of Innovative Medicine, Faculty of Medicine, The Chinese University of Hong Kong
Musculoskeletal Regeneration Research Network (MRN)
Stem Cell and Regeneration Theme, School of Biomedical Sciences, The Chinese University of Hong Kong
Key Laboratory for Regenerative Medicine (Jinan University-CUHK), Ministry of Education, China

Organizers

CU Medicine HONG KONG

SMART

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Welcome Message

Message from

Professor Joseph J Y Sung
Vice-Chancellor
The Chinese University of Hong Kong

It is with great pleasure that I welcome you all to the 2015 CUHK International Symposium on Stem Cell and Regenerative Medicine Symposium.

Regenerative medicine is one of the modern medical advancements in the 21th century. The discovery of embryonic, adult stem cell, and biomaterials make it possible for the damaged tissues to regrow and regenerate fully. The significant accomplishment including transplants of stem cells, manipulation of the patient's own stem cells, and the use of scaffold materials that emit biochemical signals to spur stem cells into action. Regenerative therapies have been demonstrated to heal many difficult medical conditions such as broken bone, severe burns, blindness, heart disease, Parkinson's disease, and degenerative diseases.

In the past 5 years, CUHK have been expanding its research potentials and capacities in the field of regenerative medicine. Dedicated research teams and research projects are being set up and state-of-the-art research facilities are built to facilitate the needs of research and clinical applications in this field.

With the generous donation from the Lui Che-Woo (吕志和) Foundation, the Lui Che Woo Institute of Innovative Medicine (IIM) has already been operating with success since 2013 summer. The SMART (Sports Medicine and Regenerative Technology) initiatives have made tremendous progress, to name but a few, the LCWIIM-SMART programme has signed MOU with Karolinska Institutet (Sweden), University Medical Centre (Utrecht), Standford University (USA) and Odense University Hospital (Denmark) respectively; CUHK delegation had made a fruitful academic visits at these institutes in June 2015, a number of staff/student exchanges and collaborative research in tendon, ligaments and cartilage have also taken place. I am also glad that Musculoskeletal Regeneration Research Network (MRN) has already brought many creditable partners to work together in the field of musculoskeletal regeneration.

The main topics of the symposium this year includes an overview on musculoskeletal regeneration and translational research and the latest development of MRN, to be followed by specific areas namely, Stem Cell Biology, Muscle, Cartilage, Tendon, and Ligament & Bone-Tendon Junction.

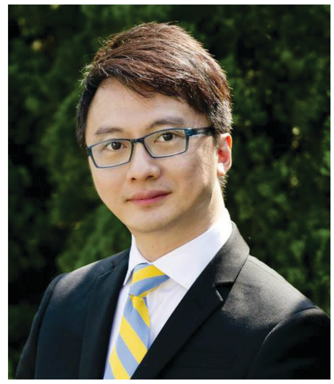
I am most delighted to see that such a great number of respectable scientists and clinicians along with many young and energetic researchers joining us to utilize this platform and to share their expertise and experience.

I wish you a most enjoyable stay in Hong Kong and stimulating and successful symposium!

Professor Joseph J Y Sung
Vice-Chancellor
The Chinese University of Hong Kong

Message from

Professor Francis K L Chan
Dean, Faculty of Medicine
The Chinese University of Hong Kong



Dear colleagues and friends,

Welcome to the 5th CUHK International Symposium on Stem Cell Biology and Regenerative Medicine.

In the 21st century, one of the major challenges is the growth of aging population in both developed and less developed countries. The socio and economic impact arising from taking care of the elderly is high on the agenda of any government. Regenerative medicine has the potential to help mitigate rising healthcare-related costs as innovations in regenerative medicine open the doors to obviating the need for organ replacement, reducing dependence on invasive procedures and improving treatments for currently intractable and incurable diseases.

Driven by societal expectations, clinicians and research scientists from clinical and pre-clinical departments have been working closely in the upstream and downstream innovative research in stem cell biology and regenerative medicine. Such collaborative research efforts have been speeding up the translational research in various specialties in medicine.

As the Director of Lui Che Woo Institute of Innovative Medicine, I would like to take this opportunity to express our indebtedness to Dr Lui Che Woo whose generous donation has made possible the organization of this annual symposium. My special thanks also go to the Organizing Committee as well as all the administrative support staff who have worked tirelessly to ensure the success of the symposium.

I trust that this platform will connect you with the best minds to develop multi-disciplinary and cross-professional synergy, further pushing the frontiers of regenerative medicine for the benefits of humanity. Once again, I am extending a warm welcome to every participant. For those from overseas, I wish you an enjoyable stay in Hong Kong.

Yours sincerely,

Professor Francis K L Chan
Dean, Faculty of Medicine
The Chinese University of Hong Kong

Welcome Message

Message from

Organizing Committee

Dear colleagues and friends:

The 5th SCRM (5th CUHK International Symposium on Stem Cell Biology and Regenerative Medicine) continues with the momentum of the previous ones with special highlights in musculoskeletal regeneration as the theme, focusing on the translation from new technology to cost-effective therapy. This also brings in the international partners of the MRN (Musculoskeletal Regenerative Research Network) following the successful network meeting in Stockholm, Sweden on June 1-2, 2015.

4th SCRM Symposium (Nov 17-18, 2014 Hong Kong)

1st MRN Symposium (June 1-2, 2015 Stockholm, Sweden)

The strategic development of MRN will be highlighted; in order to share the collaboration efforts and network we have developed, in pursuit of our vision to advocate a strong voice in the field of MSK regenerative research and a collective opinion leader in the field. We would also like to share the success of bringing together like-minded individuals with strong track records in the fields of Orthopaedics and Translational medicine, and the benefits this offers to the Orthopaedics arena as a whole. All network p artners will continue their deliberation on collaborative projects. For the specific topic in the musculoskeletal arena, we have invited key anchor person to develop the program with a balanced approach in basic research, translational approach and clinical applications.

This SCRM welcomes professionals and academics in the field of regenerative medicine, orthopaedics, neurology, biomedical science and engineering and other related disciplines. On behalf of the symposium organizers, I warmly welcome you to join us in the symposium and wish you all an enjoyable stay in Hong Kong!

Organizing Committee
The 5th CUHK International Symposium on Stem Cell Biology and Regenerative Medicine

Co-Charimen:

Prof. Kai-Ming Chan
Chair Professor
CUHK-ORT

Prof. Gang Li
Professor
CUHK-ORT
CUHK-SBS-SCR

Prof. Wai-Yee Chan
Director
Chair Professor
CUHK-SBS

Prof.Jack Chun-Yiu Cheng
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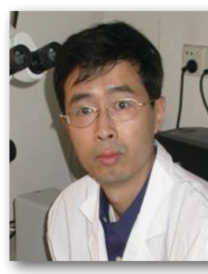
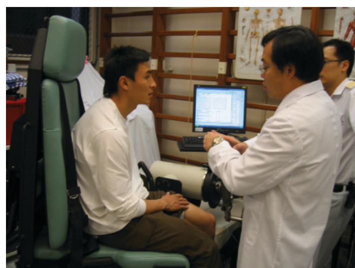


Prof. Dong-Qing Cai
Co-Director,
Jinan-CUHK Key Lab for
Regenerative Medicine,
Ministry of Education, China

Department of Orthopaedics and Traumatology
The Chinese University of Hong Kong

The department was established in 1982 under the foundation Chairmanship of Professor PC Leung. The first batch of medical students started to have their clinical orthopaedic teaching in 1983. Throughout the years, the department has grown and developed under the clear Mission and Vision "to provide the highest quality service in patient care, research, education and teaching for medical students and postgraduate training".

The department has grown from a single professor team to more than 40 clinical colleagues and 60 supporting clerical, technical and research staff now. It would be appropriate to divide the development of the department into three different phases, namely the establishment, the expansion and the consolidation phases. The initial establishment phase stretched from 1982 to 1990 and could be regarded as the infancy and childhood phase. This was followed by a rapid expansion phases from 1991 to 1996 by "hundred flowers blooming" phase which was quite similar to the pre - adolescent and adolescent phase. The past few years, from 1997-2001 featured the early consolidation and sustained growth of the department with the analogy of early and young adulthood phase.



On the clinical services, the department has developed along the major fields of subspecialties in orthopaedics, from Hand and Microsurgery, Sports Medicine, Traumatology, Paediatric Orthopaedics to Orthopaedic Oncology, Spinal injury, Orthopaedic Rehabilitation, Joint Reconstruction Surgery to the latest addition of Foot and Ankle surgery 3 years ago. Many of these subspecialties enjoy significant local, regional and international professional and academic recognition and achievements.

Commitment to quality teaching of medical students is one of the main keystones of the department. The department has been involving in the teaching of musculoskeletal system and orthopaedics in Med 3 and Med 5 students and with the introduction of the new curriculum in 2001, teaching has been extended further into year 1 and 2. With the setting up of a formal teaching committee and departmental teaching coordinator, the curriculum in musculoskeletal system is regularly reviewed and updated. Regular teaching quality assessment, meeting with students and annual curriculum review with honorary teachers has helped not only to update but continuous improvement of the quality of teaching as reflected by the evaluation results and recognition by the faculty and university.

Significant growth has been achieved in the research area. From purely clinical reviews and research, the department has steadily expanded in the years to cover different areas of basic and applied basic research that spread from soft tissue, bone and cartilage to biomaterials, osteoporosis and traditional Chinese medicine. The research committee and the musculoskeletal research laboratory structure now have clear responsibility and function to plan, advice and implement defined policies related to research. Three main focused research programs and functionalisation have been established to incorporate all teaching and research staff of the department. The research output and research grants have increased significantly over the years both in quantity and quality. Up to now, 50 Mphil, 23 PhD and 2 MD have graduated from the department. Active collaborations with other departments, universities and research institutions locally, regionally and with other countries have opened up many new and important areas of research.

The department has put great emphasis on the development of information technology and audiovisual supporting services to all staff from administration to training, teaching, research to clinical services. The whole department is now connected by a sophisticated system of high-speed Intranet. Active research and application of IT in enhancement of web-based interactive teaching is well supported. One of the most important highlights of the department is the establishment of the Orthopaedic Learning Centre from generous donations around 2 million US$ in total. Since it's opening in April 1999, over 5,000 local, regional and international participants have attended different courses and workshops conducted in the centre. The centre has also been recognised as advanced training centre by various societies and also a favorite center for visit by any outside guest to the Faculty of Medicine.

Throughout the years, colleagues of the department have and will continue to be actively committed to the university, the professional and specialty development, and play important roles in public services, voluntary services and services to the community.

With the support, spirit and dedication of colleagues at all levels, we can proudly look forward into the future, continue to strive, seek and develop "to provide the highest quality service in patient care, research, education and teaching for medical students and postgraduate training".

SMART Programme
Lui Che Woo Institute of Innovative Medicine
Faculty of Medicine
The Chinese University of Hong Kong

LCW IIM SMART Programme is a new initiative of Hong Kong Centre of Sports Medicine and Sports Science, CUHK

Mission
To provide top-quality clinical service with educational objectives to both undergraduates and post-graduates, and to conduct comprehensive research programmes in clinical, basic and applied domains

Vision
To assume regional leadership with international highlights of excellence and achievement

We are the pioneer in Sports Medicine and Health Science, with important Milestones:

1983	First Sports Clinic in Jubilee Sports Centre (now known as the Hong Kong Sports Institute)
1984	First Sports Injuries Clinic in Hong Kong established at the Prince of Wales Hospital and first to promote the development of arthroscopic surgery
1988	First Founding President of the Hong Kong Association of Sports Medicine (HKASMSS)
1990	First pioneer to establish Asian Federation of Sports Medicine (AFSM)
1995	First pioneer to establish the Asia-Pacific Orthopaedic Society for Sports Medicine (APOSSM)
1996	First Sports Medicine Centre designated as the WHO Collaborating Centre in Sports Medicine and Health Promotion (1996-2009)
2002	First Asian Presidency of International Federation of Sports Medicine (FIMS) (2002-2006)
2004	First Taught Programs (MSc & PgDip) in Sports Medicine & Health Sciences organized by a university in Hong Kong
2007	First SMART (Sports Medicine and Rehabilitation Therapy) Convention to promote knowledge transfer and community education
2008	First World Congress of Sports Trauma (WCST) held in Hong Kong, with over 1000 attendance First established centre in Sports Medicine and Health Sciences with the generous donation of HKD 88.72 million from Hong Kong Jockey Club Charities Trust
2010	First International Symposium of Ligaments and Tendons (ISL&T) held in Hong Kong
2011	First CUHK Stem Cell & Regenerative Medicine (SCRM) Conference held in Hong Kong
2013	First launch of Sport Medicine And Regenerative Technology (SMART) programme in the Institute of Innovative Medicine (IIM) and Musculoskeletal Regenerative Research Network (MRN)
2014	Academic visits to Karolinska Institutet, UMC Utrecht and Stanford Unviersity - three key collaborators of LCWIIM-SMART programme and MRN. Signed a MOU with UMC Utrecht in June and with Stanford University in November respectively
2015	Co-organized the 1st International Symposium of Musculoskeletal Regenerative Research Network (MRN), June 1-2, 2015, Karolinska Institutet, Sweden. Academic visit to Odense University Hospital, Denmark and signed a MOU in June.

Clinical Service

Sport Team has been the pioneer dedicated to the prevention, treatment and rehabilitation of sports-related injuries since its establishment in 1983. Through close collaborations with various clinical departments, a one-roof, one-stop comprehensive and multi-disciplinary diagnostic, treatment and rehabilitation service is provided not only to the general population, but also to professional and amateur athletes. A full spectrum of sports-related injuries, including ligament, meniscus & cartilage injuries around the knee; instability, rotator cuff and bicep tendon injuries around the shoulder; cartilage injuries, instability, impingement and tendon problems around the ankle, and labrum injuries, impingement, cartilage and tendon problems around the hip are managed by us. We are now taking care of over 5000 sports injury cases in our clinic every year. At the Hong Kong Sports Institute, we provide general medical and orthopaedic consultations, sports injury management and rehabilitation programmes, high-risk group screening in particular sports and injury prevention programmes. Each year, about 300 elite Hong Kong Team athletes receive our care in Hong Kong Sports Institute.

We are also the pioneers in arthroscopic surgeries for treatment of sports injuries through our introduction of the first knee arthroscopy in Hong Kong, and we continue to take the lead in the field. With our expertise and state-of-art technology developed, arthroscopic surgeries are very safe and effective surgeries, and allowing patients return to sports much earlier than before. Our knee arthroscopic surgeries include Anterior Cruciate Ligament (ACL) reconstructions, Posterior Cruciate Ligament (PCL) reconstructions, multi-ligament reconstructions and reconstructions for patellofemoral joint (PFJ) instability, while shoulder arthroscopic operations consist of rotator cuff repairs, arthroscopic stabilization for recurrent shoulder dislocations and SLAP repairs etc. With the aid of computer navigation system and high-definition camera system, higher level of precision and better surgical outcome particularly for knee operations is guaranteed. With close collaborations with Foot & Ankle Team and Hand team, our arena of arthroscopic service extends to ankle arthroscopy, wrist arthroscopy and elbow arthroscopy. Each year, with our operative services provided at Prince of Wales Hospital and Alice Ho Miu-Ling Nethersole Hospital, we operate on more than 350 sports injuries cases, with about 250 ACL cases and 50 shoulder arthroscopic procedures. Our team holds various arthroscopy workshops such as the advanced cadaveric arthroscopy workshops of the knee and shoulders annually with a view to sharing our surgical experiences with orthopaedic surgeons from Hong Kong, China and over the world. Our close collaboration with experts from renowned orthopaedic centres around the world has granted us ample opportunities for the exchange of new surgical technologies.

