7th CUHK International Symposium on Stem Cell Biology & Regenerative Medicine

Musculo-Skeletal Regeneration: From Technology to Therapy

13 November 2017

1/F Auditorium
Main Clinical Block and Trauma Centre
Prince of Wales Hospital, Shatin

Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong
SMART Program, Lui Che Woo Institute of Innovative Medicine, Faculty of Medicine, The Chinese University of Hong Kong
Key Laboratory for Regenerative Medicine (Jinan University-CUHK), Ministry of Education China

Organizer:

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Message from organizing committee

Dear Colleagues and friends:

The 7th SCRM (7th 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.

6th SCRM Symposium (Nov 11, 2016 Hong Kong)

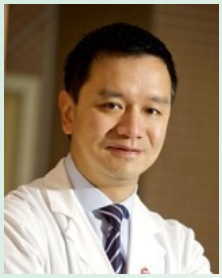
5th SCRM Symposium (Nov 12, 2015 Hong Kong)

The main topics of the symposium this year consist of new thoughts from and for musculoskeletal system, stem cells biology study, emerging technologies development as well as clinical and translational research. There are other 20 plus speakers have confirmed to attend our meeting from Taiwan, Hong Kong and mainland China.

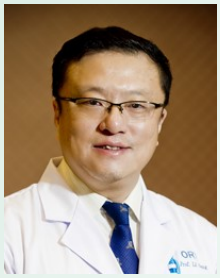
We hope this symposium will provide a communication platform for stem cell biology and regenerative medicine in Hong Kong, Taiwan and China. In addition, Hong Kong is a city where East meets West. There are many excellent shops, restaurants and tourist attractions here to be explored.

This SCRM welcome s professional s and academics in the field of regenerative medicine, orthopaedics, bio-medical science and engineering and other related disciplines. On behalf of 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 7th CUHK International Symposium on Stem Cell Biology and Regenerative Medicine



Prof. Patrick Yung
Professor
CUHK-ORT



Prof. Gang Li
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Prof. Wai-Yee Chan
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Chair Professor
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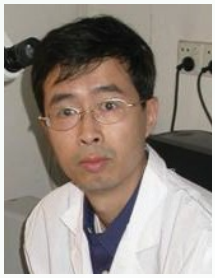

Prof. Dong-Qing Cai
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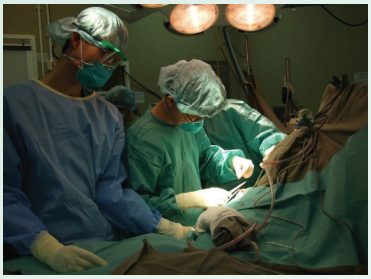
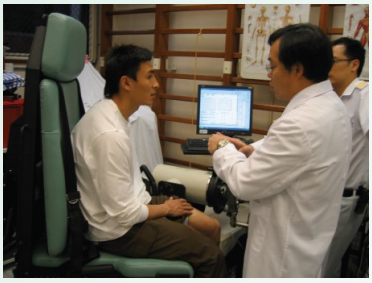
The Chinese University of Hong Kong



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 functionalization 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 recognized 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".

About Organizers

SMART Programme
Lui Che Woo Institute of Innovative Medicine
Faculty of MedicineThe 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.
2016	Co-organized the 2nd International Symposium of Musculoskeletal Regenerative Research Network (MRN), June 16, 2016, UMC Utrecht University, the Netherlands.
2017	Co-organized the 3rd International Symposium of Musculoskeletal Regenerative Research Network (MRN), June 25, 2017, Davos, Switzerland.

About Organizers

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 honoured 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 centre 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

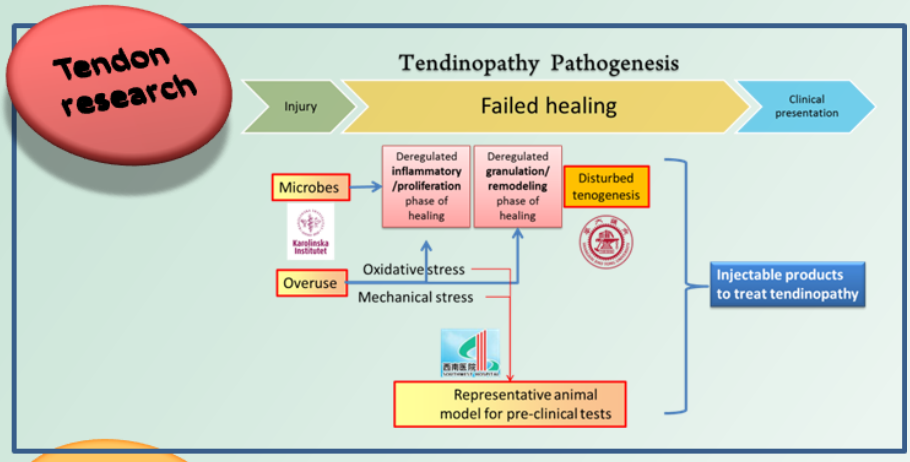
Orthopedic sport medicine is an integral part of orthopedics. It is a vibrant and emerging sub-specialty that traverses boundaries in other disciplines in medicine in general and orthopedics in particular. A well-trained orthopedic surgeon will benefit from a comprehensive program of training as highlighted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

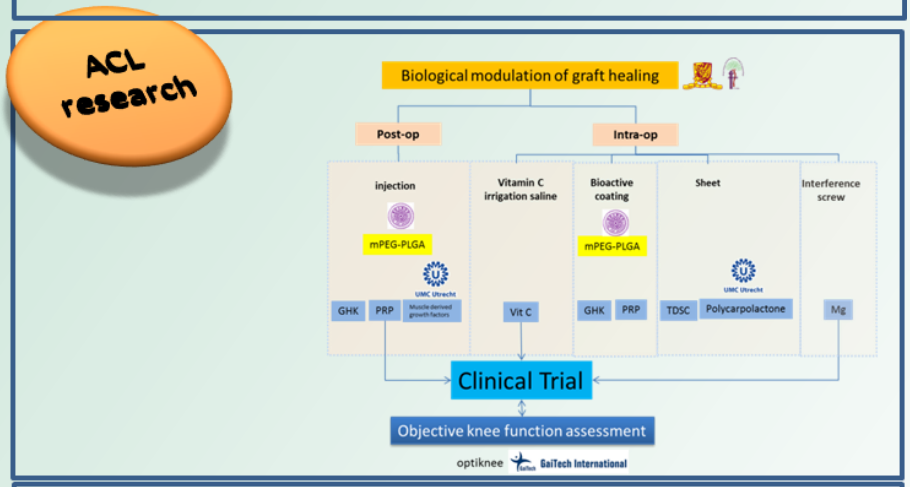
The CUHK Sport Medicine Centre will maintain this momentum of sporting spirit to achieve "Higher, Faster and Stronger" goals to reach new height in clinical service, education and research. We shall bring the next generation of clinician and scientist to a new platform of opinion leadership in this discipline.

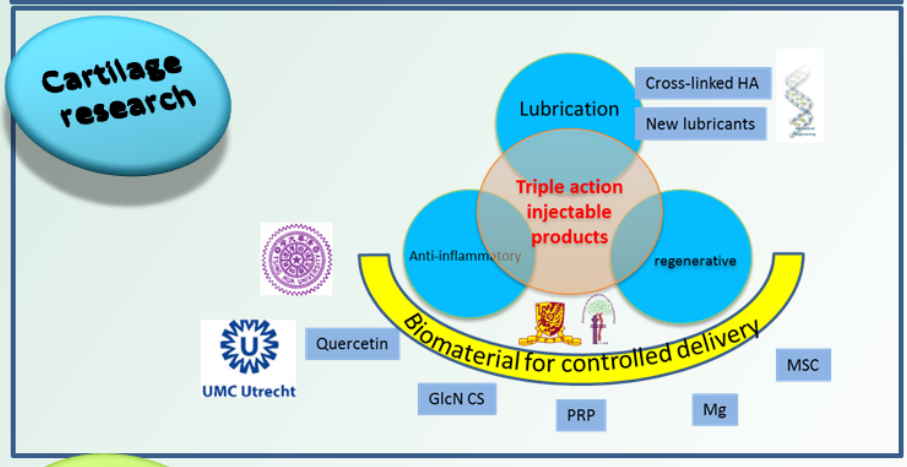
About Organizers

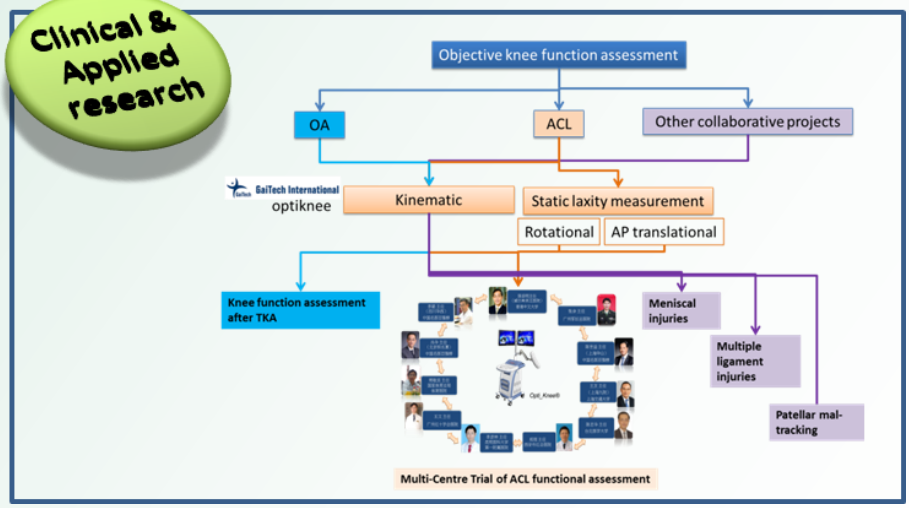
IIM-SMART International Collaboration

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.









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.

School of Biomedical Sciences
Faculty of Medicine
The Chinese University of Hong Kong

Through amalgamating the former four pre-clinical Departments of Anatomy, Biochemistry (Medicine), Pharmacology and Physiology, the School of Biomedical Sciences was formed under the Faculty of Medicine, The Chinese University of Hong Kong on 1 June 2009. Since its formation, our School has put tremendous efforts and resources in promoting cutting-edge and translational research through interdisciplinary collaboration as well as quality graduate and undergraduate education.

Wai-Yee CHAN, Director
School of Biomedical Sciences

Being the first of its kind in Hong Kong, our School has established three Thematic Research Programs (TRPs), namely:

Cancer Biology and Experimental Therapeutics
Developmental and Regenerative Biology
Neural, Vascular, and Metabolic Biology

Members of these three Programs, including those clinical Associate Members, have been supported by our Core Laboratories which provide state-of-the-art equipment and specialized technologies. The different theme-based seminars and the annual School of Biomedical Sciences Research Day are two of the examples showing our commitment to the pursuit of research excellence.

Similarly, we have placed great importance on the provision of quality teaching and learning environment to our graduate and undergraduate students. With the consolidation of teaching manpower, synergies in graduate and undergraduate teaching have been made possible. The MPhil-PhD in Biomedical Sciences Program admitted its first cohort of students in 2010-11. The establishment of the Teaching and Learning Unit and the annual School of Biomedical Sciences Postgraduate Research Day are yet another two prominent examples showcasing our dedication to the quest of excellence in education. In the academic year 2016-17, our School will introduce the new BSc in Biomedical Sciences Programme with a view to nurturing young talents conversant with biomedical sciences knowledge and skills who can engage themselves upon graduation in multiple career paths such as scientific research, health system policy and management, or clinical, pharmaceutical, diagnostics and healthcare related professions.

