3rd CUHK International Symposium on Stem Cell Biology & Regenerative Medicine

11-12 November 2013

The Postgraduate Education Centre
Prince of Wales Hospital
Shatin, Hong Kong

Organizers

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

Organizers:

Sponsored by :

呂志和基金有限公司
LUI CHE WOO FOUNDATION LIMITED

嘉華集團
K. WAH GROUP

何善衡慈善基金會有限公司
THE S. H. HO FOUNDATION LIMITED

Contents

Contents

Welcome Message

Message from

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

It is with great pleasure that I welcome you all to the 2013 Stem Cell and Regenerative Medicine International Symposium.

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

In the last 3 years, CUHK have been expanding our research potentials and capacities in the field of regenerative medicine. Dedicated research teams and research projects are being set up and state-of-the-art research facilities are built to facilitate the needs of research and clinical applications in this field.

I am delighted to announce that a new Institute of Innovative Medicine (IIM) has been established at CUHK with a generous donation of the Lui Che-Woo Foundation (吕志和基金). Three main research themes are identified: Sport Medicine and Regenerative Technologies (SMART); Brain Research and Innovative Neuroscience (BRAIN) and Cardiovascular Advancement, Research and Education (CARE).

The main theme of this year's symposium is musculoskeletal regeneration and I am glad to see the formation of A Musculoskeletal Regeneration Research Network (MRN), which is an unique platform bringing many creditable partners together to share innovative research in the field of musculoskeletal regeneration.

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

I wish you a most enjoyable stay in Hong Kong and that the symposium will be very stimulating and successful!

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

Message from

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

Dear colleagues and friends:

Welcome to the 3rd CUHK International Symposium on Stem Cell Biology and Regenerative Medicine.

Regenerative medicine is an emerging discipline using cells, genes, other biological factors and tissue engineering to repair or regenerate cells, tissues, and organs. It has enormous potential to develop new paradigms for medicine focusing on tissue repair and regeneration obviating the need for organ replacement. This specialty will transform clinical practice, reducing dependence on invasive procedures and providing the potential to treat currently intractable diseases. As such it is of great societal and economic importance. Stem cell biology and regenerative medicine research bring together the clinicians and research scientists from clinical and preclinical departments which are interdisciplinary research efforts.

I hope that you take this opportunity to share research findings and make friends, and also enjoy the hospitality of our colleagues at CUHK.

I wish you enjoy your stay in Hong Kong and the symposium to be very fruitful and successful!

Yours sincerely,

Francis Chan

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

Welcome Message

Message from

Organizing Committee

Dear colleagues and friends:

The 3rd CUHK International Symposium on Stem Cell Biology and Regenerative Medicine will be held in Prince of Wales Hospital, the Chinese University of Hong Kong on 11-12 November 2013.

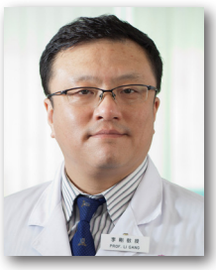
First, we would like to thank sincerely for all the guest speakers to join us on this occasion and show your support. Your presence has made this symposium a truly international one. Research on stem cell biology and regenerative medicine in Hong Kong develops rapidly. More and more staff are interested or involved in the research fields of stem cell biology, biomaterials, tissue engineering under the broader term of regenerative medicine. We hope that the symposium will provide a platform for us to share and learn new research ideas, findings and techniques from each other.

The symposium is divided into 4 main parts: biology of tissue regeneration; topics of regenerative medicine; technological advancements and translational medicine related topics. Experts from Europe, USA, Taiwan, Singapore, China as well as from CUHK will share their latest discoveries, research ideas and techniques on various fronts of regenerative medicine research. This symposium is an ideal opportunity for researchers, students, clinicians and people who are interested in regenerative medicine to learn and to share.

On behalf of the symposium organizers, we warmly welcome you to join us in Hong Kong and enjoy the symposium as well as the stay in Hong Kong!

Organizing Committee
The 3rd CUHK International Symposium on Stem Cell Biology and Regenerative Medicine

Co-Charimen:

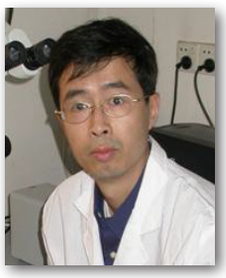


Prof. Gang Li
Professor
CUHK-ORT
CUHK-SBS-SCR

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

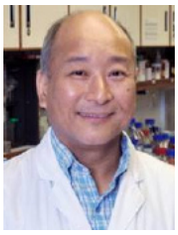
Prof. Kai-Ming Chan
Chair Professor
CUHK-ORT

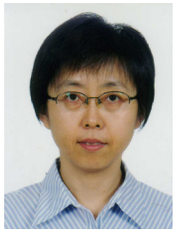
Prof.Jack Chun-Yiu Cheng
Chairman
CUHK-ORT

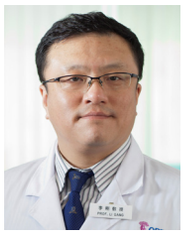


Prof. Dong-Qing Cai
Co-Director,
Jinan-CUHK Key Lab for
Regenerative Medicine,
Ministry of Education, China

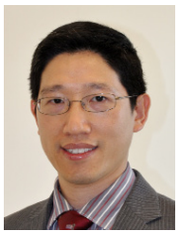
Stem Cells and Regeneration (SCR) Theme
School of Biomedical Sciences
The Chinese University of Hong Kong


Prof. Kenneth LEE


Prof. Bo FENG


Prof. Gang LI


Prof. Kingston MAK


Prof. Chao WAN


Prof. KM CHAN


Prof. Ling QIN


Prof. Xiaohua JIANG


Prof. Faye TSANG


Prof. Ping YUAN

Members of SCR:

Position	Name	Contact Email
Chief	Prof. LEE Ka Ho Kenneth 李嘉豪	kaholee@cuhk.edu.hk
Deputy Chief	Prof. LI Gang 李剛	gangli@ort.cuhk.edu.hk
Members	Prof. FENG Bo 馮波	fengbo@cuhk.edu.hk
	Prof. MAK King Lun Kingston 麥經綸	kmak@cuhk.edu.hk
	Prof. JIANG Xiaohua 蔣曉華	xjiang@cuhk.edu.hk
	Prof. LU Gang 路鋼	lugang@surgery.cuhk.edu.hk
	Prof. WAN Chao 萬超	cwan@cuhk.edu.hk
Associate Members	Prof. CHAN Kai Ming Cavor 陳啓明	kmchan@ort.cuhk.edu.hk
	Prof. CHEUNG Wing Hoi Louis 張穎愷	louis@ort.cuhk.edu.hk
	Prof. CHENG Chun Yiu Jack 鄭振耀	jackcheng@cuhk.edu.hk
	Prof. LU Weijia William 呂維加	wwlu@hkusua.hku.hkc
	Prof. MAK Fuk Tat Arthur 麥福達	arthurmak@cuhk.edu.hk
	Prof. POON Wai Sang 潘偉生	wpoon@cuhk.edu.hk
	Prof. QIN Ling 秦嶺	lingqin@cuhk.edu.hk
	Prof. TSANG Suk Ying Faye 曾淑瑩	fayetsang@cuhk.edu.hk
	Prof. WANG Huating 王華婷	huating.wang@cuhk.edu.hk
	Prof. YUAN Ping 袁平	pyuan@cuhk.edu.hk

Mission and Vision of SCR:

To co-ordinate and facilitate research, education, and clinical application of stem cells and regeneration technologies in the Faculty of Medicine, the Chinese University of Hong Kong and to implement a new, multidisciplinary, and sustainable program in translational research in regenerative biology, which will form the basis for incorporating clinical service with cutting edge technology into these disciplines.
More specifically we view as our missions:

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

Research Focus of SCR:

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

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

Core technology and research platforms of SCR:

The followings are some existing technologies that we have in the theme:

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

For the research interests of each members, please check at the following website:
http://www.sbs.cuhk.edu.hk/Research_Scr.asp

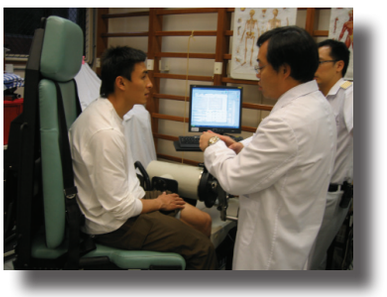
Department of Orthopaedics and Traumatology
The Chinese University of Hong Kong

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

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

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

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



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

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

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

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

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

IIM SMART 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 & 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 & 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 (MSKRRN)

Clinical Service

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

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

Research

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

Our Clinical team is actively participating in clinical researches. We have a very broad spectrum of interests, from sports injuries epidemiology, diagnostic skills, injury prevention programme, surgical technique development to rehabilitation and performance enhancement program. Our current main focus essentially is

on Knee and shoulder sports injuries, with special interests in ACL injuries particularly randomize-controlled trials in single-bindle ACL versus double-bundle ACL reconstructions etc. We have published more than 30 clinical papers in different peer-reviewed international journals.

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

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

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

Education

We are a leading center for sports medicine education. For Undergraduate teaching, we are dedicated in educating CUHK MB,ChB Med I, III and V students. We were awarded the University Grants Council (UGC) Restructuring and Collaboration Fund (RCF) to set up the Joint Universities Sports Medicine and Rehabilitation centre with the Rehabilitation department of Hong Kong Polytechnic University in 2007. 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.

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.

We would like to thank our generous sponsors:

Croucher Foundation
裘槎基金會

THE UNITED COLLEGE OF HONG KONG
新民 明德
聯合書院

life technologies™

天恒

Session 1: Stem Cell Biology in Musculoskeletal Diseases and Regeneration

Human Globin Gene Regulation and iPSC Therapy for Sickle Cell Disease

Prof. Tim M. Townes
Chairman, Department of Biochemistry and Molecular Genetics,
Director, UAB Stem Cell Institute,
Schools of Medicine and Dentistry,
University of Alabama at Birmingham,
USA

In 2006, we corrected sickle cell disease in our humanized mouse model by gene replacement (Blood 108:1183). This proof of principle experiment demonstrated that the disorder can be cured without the risks associated with gene addition approaches. In 2007, we and our collaborators extended this approach to induced pluripotent stem cells (Science 318:1920. This was the first demonstration of gene replacement in iPSC and the first example of the use of iPSC to cure an inherited disorder. We have now derived iPSC from skin fibroblasts of 9 sickle cell patients at UAB and have corrected the sickle mutation by homologous recombination. These corrected iPSC express fetal hemoglobin instead of adult hemoglobin. We have demonstrated that the level of a critical transcription factor (KLF1) is low in iPSC-derived erythroid cells and that enhancing KLF1 levels results in correct globin gene switching. Finally, we have defined kinases that control KLF1 levels. Inhibitors and stimulators of these kinases are potential therapeutic drugs for sickle cell disease. These studies provide a foundation for the development of both genetic and drug therapies for this devastating disorder.

Brief CV
Dr. Townes is Director of the UAB Stem Cell Institute and Chairman of the Department of Biochemistry and Molecular Genetics at the UAB Schools of Medicine and Dentistry. His research on sickle cell disease has been funded by the National Institutes of Health since 1985. His research is designed to develop novel, safe and effective therapies for sickle cell disease and beta-thalassemia.

Stem cells for Intervetebral disc regeneration: Which Cells? At what time? How to deliver?

Prof. Mauro Alini
AO Research Institute Davos,
Swizerland

There is evidence that implantation of bone marrow derived mesenchymal stem cells (MSCs) into damaged discs may regenerate the tissue. MSCs have increasingly been recognized as a promising source of stem cells for tissue repair and regeneration therapies. Indeed, recent studies have shown that human MSCs have the capability to survive within the disc. Injection of human MSCs into injured porcine spinal discs, rat disc degeneration models, and bovine caudal discs in vitro demonstrated MSC survival and differentiation towards a disc-like phenotype. It is, however, not yet clear whether MSCs could also release biological factors, which will be able to stimulate the resident disc cells or activate the potential progenitor cells present within the disc

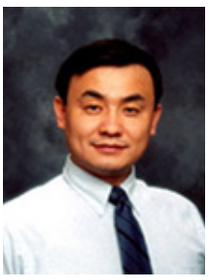
Anyhow, the present delivery approach of MSCs within the IVD has to be through injection, via the annular or end-plate route. In both cases, it would require to injure intact tissues, which would subsequently lead to further degeneration, as recently shown by (Carragee et al., Spine 2009).

We have now shown that MSCs have the ability to migrate (homing) towards sites of injury and aid wound healing and tissue repair, using our whole organ culture system. This alternative finding is opening new potential strategies for the systemic delivery of MSCs within the IVD without damaging neither the annulus fibrosus nor the end-plate tissues.

Brief CV

Mauro Alini graduated in Chemistry from the University of Lausanne (Switzerland) in 1983. Since then he has been involved in connective tissue research, starting form his Ph.D. research work, done at the Laboratory of Cellular Pathology in Locarno (Switzerland), which focused on the isolation and characterization of proteoglycans extracted from both normal human mammary gland and carcinomas thereof. In September 1988, he joined the Joint Diseases Laboratory (under Dr. A. R. Poole's direction) at the Shriners Hospital in Montreal to work on quantitative and qualitative changes in extracellular matrix proteins (particularly proteoglycans and collagens) of the growth plate tissue before and at the time of cartilage matrix calcification during endochondral bone formation. In January 1995, he was appointed as an Assistant Professor at the Division of Orthopaedic Surgery of the McGill University (Chair Prof. M. Aebi) and head of the Biochemistry Unit of the Orthopaedic Research Laboratory, working to develop new biological approaches to treating intervertebral disc damage. Since July 2000, he is in charge of the Musculoskeletal Regeneration Program at the AO Research Institute (Davos, Switzerland), focusing on cartilage, bone and intervertebral disc tissue engineering. Since September 2009 is also the Vice-Director of the same Research Institute.

MSCs in Bone Remodeling and Osteoarthritis



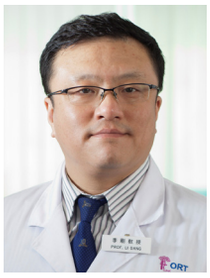
Prof. Cao Xu
Department of Orthopaedic Surgery,
Johns Hopkins University,
USA

Osteoarthritis (OA) is a highly prevalent joint cartilage degeneration disorder. Articular cartilage has been the focus for OA study, but there is no effective disease modifying treatment for OA. In this study, we investigated subchondral bone-articular cartilage as a functional unit in the joints during progression of OA. We found uncoupled osteoclastic bone resorption in the subchondral bone 7 days post anterior cruciate ligament transaction (ACLT) of an OA mouse model. The levels of active TGFβ1 were significantly increased in the subchondral bone, which induced increase of mesenchymal stem cells (MSCs) and osterix+ osteoprogenitors significantly in the subchondral bone marrow one month post ACLT. Injection of TβRI inhibitor (1mg/kg for 1 month) improved subchondral bone structure, decreased angiogenesis and partially attenuated articular cartilage degeneration. Furthermore, local administration of TGFβ antibody in the subchondral bone of ACLT rats prevented articular cartilage degeneration, indicating that the pathological changes in subchondral bone contribute to the progression of articular cartilage degeneration. Moreover, we knocked out TGFβ type II receptor (TβRII) specifically in nestin+ MSCs by inducible nestin-CreER to further validate the role of nestin+ cells in the onset of OA. The microarchitecture was significantly improved in KO mice. Importantly, proteoglycan loss, advances of calcified cartilage zone, MMP13 and type X collagen expression in chondrocytes were prevented in ACLT TβRII knockout mice. This study demonstrates that high levels of active TGFβ1 in the subchondral bone contribute to the pathological changes seen at the onset of OA. Inhibition of TGFβ1 prevented OA progression and could an effective therapy of OA.

Brief CV

Dr. Cao was initially trained in cartilage biology during my Ph.D study. I studied osteoclasts in my postdoctoral training at Washington University. My lab is currently working on the mechanisms of bone remodeling. My own career development has greatly benefited from membership in ASBMR. In the past 23 years of my skeletal research career, I have actively participated in ASBMR activities and services. I have served on the Membership Development Committee, Special Task Forces, session chair for the ASBMR Annual Meeting and Editorial Board member and Senior Associate Editor for the JBMR. I also served as the program Co-Chair for the 2012 ASBMR Annual Meeting. With my bone research experience and my years of service in the Society, I feel confident that I understand the future direction for the development of the ASBMR, and I will do my best for the ASBMR as a Councilor if I am elected.

Circulating stem cells and its clinical implications



Prof. Gang Li, MBBS, DPhil (Oxon)
School of Biomedical Sciences,
Department of Orthopaedics and Traumatology,
The Chinese University of Hong Kong,
Hong Kong, China

Mesenchymal stem cells (MSCs) have been found in cord blood and peripheral blood (PB) of mammalian species including human, guinea pig, mice, rat, dog, horse and rabbit. The number of MSCs in PB (PB-MSCs) is rare and their biological role was not fully defined. We have found increased numbers of circulating MSCs in peripheral blood in patients with long bone fracture, non-union and in patients with cancers. The number of PB-MSCs was approximately 9 times higher in the cancer patients, suggesting there is systemic recruitment of MSCs during cancer development. We have compared the difference between the circulating MSCs and bone marrow derived MSCs and found that they share similar phenotype in vitro, but the gene expression profile between the two cell populations was significantly different. cDNA microarray analysis and quantitative RT-PCR confirmed some genes that are differentially expressed with more than 10 folds difference, such as cellular retinol-binding protein 1 (CRBP1), N-cadherin, SRY-box containing gene 11 (Sox11), the aquaporin 1 (AQP1), et al. These genes are now being further investigated for their role in MSCs migration, homing and multiple-differentiation potential. We have demonstrated that systemically administrated MSCs could home to tumor sites and participated tumor growth. We are now working on using MSCs as a systemic gene delivery vehicle for management of wound healing and cancer therapy, and the ways of enhancing the homing and recruitment of MSCs toward specific sites after their systemic delivery. In conclusion, PB-MSCs are new cell source of cells that may play very important roles in development, repair and disease progression. PB-MSCs may be used for disease monitoring, diagnosis, cell and gene therapy application.

Brief CV

Prof. Li Gang received his MBBS degree from the 4th Military Medical University, Xian, China (1985-1991). In 1997, he received D.Phil. degree from University of Oxford Medical School. After post-doctoral training at the MRC Bone Research Laboratory in the University of Oxford, he took up a lectureship (1998), Senior Lectureship (2001) and Readership (2004) in the School of Medicine, Queen's University Belfast, UK. Dr. Li is currently a Professor at the Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong (2009-). His main research interests are on biological mechanisms of distraction osteogenesis, fracture healing, musculoskeletal tissue regeneration with emphasis on stem cell biology and clinical applications. He has published more than 95 peer-reviewed SCI articles, 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 International Chinese Musculoskeletal Research Society (ICMRS). Prof, Li is 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.

Key Reference (Prof. Gang Li's work in relation to PB-MSCs):
Meng FB, Rui YF, Xu LL, Wan C, Jiang XH, Li G. Aqp1 enhances migration of bone marrow mesenchymal stem cells through regulation of FAK and β-catenin. Stem Cells and Development, 2013 (in press)
Xu LL, Meng FB, Ni M, Lee YW, Li G. N-cadherin regulates osteogenesis and migration of bone marrow-derived mesenchymal stem cells. Molecular Biology Report, 2013 (online 29 November 2012).
Xu LL, Song C, Ni M, Meng, FB, Xie HQ, Li G. Cellular retinol-binding protein 1 (CRBP-1) regulates osteogenenesis and adipogenesis of mesenchymal stem cells through inhibiting RXR-a-induced ß-catenin degradation The International Journal of Biochemistry & Cell Biology, 2012:44:612-619.
Ma LL, Meng FB, Shi P, Li G, Pang XN. Quantity and proliferation rate of mesenchymal stem cells in human cord blood during gestation. Cell Biology International, 2012; 36:415-418.
Bian ZY, et al, Li G, Tang TT. Increased number of mesenchymal stem cell-like cells in peripheral blood of patients with bone sarcomas. Archives of Medical Research; 2009; 40(3):163-8.
He Q, Wan C, Li G. Multi-potent mesenchymal stem cells in blood. Stem Cells; 2007; 25:69-77.
Wan C, He Q, Li G. Allogenic peripheral blood derived mesenchymal stem cells (MSCs) enhance bone regeneration in rabbit ulna critical-sized bone defect model. Journal of Orthopaedic Research; 2006; 24(4):610-8.

Session 4

Keynote Speech

New Frontiers of Skeletal Regeneration: Stem Cells, Extracellular Matrix, and Biomaterial Scaffolds

Prof. Rocky S. Tuan
Director, Center for Cellular and Molecular Engineering,
Arthur J. Rooney, SR. Professor and Executive vice chair
Department of Orthopaedics Surgery
Associate director, McGowan Institute for Regenerative Medicine,
Director, Center for Military Medicine Research
Professor, Department of Bioengineering and Mechanical Engineering & Materials Science
University of Pittsburgh, Pittsburgh, USA

The intrinsically low capacity of cartilage for tissue repair and regeneration is a clinical challenge to effective treatment of degenerative joint diseases, such as osteoarthritis, the main cause of physical disability. Tissue engineering and regenerative medicine represents a potentially promising approach. The principal requirements are cells, scaffolds, and biological signals. Adult stem cells, such as mesenchymal stem cells (MSCs), may be harvested from autologous tissues sources, including bone marrow and adipose. MSCs have the ability to undergo multi-lineage differentiation, including chondrogenesis, osteogenesis and tenogenesis, and are actively being investigated as a candidate cell type for skeletal repair. Critical to successful cell-based tissue engineering is the use of a biocompatible biomaterial scaffold that ideally also enhances proliferation and differentiation of the seeded cells. Biomimetic scaffolds that simulate the structure of native extracellular matrix, e.g., the nanoscalar fibrous nature of collagen, have shown promise in skeletal tissue engineering using MSCs both in vitro and in vivo. Our recent work utilizing of custom-designed, photo-crosslinked hydrogel scaffolds, which allows cell encapsulation during fabrication, demonstrates high fidelity reproduction of internal structure and excellent cell retention, viability, and differentiation. Specifically, we are currently applying a 3D printing approach and a custom-designed microbioreactor to construct a microtissue analogue of the osteochondral junction, based entirely on MSC-derived components, to model the pathogenesis of osteoarthritis. In addition, our recent work also demonstrates that extracellular matrices derived from MSCs and from adult skeletal tissues, such as that from tendon, regulate MSC activity and/or tissue-specific MSC differentiation, suggesting their utility as a potential enhancer of skeletal regeneration. Taken together with their differentiation potential and recently discovered trophic activities, adult stem cells thus present a powerful platform for regenerative, therapeutic, and disease modeling applications in biomedicine.

References
Lin H, Taboas JM, Tan J, Yang G, Tuan RS. Decellularized matrix derived from human mesenchymal stem cells enhances their proliferation, migration and multi-lineage differentiation potential. Biomaterials. 2012. 33(18):4480-4489.
Xie X, Wang Y, Zhao C, Guo S, Liu S, Jia W, Tuan RS, Zhang C. Comparative evaluation of MSCs from bone marrow and adipose tissue seeded in PRP-derived scaffold for cartilage regeneration. Biomaterials. 2012. 33(29):7008-7018.
Diederichs S, Shine KM, Tuan RS. The promise and challenges of stem cell-based therapies for skeletal diseases - Stem cell applications in applications in skeletal diseases: Potential, cell sources and characteristics, and challenges of clinical translation. BioEssays. 2013. 35(3):220-230.
Lin H, Zhang D, Alexander PG, Yang G, Tan J, Cheng AW, Tuan RS. Application of visible light-based projection stereolithography for live cell-scaffold fabrication with designed architecture. Biomaterials. 2013. 34(2):331-339.
Rothrauff BB, Lin H, Gottardi R, Alexander PG, Tuan RS. Enhancement of tenogenic differentiation of human adipose stem cells by tendon-drived extracellular matrix. Biomaterials. 2013. In press.

Brief CV

Rocky S. Tuan, PhD, received his PhD in 1977 from the Rockefeller University in New York, under the mentorship of the late Zanvil A. Cohn, MD. His postdoctoral research fellowship was at Harvard Medical School in Boston, first with Melvin J. Glimcher, MD in the Department of Orthopaedic Surgery at the Children's Hospital, and then from 1978 to 1980 with Jerome Gross, MD, in the Developmental Biology Laboratory at the Massachusetts General Hospital. In 1980, Dr. Tuan was appointed as Assistant Professor in the Department of Biology, University of Pennsylvania in Philadelphia, and was promoted to Associate Professor in 1986. In 1988, Dr. Tuan joined Thomas Jefferson University, Philadelphia, to be the Director of Orthopaedic Research and Professor and Vice Chairman in the Department of Orthopaedic Surgery with a joint appointment in the Department of Biochemistry and Molecular Biology. From 1992-1995, Dr. Tuan was the Academic Director of the MD/PhD program at Jefferson, and in 1997, he established the USA's first Cell and Tissue Engineering PhD program at Jefferson, with the mission of training the next generation of "cross-cultural" biomedical scientists committed to regenerative medicine and the development of functional tissue substitutes. In the fall of 2001, Dr. Tuan joined the Intramural Research Program of the National Institute of Arthritis, and Musculoskeletal and Skin Diseases (NIAMS), National Institutes of Health (NIH), as Chief of the newly created Cartilage Biology and Orthopaedics Branch. In 2004, Dr. Tuan received the Marshall Urist Award for Excellence in Tissue Regeneration Research of the Orthopaedic Research Society. In the Fall of 2009, Dr. Tuan was recruited by the University of Pittsburgh School of Medicine to be the Founding Director of the Center for Cellular and Molecular Engineering, and as Arthur J. Rooney, Sr Chair Professor and Executive Vice Chairman of the Department of Orthopaedic Surgery, with a joint appointment as Professor in the Department of Bioengineering. Dr. Tuan is currently Co-Director of the Wake Forest University/University of Pittsburgh Consortium of the Armed Forces Institute of Regenerative Medicine, a Department of Defense funded, multi-institutional consortium focused on developing regenerative therapies for battlefield injuries. Two recent appointments at Pitt include (1) Associate Director of the McGowan Institute for Regenerative Medicine, and (2) Founding Director of the Center for Military Medicine, both at the University of Pittsburgh. Dr. Tuan has published over 400 research papers, has lectured extensively, and is currently Editor of the developmental biology journal, BDRC: EMBRYO TODAY, and the Founding Editor-in-Chief of STEM CELL RESEARCH AND THERAPY.