Research

Research in sport team is bon marriage of clinical, applied and basic science research. Our major research focuses are prevention and treatments for sports injuries. We have published more than 264 articles in SCI journals. We have successfully secured 17 (General Research Fund) grants and 9 ITF (Innovation and Technology) grants in the past 30 years. In 2006, we were also awarded a 12 million UGC grant in developing a joint university centre in Sport medicine and rehabilitation. In 2008, the establishment of the CUHK-Jockey Club Sports Medicine and Health Sciences Centre (with a funding of 88 million) has significantly enhanced our research capabilities, with the state-of-the-art facilities such as animal gait analysis; in-vivo cell imaging system; multi-channel flow cytometer and high resolution ultrasound imaging system. To achieve innovative solutions for management of orthopaedic sport medicine conditions and musculoskeletal disorders and to provide platform for multi-disciplinary research on musculoskeletal regeneration, the Sport Medicine And Regenerative Technology (SMART) programme was established under the Institute of Innovative Medicine (IIM) in 2013.

Our Clinical team is actively participating in clinical researches. We have a very broad spectrum of interests, from sports injuries epidemiology, diagnostic skills, injury prevention programme, surgical technique development to rehabilitation and performance enhancement program. Our current main focus essentially is on Knee and shoulder sports injuries, with special interests in ACL injuries particularly randomize-controlled trials in single-bindle ACL versus double-bundle ACL reconstructions etc. We have published more than 30 clinical papers in different peer-reviewed international journals.

Our Basic Science team is one of the prominent tendinopathy research groups in the world and we pioneered the studies on clinical samples of tendinopathies. We also investigated various strategies to promote tendon healing, including growth factors, stem cells, traditional Chinese medicine and biophysical intervention. With respect to ACL injuries, the basic research team works closely with the clinical and applied research team in order to achieve clinical translation of research findings. A number of patents are filed and we looking forward to bringing more research findings into clinical application.

Our Applied team established the CUHK Sports Performance and Biomechanics Laboratory. We apply the technology of biomechanics to predict the occurrence of ankle sprain, and by micro-electrical muscle stimulation, excessive joint motion could be prevented. This innovative idea has led to the development of anti-sprain shoe and hopefully a series of anti-sprain "smart" devices will be launched into the market in the near future. We have also newly invented a new knee rotational laxity meter to assess the dynamic and static rotational stability of the ACL, which provides an innovative objective biomechanical assessment technique of the knee.

We are honored to be the regional hub of knowledge transfer with respect to tendon and ligament research. We have hosted the world renowned "International Symposium of Tendon and Ligament (ISL&T) in 2008 and 2010. In 2013, the 3rd CUHK Stem Cell & Regenerative Medicine Conference will continue to have the top scientists in the fields of regenerative medicine to join us. With the establishment of musculoskeletal research network, we shall be able to enhance the academic, professional and scientific output of members by facilitating more international collaboration.

Education

We are a leading center for sports medicine education. For Undergraduate teaching, we are dedicated in educating CUHK MB,ChB Med I, III and V students. We were awarded the University Grants Council (UGC) Restructuring and Collaboration Fund (RCF) to set up the Joint Universities Sports Medicine and Rehabilitation centre with the Rehabilitation department of Hong Kong Polytechnic University in 2007. Though this collaboration, our medical students from CUHK and physiotherapist students from HKPU is now having the opportunities to enjoy a two-way learning, particularly acquiring more knowledge on the principle and applications of rehabilitation in sports injuries, as well as developing good long term working relationship. For post-graduate education, 21 research master students and 15 PhD students have completed their research projects on areas such as tendon and ligament regenerations and biomechanics studies. Our team successfully launched the first ever Master Course in sports Medicine & Health Science in Hong Kong in 2004. With a strong teaching international faculty equipped with collective expertise in research and education, rigorous trainings were provided to learners from a diversified background such as medical doctors, physiotherapists, nurses, sports scientists, allied health, fitness professionals and sports enthusiasts. We have now trained more than 400 people with our MSc course. Many of these alumni are contributing and playing a significant role in the sports medicine profession and industry in HK and around the world.

Future

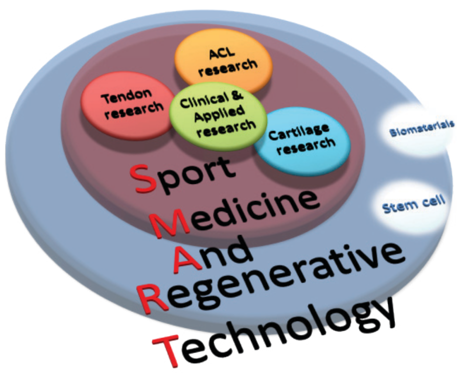
Orthopedic sport medicine is an integral part of orthopedics. It is a vibrant and emerging sub-specialty that traverses boundaries in other disciplines in medicine in general and orthopedics in particular. A well-trained orthopedic surgeon will benefit from a comprehensive program of training as highlighted in this discipline with knowledge and skill applicable to other sub-specialties.

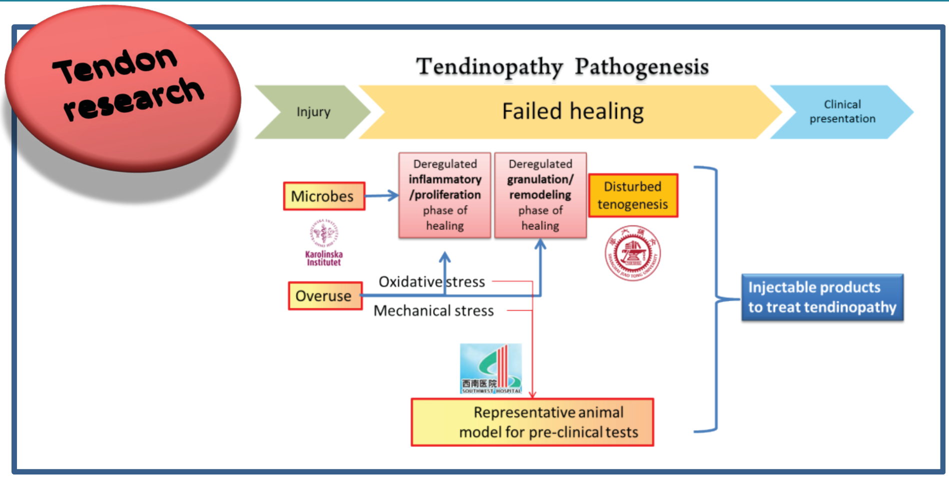
The CUHK Sport Medicine Centre will maintain this momentum of sporting spirit to achieve "Higher, Faster and Stronger" goals to reach new height in clinical service, education and research. We shall bring the next generation of clinician and scientist to a new platform of opinion leadership in this discipline.

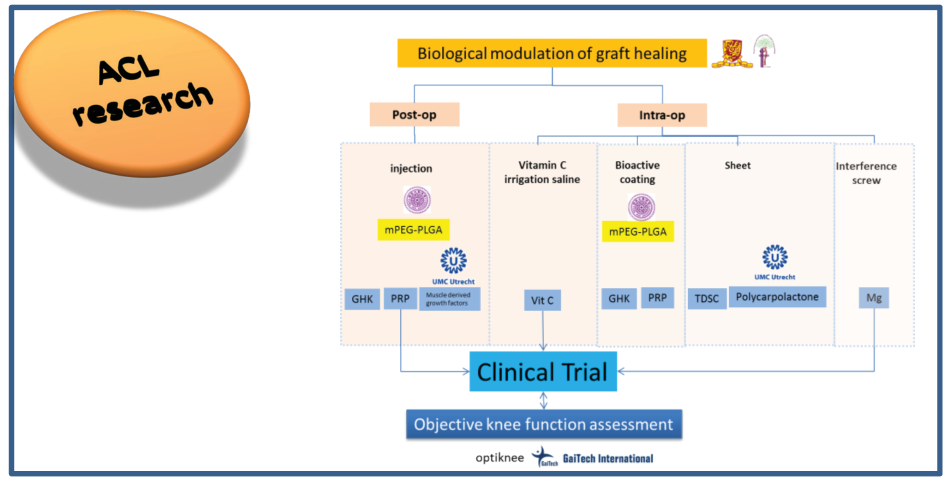
SMART

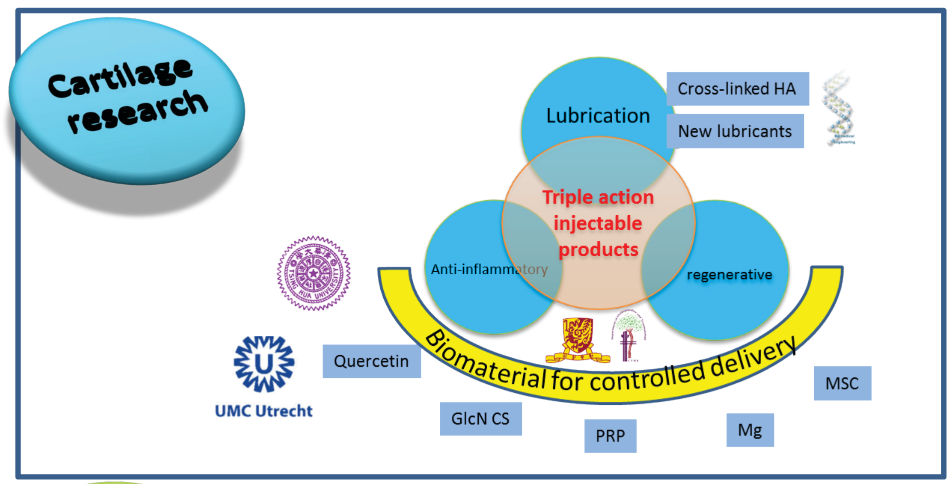
IIM-SMART International Collaboration

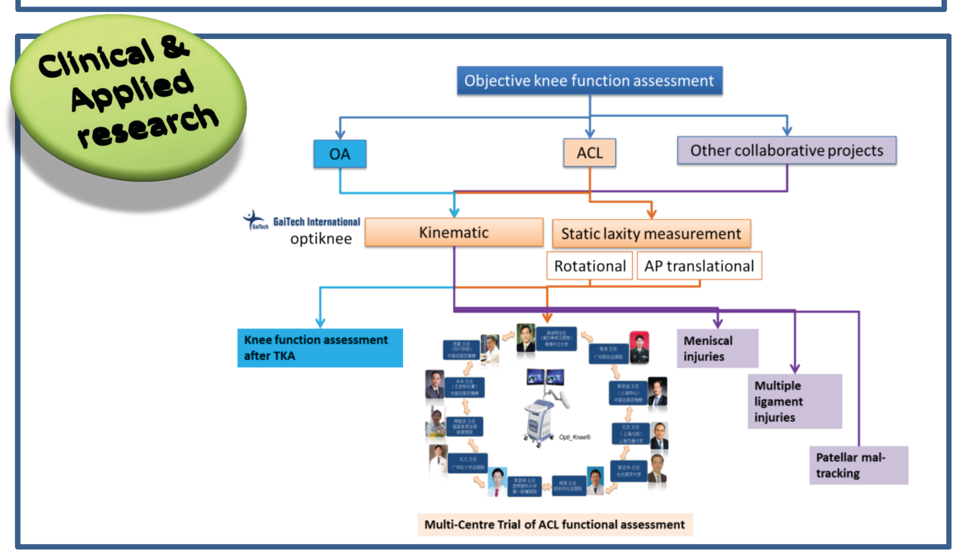
Sport Medicine and Regenerative Technology (SMART) research programme focuses on prevention and treatments for sports injuries. Apart from clinical and applied research, we chiefly devote to translational research on tendon, ACL and cartilage healing.



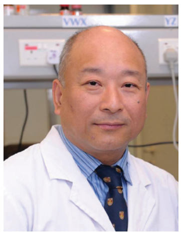




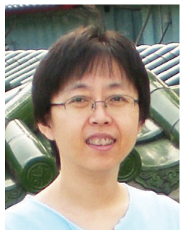




Stem Cells and Regeneration (SCR) Theme
School of Biomedical Sciences
The Chinese University of Hong Kong


Prof. Kenneth LEE


Prof. Jack CHENG


Prof. Bo FENG


Prof. Xiaohua JIANG


Prof. Gang LU


Prof. Kingston MAK


Prof. Chao WAN


Prof. KM CHAN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Mission and Vision of SCR:
To co-ordinate and facilitate research, education, and clinical application of stem cells and regeneration technologies in the Faculty of Medicine, The Chinese University of Hong Kong and to implement a new, multidisciplinary and sustainable program in translational research in regenerative biology, which will form the basis for incorporating clinical service with cutting edge technology into these disciplines.

More specifically we view as our missions:

- To provide a platform for interaction among investigators working on different aspects of stem cell biology and regenerative medicine in the Faculty of Medicine, CUHK.
- To enhance and facilitate collaboration between investigators.
- To serve as the representative body of all clinical and basic investigators in stem cell and regenerative biology at The Chinese University of Hong Kong when dealing with outside institutions.
- To provide a platform for collaborations with scientists in North America, Europe, Asia, Taiwan, Hong Kong and China mainland.
- To enhance international profiles of CUHK.

Research Focus of SCR:
The host reaction to tissue injury involves a complex interplay of local and systemic, cellular and hormonal responses. Mesenchymal stem cells (MSCs) present in many adult tissues can generate new cells either continuously or in response to injury/inflammation/cancer. The main research focus of this group is to understand the role of stem cells in diseases and development and to use MSCs for clinical translational research. The main research interests include:

- Study the fundamental biological/mechanical factors that control/regulate MSCs proliferation, differentiation and fate.
- MSCs as a source for tissue engineering and regeneration such as bone-tendon healing, tendon repair, fracture healing, cardiac tissue repair, etc.
- The role of MSCs in cancer development and the use of MSCs as carriers for anti-cancer gene therapy.
- Reprogram the somatic cells into induced pluripotent stem cell (iPS) and the use of iPS as models for studying diseases and developmental process.
- To use GMP stem cell facility to carry out cell therapy clinical trials.

Core technology and research platforms of SCR:
The following are some existing technologies that we have in the theme:

1. MSCs, iPS and embryonic cell culture techniques and standard characterization of various stem cells by flowcytometry, immunohistochemistry and morphology.
2. Multi-differentiation potential assays for stem cells, such as osteogenesis, chondrogenesis, adipogenesis, neurogenesis, angiogenesis and differentiation into cadivascualr muscles.
3. In vivo imaging techniques to trace stem cell migration in vivo.
4. Chemotaxis analysis techniques and imaging techniques including microCT, VivaCT and ultrasound imaging.
5. Transgenic animal models of GFP rat, Luciferase mice, and BMP-4 promoter driver Luc-mouse.
6. Animal models of stem cell transplant, animal models of muscle, tendon, bone and cartilage, spinal card injury and repair and assessments.
7. Bioreactor platform for stem cell culture.
8. GMP standard clinical grade clean room for human stem cell culture and clinical cell therapy applications.