To promote stronger academic and scientific collaboration with overseas universities and research institutes and to further broaden the international outlook of our investigators and students, we have signed Memoranda of Understanding (MOU) with a number of prestigious higher education and research institutions in the Mainland and overseas. Our School has also actively taken part in many outgoing and incoming visits to explore possible research and educational collaborations.

The different pages of this new website will give you more details on our School, including the profiles of our academic and teaching staff. Meanwhile, our SBS 5th Anniversary Booklet - Reminiscences of the First Quinquennium and other publications can give you more ideas on the efforts and achievements we have made so far in different domains. If you have any comments or need any information, please feel free to write to us at sbs.med@cuhk.edu.hk.

Theme-based Research Scheme Project: Functional Bone Regeneration in Challenging Bone Disorders and Defects

The world population is ageing. Ageing is associated with many musculoskeletal problems, including osteoporosis (OP), osteoarthritis (OA) and chronic tendon-bone insertion disorder and injury, which often lead to bone fractures, joint deformity and disability.

We are very fortunate to have our project granted in the Theme-based Research Scheme (TRS). This TRS project, titled "**Functional Bone Regeneration in Challenging Bone Disorders and Defects**" (RGC Reference No. T13-402/17N) is a collaboration of four research institutes in Hong Kong and a few international partners (Please refer to the below figure for our team management). Our current research will focus on these skeletal disorders and injuries with limited repair and healing potential, including osteoporotic fracture, avascular osteoneocrosis (AVN) around joints with extremely high incidence of OA, and tendon-bone insertion reconstruction. A significant reduction in number and regeneration potential of stem cells, especially bone marrow stem cells (BMSCs), are the most common features of these disorders. Our research focuses on healing enhancement of these skeletal disorders and injuries by augmenting the regenerative potential of autologous BMSCs and mobilizing circulating stem cells to bone defects for regeneration. To enhance osteogenesis, we will investigate the recruitment of circulating stem cells, mobilization of local BMSCs onto material surface, and cell-matrix signalling with or without the modulation of biophysical stimulation.

This project will be divided into three stages: 1) Osteogenic modulation of BMSCs for skeletal tissue engineering; 2) Investigation on the treatment efficacy of implanted innovative biomaterials and postoperative non-invasive biophysical modulation for maximizing the osteogenic efficacy using our well-established preclinical animal models; 3) Completion of the required biosafety testing for Class III medical implants for product registration and subsequent preparation for clinical trials. This TRS project will synergize our research expertise and resources to achieve functional bone regeneration in challenging bone disorders. Ultimately, our developed biomaterials and treatment protocols will benefit our patients and society.

Glucocorticoids, bone and systemic metabolism

Prof. Hong Zhou
Bone Research Program, ANZAC Research Institute
The University of Sydney, Gate 3 Hospital Road, Concord
NSW 2139, Australia

Glucocorticoids are pleiotropic hormones with regulatory roles in fuel metabolism, immune defence, bone and connective tissue homeostasis as well as growth and development. Clinically, glucocorticoids are widely used for their unsurpassed anti-inflammatory and immunomodulatory effects. However, the therapeutic use of glucocorticoids is almost always limited by significant adverse effects such as osteoporosis, diabetes and obesity. Recent insights into the mechanisms of action of both endogenous and exogenous glucocorticoids in bone cells have unlocked new potential approaches for the prevention and treatment of glucocorticoid-induced osteoporosis. Furthermore, studies in rodents indicate that the osteoblast-derived peptide, osteocalcin, plays a central role in the pathogenesis of glucocorticoid-induced diabetes and obesity. More recently, glucocorticoid signalling in bone cells has been found to be central in the regulation of aging-associated changes and high-fat diet induced changes in body composition and glucose metabolism.

This presentation will review the glucocorticoid action and discuss emerging concepts regarding the molecular mechanisms underlying the adverse effects of glucocorticoid excess.

Professor Hong Zhou is a Senior Principal Research Fellow at the University of Sydney and Head of the Molecular Bone Biology Laboratory at the ANZAC Research Institute, Sydney. She received her Ph.D. at the University of Melbourne, Australia. Her scientific interests include glucocorticoid action on bone in the use and analysis of animal models of normal and abnormal bone metabolism, skeletal development, bone and cartilage biology, bone regulated systematic matabolic metabolism, autoimmune arthritis, surgically induced osteoarthritis. Her current research is focused on molecular Mechanisms by which glucocorticoid action on bone development, bone and fuel metabolism and inflammation arthritis via osteoblast and osteocytes. In past 5 years, her research was supported by 6 NHMRC project grant. Over the course of her career, she has published 98 scientific reports (29 in the past 5 years), many of which appeared in top-ranking journals such as J Clin Invest, J Exp Med, PNAS, Development, Arthritis Rheum, JBMR, Diabetes, Cancer Res, Bone Research, JBC, Oncotarget and Bone. Her research has received 2509 citations since 2012. Her current H-Index is 40 (Google Scholar).

Critical roles of Kindlin-2 signaling in skeleton

Prof. Guo-Zhi Xiao

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Shenzhen 518052, China

The signals that control the skeletal homeostasis are incompletely understood. Here we show that inducible deletion of Kindlin-2 in articular chondrocytes using the Aggrecan-Cre transgenic mice caused multifaceted osteoarthritis-like changes of knee joint, including deformation, osteophyte formation and hyperalgesia, and progressive loss of articular cartilage in adult animals. Kindlin-2 deletion initiated a catabolic response in articular cartilage as demonstrated by increases in Mmp13 and Adamts5 expression in articular chondrocytes. Kindlin-2 ablation increased Runx2 and Col10 expression and accelerated chondrocyte differentiation. Interestingly, the level of Vegf expression in articular chondrocytes and meniscus cells and microvascular density were markedly increased in surrounding tissues of the knee joint of Kindlin-2Aggrecan mice. Osteocytes embedded in the bone matrix modulate bone homeostasis by coordinating osteoblast and osteoclast activity located on bone surfaces through mechanisms still unclear. We found that deleting Kindlin-2 in osteocytes using the Dmp1-Cre transgenic mice resulted in dramatic decreases in bone mineral density and volume. Kindlin-2Dmp1 mice displayed reduced bone formation markers, low number of osteoblasts, and markedly decreased metaphyseal trabecular and periosteal cortical bone formation. In the absence of Kindlin-2, osteocyte apoptosis was dramatically accelerated, resulting in significantly lower osteocyte density in Kindlin-2Dmp1 bone. Finally, loss of Kindlin-2 severely impaired the recovery of tail suspension-induced bone loss in adult mice. Collectively, these findings demonstrate a critical role of Kindlin-2 in control of cartilage and bone homeostasis.

Professor Guo-Zhi Xiao is a bone biologist. He obtained his PhD degree in biochemistry and molecular biology from Peking University in 1994 and finished his post-doc training (1994-1998) and worked as a research scientist (1998-2005) at the University of Michigan Ann Arbor. In 2005, he assumed an independent faculty position as a tenure-track assistant professor at the University of Pittsburgh School of Medicine and was promoted to the level of associate professor with tenure in 2011. In 2012, he joined Rush University Medical Center in Chicago and assumed a prominent academic position as the Dr. Ralph and Marian C. Falk Endowed Chair Professor of Biochemistry and served as the director of research of the department of biochemistry. In 2013, he joined the SUSTech as a tenured full professor and later became the chair of the biological department. Dr. Xiao has made several contributions to our understanding the molecular control of skeletal development and homeostasis. His work is reported in more than 100 peer-reviewed publications, many in high profile journals such as the Journal of Clinical Investigation and Nature Communications. He serves as a reviewer for the US National Science Foundation (NSF), the Italian Ministry of Health and the National Natural Science Foundation of China (NSFC) and sits on the editorial boards of the Journal of Bone and Mineral Research (JBMR) and the Journal of Biological Chemistry (JBC). Dr. Xiao's research interests mainly focus in the following areas: (1) to determine how osteoblast, osteoclast, and chondrocyte formation is controlled during skeletal development and homeostasis under physiological and pathological conditions; (2) to define the mechanisms that modulate bone angiogenesis; and more recently, (4) to study the role of cell adhesion signaling molecules, such as Kindlin-2 and Migfilin, in skeletal development and homeostasis. By working on these projects, Xiao laboratory has also maintained a focus on important medical issues involving bone –osteoarthritis, osteoporosis, metastatic osteolytic lesions, and fracture healing. Information obtained from these studies will enhance our understanding of these pathological processes.

Novel TNFR2 Anabolic Signaling in Cartilage and Bone Regeneration

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TNFR1 primarily mediates inflammatory activity of TNFα and is responsible for delayed cartilage and bone regeneration in various diseases/conditions, in particular under inflammatory conditions. Growing evidences indicate that TNFR2 plays a protective and anti-inflammatory role in various disorders; however, the role of the TNFR2 pathway in cartilage and bone regeneration remains largely unknown. Thus, a molecular understanding of the anabolic TNFR2 pathway in musculoskeletal regeneration will provide new insights into regenerative medicine and invaluable information in for the pursuit of novel therapeutic targets to prevent and treat fractures. Our genetic screen for the binding partners of progranulin (PGRN) growth factor led to the isolation of TNFR2 as the PGRN-binding receptor. Remarkably, PGRN exhibits an approximately 600-fold higher binding affinity to TNFR2 than does TNFα. PGRN stimulated chondrogenesis of mesenchymal stem cells in vitro and deficiency of PGRN in mesenchymal stem cells leads to defects in cartilage development in vivo. Moreover, loss of PGRN delayed, whereas recombinant PGRN promoted, bone regeneration in animal models and recombinant PGRN also induced the formation of hyaline cartilage in a rabbit cartilage regeneration model. Importantly, PGRN-stimulated cartilage and bone regeneration is largely lost in TNFR2$^{-/-}$ mice, indicating that the PGRN/TNFR2 pathway plays a central role in PGRN-stimulated musculoskeletal regeneration. Further, 14-3-3ε was identified as a novel component of TNFR2 receptor complex in response to PGRN stimulation in a proteomics screen. More excitingly, Tgfbr1, Tgfbr2 and Sostdc1, an antagonist of both BMPs and Wnt signaling, were isolated as the critical mediators of PGRN-stimulated endochondral bone formation in a whole genome microarray and a comparative proteomics. These findings not only advance our understanding of regeneration biology, but may also lead to the development of novel interventions for cartilage and bone regeneration.

Dr. Chuan-Ju Liu is a Professor of Orthopaedic Surgery and Cell Biology at NYU School of Medicine. He was awarded his doctorate in cellular and developmental biology from Shandong University and Shanghai Institute of Cell Biology, Chinese Academy of Science. He received his postdoctoral training in the Department of Molecular Biophysics and Biochemistry at Yale University. He held a dual appointment as an Assistant Professor from Department of Orthopaedic Surgery and Department of Cell Biology at NYU School of Medicine since 2002, and was promoted to Associate Professor with Tenure and Professor with Tenure in 2007 and 2013, respectively. He is the current Editor-in-Chief of *Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders* and *Rheumatology Research and Review*, and serves on a number of Editorial Boards. He is also a highly active participant in peer review of manuscripts and grant applications to government agencies (NIH, DOD, National Science Foundation of China, Research Grants Council of Hong Kong, Medical Research Council of UK, Italian Ministry of Health, The Israel Science Foundation; Innovational Research Incentive Scheme of Netherlands, Research Foundation of Belgium, etc.) and private foundations. His current research focuses on osteoarthritis, inflammatory arthritis, and cartilage/bone regeneration. He has published over 130 papers in prestigious journals, including *Science, ARD, EMBO J, and PNAS*. In addition, he is the recipient of numerous awards, including the American Society for Bone and Mineral Research's Harold M. Frost Award, the Arthritis Foundation's Dorothy W. Goldstein Award, the NIH Career Development Award, the Kappa Delta Award from the American Academy of Orthopaedic Surgeons, the Innovative Research Award from the American College of Rheumatology, and the very recent STAR Award from NIH/NIAMS.

