4th CUHK International Symposium on Stem Cell Biology & Regenerative Medicine

17-18 November 2014

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

SMART Programme, 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

Sponsors

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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 2014 CUHK International Symposium on Stem Cell and Regenerative Medicine Symposium.

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

In the past 4 years, CUHK has been expanding its research potentials and capacities in the field of regenerative medicine. Dedicated research teams and research projects are being set up and state-of-the-art research facilities are built to facilitate the needs of research and clinical applications in this field.

With the generous donation from the Lui Che-Woo (吕志和) Foundation, the Institute of Innovative Medicine (IIM) has already been operating with success since 2013 summer. The SMART (Sports Medicine and Regenerative Technology) programme has made tremendous progress, to name but a few, SMART programme has signed an MOU with Karolinska Institute, Sweden and University Medical Centre, Utrecht respectively; CUHK delegation had made a fruitful academic visit at both institutes in June 2014, staff and student exchanges and collaborative research in tendon, ligaments and cartilage are also underway.

The main topics of the symposium this year consist of biology of regenerative medicine, musculoskeletal regeneration and translational research, and musculoskeletal regeneration network sections. And I am glad to see the Musculoskeletal Regeneration Research Network (MRN) has already brought many creditable partners to work together in the field of musculoskeletal regeneration.

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

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

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

Message from

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

Dear colleagues and friends:

Welcome to the 4th CUHK International Symposium on Stem Cell Biology and Regenerative Medicine.

The groundbreaking research undertaken by the 2012 Nobel Laureates in Physiology or Medicine, Dr John Gurdon and Dr Shinya Yamanaka has opened up new frontiers in the understanding of degenerative diseases such as stroke, Parkinson's, and diabetes. An aging population in developed countries requires a new perspective on treatments that address major health conditions caused by degenerative diseases. Conventional medicine treats the cause of diseases but does not repair damaged cells, tissues and organs. Their pioneering and revolutionary work has ushered in a new era which the enormous potential of developing more effective treatments and cures for patients is to be fully tapped.

The society, the clinical and scientific communities, and patients hold high hopes for regenerative medicine, which is driving the advancements in cell biology and allied basic sciences research and speeding up the turning of translational research into clinical applications in various specialties in medicine.

It is our great honour to have Professor Shinya Yamanaka as the Dr Lui Che Woo Distinguished Professor to give an Open Lecture on "New Era of Medicine with iPS Cells" this late afternoon. I am sure you are very much looking forward to hearing this most intellectually stimulating lecture.

I would like to take this opportunity to acknowledge the generous donation from Dr Lui Che Woo which has made possible the organization of the annual Distinguished Professor Public Lecture.

My special thanks also go to the Organizing Committee as well as all the administrative support staff who have worked tirelessly to attend to every detail to ensure the success of the symposium.

I trust that you will meet and connect with as many like-minded individuals as possible at the symposium to share research findings, to cement links for more collaborative research and equally important, to foster lasting friendship.

We are extending a warm welcome and gracious hospitality to every participant. For those who journey away from home to here, I also wish you an enjoyable stay in Hong Kong.

Yours sincerely,

Francis Chan

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

Message from

Organizing Committee

Dear colleagues and friends:

The 4th CUHK International Symposium on Stem Cell and Regenerative Medicine is held in Hong Kong (17-18 November, 2014) following 3 previous successful ones in 2011, 2012 and 2013.

The main topics of the symposium this year consist of biology of regenerative medicine, musculoskeletal regeneration and translational research, and musculoskeletal regeneration network sections. We are pleased to announce that Prof. Shinya Yamanaka, MD, PhD, Nobel Laureate of 2012 Medicine and Physiology will be our guest of honor and give a talk on "New Era of Medicine with iPS Cells". There are over 30 speakers have confirmed to attend our meeting from USA, Europe, Australia, Japan, Taiwan, Hong Kong and China.

We hope that the symposium will provide a platform to share and learn new research ideas, findings and techniques from each other in Hong Kong and greater China areas. In addition, Hong Kong is a city where East meets West. There are many excellent shops, restaurants and tourist attractions here to be explored.

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 4th CUHK International Symposium on Stem Cell Biology and Regenerative Medicine

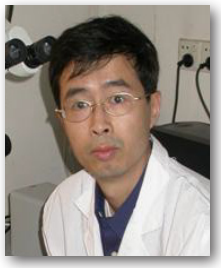
Co-Charimen:

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

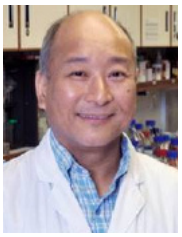
Prof.Jack Chun-Yiu Cheng
Chairman
CUHK-ORT

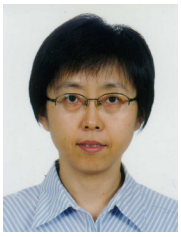


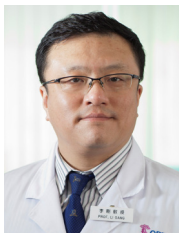
Prof. Dong-Qing Cai
Co-Director,
Jinan-CUHK Key Lab for
Regenerative Medicine,
Ministry of Education, China

香港中文大學 生物醫學學院 CUSBS

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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Prof. Xiaohua JIANG


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

More specifically we view as our missions:

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

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

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

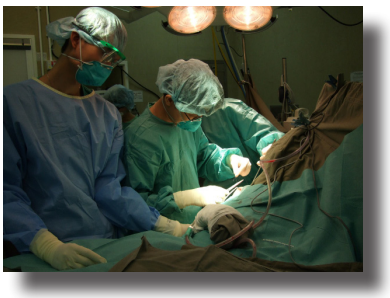
Core technology and research platforms of SCR:
The following are some existing technologies that we have in the theme:

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

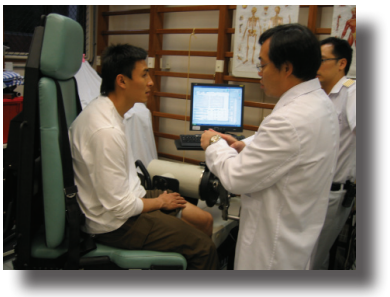
For the research interests of each member, please visit http://www.sbs.cuhk.edu.hk/Research_Scr.asp

Department of Orthopaedics and Traumatology
The Chinese University of Hong Kong

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



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



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

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

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

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

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

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

SMART 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 and first to promote the development of arthroscopic surgery
1988	First Founding President of the Hong Kong Association of Sports Medicine (HKASMSS)
1990	First pioneer to establish Asian Federation of Sports Medicine (AFSM)
1995	First pioneer to establish the Asia-Pacific Orthopaedic Society for Sports Medicine (APOSSM)
1996	First Sports Medicine Centre designated as the WHO Collaborating Centre in Sports Medicine and Health Promotion (1996-2009)
2002	First Asian Presidency of International Federation of Sports Medicine (FIMS) (2002-2006)
2004	First Taught Programs (MSc & PgDip) in Sports Medicine & Health Sciences organized by a university in Hong Kong
2007	First SMART (Sports Medicine and Rehabilitation Therapy) Convention to promote knowledge transfer and community education
2008	First World Congress of Sports Trauma (WCST) held in Hong Kong, with over 1000 attendance First established centre in Sports Medicine and Health Sciences with the generous donation of HKD 88.72 million from Hong Kong Jockey Club Charities Trust
2010	First International Symposium of Ligaments and Tendons (ISL&T) held in Hong Kong
2011	First CUHK Stem Cell & Regenerative Medicine (SCRM) Conference held in Hong Kong
2013	First launch of Sport Medicine And Regenerative Technology (SMART) programme in the Institute of Innovative Medicine (IIM) and Musculoskeletal Regenerative Research Network (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. Though this collaboration, our medical students from CUHK and physiotherapist students from HKPU is now having the opportunities to enjoy a two-way learning, particularly acquiring more knowledge on the principle and applications of rehabilitation in sports injuries, as well as developing good long term working relationship. For post-graduate education, 21 research master students and 15 PhD students have completed their research projects on areas such as tendon and ligament regenerations and biomechanics studies. Our team successfully launched the first ever Master Course in sports Medicine & Health Science in Hong Kong in 2004. With a strong teaching international faculty equipped with collective expertise in research and education, rigorous trainings were provided to learners from a diversified background such as medical doctors, physiotherapists, nurses, sports scientists, allied health, fitness professionals and sports enthusiasts. We have now trained more than 400 people with our MSc course. Many of these alumni are contributing and playing a significant role in the sports medicine profession and industry in HK and around the world.

Future

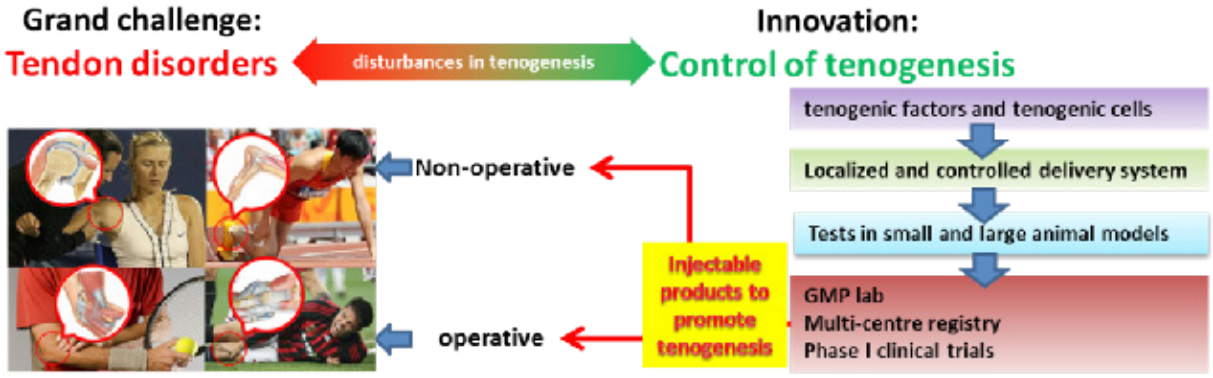
Orthopedic sport medicine is an integral part of orthopedics. It is a vibrant and emerging sub-specialty that traverses boundaries in other disciplines in medicine in general and orthopedics in particular. A well-trained orthopedic surgeon will benefit from a comprehensive program of training as highlighted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