For the research interests of each member, please visit http://www.sbs.cuhk.edu.hk/Research_Scr.asp

Key Laboratory for Regenerative Medicine
(Ji Nan University - The Chinese University of Hong Kong)
Ministry of Education, China

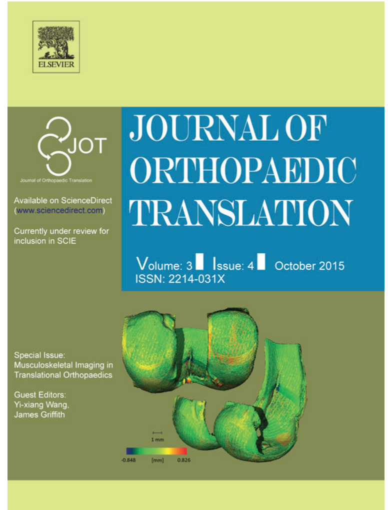
The Key Laboratory for Regenerative Medicine, Ministry of Education (Ji Nan University-The Chinese University of Hong Kong), was established by Ji Nan University, Guang Zhou, and the Chinese University of Hong Kong, Hong Kong, on the basis of the previously established Joint CUHK-JNU Lab for Regenerative Medicine in April 17th 2007. To further strengthen the expertise and resources of both universities, the Lab then applied for as a Key Lab of Regenerative Medicine, in the Ministry of Education, which was approved in Dec. 2007 to start building the Lab. Moreover, the Key Lab was approved in 2008 as an International Collaborative Base for Science and Technology, by the Department of Science and Technology, Guang Dong Province. In 2009, the key lab was further approved as International Collaborative Base for Science and Technology, by the Department of Science and Technology, P.R.China. Currently, the Key Lab has 31 permanent staffs with an average age of 45 years old. There are 20 high ranking members (Professor), 1 member with title in the "New Century National Hundred, Thousand and Ten Thousand Talent Project", 1 member of Oversea Outstanding-Youth. Almost all of the principal investigators have been trained oversea. The expertise of the staffs includes almost all areas of regenerative medicine, which are medical regeneration, developmental biology, regenerative biology, cell and molecular biology, tissue engineering, physiology, and immunology etc. The total lab space is about 3600 m^2 , which includes laboratories for molecular biology, cell biology, stem cells, biological imaging, morphology, functional analysis, and up-to 1000-grade cell culture rooms. The labs are furnished with state-of-the–art equipment. The equipment and apparatus procured are worth about 50 million RMB. Post-graduate students from both laboratories move freely and conduct research at both sites. Our mission is to improve the lives of our community by conducting research to find cures for degenerative diseases, such as ischemic heart diseases, skeletomuscular degeneration, eye disease and tissue degeneration caused by cancer/aging. Stem cell- and small molecule- based therapies are currently being developed by principle investigators in the Key Lab to treat the various forms of degenerative diseases mentioned.

Musculoskeletal Regeneration Research Network (MRN)

<u>**Editorial Article**</u>
<u>**Musculoskeletal Regeneration Research Network – A Global Initiative**</u>

This article is adapted from an article published in Journal of Orthopaedic Translation in October 2015 with permission of the Journal.

Chan KM, Rolf CG, Qin L, Felländer-Tsai L, Castelein R, Saris D, Malda J, Richards RG, Goodman S, Tuan RS, Maloney W, Lidgren L, Hopkins C, Fu SC, Li G, Ding M, Tang TT, Zhang XL, Lei W, Sun H, Ouyang HW



Abstract
The Musculoskeletal Regeneration Research Network was founded in 2013 and has been growing and developing since. In order to gain greater awareness for musculoskeletal conditions, we have organised a global network to promote collaboration and through this, enhance achievements in musculoskeletal regeneration and translational research.

Global Impact of Musculoskeletal Disorders
The World Health Organisation (WHO) has identified the four most lethal, non-communicable diseases (NCDs) affecting the greatest proportion of the world population as: cardiovascular diseases, cancer, respiratory diseases and diabetes. While musculoskeletal (MSK) conditions are the second greatest cause of disability and account for 1/3 of all work sick-leave [1], the WHO does not place the same awareness on musculoskeletal conditions. Greater awareness of diseases maintains visibility which leads to greater funding for research and education, making it more difficult for the under-recognised diseases to gain the necessary resources to make an impact in the field [2].

It is thus imperative for musculoskeletal interest groups to appeal to not only the WHO but also governments, pharmaceutical companies and regulatory bodies to give greater attention to musculoskeletal conditions. For instance, the Bone and Joint Decade (BJD) has contributed to the WHO Global Disability Action Plan which is a systematic review similar to that of the highlighted NCDs. BJD has also contributed to the WHO report on ageing and health, which will be followed by an action plan [3]. While BJD has done an excellent job in promoting global awareness of musculoskeletal conditions, especially with larger organisations, the question about how advantageous this is for individual institutions in making a translational difference remains controversial. For this reason, smaller groups who are able to establish in-depth discussions and co-ordinate themselves around a centralised goal are essential.

Some organisations are already recognising this need to support the study of numerous diseases. Horizon 2020 is the largest EU Research and Innovation programme, with explicit recognition of musculoskeletal conditions. This programme not only funds orthopaedic projects, but encourages cross-disciplinary research, thus allowing for a disease to be holistically studied and treated [4, 5], and access to such grants will be greater achieved by groups focused on one goal with multiple fields of expertise.

Background and Launch
The Musculoskeletal Research Regeneration Network (MRN) is an International Consortium to promote Musculoskeletal Regeneration & Translational Research to encourage collaboration to enhance achievement. It was inaugurated on Nov 11, 2013 during the 3rd CUHK International Symposium on Stem Cell Biology and Regenerative Medicine (SCRM) [Fig. 1A, 1B].

With the vision to advocate a strong voice in the field of MSK regenerative research and a collective opinion leader in the field, the Musculoskeletal Research Regeneration Network (MRN) is an ideal platform to establish a taskforce to translate the research conducted by participating members into clinical practice. By building a strong network with like-minded teams and institutions, members of this network will gain unique opportunities to enhance their research and clinical practice and outcomes, as well as enabling assistance in applying for grants, through their MRN collaborations. MRN will also be able to form active relationships with industries, in order to bring academic research into the clinical realm. Ultimately, such interactions will lead to effective knowledge transfer among the MRN members, to ensure projects remain on track and achieve their ultimate goals.

The Mission of the MRN is:
1. to establish an effective, collaborative platform to facilitate musculoskeletal regenerative research;
2. to bridge the gap in translation in MSK regenerative research between professional bodies and industries;
3. to enhance the academic and professional output of members of the Network; and
4. to host high quality meetings in strategic global sites to promulgate the impact of MSK regenerative research

Fig. 1A: 3rd CUHK International Symposium on Stem Cell Biology and Regenerative Medicine (SCRM), 11-12 November 2013.

Fig. 1B: Launch of MRN, 11 November 2013.

Musculoskeletal Regeneration Research Network – Progress Update
Based on the Fragility Fracture Network model [6], the MRN aims at bringing together like-minded researchers from global institutions, focusing on musculoskeletal regeneration and turning basic science into translatable results. In the past 5 years, MRN has taken the necessary steps to build a firm foundation and expand to include illustrious institutions, allowing access to new grants, publication of more research, and providing staff and students the opportunity to learn and share expertise and knowledge beneficial to both the host and home institutions [7]. For example, the collaboration between The Chinese University of Hong Kong (CUHK) and Karolinska Institute (KI) has already achieved numerous benefits. KI has access to a large number of human tendinopathy samples for the analysis of microbial presence, while CUHK has cell culture facilities to study the pathogenesis of microbes on the development of tendinopathy. The project has expanded its collaborative efforts to Uppsala University, by virtue of its bioinformatics facilities. Furthermore, the collaborating institutions were approached by the University Hospital of Trondheim, Norway, supplying additional tendinopathy samples to increase sample and demographic size in the study. A similar collaborative platform has been established between CUHK and University Medical Centre (UMC) Utrecht. UMC Utrecht has developed hydrogel 3D printing technology for regeneration of focal chondral defects, while CUHK is working on injectable products to treat degenerative osteoarthritis, with a shared interest in developing value-added biomaterials for these applications. Recently, CUHK researchers visited the University of Southern Denmark and held a joint symposium on "Musculoskeletal Regeneration". A formal MOU has been signed and a project is being planned for development of bioactive constructs, wherein both institutions will apply for research grants, establish a joint PhD programme, and share resources and facilities. Delegates from CUHK recently visited Stanford University, California, U.S.A. (Stanford delegates have previously visited CUHK), under the auspices of a signed MOU between the two institutions, to initiate lectures and formulate new research bonds in various musculoskeletal fields. A similar, research focused MOU is also in place between the University of Pittsburgh, Pennsylvania, U.S.A, and CUHK. In addition, opportunities for collaboration in research, education, grants and publication in both academia and industry are also being developed. Researchers from AO Foundation, Shanghai Jiao Tong University and CUHK have formed the European and Chinese RAPIDOS consortium, to collaborate on the project titled "rapid prototyping of custom-made bone-forming tissue engineering constructs", which received funding from the European Commission and the National Natural Science Foundation of China in 2013 [8]. Furthermore, the collaboration between Shanghai Jiao Tong University and CUHK has produced

another study on tendinopathy and tendon regeneration, which has resulted in the sharing of resources and facilities, education opportunities and a number of publications [9, 10, 11]. Further collaboration is also under development with Brown University and CUHK, in which a publication studying SDF-1 and osteoarthritis has been published [12], as well as facilitating scholars and students from CUHK to visit Brown University.

Through this growing network of international collaborators and promising research opportunities, the 1st International Symposium of Musculoskeletal Regeneration Research Network (MRN) [Fig. 1C] was held at KI on the 1-2 June, 2015, for member institutions to share recent work, as well as discuss and develop future research opportunities and collaborations, such as acute and chronic inflammation and infection in musculoskeletal disease, and tissue regeneration. Participants also discussed how MRN can move forward to accomplish its goals. It is believed that MRN not only presents opportunities for collaborative ventures among similar institutions, but also enables collaboration with pharmaceutical and governmental regulatory bodies to implement systems towards effective translational activities. The Albert Einstein College of Medicine expressed their excitement for recently joining MRN, emphasising specifically the opportunity of interaction with other international institutions and potential collaborations with other members of the MRN. Following the success of the 1st MRN meeting, annual meetings are planned for 2016 (Utrecht, The Netherlands) and 2017 (Davos, Switzerland).

MRN holds a unique position in that it has a diverse group of members who have specialised knowledge, systems and facilities in place, to bring research from bench-to-bedside. MRN has the advantage of maintaining a small, tight-knit community to maintain specific, focused discussions and allowing stronger, effective collaborations. Such collaborations have already shown significant mutual benefits for both musculoskeletal investigators and their institutions. The overall outcome of greater access to facilities, knowledge, resources, grants, publications and technology, enabled by the MRN, will bring about substantive advancements in making bench-to-bedside translational research a reality.

Fig. 1C: 1st International Symposium on Musculoskeletal Regeneration Research Network, 1-2 June 2015

Institution	Department/Division	Personnel
The Chinese University of Hong Kong	The Department of Orthopaedics and Traumatology	Prof. K.M. Chan, Prof. Qin Ling, Prof. Li Gang, Dr Bruma Fu, Ms Chelsea Hopkins
Karolinska Institute	Department of Clinical Science, Intervention and Technology	Prof. Christer Rolf, Prof. Li Felländer-Tsai
University Medical Centre (UMC) Utrecht	Department of Orthopaedics	Prof. Rene Castelein, Prof. Jos Malda, Prof. Daniël Saris
AO Foundation Davos Switzerland	AO Research Institute (ARI)	Prof. Geoff Richards
University of Pittsburgh	Center for Cellular and Molecular Engineering, Department of Orthopaedic Surgery	Prof. Rocky Tuan
Stanford University	Orthopaedic Surgery	Prof. Stuart Goodman, Prof. William Maloney
Lund University Sweden	Department of Orthopaedics	Prof. Lars Lidgren
University of Southern Denmark	Department of Orthopaedic Surgery and Traumatology	Prof. Ming Ding
Zhejiang University	School of Basic Medical Science	Prof. H.W. Ouyang
Shanghai Jiao Tong University	Shanghai Key Laboratory of Orthopaedic Implants, Department of Orthopaedic Surgery	Prof. T.T. Tang, Prof. XiaoLing Zhang
Brown University	Department of Orthopaedics	Dr Lei Wei
Albert Einstein Institute	Department of Orthopaedic Surgery	Dr Herb Sun

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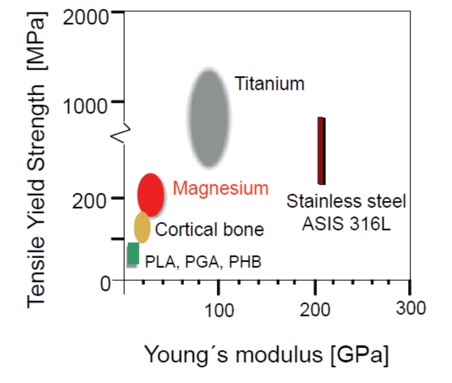
Institute of Tissue Engineering and Regeneration Medicine (iTERM)

The tremendous advancements in life sciences, engineering and information technology that have taken place in the last several decades have combined to make biomedicine a uniquely promising research discipline. Recent advances in biomedicine, in areas such as stem cells and molecular biology, and in bioengineering and biomaterials, have led to the emergence of the field of tissue engineering and regeneration medicine. The field has captured the attention and imagination of young and established scientists, as well as the general public and medical and biotech industries, and is one of the most rapidly developing fields in biomedicine. There is keen interest and commitment at CUHK in developing tissue engineering and regenerative medicine on campus, supported by existing strengths. There is a timely and justified need to establish an infrastructural component, the Institute of Tissue Engineering and Regeneration Medicine (iTERM) (組織工程與再生醫學研究所), building on existing excellence and strengths in CUHK to make high impact advances in neuromusculoskeletal tissue engineering and regeneration medicine. The founding of this institute has been endorsed with seeding fund and strategic support from the university . The goal of iTERM at CUHK is to integrate multiple disciplines in biomedical sciences, engineering, and clinical medicine, develop novel and enabling technologies, and build and maintain an educational infrastructure that attracts the best and brightest into the field. The initial targeted program areas will include (i) Stem Cells and Cell-based Therapies; (ii) Tissue Engineering for Regenerative Medicine; (iii) Microphysiological Tissue Models; and (iv) Clinical Trials and Precision Medicine. iTERM will capitalize on the support from both the government and the private sector to develop tissue engineering and regeneration medicine and to form close alliance with enterprises in the Science Park as well as other parts of Hong Kong and the region. Since the majority of research work on stem cell biology and regenerative medicine in CUHK are being conducted by various individuals in the Faculty of Medicine with tissue engineers from the Biomedical Engineering Program in the Faculty of Engineering, key members of iTERM will be mainly from Faculties of Medicine and Engineering, and the Faculty of Medicine will assume administrative responsibilities for its operation.

Research and Development of Magnesium-based Biometal as Class III Medical Implants for Orthopaedic Applications

Prof. Ling QIN is one of the leading scientists in the Orthopaedic Innovative Drug and Biomaterials Program, Musculoskeletal Research Laboratory, Department of Orthopaedics and Traumatology, the Chinese University of Hong Kong, Hong Kong SAR

Conventional orthopaedic implants that are made of permanent and rigid metals, such as stainless steel and/or titanium (Ti), may create stress shielding to the healing tissues and may impair the healing process. Furthermore, a second operation for removal of these permanent implants is required and may weaken the bone especially used for osteoporotic fracture that often results in refracturing. Magnesium (Mg), the eighth most common element in the crust of the earth, has attracted great attention to be developed into biodegradable or biocorrosive biometals as medical implants for both cardiovascular and orthopaedic applications (Fig. 1). However, Mg and its alloys may not provide enough mechanical support for some orthopaedic applications, such as for fixation of weight-bearing bones. Besides, mechanical properties of the current Mg-based implant would deteriorate rapidly due to the insufficient corrosion resistance after implantation in fractured bone. Fast degradation will be accompanied by gas bubble formation. Therefore, it is important to reduce the corrosion rate of Mg.