Chondrogenesis, chondrogenic differentiation, and cartilage injury & repair

Prof. Xue-Song Yang

Division of Histology & Embryology
Key Laboratory for Regenerative Medicine of the Ministry of Education
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Since articular cartilage can not regenerate, people continuously look for new tissue-engineering approaches to treat articular cartilage defects. In spite of various approaches have been reported, there has not been an perfect scenario at moment. In this study, we screened the optimal concentration of chorogenic acid (CGA) using in vitro primary culture of chondrocyte, and then confirmed that CGA in alginate could stimulate chondrogenesis in vitro. After the application of the complexes containing chondrocytes and CGA with alginate in articular cartilage injury model of chick knees, we assessed the functional recovery on day 7. 14, 21 using gait analysis, which showed that the complexes application dramatically accelerate the recovery of injury-induced dysfunction. The following histochemical analysis demonstrated that less vasculature and more chondrocyte proliferation and cartilage matrix synthesis in presence of the complexes containing CGA. In search for the underlying mechanisms, we discovered that CGA-activated the expressions of Sox9 and Col2a1 might be responsible for the stimulation of chondrogenesis. Furthermore, the complexes application containing CGA could suppress the increase of IL-1β and TNF-α as well as p-p65, which is achieved through adjusting cellular redox homeostasis. Taken together, the current study suggest that the combinational administration of chondrocytes and CGA on alginate scaffold could dramatically improve the recovery of articular cartilage defects.

Xue-Song Yang is currently a professor in Jinan University Medical College, China. He received his bachelor's and master's degree in Harbin Medical University, China and then received his doctorate in Tokyo Medical and Dental University School of Medicine, Japan. After having worked in University of Manchester and University of Dundee University, UK for 11 years, he took the position in Jinan University Medical College. His research interests contain: 1) exploring embryos as the possible models for stem cell applications on regenerative medicine. 2) the regulations of coordinated signaling pathways on mesoderm and neural crest cell migration during gastrula embryo development. 3) the investigation of gene-regulatory elements on birth defects. So far, he has published 94 SCI scientific papers including Developmental Cell, PNAS, Current Biology and Development, Developmental Biology and Oncogene.

New approaches in bone regeneration by therapeutically stimulating endochondral ossification

Prof. Chelsea S Bahney

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University of California, San Francisco & Zuckerberg San Francisco General
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Fractures are one of the most common injuries, affecting ~15 million people/year in the US alone. While most bone injuries regenerate well, 10-15% of normal fractures demonstrate impaired healing in the form of delayed- or non-union. Non-union rates increase to 50% of fractures when coupled with vascular damage or a high co-morbidity burden. Clinically these injuries difficult to treat, as physicians are reluctant to diagnose non-union until 6-9 month without bone formation, then injury is addressed surgically with addition of bone graft. Treatment of fractures currently pose a $45 billion annual burden on our healthcare system. *There is an unmet clinical need for therapeutic biologics that could stimulate fracture healing through a non-surgical delivery platform.*

To discover novel therapeutic targets for bone regeneration we must first improve our basic understanding of the molecular and cellular mechanisms driving fracture healing. While fractures heal through a combination of direct (intramembranous) and indirect (endochondral) ossification, the cartilage callus is responsible for bridging the fracture gap, making endochondral ossification the dominant mechanism of healing. Traditionally, the cartilage callus has been viewed as a temporary structure, simply forming an osteoconductive scaffold for bone formation. In this model of endochondral ossification, chondrocytes mature to a hypertrophic state, at which point they are considered a terminally differentiated, post-mitotic cell, fated for apoptosis. According to this model, new bone is formed by osteoprogenitors invading the calcified cartilage from the vasculature. New data from our group and others utilizes genetic lineage tracing to support an alternative model for endochondral ossification in which chondrocytes transdifferentiate into osteoblasts during repair and development.

In our laboratory, we take a developmental engineering approach designed to improve our mechanistic understanding of endochondral bone repair and therapeutically modulate it. Recent data from our group demonstrates that chondrocyte become osteoblast by taking on a hyperplastic state mediated by the transcription factor *Sox2*. *Sox2* localizes to hypertrophic chondrocytes at the chondro-osseous boarder during fracture repair and conditional deletion impairs healing by increasing the cartilage fraction and decreasing the bone fraction of the fracture callus.[3] Following this hyperplastic state induced in the chondrocytes, subsequent bone formation is mediated by the Wnt/b-catenin pathway. Here we show how these pathways can be therapeutically manipulated to stimulate fracture repair.

RESEARCH INTERESTS

The focus of my laboratory is to develop novel translational technologies that promote bone and cartilage regeneration by recapitulating development and repair. We utilize engineered biomaterials to deliver cells, proteins or genes that will promote a sequence of biological milestones that parallel native repair or prevent disease progression. By utilizing interdisciplinary techniques that capitalize on engineering and developmental biology I aim to solve problems that have a direct and significant impact on human health.

Education and Training

Bachelor Science in Chemical Engineering. University of Colorado, Boulder	1997-2001
Research & Development Engineer. Medtronic, Boulder, Colorado	2000-2005
PhD Cell & Developmental Biology. Oregon Health & Science University	2005-2010
Post-Doctoral Fellowship, University of California, San Francisco	2010-2014

Other Affiliations

UCSF/UC Berkeley Bioengineering
UCSF Oral and Craniofacial Sciences Graduate Program
UCSF Core Center for Musculoskeletal Biology and Medicine
UCSF Program of Craniofacial Biology
Chair, Advocacy Committee. Orthopaedic Research Society (ORS)
Chair, Science and Education. International Section of Fracture Healing (ISFR)

Comparing human MSC chondrogenesis under static and loading conditions

Prof. Martin Stoddart

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The unique properties of mesenchymal stem cells (MSCs) and their natural presence within the bone marrow make them an attractive source of cells for orthopaedic therapies. The microenvironment the cells experience within a repair tissue will play a major role in the repair response. Within the musculoskeletal system, one of the major regulators is the mechanical load applied to the cells within the defect. Most new cartilage repair therapies are developed using static culture. However, it is clear that due to the critical role mechanics plays in vivo, a more physiological loading regime in vitro would be more appropriate and this can be achieved by the use of bioreactors. Using a multiaxial load bioreactor system, we have been investigating the effect of mechanical stimulation on human MSC differentiation. Performing studies in the absence of growth factors, specifically Transforming growth factor β (TGFβ), allows the direct effect of the mechanical strain applied to be elucidated. Our bioreactor system allows for the application of shear, compression or a combination of both stimuli to establish the phenotypic changes induced within MSCs. As a model system, human bone marrow derived MSCs are embedded in a fibrin gel, which is then retained in a macroporous biodegradable polyurethane (PU) scaffold. Neither compression alone, nor shear alone can induce a change in MSC phenotype within this system. However, a combination of compression and shear is able to induce chondrogenic differentiation and this is due to increased endogenous expression and activation of TGFβ from the stimulated cells. Using this device, we have been identifying new targets that are differentially regulated in TGFβ induced chondrogenic differentiation compared to mechanical induction. One of the most interesting being an increase in nitric oxide (NO) production during mechanical stimulation. Therefore, NO is potentially increased during rehabilitation after microfracture and this effect would not be observed during static chondrogenesis studies. Identification of novel targets that only present during chondrogenic differentiation under mechanical stimulation would offer the opportunity to enhance the current microfracture procedure, while providing a greater understanding of the underlying biology.

Since 2009 Prof. Martin Stoddart, FRSB has been working as a Principal Scientist at the AO Research Institute (ARI), where he is responsible for the Stem Cell Focus Area. His interests include the use of mesenchymal stem cells for bone and cartilage repair, in particular the role of mechanoregulation during the initiation of MSC chondrogenesis. This has led to an increased understanding of chondrogenesis under complex physiological loads in the absence of exogenous growth factors.He completed his bachelors in Biology in 1995 and M.Phil (ARI) in 1996 at the University of Aberystwyth. He completed his doctoral thesis in Oncology (University of Nottingham). In 2000 he moved to the Laboratory for experimental cartilage research, Zürich, Switzerland, initially as Post-Doc and from 2003 as Group Head, moving to ARI in 2005. In 2002 he took a sabbatical at the Centre for Molecular Orthopeadics, Harvard Medical School, Brigham and Womens Hospital, Boston, to learn viral gene transfer techniques. Dr. Stoddart was awarded an Honorary Professorship from the Albert-Ludwigs University, Freiburg, Germany in 2015 and an Honorary Professorship from the Institute for Science & Technology in Medicine, Keele University, UK in 2016. In 2016 he was elected Fellow of the Royal Society of Biology. He is Chair of the ORS Basic Science Education Committee and deputy co-chair or the ICRS Basic Science Committee. He is an Editor for Tissue Engineering Journal Parts A,B,C, Scientific Editor for eCM Journal and an organizer of the yearly eCM Conference. He has authored over 90 papers and book chapters.

The role of mechanical loading on stem cell differentiation

Prof. Ming-Hao Zheng

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The University of Western Australia, Nedlands
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Although it is well established that growth factors play a critical role in stem cell differentiation and tissue hemostasis, much less is known on the role of mechanobiological signals on stem cell differentiation. In the musculoskeletal system, tissues are constantly subjected to different forms of mechanical loading. For instance, articular cartilage and bone have shock absorption and supportive abilities, respectively upon receiving compressive force, while tendon and ligament are required to adapt tensile forces from muscle contraction and body movement. To sense the types of specific loading, these tissues must configure a specific microarchitectures which enable the mechanical loadings to regulate cell shape, migration, proliferation, and differentiation. To investigate whether mechanical stimulation can selectively drive stem cell differentiation toward cartilage, bone and tendon. We test the effect of uni-axial and bi-axial mechanical loadings on differentiation and cellular signal pathways of tendon derived stem cells (TDSC). We hypothesize that 3D uni-axial loading may closely mimic the physiological loading of the normal tendon and thus enable to induce tenogenic-specific differentiation and tendon formation of TDSCs. Our data showed that there are variations in cell signaling and cell differentiation of TDSCs in respond to uni-axial and bi-axial loadings in monolayer cultures. Uni-axial loading induced AKT phosphorylation and bi-axial loading induced ERK phosphorylation. While uni-axial loading induced TDSCs toward tenogenic and osteogenic differentiation, bi-axial loading induced osteogenic, adipogenic and chondrogenic differentiation of TDSCs. However, when uni-axial mechanical loading was applied to 3D TDSCs construct in bioreactor culture, it only induced TDSCs toward tenogenic differentiation and tendon formation. PI3K -AKT signaling pathway was involved in the induction of tenogenic differentiation and tendon-like tissue formation in a 3D bioreactor culture by un-axial mechanical loading. Our findings highlight the importance of appropriate mechanobiological stimulation in 3D cell niches on tendon-like tissue formation.