Dr. Tuan directs a multidisciplinary research program, which focuses on orthopaedic research as a study of the biological activities that are important for the development, growth, function, and health of musculoskeletal tissues, and the utilization of this knowledge to develop technologies that will regenerate and/or restore function to diseased and damaged skeletal tissues. Ongoing research projects are directed towards multiple aspects of skeletal and related biology, including skeletal development, stem cells, growth factor signaling, bone-biomaterial interaction, extracellular matrix and cell-matrix interaction, nanotechnology, biomaterials, 3D printing, mechanobiology, regenerative medicine, and tissue engineering, utilizing an integrated experimental approach combining contemporary technologies of biochemistry, cell and molecular biology, embryology and development, cellular imaging, and engineering.

Session 5: New Technologies and Advancements

Next-generation sequencing as a molecular diagnostic tool

Prof. Rossa W.K. Chiu
Department of Chemical Pathology,
The Chinese University of Hong Kong,
Hong Kong, China

Cell-free DNA and RNA molecules can be found in human plasma and are released during the process of cell death. Pathological processes associated with cell death release nucleic acid molecules with characteristic signatures that may be detectable in plasma. This forms the basis for the development of non-invasive blood-based diagnostics. An example is the detection of cancer-derived DNA molecules in plasma of cancer patients. Plasma DNA molecules exist in the circulation as short fragments. Plasma DNA fragments are amenable to analysis by next-generation sequencing whereby the genetic identities, pathological changes, relative amounts and size of plasma DNA could be profiled. By studying the DNA profile of recipients of haematopoietic stem cell transplantation, we showed that blood cells are the predominant source of plasma DNA. By measuring the relative amount of donor-derived DNA in plasma, one may monitor the progress of the transplantation and the development of rejection. With the development of sophisticated bioinformatics algorithms, we have succeeded in assembling whole genomes from sequences of plasma DNA molecules. We have assembled the genome of an unborn fetus by sequencing fetal DNA molecules that are present in the plasma of a pregnant woman. We have detected copy number aberrations associated with cancers directly through the analysis of plasma DNA. Recently, we achieved the non-invasive determination of the fetal methylome by performing genome-wide bisulfite sequencing on maternal plasma DNA samples. Plasma DNA methylation analysis enables one to distinguish the tissue origin of plasma DNA molecules. The newly developed molecular analysis tools could potentially be applied to stem cell research to study the associated epigenetic profile or to assess the differentiated lineage of the cells.

Brief CV
Rossa Chiu is currently Professor at the Department of Chemical Pathology and Assistant Dean (Research) at the Faculty of Medicine, The Chinese University of Hong Kong. She is also an Honorary Consultant Chemical Pathologist at the New Territories East Cluster of Hospitals. Prof Chiu graduated in 1997 with First Class Honours in Bachelor of Medicine and Bachelor of Surgery from the University of Queensland, Australia. Between 2004 and 2005, she became a Fellow of the Royal College of Pathologists of Australasia, the Hong Kong College of Pathologists and the Hong Kong Academy of Medicine (Pathology). She was awarded Doctor of Philosophy by The Chinese University of Hong Kong in 2004.

Prof Chiu has made significant contributions to research on circulating fetal nucleic acids for non-invasive prenatal diagnosis. She was the first to apply cell-free fetal DNA analysis in maternal plasma for the non-invasive prenatal diagnosis of autosomal recessive diseases. Prof Chiu developed a number of approaches for the non-invasive prenatal diagnosis of fetal aneuploidies. She was the first to perform a large scale study to demonstrate the effectiveness of the massively parallel maternal plasma DNA sequencing approach for the non-invasive prenatal screening of Down syndrome. Since 2011,

the approach has been adopted for clinical use worldwide and has resulted in major changes in the conventional practices of prenatal diagnosis.

To date, Prof Chiu has published over 115 peer-reviewed research articles, 15 books or book chapters, delivered over 65 invited presentations and has 20 granted patents or patent applications. Prof Chiu has received a number of awards for her research, including the 2011 International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Young Investigator Award, the 2011 Professors' Prize endowed by the Association of Academic Heads of Clinical Biochemistry Departments in the UK, the 2012 Asia Pacific Economic Cooperation (APEC) Science Prize for Innovation, Research and Education, the 2012 China Women in Science Fellowship and the 2013 American Association of Clinical Chemistry Outstanding Scientific Contributions for a Young Investigator. She served as the President of the Hong Kong Society of Clinical Chemistry between 2003 and 2004. She is an Associate Editor of Clinical Biochemistry, an Editorial Board member of, Clinical Chemistry, Clinical Chemistry and Laboratory Medicine, and an Editorial Advisory Board member of Critical Reviews in Clinical Laboratory Sciences.

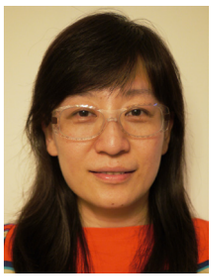
A key network approach reveals new insights in bone cell development and osteoporosis

Prof. Zhou Guang Qian
Shenzhen University Medical School,
China

A large number of molecular, genetic and environmental factors underlie osteoporosis mechanisms. Osteocytes from animal models of osteoporosis exhibit that amorphis and abnormal endomembrane system morphology as the main pathological features. Based on the fundamental nature of biological systems, we demonstrate that gross structure of physiologic developments as well as osteoporosis can be obtained from a simple coarse grained core regulatory network. Gene expression profiling further demonstrates that amorphis related genes and lipid metabolism genes are differentially expressed in osteoporotic osteoblasts. Interactions of these genes form a series of positive loops to maintain their own expression, including lipid metabolism and Ca^{2+} pump loops. Based on the proposed network and further mathematic calculations, it is proposed that abnormal lipid metabolism is a most prominent weakness of cellular molecular regulatory mechanisms and that lipid consumption and Ca2+-drived exocytosis may be the cause of membrane loss and subsequent damage of mitochondria, endoplasmic reticulum and Golgi apparatus. The key regulators for the physiologic functions related to osteoblast proliferation and differentiation are also included in this network. On the global scale this network contains three clusters, through interactions among which, a rather clear picture for cell proliferation, differentiation, cell cycle arrest process emerge. A series of experiments are being carried out in order to provide more evidences to prove our insights.

Brief CV
Guang-Qian has a bachelor's degree in Medicine and obtained his PhD in molecular immunology from Umea University, Sweden. He then worked as a postdoctoral researcher at the University of Oxford, where he started his interests in stem cells. Dr Zhou was a lecturer at Queens University Belfast during 2003-2006, an assistant professor at University of Hong Kong during 2006-2010, and joined in Shenzhen University in 2010. He is currently a professor in medical cell biology and leads research activities in anti-aging regenerative medicine. Dr Zhou has published some 40 papers in peer-reviewed international scientific journals in areas of stem cells, disease mechanisms and regeneration of musculoskeletal and nervous system organs. Particularly, Dr Zhou is interested in tissue-residing stem cells that are responsible for tissue turnover and homeostasis and rigorously impaired in the age- or disease-related degeneration of various tissue types, such as cartilage, intervertebral disc and central nervous system tissues. Dr Zhou is working to reveal key signaling pathways as well as epigenetic mechanisms regulating functionalities of such stem cells and search for extracellular molecular components to re-activate endogenous stem cells. Dr Zhou is financially supported by several international and major national funding bodies, including Natural Science Foundation of China (NSFC) and of Guangdong province (NSFG), National High-Tech "863"program, Scoliosis Research Society (SRS), Research Grant Council (RGC) of Hong Kong, and the AOSpine International.
Dr Zhou is the member of British Society for Cell Biology (BSCB), American Society for Cell Biology (ASCB), International Society for Stem Cell Research (ISSCR), International Society for Cell Transplantation (ISCT), International Chinese Mineral Research Society (ICMRS), and the AOSpine Asia. He served as an executive member of Laboratory Practice group, ISCT during 2006-2010. Dr Zhou has been a reviewer for a number of international journals, including Cytotherapy, Cell Transplantation, Biomaterials, Chinese Medical Journal, and for several national and international funding agents, including NSFC and the AO Foundation.

Extracellular matrix niche for stem cells



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

Scaffold in engineered tissues plays important functions analogous to that of extracellular matrix in native tissues. Apart from providing structural support for cells, scaffolds should also interact with cells by providing or mediating suitable biological and physical cues in their microenvironment, and act as a remodelable template for neotissue formation. The significance of major signals including soluble factors, insoluble extracellular matrix components, mechanical and topological signals in affecting stem cell fate processes will be discussed. A summary on the practical approaches to incorporate or "engineer" these niche signals into various scaffolding systems will be given with specific examples. Finally, future perspectives and technological challenges in engineering stem cell niche will be discussed.

Brief CV
Dr. Chan completed her undergraduate studies in Biochemistry at the Chinese University of Hong Kong in 1994. She obtained her Ph.D. in Surgical Science Division of the Faculty of Medicine from CUHK in 1998 and finished her first post-doctoral fellowship in Orthopaedics and Traumatology in the same institution in 1999. Dr. Chan then joined the Innovation and Technology Commission participating in the operation of the Small Entrepreneur Research Assistant Program under the Innovation and Technology Fund. After a one-year service in the government, she received her second postdoctoral fellowship in the Wellman Laboratories for Photomedicine, Massachusetts General Hospital in Harvard Medical School. Dr. Chan moved back to Hong Kong in 2002 and worked in the CK Life Sciences Int'l Inc. as a project manager. She joined the Department of Mechanical Engineering in the University of Hong Kong in 2003. Her main research interests are tissue engineering and regeneration, biosurgery, laser medicine, stem cells and biomaterial interactions, and mechanoregulation.

Session 6

Keynote Speech

Translational challenges in musculoskeletal tissue engineering

Prof. Wouter J.A. Dhert, MD, PhD, FBSE
Utrecht University,
Netherland

Diseases of the musculoskeletal system system such as osteoarthritis, trauma or cancer have a high impact to the well-being of an individual patient and form an important burden to our ageing and/or active society. During the past two decades, the emerging field of tissue engineering and regenerative medicine has made large progress and new solutions to regenerate bone or cartilage have been developed or are under current development. However, the pathway from new developments in basic science to implementation in patient care has presented many hurdles. Examples of hurdles to be addressed are the characteristics of an individual patient to receive a new treatment, the high level of complexity in the clinical situation in comparison to the well-controlled and usually simplified situation in a preclinical or laboratory setting, but also questions related to the design of clinical trials, and finally ethical and economic dilemmas. It is important to take all these aspects in consideration in the translation to patient care, not only to follow this pathway as optimal as possible, but also to prevent promising new potential treatments to fail at some point during his trajectory. For instance this has resulted in recent debate on the applications of growth factors, but also several new treatments did not reach the ultimate goal, i.e. application in the patient. In the current presentation, several aspects and possible solutions in the translation to the patient related to musculoskeletal tissue regeneration will be addressed.

Brief CV
Wouter Dhert is full professor of translational musculoskeletal research at the University Medical Center Utrecht, as well as part-time professor of tissue repair at the Faculty of Veterinary Medicine, Utrecht University. He studied Medicine at Leiden University and obtained a PhD at the Leiden Biomaterials Research Group. Currently he is chair of the UMC Utrecht research program 'Regenerative Medicine & Stem Cells'. He serves at several international committees/boards, such as the Tissue Engineering journal (executive editorial board), Netherlands Institute for Regenerative Medicine (NIRM), the AO Research Review Commission (AORRC). In 2000 he was acknowledged as international Fellow in Biomaterials Science and Engineering (FBSE). His main research focus is on regeneration of tissues of the musculoskeletal system, in particular bone and cartilaginous tissues. Since 2004 he is actively involved in applying biofabrication/ additive tissue manufacturing technology in regenerative medicine. Wouter Dhert is (co)author of approximately 190 peer reviewed papers.

Session 7: Clinical Perspectives of Regenerative Medicine: The Reality and Challenges

Towards intra-operative cell repair

Prof. R.Geoff Richards
AO Research Institute Davos,
Swizerland

Cell based therapies still have major challenges that need to be overcome in order to be able to reliably apply them within the clinic. The current pre-clinical strategies under investigation often include a monolayer expansion step. This increases time and cost, especially when regulatory requirements and logistics are taken into account. This has driven investigation into applications using freshly isolated cells which would be readily available within the clinical environment. As the biology of the mixed population of freshly isolated cells is different to those routinely used after monolayer expansion, a greater understanding of the differences will be needed. In addition, as there are fewer mesenchymal stem cells found within the freshly isolated mononuclear fraction, emphasis must be changed to take into account the lower cell numbers being applied. However, a smaller number of freshly isolated cells may be functionally more effective than a larger number of monolayer expanded cells. Mononuclear cell concentrators for intra-operative cell harvest are already available and the challenge is how to best use the cells obtained. A combination of fresh cells with a suitable biomaterial carrier, approved gene therapy techniques and appropriate rehabilitation methods could lead to the development of a rapid, intra-operative intervention.

Brief CV
2009 > Director of AO Research Institute Davos (http://www.aofoundation.org/ari), AO Foundation, Switzerland.
1991>2009 PhD Student > Group Leader (Interface Biology) > Programme Leader (Bio-performance of Materials & Devices > Translational Research) AO Research Institute Davos, Switzerland. 87-91 B.Sc, M.Sc. University of Wales, Aberystwyth, Wales, GB.

Titles & Honours
2007 > Honorary Professor, School of Biosciences, Cardiff University, Wales (GB).
2007 > Honorary Professor, Institute of Biological Sciences, Aberystwyth University, Wales (GB).
2012 Fellow of Biomaterials Science and Engineering (FBSE).
2012 Invited as a “Swiss personality” to the World Economic Forum Annual Meeting 2012 & 2013 Davos.
2010 Life Honorary Member Swiss Society for Biomaterials.
2004 Jean Leray Award (European Society for Biomaterials) – (for a researcher under 40 who demonstrated distinctive achievement and insight in biomaterials research).

Brief CV (con't)

Current Journal, Society and Board Appointments
2013> Associate Editor of the Journal of Orthopaedic Translation.
2013> Member at Large TERMIS-Europe & European representative of the world council Tissue Engineering and Regenerative Medicine International Society.
2013 Member of the World Orthopedic Alliance organizing Committee for 1st World Congress, Beijing.
2013 > Member of executive committee of Academia Raetica (umbrella organisation for the most highly qualified research institutes and the different clinics within the Canton of Grisons).
2013> Member of executive committee of Science City Davos.
2011> Executive Committee member EORS (European Orthopaedic Research Society).
2010 Honorary life member Swiss Society for Biomaterials & Regenerative Medicine.
2009 > Director of the Board ("Stiftungsrat") of the Foundation of the AO Research Institute Davos.
1999 Founder, eCM journal. 2000> Editor-in-Chief, webmaster/ editor eCM journal.

Past Society, University and Board Appointments
2009 >end of 2013 Board of directors AO GCTM (AO Global Clinical Trials Management).
2008 > 2013 Member of AO Foundation Academic Council & ex officio member of Board of Trustees.
2011>2013 Chair of the Infection Committee, ORS (Orthopaedic Research Society).
2010 >2013 Member of Swiss Arab Postgraduate Clinical Academy Academic Advisory Board.
2006-2009 Visiting Professor Institute of Biomaterials & Bioengineering, Tokyo Medical & Dental University (J).
2000>2009 Swiss Society for Biomaterials. 2009-12 Past President, 2007-09 President, 2004-07 Vice-President, 2002-04 Secretary, 2000 Executive member.
2004-2012 Honorary Senior Research Fellow Faculty of Biomedical & Life Sciences, University of Glasgow, GB.
1999-2007 Honorary Lecturer, Institute of Biological Sciences, Aberystwyth University, Wales (GB).

Other
Author on over 100 peer reviewed papers and over 300 abstracts (over 150 invited lectures, including keynotes, faculty, award lectures, symposium main lecturer, session chair etc).
Founder, web editor/master, and Editor-in-Chief for the first online only Biomaterials (& Trauma) journal eCM (http://www.ecmjournal.org). Scope: Preclinical research in the musculoskeletal field and the cells and materials used in the replacement, repair or regeneration of these tissues. Five-year Impact Factor 2012- 5.7 Yearly Impact Factor: 2012 4.558. eCM initiated the transparent review process (now known in science as open peer review) including a transparent route to becoming a member of the Review Board.
Supervised 11 PhD's, 15 masters theses, numerous medical / vet thesis's and diploma theses. Currently manage (indirectly) over 100 employees.

Developing an "Enhanced" Bone Tissue Engineering Therapeutic Strategy for Large Bone Defect Treatment under Diseased Condition -- A pilot study in diabetic rabbit model

Prof. Zhang Zhiyong
Shanghai 9th People's Hospital, Shanghai Key Laboratory of Tissue Engineering, School of Medicine, Shanghai Jiao Tong University,
National Tissue Engineering Center of China, Shanghai, China

Large bone defect treatment still remains a major clinical challenge, requiring effective bone grafts to achieve healing. Bone tissue engineering (BTE) strategy provides a promising approach to generate tissue engineered bone grafts (TEBG) to address this ever-pressing clinical need. So far, most of the research only focus on developing BTE strategies for defect treatment under the normal healthy condition. However, in many clinical scenario, especially in the elder patients, occurrence of bone defect is usually associated with other pathological condition, such as diabetes mellitus and osteoporosis, adversely affecting the defect healing process. Here, we used diabetes as a disease model, which was well known to delay the bone defect healing, and conducted a pilot study to develop an "enhanced" BTE therapeutic strategy to promote the defect healing efficacy under the diseased condition. A diabetic rabbit model was established through alloxan injection. The in vitro cell culture study using diabetic serum(DS) or normal serum (NS) supplemented with H_2O_2 demonstrated that reactive oxygen species (ROS) play an important role in the impaired osteogenic potential and increased apoptosis of osteoblast. Whereas, scavenging ROS with NAC (a potent ROS inhibitor) anti-oxidative treatment can significantly attenuate the DS-induced osteoblast dysfunction and apoptosis in vitro and promote better bone defect healing efficacy in vivo. Our findings demonstrate that ROS overproduction under diabetic condition induces depressed osteoblasts behaviors and abundant cell apoptosis, resulting in the impaired bone regeneration process. An enhanced BTE strategy accompanying with anti-oxidative treatment may become an effective therapeutic approach for bone defect treatment in diabetic diseased condition.

Brief CV

Professor Zhang Zhiyong received his B.Sc. degree in biology from Xiamen University of China in 2004 and PhD degree in bioengineering from National University of Singapore in 2009. In 2011, he was appointed as the Senior Scientist in KK Women's and Children's Hospital of Singapore. In 2012, he joined Shanghai Jiao Tong University and National Tissue Engineering Center of China; meanwhile he was granted National "1000 Young Talent" Award by the central government of China and appointed as "Eastern Scholar" Distinguished Professor by Shanghai government.

Trained as a bioengineer at multidisciplinary interfaces, Prof. Zhang holds great passion for translational research of bone tissue engineering and regenerative medicine (TERM). He is pioneering in the use of allogenic fetal mesenchymal stem cell source for TERM application and successfully developed an off-the-shelf bone TERM strategy with the integrated use of stem cell, scaffold, bioreactor and bioimaging technologies. Currently, the first-in-man clinical trial of this strategy is under the way and this could become world's first off-the-shelf bone TERM clinical trial according the literature search in database of Pubmed and Clinicaltrial.gov. He has filed 4 patents, published more than 20 academic papers in the international top-tiered journals including Stem Cells, Biomaterials, Cell Transplantation and Tissue Engineering (Average IF: 6.1 per paper) and authored five bookchapters. He has given plenary, keynote, invited and oral presentation in more than 30 international conferences and been granted eight awards including the young scientist awards, best oral awards and so on. In addition, he has sucessfully secured 8 research grants with more than 8 million RMB research grants in China. His research effort has also led to the successful commercialization of a unique bioreactor device.

Clinical applications of MSC and NSC in neuro-degenerative disorders

Prof. William J. Maloney
Elsbach-Richards Professor of Surgery,
Professor and Chairman, Department of Orthopaedic Surgery,
Stanford University School of Medicine Chief, Orthopaedic Surgery,
Stanford University Medical Center,
USA

Dr. Maloney is currently the Elsbach-Richards Professor and Chair of the Department of Orthopaedic Surgery at Stanford University where he oversees clinical and research programs in areas including joint replacement surgery, spinal surgery, trauma and sports medicine. Prior to returning to Stanford in 2004, Dr. Maloney worked at the Washington University School of Medicine in St. Louis, where he was the Charles and Joanne Knight Professor as well as Chief of Orthopaedic Surgery at Barnes-Jewish Hospital. His clinical and research efforts concentrate on joint replacement surgery and he is internationally recognized for his work on the skeletal response to biomaterials used in total joint replacement. Dr Maloney is the Past President of the Hip Society and currently serves as the Chair of the Board of Directors of the American Joint Replacement Registry. He serves on the Board of Directors of the Knee Society, the American Association of Hip and Knee Surgeons, the Western Orthopaedic Association, Stemedica Cell Technologies, Inc. and ISTO Technologies, Inc. He has received a number of awards, including three Hip Society Research Awards, the Presidential Award of the American Association of Hip and Knee Surgeons and the American-British-Canadian Traveling Fellowship of the American Orthopaedic Association.

Inflammation and stem cell homing in musculoskeletal regeneration

Prof. Stuart Goodman, MD, MSc, PhD, FRCSC, FACS, FBSE
Stanford University,
USA

Acute and chronic inflammation, and musculoskeletal tissue organogenesis, repair and regeneration initiate the mobilization and migration of cells from distant sites. These events are orchestrated by cells of the monocyte/macrophage lineage through the local production and release of pro- and anti-inflammatory cytokines and other factors, as well chemotactic cytokines (chemokines). Gradients of chemokines generate local signaling mechanisms that cause adhesion and diapedesis of inflammatory and reparative cells to the injury site to begin the processes of destruction and phagocytosis of dead cells and debris, cellular repopulation, new matrix production, and reconstitution of host tissue. If these events fail to resolve the acute inflammatory reaction, chronic inflammation or fibrosis are the end result. The latter outcomes produce functionally deficient tissue.

Abstract (con't)

Our group has used various in vitro and in vivo models to further understand the biological events governing the initiation and resolution of inflammation, and bone tissue repair. These models include cell and organ culture experiments, in vitro and in vivo chemotaxis studies, scenarios simulating aseptic and septic inflammation, and the healing of bone defects in particular. From these studies it can be concluded that an innate series of biological events occur following tissue injury that attempt to return the organism to a position of homeostasis. These events can be modulated by local infusion of biologics to curtail the pro-inflammatory environment and facilitate host tissue repair. Future translational applications of these interventions will undoubtedly hasten the recovery of patients exposed to injurious stimuli.

Brief CV

Stuart B. Goodman is the Robert L. and Mary Ellenburg Professor of Surgery, and Professor with Tenure in the Department of Orthopaedic Surgery at Stanford University. He has a courtesy appointment in the Department of Bioengineering and is an affiliate member in the Department of Mechanical Engineering. He was Chief of Orthopaedic Surgery at Stanford University from 1994-2002. Dr. Goodman received his BSc, MD and MSc (Institute of Medical Science) from the University of Toronto, and his PhD in Orthopedic Medical Science from Lund University in Sweden. He is a Fellow of the Royal College of Surgeons (Canada), the American Academy of Orthopaedic Surgeons and the American College of Surgeons. Dr. Goodman's clinical practice concentrates on adult reconstructive surgery. His clinical research interests center on the outcome of surgery for arthritis including total joint replacement, juvenile arthritis, and osteonecrosis of the hip and knee. His basic science interests center on biocompatibility of orthopaedic implants, and musculoskeletal tissue regeneration and repair. Dr. Goodman is a member of numerous academic organizations including the Biological Implants Committee of the AAOS (Chairman), and is a former member of the AAOS Biomedical Engineering Committee. He is a member of the Hip Society and the Knee Society, a consultant to the Orthopaedic and Rehabilitation Devices Advisory Panel of the FDA, and former vice-chairman of the Musculoskeletal Tissue Engineering study section at NIH. Dr. Goodman is on the editorial board of Clinical Orthopaedics (Deputy Editor-Hip Society Liason), the Journal of Arthroplasty, The Journal of Orthopaedic Research, The Journal of Biomedical Materials Research, Biomaterials, and other journals, and is a manuscript reviewer for over 20 journals in the fields of orthopaedic surgery, arthritis, bioengineering and biomaterials. Dr. Goodman has published over 345 peer-reviewed manuscripts in medical and bioengineering journals. Dr. Goodman and co-workers have received awards for their research from the Society for Biomaterials, Orthopaedic Research Society, the American Orthopaedic Association, Western Orthopaedic Association, and the Association of Bone and Joint Surgeons. Dr. Goodman was awarded the Clemson Award for Basic Research from the Society For Biomaterials in May 2000. He was the President of the Society For Biomaterials (2001-2) and served on the Board of Directors of the Orthopaedic Research Society. Dr. Goodman served as Co-Chair for the 1995, 2000 and 2007 NIH/AAOS-sponsored workshops on Implant Wear. Dr. Goodman was recognized as a Fellow, Biomaterials Science and Engineering (FBSE) by the International Union of Societies, Biomaterials Science and Engineering in May 2004. He was elected as a Fellow of the American Institute of Medical and Biological Engineers in February 2012.