Long, Rack 1998; Wintermantel 1996; Hoeppner, Chandrasekran 1994

Fig. 1: Magnesium has a material and mechanical properties close to cortical bone that may have good potential for developing Mg-based orthopaedic implants.

Our group is collaborating with biomaterial scientists to develop innovative Mg-based implants or surface coating / surface treatment to reduce degradation rate and enhance or maintain its initial mechanical properties for fixation. The bone stimulation effects, both physiologically and biologically, of these implants were investigated using both in vitro and in vivo preclinical experimental models. We have specially designed an innovative intramedually nail containing Mg for the fixation of long bone fracture in rat model (Fig.2) and rabbit model (Fig. 3). This new material and design not

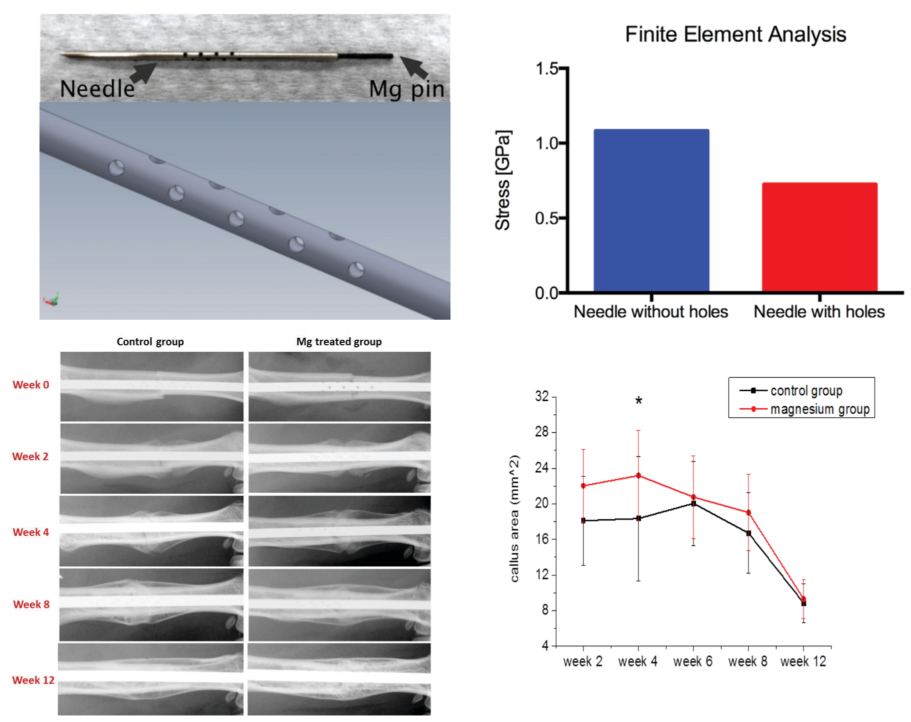


Fig. 2: Magnesium-containing intramedullary nail shows better bone shaft healing in rat femoral fracture model. Top left: Design of the implant for preclinical study in rats. Top right: Finite element analysis of the implant. The new design (needle with holes) showed 25% decrease in stress compared with the normal needle (needle without holes). Bottom left: Radiographic images of the fracture femur of rats with different implants (Stainless steel and Magnesium) at different time points. The implants provided sufficient support for fixation of femoral fracture. Bottom right: Quantification of the callus area between different treatment groups. Magnesium group showed larger callus area than the Control group.

only have proved to reduce the healing time and enhance the strength of the fractured bone, both by 30%, but also possibly avoid a second fracture. Mg-based biodegradable metals also predominantly stimulate new bone formation at the peripheral cortex of the shafts of long bones (such as the femur), rather than around the marrow cavity. The densely distributed pluripotent periosteum-derived stem cells (PDSCs) and sensory neuronal endings in periosteum might play critical roles during Mg-induced new bone formation (Fig. 4). This innovation is expected to apply to osteoporotic-related bone fracture after verification through clinical studies in the future. Our team is also investigating the application of Mg-based implants to other orthopaedic application, including Mg-based interference screws for fixation of anterior cruiciate ligament (ACL) repair, in addition to fracture fixation.

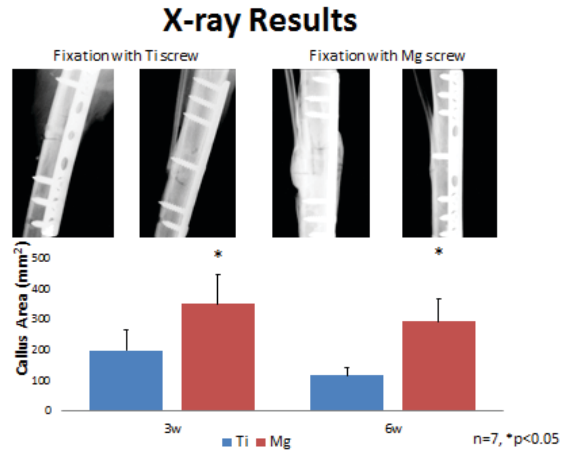


Fig. 3: Permanent metal screw-plate with inclusion of biodegradable magnesium screw enhanced callus formation of femoral shaft fracture in rabbits.

Recently, our innovative bone implant by combining biodegradable Mg and conventional metals has been awarded a silver medal in the 43rd International Exhibition of Inventions of Geneva (Fig. 5). This project has been generously supported by the Hong Kong RGC Collaborative Research Fund (CRF 2014/2015, C4028-14GF), SMART Programme of Lui Che Woo Institute of Innovative Medicine, Faculty of Medicine, the Chinese University of Hong Kong supported by Lui Che Woo Foundation Limited, and CAS-Croucher Founding Scheme for Joint Laboratories (Ref. CAS 14303).

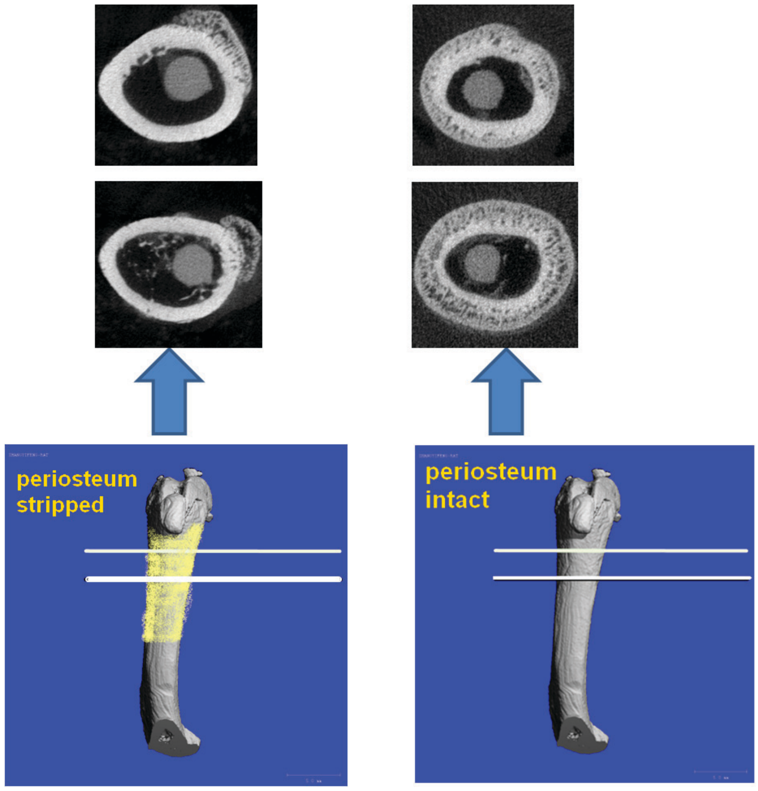


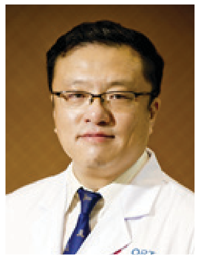
Fig. 4: Biodegradable magnesium induced new bone formation in long-bone shaft is periosteum-dependent: Left: partial removal of periosteum; Right: intact periosteum.

Fig. 5: Certificate of a silver medal in the 43rd International Exhibition of Inventions of Geneva

We would like to express our gratitude to all SCRM speakers and the following guests for their expert contributions to SCRM 2015 and for their effort to facilitate and lead an interactive discussion:

Prof. Wai-Yee Chan
School of Biomedical Science,
Faculty of Medicine,
CUHK

Prof. Jack Cheng
Department of Orthopaedics
& Traumatology,
Faculty of Medicine,
CUHK



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Prof. Arthur Mak
Division of Biomedical
Engineering,
Faculty of Engineering,
CUHK

Prof. Savio Woo
Musculoskeletal Research Center,
Department of Bioengineering,
University of Pittsburgh

We would also like to thank our generous sponsors:

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THE S. H. HO FOUNDATION LIMITED

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SESSION 1 MUSCULO-SKELETAL REGENERATION : FROM TECHNOLOGY TO THERAPY

Musculoskeletal Regeneration Research Network (MRN) - A Global Initiative with Impact

Prof. KM Chan
Department of Orthopaedics & Traumatology,
The Chinese University of Hong Kong,
Hong Kong, China

The World Health Organization (WHO) defines the four major non-communicable diseases (NCDs) as cardiovascular diseases, diabetes, respiratory diseases and cancer. The social-economic impacts of these four NCDs are poverty, unhealthy behavior, poor physical status, loss of income and high cost to the healthcare system. If we critically examine the social-economic impact of musculoskeletal conditions that they follow the same cycle in a slower but the longer period, this is the second greatest cause of disability with significant health cost worldwide.

Though musculoskeletal conditions are not usually fatal, they should be given the same attention for resource allocation if more recognition and action are taken by both the professional, academic and research communities. There is a WHO Disability Action Plan to systematically review musculoskeletal conditions with topics of osteoporosis, RA, OA, injuries and spinal conditions. To contribute to the WHO report on aging and health, we would like to add to this global movement our concerted efforts in the regeneration research as we strongly believe that through translational research from bench-to-bedside we may look for more cost-effective treatment.

The MRN was set up on November 13, 2013 in Hong Kong, following 3 successful years of SCRM. We planned to set up a platform where we can be a strong and united voice in the field of musculoskeletal regeneration research and emerge as a collective opinion leader in the field. Our tasks are to advance development of musculoskeletal regeneration research with an effective collaborative platform, to educate research personnel, and to bridge the gap in translational research. The inaugural international meeting was held at Karolinska institute, Sweden on June 1 and 2, 2015 with participation of more than 20 countries and regions.

We have also defined some collaborative projects which to be rolled out with the different consortium members. We have also mapped out international meeting to be held in 2016 in Utrecht, the Netherlands hosted by University Medical Center Utrecht (UMC Utrecht) and 2017 in Switzerland hosted by AO Foundation Center Davos. We believe that MRN will serve as a vehicle to bring together the talent and experience of research individuals and institutions. Together we will make a difference.

Prof. KM Chan is the Chair Professor of Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong. His clinical work includes arthroscopic surgery of the knee and shoulder and rehabilitation of sport injuries.

Prof Chan's research focuses on tendon and ligament regeneration, ACL healing & kinematic assessment and regenerative technology transfer. He has published more than 300 peer-reviewed scientific articles and edited more than 30 books in orthopaedics and sport medicine.

Prof Chan was the founding president of Asia-Pacific Orthopaedic Society for Sports Medicine (APOSSM) (1995-1997) (now renamed as Asian-Pacific Knee, Arthroscopy and Sports Medicine Society (APKASS)). He was the first Asian to assume President of International Federation of Sports Medicine (FIMS) (2002-2006). He was honored with the John Joyce Award of ISAKOS, FIMS Gold Medal, Alpha-Omega-Alpha Honorary Member of Stanford University, the Ambassador of the Bone & Joint Decade (BJD), and Takagi and Watanabe Award of APKASS.

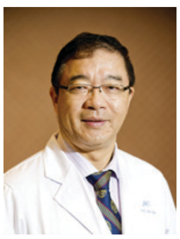
Introduction to Translational Medicine Platform in Shenzhen – SIAT Experience

Prof. Ling Qin
Department of Orthopaedics and Traumatology,
The Chinese University of Hong Kong,
Hong Kong, China

In December 2009, the Shenzhen Institutes of Advanced Technology (SIAT)of Chinese Academy of Sciences (CAS) and the Chinese University of Hong Kong (CUHK) jointly established the Center for Translational Medicine and Research and Development (TMC), which aims to promote translational research in Shenzhen and the Pearl River Delta region. TMC focus on clinical needs, utilizes granted platforms, including 1) the Shenzhen research and development of new drugs and preclinical technical service, 2) the Shenzhen bio-medical electronics and public health information technology services, and 3) the Shenzhen municipal personalized orthopedic implant production to develop orthopedic related medical devices and biomedicine. It also aims to highlight the importance of basic research on product transformation, and strive to publish major breakthroughs and findings on challenging scientific issues. The collaboration between TCM, hospitals and related enterprises focuses on projects that have the potential to be industrialized. Necessary documents and approvals, as well as preparations will be done for future clinical trials, which pave the way for any subsequent approval applications. This will also help consolidate the collaboration between government, industry, academia, research institutes and medicine.

Establishing a first-class industrial technology research institute is a goal of SIAT. The team strongly believes in the collaboration between clinicians and industry and the idea of translation. All members strive to understand the clinical needs and aim to make breakthroughs on the current core technologies and research and development concepts, in order to develop medical products that have the potential for industrialization and benefit the society. Since its establishment, the center has made good progress on building a strong team, the planning of test sites and various projects, collaborating with industrial companies, as well as foreign exchange. We are also actively collaborating with international and regional partners to further improve and consolidate the collaboration between government, industry, academic, research institutes and medicine as one transforming unit.

To build up and share the TMC platform is the focus of this presentation however, we will also share our experiences and lessons we got in the past 5 years in order to develop and collaborate towards realization of TMC's missions and objectives.



Dr. Qin is Professor and Director of Musculoskeletal Research Laboratory in the Department of Orthopaedics & Traumatology, the Chinese University of Hong and director of the Translational Medicine R&D Center of Shenzhen Institutes of Advance Technology of Chinese Academy of Sciences. Dr. Qin has been working on advanced diagnosis, prevention and treatment of musculoskeletal degenerations and injuries, in collaboration with research and clinical scientists and engineers. Dr. Qin is a number of journal editorial boards, including Co-editors-in-chief of Journal of Orthopaedic Translation, editorial member of a number of international journals, including JBMR and IJSM. He holds memberships in several international and national orthopaedic and related research organizations, including collage fellow of American Institute of Medical and Biological Engineering. He has received over 30 Research Awards and holds 4 patents. Dr. Qin published 7 monographs as editor or associate editor, over 350 journal papers in English, German, and Chinese, including 250 SCI articles, with citation over 5000 and an H-index of 40.

The Innovation, Translation and Commercialization of Orthobiologics: Opportunities and Challenges

Prof. Ming-Hao Zheng
Centre for Orthopaedic Research,
School of Surgery, University of Western Australia,
Nedlands, Western Australia

Research into orthobiologics is considering to be an emerging field that generate many attractions and interactions between academics, industries and venture capitals. With the improvement on understanding of pathogenesis of musculoskeletal diseases and process of tissue repair, many orthobiologic based substances have been developed and used clinically in the last two decades. These include the use of natural and synthetic matrix, growth factors and related extracts such as platelet rich plasma (PRP) and stem cell therapies. While academic institutions have played a major role in the development and translation of orthobiologics into clinical practices, there are many gaps and obstacles in the utilization of academic research in clinical setting.