Professor Ming-Hao Zheng graduated as Bachelor of Medicine at Shantou University in 1983, Master of Medicine at Sun Yet Sen University of Medical Science in 1987, PhD in 1993, Doctor of Medicine (MD) in 2000 at the University of Western Australia. He undertook histopathology training in China and Australia and 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 affairs), Faculty of Medicine and Health Sciences, Professor and Director of Centre for Translational Orthopaedic Research at the University of Western Australia. He is the founder and Consultant Chief Scientific Officer of Orthocell Ltd (ASX:OCC) in Australia; Executive of the Scientific Committee of Pluslife, Perth; and Chung Kong Lecturing Professor at Zhejiang University, China and visiting Professor at numbers of universities in China. He is currently member of Faculty 1000 Prime and Associate Editor of Stem Cell Research and Therapy. He has published over 180 papers and holds 7 patents and has been awarded for Vice Chancellor Senior Research award and Western Australia Innovation award in 2016. Professor Zheng's major research focus is in the molecular and cellular biology of bone cells, cell signalling and generation of gene knockout mice; development of autologous tendon cell therapy for tendon injury, clinical trials and laboratory evaluation of human tissue and cellular products. He has developed a first cell-scaffold product (MACI) for cartilage repair that has been approved by FDA in USA in 2016. His research leads toward the development of autologous stem cell and progenitor cell therapy in bone, cartilage and tendon.

Functional Role of Jmjd1a and Jmjd2c in MSC senescence and bone aging

Prof. Cynthia Xiao-Hua Jiang

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School of Biomedical Sciences, Faculty of Medicine,
The Chinese University of Hong Kong

Epigenomic changes and stem cell exhaustion are two hallmarks of aging. Accumulating evidence suggest that MSC senescence could perpetuate aging or age-related diseases. Here we show that MSC senescence is accompanied by a dynamic change of heterochromatin structure. We have identified two H3K9 demethylases Jmjd1a and Jmjd2c, which cooperatively mediate the heterochromatin remodeling and homeostasis during MSC senescence. Mechanistically, Jmjd1a and Jmjd2c transcriptionally activate chromosome condensation genes via the demethylase activity. Deficiency of Jmjd1a or Jmjd2c results in defective chromosome organization and exacerbated DNA damage response. In addition, loss of Jmjd1a leads to accelerated MSC senescence and bone aging in *Jmjd1a* knockout mice. More importantly, a marked downregulation of Jmjd1a and Jmjd2c associated with a decrease in H3K9me3/2, HP1g and chromosome organization genes is found in MSCs derived from old individuals. Thus, for the first time, we have revealed a previously unrecognized epigenetic mechanism underlying dynamic heterochromatin remodeling and stem cell senescence, which may underlie the bone aging process.

Dr. Jiang Cynthia Xiaohua graduated from Shanghai Second Medical University (currently School of Medicine, Shanghai JiaoTong University), and completed her internship and residency at RuiJin Hospital in Shanghai. She obtained her PhD degree from the Department of Medicine, the University of Hong Kong. Dr. Jiang undertook her postdoctoral training at the Department of Medicine, UCLA. Her work focused on the role of protein kinases in cancer development. After that, she joined the University of Southern California as a CIRM (California Institute for Regenerative Medicine) fellow and her research focused on understanding the origin and genetics of pediatric cancers by using human embryonic stem cells as an innovative model. Currently, Dr. Jiang is a PI in the School of Biomedical Sciences, Faculty of Medicine, CUHK. Dr. Jiang's research themes focus on the molecular mechanisms that control stem cell properties and application of adult stem cells in tissue regeneration and cancer targeting. Dr. Jiang has published 70 papers in peer-reviewed journals, including Nature Medicine, Stem Cells, Stem Cell Reports, Cell Research, Cancer Research, Gastroenterology and Oncogenes.

Progenitor cells of cartilaginous tissues

Prof. Brian Johnstone

Dept of Orthopaedics and Rehabilitation, OP31
Oregon health & Science University
Portland, OR 97239, USA

Articular cartilage progenitor cells remaining in the tissue after growth has ceased provide another possible cell source for articular cartilage regeneration. Features of these cells make them particularly attractive for tissue engineering: they are clonable and expandable with retention of differentiation potential, and when stimulated, most clones create a matrix closer to that of stable articular cartilage rather than the endochondral cartilage produced from other stem/progenitor cell types. This talk will cover characterization of these progenitor cells as well as comparative cell-based tissue engineering studies with these and other stem/progenitor cells, focusing on the differential influence of environmental parameters.

Brian Johnstone, PhD, FIOR, did his predoctoral research at the Kennedy Institute of Rheumatology, London, England and postdoctoral work at West Virginia University and the University of North Carolina at Chapel Hill, USA. His work on intervertebral disc biology was acknowledged with two Volvo prizes for spine research. He moved to Case Western Reserve University in 1993 and developed the *in vitro* system for the chondrogenic induction of adult stem cells. In 2004, he became Director of Research in the Department of Orthopaedics at Oregon Health & Science University, Portland, Oregon where he continues his work on stem cells in skeletal tissue repair and regeneration. He was the President of the Orthopaedic Research Society for 2011-2012, elected to the inaugural class of the Fellows of International Orthopaedic Research in 2016, and was awarded the Marshall R. Urist Award for his tissue regeneration research in 2017.

Stem Cell Niche: Secreted Proteins of Human Stromal Stem Cells

Prof. Li Chen

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DK-5000 Odense C, Denmark

Understanding mechanisms controlling stem cell differentiation into a specific lineage is a pre-requisite for clinical use of stem cells in therapy. The microenvironment of stem cells (i.e. the stem niche) controls their differentiation fate, and the secreted proteins by the stem cells are important regulators of stem cell niche composition. However, the type and the function of the secreted proteins by stem cells are poorly studied. We study the profile of the secreted proteins (secretome) of skeletal (mesenchymal) stem cells as revealed by quantitative mass spectrometry (MS) and their roles in stem cell self-renewal and multi-lineage differentiation (osteogenesis, chodroogenesis, and adipogenesis) by both in vitro and in vivo models. The overall aim is to identify novel factors that “druggable” and can be used for bone and cartilage regeneration.

Li Chen, Ph.D., (born in 1971) is an assistant professor at Molecular Endocrinology Laboratory (KMEB), Odense University Hospital, and University of South Denmark. She earned her BS at Fudan University, Shanghai, China (1993), and work as researcher and lecturer at the Medical College at Fudan University, and got her MS at National Laboratory of Medical Neurobiology, Fudan University (2000). She gained her Ph.D. at Aalborg University, Denmark (2005). She had the post-doctoral fellowship at the NCI, NIH, Bethesda, MD, USA where she worked at signaling regulation at cell apoptosis and necrosis. Li Chen's research focus on the molecular mechanisms of stem cell differentiation that regulated by kinases, miRNA, secretome, small chemical molecule, and materials; and the use of MSCs for cell therapy in aging, osteoporosis and diabetes.

Novel angiogenic factors in bone microenvironment: potential therapeutic targets for bone regeneration

Prof. Jia-Ke Xu

Division of Regenerative Medicine
School of Biomedical Sciences
The University of Western Australia

Angiogenesis plays an important role in physiological bone growth and remodeling, as well as in pathological bone disorders such as delayed fracture repair, osteonecrosis, and tumor metastasis to bone. Angiogenic factors, produced by cells from a basic multicellular unit (BMU) within the bone remodeling compartment (BRC) regulate local endothelial cells and pericytes. The expression of angiogenic factors by osteoclasts, osteoblasts and osteocytes in the BMU and in the cartilage-bone interface is evident. These include vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), BMP7, and epidermal growth factor (EGF)-like family members. In addition, the expression of EGFL2, EGFL3, EGFL5, EGFL6, EGFL7, EGFL8 and EGFL9 has been recently identified in the bone local environment, giving important clues to their roles in angiogenesis and bone homeostasis. EGFL7, is a secreted factor produced by osteoclasts and osteoblasts and promotes angiogenesis. EGFL6 is expressed by osteoblasts and regulate angiogenesis via a paracrine mode of action. Using EGFL6 KO mouse model, and neutralizing antibody approach, we found that EGFL6 plays an important role in bone fracture healing. In addition, we identified that Nephronectin (NPNT), a homologue of EGFL6, is expressed in osteoblasts, and exert a paracrine effect on endothelial cells. Intriguingly, the expression of NPNT is reduced in the bone of ovariectomised mice and in osteoporosis patients. Exogenous addition of mouse recombinant NPNT on SVEC (a simian virus 40-transformed mouse microvascular endothelial cell line) stimulates endothelial cell migration and tube-like structure formation *in vitro*. Furthermore, NPNT promotes angiogenesis in an *ex vivo* fetal mouse metatarsal angiogenesis assay. We show that NPNT stimulates the phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 mitogen-activated kinase (MAPK) in SVEC cells. Inhibition of ERK1/2 impaired NPNT-induced endothelial cell migration, tube-like structure formation and angiogenesis. Understanding the role of angiogenic factors in the bone microenvironment may help to develop novel therapeutic targets and diagnostic biomarkers for bone and joint diseases, such as osteoporosis, osteonecrosis, osteoarthritis, and delayed fracture healing.

Dr. Jia-Ke Xu is currently Winthrop Professor and Head of molecular Laboratory and Head of the Division of Regenerative Biology at the University of Western Australia (UWA). (http://www.web.uwa.edu.au/people/jiake.xu). He is also a founding Fellow, Faculty of Science, the Royal College of Pathologists of Australia. He served as the President of the Australian and New Zealand Orthopaedic Research Society (ANZORS, 2012-2015). He completed his PhD studies at UWA in 1994, and carried out his postdoctoral research at Stanford University from 1994 to 1998. His current research activities are focused on regenerative biology, bone and joint pathology related to orthopaedic conditions, and he has published over 160 SCI papers; including Nature Medicine, Endocrine Reviews, Nature Comm. PNAS, J Bone Miner Res., Mol. Cell. Biol., J Biol. Chem., Arthritis Rheum. Stem Cells, and Biomaterials.

Bone tissue engineering and regenerative medicine 2.0 --Paradigm shift from "Proof-of-concept" to "Proof-of-value"

Prof. Zhi-Yong Zhang

1. Translational Research Centre of Regenerative Medicine and 3D Printing Technologies, Guangzhou Medical University
2. The Third Affiliated Hospital of Guangzhou Medical University

Bone tissue engineering (BTE) strategy provides a promising approach for large bone defect treatment. Despite its first clinical application report in 2001, BTE strategy still stays as a laboratory technique rather than a regular clinical practice, with very limited clinical impact so far. In order to understand the major bottlenecking factors that hinder the fast clinical translation of BTE technology, the development of tissue engineering technology will be compared with computer technology in order to illustrate the influence of "Proof-of-concept (POC)" and "Proof-of-value (POV)" oriented research strategy on the translation of new technology. Generally, it can be regarded as the BTE 1.0 development stage for the past thirty-year's R&D effort. BTE 1.0 stage is the POC oriented with the goal to prove the scientific feasibility and clinical efficacy and safety of BTE concept. In order to facilitate its wider clinical application and the final translation from a lab technique into a routine clinical therapeutic practice, we believe, in the subsequential BTE 2.0 stage, the focus of our research should be shift from POC to POV, whose mission is to improve and achieve sufficient clinical and commercial value of BTE strategy to replace the current technique. I will discuss and illustrate the Low-Value points of current BTE strategy, such as unavailability off-the-shelf, high cost, complicated manufacturing process and so on and share with you our POV research efforts and thoughts on how to conquer these problems one by one. We believe, similar to the development of computer industry, the next stage of POV-orientated R&D effort (BTE 2.0 stage) will be the most critical and essential stage in order to boost up the final translation of BTE strategy into the real clinical technique, and facilitate the commercialization and maturation of the new industry of tissue engineering and regenerative medicine.