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

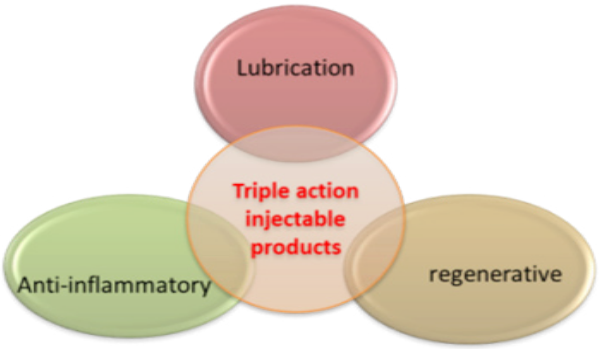
IIM-SMART International Collaboration

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

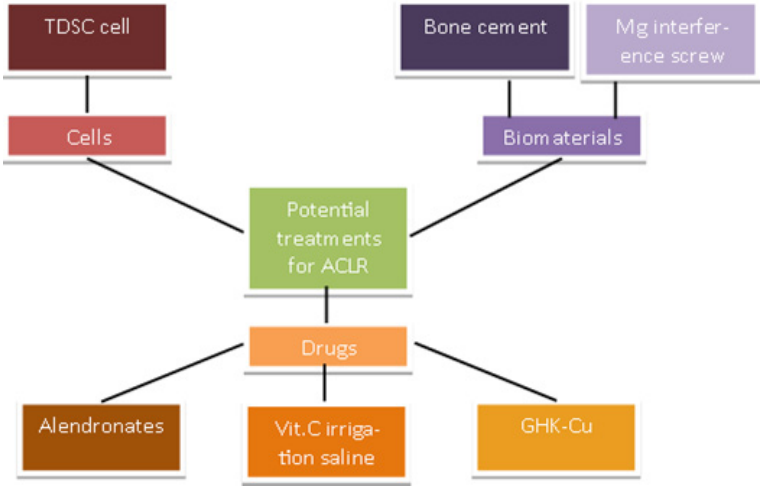
Tendon research



Cartilage research

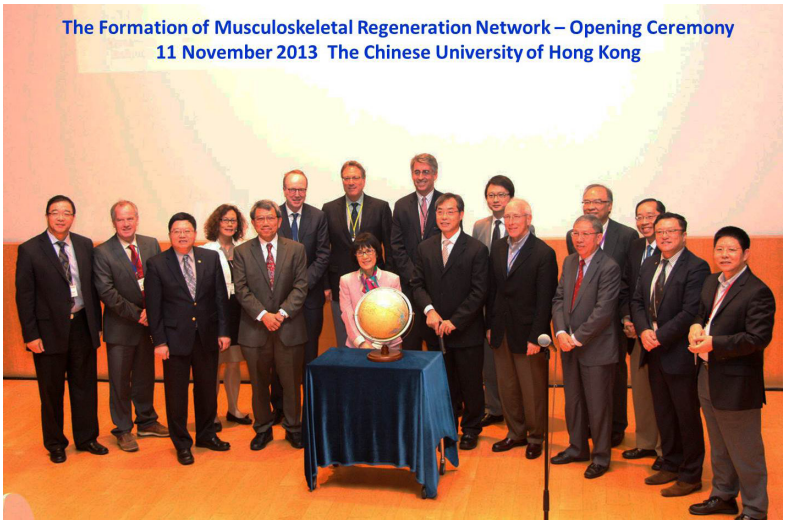


ACL research



Clinical & applied research

Musculoskeletal Regeneration Network (MRN)



Visit to Karolinska Institute

Joint research symposium in musculoskeletal regeneration

KI presentations

- Fetal MSC research (Prof. Cecilia Gotherstrom)
- CT imaging and knee function in knee OA (Prof. Hans Berg)
- Epidemiology of tendon and ligament injury (Prof. Ville Matilla)
- The role of infection in Tendinopathy (Prof. Goran Friman)
- PGC-1alpha: transcriptional context in muscle adaptation to exercise (Prof. Jorge Ruas)

CUHK presentations

- Tenogenic differentiation of MSC:s and TDSC:s and their applications (Prof. Gang Li)
- Current concepts in pathogenesis of tendinopathies (Dr. Bruma Fu)
- Tissue analyses and tendon rupture (Dr. Luan Ju)

Visit to University Medical Center Utrecht

Seminar "Exploring the CUHK-Utrecht collaboration"

UMC Utrecht presentations
- Welcome (Prof. Rene Castelein)
- Introduction (Prof. Wouter Dhert)
- Musculoskeletal small animal imaging (Prof. Harrie Weinans)
- Biofabrication of osteochondral construct (Dr. Jos Malda)
- Impact: First in human trial in single stage cartilage repair (Mr Tommy de Windt/ Dr. Daniel Saris)

CUHK presentations
- CUHK-UU collaborative research on SMART (Prof. Chan KM)
- The Use of chondrogenic de-differentiated MSCs for cartilage tissue engineering (Prof. Li Gang)
- Development of triple action hydrogel to treat OA (Dr. Bruma Fu)
- Functional biomaterials for cartilage repair (Prof. Bian LM)

Visit to Stanford University

With the support of SH Ho Visiting Professorship Exchange Programme, Prof. Li Gang visited the department of orthopaedic surgery of Stanford University for a month. He attended laboratory meetings, seminars and gained a deeper understanding of the research work carried out at Stanford university. He also gave a departmental lecture and a lecture for the Grand Round talk.

Outcome
- Start 3 joint/collaborative research projects between PIs of the two departments
- Publish a paper with Stanford University group
- Prepare and sign an MOU between Stanford Orthopaedic Surgery Department and CUHK-ORT for research collaborations and personnel exchanges

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.

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Session 1: Stem Cells in Tendon and Intervertebral Regeneration

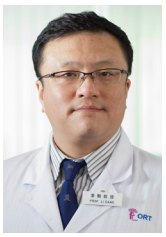
TENDON STEM CELL AGING AND REJUVENATION

Prof. Herb Sun
Director of Orthopaedic Research
Albert Einstein College of Medicine
USA

Age is a major risk factor for tendon injury and impaired tendon healing. Aged tendons undergo degenerative changes in structure and biomechanics, accompanied by reductions in the number and function of tenocytes, the tendon cells principally responsible for production and remodeling of tendon extracellular matrix (ECM). Previous studies found that with age, tendon stem/progenitor cells (TSPCs) exhibit declines in number, reduced proliferation rate, diminished differentiation potential into tenocytes, and increased cellular senescence. In this presentation, we will reveal the current evidence of aging-related declines in TSPC function, focus on its regulation by transcriptional regulator CITED2, discuss recent evidence of CITED2 deficiency on mimicking the aged phenotype, and the ability of CITED2 to enhance the reparation of aged human TSPCs and promote its rejuvenation.

Brief CV
I have been conducting musculoskeletal academic research and education for many years, in many institutes in the United States, China, and Japan, and have gained an extensive experience in biomedical research, in particular, in the musculoskeletal system and orthopaedics. My research program involves elucidating the cellular and molecular mechanisms underlying pathologies of musculoskeletal disorders. My current studies involve elucidating the role of transcriptional regulator CITED2 in the context of tendon stem cell aging and in the maintenance of cartilage integrity, with a goal of translating the knowledge gained into prevention and treatment of musculoskeletal diseases such as arthritis and tendinopathy.