Here we will discuss the general overview of orthobiologics followed by the summary of potential development of new biologic based products. Using PRP and cell therapies in bone, cartilage and tendon repair as examples, we will discuss the challenges in the development of orthobiologics for commercial use. We will also propose a step wise introduction on the development of orthobiologic product from scientific based approach in preclinical study into evidence based clinical approach in human trial. A recommendation of utilising the IDEAL framework as a standard international guideline for the introduction of new intervention of orthobiologics in clinical setting is proposed.

Professor Ming-Hao Zheng graduated from Shantou University and Sun Yet Sen University of Medical Science and obtained PhD (1993) and Doctor of Medicine (1999) at the University of Western Australia. He has admitted as fellow at the Royal College of Pathologists, UK and the Royal College of Pathologists of Australasia. Professor Zheng is currently the Associate Dean (International), Faculty of Medicine, Dentistry and Health Sciences, Winthrop Professor and Director of Centre for Orthopaedic Research at the University of Western Australia. He is the Chair of Western Australia Premier's Award Committee (Western Australia in Asia), Consultant Chief Scientific Officer of Orthocell Ltd. and Chung Kong Lecturing Professor at Zhejiang University, China. He has published 150 papers and holds 7 patents. Professor Zheng's major research focus is in the molecular and cellular biology of bone cells, development of autologous tendon cell therapy and cell-scaffold technology for cartilage, tendon and bone regeneration.

SESSION 2 STEM CELL BIOLOGY

Harnessing Skeletal Stem Cells and Environmental Niches for Bone Repair – From Bench to Clinic

Prof. Richard Oreffo
Bone and Joint Research Group, Centre for Human Development,
Stem Cells and Regeneration, Institute of Developmental Sciences,
University of Southampton,
Southampton, UK

Medical advances have led to a welcome increase in world population demographics. However, increased aging populations pose new challenges and emphasize the need for innovative approaches to augment and repair tissue lost through trauma or disease.

We have developed protocols for the isolation, expansion and translational application of skeletal stem cell populations with cues from developmental biology, nanotopography and nanoscale architecture as well as biomimetic niche development informing our skeletal tissue engineering approaches. We have developed ex vivo approaches to bone formation evaluation and analysis and central are large animal in vivo translational studies to examine the efficacy of skeletal stem and cell populations in innovative scaffold compositions for orthopaedics. The talk will also highlight current clinical translational studies to examine the efficacy of skeletal populations for orthopaedic application. Advances in our understanding of skeletal stem cells and their role in bone development and repair, offer the potential to open new frontiers in bone regeneration and offer exciting opportunities to improve the quality of life of many.

Funding from the BBSRC, MRC and EU FP7 (Biodesign) is gratefully acknowledged

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Prof. Richard Oreffo holds the chair of Musculoskeletal Science a is co-founder and current Director of the Centre for Human Development, Stem Cells and Regeneration at the University of Southampton.

Richard leads a multidisciplinary research group focused on developing strategies to repair bone & cartilage and understanding bone development; including the role of epigenetics in musculoskeletal diseases. He is internationally-recognised for his work on skeletal biology and the mechanisms involved in skeletal stem cell differentiation and bone regeneration through to the clinic. He has published over 225 papers (h-index 49; >9,000 citations) including breakthrough publications on skeletal cells and nanotopography, bone regeneration and epigenetics in Osteoarthritis in Nature Materials, ACS Nano, Stem Cells, Arthritis and Rheumatism and holds six patents.

Richard is the recipient of a number of awards, holds several visiting professorships, is on the editorial boards of six journals and is a Fellow of the Royal Society of Biology.

Cell Surgery Robotics in Cell Fusion Application

Prof. Dong Sun
Department of Mechanical and Biomedical Engineering,
City University of Hong Kong,
Hong Kong, China

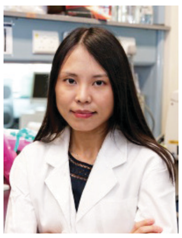
Cell surgery robotics, enabled with special bio-manipulation tools capable of operation at the single cell level, is an innovation based on traditional surgery robotics into the areas of precision medicine and regenerative medicine. This talk will present the application of cell surgery robotics equipped with optical tweezers manipulator to achieving engineered laser-induced cell fusion. Cell fusion is a process by which two or multiple cells combine to form a single entity. This process is important in numerous biological events and applications, such as tissue regeneration and cell reprogramming. Laser-induced cell surgery robotic system, in which optical tweezers is used to trap and transport cells and optical scissors is used to cut cells, can achieve specific cell fusion artificially with high selectivity and fusion efficiency. Our research on the fusion between hepatocellular carcinoma cell (HepG2) and human embryonic stem cell (hESC), has demonstrated that the generated fused cells can have both stemness and cancer characteristics, and hence more like tumor-initiative cells. Experimental results showed that the fused cells expressed both cancer markers and stemness markers, exhibited increased resistance to drug treatment and enhanced tumorigenesis. This case study has evidenced that the laser-induced cell surgery robotic system will provide a new opportunity to study fusion during cell differentiation, maturation, reprogramming, and canceration.

Professor Sun is an internationally renowned scholar in robotics and the related area of biomedical engineering. He graduated from Tsinghua University and The Chinese University of Hong Kong, and then performed his post-doc research at the University of Toronto, Canada. He joined the City University of Hong Kong in 2000, and is now Chair Professor and Head of the Department of Mechanical and Biomedical Engineering. He has successfully led many research projects supported by external grants including the Collaborative Research Fund of Hong Kong, with outcomes in both fundamental and applied research. He received numerous best paper awards, as well as industrial awards such as Hong Kong Awards for Industry. He received the 2014 Outstanding Research Award of City University of Hong Kong. He has served editorial boards for several international journals including the IEEE Transactions on Robotics, and organized international conferences as General or Program Chair. He is Fellow of the IEEE.

Driving Vascular Regeneration against Diabetic Limb Ischemia with Immune Intervention

Prof. Kathy Lui
Department of Chemical Pathology,
The Chinese University of Hong Kong,
Hong Kong, China

Type-2 diabetes (T2D) is a major risk factor for development of cardiovascular diseases and peripheral arterial disease. Using the leptin receptor-deficient mouse model as a surrogate for obesity-induced type 2 diabetes, we observed that the T2D mice had impaired arteriogenesis and angiogenesis following unilateral hindlimb ischemia induced by ligation of the femoral artery. Genome-wide transcriptome profiling via RNA-sequencing of endothelial cells purified from the T2D mice revealed a pro-inflammatory signature compared to that of the wildtype littermates. Moreover, we observed elevated gene expression levels of the pro-inflammatory cytokines in endothelial cells purified from the ischemic muscle of T2D mice compared to that of the wildtype control. We also observed, by flow cytometry, significantly more infiltration of macrophages, CD4+ helper and CD8+ cytotoxic T cells in the ischemic muscle of the T2D mice compared to that of the wildtype littermates. Therefore, we hypothesize that tipping the balance of the immune system away from the pro-inflammatory state yet towards the anti-inflammatory, proangiogenic state could promote vascular regeneration against diabetic limb ischemia.



Dr. Kathy Lui received her Bachelor of Science and Master of Philosophy degrees from the Department of Biochemistry, The Chinese University of Hong Kong. With support from the full scholarship, Dorothy Hodgkin Postgraduate Award, Dr. Lui completed her Ph.D in the field of Stem Cell Immunology at Sir William Dunn School of Pathology, University of Oxford, U.K. Dr. Lui was also the recipient of Senior Scholarship at Lincoln College, Oxford, U.K. and Peter Beaconsfield Prize in Physiological Sciences, Oxford, U.K. which is awarded specifically to young researchers who are 'capable of escaping from the stereotype of narrow specialization, and who display a wider grasp of the significance and potential applicability of their research'. Thereafter, Dr. Lui received the Croucher Foundation Fellowship and continued her postdoctoral training in the field of Stem Cells and Vascular Regeneration at Massachusetts General Hospital and Department of Stem Cell and Regenerative Biology, Harvard University, U.S.

Dr. Lui is now an Assistant Professor at Department of Chemical Pathology and a principal investigator at Li Ka Shing Institute of Health Sciences, Prince of Wales Hospital, CUHK. Dr. Lui's laboratory studies organ regeneration via human pluripotent stem cells and vascular signaling.

Pharmacological Inhibition of Protein Kinase G1 Enhances Bone Formation by Human Skeletal Stem Cells through Activation of RhoA-Akt Signaling

Prof. Li Chen
Medical Biotechnology Center,
Odense University Hospital,
Odense, Denmark

Development of novel approaches to enhance bone regeneration is needed for efficient treatment of bone defects. Protein kinases play a key role in regulation of intracellular signal transduction pathways, and pharmacological targeting of protein kinases has led to development of novel treatments for several malignant and nonmalignant conditions. We screened a library of kinase inhibitors to identify small molecules that enhance bone formation by human skeletal (stromal or mesenchymal) stem cells (hMSC). We identified H-8 (known to inhibit protein kinases A, C, and G) as a potent enhancer of ex vivo osteoblast (OB) differentiation of hMSC, in a stage- and cell type-specific manner, without affecting adipogenesis or osteoclastogenesis. Furthermore, we showed that systemic administration of H-8 enhances in vivo bone formation by hMSC, using a preclinical ectopic bone formation model in mice. Using functional screening of known H-8 targets, we demonstrated that inhibition of protein kinase G1 (PRKG1) and consequent activation of RhoA-Akt signaling is the main mechanism through which H-8 enhances osteogenesis. Our studies revealed PRKG1 as a novel negative regulator of OB differentiation and suggest that pharmacological inhibition of PRKG1 in hMSC implanted at the site of bone defect can enhance bone regeneration.

Dr. Li Chen obtained a BSc. and MEd from the Fudan University (Shanghai, China) with major in Microbiology and Neurobilogy, and PhD in 2005 from the Aalborg University, majored in stem cell differentiation. She then worked as postdoctoral fellow in the NCI/NIH in USA from 2006-2009. She joined the Dept. of Endocrinology and Metabolism, Endocrine Research Laboratory (KMEB), Odense University Hospital & University of Southern Denmark in 2009. Now she is an assistant professor, senior investiagtor and PhD supervisor. Her current studies focus at druggable targets for enhancing bone formation (small chemical molecular, miRNAs, siRNAs), Stem cell niche (cell and cell crosstalk, secreted factors of MSCs), Stem cell homing, Stem cell tissue engineering (biomaterials and markers of MSCs).

SESSION 3 MUSCLE

Functional Characterization of Malat1 in Skeletal Myogenic Differentiation and Muscle Regeneration

Prof. Hua-Ting Wang
Department of Orthopaedics & Traumatology,
The Chinese University of Hong Kong,
Hong Kong, China

As one of the most abundant lncRNAs in various cell types the exact cellular function of Malat1 is a matter of intense investigation. In this study we characterized the functional roles of Malat1 in skeletal muscle cell and muscle regeneration. Utilizing both cell culture (mouse myoblast cell line and freshly isolated muscle satellite cells) and a knock-out mouse model, our findings demonstrate that Malat1 plays a critical role in regulating gene expression during myogenic differentiation of satellite cells. Specifically, we found that knock-down of Malat1 accelerated myoblast differentiation in cultured cells. Consistently in vivo Malat1 knock-out mice displayed enhanced limb muscle regeneration after injury and deletion of Malat1 in dystrophic Mdx mouse also improved the muscle regeneration. Mechanistically, we showed that in the proliferating myoblasts, Malat1 recruits Suv39h1 to MyoD binding loci, causing trimethylation of histone 3 lysine 9 (H3K9me3) which suppresses the target gene expression. At the onset of the differentiation, miR-181a expression increases and targets the nuclear Malat1 transcripts for degradation through an Ago2 dependent pathway; the Malat1 decrease subsequently leads to the destabilization of Suv39h1/HP1β/HDAC1 repressive complex and displacement by a Set7 containing activating complex, which allows MyoD trans-activation to occur. Together our findings identify a novel regulatory axis of miR-181a-Malat1-MyoD/Suv39h1 in myogenesis and discover a novel molecular mechanism of Malat1 action.

Dr. Wang is currently an Associate Professor at Li Ka Shing Institute of Health Sciences, Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong. She received her B.S degree from Nanjing University, China and PhD at the Ohio State University (OSU), USA. Since joining Dr. Denis Guttridge's lab as a Postdoctoral researcher at OSU in 2004, she has been working on dissecting gene regulatory mechanisms using skeletal muscle cell as a model system. She is currently interested in studying the functional roles of non-coding RNAs in regulating gene expression in skeletal muscle stem cells and muscle regeneration.

Molecular Regulation of Muscle Stem Cell Quiescence and Activation

Prof. Tom Hiu-Tung Cheung
Division of Life Science,
The Hong Kong University of Science and Technology,
Hong Kong, China

Adult stem cells are unique in their ability to produce differentiated daughter cells while retaining their stem cell identity by self-renewal. The quiescent state of stem cells has long been viewed as a dormant state, but our understanding of the molecular regulation and physiological significance of this state remains limited. Dysregulation of quiescence results in the depletion of the stem cell pool. Deciphering the molecular mechanisms regulating the quiescent state will enable us to better devise approaches for stem cell therapies for degenerative diseases such as muscular dystrophy. Muscle stem cells, or "satellite cells", are a population of adult stem cells that are primarily quiescent in the absence of injury, making them an excellent model to study stem cell quiescence. We hypothesize that the state of quiescence is a poised state awaiting extrinsic signals for activation. Our data showed that the state of quiescence is actively controlled at the post-transcriptional level by microRNAs. Interestingly, we have identified microRNA-dependent pathways that regulate stem cell quiescence and underlie the functional heterogeneity of adult stem cells. Collectively, our data provides strong support for the hypothesis that the quiescent state is an actively regulated state.

Dr. Tom Cheung is an assistant professor in the Division of Life Science at the Hong Kong University of Science and Technology. He is currently a member of the Center for Stem Cell Research, the State Key Laboratory of Molecular Neuroscience, the Center for Systems Biology and Human Health and an affiliated member of the Division of Biomedical Engineering and Bioengineering Graduate Program at HKUST.

The main area of research interest of the Cheung laboratory at HKUST is somatic stem cell biology. The focus of the laboratory is to specify the molecular pathways that control stem cell quiescence and stem cell-mediated tissue regeneration to achieve a better understanding of somatic stem cell function in the context of tissue regeneration and diseases. The long-term goal of the Cheung laboratory is to understand molecular pathways that are essential for stem cell function during the process of biological ageing.

miRNAs Role in Regulating Stem Cell Heterogeneity of Skeletal Muscle Stem Cells

Prof. Da-Hai Zhu
National Laboratory of Medical Molecular Biology,
Department of Biochemistry and Molecular Biology,
Institute of Basic Medical Science, Peking Union Medical College,
Beijing, China

Skeletal muscle stem cells, called satellite cells, are quiescent and considered a heterogeneous population. Recent studies demonstrate that Pax7, a well-defined transcriptional regulator of satellite cell functions, influences the heterogeneity of satellite cell subpopulations (Pax7^{Hi} and Pax7^{Low}). However, the mechanism by which Pax7^{Hi} and Pax7^{Low} subpopulations are established and maintained during myogenesis remains elusive. Recently, we found that miRNA-431, predominantly expressed in skeletal muscle, mediates satellite cell heterogeneity by fine-tuning Pax7 levels during muscle development and regeneration. By generating the transgenic mice and knockout mice of this miRAN, we have established unique genetic models in which the Pax7^{hi} satellite cell subpopulation was enriched during development. With those mice models, we have investigated functional role of the subpopulation and the molecular mechanism for establishing and maintaining the subpopulations. Together, those mice models provide unique genetic system for investigating the cellular features and biological functions of Pax7^{Low} and Pax7^{hi} satellite cells during muscle development and regeneration.