Autologous Human Mesenchymal Stem Cells for Cartilage Repair: From Bench to Bedside

Prof. James Hui, MBBS, FRCS (Edin), FAMS, MD (Research)
Department of Orthopaedic Surgery
National University of Singapore
Singapore

Mesenchymal stem cells (MSCs) research demonstrated therapeutic potential of the cells. They can be used to treat diversified clinical conditions, from immune modulation to tissue regeneration. We have focused on the translational development of using MSCs clinically for cartilage repair. Earlier, we have demonstrated through in vitro research that human bone marrow (BM) is better source of MSCs than adipose tissue (Tissue Eng 2007). In the study, BM and adipose MSCs were cultured from the same sets of donors. Results showed that BM MSCs produced significantly more collagen II and s-GAG. We further demonstrated, in small and large animal, that MSCs were capable of enhancing cartilage repair (Am J Sports Med 2007, Stem Cells 2007, JBJS 2010). Especially in porcine, biomechanical testing showed that meniscus repaired with the addition of MSCs was significantly stronger that of the control animals. A clinical trial comparing MSCs and chondrocytes (Am J Sports Med 2010) showed that both cell types were capable of improving cartilage repair. However, MSCs appeared to be superior in longer term follow up, work just as well in older patients (> 45 yr) and require 1 less knee surgery (cost saving with lower risk potentially). Clinical trials (IRB approved) are now open and accruing patients at the National University Hospital in Singapore to evaluate the safety and efficiency of autologous BM MSCs in cartilage repair. Harvested bone marrow samples (during knee surgery) are processed in clean room environment (cGMP cell processing facility recently re-modeled and upgraded) and cultured for 3 weeks. The cells are injected locally in the knee with hyaluronic acid. Preliminary results showed that MSCs injection is a safe procedure (in terms of serious adverse events during administration of MSCs) and the rate of microbial contamination is low (1 in 218 processes during a 6-year span from 2006 to 2012). Our research and development has demonstrated that, in the setting of cartilage repair, it is feasible to translate longitudinally from laboratory to clinical studies using animal models (small and large) to validate in vitro results prior to design and initiation of human trials. Recent completion of patient accrual and final analysis of the trials demonstrated efficacy of autologous MSCs in cartilage repair. (Arthroscopy 2013).

Brief CV

Prof James Hui received his MBBS degree from National University of Singapore in 1990. He received his FRCS (Royal College of Surgeons, (Edinburgh UK)) in 1994, FAMS (Academy of Medicine, Singapore) in 1999 and Doctor of Medicine (National University of Singapore) in 2008. Dr Hui is currently an Associate Professor at the Department of Orthopaedic Surgery, National University of Singapore. He is heading Division of Paediatric Orthopaedics and is Director of Clinical Services for Department of Orthopaedic Surgery, National University Hospital. He is also appointed as Director for Tissue Engineering and Cell Therapy (GMP) Laboratory, National University Health System, Singapore and is a Group Leader for Cartilage Division of National University of Singapore, Tissue Engineering Programme (NUSTEP). His main research interests are on musculoskeletal tissue engineering and reconstructive surgery in paediatric orthopaedics.

Session 8: Ligament, Tendon and Muscle Highlights Symposium

The association between Cruciate Ligament injury and development of post-traumatic osteoarthritis, a population based nationwide study in Sweden, 1987-2009

Prof. Li Felländer-Tsai
Department of Orthopaedics,
Karolinska Institutet, Stockholm
Sweden

Objective: To study the association between Cruciate Ligament (CL) reconstruction and development of post-traumatic osteoarthritis in the knee.
Design: Cohort study; Level of evidence II-2
Setting: Sweden, 1987-2009.
Participants: All patients being diagnosed and registered with a CL injury in The National Swedish Patient Register between 1987 and 2009.
Main outcome measures: Knee osteoarthritis
Results: 79,442 incident cases of patients diagnosed with CL injury in Sweden between 1987 and 2009 were included in the study and 10% of the patients were diagnosed with knee OA. There was a difference in risk to develop OA depending on treatment. Early CL-R was not superior to late CL-R. The risk to develop OA was not affected by sex. Higher age and meniscal injury increased the risk. CL-R had a more protective effect on those that had a meniscal injury compared to those that had not. CL-R was not more beneficial depending on sex.
Conclusion: This is the first population based nationwide study demonstrating the development of OA in patients diagnosed with a CL injury and the impact of sex, age, concomitant meniscal injury and choice of treatment.

Brief CV
Li Felländer-Tsai, is a professor of orthopaedics at the Karolinska Institutet, and senior consultant at Karolinska University Hospital in Stockholm, Sweden. She is the chairman of the Department of Clinical Science, Intervention and Technology at Karolinska Institutet and head of orthopaedics and biotechnology. She is also the Director of the Center for Advanced Medical Simulation and Training at Karolinska.
She is also president of the Swedish Orthopaedic Association and was previously registrar and board member of the Swedish ACL Register (Quality registry for cruciate ligament reconstruction). Since 2010 she is a member of the University Board at the KTH, The Royal Institute of Technology in Stockholm.

Identification of cartilage progenitor cells and translational research on cartilage tissue engineering

Prof. Hong-Wei Ouyang
Center for stem cell and tissue engineering, Zhejiang University, China

Osteoarthritis and cartilage injuries are the challenge in orthopedic clinical practice. Tissue engineering approach provides a promising strategy to develop new therapeutics. Numerous researches developed a number of cell sources and scaffolds for cartilage tissue engineering. Most of them focused on the small portion of patients with limited full-thickness cartilage defect. But more than 90% of clinical cases are unlimited area of heterogeneous partial-thickness cartilage defect which cannot be self-repair or repaired by cell-scaffold structure. It requires us to further understand cartilage progenitor cells. Some progress was achieved on the identification of CPC and the repair of partial-thickness cartilage defect after We modified the local niche for CPC and MSCs. On the other hand, the ACI/MACI is a relative mature therapeutic for limited cartilage defect which has more than 20 year's history. However, it is hindered in China due to lack of official approval channels. Here we introduce the neo-build regulatory of new therapeutics of engineered tissue transplantation. Following the guideline Zhejiang university and 5 hospitals have successfully got the official approval in 2010. Since then more than 20 patients has been treated by Tissue Engineered Cartilage (TEC). In brief, the translational procedure of tissue engineered research in China includes preparing preclinical research data, samples of seed cells and scaffold, a series of SOPs, clinical research data, and application for the approval on clinical entry as well as the price of the therapeutics. It is a long lasting work, translation researcher need to coordinate with officers from different government departments as well as technicians, doctors and patients.

Brief CV
Professor in Sports medicine & Stem Cells and Regenerative Medicine
Director for School of Basic Medical Science, Zhejiang University
Vice-Dean for College of Mecine, Zhejiang University
Awardees of the National Science Fund for Distinguished Young Scholars (Jie-Qin)
Awardees of National "1000-talent"plan (Qian-Ren)
The "Qiu-shi" Distinguished Professor, Zhejiang University
Adjunct Professor, School of Biomedical Sciences, Chinese University of Hong Kong
Professor Ouyang focuses on the research of tissue engineering and regenerative therapy of tendon and cartilage. With the development of a functional silk scaffolds as well as the stepwise differentiation of embryonic or adult stem cells with the combination of biochemical and mechanical strategies, Prof Ouyang's researches improved structural and functional tendon and cartilage regeneration significantly in vitro and in vivo. He has filed ten national patents applications (four approved) and published more than thirty original research papers in the international journals. Among these papers, more than fouty papers corresponded by Prof Ouyang were published in the leading journals of particular fields, such as Stem Cells, Biomaterials, Cell Transplantation(Incitations >1000, Average IF=5.6). In 2008, authorized by State Food and Drug Administration, he was involved in drafting the Guide for in vivo assessment of implants for cartilage repair and regeneration YY/T 0606.10-2008, Chapter 10 of Tissue Engineering Medical Products, Pharmaceutical Industry Standard of People's Republic of China. In 2009, he was again involved in formulating the Provisions for Therapeutic Transplantation of Engineered Tissues announced by the Ministry of Health (MOH). In March of 2010, under the new regulations of the Ministry of Public Health in China, Prof Ouyang established a standard approach for tissue engineered cartilage (TEC) transplantation, and set up the clinical application network of cartilage tissue engineering technology in orthopedics from five third-grade class-A hospitals in Zhejiang.

The role of infection and genetic predisposition of failed healing in chronic tendon ailments

Prof. Christer Rolf MD, PhD
Department of Orthopedics,
Karolinska University Hospital, Clintec,
Karolinska Institutet, Stockholm,
Sweden

There is a rationale to suggest that some pathogens can trigger and control an active "non-healing" process by reprogramming tendon cells, in particular in genetically predisposed individuals. Human data of failed tendon healing and tendinopathy is limited by the fact that collection of tissue samples occurs at one specific point in time, during surgery, which usually is long time after onset of this failed healing process. The duration is not known, neither is the natural course. At that time of surgery for a tendon rupture the tendon structure is usually severely deteriorated with or without preceding symptoms. Normal collagen is not restored after surgery but replaced with fibrotic structures. Novel analytic techniques allow us to revert into the phase of some of possibly etiologic factors which may be involved in triggering such process. The new techniques are based on the simultaneous detection of nucleic acids in affected tissues and the corresponding antibodies in serum. A new technique allows a sensitive and multiplex detection of relevant microbes. Another new serological technique (Suspension multiplex immunoassay, SMIA) has been developed by researchers at Uppsala University. It allows rational and simultaneous detection of antibodies to most of the targeted pathogens. 16S rRNA sequencing is a well-established method that enables the detection of unknown bacteria in sterile body sites. A corresponding tissue bank for human surgical samples has recently been developed at Karolinska Institutet. This study is currently undertaken in close collaboration between Karolinska Institutet, Chinese University of Hong Kong and Uppsala University.

Brief CV
Consultant Orthopaedic Surgeon, Head of Arthroscopy and Sport Injury Section,
Department of Orthopaedics, Karolinska University Hospital
Professor of Sports Medicine Department of Clinical Science, Intervention and Biotechnology, Karolinska Institutet, Stockholm, Sweden

Effect of post-operative GHK-Cu intra-articular injections on graft healing in ACL reconstruction

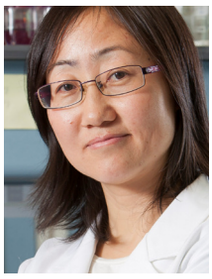
Dr. Fu, Sai Chuen Bruma
Department of Orthopaedics & Traumatology,
The Chinese University of Hong Kong,
Hong Kong, China

Anterior cruciate ligament reconstruction (ACLR) is the standard treatment to restore knee function. However, the biological healing of the graft is poor, which can lead to ACLR failure and excessive knee laxity. Glycyl-Histidyl-Lysine tripeptide in its copper (II) chelated form (GHK-Cu) is a well-known activator of tissue remodeling. In the present study, we investigated the effects of GHK-Cu to promote graft healing in ACLR. Seventy-two male Sprague Dawley rats (12 weeks old, 400-450g) were used. Intra-articular injections (50μl per injection) of saline or GHK-Cu solution (0.3 or 3 mg/ml) were performed weekly from 2nd week to 5th week post operation. At 6 or 12 weeks post-operation, t knee specimens were harvested for anterior-posterior (AP) knee laxity test, graft pull-out test and histological scoring. We found that rats treated with 0.3 or 3 mg/ml GHK-Cu resulted in a significantly smaller side-to-side difference in AP-knee laxity at 6 weeks post operation, but no difference was detected at 12 weeks post operation. There was no significant improvement in pull-out strength of the graft complex. Histological examination showed that graft incorporation and bone healing inside tunnels was significantly better in the GHK-Cu treated groups. Graft degeneration was less severe in the 0.3 mg/ml GHK-Cu group as compared to saline group, but significantly increased cell recruitment to graft mid-substance in 3 mg/ml GHK-Cu group also rendered poor graft integrity. Our study suggests that GHK-Cu may improve graft healing in ACLR. Further studies are necessary to investigate the underlying mechanisms for the observed effects of GHK-Cu.

Brief CV

Dr. Fu Sai Chuen, Bruma is currently an honorary research associate at the Department of Orthopaedics and Traumatology, the Chinese University of Hong Kong. His main research interests are on pathogenesis of tendinopathy, development of strategies to promote tendon healing and graft healing in anterior cruciate ligament reconstruction.

Identification and Characterization of Long non-coding RNA in Skeletal Myogenesis



Prof. Wang Huating
Department of Obstetrics and Gynaecology,
The Chinese University of Hong Kong

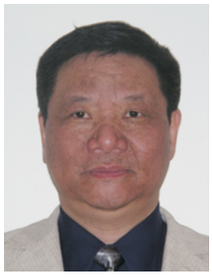
Large portion of mammalian genome was thought to be "junk" regions while only ~3% are useful in coding proteins. However, recent efforts in high throughput analyses of the mouse and human genomes have revealed that these "junk" regions are transcribed into a wide variety of non-coding RNA (ncRNA) transcripts. Long ncRNAs (>200nt in length, lncRNAs) are emerging as potent regulators of gene expression. Spurring efforts have been made to identify and characterize their functions in various cells and tissues. However, little was known whether lncRNAs are involved in skeletal muscle stem cells or muscle regeneration. Here we describe ab initio identification of novel lncRNAs through analyzing a combination of genome-wide chromatin mapping and transcriptome sequencing data. Further functional characterization demonstrated that these lncRNAs are critical regulators of myogenesis through various molecular mechanisms.

Brief CV

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

Session 9: Tissue Specific Functions of Stem Cells

A Stem Cell–Based Approach to Cartilage Repair in mouse Osteoarthritis disease Model



Prof. Yi-Ping Li
Department of Pathology,
University of Alabama at Birmingham,
USA

Osteoarthritis (OA) is a frequent cause of joint pain and is the most common cause of disability for persons older than 55 years in the US. OA was previously thought to be a normal consequence of aging. However, now we know that osteoarthritis has multiple risk factors, including joint instability, genetic predisposition, local inflammation, mechanical forces, and cellular and biochemical processes and is a degenerative joint disease that involves the destruction of articular cartilage and eventually leads to disability. The molecules that promote the selective differentiation of multipotent mesenchymal stem cells (MSCs) into chondrocytes may stimulate the repair of damaged cartilage and remain unknown. Using AAV mediated genetically-engineered MSC expressing the transcription factor RUNX1 and CBFb shows chondroprotective effects in vitro, and is efficacious OA animal model. AAV-RUNX1 expression and AAV- CBFb expression virus induces chondrogenesis by regulating the CBFb-RUNX1 transcriptional program. This work provides new insights into the control of chondrogenesis that may ultimately lead to a stem cell—based therapy for steoarthritis

Brief CV

Institution and location	Degree	MM/YY	Field of study
Zhejiang University, China	B.S.	07/79	Chemistry
Shanghai Institute of Biochemistry, Chinese Academy of Sciences, Shanghai, China	Ph.D.	10/88	Molecular Genetics
Ctr. Biomedical Res, Rockefeller University, NY	Postdoctoral Fellow	02/89 - 04/90	Molecular Biology
The Forsyth Institute; Harvard School of Dental Medicine, Boston	Postdoctoral Fellow	05/90 05/93	Bone and Cell Biology

Brief CV (con't)

Positions and Employment

1989 - 1990	Assistant Professor, Shanghai Institute of Biochemistry, The Academy of Sciences of China
1990 - 1993	Staff Associate, Cytokine Biology Department, Forsyth Dental Center (now The Forsyth Institute), Harvard School of Dental Medicine, Boston, MA
1993 - 1994	Research Associate, Cytokine Biology Department, The Forsyth Institute, Harvard School of Dental Medicine Boston, MA
1994 - 1995	Assistant Member of the Staff, Cytokine Biology Department, the Forsyth Institute. Harvard School of Dental Medicine
1994 - 1999	Lecturer, Oral Biology and Pathophysiology, Harvard School of Dental Medicine, Boston, MA
1995 - 1998	Assistant Member of the Staff II (equivalent to Assistant Professor), Cytokine Biology Department, The Forsyth Institute, Harvard School of Dental Medicine
1999 - 2010	Assistant Professor, Developmental Biology Department, Harvard School of Dental Medicine
1999 - 2007	Associate Member of the Staff (equivalent to Associate Professor), Cytokine Biology Department, The Forsyth Institute, Harvard School of Dental Medicine, Boston, MA
2007- 2010	Senior Member of the Staff (equivalent to Tenured Professor), Cytokine Biology Department, The Forsyth Institute, Harvard School of Dental Medicine, Boston, MA
2010 - present	Adjunct Senior Research Investigator, Cytokine Biology Department, The Forsyth Institute, Harvard School of Dental Medicine, Boston, MA
2010 - present	Jay M. McDonald Endowed Professor in Bone Biology, University of Alabama at Birmingham, Birmingham, AL
2010 - present	Senior Vice Director for Research, Center for Metabolic Bone Disease, University of Alabama at Birmingham, Birmingham, AL
2013 - present	Professor, UAB Dental School Secondary Appointment

Blocking SDF-1/CXCR4 pathway attenuates OA development

Prof. Wei Lei
Department of Orthopedics,
Brown Medical School/Rhode Island Hospital,
USA

To test whether blocking stromal cell-derived factor-1 (SDF-1)/CXCR4 pathway with AMD3100 can attenuate Osteoarthritic (OA) pathogenesis in Guinea pig OA model. OA chondrocytes and cartilage explants were incubated with SDF-1, siRNA CXCR4, or anti-CXCR4 antibody prior to treatment with SDF-1. Matrix metalloproteases (MMPs) mRNA and protein levels were measured with RT-PCR and ELISA, respectively. 35 nine-month-old male Hartley guinea pigs (0.88kg±0.21kg) were divided into three groups: AMD treated Group (n=13); OA Group (n=11); and Sham Group (n=11). At three months post-treatment, knee joints, synovial fluid, and serum were collected for histological and biochemical analysis. The severity of cartilage damage was assessed using the modified Mankin score. The levels of SDF-1, GAG, MMP-1, MMP-13 and Interleukin-1 (IL-1β) were quantified by ELISA. SDF-1 infiltrated cartilage and decreased proteoglycan staining. Increased glycosaminoglycans and MMP-13 activity were found in the culture media in response to SDF-1 treatment. Disrupting the interaction between SDF-1 and CXCR4 with siRNA CXCR4 or CXCR4 antibody attenuated the effect of SDF-1. Safranin-O staining revealed less cartilage damage in the AMD3100 treated animals with the lowest Mankin score compared to the control animals. The levels of SDF-1, GAG, MMP1, MMP-13, and IL-1β were much lower in the synovial fluid of AMD3100 group than that of control group. These findings raise the possibility that disruption of the SDF-1/CXCR4 signaling can be used as a therapeutic approach to attenuate cartilage degeneration.

Brief CV
Dr. Lei Wei obtained his M.D. from Guiyang Medical College in China, and his Ph.D. degree from Karolinska Institute in Stockholm, Sweden. He completed his post-doctoral fellowship in Hershey Medical School of Penn State University. Currently, Dr. Wei is an Associate professor in Orthopaedic Research at Brown Medical School/ Rhode Island Hospital. Dr. Wei's research has been supported by several grants from NIH, Aircast foundation and Arthritis foundation. Dr. Wei's research interest includes cartilage molecular biology, growth plate development, and cartilage degeneration (i.e., osteoarthritis). Throughout Dr. Wei's research career, he received several Scientist Awards, including New Investigator Recognition Awards from Orthopaedic Research Society, Young Investigator Award from Osteoarthritis Research Society International (OARSI) (2002 and 2005). OA, the degeneration of articular cartilage, is the most common cause of joint pain and disability in the elderly. Unfortunately, there is little effective pharmacological therapy aiming at the mechanism of the disease, largely because the etiology and pathogenesis of OA still remain unknown. The goal of my study is understand the molecular mechanisms of primary and traumatic OA development and to develop a novel therapy for treating and preventing primary and traumatic osteoarthritis (OA) in vivo. Currently, our group focuses on several targets for OA diagnosis and treatment, including SDF/CXCR4 pathway, Ihh signaling, and HDAC4 protein.

Functional Arterial grafts generated from human hair follicle stem cells and de-cellular umbilical cord arteries

Prof. Jin Yu Liu
Department of Pathobiology, Key Lab of Ministry of Education,
Jilin University, China

Increasing evidences have shown tissue engineered vascular grafts hold promises in cardiovascular repair and regeneration. The cell source of stem cells, the preparation of scaffolds and commitment of stem cells into smooth muscle and endothelial cell lineages by growth factors are the determinants in cardiovascular tissue engineering. By using easily accessible and rich source of human hair follicle derived mesenchymal stem cells (HF-MSCs) as cell sources and decellular human cord arteries (De-CAs) as scaffolds, we engineered functional small diameter arterial grafts(TE-AGs). H&E, Masson and Van Giesan staining showed De-CAs exhibited similar histology and ECM distribution as native cord arteries. Biochemical quantification showed the De-CAs remained very similar collagen and proteoglycan contents before and after de-cellularization. Mechanical property analysis demonstrated De-CAs retained robust elastic modulus and burst pressures, comparable to native cord arteries. Very promisingly HF-MSCs proliferated, migrated in the De-CAs, expressed α-actin and calponin under the treatment of TGF-ß1 and exerted systolic or diastolic forces in response to potassium chloride and norepinephrine or sodium nitroprusside. Our research showed HF-MSCs can be used as cell sources and De-CAs as scaffolds to engineer functional cardiovascular grafts, offering alternatives to autologous vascular grafts in cardiovascular repair and regeneration.

Brief CV

Education

1995 - 1999	Ph. D in Biochemistry, Institute of Regenerative Medicine, N. Bethune University of Medical Sciences
1988 - 1991	Master in Toxicology, School of Preventive Medicine N. Bethune University of Medical Sciences
1983 - 1988	MD, N. Bethune University of Medical Sciences

Research experiences

2009 - present	Professor and Vice Director Department of Pathobiology, Key Lab of Ministry of Education Jilin University, Changchun, China
2004 - 2008	Research Assistant Professor Department of Biological and Chemical Engineering State University of New York at Buffalo, USA
1999 - 2004	Postdoctoral Associate, Department of Dermatology Zurich University Hospital, Switzerland
1991 - 1995	Environmental Protection Engineer Songliao Water Conservancy Agency, Changchun, China

Research fields

Stem cell tissue engineering, wound healings and gene therapy

Stem Cell Therapy for Infarcted Myocardium — Stem Cells or other Cells

Prof. Cai Dongqing
Key Laboratory for Regenerative Medicine, Ministry of Education, Ji Nan University, International Base of Collaboration for Science and Technology (JNU), The Ministry of Science and Technology & Guangdong Province, Department of Developmental & Regenerative Biology, Ji Nan University, China

Regeneration of damaged myocardium is still a big challenge now. Stem cell therapy has shed light to regenerate the ischemic myocardium. However, low survival rate of transplanted stem cells, very low terminal differentiation of transplanted stem cells, and serious fibrosis of infarcted zone limit therapeutic effects of stem cell to achieve functional and structural regeneration of ischemic myocardium. Recent studies have shown that supporting niche cells which are consisted in cardiac unit in myocardium might play an important role in regeneration of myocardium. A novel interstitial cell, named as telocytes, have been identified recently in heart interstitium. Within cardiac stem cell niche, cardiac telocytes (CTs) play an essential role as niche-supporting cell to nurse the cardiac stem cells and angiogenic cells in myocardium, which might play an important role in regeneration of myocardium. Recently we reported that cardiac telocyte network in myocardium was impaired during myocardial infarction (MI). In addition, transplantation of CTs in both infarcted and border zone of myocardium simultaneously was able to decrease the infarct size and improve the myocardial function. Our up-to-date study further revealed that the therapeutic effects (decrease of infarct size and improve myocardial function) of CTs transplantation for MI was similar to or even better than that of transplantation of bone marrow derived stem cells (MSCs). In addition, therapeutic effects of transplantation of CTs+MSCs for MI were better than that of MSCs alone or CTs alone. The finding of our study suggested that CTs might be considered as one of the potential cell types for cell mediated therapy to regenerate MI used alone or tandem stem cells.