Professor Zhang Zhi-Yong received his B.Sc. degree in biology from Xiamen University of China and PhD degree in bioengineering from National University of Singapore in 2009. From 2010 to 2012, he held an adjunct position in Fourth Military Medical University as Associate Professor. In 2012-2016, he worked as Professor and Group Leader in Shanghai Jiao Tong University and National Tissue Engineering Center of China. In 2017, he joined Guangzhou Medical University as the founding director of the Translational Research Centre of Regenerative Medicine and 3D Printing Technologies, which pursue the "Proof-of-Value" translation strategy to promote the fast bench-to-bed translation of next generation of medical technologies. Due to his contribution, Professor Zhang has been granted a number of talent scheme program awards including the National "One Thousand Young Talents" (Chinas Recruitment Program of Global Experts Award) by the central government of China, Eastern Scholar Distinguished Professor award by Shanghai government and the "Outstanding Medical Academic Leader" award by Guangzhou government. Ever since his postgraduate training, Prof. Zhang has actively served in more than 15 international and national academic societies such as the SYIS Chair of TERMIS-AP (2009-2012), Education Committee Member of International Chinese Musculoskeletal Research Society(ICMRS), Committee Member of Chinese Society of Tissue Engineering and Regenerative Medicine, Editorial Board member of Cogent Engineering Journal and so on. In addition, he has contributed significantly to the success of organizing a couple of international conferences in the field of TERM, including the TERMIS-AP 2013 as the General Secretary, the 2016 Cross-Strait Conference of TERM as Scientific Chair and TERMIS-AP 2016 as Organization Committee Member.

Electromagnetic stimulation effects on rotator cuff repair: From the lab to the clinic

Dr. Erik Waldorff

3451 Plano Parkway Lewisville, TX 75056, USA

Clinical application of pulsed electromagnetic fields (PEMFs) has been approved by the US Food & Drug Administration (FDA) for adjunct treatment to lumbar or cervical spine fusion and for treatment of long-bone non-unions. Common for all of these clinical applications is the need for a clinical trial prior to FDA approval. The optimization of PEMFs for improvement in efficacy for current indications, in addition to the expansion into new indications, is therefore not trivial. Moving directly into a clinical trial can be costly and carries little guarantee for success, necessitating the need for preclinical studies. This talk will cover the translational path from pre-clinical research/basic science to clinical research of pulsed electromagnetic field (PEMF) application as an adjunctive treatment to rotator cuff repair:

Initial considerations:
A discussion of the initial considerations (prior to pre-clinical studies) for why PEMF would work as an adjunctive treatment to rotator cuff repair will be reviewed. In addition factors that were considered prior to performing any pre-clinical studies will be covered.

Pre-clinical studies:
A presentation of the associated pre-clinical in-vitro studies will show the effects of PEMF on tenocyte and myocyte proliferation and differentiation which have been studied using human rotator cuff tenocytes and C2C12 murine myoblasts. Specifically it was seen that three hours of daily PEMF exposure for two weeks enhanced gene expression of growth factors in human rotator cuff tenocytes and myocytes (MyoD) under inflammatory conditions but not under normal conditions. In addition, it was found that myotube formation was increased under both normal and inflammatory conditions. Results from pre-clinical in-vivo studies will furthermore show that daily PEMF exposure (3 hours of Physio-Stim) led to improvements in tendon-to-bone healing in an acute rotator cuff repair model in rats. Specifically the tendon modulus increased significantly at early time periods (100% and 60% at 4 weeks and 8 weeks, respectively) with increased maximum stress (4 weeks) and subsequent improved bone quality at 16 weeks (increased bone volume fraction, trabecular thickness, and bone mineral density). Further in-vivo investigations also revealed that using PEMFs with varying fundamental frequencies (3.85 kHz or 40.85 kHz) or exposure durations (1 hours/day, 3 hours/day, or 6 hours/day) led to improvements in tendon properties for both types of PEMF and all exposure durations compared to non-PEMF controls. However early (4 weeks) improvements in tendon modulus was only found for PEMFs at lower fundamental frequencies (for all exposure durations).

Clinical study:
A discussion of how the pre-clinical results were translated into a recent FDA approved Investigational Device Exemption (IDE) clinical trial will be done. Clinical study design factors and outcome measures will be also presented.

Erik Waldorff, PhD is the Principal Scientist & Research Manager for Orthofix, Inc., an orthopedic medical device company based in Lewisville, Texas, USA. At Orthofix he develops and manages the strategies, protocols and projects for all company sponsored pre-clinical research activities to support technology innovation for new and existing product development for all four company divisions (BioStim, Biologics, Extremity Fixation and Spine Fixation). In addition he supports the transition from pre-clinical to human trials, assists with clinical research (post-market clinical studies/Investigational Device Exemptions (IDEs)), and serves as company liaison to outside research institutions, research consultants, and clinicians. Before joining Orthofix, he served as a Clinical Research Scientist for the Neuromodulation Division at St. Jude Medical where he performed pre-clinical studies in addition to post-market clinical trials on spinal cord stimulation and deep brain stimulation patients. Prior to that Dr. Waldorff held a position as a Postdoctoral Fellow in the Post-Doctoral Translational Scholars Program (PTSP) at the Michigan Institute for Clinical and Health Research (MICHR) at the University of Michigan where he led orthopedic human and animal studies. Dr. Waldorff holds a Ph.D. and M.S.E. degree in Biomedical Engineering, and an M.S.E. and B.S.E. in Aerospace Engineering from the University of Michigan (Ann Arbor, Michigan, USA).

Self-assembled injectable nanocomposite hydrogels stabilized by bisphosphonate-magnesium (Mg2+) coordination for 3D cell culture and controlled release of bioactive ions

Prof. Li-Ming Bian

Room 213
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The Chinese University of Hong Kong

Nanocomposite hydrogels consist of a polymer matrix embedded with nanoparticles (NPs), which provide the hydrogels with unique bioactivities and mechanical properties. Incorporation of NPs via in situ precipitation in the polymer matrix further enhances these desirable hydrogel properties. However, the non-cytocompatible pH, osmolality and lengthy duration typically required for such in situ precipitation strategies precludes cell encapsulation in the resultant hydrogels. Bisphosphonate (BP) exhibits a variety of specific bioactivities and excellent binding affinity to multivalent cations such as magnesium ions (Mg2+). Herein, we describe the preparation of nanocomposite hydrogels via self-assembly driven by bisphosphonate-Mg2+ coordination (Scheme 1). Upon mixing solutions of polymer bearing BPs, BP monomer (Ac-BP), and Mg2+, this effective and dynamic coordination leads to the rapid self-assembly of Ac-BP-Mg NPs which function as multivalent crosslinkers stabilize the resultant hydrogel structure at physiological pH (Figure 1). The obtained nanocomposite hydrogels are self-healing and exhibit improved mechanical properties compared to hydrogels prepared by blending pre-fabricated NPs. Importantly, our hydrogels allow the encapsulation of cells and subsequent injection without compromising the viability of seeded cells (Figure 2). Furthermore, the acrylate groups on the surface of Ac-BP-Mg NPs enable facile temporal control over the stiffness and crosslinking density of hydrogels via UV-induced secondary crosslinking, and we find that the delayed introduction of this secondary crosslinking enhances cell spreading and osteogenesis.

Dr. Bian received his B. Eng and MSc degree from the National University of Singapore in 2002 and 2004, respectively. Dr. Bian completed his Ph.D. study in Biomedical Engineering at Columbia University in 2009. Dr. Liming Bian then conducted his postdoctoral research in the Department of Bioengineering, the University of Pennsylvania from 2009 to 2012. In 2012, Dr. Bian joined the Chinese University of Hong Kong as an assistant professor. Dr. Bian's research focuses on the development of novel multiscale biomaterials not only for investigating the role of cell microenvironment factors on stem cell behaviors but also for facilitating the regeneration of diseased or injured tissues and organs. Dr. Bian's research work has been published in the leading journals including PNAS, JACS, Nano Letters, Biomaterials, Advanced Functional Materials, ACS Nano, Macromolecules, Advanced Healthcare Materials, etc.

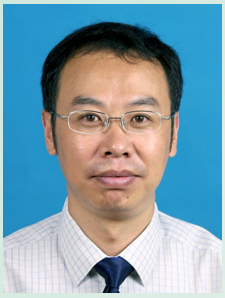
Biomaterial based stem cells enrichment for bone regeneration: from bench to bedside

Prof. Ting-Ting Tang

Shanghai Jiaotong University
Shanghai, China

Previously, we have developed several stem cells based therapies to promote bone regeneration, including the gene therapy with BMP2 gene modified stem cells, perfusion bioreactors to construct tissue engineering bone and stem cells enrichment techniques. Although all these therapies have demonstrated their efficiency to promote the bone regeneration in varied animal models with bone defects or bone diseases, stem cells enrichment without cell expansion *in vitro* represents a safe and convenient approach to be used in clinic trial.

Recently we developed a biomaterial based technique to enrich the mesenchymal stem cells (MSCS) from bone marrow, which takes advantage of the adherent properties of MSCs on material surface. We designed an innovative appliance named the stem cell screen–enrich–combine(-biomaterials) circulating system (SECCS). By the circulation of bone marrow in the SECCS through porous biomaterials acting as bone marrow filters, MSCs could be rapidly screened, enriched, and combined with biomaterials. In present study, 42 patients with fractures or non-unions were enrolled in the clinical trial. Their bone marrow samples and beta-tricalcium phosphate (β-TCP) granules were processed in the SECCS for 10-15 minutes, to produce MSC/β-TCP composites. The composite was grafted in the bone defect. Our results showed that MSC/β-TCP composites were capable of enhancing fracture healing and bone regeneration in the patients with delayed union. We believe that this biomaterial based cell enrichment approach is a promising regeneration strategy to be widely used in orthopaedic clinics.



Dr. Tang is professor, doctoral supervisor, director of Shanghai Key Laboratory of Orthopeadic Implants, vice chairman of Orthopedic Department of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. He had been awarded as candidate of New Century Excellent Talent Program of Ministry of Education, New Century Hundred, Thousand and Ten Thousand Talent Program in China. Currently he also serves as President of International Chinese Musculoskeletal Research Society (ICMRS), Board member of China Biomaterial Society, Committee member of China Biomechanics Society, Associate Committee Chairman of Chinese Orthopedic Research Society of CAOS, Editorial board members of over 15 international and Chinese journals including Journal of Orthopedic Translation, Bone Research, JBMR et al. His main research interests include orthopedic implants and biomaterials, stem cells research related to musculoskeletal degeneration and regeneration, cancer and bone disease. He had been the Principal Investigators of over 30 grants and currently is the leading scientist of National Key R&D program. He has over 170 peer-reviewed SCI indexed international publications and 15 authorized National invention patents.

Engineered hair follicle mesenchymal stem cells overexpressing controlled-release insulin reverse hyperglycemia in mice with type l diabetes

Prof. Jin-Yu Liu

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Genetically engineered stem cells that overexpress genes encoding therapeutic products can be exploited to correct metabolic disorders by repairing and regenerating diseased organs or restoring their function. Hair follicles are readily accessible and serve as a rich source of autologous stem cells for cell-based gene therapy. Here we isolated mesenchymal stem cells from human hair follicles (HF-MSCs) and engineered them to overexpress the human insulin gene and release human insulin in a time- and dose-dependent manner in response to rapamycin. The engineered HF-MSCs retained their characteristic cell surface markers and retained their potential to differentiate into adipocytes and osteoblasts. When mice with streptozotocin-induced type 1 diabetes were engrafted with these engineered HF-MSCs, these cells expressed and released a dose of human insulin, dramatically reversed hyperglycemia, and significantly reduced death rate. Moreover, the engineered HF-MSCs did not form detectable tumors throughout the 120-day animal tests in our experiment. Our results show that HF-MSCs can be used to safely and efficiently express therapeutic transgenes and therefore show promise for cell-based gene therapy of human disease.