Prof. Dahai Zhu is a Professor in National Laboratory of Medical Molecular Biology, Department of Biochemistry and Molecular Biology, Institute of Basic Medical Science, Peking Union Medical College Beijing China. He obtained his Ph.D. in molecular genetics at North Carolina Sate University and did his postdoctoral research in Howard Hughes Medical Institute, Duke University Medical Center. He has received several awards including NIH Merit Award, Fellow Award for Research Excellence of NIH. His research focus on

1) Establishment of heterogeneity of muscle stem cells during muscle development and regeneration;

2) Myofibers as a endocrine organ in regulating muscle stem sells. The work in his laboratory has been published in *Nature Communications; PNAS: Development: Cancer Research; Nucleic Acids Res.; Cell Research; Oncogene; Cell Death and Disease; BMC Genomics; J. Biol. Chem.: Cellular and Molecular Life Sciences; Molecular Pharmacology, Cellular Signaling ect.*

A Molecular Switch that Regulates the Cell Fate Choice between Muscle Progenitor Cells and Brown Adipocytes

Prof. Zhen-Guo Wu
Division of Life Science,
The Hong Kong University of Science and Technology,
Hong Kong, China

During mouse embryonic development, skeletal muscle progenitor cells (MPC) and brown adipocytes (BA) are known to be derived from the same Pax7+/Myf5+ progenitor cells. However, it remains unclear how each cell fate is selected and stably maintained. Unexpectedly, in *Pax7*-null MPC, we found that a group of BA-specific genes including *Prdm16* and *Ucp1* were upregulated with a concomitant reduction of key muscle-determination genes, indicative of a cell fate change from MPC to BA. Consistently, the Pax7-null MPC freshly isolated from the mutant mice efficiently formed UCP1+ BA in culture. Importantly, we showed that some Pax7-null MPC could also be converted to UCP1+ BA in vivo. Our mechanistic studies revealed a molecular switch that regulates the cell fate choice between MPC and BA. Our work provides the basis for potential cell-based therapy for treatment of obesity and diabetes in the future.

(This work was supported by a CRF grant (C6015-14G) from the Hong Kong Research Grant Council)

Dr. Zhenguo Wu received his Bachelor degree in 1986 from Nanjing University in China and his Ph.D. degree in Biochemistry in 1995 from the University of Western Ontario in Canada. He did his postdoctoral training with Prof. Michael Karin in the University of California at San Diego from 1996 to 1999 to study the MAP kinase-mediated cell signaling. He set up his own laboratory in the Hong Kong University of Science $& Technology in 1999.

Dr. Wu's laboratory has a long-standing interest in elucidating the roles of different intracellular signaling pathways in regulating muscle stem cells and muscle differentiation using both primary and immortalized mouse myoblasts as well as different mouse models.

Dr. Wu is currently a co-director in the Center for Stem Cell research, and a member in the Center for Systems Biology and Human Health at HKUST.

SESSION 4 CARTILAGE

Mesenchymal Progenitor Cells Derived from Blast-Traumatized Muscle: A Unique Cell Source for Tissue Engineering and Regeneration

Prof. Rocky Tuan
Center for Cellular and Molecular Engineering,
Department of Orthopaedic Surgery,
University of Pittsburgh School of Medicine,
Pittsburgh, USA

Blast trauma, such as those resulting from battlefield activities or industrial accidents, result in large scale extremity injuries. Massive tissue debridement is a standard of care for such injuries, which often result in amputations. A common, associated complication is heterotopic ossification (HO), the abnormal formation of ectopic bone in muscle tissue sites, which compromises tissue healing, vascularity, and proper fitting of prosthetics, and increases tissue morbidity. At present, the etiology of HO remains large unknown. Our recent studies have revealed that exposure to blast trauma results in the appearance of a population of multipotent progenitor cells (MPCs) in fibrotic regions within the traumatized muscle that are presumptive initiation sites of HO. The traumatized muscle-derived MPCs (TM-MPCs) display phenotypic characteristics of adult mesenchymal stem cells (MSCs), and their gene expression and growth factor profiles suggest the ability of these cells to initiate osteogenesis, both cell-autonomously or in a paracrine manner. In addition, our recent findings show that the TM-MPCs also exhibit neurotrophic and pro-angiogenesis activities, with vascular endothelial growth factor (VEGF) being involved in both activities. Our current research is focused on developing technologies to apply TM-MPCs as a readily available, autologous therapeutic cell source in individuals who have suffered blast trauma injuries.

(Support: NIH, US Department of Defense, Commonwealth of Pennsylvania)

Dr. Tuan (Ph.D., Rockefeller University; postdoctoral fellowship, Harvard Medical School) was a professor at the University of Pennsylvania and Thomas Jefferson University, before he was recruited to the NIH (NIAMS) as Chief of the Cartilage Biology and Orthopedics Branch in 2001. In 2009, he joined the University of Pittsburgh as Founding Director, Center for Cellular and Molecular Engineering, and Arthur J. Rooney, Sr. Chair and Professor and Executive Vice-Chair, Department of Orthopaedic Surgery, and Professor in Department of Bioengineering. Currently Dr. Tuan is the editor of *BDRC: Embryo Today*, and founding editor-in-chief of *Stem Cell Research and Therapy*. Since 2010, Dr. Tuan has served as Co-Director of the U.S. Armed Forces Institute of Regenerative Medicine. In 2012, he became the Founding Director of Center for Military Medicine Research and Associate Director of McGowan Institute for Regenerative Medicine. Dr. Tuan was appointed a Distinguished Professor in 2014 and received Chancellor's Distinguished Research Award in 2015. An author of more than 450 research publications, Dr. Tuan directs a multidisciplinary program focusing on the development, growth, function, and health of musculoskeletal system, the biology of adult stem cells, and developing stem cell- and smart biomaterial-based technologies that regenerate and/or restore function to musculoskeletal tissues.

Induction of Articular Cartilage Stem Cells and Cartilage Egeneration by Inhibiting NF-κB Signaling in Osteoarthritis

Prof. Xiao-Ling Zhang
Professor of Institute of Health Sciences,
Shanghai Jiao Tong University School of Medicine (SJTUSM) &
Shanghai Institutes for Biological Sciences (SIBS),
Chinese Academy of Sciences (CAS),
Shanghai, China

The presence of mesenchymal stem cells (MSCs) is a key component for a rapid and successful regeneration of various tissues. The articular cartilage appears to be hypocellular and avascular depending on the diffusion for its nutrient delivery and to be realized lack of stem cells before. Recently, the increased activation of Notch, Stro-1, vascular cell adhesion molecule-1, and Sox9 in osteoarthritis (OA) cartilage can indicate a regeneration response signaling in cartilage. Nevertheless, no in situ studies have identified that ACSCs were activated in OA and elucidated the signaling pathway may be involved during this process. In our study, we directly confirmed the existence of articular cartilage stem cells (ACSCs) in vivo and in situ for the first time both in normal and OA articular cartilage, we found an interesting phenomenon that ACSCs were activated and exhibited a transient proliferative response in early OA as an initial attempt for self-repair. Using in vitro and in vivo experiments, we discovered IL-1β can efficiently activate the NF-κB pathway and potently impair the responsiveness of ACSCs, whereas the NF-κB pathway inhibitor rescued the ACSCs chondrogenesis and induced cartilage regeneration in an OA animal model. Our results provided in vivo evidence of the presence of ACSCs and demonstrated the feasibility of inducing endogenous adult tissue-specific mesenchymal stem cells for articular cartilage repair and OA therapy.

Acknowledgement. This work was supported by grants from National Natural Science Foundation of China (No. 81190133), Chinese Academy of Sciences (No. XDA01030502), Science and Technology Commission of Shanghai Municipality (No. 12411951100, No. 13430710700), Shanghai Municipal Commission of Health and Family Planning (No. 2013ZYJB0501), Shanghai Municipal Education Commission (Grant No.J50206), Shanghai Jiao Tong University (No.2013SMC-A-6).

Prof. Xiaoling Zhang, Ph.D. , Professor of Institute of Health Sciences, Shanghai Jiao Tong University School of Medicine (SJTUSM) & Shanghai Institutes for Biological Sciences (SIBS), Chinese Academy of Sciences (CAS). Dr. Zhang's research mainly focuses on the therapy and mechanism of bone and cartilage degeneration, stem cells and bone and joint regeneration and repair. Dr. Zhang got many awards, such as, Best Paper Awards for Young Investigator of 29th FIMS World congress of Sport Medicine (2006), Shanghai Rising-star Program of Science and Technology Commission of Shanghai Municipality (2007), Raine International Visiting Research Fellowship of University of Western Australia (2008), Shanghai Aurora talent program of Shanghai Municipal Education Commission (2010). Dr. Zhang has authored over 58 scientific papers including some in J Bone Miner Res, stem cells, *Biomaterials, J Cell Mol Med*, J Control Release. Her papers have been cited 1206 times, H-index 20.

Collagen-Assisted Mesenchymal Stem Cell (MSC)-based Osteochondral Tissue Engineering

Prof. Barbara Chan
Medical Engineering Laboratory,
Department of Mechanical Engineering,
The University Hong Kong,
Hong Kong, China

Mesenchymal stem cells (MSCs) present a promising cell source for tissue engineering. We established a microencapsulation scaffolding technology to entrap MSCs in collagen microspheres and found the collagen fibrous meshwork an excellent scaffold in supporting MSC survival, growth and differentiation. Mesenchymal condensation is a critical transitional stage that precedes cartilage or bone formation. We hypothesize that collagen microencapsulation process recapitulates some early events of mesenchymal condensation and hence facilitated commitment towards chondrogenic and osteogenic lineages. Over the years, we have investigated the potential of using collagen-MSC microspheres for cartilage regeneration using in vitro and in vivo models. The importance of critical design parameters including the cell density, the chondrogenic pre-differentiation, the timing for differentiation induction and the hierarchical organization of the osteochondral tissues will also be discussed.

Dr. B. Chan obtained her B.Sc. in Biochemistry and Ph.D. in Surgical Science Division of the Faculty of Medicine at the Chinese University of Hong Kong. Dr. Chan received her postdoctoral fellowship in the Wellman Laboratories for Photomedicine, Massachusetts General Hospital in Harvard Medical School. Dr. Chan joined the University of Hong Kong in 2003 and is one of the core members in the Medical Engineering program. Her research interests include tissue engineering and regenerative medicine, natural biomaterials, stem cells, mechanoregulation and laser medicine.

Stem Cell Therapy for Osteoarthritis: Dream or Fantasy?

Prof. James Hui
Department of Orthopaedic Surgery,
National University of Singapore,
Singapore

Osteoarthritis (OA) is the most prevalent joint disease and a common cause of joint pain, functional loss, and disability that will affect an ever increasing number of patients, especially the elderly and the obese. While conventional treatments like physiotherapy or drugs offer temporary relief of clinical symptoms, restoration of normal cartilage function has been difficult to achieve. Mesenchymal Stem Cells (MSC) are a multipotent endogenous population of progenitors capable of differentiation to musculoskeletal tissues. MSCs have a well-documented immunomodulatory role, managing the inflammatory response primarily through paracrine signaling. MSCs related therapeutic approaches have shown feasibility, safety, and strong indications for clinical efficacy, which have a significant advantage to traditional surgical approaches such as autologous chondrocyte transplantation: no cartilage biopsy is necessary, thus no external stress and cellular damage are applied at the donorsite articular surface. However, based on the status of clinical investigations regarding stem cell therapy for OA, some authors have expressed concerns about the issues of dosing, timing of intervention, type of MSCs, mode and route of delivery of MSCs in clinical studies. We have performed comprehensive study on MSCs for cartilage regeneration. Different sources (bone marrow, adipose and peripheral blood) of MSCs were tested for chondrogenic differentiation and bone marrow was chosen for clinical application because of preservation of good proliferation and multiple lineage differentiation capacity. We developed a validated methodology for MSCs culture and administration route for clinical application. Hundreds of OA patients have benefited from this treatment over years. However, currently there are no established guide lines from governmental and intergovernmental agencies for stem cell use in clinical applications. More study is needed for better understanding of MSCs to improve future cell-based therapies and tissue engineering strategies.

Prof. James Hui received his MBBS degree from National University of Singapore in 1990. He received his FRCS (Royal College of Surgeons, (Edinburgh UK) in 1994, FAMS (Academy of Medicine, Singapore) in 1999 and Doctor of Medicine (National University of Singapore) in 2008. Dr Hui is currently a Professor at the Department of Orthopaedic Surgery, National University of Singapore. He is heading Division of Paediatric Orthopaedics and is Director of Clinical Services for Department of Orthopaedic Surgery, National University Hospital. He was also appointed as Director for Tissue Engineering and Cell Therapy Laboratory, National University Health System, Singapore and is a Group Leader for Cartilage Division of National University of Singapore, Tissue Engineering Programme (NUSTEP). He is also currently the vice-president of Asian Cartilage Repair Society.

SESSION 5 TENDON

Achilles' Tendon Rupture Caused by Microbial Influences: A Feasible Aetiology?

Prof. Christer Rolf
Department of Clinical Science,
Intervention and Biotechnology, Karolinska Institute,
Stockholm, Sweden

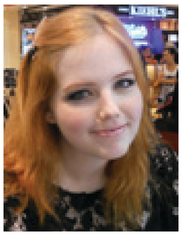
Ms. Chelsea Hopkins
Department of Orthopaedics & Traumatology,
The Chinese University of Hong Kong,
Hong Kong, China

Achilles' tendon ruptures are typically associated with chronic Tendinopathic structural alterations. Given the insidious nature of Tendinopathy, failed tendon healing may result from exposure to direct or indirect risk factors with long incubation periods such as microbes. There are a number of examples of microbe-induced matrix degeneration, for example, chronic myocarditis may, in some cases, be linked to viruses and bacteria, which lead to activation of nucleotide-binding oligomerisation domain (NOD) containing proteins and results in cell apoptosis and matrix disturbance similar to that in Tendinopathy in peripheral tendons. At least three reported cases of Tendinopathy were found to be linked to bacteria, two cases to *Borrelia burgdorferi* (Lyme disease) and one case to *Mycobacterium tuberculosis*. We propose a theory that microbial influences may play a role in the development of chronic Tendinopathic changes, occasionally leading to complete tendon rupture.

We detected the presence of microbial footprints in 8 out of 24 operated Achilles' tendon rupture samples, being positive for 16S rRNA (33.3%), while healthy hamstring tendon samples (n=24) were all negative. Serological findings also suggest higher microbial exposure in a similar sized group of patients with Achilles' tendon rupture, than that in a control group of healthy subjects. As expression of NOD1 is prevalent in many Tendinopathy samples but not in healthy tendon samples, it is possible that these findings combined reflect an activation of NOD pathways in tendon cells which could contribute to pathological structural changes associated with failed tendon healing. In an experimental model, we treated cultured healthy tendon-derived stem cells with diaminopimelic acid (DAP; an agonist of NOD1) and demonstrated a significant up-regulation in NOD1 and interleukin-1 beta (IL-1β). As cyclic stretching (mimicking overuse) on tendon cells also leads to increased IL-1β expression and altered cellular activities related to failed tendon healing, the current evidences suggest that microbes may play a role in the pathogenesis of Tendinopathy.