Acknowledgements
This work was supported by the Collaborated grant for HK-Macao-TW of Ministry of Science and Technology (2012DFH30060); Research grant of Department of Education of Guangdong (2012gjhz0003); the National Natural Science Foundation of China (30770886, 30570369, 30340038, 30973158, 81170324); 863 grant (2007AA02Z105); Guangdong Key grant for Natural Science Foundation (04105826; S2012020010895); Guangdong grant for Science and Technology Development (2004B30601007); International collaborated grant of Guangdong (2009B050900007).

Brief CV
Professor Cai Dong-qing: Education: M.D. (Guangzhou Medical College; 1987), Ph.D. (The Chinese University of Hong Kong; 2000), Postdoctoral Associate (Weill Medical College of Cornell University [U.S.A.]; 2000-2003). Employment: Professor and Director, Key Laboratory for Regenerative Medicine, Ministry of Education, Ji Nan University; Director, Department of Developmental and Regenerative Biology, Ji Nan University. Scientific interests: 1) Aging and microenvironment in regeneration of myocardial infarction (MI); 2) Cardiac vascular specific targeting and therapy (stem cell and therapeutic angiogenesis) for MI; 3) Aging and regeneration of Tissue & Organ. Grant: 2003-present: 863, International collaboration grant of Ministry of Science & Technology, five NSFC-grants, two Key grant of GDZRKXJJ and other five Guangdong and Guangzhou government grants. Publication: 35 SCI papers have been published (included: JCMM, Proteomics, Am J Physiol Heart Circ Physiol and Physiological Genomics etc). Referee: referee for Six SCI journals (JCMM, Physiological Genomics etc)

Role of BRE Gene is Stem Cell and Development

Prof. Kenneth Lee
School of Biomedical Sciences,
The Chinese University of Hong Kong,
Hong Kong, China

BRE is a multifunctional protein involved in DNA repair and apoptosis in tumor cells. It is a component of the BRCA1/BARD1 complex which positively regulates DNA repair upon ionization radiation to enhance cellular survival. BRE also binds to the cytoplasmic region of death receptors TNF-R1 and Fas to inhibit mitochondrial apoptosis. To date, most studies of this protein have been focused in the tumor model. The role of BRE in stem cells has never been examined. Hence, we employed HUCPV cells to elucidate the function of BRE. HUCPV cells are fetal progenitor cells which possess the ability to differentiate into various mesenchymal cell lineages when chemically induced and can be more easily amplified in culture.

We have established that BRE expression was down-regulated when HUCPV cells were induced to differentiate. In addition, silencing BRE expression, using BRE-siRNA, in HUCPV cells could accelerate induced chondrogenic and osteogenic differentiation. Hence, we postulated that BRE played an important role in maintaining the stemness of HUCPV cells. We used microarray analysis to examine the transcriptome of BRE-silenced cells. BRE-silencing negatively regulated OCT4, FGF5 and FOXO1A. BRE-silencing also altered the expression of epigenetic genes and components of the TGF-β/BMP and FGF signaling pathways which are crucially involved in maintaining stem cell self-renewal. Comparative proteomic profiling also revealed that BRE-silencing resulted in decreased expressions of actin-binding proteins. In sum, we propose that BRE acts like an adaptor protein that promotes stemness and at the same time inhibits the differentiation of HUCPV cells.

Brief CV

Current position

Professor and Chief of Stem Cell and Regeneration Thematic Research Programme,
School of Biomedical Sciences, Chinese University of Hong Kong

Director

Key laboratory for Regenerative Medicine (Hong Kong), Ministry of Education

Qualifications

1982	BSc, Department of Developmental Biology, University of Aberdeen, Scotland
1986	PhD, Developmental Biology Unit, University of Glasgow, Scotland

Academic appointments

1986 - 1989	Post-doctoral Fellow, University of Edinburgh, Scotland
1989 - 1995	Lecturer, Department of Anatomy, Chinese University of Hong Kong
1995 - 2002	Associate Professor, Department of Anatomy, Chinese University of Hong Kong
2002 - 2008	Professor, Department of Anatomy, Chinese University of Hong Kong

Publications

98 peer reviewed papers, 5 chapters in books and 2 PCT patents

Session 10: Cartilage Regeneration and Osteoarthritis

Molecular regulation of opposing anabolic and catabolic signaling pathways in mesenchymal chondroprogenitors

Prof. Chen Qian
Department of Orthopaedics,
Alpert Medical School of Brown University/Rhode Island Hospital,
USA

In this study, we test the hypothesis that epidermal growth factor receptor (EGFR) signaling is required to mediate regulation of mesenchymal chondroprogenitors by matrilin-3 (MATN3), whose mutation in the EGF-like domain is associated with hand osteoarthritis (HOA). EGFR signaling has been shown to be a key regulator of cartilage development and homeostasis although its exact role is not fully understood. Here we show for the first time that the absence of EGFR leads to the activation of IL-1 pathway, which in turn results in down-regulation of chondrogenesis markers Col II and aggrecan and up-regulation of hypertrophic marker Col X in chondroprogenitors. Furthermore, MATN3 appears to regulate chondrogenesis through up-regulation of EGFR, since knocking down EGFR abolishes MATN3 stimulation of Col II and aggrecan. The HOA-MATN3 mutant was incapable of regulating these markers in the presence or absence of EGFR. This strongly suggests that MATN3 mediate these regulatory effects through EGFR signaling, while HOA-MATN3 cannot do so due to its EGF-like domain mutation. Our result indicates that the lack of regulation of chondrogenesis through EGFR signaling may contribute to pathogenesis of osteoarthritis, as we demonstrated in the chondroprogenitors harboring the hand OA MATN3 mutation. Our study reveals an underlying mechanism connecting EGFR signaling with the ECM protein MATN3 and the IL-1 pathway in chondrogenesis and hypertrophy of chondroprogenitors, which play a major role in development of osteoarthritis.

Brief CV

Dr. Qian Chen is the Michael G. Ehrlich, MD Endowed Chair in Orthopaedic Research, Professor of Medical Science, and Vice Chair for Research in the Department of Orthopaedics at the Warren Alpert Medical School of Brown University. He is the director of Center of Biomedical Research Excellence in Skeletal Health and Repair in Rhode Island Hospital, a multi-disciplinary translational research center established by National Institute of Health. Dr. Chen was born and raised in Shanghai, China. He received PhD degree in cell, molecular, and developmental biology from Tufts University School of Medicine in Boston, and performed post-doctoral fellowship at Harvard Medical School and Massachusetts General Hospital. Dr. Chen's research interest includes cartilage molecular biology, mechanotransduction, and osteoarthritis. Throughout Dr. Chen's research career, he received the Independent Scientist Award from NIH, the Satterfield Arthritis Investigator Award from Arthritis Foundation, and the Kappa Delta Award from American Academy of Orthopaedic Surgeons. Dr. Chen served on multiple NIH study sections and advisory panels. He served as the Basic Science Section Editor of the journal Current Opinions in Orthopaedics, and the topic Chair of Cartilage, Synovium, and Meniscus for the annual meeting of the Orthopaedic Research Society. He served as the Chairman of the Board of Directors of the International Chinese Hard Tissue Society (currently the International Chinese Musculoskeletal Research Society).

Recreating microenvironment cues via biomimetic biomaterials to guide mesenchymal stem cell chondrogenesis for cartilage regeneration

Prof. Bian Liming
Department of Mechanical & Automation Engineering
The Chinese University of Hong Kong,
Hong Kong, China

The incidence of osteoarthritis among Chinese population has been increasing significantly in the recent decades. Human mesenchymal stem cells (hMSCs) have emerged as a clinically relevant cell source for cartilage repair, due to their multipotency and easy availability. However, after firstly differentiating (chondrogenesis) into chondrocytes like cells, hMSCs continue to differentiate toward a hypertrophic phenotype, resulting in extensive mineralization of the neocartilage formed, which should be free of mineralization. This problem is now being recognized as a major obstacle to the widespread adoption of hMSCs as a clinically viable cell source for cartilage repair. Furthermore, basic science studies have shown that the survival, maintenance and differentiation of stem cells are tightly regulated by a plethora of signals from their local microenvironment. This talk focuses on the design and development of biomimetic biomaterial scaffold to enhance chondrogenesis of hMSCs for cartilage repair. Our findings demonstrate that biomimetic scaffold materials and appropriate developmental cues are crucial to the development of tissue engineered cartilage using MSCs. These findings provide important insights into clinical translation of stem cell therapy for cartilage repair.

Brief CV

Academic Qualifications

2009 - 2012	Postdoctoral researcher, Polymeric Biomaterials Laboratory The University of Pennsylvania
2004 - 2009	Ph.D., Biomedical Engineering, Columbia University
2002 - 2004	M.Sc., Bioengineering, National University of Singapore
1998 - 2002	B.Eng. (Hons), National University of Singapore
2012 - present	Assistant professor, Department of Mechanical & Automation Engineering, CUHK

Brief CV (con't)

Selected publications

Section A–Five most representative (relevant) publications in recent five years

1. Bian, L.; Guvendiren, M.; Mauck, R.L.; Burdick, J.A. Hydrogels that mimic developmentally relevant matrix and N-cadherin interactions enhance MSC chondrogenesis. PNAS, 2013 Jun 18;110(25):10117-22
2. Bian, L.; Hou, C., Tous, E.; Rai R.; Mauck, R.L.; Burdick, J.A. The Influence of Hyaluronic Acid Hydrogel Crosslinking Density and Macromolecular Diffusivity on Human MSC Chondrogenesis and Hypertrophy. Biomaterials, 2013 Jan; 34(2):413-21.
3. Bian, L.; Zhai, D.Y.; Zhang, E.C.; Mauck, R.L.; Burdick, J.A. Dynamic compressive loading enhances chondrogenesis of human mesenchymal stem cells in photocrosslinkable hyaluronic acid hydrogel. Tissue Engineering Part A. 2012 Apr; 18(7-8):715-24.
4. Bian, L.; Zhai, D.Y.; Tous, E.; Rai R.; Mauck, R.L.; Burdick, J.A. Enhanced MSC chondrogenesis following delivery of TGF-β3 from alginate microspheres within hyaluronic acid hydrogels in vitro and in vivo. Biomaterials, 2011 Sep; 32(27):6425-34.
5. Bian, L.; Zhai, D.Y.; Mauck, R.L.; Burdick, J.A. Coculture of human mesenchymal stem cells and articular chondrocytes reduces hypertrophy and enhances functional properties of engineered cartilage. Tissue Engineering Part A. 2011 Apr; 17(7-8):1137-45.

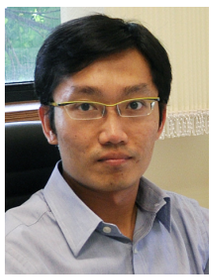
Section B–Five other representative publications

6. Bian, L., Stoker, A.M., Marberry, K.M, Ateshian, G.A., Cook, J.L., Hung, C.T. Am J Sports Med. 2010 Jan; 38(1):78-85.
7. Bian, L., Ng, K.W., Lima, E.G., Williams, D.Y., Ateshian, G.A., Hung, C.T. Tissue Engineering Part A. 2009 Aug; 15(8):2065-72.
8. Bian, L., Angione, S.L., Ng, K.W., Lima, E.G., Williams, D.Y., Mao D.Q., Ateshian, G.A., Hung, C.T. Osteoarthritis and Cartilage, 2009 May; 17(5):677-85.
9. Bian, L., Kaplun, M., Williams, D.Y., Ateshian, G.A., Hung, C.T. Journal of Biomechanics 2009 Feb 9; 42(3):286-90.
10. Bian, L., Lima, E.G., Angione, S.L., Ng, K.W., Williams, D.Y., Xu, D., Stoker, A.M., Cook, J.L., Ateshian, G.A., Hung, C.T., 2008. Journal of Biomechanics, 2008, 41 (6): 1153-1159.

Others:

- STAR award, Annual meeting of the Society for Biomaterials, 2011
- New Investigator Recognition Awards (NIRA) finalist, Orthopedic Research Society meeting, 2010

Functional roles of Wnt16b in endochondral bone development



Prof. MAK, Kingston King-Lun
School of Biomedical Sciences,
The Chinese University of Hong Kong,
Hong Kong, China

Proper joint formation relies on tight regulation of chondrocyte proliferation and differentiation and it is highly coordinated with endochondral bone formation. Wnt signaling has been previously implicated in both joint formation and endochondral ossification. However, the specific function of each individual Wnt ligand is not clear. Here, we have found that ectopic expression of Wnt16b in the developing growth plates inhibits chondrocyte hypertrophy and osteoblast differentiation but synovial joint formation is not affected. Surprisingly, these regulations of Wnt16b are independent of the canonical pathway. Our results demonstrate that Wnt16b by itself is not sufficient to affect joint formation, but it plays a role in regulate endochondral ossification primarily through the non-canonical pathway.

Brief CV

Mak received his Ph. D from the University of Hong Kong and continued his postdoctoral training at the National Institute of Health (NIH). During the training, his research interest focused on the regulation of the developing cartilage and bone. Specifically, he dissected the differential roles of Hedgehog signaling in various aspects during endochondral bone formation and postnatal bone remodeling. He received several awards for his works during postdoctoral training including American Society of Bone and Mineral Research Young Investigator Award and Webster Jee Young Investigator Award. Currently, his research focuses on studying the roles of important signaling pathways in Mesenchymal Stem cell (MSCs) differentiation and renewal for the development of skeletal related cell lineages. He also investigates the molecular mechanisms of skeletal related diseases and cancers such as osteoarthritis and osteoporosis.

In vitro cartilage regeneration and its application in repairing cartilage defects

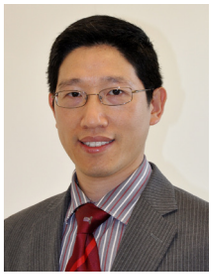
Prof. Zhou Guangdong
Department of Plastic and Reconstructive Surgery,
Shanghai 9th People's Hospital,
China

In vitro tissue regeneration is an important direction for clinical translation and industrialization of tissue engineered product. Cartilage is a kind of tissue fitting for in vitro regeneration due to lack of blood vessels and nerve in it. In the current study, several methods (such as micromass, cell sheet, co-culture, and three-dimensional scaffold) were introduced for in vitro cartilage regeneration. The cell source involved chondrocytes, bone marrow stem cells, and adipose-derived stem cells and the shape of regenerated cartilage included cylinder, meniscus, trachea, and ear. In addition, different cartilage defect model were established in large animals and the feasibility of repairing the defects with the in vitro engineered cartilage was investigated. Besides, some important issues were proposed during repairing different cartilage defect models. For example, in articular defect model, the mechanical properties of in vitro engineered cartilage and the interface healing among implanted cartilage, native cartilage, and subchondral bone might be the important issues. In tracheal defect model, the vascularization and epithelialization might be paid great concern. For ear reconstruction, however, the shape control and maintenance might be the most important points.

Brief CV
Guangdong Zhou graduated in Department of Medicine from Wei Fang Medical College, Shandong, China in 1997. He underwent another three years for his postgraduate training in the same college, majoring in Plastic Surgery. Then, He was enrolled by Shanghai Tissue Engineering Center, Shanghai Jiao Tong University School of Medicine in 2000 for his PhD training. In the following three years, under the guide of Prof. Yilin Cao (his tutor and the director of Shanghai Tissue Engineering Center), he majored in cartilage regeneration with adult stem cells. After got his PhD degree at the year of 2003, he became an Assistant Professor of Medicine at Shanghai Tissue Engineering Center and was in charge of the researches of cartilage engineering. In 2005, he promoted Associate Professor and proceeded to take charge the researches related to adult stem cells and cartilage engineering. In 2009, he got the position of professor. His researches mainly involved basic biological characteristics, purification technology, and committed differentiation of bone marrow stem cells (BMSCs) and adipose-derived stem cells (ADSCs), as well as in vitro regeneration of cartilage with adult stem cells, in vivo evaluation of stem cell regenerated cartilage, repair of cartilage defect, and development of cartilage products. He was also one of main sponsors of National Tissue Engineering Center of China and was in charge of the cartilage product program of China.

Session 11: Musculoskeletal Development and Cell Biology

Hypoxia promotes expansion of mesenchymal stem cells for skeletal tissue regeneration



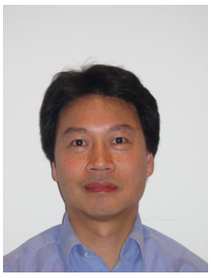
Prof. Wan Chao
School of Biomedical Sciences,
The Chinese University of Hong Kong,
Hong Kong, China

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. Our recent studies showed that HIFα serves 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 tdeletion 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. These data indicate that HIFα functions as a critical mediator for MSCs self-renewal. Next we determined whether HIFα involves in the self-renewal of human MSCs. CD146+ human umbilical cord perivascular cells (HUCPVCs) were purified and characterized as mesenchymal progenitors in vitro and in vivo. We found that hypoxic conditions suppressed osteogenic differentiation while increased cell proliferation and colony-forming efficiency of CD146+ HUCPVCs as compared to that under normoxic conditions. Re-oxygenation restored the multi-differentiation potential of the CD146+ HUCPVCs. Western blot analysis revealed an upregulation of HIF-1α, HIF-2α, and OCT-4 protein expression in CD146+ HUCPVCs under hypoxia, while there was no remarkable change in SOX2 and NANOG expression. The gene expression profile of stem cell transcription factors between cells treated by normoxia and hypoxic conditions was compared by PCR array analysis. Intriguingly, PPAR- was dramatically downregulated (20-fold) in mRNA expression under hypoxia, and was revealed to possess a putative binding site in the Hif-2 gene promoter region. Chromatin immunoprecipitation assays confirmed the binding of PPAR- protein to Hif-2 promoter and the binding was suppressed by hypoxia treatment. Luciferase reporter assays showed that the Hif-2 promoter activity was suppressed by PPAR- expression. Thus, PPAR- may involve in the regulation of HIF-2 for stemness maintenance and promoting the expansion of CD146+ HUCPVCs in response to hypoxia. CD146+ HUCPVCs could be expanded under hypoxia and serve as a potential autologous cell source for skeletal tissue regeneration.

Brief CV

Dr. Chao Wan is an Assistant Professor, Supervisor of Graduate Student in Stem Cell and Regeneration Thematic Research Program, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong (CUHK). He is also a member of Ministry of Education Key Laboratory for Regenerative Medicine, and School of Biomedical Sciences Core Laboratory, The Chinese University of Hong Kong Shenzhen Research Institute. Before that he 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, and then obtained his PhD in Shanghai Jiaotong University School of Medicine. Following that he pursued Postdoctoral training in School of Medicine, 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 and the discovery of novel therapeutic targets for skeletal tissue regeneration. He was a recipient of British Orthopaedic Research Society Travelling Award, Japanese Orthopaedic Association Fellowship, ICHTS Webster Jee Young Investigator Award, and ASBMR Harold Frost Young Investigator Award. His current research is supported by RGC GRF, NSFC, and NSFC-RGC Joint Research Scheme.

Angiogenic factors in bone microenvironment: potential therapeutic targets for bone repair



Prof. Xu Jiake
School of Pathology and Laboratory Medicine,
University of Western Australia,
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. Vascularization is required for bone remodeling along the endosteal surface of trabecular bone or Haversian canals within the cortical bone, as well as the homeostasis of the cartilage-subchondral bone interface. 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 and function of angiogenic factors produced by osteoclasts, osteoblasts and osteocytes in the BMU and in the cartilage-subchondral bone interface is evident. These include vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), BMP7, receptor activator of NF-κB ligand (RANKL) 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 possible roles in 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.

Brief CV
Dr Jiake Xu is currently Winthrop Professor and Head of Laboratory in the School of Pathology and Laboratory Medicine at the University of Western Australia.
He is also a founding Fellow, Faculty of Science, the Royal College of Pathologists of Australia, and has been appointed the President of the Australian and New Zealand Orthopaedic Research Society (ANZORS).
He finished his medical training in Guangzhou Medical College in China in 1985. After completing his PhD studies at UWA in 1994, he carried out his postdoctoral research at Stanford University from 1994 to 1998. He returned to UWA in 1998, and has since undertaken research and teaching in the Schools of Surgery and Pathology and Laboratory Medicine.
His current research activities are focused on gene discovery, molecular mechanisms of osteoclast functions and the intercellular communication in bone microenvironment between osteoclasts, osteoblasts and endothelial cells which have significant implication in bone diseases; including osteoporosis, Paget's disease of bone and malignancy-related osteolysis.

miR-214 targets ATF4 to inhibit bone formation

Prof. Zhang Ge
Institute for Advancing Translational Medicine in Bone & Joint Diseases,
Hong Kong Baptist University,
Hong Kong, China

Emerging evidence indicates that microRNAs (miRNAs) have important roles in regulating osteogenic differentiation and bone formation. Thus far, no study has established the pathophysiological role for miRNAs identified in human osteoporotic bone specimens. Here we found that elevated miR-214 levels correlated with a lower degree of bone formation in bone specimens from aged patients with fractures. We also found that osteoblast-specific manipulation of miR-214 levels by miR-214 antagomir treatment in miR-214 transgenic, ovariectomized, or hindlimb-unloaded mice revealed an inhibitory role of miR-214 in regulating bone formation. Further, in vitro osteoblast activity and matrix mineralization were promoted by antagomir-214 and decreased by agomir-214, and miR-214 directly targeted ATF4 to inhibit osteoblast activity. These data suggest that miR-214 has a crucial role in suppressing bone formation and that miR-214 inhibition in osteoblasts may be a potential anabolic strategy for ameliorating osteoporosis.

Brief CV

Academic Qualifications

1990.9 - 1995.7	B. Med	Shanghai University of Chinese Medicine, Shanghai, China
1997.9 - 2000.7	M. Med.	Institute of Orthopaedics & Traumatology, Shanghai University of Chinese Medicine, China
2000.9 - 2003.7	M.D.	Institute of Orthopaedics & Traumatology, Shanghai University of Chinese Medicine & Department of Orthopaedics & Traumatology, The Chinese University of Hong Kong

Previous academic positions held

1995.8 - 2000.11	Resident	Institute of Orthopaedics & Traumatology, Shu Guang Hospital, Shanghai University of Chinese Medicine
2000.12 - 2004.2	Physician-in-Charge	Institute of Orthopaedics & Traumatology, Shu Guang Hospital, Shanghai University of Chinese Medicine
2004.3 - 2007.6	Postdoctoral Research Fellow	Department of Orthopaedics & Traumatology, The Chinese University of Hong Kong
2007.7 - 2012.8	Research Assistant Professor	Department of Orthopaedics & Traumatology, The Chinese University of Hong Kong

Present academic position

2012.9 - present	Associate Professor / Deputy Director	Ge Zhang's Lab (www.gezhanglab.com), Institute for Advancing Translational Medicine in Bone & Joint Diseases, Hong Kong Baptist University, Hong Kong Baptist University

Brief CV (con't)

Previous relevant research work
Technical expertise
Bone bio-imaging, Bone histomorphometry, Bone biology, Bone biomechanics
Research area
Molecular understandings and RNAi-based & phytotherapy-based translational research in osteoporosis, osteonecrosis, osteoarthritis, rheumatoid arthritis and facture repair

Publication Records
3 Theses; 9 Book Chapters; 106 SCI Papers; Sum of the Times cited (excluding self-citation): 220; h-index: 9

Six Representative publications in the past six years

1. Wang X, Guo B, …, Zhang G (Corresponding Author), Li Y (Corresponding Author). miR-214 targets ATF4 to inhibit bone formation. Nat Med. 2013 Jan;19(1):93-100
2. Zhang G (Corresponding Author), Guo B, Wu H, Tang T, Zhang BT, …, Zhang L (Corresponding Author), Qin L (Corresponding Author). A delivery system targeting bone formation surfaces to facilitate RNAi-based anabolic therapy. Nat Med. 2012 Jan 29;18(2):307-14
3. Xie XH, Wang XL, He YX, Liu Z, Sheng H, Zhang G (Corresponding Author), Qin L (Corresponding Author). Promotion of bone repair by implantation of cryopreserved bone marrow-derived mononuclear cells in a rabbit model of steroid-associated osteonecrosis. Arthritis Rheum. 2012 May;64(5):1562-71
4. He YX, Liu Z, Pan XH, Tang T, Guo BS, Zheng LZ, Xie XH, Wang XL, Lee KM, Li G, Cao YP, Wei L, Chen Y, Yang ZJ, Hung LK, Qin L, Zhang G (Corresponding Author). Deletion of estrogen receptor beta accelerates early stage of bone healing in a mouse osteotomy model. Osteoporosis Int. 2012 Jan;23(1):377-89.
5. Zhang G, Sheng H, et al. Continuous occurrence of both insufficient neovascularization and elevated vascular permeability in rabbit proximal femur during inadequate repair of steroid-associated osteonecrotic lesions. Arthritis Rheum. 2009 Oct;60(10):2966-77.
6. Zhang G, Qin L, Shi Y. Epimedium-derived phytoestrogen flavonoids exert beneficial effect on preventing bone loss in late postmenopausal women: a 24-month randomized, double-blind and placebo-controlled trial. J Bone Miner Res. 2007 Jul;22(7):1072-9.