Dr. Jin-Yu Liu earned his MD and Ph.D in Norman Bethune University of Medical Sciences. From 1999-2004 he worked as postdoctoral with Professor Gunter Burg at Department of Dermatology, Zurich University Hospital, Switzerland with major in skin tissue engineering and wound healing. From 2004-2008 he worked as research assistant professor at Department of Chemical and Biological Engineering, Sate University of New York at Buffalo with major in stem cell biology and cardiovascular tissue engineering. Since 2009 he worked as professor at Jilin University with research focus on cell-based translational medicine. Dr. Liu published 27 SCI papers, won national scientific and technological progress award (second prize) and the Chinese medicine award (first prize).

Fracture Healing: New challenges to the old paradigm

Prof. Theodore Miclau

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The burden of musculoskeletal disease has surpassed cardiovascular disease as the major health burden in the world, and bone fractures contribute substantially to the overall burden of musculoskeletal disease. In the US, there are over 600,000 fractures per year with a substantial number of these fractures exhibiting delayed healing or non-union. The gold standard to stimulate bone union been autologous bone grafting, which although generally good, remains problematic due to limited graft supply, donor site morbidity, and potential complications. Therefore, understanding mechanisms of normal fracture healing to develop effective therapies to treat patients is imperative. Generally, fracture repair occurs through two processes: direct bone (intramembranous ossification) and the formation of bone through a cartilage intermediate (endochondral ossification). With the exception of an initial inflammatory process, adult healing is similar to that observed during bone development. Previous work suggested that in adult repair, stem cells in the periosteum and endosteum give rise to chondrocytes that form the soft callus during endochondral ossification, and subsequently, during vascular invasion of the cartilage callus, osteoprogenitor cells are delivered to the fracture site to form new bone. Recent findings, however, challenge this assumption. Our preliminary and published data suggest that stem cells at the fracture site give rise to an amplifying population of chondroprogenitor cells that maintain their stem cell lineage in the newly healed bone. Further, the chondrocytes that are produced are the primary source of osteocytes during bone fracture healing and transform into osteocytes from signals derived from the invading endothelial cells, which turn on the core transcription factors that promote pluripotency (*Sox2*, *Oct4A*, *Nanog*). Traditionally, strategies for stimulating bone repair seek to stimulate the process of direct bone formation. However, given that the majority of long bone fractures heal with some degree of callus formation (with the exception of those treated with absolute stability) and the above mentioned findings, successful fracture repair therapies might target the endochondral rather than intramembranous ossification process. This presentation will review these potentially paradigm-shifting research findings, which have the potential to affect the way fracture healing, bone incorporation, and bone tissue engineering strategies are developed and employed.

After graduating from Yale College and Yale University School of Medicine, Theodore Miclau III, MD, completed his residency in orthopaedic surgery at the University of North Carolina at Chapel Hill in 1994. During his residency, he spent nearly one year at the AO Research Institute in Davos, Switzerland studying fracture healing. After finishing an orthopaedic trauma fellowship at the Baylor College of Medicine in Houston, Texas in 1995, he was awarded the AO-Jack McDaniel fellowship and visited prominent trauma centers in St. Gallen, Switzerland and Berlin, Germany. In 1996, Miclau joined the faculty of the Department of Orthopaedic Surgery at the University of California, San Francisco (UCSF) as an orthopaedic traumatologist at the Zuckerberg San Francisco General Hospital and (ZSFG). In 2000, he received a five-year Career Development Award (K08) from the National Institutes of Health and the Musculoskeletal Transplant Foundation to study the role of angiogenesis in fracture repair; he has had funding from NIH for that program since that time. He also received the North American and American-British-Canadian traveling fellowship awards from the American Orthopaedic Association. In 2002, Dr. Miclau became the Acting Chief of Orthopaedic Surgery at SFGH, and subsequently became the Chief of Orthopaedic Surgery at SFGH in 2004. He also became a full-tenured professor in 2004. He was named Vice Chairman and Director of Orthopaedic Trauma of the Department of Orthopaedic Surgery at UCSF in 2003. He became Director of the UCSF/SFGH Orthopaedic Trauma Institute (OTI) when it opened in 2009. The OTI is home to the largest number of orthopaedic trauma fellowship trained surgeons in the US and has robust, research programs that include biomechanics, molecular biology, and clinical research. Dr. Miclau serves on many local and national committees, and editorial and grant-review panels. He served as president of the Orthopaedic Research Society in 2012, and as president of the Orthopaedic Trauma Association in 2015. He also serves as the OTA Governance Council Chair, and is the former Chair of the OTA Basic Science Committee, Annual Basic Science Focus Forum, and Research Committee. He is the course chair for the Annual UCSF Orthopaedic Trauma conference, and several other conferences nationally and internationally. For the ORS, he serves as the International Committee Co-Chair. He is the President of the International Combined Orthopaedic Research Societies organization, and the chair of two international research committees, the Osteosynthesis and Trauma Care Foundation Research Committee and the AO Research Institute Advisory Committee. He has recently been named Chair of the Steering Committee for the International Orthopaedic Trauma Societies. He has published over 120 peer-reviewed research papers and 10 book chapters.

Mg-based bimetal: from bench to bed

Prof. Qin Ling

Department of Orthopaedics and Traumatology
Faculty of Medicine, The Chinese University of Hong Kong

Professor Qin is Professor and Director of Musculoskeletal Research Laboratory in the Department of Orthopaedics & Traumatology, the Chinese University of Hong Kong. Professor Qin also holds joint professorship in Shenzhen Institutes of Advance Technology (SIAT) of Chinese Academy of Sciences (CAS) and serves Director of the Translational Medicine Research & Development Center of Institute of Biomedical & Health Engineering of SIAT (http://www.siat.cas.cn). He received his BA and M.Phil. in basic medical and life sciences in physical education at the Beijing Sports University in China, and his PhD from German Sports University, Cologne, Germany and postdoctoral training in AO-Research Institute, Davos, Switzerland. Professor Qin was research scientist in the Department of Trauma & Reconstructive Surgery, University Clinic Rudolf Virchow, Free University Berlin (now known as Charite Medical University) Germany before joining CUHK in late 1994.

Professor Qin is the past President of the International Chinese Musculoskeletal Research Society (ICMRS) (http://www.icmrs.net) and member of a number of journal editorial boards, including Editor-in-chief of Journal of Orthopaedic Translation (http://ees.elsevier.com/jot); Associate Editor of Clinical Biomechanics and Chinese Journal of Orthopaedic Surgery; board member of a number of international journals, including Journal of Bone and Mineral Research (http://www.jbmr.org) and International Journal of Sports Medicine (http://www.thieme.de/sportsmed). He holds memberships in several international and national orthopaedic and related research organizations, including collage fellow of American Institute of Medical and Biological Engineering (http://www.aimbe.org). He has received over 30 Research Awards and holds 6 patents.

Professor Qin published 10 monographs as editor or associate editor, 5 conference proceedings, 80 book chapters, and over 400 journal papers in English, German, and Chinese, including around 300 SCI articles published in Nat Med, JBMR, Osteoporosis Int, Bone, A&R, Biomaterials, Acta Biomaterialia, Am J Sports Med, Int J Sports Med, etc. with citation over 5000 and a H-index of 42.

In vitro cartilage regeneration and its clinical translation

Prof. Guang-Dong Zhou

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Shanghai 9th People's Hospital, Shanghai Jiao Tong University
School of Medicine, 639 Zhi Zao Ju Road, Shanghai 200011, PR China
National Tissue Engineering Center of China, Shanghai, PR China

Cartilage regeneration and its functional reconstruction is always a great challenge in clinical treatment. Tissue engineering provides a new strategy for solving this issue. During the past ten years, our group performed a series of basic research, established a number of critical techniques for *in vitro* cartilage construction, and finally realized clinical translation of cartilage regeneration technologies. The main advances includes: 1) To establish a novel chondrogenic induction system by mimicking the chondrogenic microenvironment through *in vitro* co-culture or *in vivo* co-transplantation of chondrocytes and mesenchymal stem cells, which could efficiently regulate chondrogenesis and cartilage regeneration of stem cells and thus help to solve the problem of seed cell source; 2) To establish a series of technological system of *in vitro* 3D cartilage regeneration, and to realize accurate shape control of *in vitro* regenerated cartilage by combining with 3D print techniques; 3) To develop bioreactor to be used specially for cartilage regeneration, which efficiently enhanced the mechanical properties of *in vitro* regenerated cartilage; 4) To establish and successfully repair various cartilage defect models (such as articular osteochondral defects, tracheal defects, meniscus defects etc.) in large animals; 5) To successfully perform various clinical trials of cartilage regeneration and its functional reconstruction based on *in vitro* regenerated cartilage, including reconstruction of external ear, repair and reconstruction of nasal cartilage defects, repair of tarsal plate defects, repair of articular cartilage defects as well as repair of articular osteochondral defects.

Mesenchymal Stem Cells and Skeletal Tissue Engineering

Prof. Oscar Kuang-Sheng Lee

Taipei City Hospital, No.145, Zhengzhou Road, Datong District
Taipei City 10341, Taiwan (R.O.C.)

It was not until the late 80's that tissue engineering was regarded as an independent branch of science. The term tissue engineering was initially defined by the attendees of the first National Science Foundation of the United States sponsored meeting in 1988 as "application of the principles and methods of engineering and life sciences toward fundamental understanding of structure-function relationship in normal and pathologic mammalian tissues and the development of biological substitutes for the repair and regeneration of tissue or organ function". In 1993, Langer and Vacanti summarized the early development in this field and defined tissue engineering as "an interdisciplinary field that applies the principles of engineering and life sciences towards the development of biological substitutes that restore, maintain, or improve tissues or organ function. The exercise of interdigitating these different functional talents into a coherent device has produced the working definition of tissue engineering: "Tissue engineering is an art and science by which synthetic compounds are manipulated into anatomically and/or functionally specific architectures and, when required, may be integrated with biologically active agents and/or living cells such that resultant properties of the whole are precisely suited to support the specific cell life prescribed for recipient tissues". Consequently, tissue engineering has now emerged as a potential alternative to tissue or organ transplantation. Based on the above mentioned principles of tissue regeneration, reconstructing segmental bone defects after resection of malignant bone tumors, a long-standing challenge for orthopaedic surgeons, was an excellent demonstration of the application of mesenchymal stem cells (MSCs) in orthopaedic tissue engineering. With the increased knowledge of MSCs, we have demonstrated that it is possible to reconstruct segmental bone defects using a tissue engineering approach. Also, the combination of nano-technology with MSCs for skeletal regeneration is another good example. We have cultured MSCs on biomimetic electrospun Type 1 collagen nanofiber scaffold, making the composite an excellent advanced therapy product for reconstruction of flat bones. Future efforts will be made to further validate the safety and efficacy of applying MSC technology for skeletal regeneration in both pre-clinical and clinical settings.