TENOGENIC DIFFERENTIATION OF MSCs AND THEIR APPLICATIONS



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

Tendon contains stem cells (TDSCs) and they are unique mechymal stem cells (MSCs). We have compared the tenogenic differentiation of bone marrow derived MSCs among the reported factors, such as CTGF, BMp-12 and TGF-b1, and tried to define a set of specific tenogenic markers. We showed that TDSCs have the spontaneous tenogenic differentiation potential and three key tenogenic transcription factors, Egr1, Eya1 and Mkx, are highly expressed during tenogenic differentiation processes. Through bioinformatics analysis, miR-124-3p is predicted to target Egr1, Eya1 and Mkx through the possible common binding sites. The expression level of miR-124-3p is much higher in the TDSCs compared to that of intact tendon as determined by RT-qPCR. In addition, miR-124-3p expression level is declining as the expression levels of Egr1, Eya1 and Mkx increased along with the process of spontaneous tenogenic differentiation. We will further investigate whether miR-124 can regulate tenogenic differentiation through binding its targets directly. These findings will give insights into the regulatory mechanisms of tenogenic differentiation and provide new promising targets for the treatment of tendon disorders. We also tested the use of TDSCs or TDSCs cell sheet to repair tendon injury. The TDSCs cell sheet could form neo-tendon tissue in vivo, and promote tendon regeneration in a rat acute patellar tendon injury model. The TDSCs and their cell sheets may be used as a new form of cell sources and biomaterial for tendon repair.

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 100 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 team work in relation to Tendon regeneration):
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STEM CELLS FOR INTERVERTEBRAL DISC REGENERATION: WHICH CELLS? AT WHICH TIME? AND HOW TO DELIVER THEM?

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 intervertebral disc tissue (IVD). 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. Pilot human studies have also been started. It is, however, not yet clear whether MSCs directly or indirectly contribute to the healing process. Indirectly, MSC could also release biological factors, which will be able to stimulate the resident disc cells or activate the potential progenitor cells present within the IVD. Therefore, stem cell homing into damaged tissues may be seen as a promising therapeutic method for tissue regeneration. We have recently shown that MSCs have such ability to migrate (homing) towards sites of IVD 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. However, it needs to be elucidated whether the identified homing factors, CCL5 and/or CXCL6 are specific for the disc or other tissues and whether systemic administration of MSCs can be used to regenerate the tissue. Furthermore, such systemic approach could avoid the damaging of the annulus fibrosus (AF) tissue, the current route to access the IVD space.
As mentioned above, the present delivery approach of MSCs within the IVD has to be through injection, via the annular route. This requires injuring intact AF tissue, which would subsequently lead to further degeneration, as recently shown in human by (Carragee et al., Spine 2009). We have recently developed a new approach to the IVD space, via the transpedicular route, which may be less damaging compare to the AF access.
The three routes (AF, Transpedicular and systemic) will be presented and advantages and disadvantages will be discussed.

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 from 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.
http://scholar.google.com/citations?user=9_h6-YgAAAAJ&hl=en

NOTCH SIGNALING IN DEVELOPMENT AND DISEASE

Prof. Urban Lendahl
Department of Cell and Molecular Biology
Karolinska Institutet, Stockholm
Sweden

The Notch signaling pathway is an evolutionarily highly conserved cell-cell communication system that controls cell fate decisions in a variety of organs, including skeletal muscle. We have a long-standing interest in Notch signaling, both in decoding the core signaling mechanism and understanding how Notch signaling intersects with other signaling mechanisms, such as BMP/TGF-beta signaling and the cellular hypoxic response, to control cell fate decisions. For example, during myogenesis we have shown that Notch and BMP signaling synergizes to prevent myoblast differentiation.
In more recent research, we also focus on how deregulated Notch signaling leads to disease. Mutations in the Notch signaling pathway lead to diseases as different as T-cell leukemia, the multi-organ disease Alagille syndrome and the stroke and dementia syndrome CADASIL. Common to Alagille syndrome and CADASIL is that the vasculature becomes dysfunctional, and to gain insights into the role of Notch signaling in the formation and homeostasis of vasculature is of interest also for regenerative medicine purposes, as vascularization of engineered tissues is a critical factor for transplantation success.
In the presentation, I will describe data on how Notch signaling controls vascular smooth muscle cell (VSMC) differentiation and maintenance and critical roles for the Notch3 receptor and the Jagged1 ligand in this process. In Notch3-deficient mice we have recently demonstrated that there is a progressive loss of VSMC degenerate over time, and that this loss is accompanied by leakage across the blood-brain barrier. In a mouse model carrying a missense mutation in the Jagged1 gene (aka Nodder mice), we show that they phenocopy the spectrum of symptoms observed in patients with Alagille syndrome, for example in the heart, thymus, lens, kidneys and the vasculature. We provide data indicating that this is a result of a hypomorphic function of the mutated Jagged1 ligand.
In conclusion, our data shed new light on the importance of functional Notch signaling for a variety of organs, including skeletal muscle and the vasculature, and we hope that our data can provide the basis for rational therapies to diseases caused by Notch mutations in the future.