Life-dependent primitive neural stem cells derived from mouse ES cells represent a reversible stage of neural commitment

Prof. Feng Bo
School of Biomedical Sciences,
The Chinese University of Hong Kong,
Hong Kong, China

Primitive neural stem cells (NSCs) define an early stage of neural induction, thus provide a model to understand the mechanism that controls initial neural commitment. In this study, we investigated primitive NSCs derived from mouse embryonic stem cells (ESCs). By genome-wide transcriptional profiling, we revealed their unique signature and depicted the molecular changes underlying critical cell fate transitions during early neural induction at a global level. Together with qRT-PCR analysis, our data illustrated that primitive NSCs retained expression of key pluripotency genes Oct4 and Nanog, while exhibiting repression of other pluripotency-related genes Zscan4, Foxp1, Dusp9 and up-regulation of neural markers Sox1 and Hes1. The early differentiation feature in primitive NSCs was also supported by their intermediate characters on cell cycle profiles. Moreover, re-plating primitive NSCs back to ESC culture condition could reverse them back to ESC stage, as shown by reversible regulation of marker genes, cell cycle profiles changes and enhanced embryoid body formation. In addition, our microarray analysis also identified genes differentially expressed in primitive NSCs, and loss-of-function analysis demonstrated that Hes1 and Ccdc141 play important function at this stage, opening up an opportunity to further understand the regulation of early neural commitment.

Brief CV

Academic Qualifications

2002.2 - 2006.10	PhD in Developmental Neurobiology, Temasek Life Sciences Laboratory, National University of Singapore
1993.9 - 1996.7	MSc in Microbiology, Nankai University, China
1989.9 - 1993.7	BSc in Microbiology, Nankai University, China

Academic positions

2010.10 - present	Assistant Professor, School of Biomedical Sciences, CUHK
2007.1 - 2010.9	Postdoctoral Fellow & Research Associate, Genome Institute of Singapore
1996.7 - 1999.2	Tutor, Department of Microbiology, Tianjin Normal University, China

Previous research work

(1) Identification of Esrrb and Nr5a2 as new factor to reprogram mouse fibroblasts into iPSCs;
(2) Characterization of new factors that control human ESCs identity by reprogramming;
(3) Study on primitive neural stem cells differentiated from mouse ES cells

Brief CV (con't)

Publications
Section A (in recent 5 years)

1. Tsang, W.H., Wang, B., Wong, W.K., Shi, S., Chen, X., He, X., Gu, S., Hu, J., Wang, C., Liu, P.C., Lu, G., Zhao, H., Poon, W.S., Chan, W.Y. & Feng, B. LIF-dependent primitive neural stem cells derived from mouse ES cells represent a reversible stage of neural commitment. Stem Cell Res 11, 1091-1102 (2013).
2. Chia NY*, Chan YS*, Feng B*, Lu X, Orlov YL, Moreau D, Kumer P, Yang L, Jiang J, Lau MS, Huss M, Soh BS, Kraus P, Li P, Lufkin T, Lim B, Clarke ND, Bard F, Ng HH., A genome-wide RNAi screen reveals determinants of human ES cell identity. Nature 468, 316-20 (2010) (*Co-first authors)
3. Heng JC*, Feng B*, Han J, Jiang J, Kraus P, Ng JH, Orlov YL, Huss M, Yang L, Lufkin T, Lim B, Ng HH., The nuclear receptor Nr5a2 can replace Oct4 in the reprogramming of murine somatic cells to pluripotent cells. Cell Stem Cell. 6, 167-74 (2010). (*Co-first authors)
4. Feng B, Ng JH, Heng JC, Ng HH., Molecules that promote or enhance reprogramming of somatic cells to induced pluripotent stem cells, Cell Stem Cell. 4, 301-12 (2009). Review.
5. Feng B, Jiang J, et al., Lufkin T, Ng HH., Reprogramming of fibroblasts into induced pluripotent stem cells with orphan nuclear receptor Esrrb. Nat Cell Biol. 11, 197-203 (2009).

Section B (beyond 5 years)

1. Feng B., Bulchand S., Yaksi E., Friedrich R. W. and Jesuthasan S., The recombination activation gene 1 (Rag1) is expressed in a subset of zebrafish olfactory neurons but is not essential for axon targeting or amino acid detection. BMC Neurosci. 6, 46 (2005).
2. Feng B., Schwarz H. and Jesuthasan S., Furrow-specific endocytosis during cytokinesis of zebrafish blastomeres. Exp Cell Res, 279, 14-20 (2002).

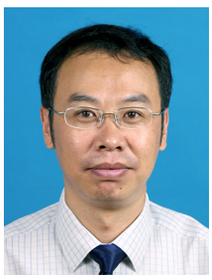
Patents

1. WO2011152798 A1: "Method for inducing pluripotency in human somatic cells with PRDM14 or NRFKB" Ng Huck Hui; Chia Na Yu; Feng Bo
2. US 20110165570A1: "Method of effecting de-differentiation of a cell" Feng Bo; Jiang Jianming; Ng Huck Hui; Thomas Lufkin; Petra Kraus

Mentoring experience
Undergraduate students 4; postgraduate students 3; Research assistants 5.

Session 12: Stem cells de-differentiation in cancer development and treatment

Mesenchymal stem cells contribute to the growth and metastasis of osteosarcoma



Prof. Tang Tingting
Shanghai Ninth People's Hospital,
China

Stem cells, especially for the bone marrow derived mesenchymal stem cells (MSCs), can promote the tissue repair or regeneration with great application potential in orthopaedic clinic. However, recent studies indicated that stem cells could contribute to the tumor growth. We have investigated the interactions of MSCs with osteosarcoma(OS) cell line (Saos-2 cells) in tumor microenvironment. We found that the co-injection of MSCs and Saos-2 cells into nude mice could promote the tumor growth and progression. In vitro, the proliferation of Saos-2 and MSCs was promoted by each other's conditioned medium, in which IL-6 played an important role. The STAT3 signal pathway in Saos-2 was activated by IL-6 from MSCs. The inhibition of STAT3 in Saos-2 cells by siRNA or AG490 (a JAK2 inhibitor) decreased the proliferation, migration and invasion, down-regulated the mRNA expression of Cyclin D, Bcl-xL and Survivin and enhanced the apoptotic response of Saos-2 cells. Furthermore, AG490 could inhibit the growth and pulmonary metastasis of OS in an nude mice model and prolong the survival time of these mice. MSCs also promoted the anoikis resistance of Saos-2 cells in vitro and in vivo, which contributed to the pulmonary metastasis of OS. IL8-CXCR1-Akt pathway played an important role in the regulation of the anoikis resistance, and blocking the IL8-CXCR1-Akt pathway with shRNA targeting at CXCR1 could inhibit the pulmonary metastasis of OS and prolong the survival time of tumor-bearing mice. Altogether, our data demonstrated that MSCs contribute to the growth and metastasis of OS and the involved signal pathway would be a new target for the OS treatment.

Brief CV
Prof.Ting-ting Tang, is professor, doctoral supervisor, candidate of New Century Excellent Talent Program of Ministry of Education, New Century Hundred, Thousand and Ten Thousand Talent Project. Currently he serves as Director of Shanghai Key Laboratory of Orthopeadic Implants, vice Director of Orthopedic Department of Shanghai Ninth People's Hospital affiliated to Shanghai Jiao Tong University School of Medicine. Also he is Board member and chairman of China Development Committee of International Chinese Musculoskeletal Research Society, Board member of China Biomaterial Society, committee member of China Biomechanics Society, editorial member of over 10 international and Chinese journals including Journal of Orthopaedic Translation, Chinese Journal of Orthopaedic Trauma, et al. The main research field includes orthopedic implants and bone repair materials, stem cell research related bone repair and bone tumor.

Reprogramming MSCs for cancer targeting

Prof. Cynthia Xiaohua Jiang
School of Biomedical Sciences,
The Chinese University of Hong Kong,
Hong Kong, China

Successful treatment of human glioma, the most deadly brain tumor, has not been achieved largely due to deficiencies in current delivery strategies. Recently, MSC mediated gene delivery has been shown to be a promising strategy for improving the efficacy and minimizing the toxicity of gene therapy approaches in the treatment of glioma. However, for clinical applications, it would be desirable if a sufficient quantity of engineered MSCs that localize within tumors is achieved. This requires the development of methods to improve the migratory capacity of MSCs to tumors, which would thereby increase the delivery of the therapeutic genes.

Interestingly, previous studies from both our group and others have demonstrated that after neuronal commitment, differentiated-MSCs can be induced to dedifferentiate and revert back to MSC morphologically under appropriate condition. In addition, we have shown that these dedifferentiated MSCs (De-MSCs) present a variety of distinguishing genetic and phenotypic characteristics distinct from their original counterparts. Strikingly, we have found that De-MSCs express significantly higher levels of chemokines and cytokines, and display enhanced tropism to cancer both in vitro and in vivo. Furthermore, we have revealed that the enhanced migratory capability of De-MSCs is attributed to upregulated CCL5/MAPK pathway. Currently, we are evaluating the therapeutic efficacy of De-MSCs expressing thymidine kinase (TK) in xenograft intracranial models of glioma. Successful use of induced dedifferentiated MSCs to deliver therapeutic proteins to brain tumors will represent a major step forward in enhancing treatments of patients with the deadly disease for whom only minimally-effective therapies are currently available.

Brief CV

Dr. Jiang Cynthia Xiaohua graduated from Shanghai Second Medical University (currently School of Medicine, Shanghai JiaoTong University) in 1994, and completed her internship and residency at RuiJin Hospital, Shanghai in 1998. She obtained her PhD degree in cell biology from the University of Hong Kong in 2003. Dr. Jiang undertook her postdoctoral training at the Department of Medicine, UCLA, from 2003-2006. Her work focused on the role of protein kinase cascades 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 Ewing sarcoma by using human embryonic stem cells as an innovative model. Currently, Dr. Jiang is a PI in the Stem Cells and Regeneration theme of School of Biomedical Sciences. Dr. Jiang's research interest focuses on the interface of stem cell biology and cancer, studying the mechanisms that regulate the function of stem cells and the ways in which those mechanisms are hijacked by cancer cells to generate tumors. Dr. Jiang has published forty papers in peer-reviewed journals, including Nature Medicine, Stem Cells, Cell Research, Cancer Research, Gastroenterology and Oncogenes.

Combination cancer therapy: The use of TK-MSCs and Doxorubicin

Dr. Wayne YW Lee
Department of Orthopaedics & Traumatology,
The Chinese University of Hong Kong,
Hong Kong, China

Bone marrow mesenchymal stem cells (MSCs) are able to migrate specifically to sites of tumors and contribute to the formation of tumor-associated stroma. These properties make MSCs good candidates as anti-tumor agent delivery vehicles and lead to a great interest in manipulating MSCs genetically to express anti-tumor molecules. We have developed immortalized human fetal MSCs stably expressing HSV-thymidine kinase (SV40-TK-hfBMSCs). Repeated injection of SV40-TK-hfBMSCs and subsequent consecutive administration of ganciclovir (GCV, a prodrug catalyzed by TK into cytotoxic molecules) could suppress tumor growth of human prostate tumors (DU145 and PC3) in xenograft nude mice model. Alternative strategy has been pursued in this study by the use of combination therapy with conventional chemotherapy to enhance the overall efficiency of this MSCs-directed anti-tumor therapy. The anti-tumor effect of SV40-TK-hfBMSCs/GCV was evaluated alone or combined with low dosage of doxorubicin (DOX) in DU145 xenograft model. Tumor tissues were subject to immunocytochemistry for tumor cell proliferation and apoptosis. Transwell migration assay was used to determine the migratory ability of the cells to tumor upon DOX treatment. Combination therapy resulted in significant growth inhibition, increased caspase 3 activity and lower tumor cell proliferation when compared with cells or DOX alone treatment. In conclusion, the study has demonstrated that cytotoxic chemotherapeutic agent is able to enhance the anti-tumor efficiency of MSCs/GCV system. The underlying mechanism leading to this enhancement requires further elucidation.

Brief CV

Academic Qualifications

2005	B.Sc. in Applied Biology (HKBU)
2009	Ph.D. in Pharmacology (CUHK)

Academic honours

2005	President's Honour Roll
2003 - 2005	Pisces Biology Scholarship

Current position

2010 - present	Postdoctoral fellow, Department of Orthopaedics & Traumatology, The Chinese University of Hong Kong.

Research work

Stem cell biology, functional tissue engineering, etiopathogenesis of adolescent idiopathic scoliosis, TCM.

Number of publications in peer-reviewed SCI indexed journals (19)
Number of publication in conference (7)
Number of filed patents (1)

Brief CV (con't)

Selected publications

- Lee WYW, Zhang T, Lau CPY, Wang CC, Chan KM, Li G (2013) Immortalized human fetal bone marrow-derived mesenchymal stem cell expressing anti-tumor suicide gene for anti-tumor therapy in vitro and in vivo. Cytotherapy (in press).
- Zhang T, Lee YW, Rui YF, Cheng TY, Jiang XH, Li G (2013) Bone marrow-derived mesenchymal stem cells promote growth and angiogenesis of breast and prostate tumors. Stem Cell Research & Therapy in press.
- Meng XM, Su RJ, Baylink DJ, Neises A, Kiroyan JB, Lee WYW, Payne KJ, Gridley DS, Wang J, Lau KHW, Li G, Zhang XB (2013) Rapid and efficient reprogramming of human fetal and adult blood CD34+ cells into mesenchymal stem cells with a single factor. Cell Research in press.
- Lee WY, Lui PP, Rui YF (2011) Hypoxia-mediated efficient expansion of human tandem-derived stem cells in vitro. Tissue Engineering part A 18, 484-498.
- Lee WY, Zhou X, Or PM, Kwan YW, Yeung JH (2011) Tanshinone I increases CYP1A2 protein expression and enzyme activity in primary rat hepatocytes. Phytomedicine 19, 169-176.
- Lee WY, Cheung CC, Liu KW, Fung KP, Wong J, Lai PB and Yeung JH (2010). Cytotoxic effects of tanshinones from Salvia miltiorrhiza on doxorubicin-resistant human liver cancer cells. J Nat Prod 73, 854-859.
- Lee WY, Liu KW and Yeung JH (2009). Reactive oxygen species-mediated kinase activation by dihydrotanshinone in tanshinones-induced apoptosis in HepG2 cells. Cancer Lett 18, 46-57.
- Lee WY, Chiu LC and Yeung JH (2008). Cytotoxicity of major tanshinones isolated from Danshen (Salvia miltiorrhiza) on HepG2 cells in relation to glutathione perturbation. Food Chem Toxicol 46, 328-338.

Improved osteogenesis of de-differentiation mesenchymal stem cells

Prof. Qin Shi
The First Affiliated Hospital of Soochow University, China

Methods: Mesenchymal stem cells (MSCs) were prepared from the bone marrow of healthy adults. De-MSCs were developed by alternating the growth factors in cell culture medium. Morphological characteristics were observed and cell surface markers of De-MSCs were analysised by flow cytometry (FCM). The proliferation capacity was detected using Cell count kit-8(CCK8). After De-MSCs were induced in osteogeneticlly cell medium, osteogenic related-gene expression of De-MSCs were detected using semi-quantized PCR (qPCR) assay at day 7. Meanwhile the osteogenic redifferentiation potential was measured by alkaline phosphatase (ALP) activity assay and the bone formation was confirmed by morphology observed and Alizarin red staining.
Results: De-MSCs displayed the spindle-shape morphology and expressed stem cells markers. The proliferation capacity was obviously higher than MSCs statistically ($p<0.05$). The expression levels of osteogenic related genes and ALP activities were significantly increased compared with MSCs ($p<0.05$). Red nodules were observed with Alizarin red staining after De-MSCs were cultured in osteogenic medium for 28 days.
Conclusions: De-MSCs remained the characteristics of MSCs, but had a higher proliferation and osteogenic potential than MSCs. De-MSCs show improved osteogenesis than MSCs in vitro and could be an alternative potential seed cells in tissue engineering.

Brief CV

Education

09,2000 - 07,2003	MD&Ph.D	School of Medicine, Soochow University, Jiangsu Province, P. R. China
09,1996 - 07,1999	Master	School of Medicine, Soochow University, Jiangsu Province, P. R. China
09,1989 - 07,1994	Bachelor	School of Medicine, Soochow University, Jiangsu Province, P. R. China

Work Experience

02,2008 - present	Associated Professor	Orthopedic Department, the First Affiliated Hospital of Soochow University
02,2005 - 01,2008	Postdoctoral Researcher	Division of Rheumatology, University of Pennsylvania School of Medicine
09,1996 - 01,2005	Research Assistant and Assistant Professor	Immunology Department, School of medicine, Soochow University
07,1994 - 08,1996	Residential doctor	Southwest Institute Staff Hospital

Session 13: Novel Technologies and Biomaterials in Regeneration

Oxidative Stress and Cell Mechanics

Prof. Arthur Mak
Department of Biomedical Engineering,
The Chinese University of Hong Kong,
Hong Kong, China

Reactive oxygen species such as superoxide radicals and hydrogen peroxides are products of metabolic processes. They appear naturally and exist in a dynamic equilibrium of various REDOX processes in normal situations. Antioxidants such as glutathione, Vitamins C and E serve as free radicals scavengers to maintain such a dynamic equilibrium. Oxidative stress arises when the oxidative agents surge beyond the coping capacity of the involved cells and tissues in metabolically challenging and pathological situations. Examples include skeletal muscles in demanding sports and rehabilitation contexts, and cardiac muscles during post-ischemic reperfusion. It is known that oxidative stress surges in inflammatory responses and when blood reperfuse an ischemic organ. In spite of these challenges, muscle cells in such situations need to continue its biomechanical functions. It is important to understand how the load-carrying capacity of muscle cells and their resistance to mechanical damage can be affected in oxidative environments. In the context of stem cell biology and regenerative medicine, it is known that stem cell differentiation can be significantly affected by their mechanics and their interaction with the extracellular matrix. Tissue regeneration often needs to be conducted in challenging oxidative and biomechanical environments. It is important to address the question how continued exposure to oxidative and mechanical stresses may affect stem cell differentiation. This lecture will summarize our recent in-vitro studies on how cells respond to different oxidative environments – changes in the cytoskeletons, cell stiffness, cell adhesion, and cell resistance to biophysical damages.

Brief CV
Prof Arthur Mak obtained his BSc in Engineering Mechanics with highest honor from University of Illinois at Urbana-Champaign in 1976 and earned his PhD in Biomechanics at Northwestern University in 1980. After spending 3 years of postdoctoral fellowship in Tissues Mechanics under Professor Van Mow at Rensselaer Polytechnic Institute in New York, he took up an Assistant Professorship in Bioengineering and Orthopedic Research at University of Pennsylvania. Prof. Mak joined the Jockey Club Rehabilitation Engineering Center at Hong Kong Polytechnic University in 1988 and became Chair Professor of Rehabilitation Engineering in 1997 and in the same year was appointed as the Head of the Center. In 2005-2009, Prof Mak served as the Founding Head of the Department of Health Technology and Informatics. Prof Mak was PolyU's Associate Vice President (Academic Development) in 2006-2010 and Founding Dean of Students in 2008-2011. In 2011, Prof. Mak joined CUHK as Professor in Biomedical Engineering, both in the Departments of Electronic Engineering and Mechanical & Automation Engineering. Prof Mak is serving in the editorial boards of a number of international journals on biomedical engineering and rehabilitation engineering. He is a member of the World Council on Biomechanics. He was President of the World Association for Chinese Biomedical Engineers in 2008-2010.

Development of Combinatory Drugs from Traditional Chinese Medicine by Using Closed-loop Feedback Control

Prof. Yi-Kuen Lee
Department of Mechanical and Aerospace Engineering &
Division of Biomedical Engineering,
The Hong Kong University of Science & Technology,
Hong Kong, China

Traditional Chinese medicine (TCM) is a great treasure that has contributed greatly to the prosperity of the Chinese population for several thousand years, and to the development of herbal medicine worldwide. One of the major challenging tasks in studying these combinatory TCM drugs is that the number of possible combinations of drugs is too large to be systematically investigated. On the other hand, closed-loop feedback control (CFC), originally developed for long-distance telecommunication systems in 1930, has been widely used in modern electronics and machines (airplanes, rockets and robotics). Recently, CFC has been used to biomedical applications. With the help of CFC, Wong et al. (PNAS 2008) demonstrated that only tens of searches instead of 1,000,000 cases are needed to identify the optimized drug cocktail. We successfully identified two unique combinations of four flavonoids in Astragali Radix (AR; Huangqi;黃芪), the dried root of Astragalus membranaceus (Fisch.) Bunge, one of the most widely used Chinese herbs to reinforce vital energy. Out of 1,000 possible combinations, only several tens of trials were needed to optimize the flavonoid combinations that stimulated the expression of erythropoietin (EPO) in cultured human embryonic kidney fibroblast (HEK293T). Application of the optimized flavonoid combination onto pHRE-Luc-transfected cells increased the hypoxia response element (HRE) mediated transcriptional activity by ~3-fold comparing with AR and individual flavonoid. Our study suggests that the CFC method is able to serve as an efficient and model-free approach to optimize the drug combination of ingredients within herbal medicine, and identified unique flavonoid combinations in enhancing hematopoietic functions. It is expected that the CFC method can be widely used in various biomedical fields: optimization of culturing and differentiation of stem cells, combinatory drugs for cancer and viral infections, etc.

References

1. P. K. Wong, F. Yu, A. Shahangian, G. Cheng, R. Sun, and C.-M. Ho, "Closed-loop control of cellular functions using combinatory drugs guided by a stochastic search algorithm,PNAS, 105, 5105-5110, 2008.
2. H. Yu, W.L. Zhang, X. Ding, K.Y.Z. Zheng, C.-M. Ho, K.W.K. Tsim, Y.-K. Lee, "Optimizing Combinations of Flavonoids Deriving from Astragali Radix In Activating the Regulatory Element of Erythropoietin By a Feedback System Control Scheme," Network Pharmacology in Traditional Chinese Medicine, ID 541436, 2013 (dx.doi.org/10.1155/2013/541436).
3. Y.-K. Lee, K.W.K. Tsim, C.-M. Ho, et al. "TCM formula from combinatory flavnoids for treating anemia," Chinese patent pending, Ref No. 201210369803.5, Date: 27 Sep 2012.
4.H. Tsutsui et al. "An Optimized Small Molecule Inhibitor Cocktail Supports Long-term Maintenance of Human Embryonic Stem Cells," Nature Communications, 2:167, 2011.

Brief CV (con't)

Dr. Yi-Kuen Lee received his BS degree in Bio-Industrial Mechatronics Engineering Department (formerly Agricultural Machinery Engineering Department), National Taiwan University (NTU) in 1992. He received his MS degree in the Institute of Applied Mechanics, NTU in 1995. After finishing two-year military service, he went to US and obtained Ph.D. degree in Mechanical Engineering with Major in MEMS under the guidance of Prof Chih-Ming Ho (member of US NAE and Academia Sinica) at UCLA in 2001. He was an Assistant Professor from 2001 to 2007 at HKUST. He received substantiation and was promoted to Associate Professor in 2007. He was a Visiting Associate at Caltech in 2011. He has published two book chapters, 38 refereed journal papers and 57 refereed international conference papers. His current research topics include microfluidics for enumeration of Circulation Tumor Cells (CTCs) for cancer diagnostics, microchips for DNA transfection, micro/nano heat transfer, micro/nano electrophoresis for large DNA molecules, MEMS sensors for environmental monitoring and energy-efficiency building. He was also the Chair for the 5th International Workshop on Innovation and Commercialization of Micro & Nano Technologies (ICMAN 2011), Shenzhen, 5-8 Nov 2011. He is currently the Vice President of Hong Kong Society of Theoretical and Applied Mechanics (HKSTAM) since Mar 2012. He was the co-founder of the annual Nano/Micro Engineered and Molecular Systems (IEEE NEMS) conferences since 2006; Technical Program Committee (TPC) member of IEEE MEMS 2007, Kobe, Japan; TPC member of IEEE Nano 2007; TPC member of APCOT 2008, 2010 & 2012, TPC member of IEEE NEMS 2009-2013, IEEE Transducers 2009, 2011 & 2013.

Magnesium As Bioactive and Biocorrosive Orthopaedic Implants

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

It is known that magnesium (Mg) is the eighth most common element in the crust of the earth and now attracts great attention to become biodegradable or biocorrosive medical implants that avoid a second surgical procedure to remove the temporary metallic parts for fixation after the tissue has sufficiently healed, apart from lowering overall associated health care costs.

Recently, Mg and its alloys are mainly considered suitable for degradable bone implants with high initial stability. Safety concerns are also raised although Mg dissolution is unlikely to have adverse or side effects since Mg is the fourth most plentiful cation in the human body, including involvement in the formation of biological crystal apatite; it is also a co-factor for many enzymes and stabilizes the structures of DNA and RNA; beneficial from a physiological standpoint, since Mg deficiencies in human body will result in disorders of metabolic organs and cardiovascular system as well.

The author's group is developing orthopaedic implants, with great efforts to collaborate with scientists of metallurgy for developing Mg and its alloys as biocorrosive orthopaedic implants and investigating their bone stimulation effects physiologically and biologically using both in vitro and in vivo preclinical experimental models. Renal failure model is also established to investigate concerns on its role in physiological regulation by kidney. Human pilot or Phase I studies are also conducted to investigate its biosafety as well as its efficacy for adequate orthopaedic indications.