After obtaining medical degree and finishing residency training in orthopaedic surgery, I went to University College London, England for PhD study, where I used bone marrow mesenchymal stem cells (MSCs) isolated from bone marrow to treat severe nonunion fractures using animal models. After finishing my research training in England, I returned to Taiwan and started my own lab at the Taipei Veterans General Hospital in 2002. The major research theme is plasticity and application of MSCs. Being a clinician and a stem cell scientist, I am particularly interested in developing new application of MSCs to treat diseases that currently lack cures. Over the years, I and my team members reported the successful isolation of multipotent MSCs from human bone marrow and umbilical cord blood capable of differentiating into different lineages. The multi-germ-layer differentiation potential was further demonstrated using an in utero transplantation model. We also reported the differentiation potential of MSCs into hepatocytes in vitro under defined conditions. Subsequently, the therapeutic potential of MSCs for treatment of liver disease was demonstrated using a mouse model of fulminant hepatic failure. To further look into the possibility of MSCs for bone tissue engineering, we studied the growth and differentiation of mesenchymal stem cells on Type 1 collagen nanofibers. In addition, molecular mechanisms and changes of mitochondrial biogenesis during osteogenic differentiation of MSCs have also been investigated. Other research achievements include the isolation of stem cells from human parathyroid gland, fat tissues and the cruciate ligaments of the knee joint. We have also studied the role of MSCs in the immune system and have successfully used MSCs to treat lupus nephritis in experimental animal model. Besides, biophysical effects of MSCs have also been investigated, and the molecular mechanisms governing matrix stiffness-induced differentiation of MSCs have been studied.

Annulus fibrosus regeneration using a multimodal mechano-modulation and layered assembly strategy

Prof. Bin Li

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Suzhou, Jiangsu 215007, China

Degenerative disc disease (DDD) is the leading cause of low back pain, a serious global health problem which contributes to healthcare costs significantly. While it is promising to repair degenerated intervertebral discs (IVDs) using tissue engineering techniques, such an approach largely relies on the effective construction of annulus fibrosus (AF), a major load-bearing component of IVD. However, because of the tremendous cellular, biochemical, microstructural, and biomechanical heterogeneity of AF tissue, it remains challenging to fabricate AF replacements that are biologically and functionally comparable to native AF tissue. Recently, we started to employ a tissue engineering strategy based upon layer-by-layer assembly and multimodal mechano-modulation in order to mimic the layered structure and to address the heterogeneity feature of AF tissue as well. In brief, we isolated multipotent AF-derived stem cells (AFSCs) for AF tissue engineering. We then synthesized a series of biodegradable polyurethanes and hydrogels with similar elastic modulus as AF tissue. We found that the biochemical and biomechanical profiles of AFSCs were markedly affected by the elastic modulus of scaffolds, implying the feasibility to induce differentiation of AFSCs into cells at different regions of native AF tissue. We also obtained AFSC sheets, i.e., cell monolayers together with the underlying matrix, using novel cell sheet culture techniques. Further, we applied dynamic mechanical stimulation to AFSCs and found that their anabolic and catabolic metabolisms were significantly dependent on the magnitude, frequency and duration of mechanical stimulation. Following these, we will assembly engineered AF tissue, through a layer-by-layer approach, using AFSC sheets primed with substrates of various elasticity and conditioned with appropriate mechanical stimulation. Findings from these studies may provide new insights toward developing engineered AFs whose biological features and mechanical functions approximate those of native AF tissue.

Professor Bin Li received the bachelor degree in Polymeric Materials Science and Chemical Engineering from the Department of Chemical Engineering of Tsinghua University in 1996. He received the PhD degree in Materials Science from Tsinghua University in 2001. He then worked as a Research Associate at the Institute of Materials Research and Engineering, Singapore from 2001 to 2004. After that he pursued postdoctoral training at the Department of Orthopaedics, University of Pittsburgh School of Medicine in USA from 2005 to 2009. He also completed two short-term trainings as a visiting research scientist at Carnegie Mellon University in 2004 and Harvard University in 2009, respectively. He joined Soochow University in 2009 as a Specially Appointed Professor and director of the Biomaterials and Cell Mechanics Laboratory (BCML) of Orthopedic Institute. He is the recipient of a number of awards such as the Suzhou Science & Technology Development Award, Orthopaedics Research Award (1st class) from Chinese Orthopaedic Association, Xu Guangqi Program from the French Embassy in China, and France Talent Innovation from the Consulate General of France in Shanghai. He currently serves as the chair of China Development Committee of the International Chinese Musculoskeletal Research Society (ICMRS). He is a fellow of Chinese Orthopaedic Research Society (CORS), Chinese Association of Orthopaedic Surgeons (CAOS), Chinese Association of Rehabilitation Medicine (CARM), and International Society of Orthopaedic Surgery and Traumatology (SICOT). He is also a member of the Orthopedic Research Society (ORS), Tissue Engineering and Regenerative Medicine International Society (TERMIS), Society For Biomaterials (SFB), Chinese Society for Biomaterials (CSBM), and Chinese Materials Research Society (CMRS). He serves on the editorial board of 9 journals, and is guest editor of 2 journals and reviewer for over 40 journals. He serves as the organizing committee and executive chairs of the International Chinese Musculoskeletal Research Conferences (Shihezi, 2017; Suzhou, 2013). He has delivered more than 70 invited talks and is the author of 80 journal articles and 10 book chapters. His research interests include biomaterials for orthopaedic applications, degenerative disc disease, stem cells and tissue engineering, smart molecular recognition and controlled release, surface modification and functionalization, cellular biomechanics and mechanobiology.

Microstructure of bone-tendon junction -- A new micro-imaging technology introduction

Prof. Hong-Bin Lu

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Central South University, Changsha, China, 410008

A tendon integrates with bone through an ordered transitional interface, which is composed of a complex mixture of hard, bony, and soft connective tissues. This multi-tissue interface, known as the bone-tendon junction (BTJ), is morphologically categorized into four distinct yet continuous tissue zones: tendon, uncalcified fibrocartilage, calcified fibrocartilage, and bone. This highly specialized and organized interface is beneficial for mediating the load transfer and minimizing concentrated stress between the tendon and bone. Unfortunately, the BTJ is easily injured in sports activities involving jumping, cutting, and pivoting, while its healing is a slow process. Until now, no effective way can functionally and quickly restore BTJ injuries. The reason for its complicated healing is not only because the junctional fibrocartilage layer of BTJ is regenerated slowly and incompletely at the healing interface but also more importantly because the microstructure of BTJ have not been totally understood. A new 3D micro-imaging technology, which is synchrotron radiation imaging, was used to analyze the microstructure of BTJ. Firstly, synchrotron radiation micro-CT (SR-μCT) was successfully used to visualize the three-dimensional morphology of BTJ with high-resolution (0.65 μm). In addition, an in-vivo three-dimensional high-resolution morphological evaluation method was innovatively established for mouse Achilles tendon insertion. Secondly, based on synchrotron radiation, characterization of mineral element spatial distributions at the fibrocartilage zone of BTJ was elucidated by synchrotron radiation micro X-ray fluorescence (SR-μXRF). Thirdly, region-dependent changes of BTJ in collagen, proteoglycan, and mineral distribution, as well as collagen organization were mapped using synchrotron radiation-Fourier transform infrared spectroscopic imaging (SR-FTIR). In summary, microstructure of BTJ was characterized by synchrotron radiation micro-imaging technology, and these observations will serve as critical benchmark parameters for current efforts in BTJ repair.

1. Current post

2003-present Master supervisor in Department of Sports Medicine of Xiangya hospital, Central South University, Hunan, China
2007-present Director of Research Center of Sports Medicine, Xiangya Hospital, Central South University, Hunan, China
2008-present Professor in Department of Sports Medicine of Xiangya hospital, Central South University, Hunan, China
2009-present Professor of "Sublimation Scholars Program" of Central South University & Doctoral supervisor in Department of Sports Medicine of Xiangya hospital, Central South University, Hunan, China
2011-present Academic leader of key discipline (sports medicine) in Hunan Province
2012-present Director of Department of Sports Medicine at Xiangya Hospital, Central South University, Hunan, China
2013-present Academic leader of National Key Clinical Specialty (sports medicine)
2016-present Director of Key Laboratory of Organ Injury, Aging and Regenerative Medicine of Hunan Province
2017-present Director of Xiangya Hospital of Central South University-International Chinese Musculoskeletal Research Society Collaborating Center for Sports Medicine

2. Specialties

Clinical and basic research on injuries of musculoskeletal system
Rich experience in clinical diagnosis and treatment of a variety of sports injuries

3. Professional affiliations

Member of Sports Medicine Society of Chinese Medical Association
Vice chairman of sports rehabilitation group of Sports Medicine Society of Chinese Medical Association
Chairman of Sports Medicine Professional Committee of Hunan Medical Association
Invited reviewer of projects of Swiss AO Foundation
Peer reviewer National Natural Science Foundation of China

Regulation of hypoxia microenvironment during skeletal regeneration

Prof. Chao Wan

School of Biomedical Sciences, Faculty of Medicine
The Chinese University of Hong Kong, Hong Kong SAR

Oxygen is a fundamental requirement for organogenesis and tissue regeneration. Hypoxia inducible factors (HIFs) are essential mediators of cellular adaptation to oxygen fluctuations and critical for proliferation and differentiation of stem/progenitor cell populations. We previously showed that HIF-α served as a key to couple angiogenesis to osteogenesis during skeletal development and regeneration. We further analyzed the role HIF-1α in the development of condensing mesenchyme, and found that the bones of the mutant mice were smaller and less mineralized than the controls, with disorganized mesenchymal condensation. Deletion of HIF-1α impaired self-renewal and osteoblast lineage differentiation of mesenchymal stem cells (MSCs) indexed by colony forming unit assay and reduced expression of osteogenic marker genes, in accord with our findings *in vivo*. Chromatin immunoprecipitation assays showed direct occupancy of the osterix promoter by HIF-1α. In an effort to searching for small molecules for regulating repairing microenvironment and enhancing skeletal repair, we identify tetramethylpyrazine (TMP), a bioactive compound isolated from Ligusticum wallichii as an activator of HIF-1α. TMP stimulates HIF-1α nuclear translocation, promotes osteoblastic differentiation and endothelial sprouting *in vitro*. In an OVX-induced osteoporosis mouse model, TMP functions as an anabolic agent to promote bone formation. Our results suggest that pharmacological manipulation of the HIF-1α pathway might serve as a promising approach for regulating the microenvironment of repair to promote skeletal tissue regeneration.

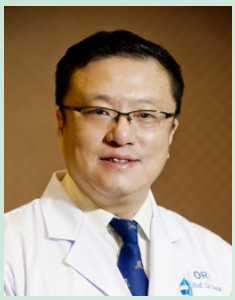
Dr. Chao Wan is an Associate Professor in School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong (CUHK). Dr. Wan serves as Deputy Director of Management Committee, School of Biomedical Sciences Core Laboratory, CUHK, and Director of School of Biomedical Sciences Core Laboratory, CUHK Shenzhen Research Institute. Before joining CUHK as Assistant Professor in 2009, Dr. Wan was an Instructor in Department of Orthopaedic Surgery, Johns Hopkins University School of Medicine, and an Instructor in Department of Pathology, University of Alabama at Birmingham (UAB). Dr. Wan was trained as an Orthopaedic Surgeon in Shandong University of TCM, and then obtained PhD in Shanghai Jiaotong University School of Medicine (2002). Following that he pursued Postdoctoral training in School of Medicine, The Queen's University of Belfast, UK, and in Department of Pathology, UAB, USA. His research interests include the molecular and cellular mechanisms of the oxygen sensing pathway in stem cell biology, tissue repair microenvironment, and discovery of novel therapeutic targets for skeletal tissue regeneration. As a collaborator, he was awarded Shanghai Medical Science and Technology Award (First Grade), National Medical Science and Technology Award (Second Grade). He was a recipient of British Orthopaedic Research Society Travelling Award, Japanese Orthopaedic Association Fellowship, ICHTS (ICMRS) Webster Jee Young Investigator Award, and ASBMR Harold Frost Young Investigator Award. He is a Member of American Society for Bone and Mineral Research (ASBMR), Orthopaedic Research Society (ORS), China Orthopaedic Association (COA), and ICMRS lifetime member. His research was supported by Hong Kong RGC GRF, HMRF, NSFC, 973 Sub-project and NSFC-RGC Joint Research Scheme. Recent developments include defining cellular and molecular mechanisms for stem cell microenvironment, self-renewal and stem cell based therapy for skeletal tissue regeneration.