Brief CV
Urban Lendahl was born in Stockholm in 1957 and studied biology at Stockholm University from 1978-1982, specializing in molecular biology. After earning his PhD at the Karolinska Institute in 1987, Lendahl was a postdoctoral fellow at MIT 1987-1989 with professor Ron McKay as mentor. After returning to the Karolinska Institute, Lendahl became Professor of Genetics in 1997. Lendahl is a member of the Nobel Assembly for Physiology or Medicine since 2001, and was Chairman of the Nobel Committee in Physiology or Medicine in 2012. Lendahl's research is focused on stem cells, developmental biology and intracellular signaling pathways. Lendahl has served as head of the review committee at the Human Frontiers Science Foundation, and serves at evaluation committees at the Swedish Research Council and the Swedish Cancer Society. Lendahl is currently director of two research centers in stem cell research and regenerative medicine: DBRM (www.dbrm.se) and WIRM (the Wallenberg Institute for Regenerative Medicine). Since 2012, Lendahl holds a Distinguished Professor Award at the Karolinska Institute. He is a Member of the Board of Trustees for the Koerber European Science Award. From 2013 he leads the Advisory Panel for Stem Cell Research in Norway and is a member of the Board of Directors at ISSCR.

Session 3: Musculoskeletal Regeneration Research Network (MRN)

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

Prof KM Chan is the Chair Professor of Department of Orthopaedics and Traumatology, Prince of Wales Hospital, The Chinese University of Hong Kong. He was the past Chairman and Chief of Service. He is a pioneer in orthopaedic sport medicine, the founding president of the Hong Kong Association of Sport Medicine and Sport Science (HKASMSS) and Asia-Pacific Orthopaedic Society for Sports Medicine (APOSSM), now renamed as Asian-Pacific Knee, Arthroscopy and Sports Medicine Society (APKASS). He was the first Asian to assume President of International Federation of Sports Medicine (FIMS). Prof Chan clinical work includes arthroscopic surgery of the knee and shoulder, tendinopathies and rehabilitation of sporting injuries. His research work focuses on tendon and ligament tissue engineering, ACL healing & kinematic assessment and regenerative technology transfer. Prof Chan has published more than 300 peer-reviewed scientific articles and edited more than 30 books in the discipline of orthopaedic and sport medicine. He is a past president of the Hong Kong Orthopaedic Association (HKOA), Hong Kong College of Orthopaedic Surgeon (HKCOS), Chinese Speaking Orthopaedic Society (CSOS). He was honored with the John Joyce Award of ISAKOS, FIMS Gold Medal, Alpha-Omega-Alpha Honorary Member of Stanford University, USA, the Ambassador of the Bone & Joint Decade (BJD) and Takagi and Watanabe Award of APKASS.

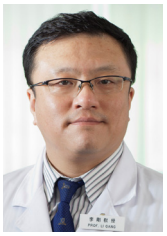
Prof. Wouter J.A. Dhert, MD, PhD, FBSE
Utrecht University
Netherlands

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.

Prof. Christer Rolf
Division of Orthopaedics
Karolinska Institutet
Sweden

Prof. Christer Rolf received his M.D. in the Umeå University in 1983, and then obtained his Full Medical License to practice, Board of Health in Sweden in 1986. He received his Ph.D in Orthopedics och Rehabilitation of Umeå University in 1987. From 1991 to 1993, Prof. Christer Rolf worked as Specialist Orthopedic Surgery in Karolinska University Hospital, and then Consultant Orthopedic Surgeon in Karolinska University Hospital (1993-1997). Prof. Christer Rolf used to be the Visiting Clinical Professor of Sports Medicine Department Orthopedics in Prince Of Wales Hospital, The Chinese University of Hong Kong (1997-2000). From 2000-2010, he was appointed as the Founding Clinical Chair in Sports Medicine in the University of Sheffield. Meantime, he was also the Foreign Adjunct Professor of Sports Medicine of Karolinska Institutet (2008-2014). Prof. Christer Rolf also served as the Chairman of FIMS International Federation of Sports Medicine Scientific and Education Committee (1998-2002) and European Federation of Sports Medicine Associations Scientific and Education Committee (2000-2010). He is currently the Consultant Orthopedic Surgeon in the Head Arthroscopy and Sport Injury Section in the Department of Orthopedics of Karolinska Universitetssjukhuset, and also the Clinical Head Karolinska University Hospital Multidisciplinary Day Case Centre, and the Professor of Sports Medicine in Clintec of Karolinska Institutet. He is also the honorary Visiting Professor in Department Orthopedics, Prince of Wales Hospital, Chinese University of Hong Kong (2013-present). In 2013, he became the Joint Coordinator and Principal Investigator (KI) with Prof KM Chan (CUHK) of an MOU and Joint Research Program in Musculoskeletal Regenerative Medicine between Karolinska Institutet and Chinese University of Hong Kong (2013-2018). Prof. Christer Rolf is 125 peer reviewed articles in international Journals, 23 books, 6 book chapters.

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



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 100 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.

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

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 Experimental Morphology 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 past President of the International Chinese Musculoskeletal Research Society (ICMRS) (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) and International Journal of Sports Medicine (http://www.thieme.de/sportsmed) . He holds memberships in several international and national orthopaedic and related research organizations, including collage fellow of American Institute of Medical and Biological Engineering (http://www.aimbe.org). He has received over 30 Research Awards and holds 4 patents. Dr. Qin published 7 monographs as editor or associate editor, 3 conference proceedings, 80 book chapters, over 300 journal papers in English, German, and Chinese, including 220 SCI articles published in Nat Med, JBMR, Osteoporosis Int, Bone, A&R, Biomaterials, Acta Biomateralia, Am J Sports Med, etc. with citation over 4000 and a H-index of 37.

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

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.