Acknowledgement: This research is jointly funded by NSFC-DG-RTD Joint Scheme (Project No. 51361130034) and EU-NSFC under the European Union's 7th Framework Program (NMP-2013-EU-China proposal, project No. 604517).

Brief CV

Dr. Qin is Professor and Director of Musculoskeletal Research Laboratory in the Department of Orthopaedics & Traumatology, Chinese University of Hong (www.ort.cuhk.edu.hk). Dr. 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 (www.siat.cas.cn). He received his B.Ed and M.Ed. in sports medical sciences at the Beijing University of Physical Education in China, and his Ph.D. at the Institute of Biomechanics and Orthopaedics at the German Sports University, Cologne, Germany and postdoc in AO-Research Institute, Davos, Switzerland. Dr. Qin was research scientist in the Department of Trauma & Reconstructive Surgery, University Clinic Rudolf Virchow, Free University Berlin, Germany before joining CUHK in late 1994.

Dr. Qin has been working on advanced diagnosis, prevention and treatment of bone metabolic disorders, especially osteoporosis and osteonecrosis, in collaboration with research and clinical scientists in medicine, geriatrics, rheumatologists, traditional medicine, and biomaterials. Dr. Qin is the immediate-past President of the International Chinese Hard Tissue Society (ICHTS) (www.icmrs.net) and member of a number of journal editorial boards, including Co-editor-in-chief of Journal of Orthopaedic Translation (http://ees.elsevier.com/jot) , Associate Editor of the Chinese Journal of Osteoporosis and Clinical Biomechanics, editorial member of a number of international journals, including Journal of Bone and Mineral Research (www.jbmr.org). 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 20 Research Awards and holds 5 patents.

Dr. Qin published 7 monographs as editor or associate editor, 3 conference proceedings, 50 book chapters, around 300 journal papers in English, German, and Chinese, including 186 SCI articles published in Nat Med, JOR, JBJS, JBMR, Osteoporosis Int, Bone, A&R, Biomaterials, etc. with citation over 3000 and H-index of 33.

Novel Multifunctional Scaffolds for Tissue Regeneration

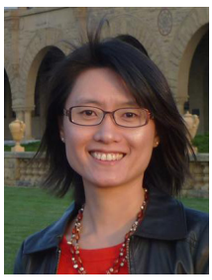
Prof. Min Wang
Department of Mechanical Engineering,
The University of Hong Kong,
Hong Kong, China

In scaffold-based tissue engineering, scaffold materials and scaffolds themselves underpin the success of any strategy for the regeneration of human body tissues. Biodegradable tissue engineering scaffolds provide a microenvironment for cells to adhere, proliferate and differentiate, leading to new tissue formation. Traditional materials for tissue engineering show their limitations and many groups around the world adopt the composite approach in developing new tissue engineering materials. On the other hand, multifunctionality of tissue engineering scaffolds is constantly pursued now, spurring the development of new, multifunctional scaffolds. For example, by employing controlled release strategies that are successfully used in the drug delivery field, growth factors can be encapsulated in tissue engineering scaffolds during scaffold manufacture and then released in vitro or in vivo in a controlled manner, which greatly assists new tissue formation. In regenerating complex body tissues, the temporal and spatial control of biomolecule release is important. Using the hybrid approach, multicomponent scaffolds can be constructed, with each component in the scaffold acting separately as a delivery vehicle for respective bioactive agent. In many circumstances, the selection of a scaffold fabrication technology and the design of novel nanocomposite for scaffolds must be considered together. Many techniques are now available for fabricating tissue engineering scaffolds. However, not all of them are suitable for encapsulating biomolecules in scaffolds. This talk introduces our strategies, approaches and work in the development of multifunctional tissue engineering scaffolds. A few critical issues in biomaterial and scaffold design, fabrication and evaluation will be discussed.

Brief CV
Min Wang was awarded BSc in Materials Science and Engineering in 1985 by Shanghai Jiao Tong University (SJTU), China, and earned his PhD in Materials Science and Engineering in 1991 at the University of London, U.K. He is a Chartered Scientist (CSci, 2005, U.K.), a Chartered Engineer (CEng, 1995, U.K.), a fellow (FIMMM, elected in 2001) of the Institute of Materials, Minerals and Mining, U.K., a fellow (FIMechE, elected in 2007) of the Institution of Mechanical Engineers, U.K., a fellow (FHKIE, elected in 2010) of the Hong Kong Institution of Engineers, Hong Kong, Fellow of Biomaterials Science and Engineering (FBSE, elected in 2011) by the International Union of Societies for Biomaterials Science and Engineering, a fellow (FAIMBE, elected in 2012) of the American Institute for Medical and Biological Engineering, U.S.A., and Academician (WAC Academician, elected in 2013) of the World Academy of Ceramics. Dr. Wang was a founding member of the Interdisciplinary Research Centre (IRC) in Biomedical Materials of the University of London, U.K., and worked on various projects in the IRC (at Queen Mary, University of London) between 1991 and 1997. Before joining The University of Hong Kong (HKU) in June 2003, Dr. Wang conducted teaching and research in Nanyang Technological University (NTU) (1997-2002), Singapore, and The Hong Kong Polytechnic University (PolyU) (2002-2003), Hong Kong. At Nanyang Technological University, he set up and led the Biomaterials Strategic Research Programme and the Tissue Engineering Laboratory. At The Hong Kong Polytechnic University, he helped to set up facilities in the Biomaterials and Tissue Engineering Laboratories. At The University of Hong Kong, he has played a key role in the administration and development of the interfaculty BEng (MedE) Programme and setting up Faculty of Engineering's Medical Engineering Laboratory. In various places, Dr. Wang set up courses in biomaterials and tissue engineering, biomechanics, and biomedical engineering. Dr. Wang is also a guest professor or adjunct professor of Wuhan University of Technology, Shanghai Jiao Tong University, Dong Hua University, Tianjin University, Zhejiang University, and Southwest Jiaotong University, China. Over the years, Dr. Wang and his co-workers have investigated and developed various biomaterials for medical applications. The biomaterials that he and

Brief CV (con't)
his co-workers have worked on include bioactive calcium phosphates (hydroxyapatite (HA), tricalcium phosphate (TCP), etc.), Bioglass, A-W glass-ceramic (Cerabone A-W), as well as nonporous composites (such as hydroxyapatite reinforced polyethylene (HAPEXTM)), coatings and porous scaffolds containing these bioactive materials. The bioactive composites that he and his colleagues developed have been patented in the U.S.A. For developing tissue engineering scaffolds, his group has been using various fabrication techniques, including emulsion freezing and freeze-drying, selective laser sintering (SLS), and electrospinning. He and his research staff/students have won a number of awards at international conferences for their research. Dr. Wang has authored/co-authored a large number of research papers as well as many book chapters. His research has been widely cited by other researchers. He is ranked by the ISI as being among the world top 1% of scientists according to the number of citations recorded for their publications (ISI's Essential Science Indicators) (http://hub.hku.hk/local/top1pc/top1pc.jsp). For his research work, he has given many presentations, including more than 100 invited talks, at various conferences. He has also given more than 90 research seminars in universities, research institutes or hospitals in Western Europe, North America, Asia and Australia. He has provided consultancy on biomaterials and biomedical engineering to multinational companies based in the U.K., U.S.A. and Hong Kong. Since 1990, Dr. Wang has served as a reviewer for more than 70 international scientific journals in the fields of materials science and engineering, biomaterials and tissue engineering, physics, chemistry, medicine, dentistry, medical devices, biofabrication, nanoscience, and nanotechnology. He has also reviewed research grant applications for national research councils/funding agencies of a few countries (U.S.A., Singapore, Australia, etc.). Since 2012, Dr. Wang is the Series Editor of Springer's books series, Springer Series in Biomaterials Science and Engineering(http://www.springer.com/series/10955), and also Editor of Elsevier's journal Materials Letters (http://www.sciencedirect.com/science/journal/0167577X). He has been an Editorial Board member of many international printed journals, including (1) Journal of the Royal Society Interface (http://rsif.royalsocietypublishing.org/), (2) Journal of Materials Science: Materials in Medicine(http://springerlink.metapress.com/content/100192/), (3) Biomedical Materials: Materials for Tissue Engineering & Regenerative Medicine(http://www.iop.org/EJ/journal/BMM) (2006 - 2012), (4) Composites Science and Technology (http://www.elsevier.com/locate/compscitech), (5) Surface and Coatings Technology (http://www.elsevier.com/locate/surfcoat), (6) IET Nanobiotechnology(http://www.ieedl.org/IP-NBT), (7) Frontiers of Materials Science(http://www.springer.com/materials/journal/11706), (8) Journal of Biomimetics, Biomaterials and Tissue Engineering (http://www.scientific.net/JBBTE/), (9) Nano LIFE (http://www.worldscinet.com/nl/nl.shtml), (10) Bioceramics Development and Applications (http://www.ashdin.com/journals/bda/bda.aspx), (11) Journal of Bionanoscience (http://www.aspbs.com/jbns) (2008 - 2012), (12) Journal of Biomaterials and Tissue Engineering (http://www.aspbs.com/jbt.html), and several other printed journals or Open Access (OA) journals. Dr. Wang served as an expert member (2003 - 2007) of the Project Selection/Awarding Panel for Biophysics and Biomedical Engineering of the National Natural Science Foundation of China (http://www.nsfc.gov.cn). He has served in three Technical Committees (TC) of the International Organization for Standardization (ISO). Since 1999, Dr. Wang has served as Chairman and/or Organizer (or Co-Chair/Co-organizer) of 15 international conferences/symposia/workshops, including symposia in the 7th World Biomaterials Congress (Sydney, 2004), the 8th World Biomaterials Congress (Amsterdam, 2008) and the 9th World Biomaterials Congress (Chengdu, 2012) and the 2nd International Symposium on Surface and Interface of Biomaterials (ISSIB-II, Hong Kong, 2010, http://www.hku.hk/issib2010), as well as serving in committees of more than 50 conferences. Dr. Wang also actively participates in professional societies' activities and has served in these societies, including Institute of Materials (East Asia), Hong Kong Institution of Engineers, and Asian Biomaterials Federation. Dr. Wang's current research interests include biomedical materials, biological materials, and tissue engineering. He teaches courses in materials science and engineering, biomaterials and tissue engineering, biomechanics, and biomedical engineering for undergraduates, graduates and clinicians. To promote the engineering profession in general and both materials science and engineering and biomedical engineering in particular, Dr. Wang also goes to local schools to give talks of various topics to high school students. (Updated: July 2013)

Photocrosslinkable Microribbons for Forming Highly Flexible 3D Macroporous Scaffolds for Musculoskeletal Tissue Engineering



Fan Yang[1, 2], Li-Hsin Han[1], Xinming Tong[1]
[1] Department of Orthopedic Surgery, 2 Department of Bioengineering, Stanford University

Introduction: Hydrogels have been widely used as 3D scaffolds for culturing cells in 3D. However, most hydrogels are associated with poor flexibility when subject to cyclic loading, which limit their applications for engineering load-bearing tissues such as cartilage and bone. Furthermore, few hydrogels developed-to-date allow independent tuning of niche cues such as biochemical, mechanical and topographical cues. Here we report the development of a novel method for fabricating microribbon-shaped hydrogels as building blocks with decoupled biochemical and mechanical properties, which can crosslink into 3D macroporous scaffolds with high flexibility in a cell-friendly manner.
Materials and Methods: We first produced PEG hydrogels with microribbon-like structures by wet-spinning 8-arm PEG structures with different end-group chemistry. The stiffness of the microribbons can be tuned by varying the ratios of PEG components with different end-group chemistry. The biochemical cue on microribbons was subsequently introduced by covalently linking biochemical ligands of choice. Human adipose-derived stromal cells (hADSCs) were encapsulated in 3D scaffolds with decoupled niche properties. Outcomes were examined using scanning electron microscope (SEM), cell proliferation, immunostaining and mechanical testing.
Results and Discussion: Here we developed a novel method for fabricating PEG-based, microribbon-like elastomers that can photocrosslink into 3D macroporous scaffolds with independently tunable niche properties. This method allows direct cell encapsulation, and result highly flexible scaffolds that mimic the mechanical properties of load-bearing tissues such as cartilage. Such biomaterials platforms could provide facilitate the analyses of how the interactive niche signaling influences cell fate in 3D. Finally, our platform also supports facile spatial patterning of biochemical cues in 3D, which can facilitate recreating the zonal organization observed in many musculoskeletal tissue types.

Brief CV
Fan Yang is currently an Assistant Professor at Stanford University in the Departments of Bioengineering and Orthopaedic Surgery. Prior to joining Stanford, Dr. Yang received her Ph.D. in Biomedical Engineering from the Johns Hopkins University School of Medicine, and then completed a postdoctoral fellowship in the laboratory of Prof. Robert Langer at MIT. Her research seeks to understand how microenvironmental cues regulate stem cell fate, and to develop novel biomaterials and stem cell-based therapeutics for tissue engineering and regenerative medicine. Examples of applications include therapies for musculoskeletal diseases, cardiovascular diseases and cancer. Dr. Yang has been recognized by multiple awards including the Mission for Learning Faculty Scholar Award in Pediatric Translational Medicine, Donald E. and Delia B. Baxter Faculty Scholar Award, the McCormick Faculty Award, Stanford Asian American Faculty Award, the 3M Nonteured Faculty Award, the National Scientist Development Grant Award, the Basil O'Connor Starter Scholar Research Award, and Ruth L. Kirschstein National Research Service Award. In recognition of her innovation, she was also selected to be one of 2011 TR35 Global list honorees by Technology Review, which recognizes the world's 35 most outstanding innovators who are younger than 35.

Epigenetic regulation of Nanog and Oct4 contributes to enhanced osteogenesis in de-differentiated MSCs

Liangliang Xu[1], Cynthia Xiaohua Jiang[2], Gang Li[1, 2]
[1]Department of Orthopaedics & Traumatology, Li Ka Shing Institute of Health Sciences, Faculty of Medicine, The Chinese University of Hong Kong.
[2]School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong

Objective: The potential of mesenchymal stem cells (MSCs) in osteoblast differentiation and homing to the sites of injury make it a promising cell resource for tissue engineering. Our previous result has shown that the osteogenesis of MSCs is enhanced in de-osteogenic differentiated MSCs. In the present study, we aim to investigate the relavant mechanism involved in regulating de-differentiated MSCs.

Methods: Cultures of bone marrow-derived MSCs were established from 6-8 weeks SD rats. The MSCs were treated with osteogenic induction medium for 10 days, and then cultured in normal α-MEM for 7 days. The genomic DNA were extracted and treated with bisulfite solution as described previously. The bisulfite-modified genomic DNA was analyzed using primer sets spanning the CpG island region in the promoters of Nanog and Oct4. CHIP-PCR assay was also performed to check the binding status of H3K4me3 and H3K27me3 in the promoter regions of Oct4 and Nanog. The shRNA targeting Nanog (shNanog) was constructed for silencing endogenous Nanog gene in MSCs. The pseudo-lentivirus was produced by transient transfection of 293FT cells. MSCs were transduced with lentivirus carrying shNanog and go through the progress of de-differentiation as mentioned above. Alizarin red S staining was used to check the calcium deposit formation during osteogenesis. qRT-PCR was used to evaluate the mRNA levels of target genes.

Results: Alizarin red S staining showed the osteogenic differentiation ability of MSCs was significantly enhanced. In addition, the qRT-PCR result demonstrated that the expression levels of pluripotency makers (Nanog, Oct4 and Sox2) were significantly increased in de-differentiated MSCs. And the bisulfite genomic DNA sequencing data showed that the methylation status of Nanog and Oct4 promoter in de-differentiated MSCs was significantly lower than that of control. The CHIP-PCR assay using specific PCR primer sets indicated that the binding status of H3K4 was increased in de-differentiated MSCs, while the binding status of H3K27 was decreased, implying that transcription factors can bind to the Oct4 promoter much more easily. The relationship between Oct4 and Nanog has been intensively studied in ESCs. Oct4 can bind to the promoter region of Nanog and regulate its transcriptional level. In the present study, we also showed that silencing Nanog could significantly down regulate the mRNA level of Oct4 and Sox2, and the enhanced osteogenic differentiation potential in de-differentiated MSCs was also significantly impaired.

Conclusion: In conclusion, our study showed that the epigenetic regulation of Nanog and Oct4 may be one of the mechanisms involved in enhancing the osteogenesis in de-differentiated MSCs. Oct4 and Nanog may play other roles in MSCs especially in MSCs fate deternimation.

Effects of small molecule, miR-29b, on mice femoral fracture healing

Wayne YW Lee[1], Sien Lin[1], Bin Wang[1], Yang Liu[1], HY Lan[2,3],Gang Li[1,3,4]
[1]Department of Orthopaedics & Traumatology, The Chinese University of Hong Kong
[2]Department of Medicine & Therapeutics, The Chinese University of Hong Kong
[3]Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong
[4]School of Biomedical Sciences, The Chinese University of Hong Kong

Introduction: Fracture healing is a complex physiological repair process. About 5% of long bone fractures have poor healing outcomes; result in delayed unions and non-unions. miR-29b has been found to support differentiation and to facilitate mineralization of osteoblast cells, but the efficacy of these micro RNAs in bone fracture repair remains unclear. In this study, we hypothesized that administration of miR-29b to fracture site could promote MSC-mediated osteogenesis, thus improve healing outcome.

Materials and Methods: Bone marrow-derived MSC was isolated from Luc-mBMSC. Mouse femoral open fracture model was used in this study. After surgery, the mice were divided randomly into seven groups, i.e. (A) control; (B) MSC; (C) scrabmle; (D) miR-29b; (E) MSC plus scramble; (F) MSC plus miR-29b and (G) repeated administration of miR-29b. All mice (n = 10) were sacrificed on week 6 for CT-based histomorphometry examination, mechanical testing and immunohistochemistry staining.

Results: Transient transfection of miR-29b/tet-on plasmids promoted osteogenic differentiation of Luc-BMSC in vitro. The promoting effect remained effective 13 days post-transfection. Three-point bending test showed significant increase in relative (i.e., fracture/intact) maxloading and stiffness in MSC treatment group, while single administration of miR-29b could promote stiffness.

Discussion and conclusion: Single injection of miR-29b could enhance healing parameter to certain extend, and such prolonged effect was similar to in vitro observation. In conclusion, this study has demonstrated the feasibility of introducing micro RNAs in promoting bone fracture healing with a site-specific delivery method. This approach could be further explored in other musculoskeletal disorders wherever vascularity available.

The effects of systemic administration of allogeneic mesenchymal stem cells in bone repair

Shuo Huang[1], Gang Li[1,2]
[1] Department of Orthopaedics & Traumatology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, PR China
[2] Stem Cells and Regeneration Program, School of Biomedical Sciences, Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, PR China

Mesenchymal stem cells (MSCs) are multipotent stem cells that have the potential to give rise to a variety of specialized cell types such as osteoblasts, chondrocytes, adipocytes, myoblasts, fibroblasts, muscle and neural cells. MSCs have many advantages for clinical applications: 1) MSCs are easy to obtain by bone marrow aspiration, and culture for expansion in vitro. 2) MSCs can target specific damaged tissues and tumors. 3)MSCs have anti-inflammatory and immunosuppressive characteristics and allogeneic MSCs do not elicit immediate immune responses. MSCs are one of the most promising candidates for stem cell therapy, tissue engineering, and cell-based gene therapy. Our previous studies showed that there is a systemic mobilization and recruitment of osteoblastic precursors to the fracture site via the peripheral circulation, on this basis, we hypothesized that systemic administration of allogeneic MSCs promotes fracture healing. In this study, Our data showed that both systemic and local injection of allogeneic MSCs promoted fracture healing, through enhancing biomechanical properties, bone content, and enlarged callus sizes. Immunohistochemistry and Immunofluorescence confirmed that both in MSCs systemic injection group and MSCs local injection group, the injected allogeneic MSCs were still present in the fracture site and participate in fracture healing even at 5 weeks following the fracture. These findings offer therapeutic promise for systemic application of allogeneic MSCs, which could be an alternative therapy for local MSCs administration in conditions such as multi-fractures and osteoporotic fractures.

An Improved protocol for isolation and culture of Mesenchymal stem cells from mouse bone marrow

Shuo Huang[1], Gang Li[1]
[1]Department of Orthopedics & Traumatology, the Chinese University of Hong Kong, Hong Kong. Correspondence should be addressed to G. L. (gangli@cuhk.edu.hk)

Mesenchymal stem cells (MSCs) are an attractive cell source for tissue repairing and engineering, and vehicles of cell-based gene therapy. Bone marrow is an important source of MSCs. Unlike rats, mouse bone marrow derived Mesenchymal stem cells (BM-MSCs) cannot be easily harvested due to the low MSCs yield. We explain here a design of standardized, reliable and uncomplicated protocol for isolation of mouse MSCs from bone marrow. The protocol is consulted and developed from established standard protocols and years of cell culture experience from our researchers. The homogenous mouse BM-MSCs isolated as our protocol are strongly positive for CD44, CD90, but negative for the hematopoietic surface marker CD31 and endothelial cells marker CD34, and exhibited tri-lineage differentiation potential. Our easy and reproducible method would provide a highly ethical source of BM-MSCs for research experiments.

The role of Smad7 in bone formation, mBM-MSCs differentiation and osteoclastogenesis

Li Nan[1], Gang Li[1, 2]
[1]School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong
[2]Department of Orthopaedics & Traumatology, Faculty of Medicine,The Chinese University of Hong Kong

Although Smad7 has been well demonstrated to be a negative regulator of TGF-β signaling, and the its altered expression often causes some human diseases such as cancer and fibrosis, the role of the TGF-β/Smad7 signaling in the process of bone development remains unclear. We performed a serious of in-vivo and in-vitro experiments as well as disease model using wild-type (WT) and Smad7ΔE1 mice (KO) to test the hypothesis that Smad7 may play an important role in bone remodeling and MSCs characterization.

The KO mice were generated as reported (The translated part of exon I and part of intron I of Smad7 genomic sequence are replaced by a PGKneobpA expression cassette), and genotyped by PCR. The bone marrow derived mesenchymal stem cells (BM-MSCs) were subjected to flow cytometry to detect the cell surface expression of positive markers CD90, CD44, Scar1, and negative markers CD34 and CD45. After the confirmation of mBM-MSCs, multi-differentiation study and specific staining were used to compare the characterization between the KO and WT mBM-MSCs. The osteogenic potential detected at day 7 and 14 by Alizarin Red S staining and the quantitative acetic acid extraction method of the KO group showed less mineralized nodules, and the mRNA expression of collagen1A1 and RUNX2 were also lower. The adipogenic potential detected at day 7, 14 and 21 by Oil Red O staining showed much more and earlier lipid droplets formation in the KO group, and the mRNA expression detection including PPARγ and C/EBPα also showed much higher expression. The osteoclastogenic potential of KO mBMMs was much stronger than WT, and the osteoclasts were also significantly more and larger than WT detected by TRAP staining. The mRNA expression of TRAP and CTR were also significantly higher. The in-vivo study using micro-CT showed that KO group has significant decreased trabecular number (TbN), thickness (TbTh), and increased trabecular spacing (TbSp) in metaphysic region of the femurs at 6, 12, 24-weeks old. The study of the OVX mice model indicate that the KO group has significantly lower BMD, BV/TV, ThN, ThTh, and higher ThSp than WT group at 1m, 2m & 4m after OVX; the ratio of each parameter of OVX to sham of the KO group are also lower than the WT group at the three time points.

Both the in-vivo and in-vitro studies show that Smad7 may play a protective role in the bone development. Loss of Smad7 can lead to the worse bone remodeling and MSCs characterization. Overexpression of smad7 may represent a novel target for the therapeutical strategies of bone healing.

Effect of secretions from umbilical cord-derived MSCs on BM-MSCs differentiation

Wang Kuixing [1], Gang Li [1, 2]
[1]School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong
[2]Department of Orthopaedics & Traumatology, Faculty of Medicine,The Chinese University of Hong Kong

Objective: Stem cell secretions were made from conditioned medium of stem cells collected from human tissues, they may promote multiple differentiation of mesenchymal stem cells, also enhance the regeneration of musculoskeletal tissues.

Methods: Stainings and qRT-PCR were used to test osteogenesis, chondrogenesis and tenogenesis of Human bone marrow mesenchymal stem cells after treated by differential medium and/or secretion. Rat calvarial bone defect model, femoral fracture model, articular cartilage defect model and patella tendon defect model were used for in vivo study.

Results: Dose-dependent in vitro experiment revealed that 20ug/ml umbilical cord stem cells(UCSC) secretion could promote osteogenic differentiation of hBMSCs. It showed positive effect of 1ug UCSC secretion on bone repair by rat calvarial bone defect model, but the difference between UCSC secretion and control was not significant by rat femoral fracture model. Rat articular cartilage defect study indicated 1ug UCSC secretion with 20ul alginate gel group recovered better than alginate gel group in 6 weeks, but the difference of cartilage healing was not significant between other groups. Moreover, there were more compact collagen fibers when treated by 1ug umbilical cord secretion in rat patella tendon defect experiments, but the alignment of the new tissues were not as good as control.

Conclusion: The umbilical cord stem cell secretion could promote osteogenic differentiation in vitro. It also demonstrated positive effect on bone, cartilage and tendon regeneration.