Distraction osteogenesis for the management of cranial bone defect and neurological disorders: what is behind the magic?

Prof. Gang Li

Department of Orthopaedics & Traumatology

Distraction osteogenesis (DO) technique has been widely applied for the management of many difficult orthopaedic conditions. The novel applications of DO technology have extended to new areas such as management of avascular peripheral diseases and cranial bone defect. We have explored the use of DO technique for treatment of cranial bone defect and associated neurological disorders. A novel cranial bone distraction device has been developed and applied in 2 cases of severe cranial bone defect patients with neurological disorder, and a stroke patient with severe neurological disorder. The two cases of cranial defects have been successfully repaired and all 3 cases had also showed unexpected significant improvements of neurological functions. We further carried out a pilot animal study in a rat stroke model with cranial DO treatment to investigate the underlying mechanisms; the preliminary results showed that improvement of neurological functions is strongly associated with enhanced angiogenesis and neuronal repair in the brain. Other possible mechanisms include change of cerebrospinal fluid circulation and improvement of neuronal nutrition, etc., which are still under investigation. The cranial DO may be an exciting novel treatment strategy for neurological disorders such as stroke and other degenerative diseases.



Gang Li is a full professor (since 2009) in the Department of Orthopedics and Traumatology, Faculty of Medicine, The Chinese University of Hong Kong. Previous to this appointment, he was Lecturer, Senior Lecturer and Reader (1998-2009), at Department of Orthopaedic Surgery, School of Medicine, Queen's University, Belfast, UK.

Prof. Li earned an MBBS at the Fourth Military Medical University, Xian, China (1991), and a D. Phil at the University of Oxford School of Medicine, England, UK (1998). The focus of his research are on studies of the biological mechanisms and noval applications of distraction osteogenesis, stem cell biology, circulating mesenchymal stem cells (MSCs), the use of MSCs for cell therapy applications, musculoskeletal tissue regeneration and repair.

Prof. Li has published more than 140 peer-reviewed SCI articles with citations over 4500 and H index 34; 15 book chapters, edited 3 books on tissue engineering, distraction histogenesis, leg-lengthening and Ilizarov techniques. He served as Honorary Treasurer of British Orthopaedic Research Society (2004-2006); Member of Programe Committee of American Orthopaedic Research Society (2006-2007) and currently is the general secretary of Limb Reconstruction society, Chinese Association of Orthopaedic Surgeons. Prof. Li is also a council member of Chinese Orthopaedic Research Society, Chinese Medical Association; council member of Tissue Engineering and Regenerative Medicine Society, Chinese Association of Biomedical Engineering. Prof. Li holds honorary Professorship at Sichuan University, China; Shanxi Medical University, China; China Medical University; South-East University Medical School, China; The Forth Military Medical University, China; Guangdong Medical College, China.

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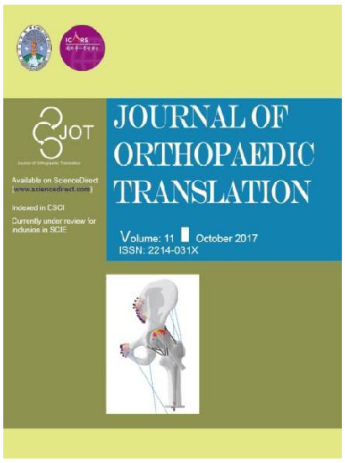

Journal of Orthopaedic Translation

The main goal of *JOT* is to publish papers that identify and fill scientific knowledge gaps at the junction of basic research and clinical application (from bench to bedside) or community application (from bench to community). In this vein, original research should report significant progress toward the prevention, diagnosis, and treatment of musculoskeletal disorders and serve as templates for future exploration and investments in translational orthopaedics.

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- Animal models
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- Industries and markets
- Medical devices and implants
- Nutrition and drugs
- Regenerative medicine
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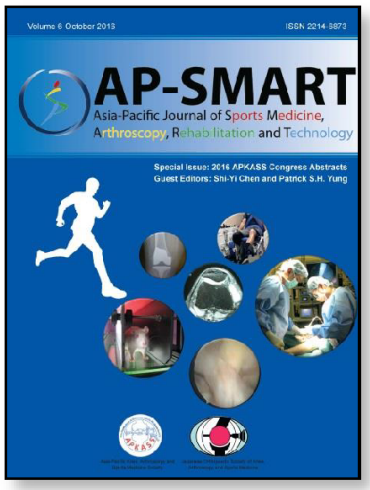

Asia-Pacific Journal of Sports Medicine, Arthroscopy, Rehabilitation and Technology

The missions of *AP-SMART* are to promote multidisciplinary research and collaboration amongst clinicians, practitioners, scientists and engineers from different disciplines and to provide a platform for the timely exchange of new clinical and scientific findings to achieve cross-fertilization of ideas.

The information presented aims to provide a scientific yet practical approach to these five areas:

- Sports medicine
- Arthroscopy
- Rehabilitation
- Sports technology
- Reconstructive surgery of the knee, shoulder and ankle

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1/F Auditorium, Main Clinical Block and Trauma Centre
Prince of Wales Hospital, Shatin
November 13, 2017

09:00-09:20	**Welcome addresses, history of CUHK SCRM meeting, SMART and iTERM program and photo taken**	**Prof. Gang Li** **Prof. Patrick Yung** **Prof. Jack Cheng**
	Session 1: New thoughts from and for musculoskeletal system	**Moderator:** **Prof. Jack Cheng** **Prof. Geoff Richards**
09:20-09:40	Glucocorticoids, bone and systemic metabolism	**Prof. Hong Zhou** University of Sydney, Australia
09:40-10:00	Critical roles of Kindlin-2 signaling in skeleton	**Prof. Guo-Zhi Xiao** *University of Sciences and Technology, China*
10:00-10:20	Novel TNFR2 anabolic signaling in cartilage and bone regeneration	**Prof. Chuan-Ju Liu** *New York University, USA*
10:20-10:40	Chondrogenesis, chondrogenic differentiation, and cartilage injury & repair	**Prof. Xue-Song Yang** *Jinan University, China*
10:40-11:00	New approaches in bone regeneration by therapeutically stimulating endochondral ossification	**Prof. Chelsea Bahney** *University of California, USA*
11:00-11:10	Tea break	
	Session 2: Stem Cells Biology	**Moderator:** **Prof. Dong-Qing Cai** **Prof. Hua-Ting Wang**
11:10-11:30	Comparing human MSC chondrogenesis under static and loading conditions	**Prof. Martin Stoddart** *AO Foundation Research Institute, Switzerland*
11:30-11:50	The role of mechanical loading on stem cell differentiation	**Prof. Ming-Hao Zheng** *University of Western Australia*
11:50-12:10	Functional Role of Jmjd1a and Jmjd2c in MSC senescence and bone aging	**Prof. Cynthia Xiao-Hua Jiang** *The Chinese University of Hong Kong, HKSAR*
12:10-12:30	Progenitor cells of cartilaginous tissues	**Prof. Brian Johnstone** *Oregon Health & Science University, USA*
12:30-12:50	Stem cell niche: secreted proteins of human stromal stem cells	**Prof. Li Chen** *University of South Denmark, Denmark*
12:50-13:10	Novel angiogenic factors in bone microenvironment: potential therapeutic targets for bone regeneration	**Prof. Jia-Ke Xu** *University of Western Australia, Australia*
13:10-14:00	Lunch break/Lunch seminar	

	Session 3: Emerging Technologies	**Moderator:** **Prof. Louis Cheung** **Dr. Nan-Li Zhang**
14:00-14:20	Bone tissue engineering and regenerative medicine 2.0--Paradigm shift from "Proof-of-concept" to "Proof-of-value"	**Prof. Zhi-Yong Zhang** *Guangzhou Medical University, China*
14:20-14:40	Electromagnetic stimulation effects on rotator cuff repair: From the lab to the clinic	**Dr. Erik Waldorff** *Orthofix Inc, USA*
14:40-15:00	Self-assembled injectable nanocomposite hydrogel stabilized by bisphosphonate-magnesium (Mg^{2+}) coordination for 3D cell culture and controlled release of bioactive ions	**Prof. Li-Ming Bian** *The Chinese University of Hong Kong, HKSAR*
15:00-15:20	Biomaterial based stem cells enrichment for bone regeneration: from bench to bedside	**Prof. Ting-Ting Tang** *Shanghai Jiatong University, China*
15:20-15:40	Engineered hair follicle mesenchymal stem cells overexpressing controlled-release insulin reverse hyperglycemia in mice with type 1 diabetes	**Prof. Jin-Yu Liu** *Jilin University, China*
15:40-15:50	Tea break	
	Session 4: Clinical and translational research	**Moderator:** **Prof. Patrick Yung** **Prof. Ming-Hao Zheng**
15:50-16:10	Fracture Healing: New challenges to the old paradigm	**Prof. Theodore Miclau** *University of California, USA*
16:10-16:30	Mg-based bimetal: From bench to bed	**Prof. Ling Qin** *The Chinese University of Hong Kong, HKSAR*
16:30-16:50	In vitro cartilage regeneration and its clinical translation	**Prof. Guang-Dong Zhou** *National Tissue Engineering Center of China, China*
16:50-17:10	Mesenchymal stem cells and skeletal tissue engineering	**Prof. Oscar Kuang-Sheng Lee** *Yangming University, Taiwan*
17:10-17:30	Annulus fibrosus regeneration using a multimodal mechano-modulation and layered assembly strategy	**Prof. Bin Li** *Soochow University, China*
17:30-17:50	Microstructure of bone-tendon junction: A new micro-imaging technology introduction	**Prof. Hong-Bin Lu** *Xiangya Medical School, China*
17:50-18:10	Regulation of hypoxia microenvironment during skeletal regeneration	**Prof. Chao Wan** *The Chinese University of Hong Kong, HKSAR*
18:10-18:30	Distraction osteogenesis for the management of cranial bone defect and neurological disorders: what is behind the magic?	**Prof. Gang Li** *The Chinese University of Hong Kong, HKSAR*
18:30-18:45	Conclusion remarks	**Prof. Gang Li** **Prof. Patrick Yung** **Prof. Theodore Miclau** **Prof. Geoff Richards**
	Meeting Adjourns	

7th CUHK International Symposium on Stem Cell Biology and Regenerative Medicine

Location (Site):

1/F Auditorium

Main Clinical Block and Trauma Centre

Prince of Wales Hospital,

30-32 Ngan Shing St. Shatin, New Territories, Hong Kong

香港新界沙田銀城街30-32號威爾斯親王醫院住院主樓暨創傷中心1樓會議廳

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The Lui Che Woo Foundation made a generous donation to CUHK for the establishment of the Lui Che Woo Institute of Innovative Medicine which integrates multiple disciplines in clinical medicine and combines the strengths of basic research and clinical studies, with the aims of exploring innovative methods of diagnosis and treatment, and bringing new hopes to patients.

"Sports Medicine and Regenerative Technology" (SMART) is one of the three focused initiatives that emphasizes inter-disciplinary collaboration and joint research to develop innovative diagnostic or therapeutic methods and devices, to advance clinical service through translational research and to promote health through community and professional education programs.

The annual CUHK International Symposium on Stem Cell Biology & Regenerative Medicine is achieving the Institute's objective of "Knowledge Transfer".

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