Prof. René Castelein
Chairman
Division of Surgical Specialties
UMC Utrecht
Netherlands

Prof. René Castelein, MD, PhD (1954) trained as a general Orthopaedic surgeon, he has always had a broad field of interest within the specialty of Orthopaedics. Throughout his professional life, however, spine surgery and paediatric orthopaedics have been foremost. During his training years, he worked as a fellow in paediatric and spine surgery at the Alfred I du Pont Institute of the Nemours Foundation, in Wilmington, Delware. Also during training, he did research at the department of Anatomy in Leiden, the Netherlands, on the subject of idiopathic scoliosis. At the same time, a PhD thesis on ultrasound screening in developmental hip dysplasia was completed. After a number of very enjoyable years as an Orthopaedic surgeon and director of the orthopaedic training programme at the Isala Clinics in Zwolle, the Netherlands, he became Professor of Paediatric Orthopaedics in 2002 at the University Medical Centre in Utrecht, and soon after Professor of Orthopaedic Surgery and Chairman of the department of Orthopaedic Surgery. In 2007, he was appointed by the Board of Directors as Chairman of the Surgical Division, at he end of 2011 he gave up this responsibility to remain close to his core business as Head of the Department of Orthopaedic Surgery. Main fields of interest are etio-pathogenesis of idiopathic scoliosis, spinal trauma and oncology, orthopaedic imaging, orthopaedic infections and paediatric orthopaedics.

Prof. Stuart B Goodman MD, PhD, FRCSC, FACS, FBSE
Robert L. and Mary Ellenburg Professor of Surgery
Professor, Department of Orthopaedic Surgery and (by courtesy) Bioengineering
Stanford University Medical Center Outpatient Center
USA

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 370 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.

Session 4: Keynote Speech 1

APPLICATION OF iPS CELL TECHNOLOGIES TO CARTILAGE REGENERATION

Prof. Noriyuki Tsumaki
Professor of Cell Induction and Regulation Field
Dept. of Cell Growth and Differentiation
Center for iPS Cell Research and Application
Kyoto University
Japan

Articular cartilage covers the ends of bones and provides shock absorption and lubrication. Cartilage consists of chondrocytes embedded in an extracellular matrix. Articular cartilage is an avascular tissue, and has limited capacity for repair. The repair of cartilage injury with healthy hyaline cartilage continues to be a challenging clinical problem. There is a significant need to develop sources of chondrocytes that can be used for cell transplantation in regenerative medicine. We have been trying to generate chondrocytic cells using cell reprogramming technologies. One approach is to convert somatic cells, such as dermal fibroblasts or blood cells, into induced pluripotent stem cells (iPSCs), followed by inducing their differentiation into chondrocytes. The methods used to induce the differentiation of embryonic stem cells (ESCs) toward chondrocytes can be applied for the differentiation of iPSCs. However, there are still no methods available that can yield hyaline cartilage, rather than fibrocartilage, and that can minimize the risk of tumor formation when the cells are transplanted. In the present study, we generated a human iPSC lines that expresses EGFP when the cells have differentiated into chondrocytes, and have been using them to determine the optimal conditions for the chondrogenic differentiation of human iPSCs. Another approach is direct cell type conversion. We found that the transduction of dermal fibroblasts with two reprogramming factors (c-Myc and Klf4) and one chondrogenic factor (Sox9) results in the direct induction of chondrogenic cells without the need for them to go through the iPS cell state. This approach may also provide a candidate cell source for chondrocytes that can be used for cartilage regeneration.

Brief CV
Prof. Noriyuki Tsumaki received his M.D. from Osaka University Medical School (1989), and obtained his Ph.D in Osaka University with degree of Dr. of Medical Science in 1996. He then became a resident in Orthopaedics Surgery in Osaka University and affiliated hospitals (1989-1992). He was also a postgraduate student in Osaka University Graduate School of Medicine (1992-1996). From 1996 to 1997, he was in National Institute of Dental Research, National Institutes of Health in USA as a visiting fellow. Prof. Noriyuki Tsumaki became an Assistant Professor in Osaka University Medical School (1998-1999), and then Assistant Professor in Osaka University Graduate School of Medicine (2002-2011). In 1999-2002, he was also appointed as a medical staff in Orthepaedics Surgery, Osaka Police Hospital. Prof. Noriyuki Tsumaki is currently a Professor in Center for iPS Cell Research and Application, Kyoto University.

Session 5: New Technologies and Advancements

3D PRINTING TECHNOLOGY AND APPLICATIONS IN ORTHOPAEDICS

Prof. Jos Malda
Department of Orthopaedics
Department of Equine Sciences
University of Utrecht
Netherlands

The global market for additive manufacturing (that includes three-dimensional (3D) printing) in medical applications is already estimated to exceed $300 million, and expected to be over one billion USD in 2020. Indeed, the introduction of 3D printing in the field of orthopaedics has enabled the generation of patient-specific saw and drill guides, as well as custom-designed plastic and metal implants. It may, however, also provide opportunities for the generation of cell-containing tissue constructs.
For the long term, the ideal solution to joint injury is to successfully regenerate rather than replace the damaged cartilage with synthetic implants. Recent advances in key technologies are now bringing this "holy grail" within reach; regenerative approaches, based on cell therapy, are already clinically available albeit predominantly for focal cartilage defects. The application of 3D bio-printing does enable the generation of custom regenerative cartilage implants that address both the shape and organization of the native tissue by providing control over the layer-by-layer placement of living cells.
The objective of bioprinting is to assemble living cells or biological materials for the preparation of tissue constructs for e.g. drug and toxicity screening or transplantation. Hydrogels are particularly attractive as "bioinks" for biofabrication as they recapitulate several features of the natural extracellular matrix and allow cell encapsulation in a highly hydrated mechanically supportive three-dimensional environment. Additionally, they allow for efficient and homogeneous cell seeding, can provide biologically-relevant chemical and physical signals and can be formed in various shapes and biomechanical characteristics. Nevertheless, there exists a significant challenge in biofabrication: the optimization of – intrinsically weak – hydrogels to address the physico-chemical demands of the biofabrication process and the right conditions for cell survival on the one hand, and to address the harsh in vivo mechanical environment on the other.
We have developed novel hydrogel-based bioink formulations that allow for the construction of intricate 3D structures, whilst providing the cells with a biologically suitable environment. For example, we modified the rheological behaviour of gelatin gels (GelMA) by the addition of the high-molecular weight polysaccharide gellan gum at tailored salt concentrations, thereby inducing pseudo-plastic behaviour and yield stress in addition to the thermosensitivity inherent to gelatine. Cartilage formation was further optimized towards chondrogenic differentiation and tissue production by the addition of hyaluronic acid.
Biomechanical performance of the hydrogel constructs was addressed by simultaneous, layer-by-layer deposition of multiple materials. These highly organized reinforcing networks include printed hydrogel or thermoplastic strands, and melt electrospun thermoplastic polymer (poly(ε-caprolactone) (PCL)) to provide inherent strength to bioprinted hydrogel constructs.