Although a direct causal relationship between microbes, Tendinopathy and tendon rupture is not established, the implications of further supportive evidence may lead to novel, evidence-based treatment for Tendinopathy, which may potentially prevent some complete tendon ruptures, in the long-run.

Prof. Christer G Rolf is Professor of Sports Medicine at the Department of Clinical Science, Intervention and Biotechnology, Karolinska Institutet (KI), Stockholm, Sweden. He is Consultant Orthopaedic Surgeon, Head of Arthroscopy and Sport Injury at Department of Orthopaedic Surgery and Project leader of Ambulatory Surgery Developments at Karolinska University Hospital. He is member of the Steering committee of Regenerative Medicine Research and PI and Coordinator of the Joint Research Centre of Musculoskeletal Regenerative Medicine between KI and the Chinese University of Hong Kong (CUHK). He is (Hon) Professor of Sports Medicine since 2012 of CUHK, served as Visiting Professor in 1997-2000, and was Professor of Sports Medicine at University of Sheffield 2000-2009.



Ms. Chelsea Hopkins is currently enrolled as a Master of Philosophy student at the Chinese University of Hong Kong. Prof. Rolf is her co-supervisor and her project is focused on the role of microbes in the development of tendinopathy.

Autologous Tenocyte Therapy and Bioreactor for Tendinopathy: From Bench to Bedside

Prof. Ming-Hao Zheng
Centre for Orthopaedic Research,
School of Surgery, University of Western Australia,
Nedlands, Western Australia

Tendinopathies and tendon injuries are the most common soft tissue disorders. Currently available conservative treatments are not satisfactory. We and others have observed that elevated rates of apoptosis and autophagy of tenocytes leading to depletion of the functional tenocyte pool in the region of the tear may account for fatigue of the normal healing response. On the basis of the pathology studies, we proposed that restoration of the population of functional cells capable of synthesizing ECM and repairing the damaged tissue within the tendon might be an effective therapeutic strategy for tendon repair.

Based on previous pre-clinical cell tracking and animal studies, we have developed protocol for the autologous tenocyte injection technique (ATI). Patients with chronic, refractory tendinopathy were recruited for study. Patients with lateral epicondylitis , gluteal tendionpathy, rotator cuff tendon tear, Achilles tendinopathy who have failed for previous injection therapies were recruited into the case cohort. A tiny needle tendon biopsy (most often the patellar tendon) was used as the source material for autologous tendon cells. The cells are isolated from the tendon tissue by enzymatic digestion and expanded in vitro in a GMP-certified laboratory. Cell characterisation were conducted to examine the purity, potency, identify and viability. Cells are reconstituted in an assembly medium containing autologous serum and implanted in the site of tendinopathy by ultrasound-guided injection. Maximum follow up of these patients with functional score and MRI were 5 years.

Clinical outcomes were assessed from baseline up to 5 years post-treatment. Significant improvements were observed for all of site specific functional scores including QuickDASH, UEFS, Oxford hip score VAS maximum pain score and grip strength starting from one month post-treatment. These improvements were maintained for up to 5 years post-treatment. MRI scores were significantly improved up to 12 months post-treatment, and demonstrated tendon in-fill and reduction in the extent of tendinopathic lesions in LE, rotator cuff and Achilles but less in gluteal tendinopathy.

In conclusion, autologous tendon-derived cells offer a strong advantage for tendon tissue regeneration. ATI, the first homologous cell therapy technique developed for the treatment of tendinopathy, has the potential to address this unmet clinical need by replenishing the pool of functional tenocytes in the site of tendinopathy, facilitating structural repair as well as improving pain and function.

Professor Ming-Hao Zheng graduated from Shantou University and Sun Yet Sen University of Medical Science and obtained PhD (1993) and Doctor of Medicine (1999) at the University of Western Australia. He has admitted as fellow at the Royal College of Pathologists, UK and the Royal College of Pathologists of Australasia. Professor Zheng is currently the Associate Dean (International), Faculty of Medicine, Dentistry and Health Sciences, Winthrop Professor and Director of Centre for Orthopaedic Research at the University of Western Australia. He is the Chair of Western Australia Premier's Award Committee (Western Australia in Asia), Consultant Chief Scientific Officer of Orthocell Ltd. and Chung Kong Lecturing Professor at Zhejiang University, China. He has published 150 papers and holds 7 patents. Professor Zheng's major research focus is in the molecular and cellular biology of bone cells, development of autologous tendon cell therapy and cell-scaffold technology for cartilage, tendon and bone regeneration.

Low Dose Steroid and Tendinopathy

Dr. Bing-Hua Zhou
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Southwest Hospital,
Third Military Medical University,
Chongqing, China

OBJECTIVES:
Substance P (SP) is known to be involved in neuropathic pain, chronic inflammation, and tendinopathy. The present study evaluated the effects of different doses of SP on tendon-derived stem cells (TDSCs) in vitro and tendons in vivo.

METHODS:
For the in vitro study, TDSCs cultured in growth medium with different concentrations of SP (negative control, 0.1 nM, and 1.0 nM). The effects of SP on TDSCs were examined with respect to their ability to proliferate and differentiate. For the in vivo study, we injected different doses of SP (saline control, 0.5 nmol, and 5.0 nmol) into rat patella tendons to investigate the effects of SP on tendons.

RESULTS:
Low and high doses SP significantly enhanced the proliferation ability of TDSCs. Low-dose of SP induced the expression of tenocyte-related genes; however, high-dose of SP induced the expression of non-tenocyte genes, which was evident by the high expression of PPARγ and collagen type II. In the in vivo study, only high-doses of SP (5.0 nmol) induced the tendinosis-like changes in the patella tendon injection model. Low doses of SP (0.5 nmol) enhanced the tenogenesis compared with saline injection and the high-dose SP group.

Dr. Binghua Zhou, MD, PhD work for the Department of Orthopaedics, Southwest hospital, Third military medical university.

Dr. Zhou's clinical work focuses on the sports medicine, especially on the foot and shoulder surgery.

He began to perform the research of tendon stem cell on 2009, and he joined two research programs of national nature of science funding of China (NNSFC) in the last five years and won a research program of NNSFC as an applicant in 2015. He published 5 papers about tendon stem cells as the first author.

He is the fellow of foot and ankle association of Chinese association of othopaedic surgeon; shoulder association of SICOT. He also is the editor of the magazine of International Journal of Physical Therapy and Rehabilitation.

Bone Marrow Stromal Cell-Seeded Tendon Slice Constructs

Prof. Ting-Wu Qin
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State Key Laboratory of Biotherapy,
West China Hospital, Sichuan University,
Chengdu, China

The extracellular matrix (ECM) microenvironment for the stem cell niches, including the biochemical composition, matrix topography and stiffness, and mechanical stimulus, is crucial to stem cell differentiation. The purpose of the study was to explore the capacity of the decellularized tendon slices (DTSs) to induce bone marrow stromal cells (BMSCs) tenogenic differentiation and the effects of mechanical loading on BMSCs seeded on the DTSs. The DTSs were found to retain the native tendon ECM microenvironment cues, including the inherent surface topography, well-preserved tendon ECM biochemical composition and similar stiffness to native tendon. When the BMSCs were cultured on the DTSs, the results demonstrated that the DTSs have the capacity to support these cells homogeneous distribution, alignment, significant proliferation and tenogenic differentiation. Furthermore, DTSs were seeded with BMSCs and subjected to cyclic stretching. The results showed that BMSCs penetrated into the DTSs and formed dense cell sheets after 7 days of mechanical stretching. Gene expression of type I collagen, decorin, and tenomodulin significantly increased in cyclically stretched BMSC-DTS constructs compared with the unstrained control group. Taken together, the findings of the study indicate that the DTSs can provide a naturally inductive microenvironment for the tenogenic differentiation of BMSCs. Our results support the use of BMSCs seeded acellular tendon slices with cyclic mechanical stimulus to develop a method of constructing a functional engineered tendon patch for tendon repair and regeneration.

Prof. Ting-Wu Qin received his Ph.D. degree in Biomechanics from Chongqing University in 1997. In his early postdoctoral work, he was involved in tendon tissue engineering for tenocyte-biomaterial adhesion at Orthopedic Surgery of West China Hospital. In 1999, he joined the Institute of Stem Cell and Tissue Engineering, West China Hospital of Sichuan University, where he is currently a team principal research scientist. In 2007, Dr. Qin did his postdoctoral work in tendon tissue engineering at Mayo Clinic, Rochester, USA as a visiting scientist. At West China Hospital, his team has developed bio-derived biomaterials for tissue engineering, which has led to publications in Biomaterials. In particular, Dr. Qin and his co-workers have pioneered a promising platform based on native tendon slices by the decellularized tendon tissue, which provides the niche microenvironment for multiple cell types. In ongoing work, he is pursuing his interest in ECM microenvironment and stem cell differentiation.

Tendon Differentiation and Regeneration

Prof. Hong-Wei Ouyang
Faculty of Basic Medicine,
Zhejiang University School of Medicine,
Zhejiang, China

The repair of injured tendons remains a formidable clinical challenge, due to our limited understanding of tendon stem cells and the regulation of tenogenesis. Here, we investigated the role of the transcription factor Mohawk (Mkx) and show a particular role of Mkx in promoting the tenogenesis of MSCs via activating Scx and tendon extracellular matrix molecules both in vitro and in vivo, and Mkx had more profound effects than Scx in promoting tenogenic gene expression and collagen fibril growth. We also demonstrate the crucial roles of Nestin and Nesin+ TSPC in tenogenesis and the maintenance of TSPCs phenotype. These findings offered new insights into tendon differentiation and providing an alternative way of obtaining cells suitable for tendon regeneration.

Professor Ouyang HongWei is the "Qiu-Shi" professor of Zhejiang university and Chair-elected of China society of tissue engineering & regenerative medicine. His research mainly focused on musculoskeletal tissue repair and regeneration and has 60+ publications on STEM CELL, BIOMAT, TISSUE ENG, ARTH&RHEUM, etc journals as corresponding authors.

SESSION 6 LIGAMENT & BONE-TENDON JUNCTION

Enhancement in ACL Graft Healing - Where are the Missing Gaps?

Dr. Patrick Shu-Hang Yung
Department of Orthopaedics & Traumatology,
The Chinese University of Hong Kong,
Hong Kong, China

ACL reconstruction (ACLR) is successful to partially restore knee functions, but the healing outcomes are always compromised by poor biological healing responses. Currently there is a myriad of studies investigating biological enhancement of graft healing in order to yield good clinical outcomes. There are several limiting factors for graft healing in ACLR, including 1) degenerative changes associated with graft remodeling; 2) Poor peri-graft bone quality that compromises graft incorporation; and 3) Poor graft incorporation. We have characterized these processes in preclinical animal models and demonstrated the effectiveness of some treatment strategies such as vitamin C irrigation saline, supplementation of alendronate, application of tendon derived stem cell sheets, and local delivery of an activator of tissue remodeling (GHK-Cu). However, if these treatment strategies are going to be applied clinically, it is necessary to devise suitable clinical evaluation method to assess the treatment outcomes as the conventional evaluation methods we use in animal models (histology and mechanical tests) will not be applicable. Current approaches in assessing recovery after ACLR includes MRI and static knee laxity tests, which do not truly reveal functional deficit of the knee with ACL injuries. Therefore, we are now developing a new method to assess knee function after ACL reconstruction by a user-friendly motion capture system. Preliminary findings showed that patients with ACL deficiency a significantly reduced knee flexion during landing in single-legged hop landing task. Further development may lead to the establishment of quantitative assessment of knee function, which may help to evaluate the effect of biological enhancement of graft healing with respect to functional recovery after ACLR.

Dr. Yung Shu-Hang Patrick is the Consultant of Department of Orthopedics and Traumatology and the chief leader of the Sports Medicine & Arthroscopy Team of the Chinese University of Hong Kong. He assumes important positions in local & international organizations in Sport Medicine & Arthroscopy surgery, namely *International Federation of Sports Medicine*, *The Asian Federation of Sports Medicine*, and *The Asia-Pacific Knee, Arthroscopy and Sports Medicine Society.*

Dr Yung has pioneered a number of new technologies in minimal invasive & arthroscopy surgery, and published many scientific papers in international journals. He has been heading the first ever taught postgraduate program in Sports Medicine & Health Science in Hong Kong since 2005. He has been taking care of Hong Kong Elite Athletes in Hong Kong Sports Institute as the Medical Consultant for over 10 years.

In recognition of Dr. Yung's contribution to the field of sports medicine and arthroscopy surgery in Hong Kong, he was awarded the "**Ten Outstanding Young Persons of Hong Kong**" in 2009.

Use of Strontium in Enhancing Ligament - Bone Healing

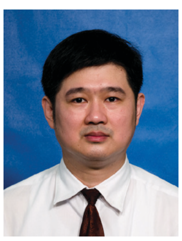
Prof. WP Yau
Department of Orthopaedics and Traumatology,
The University of Hong Kong,
Hong Kong, China

One of the major problems in anterior cruciate ligament (ACL) reconstruction using soft tissue graft is the difficulty in achieving prompt and reproducible healing of the graft. The time required for healing of the graft within the bone tunnel (graft osteointegration) and subsequent remodeling into an ACL-like structure (ligamentization) is notoriously long. Furthermore, the graft is transiently weakened during this remodeling procedure. It is prone to fail if excessive stress is applied. Graft fails in mechanical testing by pulling out from the bone tunnel in early post-operative period and mid-substance rupture during the "ligamentization" phase. This leads to the need of prolonged protection and avoidance of pivoting sport for six to nine months after surgery.

Recent attempts have been made in accelerating the "ligamentization" process of ACL graft. These include local application of platelet rich plasma, various growth factor and preserving the remnant of native ACL during the reconstruction.

We had developed a novel strontium enriched CPC cement (Sr-CPC) by incorporating 5% strontium into the CPC system. Our in vitro data suggested that the new 5% Sr-CPC was superior to traditional CPC in terms of cell adhesion study, cell proliferation study and alkaline phosphatase expression of the treated osteoblasts. The hypothesis of accelerated healing of the graft by applying Sr-CPC cement within the bone tunnel was tested in a small animal ACL reconstruction model. At 6 weeks, the tendon-bone interface in the control group was only filled up with fibrovascular tissue. However, the gap in the Strontium group had already been completely obliterated by new bone formation with evidence of early Sharpey fiber formation. At 12 weeks, Sharpey fiber started to appear in the control group. In the Sr-CPC group, the healing of the tendon graft to the bone wall was completed. Early evidence of remodeling of the tendon bone junction with tendon-fibrocartilage-bone transition was noted. At 24 weeks, mature Sharpey fiber formation was noted in the control group. For the Strontium side, complete remodeling of the tendon-bone junction into normal ligament-bone insertion was found. Histomorphometric analysis showed that the healing of the graft within the bone tunnel in the Sr-CPC treated limb was at least three to six weeks faster than the control limb.

The adoption of biological augmentation in ACL reconstruction may revolutionize the rehabilitation program in the future. However, further researches are required to demonstrate the beneficial effect before it can be recommended to the general public.



Dr. WP Yau is the Chief of Division of Sports and Arthroscopic Surgery and Clinical Associate Professor of Department of Orthopaedics and Traumatology in the University of Hong Kong. He is currently the Chief censor of Hong Kong College of Orthopaedic Surgeons and Immediate past president of Sports Medicine Chapter of Hong Kong Orthopaedic Association.