Chondrogenic Dedifferentiation Reprogrammed Human Fetal Mesenchymal Stem Cells: Better for Cartilage Regeneration?

Sien Lin[1], Ling Qin[1], Gang Li[1,2]
[1] Department of Orthopaedics and Traumatology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China
[2] Stem Cells and Regenerative Program, School of Biomedical Sciences and The Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, PR China

Introduction: To improve survival rate and enhance chondrogenic effect of human fetal mesenchymal stem cells (hfMSCs) is a challenge for functional cartilage regeneration. This study was designed to investigate whether chondrogenic dedifferentiation reprogrammed human fetal mesenchymal stem cells (hfDeMSCs) took advantages of MSCs.

Methods: This study was approved by the experimentation ethics committee of The Chinese University of Hong Kong. Human fetal mesenchymal stem cells were isolated from a placenta of 30-year-old women. hfMSCs were cultured in either normal medium or chondrogenic induction medium containing 10 ng/mL TGF-β1 for 2 weeks followed by normal medium for 1 week. Then hfMSCs and hfDeMSCs were subcultured when they reached 80% to 90% confluence. Medium was changed every 3 days. All of the assays were performed with cells from P7 to P9. For cell proliferation rate test, MTT assays were

performed at day 0, 3, and 5 after the hfMSCs and hfDeMSCs seeded in 96-well plate. For cell viability test, MTT assays were performed at 24hrs after treated by hydrogen peroxide at the concentrations of 0, 50, 150, 250, or 350 μM. Chondrognenic differentiation of hfMSCs and hfDeMSCs by monolayer culture or pellet culture were compared using standard assays. Real-time PCR were performed at 7 days after chondrogenesis to test the expression of chondrogenic markers (SOX9 and Aggrecan). Alcian blue staining or Safranin O & Fast Green staining were performed to test the expression of proteoglycan in monolayer culture or pellet culture, respectively.

Results: At day 3 or day 5, cell proliferation rate of hfDeMSCs was 117% or 210% higher than hfMSCs (Figure 1 A). After challenged with 0, 50, 150, 250, or 350 μM hydrogen peroxide, not significant higher cell viability was observed in the hfDeMSCs group than hfMSCs group (Figure 1 B). Results of real time PCR assays showed that significant higher expressions of SOX 9 and Aggrecan were observed in the hfDeMSCs group than hfMSCs group (Figure 2). It was investigated that hfDeMSCs may show chondrogenesis advantage over hfMSCs from the results of alcian blue staining (Figure 3). It was also observed that much more chondrocyte-like cells in the hfDeMSCs pellet than hfMSCs pellet. The proteoglycan which stained red was much more in the hfDeMSCs pellet than hfMSCs pellet (Figure 4). DISCUSSION AND CONCLUSION: Chondrogenic dedifferentiation reprogrammed human fetal mesenchymal stem cells takes advantages in cell proliferation, cell survival and chondrogenesis of MSCs. The hfDeMSCs may be a better choice for the functional cartilage regeneration than hfMSCs. Further studies are needed to explore the underlying mechanism and the therapeutic effect on cartilage degeneration disease animal models.

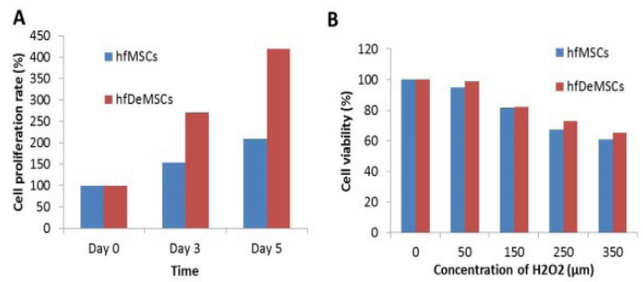


Figure 1: Cell proliferation (A) and cell survival rate (B) after challenged 24h by hydrogen peroxide.

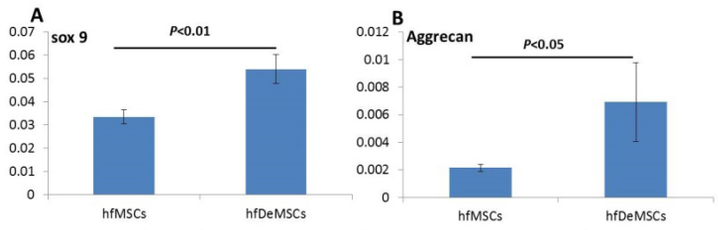


Figure 2: Chondrogenic markers (SOX9, A and Aggrecan, B) tested by Real-time PCR.

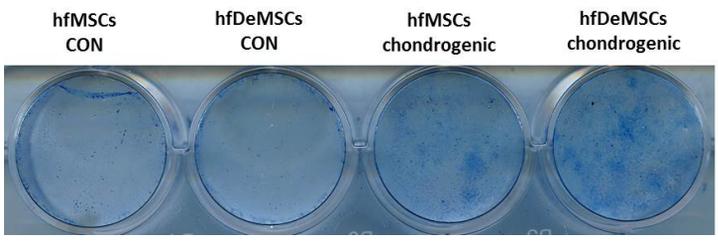


Figure 3: Representative images of alcian blue staining in monolayer culture.

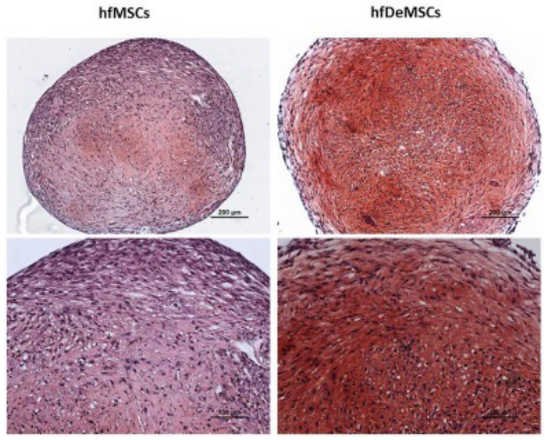


Figure 4: Representative images of Safranin O and Fast Green staining in pellet culture.

Demethylation of Nanog Promoter Contributes to the Chondrogenic and Survival Advantages of Chondrogenic Dedifferentiation Reprogrammed Mesenchymal Stem Cells

Sien Lin[1], Liangliang Xu[1], Ling Qin[1], Gang Li[1,2]
[1] Department of Orthopaedics and Traumatology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China
[2] Stem Cells and Regenerative Program, School of Biomedical Sciences and The Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, PR China.
gangli@cuhk.edu.hk

Introduction: Mesenchymal stem cells (MSCs) showed multilineage differentiation potential. Some preclinical studies and clinical trials have been performed to investigate the chondrogenic effect of MSCs on the treatment of cartilage diseases. However, MSCs showed poor viability and chondrogenic effect is still controversial. To improve survival rate and enhance chondrogenic effect of mesenchymal stem cells is a challenge for functional cartilage regeneration. This study was designed to investigate whether chondrogenic dedifferentiation reprogrammed mesenchymal stem cells (De-chondro-MSCs) took advantages of MSCs.

Methods: This study was approved by the animal experimentation ethics committee, The Chinese University of Hong Kong. Mesenchymal stem cells were isolated from femurs of a 4-week old Sprague-Dawley rat. The MSCs were cultured in either α Minimum Essential Medium (α-MEM) or chondrogenic induction medium supplemented with 10ng/ml TGF-β1 for 2 weeks followed by α-MEM for 1 week. Then MSCs and De-chondro-MSCs were subcultured when they reached 80% to 90% confluence. Medium was changed every 3 days. All of the assays were performed with cells from P3 to P5. Potentials for osteogenic, adipogenic, and chondrognenic differentiation were compared using standard assays. Flow cytometry was performed to examine MSCs surface markers profiles (CD90, CD44, CD45, and CD31). Total RNA was extracted then the expression of osteogenic markers (OPN and RUNX2), adipogenic markers (PPARγ and C/EBPα), and chondrogenic markers (SOX9, Col2α1) were measured by quantitative real-time polymerase chain reaction (qRT-PCR). Their clonogenicity and proliferative capacity were compared using colony-forming and MTT assays. Cell survival after challenged by different concentrations of hydrogen peroxide was determined by MTT assays. Cell pellets after chondrogenic for 21d or 28d were paraffin embedded and sectioned, then stained with Safranin O & Fast Green. Total genomic DNA was isolated from each sample. Bisulfite genomic sequencing was used to detected cytosine methylation of Nanog promoter.

Results: MSCs and De-chondro-MSCs showed similar osteogenic and adipogenic potentital (Fig 2), and similar expression of surface markers CD90 and CD44 (Fig 1B). De-chondro-MSCs exhibited higher clonogenicity (Fig 3A), faster proliferation (Fig 3B), and higher cell survival rate (Fig 3C) after challenged by hydrogen peroxide than MSCs. De-chondro-MSCs expressed higher SOX9, Col2a1, and Nanog RNA levels than MSCs (Fig 4 and Fig 5). De-chondro-MSCs showed higher expression of glycosaminoglycan by Safranin O & Fast Green staining (Fig 4). DNA sequencing data showed lower methylation rate of Nanog promoter in De-MSCs than MSCs (Fig 5).

Discussion: Chondrogenic dedifferentiation reprogrammed mesenchymal stem cells takes advantages in proliferation, cell survival and chondrogenesis of MSCs. The lower methylation rate of Nanog promoter of De-chondro-MSCs may contribute to the changes. De-chondro-MSCs may be a better cell source for cartilage regeneration.

Significance: De-chondro-MSCs showed higher cell proliferation, faster cell survival and better chondrogenesis than MSCs. These changes may be related to the lower methylation rate of Nanog promoter of De-chondro-MSCs.

Fig 1 Morphology (A) and surface markers (B) of MSCs and De-chondro-MSCs.
Fig 2 Osteogenic markers (OPN, B and RUNX2, C) and adipogenic (PPARγ, C and C/EBPα, D) markers and the representative images.
Fig 3 Colony formation (A), cell proliferation (B) and cell survival rate after challenged 24h (C) or 48h (D) by hydrogen peroxide.
Fig 4 Chondrogenic markers (SOX9, B and Col2a, C) and representative images (A) of Safranin O and Fast Green staining.
Fig 5 Pluripotent markers (Nonog, A and OCT4, B) and the methylation profile (C) of Nanog promoter.

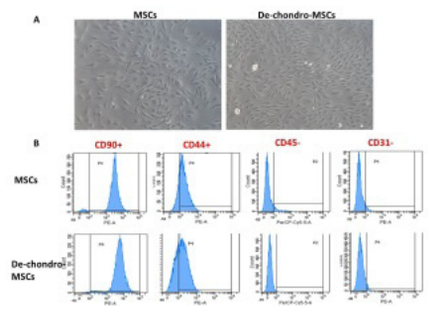


Fig 1

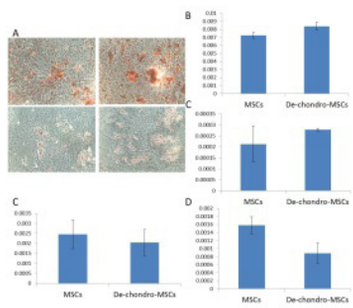


Fig 2

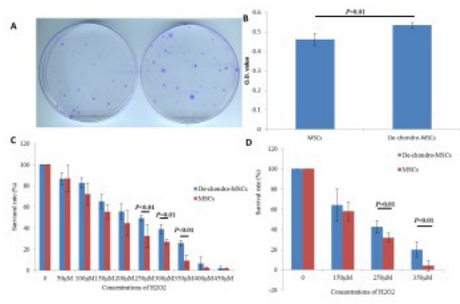


Fig 3

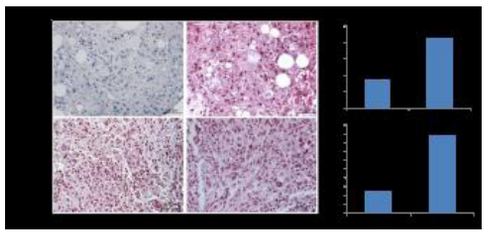


Fig 4

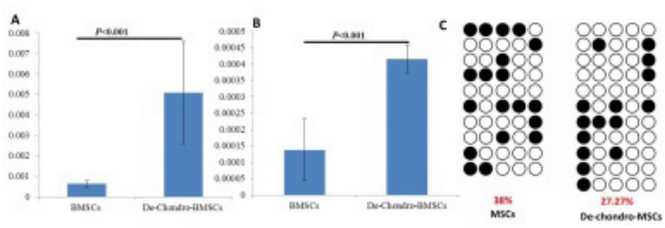


Fig 5

Examine the Role of CFTR on Tenogenic Differentiation

[1]LIU Yang, [2]Jiang Xiaohua, [1]Shekhar M Kumta, [1,2]LI Gang
[1]Department of Orthopedics and Traumatology, The Chinese University of Hong Kong, HKSAR, China
[2]Stem cell and Regeneration Program, School of Biomedical Sciences, The Chinese University of Hong Kong, HKSAR, China

Keywords: Tengenic differentiation, CFTR, mechanical loading

Introduction: Tendons are responsible for transmitting forces derived from muscle to bone and as a result, are subjected to dynamic mechanical stretching. Tendon cells respond to mechanical stretching by altering gene expression, protein synthesis, and cell phenotype. Moreover, high strain mechanical loading can also make a contribution to the tendon disease, such as tendinopathy and tendon rupture. However, how cells sense mechanical stretching and convert them into biochemical signals is not well understood. The current evidence has found that the stretching-activated ion channel may also play a role1. Recently, it has been demonstrated that Cystic Fibrosis Transmembrane conductance Regulator (CFTR) can be robustly activated by membrane stretch induced by negative pressures2. Given that CFTR can also have an unexpected function in mechanosensing, in addition to its roles as a ligand-gated anion channel and a regulator of other membrane transporters. In the current study, we first compare the tendons differences by using the most common CFTR mutation animal model (ΔF508) and its wild type mice, to examine the tendon differences at microstructure, mRNA and histology level respectively. Secondly, we examine the CFTR expression on human tendinopathy, compared its expression level with normal tendon.

Methods: Achilles tendons (AT) and patellar tendons (PT) were collected from 20-24 weeks old male CFTR mutant and wild type mice for examination. Immunofluorescence was performed on paraffin embedded patellar tendons to confirm the expression of CFTR on tendon. Transmission Electron Microscope (TEM) was performed to compare the microstructure of AT. RNA from AT was isolated for comparing the expressions of tendon related markers by qRT-PCR at mRNA level. PT was embedded for paraffin sectioning. The immunohistochemistry was also performed to compare the expressions of tenogenic markers (Tenomodulin) between CFTR mutant and wild type mice at histology level.

Results: Immunofluorescence showed that CFTR expressed on patellar tendon, especially on the cells in tendon tissue. At microstructure level, TEM indicated that tendon fibrils were loosely organized in mutant mice comparing to wild type mice, and sizes of fibrils were also unevenly distributed in mutant mice. The results of qRT-PCR showed that expressions of Tenomodulin, Scleraxis and Decorin are all lower in mutant mice comparing with wild type mice ($p<0.05$). Furthermore, the immunohistochemistry also showed lower expression of Tenomodulin in CFTR mutant mouse than that in wild type mouse.

Discussion: In the current study, we confirm the expression of CFTR on tendon tissues at microstructure, mRNA and histology level. We found that the CFTR mutant mouse showed lower expression of tenogenic markers and loosely organized tendon fibrils. We also confirmed the high expression level of CFTR on human tendinopathy, especially the region with vascular and cells in the matrix with highly degeneration.

Significance: The current results indicated that CFTR may play a role on tendon differentiation, especially during its responses to mechanical loading.

Reference

1. Wang JH, J. Biomech. 2006;39(9):1563-82.
2. WK Zhang, et al. Nat Cell Biol. 2010 May;12(5):507-12.

Develop a new approach of osteotomy in a rat distraction osteogenesis model

SUN Yuxin[1], Gang Li[1]
[1]Department of Orthopedics and Traumatology, The Chinese University of Hong Kong, HKSAR, China

Background: Despite the great amount of studies concerning distraction osteogenesis, there is still no consensus on its osteotomy approach. The objective of this research is to confirm which osteotomy approach is the optimum procedure for bone formation during distraction osteogenesis.

Materials and methods: A rat distraction osteogenesis model was generated. According to the planes and instruments of osteotomy, 40 Sprague-Dawley rats were separated averagely into 4 groups, received different osteotomy approaches (Group A: manual saw & transverse osteotomy, Group B: manual saw & S-shaped osteotomy, Group C: multidrilling & transverse osteotomy , Group D: multidrilling & S-shaped osteotomy) . Then a unilateral external fixator was fixed to the right tibia of the rats. After a 5-day latency period, limb was lengthened at 0.25 mm/12h for 10 days. The rats were sacrificed 10, 14, 17, 21, and 42 days after the operation. Radiographic examination, histological examination, micro CT and four-point bending test were performed to qualitatively and quantitatively evaluate new bone formation.

Results: New bone was emerged earlier in group C and D than that of group A and B by radiological and histological examinations. Micro CT revealed higher BMD value and BV/TV in group D than other groups at each time point. Besides, there is no different in four-point bending test among groups.

Conclusions: Application of multidrilling & S-shaped osteotomy approach in distraction osteogenesis could promote bone formation and accelerate the new bone mineralization.

Compare the anterior cruciate ligament transection alone with the cruciate ligament transection plus meniscectomized rat models of osteoarthritis

Chen Yuanfeng, Kevin Ho, Gang Li
Department of Orthopedics and Traumatology,
The Chinese University of Hong Kong, HKSAR,
China

Osteoarthritis (OA) is a chronic joint disease characterized by cartilage destruction, subchondral bone sclerosis, and osteophyte formation. Animal model have traditionally been used to study the development, progression and treatment of OA. The purpose of this study was to compare the two widely used animal model of surgically induced OA and to detect the different in time point in which pathological changes occurs.

Experimental Approach: A group (6 rats) of 6 weeks old Sprague Dawley (SD) rat were divided into two groups. In group one, the rat's right knee joint was subjected to an anterior cruciate ligament transection (ACLT) alone. In group two, the rat's right knee joint was subjected to an anterior cruciate ligament transection (ACLT) in combination with resection of the medial menisci (ACLT + MMx). The Rats were sacrificed at the 4 weeks and 6 weeks after surgery and comparison was made with the two knee joints.

Key Results: We found that articular cartilage damage has already occurred in 4 weeks post-surgery in ACLT + MMx models and progressive articular cartilage degradation could be found in 6 weeks post-surgery. However, we did not find obvious articular cartilage degradation in the ACLT models in similar time point

Conclusion: The addition of medial meniscus resection appears to accelerate the development and progression of OA in rat. This study suggested that animal model of OA condition can be seen at early as 4 weeks and disease-modifying therapies should target at a much earlier stage.

Effect of 1, 25-Dihydroxyvitamin D3 on regulatory T cells in ovariectomized mice

Junchen Liu[1,2], Chenhui Zhou[1], Xue Zhang[1], Yan Chen[1], Bilian Xu[1], CUI Liao[1], Daohua Xu1[3]
[1]Department of Pharmacology, Guangdong Medical College, Dongguan 523808, Guangdong, China
[2]The Second Affiliated Hospital(Jiande Branch), School of Medicine,ZheJiang University, Jiande 311600, Zhejiang, China
[3]Institution of Traditional Chinese Medicine and New Pharmacy Development, Guangdong, Medical College, Dongguan 523808, Guangdong, China

Objective: To investigate the relationship between regulatory T cells (Treg) and postmenopausal osteoporosis and whether the antiosteoporosis of 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) is related to Treg.

Methods: Fifty female BALB/c mice were randomly divided into five groups: the basal control (BAS), Sham, ovariectomy (OVX), OVX+diethylstilbestrol (OVX+DES), and OVX+1,25(OH)2D3. Tibias were harvested and processed with decalcification for quantitive bone histomorphometry. Femurs were stained by immunohistochemistry to detect Foxp3 protein expression. Spleens were applicated to detect Treg and Foxp3 gene expression by flow cytometry and quantitative RT-PCR, respectively.

Results: In comparison with Sham group, a significant decrease was found in OVX group in such indices as trabecular bone volume/total tissue area (BV/TV), trabecular numbe (Tb.N) and trabecular thickness (Tb.Th). 1,25(OH)2D3 and DES partly prevented the decrease in BV/TV, Tb.N, Tb.Th in OVX mouse. Treg cells number, Foxp3 mRNA expression in spleen and Foxp3 protein expression in femur significantly decreased in OVX-treated group compared with sham group. 1,25(OH)2D3 and DES significantly increase Treg cells number and Foxp3 expression. Treg cells and Foxp3 gene expression were related to bone morphology metrology index.

Conclusion: Decreased Treg cell numbers are relevant to the postmenopausal osteoporosis. The antiosteoporosis of 1,25(OH)2D3 is related to regulatory T cells.

Effects of salvianolic acid B on osteoblast and marrow stromal cells in vitro

Fan Huanqiong Liu Yuyu Zou Liyi Wu Tie Cui Liao
Department of Pharmacology, GuangDong Medical College

Objective: The purpose of this study was to investigate the effects of salvianolic acid B(Sal B) on the proliferation and differentiation of rat osteoblast, to investigate the effects of Sal B on osteogeniese and adipogenesis from MSCs in vitro, further to study whether the Sal B stimulates the osteoblastic differentiation of MSCs through Nitric oxide(NO) pathway.

Methods: To assess the effects of Sal B on the osteoblast, the osteogenesis in MSCs and assess whether the Sal B stimulate the osteogenesis of MSCs through the NO pathway, we isolated osteoblast from neonatal rat calvaria. The cell growth, alkaline phosphatase(ALP) activity, osteocalcin secretion and mineralization of osteoblasts were measure by MTT, PNPP, radioimmunoassay and atomic absorption spectrometry and alizarin red stain respectively.The mRNA expression of osteoprotegerin (OPG) and Receptor Activator nuclear Factor Kappa B Ligand (RANKL) in OB-inducted MSCs were detected by Reverse transcription-Pol-ymerase chain reaction(RT-PCR).

Results: Sal B had no significant effects on proliferation of osteoblast, it can inhibited proliferation at concentration of 10-5mol/L. However, Sal B can stimulate ALP activity in maximum in the concentration of 1×10-7mol/L for 7 days. Sal B enhanced supernatant osteocalcin secreayion at most in day 13, and enhanced mineralized node area significantly, but had no significant effect on mineralized node number.

Through density-gradient centrifugation isolation and subculture attachment selection, the cultured MSCs were became much purified. Sal B can stimulate ALP activity while MSCs do not or undergo osteogenesis. Sal B can enhanced osteocalcin content while MSCs do not or undergo osteogenesis. Sal B up-regulated OPG mRNA expression, down-regulated RANKL mRNA expression at concentration of 5×10-7mol/L and 2.5×10-6mol/L. Sal B decreased PPARγ2 mRNA expression at concentration from 5×10-7mol/L to 2.5×10-6mol/L.

The content of supernatant NO in MSCs is increased accompernied with increased of ALP activity, osteocalcin content and the OPG/RANKL equilibrium while MSCs undergo osteogenesis.

Conclusions: The studies showed that Sal B can stimulate ALP activity, enhance osteocalcin content and mineralized node area of osteoblasts in vitro. Sal B can induce the osteogenic differentiation in MSCs, stimulate ALP activity, enhance osteocalcin content in MSCs, up-regulate OPG/RANKL mRNA expression. Sal B stimulated osteoblast faction and osteogenesis of MSCs may through stimulate NO secretion from OB or MSCs.

Key Words
Salvianolic acid B; Osteoblast; Bone marrow stromal cells; Nitric oxide; Osteoporosis

The purification and use of FGF-2-binding sugar to increase the healing of critical-sized bone defects

Hui JH, Hassan A, Cool SM.
Department of Orthopedic Surgery, National University Singapore

Having successfully isolated that specifically binds to FGF-2 and proved its ability to sustain FGF2 activity so as to promote the mesenchymal stem cell (MSC) expansion presented in our previous report, we have now further elucidated the mechanism of bioactivity in human MSCs and begun in vivo studies to assess its effect in an animal bone repair model. Our present finding points toward the potential use of reagent to FGF-2 for the treatment of bone fractures due to its mitogenic effect toward MSCs. A further investigation into the in vitro effect of FGF toward the osteogenic lineage cells (osteoblasts) is in progress. We have previously shown that HS8 enhances hMSC self-renewal while maintaining multipotency. To test if HS8 supplementation in hMSC routine culture can expand the culture faster, we grew hMSCs from three individual donors separately in HS8 supplemented medium. We noted that hMSCs exposed to HS8 were able to form more colonies and FGF able to increase healing of critical-sized defect.