Brief CV
Jos Malda is an Associate Professor at the Department of Orthopaedics, University Medical Center Utrecht and the Department of Equine Sciences, University of Utrecht. He is Head of the Utrecht Biofabrication Facility and Deputy Head of Orthopaedic Research. In addition, he co-chairs the upcoming international conference Biofabrication 2015 in the Netherlands.
He received his MSc degree in Bioprocess Engineering from Wageningen University in 1999 He completed his PhD on Cartilage Tissue Engineering in 2003 (University of Twente and IsoTis bv). He subsequently accepted a research fellowship at the Institute of Health and Biomedical Innovation, (Queensland University of Technology, Brisbane, Australia), where he still holds an adjunct position. Dr Malda's research group focuses on biofabrication and biomaterials design, in particular for the regeneration of (osteo)chondral defects. He develops new biofabrication strategies and "bioinks" for 3D-printing. These hydrogel-based "inks" are both designed to drive specific differentiation of the embedded and/or endogenous cells, as well as to allow fabrication with high shape fidelity in order to generate constructs that are a blueprint of the real tissue. In addition, approaches towards the translation of the constructs in veterinary (equine) and human clinics are pursued, including its use as an in vitro platform for testing.

MIR-204 SUPPRESSES SKELETAL NEOPLASIA THROUGH INHIBITION OF RUNX2-ACTIVATED AKT SIGNALING IN MESENCHYMAL STEM CELLS

Prof. Di Chen, MD, PhD
Professor and Chairman
Department of Biochemistry
The John W. and Helen Watzek Professor of Biochemistry
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USA

Bone marrow stromal cells (BMSCs) possess the abilities to self-renew and to differentiate into different lineages such as osteoblasts, chondrocytes and adipocytes and therefore are often regarded as mesenchymal stem cells (MSCs). As their therapeutic potential is widely recognized, fundamental questions for MSCs such as their identification, isolation, expansion and differentiation remain largely elusive and even controversial. Here we demonstrated that both proliferation and differentiation of BM-resident MSCs are accelerated by conditional inhibition of miR-204 and resultant enhanced expression of Runx2, a master transcription factor in osteogenesis. These dysregulated MSCs formed tumors made up of bone and cartilage and lining the knee joints, a condition reminiscent of synovial osteochondromatosis and these growing tumors caused severe damage to the joints, i.e. an osteoarthritis-like phenotype, at later stages. Both freshly isolated and in vitro cultured BMSCs retain higher frequencies of CD45-Sca-1+CD29+CD105+ cells, which are demonstrated to have MSC properties. Of note, these MSCs with miR-204 inhibition and the joint tumors had significantly higher expression of Runx2 protein and upregulated Akt pathway, underlying the mechanisms for increased MSC differentiation and proliferation. Further, we found that elevated Runx2 expression activated mRNA transcription of nerve growth factor (NGF) and stem cell factor (SCF), two ligands respectively for NGFR and c-Kit, the receptor tyrosine kinases, and thus stimulated the Akt signaling to suppress the expression of CDK inhibitors such as p16, p21 and p57, releasing their block on cell proliferation. Our findings identify miR-204 as a crucial regulator of Runx2, which modulates MSC proliferation through Akt pathway and also control their osteoblast differentiation.

Brief CV
Prof. Chen Di is currently a Professor and Chairman in Department of Biochemistry and John W. and Helen Watzek Professor in Biochemistry in Rush University Medical Center (2011-present). Prof. Chen received his M.D degree in Tianjin Medical University, China. In 1992, he received his Ph.D degree from the University of Louisville in the field of pharmacology. After post-doctoral training at the University of Texas Health Science Center at San Antonio, he was appointed as a research scientist (1995-1998) and then senior scientist (1998-2000) in OsteoScreen Inc, San Antonio. He then became a Research Assistant Professor in the University of Texas Health Science Center at San Antonio (2000-2003), and then Assistant Professor, Associated Professor, Professor with tenure, and Dean's Professor in the Department of Orthopaedics, Center for Musculoskeletal Research, University of Rochester School of Medicine, Rochester, NY. He has published 151 peer-reviewed SCI articles, with cumulative impact factor of 794 and H-index of 44. He is former president of International Chinese Musculoskeletal Research Society (2005-2007), and is currently served as members in American Society for Bone and Mineral Research, International Bone and Mineral Society, Orthopaedic Research Society, New York Academy of Science, Osteoarthritis Research Society International, American Society for Biochemistry and Molecular Biology, American College of Rheumatology, Working Group on Outreach to Bone Scientists in China, American Association for Cancer Research, Association of Osteobiology. Prof. Chen is the member of editorial board in many journals, Journal of Orthopaedic Surgery and Research, Calcified Tissue International, Journal of Bone and Mineral Research, Journal of Cellular Biochemistry, Arthritis & Rheumatology, Osteoarthritis and Cartilage, Bone Research, Journal of Orthopaedic Translation, Scientific Reports.