Dr. Yau specializes in sports medicine and joint reconstruction surgery in shoulder, knee and hip. Dr. Yau published 60 peer-reviewed articles, 1 book chapter and over 80 conference papers and has delivered more than 50 invited lectures and close to 100 presentations in both regional and international conferences. Dr. Yau received the Author Yau Award of HKOA in 1994 and 2004, David Fang Trophy of HKOA in 2004, Harry Fang Gold Medal Award of HKCOS in 2000, Japan Orthopaedics and Traumatology Foundation Fellowship Award in 2008 and Orthopaedic Basic Science Award of HKOA in 2014.

Preclinical Studies on Biodegradable Mg and its Alloys for ACL Reconstruction

Prof. Ling Qin
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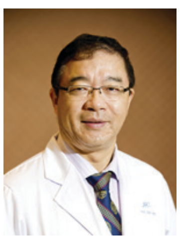
The Chinese University of Hong Kong,
Hong Kong, China

It is known that magnesium (Mg) is the eighth most common element in the crust of the earth and now attracts great attention to become biodegradable or biocorrosive medical implants for both cardiovascular and orthopaedic applications. In orthopaedics, Mg and its alloys are mainly considered suitable for degradable bone implants with good initial stability.

The author's group is conducting R&D of orthopaedic implants, in collaboration with biomaterial scientists for developing Mg and its alloys as biocorrosive orthopaedic implants and investigating their bone stimulation effects physiologically and biologically using both in vitro and in vivo preclinical experimental models, including Mg-based interference screw for its indication for ACL reconstruction. Biodegradable Mg metal, as one of the most promising osteopromotive medical device with favorable mechanical properties, has been tested for various indications using animal models by the authors and other groups. We stablished ACL reconstruction surgical model in rabbits and compared currently available Ti screw with our innovative Mg screws and evaluated in both temporal and spatial fashions. Serum Mg level was also measured. For *in vitro* studies, the effects of extracellular Mg ion level in cell culture medium on cell migration were investigated by using transwell co-culture system for incubation of bone marrow stem cells (BMSC) and tendon-derived fibroblasts.

We did not find changes in serum Mg level after implantation of Mg screws and significant changes in inflammatory response of tendon-bone interface zone in the entire experimental period. More mineralized fibrous tissues were formed in Mg group. No significant differences in the maximum load and stress between the two groups were measured although bone tunnel widening was observed more in Mg group. Wit Mg degradation overtime, early new bone formation and more mineralized fibrous tissue formation in the graft close to bone indicated that Mg could effectively enhance the graft incorporation into bone, which may be partially ascribed to promoted BMSC migration via our *in vitro* study.

Acknowledgement: This research program is funded by Hong Kong RGC Collaborative Research Fund (CRF 2014/2015, C4028-14GF), NSFC/RGC JRS project N_CUHK449/13), SMART Programme of Lui Che Woo Institute of Innovative Medicine, Faculty of Medicine, the Chinese University of Hong Kong supported by Lui Che Woo Foundation Limited.



Dr. Qin is Professor and Director of Musculoskeletal Research Laboratory in the Department of Orthopaedics & Traumatology, the Chinese University of Hong and director of the Translational Medicine R&D Center of Shenzhen Institutes of Advance Technology of Chinese Academy of Sciences. Dr. Qin has been working on advanced diagnosis, prevention and treatment of musculoskeletal degenerations and injuries, in collaboration with research and clinical scientists and engineers. Dr. Qin is a number of journal editorial boards, including Co-editors-in-chief of Journal of Orthopaedic Translation, editorial member of a number of international journals, including JBMR and IJSM. He holds memberships in several international and national orthopaedic and related research organizations, including collage fellow of American Institute of Medical and Biological Engineering. He has received over 30 Research Awards and holds 4 patents. Dr. Qin published 7 monographs as editor or associate editor, over 350 journal papers in English, German, and Chinese, including 250 SCI articles, with citation over 5000 and an H-index of 40.

Collaborative Potentials for Developing Mg-based Products for Orthopaedic Applications

Prof. Yang-De Li
Dongguan EONTEC Co Limited,
Dongguan, China

In recent years, there have been significant breakthroughs in medical applications of magnesium and its alloys. Despite the dedicated resources spent by various countries (including the USA, Japan, and South Korea) in this area of research, China and Germany remain the two dominant players in this field. In China, many research institutions and universities such as the Institute of Metals Research, Sichuan University, and Peking University have published extensively on this topic as well.

Magnesium-based medical devices are now available in several countries. Syntellix from Germany was granted the CE mark for their magnesium screw at the end of 2013, while U&I from South Korea has received permission from the KFDA to commercialize their magnesium screw earlier this year. EONTEC from China is now trying its best to gain approval for its high purity biodegradable magnesium screws and to promote the upscaling of its magnesium implants.

The applications of medical magnesium now mainly focuses on cardiovascular stents, bone screws, and bone plates. However, Prof. Lugee Li, Director of the China Medical Magnesium Association, is keen to explore the potential of magnesium in, amongst others, blood vessel connectors, spinal cages, nerve scaffolds, and anastomatic staples.

Professor Lugee Li is the Chairman of Dongguan EONTEC Co Limited (sz.300328) and the Director of the China Medical Magnesium Association. He is an energetic and creative entrepreneur who spearheaded the development and subsequent clinical trial of the first biodegradable bone screw in China. He has also worked on magnesium implants for cardiovascular applications and nerve repair. In addition, Professor Li has identified amorphous metals as the next big area of matertial research for medical implants. He always welcomes collabration with any interested parties.

A Novel Magnesium Ring Device For Anterior Cruciate Ligament Healing - An *In Vivo* Study in Goats

Dr. Kathryn Farraro
Musculoskeletal Research Center,
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Pittsburgh, USA

INTRODUCTION: In our research center, we have used biological augmentation via extracellular matrix (ECM) bioscaffolds to heal a surgically transected goat anterior cruciate ligament (ACL) [1]. However, because ACL healing remains slow, mechanical augmentation is also needed to load the ACL and prevent insertion site disuse atrophy. We thus developed a bioresorbable magnesium (Mg) ring device and surgical technique ("Mg ring repair") to repair and heal a transected ACL, to be combined with our earlier model of ECM treatment. The objective of this study was to assess ACL healing following Mg ring repair + ECM treatment.

Table 1: APTT (A) and in-situ forces in the ACL (B) of the sham-operated and Mg ring-repaired goat stifle joints (* indicates statistical significance compared to sham-operated; $P<0.05$)

	Flexion Angle		
	30°	60°	90°
A. Anterior-posterior tibial translation			
Sham-operated	3.8 ± 1.5	4.0 ± 1.5	3.4 ± 1.3
Mg ring-repaired	9.8 ± 2.3*	11.5 ± 1.9	9.4 ± 1.4*
B. In-situ forces in the ACL			
Sham-operated	63 ± 6	64 ± 6	53 ± 4
Mg ring-repaired	59 ± 16	41 ± 29	19 ± 19*

Figure 1: Gross morphology of the ACL treated with Mg ring repair + ECM (A), the normal ACL (B), and the ACL treated with ECM alone (C)

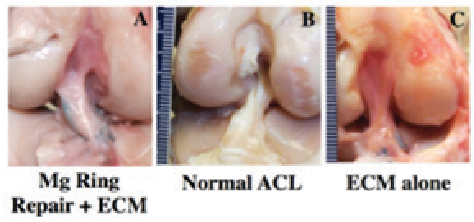

Table 2: Structural properties of the healing and sham-operated FATCs (*indicates a statistical significance compared to sham-operated; $P<0.05$)

	Healing	Sham-operated control
Stiffness (N/m)	77 ± 33	128 ± 25
Ultimate Load (N)	371 ± 240*	1070 ± 326
Ultimate Elongation (mm)	5.7 ± 0.8	10.7 ± 3.3

METHODS: Mg ring repair [2] and ECM treatment [1] were applied to transected ACLs in skeletally-mature goats (N=4), which were sacrificed at 12 weeks of healing. The resulting stifle joint kinematics and in-situ forces in the ACL of the healing and sham-operated joints were measured using a robotic/UFS testing system [3] under externally-applied loads. The gross morphology of the ACL, its cross-sectional area (CSA) [4], and the structural properties of the femur-ACL-tibia complex (FATC) were also assessed. T-tests were used to compare the data to those of the sham-operated controls, as well as to previous data using ECM treatment alone [1].

RESULTS: The healing ACL was found to be a robustly healed neo-ligament (Fig. 1A) resembling a normal ACL in both shape and CSA (Fig. 1B). The joint stability in terms of anterior-posterior tibial translation (APTT) and the in-situ force in the healing ACL were reduced compared to the sham-operated ACL (Table 1), which is consistent with other studies of ACL healing or reconstruction in this animal model [1,5,6]. In terms of the structural properties (Table 2), the stiffness of the healing FATC reached 60% of that of the control, and the ultimate load reached 35%.

Compared to joints treated with ECM alone [1], joints treated with Mg ring repair + ECM were similar in terms of joint and ACL function. However, the gross morphology of the healing ACL was greatly improved with Mg ring repair + ECM (Fig. 1C), and the normalized stiffness and ultimate load of the healing FATC were also 30% and 150% higher, respectively.
DISCUSSION: This study demonstrated the effects of a Mg ring device and ECM bioscaffolds on healing of a transected goat ACL. The results showed that the combination of biological and mechanical augmentation could enhance ACL healing compared to biological augmentation alone, leading to a stronger ACL.

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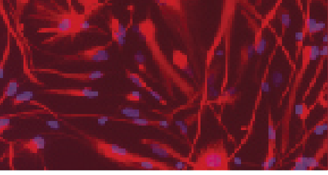
ACKNOWLEDGEMENTS: Support from an NSF Engineering Research Center Grant (#0812348) and the Commonwealth of Pennsylvania is gratefully acknowledged.

Dr. Katie Farraro is a post-doctoral researcher in the Department of Bioengineering at the University of Pittsburgh. After earning her B.S. (2008) and M.S. (2010) from the University of California, Davis, Dr. Farraro completed her Ph.D. studies at the Musculoskeletal Research Center in 2015 under renowned Professor Savio L-Y. Woo. Her Ph.D. dissertation involved the development and testing of a novel magnesium ring device for anterior cruciate ligament (ACL) healing.

During her time as a doctoral student, Dr. Farraro's achievements included First Place in the Randall Family Big Idea Competition, World Congress of Biomechanics PhD Student Competition, International Symposium on Ligaments and Tendons Best Student Paper Competition, McGowan Institute for Regenerative Medicine's Elevator Pitch Competition, and Health 2.0: The Winner's Circle Pitch Competition. She has also presented her work at multiple international conferences and has co-authored book chapters and publications in leading peer-reviewed scientific journals.



Programme Rundown

Time	Key Event	Speaker
0900-0905	**WELCOME ADDRESS**	Prof. Jack Cheng & Prof. KM Chan
	Session 1 Musculo-Skeletal Regeneration : From Technology to Therapy	Moderator: Prof. Jack Cheng & Prof. KM Chan
0905-0915	Musculoskeletal Regeneration Research Network (MRN) - A Global Initiative with Impact	Prof. KM Chan
0915-0925	Introduction to Translational Medicine Platform in Shenzhen – SIAT experience	Prof. Ling Qin
0925-0935	The Innovation, Translation and Commercialization of Orthobiologics: Opportunities and Challenges	Prof. Ming-Hao Zheng
	Session 2 Stem Cell Biology	Moderator: Prof. Arthur Mak & Prof. Gang Li
0935-0950	Harnessing Skeletal Stem Cells and Environmental Niches for Bone Repair – From Bench to Clinic	Prof. Richard Oreffo
0950-1005	Cell Surgery Robotics in Cell Fusion Applications	Prof. Dong Sun
1005-1020	Driving Vascular Regeneration against Diabetic Limb Ischemia with Immune Intervention	Prof. Kathy Lui
1020-1035	Pharmacological Inhibition of Protein Kinase G1 Enhances Bone Formation by Human Skeletal Stem Cells through Activation of RhoA-Akt Signaling	Prof. Li Chen
1035-1045	Q&A	All
1045-1100	***Break***	
	Session 3 Muscle	Moderator: Prof. Wai-Yee Chan & Prof. Hua-Ting Wang
1100-1115	Functional Characterization of Malat1 in Skeletal Myogenic Differentiation and Muscle Regeneration	Prof. Hua-Ting Wang
1115-1130	Molecular Regulation of Muscle Stem Cell Quiescence and Activation	Prof. Tom Hiu-Tung Cheung
1130-1145	miRNAs Role in Regulating Stem Cell Heterogeneity of Skeletal Muscle Stem Cells	Prof. Da-Hai Zhu
1145-1200	A Molecular Switch that Regulates the Cell Fate Choice between Muscle Progenitor Cells and Brown Adipocytes	Prof. Zhen-Guo Wu
1200-1210	Q&A	All
1210-1220	Institute of Tissue Engineering and Regeneration Medicine (iTERM)	Prof. Wai-Yee Chan
	Session 4 Cartilage	Moderator: Prof. James Hui & Prof. Barbara Chan
1220-1235	Mesenchymal Progenitor Cells Derived from Blast-Traumatized Muscle: A Unique Cell Source for Tissue Engineering and Regeneration	Prof. Rocky Tuan
1235-1250	Induction of Articular Cartilage Stem Cells and Cartilage Regeneration by Inhibiting NF-κB Signaling in Osteoarthritis	Prof. Xiao-Ling Zhang
1250-1305	Collagen-Assisted Mesenchymal Stem Cell (MSC)-based Osteochondral Tissue Engineering	Prof. Barbara Chan
1305-1320	Stem Cell Therapy for Osteoarthritis: Dream or Fantasy?	Prof. James Hui
1320-1330	Q&A	All
1330-1415	***Lunch***	
	Session 5 Tendon	Moderator: Prof. Hong-Wei Ouyang & Prof. Ming-Hao Zheng
1415-1430	Achilles' Tendon Rupture Caused By Microbial Influences: A Feasible Aetiology?	Prof. Christer Rolf & Ms. Chelsea Hopkins
1430-1445	Autologous Tenocyte Therapy and Bioreactor for Tendinopathy: From Bench to Bedside	Prof. Ming-Hao Zheng
1445-1500	Low Dose Steroid and Tendinopathy	Dr. Bing-Hua Zhou
1500-1515	Bone Marrow Stromal Cell-Seeded Tendon Slice Constructs	Prof. Ting-Wu Qin
1515-1530	Tendon Differentiation and Regeneration	Prof. Hong-Wei Ouyang
1530-1540	Q&A	All
	Session 6 Ligament & Bone-Tendon Junction	Moderator: Prof. Savio Woo, Prof. Christer Rolf & Prof. Ling Qin
1540-1555	Enhancement in ACL Graft Healing - Where are the Missing Gaps?	Dr. Patrick Shu-Hang Yung
1555-1610	Use of Strontium in Enhancing Ligament - Bone Healing	Prof. WP Yau
1610-1625	Preclinical Studies on Biodegradable Mg and its Alloys for ACL Reconstruction	Prof. Ling Qin
1625-1640	Collaborative Potentials for Developing Mg-based Products for Orthopaedic Applications	Prof. Yang-De Li
1640-1650	A Novel Magnesium Ring Device for Anterior Cruciate Ligament Healing - An *In Vivo* Study in Goats	Dr. Kathryn Farraro
1650-1700	Q&A	All

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