Mst1 and Mst2 double knockout ES cells: an important model to study Hippo pathway involved in neurogenesis, cardiogenesis and teratoma formation

Peng Li, Ping Yuan
Chemical Pathology, Faculty of Medicine, The Chinese University of Hong Kong

The Hippo pathway has emerged as a critical regulator for cell proliferation, apoptosis and organ size control. Mst1 and Mst2 are the key components of Hippo pathway. Double knockout Mst1 and Mst2 in mice results in early embryonic lethality at embryonic day 8.5. But the exact underlying cause is yet to known. As ES cells can serve as a good model to study early embryonic development, we derived Mst1 and Mst2 double knockout (Mst-/-) ES cells to completely perturb Hippo signaling. We found that depletion of Mst1 and Mst2 enhanced ES cell proliferation and the expression of pluripotent markers Nanog and unphosphorylated Yap. Interestingly, Mst-/- ES cells were prone to neural differentiation but defected in cardiac differentiation, suggesting Mst1/Mst2 repress neurogenesis but enhance cardiogenesis in pluripotent cell differentiation and embryo development. More intriguingly, although differentiated Mst-/- ES cells can express markers of three germ layer tissues, they cannot form teratoma after subcutaneously injected into nude mice, indicating Hippo pathway plays a critical role in teratoma formation. Further tracing gene expression profile during Mst-/- ES cell differentiation revealed that both non-canonical Wnt ligands and genes involved in tumorigenesis were repressed in Mst-/- ES cells, which may partially underpin the distortion of Mst-/- ES cell differentiation and the defect of teratoma formation. These results suggest that it is possible to regulate Mst1/Mst2 expression to control neurogenesis and cardiogenesis for proper cell therapy; Besides, Mst1/Mst2 may serve as important targets to inhibit teratoma formation during pluripotent cell application.

The interrelationship between HIFα pathway and estrogen receptor (ER) signaling in osteoporosis

Shu Y, Zhang F, Tsang WP, Wan C
School of Biomedical Sciences, Faculty of Medicine,
The Chinese University of Hong Kong,
Hong Kong SAR, China

Postmenopausal osteoporosis and its complications such as fracture cause severe pain to the patients and financial burdens to the society. Previous studies showed that postmenopausal osteoporosis was associated with decreased vascularity in the bone tissue. However, the underling mechanisms remain to be elucidated. This study aims to define the interrelationship between the HIFα pathway and ER signaling in the pathogenesis of postmenopausal osteoporosis. We isolated primary long bone derived osteoblasts and cultured the cells under defined osteogenic conditions. Cell proliferation was examined by BrdU incorporation assays. Cytochemistry staining for alkaline phosphatase (ALP) and quantitative real-time PCR for osteogenic marker genes were performed to determine the effects of selected HIF activators (e.g. Deferoxamine, DFO) on osteoblast differentiation. The expression of HIF-1 , HIF-2 , ER and ER in osteoblasts was detected by Western blot. The gene expression of key components of the HIFα pathway and ER signaling in the bone tissue was examined in an ovariectomized (OVX) mouse model. Our results showed that DFO increased the proliferation of osteoblasts. Continuous treatment with DFO decreased osteoblastic differentiation while intermittent treatment showed a moderate positive effect. The expression of ER and ER in osteoblasts was up-regulated when treated with DFO. In the OVX mouse model, estradiol treatment up regulated the levels of key components of the HIFα pathway (HIF-1 HIF-2 and VEGF), which was accompanied by the upregulation of osteoblast transcription factor osterix. Our results indicate that a crosstalk between the HIF pathway and ER signaling may exist in osteoblasts during the development of postmenopausal osteoporosis. Targeting the HIFα pathway may affect ER signaling during the treatment of osteoporosis yet deserves further investigation.

EPO/EPOR regulates the coupling of angiogenesis and osteogenesis during skeletal regeneration

Lin Wan[1, 2], Chao Wan[1, 2]
[1]Key Laboratory for Regenerative Medicine, Ministry of Education, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China
[2]School of Biomedical Sciences Core Laboratory, The Chinese University of Hong Kong Shenzhen Research Institute, Shenzhen, China.

Erythropoietin (EPO)/erythropoietin receptor (EPOR) signaling involves in the development and regeneration of several non-hematopoietic tissues including the skeletal tissue. It is shown that EPO enhances bone repair, while the underlying mechanisms remain unclear. This study aims to determine the role of EPO in regulating the cellular and molecular events during bone healing. Immunohistochemistry, cell proliferation assay, real-time PCR and western blot are performed to determine the role of EPO in chondrocytes in vitro. In vitro angiogenesis is determined by metatarsal endothelial sprouting assays. Histology, histomorphometry, microCT angiography and radiographic analysis are performed to determine the role of EPO in the mouse femur facture model. Our results show that EPO and EPOR are abundantly expressed in the pre-hypertrophic and hypertrophic zone of the mouse growth plates. The proliferation rate of chondrocytes is increased under EPO treatment, which is eliminated following siRNA knockdown of EPOR. EPO increases the production of proteoglycan, accompanied by upregulation of chondrogenic marker genes SOX9, SOX5, SOX6, collagen type 2, and aggrecan. EPO upregulates the phosphorylation states of Janus kinase 2 (JAK2) and signal transducer and activator of transcription 3 (STAT3) while the effects are inhibited by JAK2 inhibitor AG490. This suggests that the function of EPO in chondrocytes is partly mediated by JAK/STAT signaling. In addition, EPO promotes metatarsal endothelial sprouting in vitro, while the effects are inhibited by the EPO blockade. In vivo, EPO promotes cartilaginous callus formation at day 14, and enhances the bone healing at day 28 indexed by the radiographic examination. This is accompanied by increased vascularity during the mid-stage of bone healing (day 14). By contrast, the consolidation of the bone healing is inhibited by the treatment with soluble EPOR to block the EPO function, suggesting that the promising effect of EPO on bone regeneration is mediated by EPOR. Our results indicate that EPO/EPOR involves in the regulation of cartilaginous callus formation as well as the coupling of angiogenesis and osteogenesis during bone regeneration. EPO/EPOR may serve as a novel therapeutic target to promote skeletal regeneration.

Dedifferentiation-Reprogrammed Mesenchymal Stem Cells with Enhanced Tumor Tropism

Chen Rui[1], Cynthia Xiaohua Jiang[2]
[1]School of Biomedical Sciences, The Chinese University of Hong Kong

Objectives: Successful treatment of human glioma, the most deadly brain tumor, has not been achieved largely due to deficiencies in current delivery strategies. Recently, MSC mediated gene delivery has been appeared as a promising strategy for improving the efficacy and minimizing the toxicity of gene therapy in the treatment of glioma. However, for clinical applications, it would be desirable if a sufficient quantity of engineered MSCs that localize within tumors is achieved. This requires the development of methods to improve the migratory capacity of MSCs to tumors, which would thereby increase the delivery of the therapeutic genes.

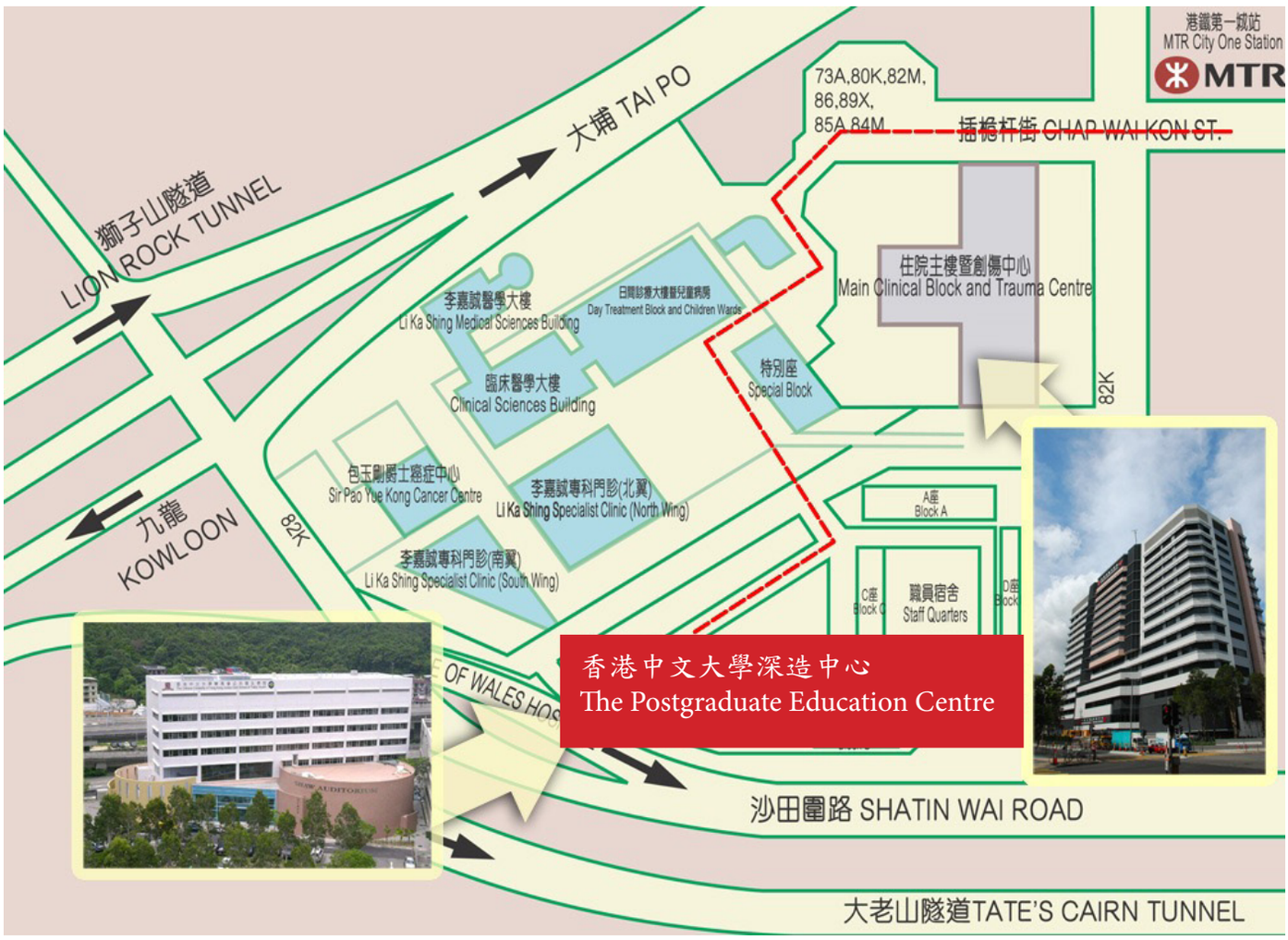
Materials and Methods: Previous studies from our group have demonstrated that after neuronal commitment, differentiated-MSCs can be induced to dedifferentiate and revert back to MSC morphologically under appropriate condition. In addition, we have shown that these dedifferentiated MSCs (De-MSCs) present a variety of distinguishing genetic and phenotypic characteristics distinct from their original counterparts. In this study, we investigated the migratory capability of De-MSCs toward glioma both in vitro and in vivo.

Results: We have found that De-MSCs express significantly higher levels of chemokines and cytokines, and display enhanced tropism to glioma both in vitro and in vivo. Furthermore, we have revealed that the enhanced migratory capability of De-MSCs is attributed to upregulated TNF-α/CCL5/CCR1/MAPK pathway. Currently, we are evaluating the therapeutic efficacy of De-MSCs expressing thymidine kinase (TK) in xenograft intracranial models of glioma.

Conclusions: Successful use of induced dedifferentiated MSCs to deliver therapeutic proteins to brain tumors will represent a major step forward in enhancing treatments of patients with the deadly disease for whom only minimally-effective therapies are currently available.

Venue Map

The Postgraduate Education Centre
Prince of Wales Hospital
Shatin, Hong Kong



Day 1 November 11, 2013 (Monday)

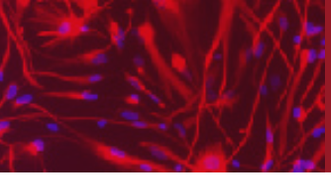
	Time	Key Event	Speaker
Venue: PEC Shaw Auditorium			
Session 1: Stem Cell Biology in Musculoskeletal Diseases and Regeneration Moderators: **Prof. Tim Townes** **Prof. Kenneth Lee**	08:30-08:50	Human Globin Gene Regulation and iPSC Therapy for Sickle Cell Disease	**Prof. Tim Townes, PhD** *University of Alabama, USA*
	08:50-09:10	Stem cells for inter-vertebral disc regeneration: Which Cells ? At what time? How to deliver?	**Prof. Mauro Alini** *AO Research Institute Davos, Switzerland*
	09:10-09:30	Mesenchymal stem cells in bone remodeling and osteoarthritis	**Prof. Xu Cao, PhD** *John Hopkins University, USA*
	09:30-09:50	Circulating mesenchymal stem cells and their clinical implications	**Prof. Gang Li, MD, PhD** *The Chinese University Hong Kong*
	09:50-10:10	Panel Discussion	
	10:10-10:30	Tea Break and Exhibitions	
Session 2: Musculoskeletal Regeneration Research Network (MRN) Moderators: **Prof. KM Chan** **Prof. Jack Cheng**	10:30-12:00	Introduction of SMART Program CUHK	**Prof. KM Chan** **Prof. Hsiao-chang Chan** **Prof. Cynthia Xiao-hua Jiang** **Prof. Kingston King-lun Mak** **Prof. Arthur Fuk-Tat Mak** **Prof. Liming Bian** **Prof. Ling Qin** **Prof. Gang Li** **Prof. Patrick Shu-hang Yung** **Prof. James Francis Griffiths** **Prof. Kevin Ki Wai Ho** **Prof. Ye Chun Ruan**
		Discussion on the goals of MRN	**Prof. Li Fellander Tsai** *Karolinska Institute, Sweden* **Prof. Qian Chen** *Brown University, USA* **Prof. William Maloney** *Stanford University, USA* **Prof. Wouter Dhert** *Utrecht University, Holland* **Prof. Tim Townes** *University of Alabama, USA* **Prof. Tingting Tang** *Shanghai Jiaotong University, China* **Prof. Guang-Qian Zhou** *Shenzhen University Medical School, China* **Prof. Hongwei Ouyang** *Zhejiang University, China* **Prof. Geoff Richards** *AO Foundation, Switzerland*
Session 3: Conference Ceremony Moderator: **Prof. KM Chan**	12:00-12:30	Opening ceremony Inauguration of MRN Group Photo	**Prof. Fanny Cheung** *Pro-Vice Chancellor & Vice- President, CUHK* **Prof. Francis Chan** *Dean of Medical Faculty* **Prof. Wai-Yee Chan** *Director SBS* **Prof. Jack Cheng** *Chairman ORT* **Prof. KM Chan** *Director, SMART-IIM*
Session 4: Keynote Speech 1 Moderator: **Prof. KM Chan**	12:30-13:00	New Frontiers of Skeletal Regeneration: Stem Cells, Extracellular Matrix, and Biomaterial Scaffolds	**Prof. Rocky Tuan** *University of Pittsburg, USA*
	13:00-14:00	Lunch Break and Exhibitions Lunch Time Seminar	
Session 5: New Technologies and Advancements Moderators: **Prof. Stuart Goodman** **Prof. Arthur Mak**	14:00-14:20	Next-generation sequencing as a molecular diagnostic tool	**Prof. Rossa Chiu** *The Chinese University of Hong Kong*
	14:20-14:40	A key network approach reveals new insights in bone cell development and osteoporosis	**Prof. Guang-Qian Zhou** *Shenzhen University, China*
	14:40-15:00	Extracellular matrix niches for stem cells	**Prof. Barbara Chan** *Hong Kong University*
	15:00-15:20	Panel Discussion	
Session 6: Keynote Speech 2 Moderator: **Prof. Gang Li**	15:20-15:50	Translational challenges in musculoskeletal tissue engineering	**Prof. Wouter Dhert** *Utrecht University, Netherland*
	15:50-16:00	Panel Discussion	
	16:00-16:20	Tea Break and Exhibitions	
Session 7: Clinical Perspectives of Regenerative Medicine: The Reality and Challenges Moderators: **Prof. Jack Cheng** **Prof. KM Chan**	16:20-16:40	Towards Intraoperative repair	**Prof. Geoff Richards** *AO Foundation Research Institute, Switzerland*
	16:40-17:00	Developing an "Enhanced" Bone Tissue Engineering Therapeutic Strategy for Large Bone Defect Treatment under Diseased Condition - A pilot study in diabetic rabbit model	**Prof. Zhi-Yong Zhang** *Shanghai Jiaotong University, China*
	17:00-17:20	Clinical applications of MSC's and NSC's in neuro-degenerative disorders	**Prof. William J. Maloney** *Stanford University, USA*
	17:20-17:40	Inflammation and stem cell homing in musculoskeletal regeneration	**Prof. Stuart Goodman** *Stanford University, USA*
	17:40-18:00	Autologous Human Mesenchymal Stem Cells for Cartilage Repair: From Bench to Bedside	**Prof. James Hui** *National University of Singapore, Singapore*
	18:00-18:20	Panel discussion	
	18:20	Meeting adjourns and bus transport to dinner venue at Shatin centre for all invited guests and speakers	
	19:00	Conference Welcome dinner for all invited guests and speakers	

Day 2 November 12, 2013 (Tueseday)

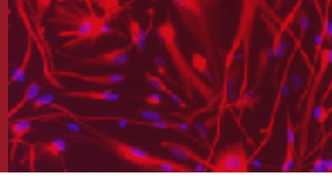
Time\Venue	PEC Kai Chong Tong		PEC Seminar Room 1-3	
	Session 8: Ligament, Tendon and Muscle Highlights Symposium	Moderators: **Prof. Christer Rolf** **Prof. KM Chan**	Session 9: Tissue Specific Functions of Stem Cells	Moderators: **Prof. Li-Ping Li** **Prof. Wan Chao**
08:30-08:50	**Prof. Li Fellander Tsai** *Karolinska Institute, Sweden* The association between Cruciate Ligament injury and development of post-traumatic osteoarthritis, a population based nationwide study in Sweden, 1987-2009		**Prof. Yi-ping Li** *Univ. Alabama, USA* A Stem Cell–Based Approach to Cartilage Repair in mouse Osteoarthritis disease Model	
08:50-09:10	**Prof. Hongwei Ouyang** *Zhejiang University, China* Identification of cartilage progenitor cells and translational research on cartilage tissue engineering		**Prof. Lei Wei** *Brown University, USA* Blocking SDF-1/CXCR4 pathway attenuates OA development	
09:10-09:30	**Prof. Christer Rolf** *Karolinska Institute, Sweden* The role of infection and genetic predisposition of failed healing in chronic tendon ailments		**Prof. Jinyu Liu** *Jilin University, China* Functional Arterial grafts generated from human hair follicle stem cells and de-cellular umbilical cord arteries	
09:30-09:50	**Dr. Bruma Fu** *The Chinese University of Hong Kong* Effect of post-operative GHK-Cu intra-articular injections on graft healing in ACL reconstruction		**Prof. Dong-Qing Cai** *Jinan University, China* Stem Cell Therapy for Infarcted Myocardium—Stem Cells or other Cells	
09:50-10:10	**Prof. Hua-Ting Wang** *The Chinese University of Hong Kong* Identification and Characterization of Long non-coding RNA in Skeletal Myogenesis		**Prof. Kenneth Lee** *The Chinese University of Hong Kong* Role of BRE Gene is Stem Cell and Development	
10:00-10:20	Panel Discussion			
10:20-10:40	Tea Break and Exhibitions			
	Session 10: Cartilage Regeneration and Osteoarthritis	Moderators: **Prof. LK Hung** **Prof. Qian Chen**	Session 11: Musculoskeletal Development and Cell Biology	Moderators: **Prof. Zhenguo Wu** **Prof. Wouter Dhert**
10:40-10:55	**Prof. Qian Chen** *Brown University, USA* Molecular regulation of opposing anabolic and catabolic signaling pathways in mesenchymal chondroprogenitors		**Prof. Chao Wan** *The Chinese University of Hong Kong* Hypoxia promotes expansion of mesenchymal stem cells for skeletal tissue regeneration	
10:55-11:10	**Prof. Li-Ming Bian** *The Chinese University of Hong Kong* Recreating microenvironment cues via biomimetic biomaterials to guide mesenchymal stem cell chondrogenesis for cartilage regeneration		**Prof. Jiake Xu** *University of Western Australia* Angiogenic factors in bone microenvironment: potential therapeutic targets for bone repair	
11:10-11:25	**Prof. Kingston Mak** *The Chinese University of Hong Kong* Functional roles of Wnt16b in endochondral bone development		**Prof. Ge Zhang** *Baptist University, Hong Kong* miR-214 targets ATF4 to inhibit bone formation	
11:25-11:40	**Prof. Zhou Gaungdong** *Shanghai Jiaotong University, China* In vitro cartilage regeneration and its application in repairing cartilage defects		**Prof. Feng Bo** *The Chinese University of Hong Kong* Life-dependent primitive neural stem cells derived from mouse ES cells represent a reversible stage of neural commitment	
11:40-12:00	Panel Discussion			
12:00-13:00	Lunch Break and Exhibitions (Buffet lunch for all in the PEC foyer area)			
	Session 12: Stem cells de-differentiation in cancer development and treatment	Moderators: **Prof. Tingting Tang** **Prof. Cynthia Xiaohua Jiang**	Session 13: Novel Technologies and Biomaterials in Regeneration	Moderator: **Prof. Yi-ping Li** **Prof. Arthur Mak**
13:00-13:15	**Prof. Tingting Tang** *Shanghai Jiaotong Univ., China* Mesenchymal stem cells contribute to the growth and metastasis of osteosarcoma		**Prof. Arthur Mak** *The Chinese University of Hong Kong* Oxidative Stress and Cell Mechanics	
13:15-13:30	**Prof. Cynthia Jiang** *The Chinese University of Hong Kong* Reprogramming MSCs for cancer targeting		**Prof. Yi-Kuen Lee** *Hong Kong University of Science and Technology* Development of Combinatory Drugs from Traditional Chinese Medicine by Using Closed-loop Feedback Control	
13:30-13:45	**Dr. Wayne Lee** *The Chinese University of Hong Kong* Combination cancer therapy: the use of TK-MSCs and Doxorubicin		**Prof. Ling Qin** *The Chinese University of Hong Kong* Magnesium as Bioactive and Biocorrosive Orthopaedic Implants	
13:45-14:00	**Prof. Shi Qin** *Suzhou University, School of Medicine, China* Improved osteogenesis of de-differentiation mesenchymal stem cells		**Prof. Min Wang** *The University of Hong Kong* Novel Multifunctional Scaffolds for Tissue Regeneration	
14:00-14:20	Panel Discussion		**Prof. Fan Yang** *Stanford University, USA* Novel Aspects of Biomaterials in Bone Regeneration	
14:20-14:40	Coffee Break			

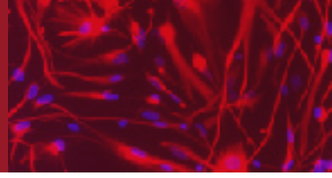
Day 2 November 12, 2013 (Tueseday)

	Time	Key Event	Speaker
Venue: PEC Kai Chong Tong			
Session 14: Free Paper and Award Paper Section 7 minutes presentation 3 minutes questions Judger and commentators: **Prof. Stuart Goodman** **Prof. Yi-Ping Li** **Prof. Kingston Mak** **Prof. Qin Ling**	14:40-14:50	Epigenetic regulation of Nanog and Oct4 contributes to enhanced osteogenesis in de-differentiated MSCs	XU Liangliang The Chinese University of Hong Kong
	14:50-15:00	The role of Smad7 in bone formation, mBM-MSCs differentiation and osteoclastogenesis	LI Nan The Chinese University of Hong Kong
	15:00-15:10	Chondrogenic Dedifferentiation Reprogrammed Human Fetal Mesenchymal Stem Cells: Better for Cartilage Regeneration?	LIN Sien The Chinese University of Hong Kong
	15:10-15:20	EPO/EPOR regulates the coupling of angiogenesis and osteogenesis during skeletal regeneration	WAN Lin The Chinese University of Hong Kong
	15:20-15:30	Mst1 and Mst2 double knockout ES cells: an important model to study Hippo pathway involved in neurogenesis, cardiogenesis and teratoma formation	LI Peng The Chinese University of Hong Kong
	15:30-15:40	Examine the Role of CFTR on Tenogenic Differentiation	LIU Yang The Chinese University of Hong Kong
	15:40-15:50	The interrelationship between HIFα pathway and estrogen receptor (ER) signaling in osteoporosis	SHU Y The Chinese University of Hong Kong
	15:50-16:00	Dedifferentiation-Reprogrammed Mesenchymal Stem Cells with Enhanced Tumor Tropism	CHEN Rui The Chinese University of Hong Kong
	16:00-16:10	Comments and questions by the judge panel members	
	16:10-16:20	Free Paper Awards Ceremony	Prof. Kingston Mak Prof. Bian Liming
	16:20-16:30	Conclusion remarks	Prof. KM Chan Prof. Gang Li
	16:30	Meeting adjourns and free evening time	



Note





Special Thanks To:

嘉華集團 K. WAH GROUP

呂志和基金有限公司
LUI CHE WOO FOUNDATION LIMITED

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".

何善衡慈善基金會有限公司
THE S. H. HO FOUNDATION LIMITED

The S. H. Ho Foundation Limited has generously sponsored the "S. H. Ho Sports Medicine Development and Education Program" of Hong Kong Centre of Sports Medicine and Sports Science, contributing to the promotion of sports medicine education and development.

Conference Secretariat

General Office
Department of Orthopaedics and Tramatology
Rm 74034, 5/F Clinical Science Building,
Prince of Wales Hospital, Shatin, Hong Kong

Tel: (852) 2632 2727 Fax: (852) 2637 7889