TOWARDS INTRAOPERATIVE CELL REPAIR

Prof. 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, which 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. With this in mind, the AO Research Institute Davos has been developing a novel three dimensional cell culture model that allows for culture of the freshly isolated mononuclear fraction from whole bone marrow. In addition, as there are fewer mesenchymal stem cells found within the freshly isolated mononuclear

fraction, compared to monolayer expanded cells, emphasis must be changed to take into account the lower cell numbers being applied. However, due to in vitro aging effects caused during monolayer expansion, a smaller number of freshly isolated cells may be functionally more effective than a larger number of monolayer expanded cells. Furthermore, the unique mechanical environment experienced within the musculoskeletal system offers further opportunities to regulate cell fate decisions using biomechanics.
There has also been a recent shift in paradigm from differentiation of cells into mature functional cells e.g. osteoblasts, to one where the secretome of the cells is used to direct a targeted healing response. This also offers new therapeutic avenues that may lead to fewer cells being need for implantation.
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
Prof. Geoff Richards is currently the Director of AO Research Institute Davos, AO Foundation. He is also the founder, web editor, webmaster and elected as the Editor-in-Chief for one of the first online open access journals in the world: "e Cells & Materials" (www.ecmjournal.org), with the scope to provide an interdisciplinary forum for publication of preclinical research in the musculoskeletal field (Impact factors 4.887, 2013). Prof. Geoff Richards received his Ph.D in UWA in the field of Cell Adhesion to implant surfaces (1997). He is currently served as Executive Committee member in European Orthopaedic Research Society, Member at Large TERMIS-Europe & European representative of the world council Tissue Engineering and Regenerative Medicine International Society (TERMIS), Associate Editor of the Journal of Orthopaedic Translation, and Scientific Member of International Combined Orthopaedic Research Societies board. He used to be the Honorary Senior Research Fellow in University of Glasgow (2004-2012), President of Swiss Society for Biomaterials (2007-2009), Visiting Professor in Tokyo Medical & Dental University (2006-2009), and Chair of the Infection Committee, ORS (2011-2013). He has published over 100 peer reviewed papers, and more than 300 abstracts of presentations & posters (since 2000, over 100 invited lectures, including keynotes, faculty, award lectures, symposium main lecturer etc). 10 book chapters, 4 patents.

Session 6: Keynote Speech 2

REGENERATIVE APPLICATIONS OF ADULT STEM CELLS: REPAIR, RENOVATE, AND RE-CREATE

Prof. Rocky Tuan
Distinguished Professor
Director, Center for Cellular and Molecular Engineering
Professor and Executive Vice Chairman for Orthopaedic Research
Arthur J. Rooney, Sr. Chair Professor in Sports Medicine
Department of Orthopaedic Surgery
Director, Center for Military Medicine Research
Associate Director, McGowan Institute for Regenerative Medicine
University of Pittsburgh School of Medicine
Professor, Departments of Bioengineering & Mechanical Engineering and Materials Science
University of Pittsburgh, Pittsburgh, Pennsylvania

Mesenchymal stem cells (MSCs), harvested from adult tissues such as bone marrow and adipose, have multi-lineage differentiation potential, including chondrogenesis, osteogenesis, and adipogenesis, and have been considered a promising candidate cell type for tissue repair and regeneration. The utility of MSCs is enhanced by the relative ease of their derivation from autologous tissue sources, such as bone marrow and adipose. We have been investigating MSC-based regenerative applications for tissues with intrinsically low reparative capacity, such as articular cartilage, which presents a significant clinical challenge to effective treatment of degenerative joint diseases, such as osteoarthritis, the main cause of physical disability. Tissue engineering and regenerative medicine, combining cells, scaffolds, and biological signals, represent a potentially promising approach. A biocompatible biomaterial scaffold that ideally also enhances proliferation and differentiation of the seeded cells is critical to successful cell-based tissue engineering. We have shown that biomimetic scaffolds that simulate the structure of native extracellular matrix, e.g., the nanoscalar fibrous nature of collagen, are effective in MSC-based skeletal tissue engineering both in vitro and in vivo. Our recent work on the use of custom-designed, photo-crosslinked hydrogel scaffolds, which allow cell encapsulation during fabrication, demonstrates high fidelity reproduction of internal structure and excellent cell retention, viability, and differentiation. Using this fabrication protocol, we have also produced gene-activated scaffolds to provide inductive factors for enhanced cell differentiation. By applying a 3D printing approach and a custom-designed microbioreactor, we have constructed a microtissue analogue of the biphasic osteochondral junction, based entirely

on MSC-derived components, to model the pathogenesis of osteoarthritis, specifically by studying the effects of biological, hormonal, pharmacological, and mechanical perturbations. Adult stem cells, with their multi-differentiation potential and recently discovered trophic activities, when used in combination with biomimetic scaffolds, present a powerful platform for regenerative, therapeutic, and disease modeling applications in biomedicine. [Funding support: NIH, U.S. Department of Defense, and Commonwealth of Pennsylvania Department of Health]

Brief CV
Rocky S. Tuan, PhD, received his PhD in 1977 from the Rockefeller University in New York, and postdoctoral training at Harvard Medical School in Boston. 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. In 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 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. Dr. Tuan is currently Co-Director of the Armed Forces Institute of Regenerative Medicine, a U.S. Department of Defense funded, national, multi-institutional consortium focused on developing translational regenerative therapies for battlefield injuries. Dr. Tuan has published over 420 research papers, has lectured extensively, and is currently Editor of the developmental biology journal, BDRC: EMBRYO TODAY, and Founding Editor of STEM CELL RESEARCH AND THERAPY.

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

FROM DEVELOPMENT TO OSTEOARTHRITIS (OA) TREATMENT

Prof. Hongwei Ouyang
Center for Stem Cell and Tissue Engineering
Zhejiang University
PR China

Traumatic rupture and a group of diseases such as osteoarthritis (OA) often result in cartilage degeneration and defects in the knee. The developmental biology of growth plate is of key importance in understanding the molecular pathology of OA, and there is much evidence indicating that signaling pathways modulating endochondral ossification (EO) during growth plate development also affect the pathogenesis of OA. We learned from the developmental biology of growth plate and uncovered the roles of several important signals including Rho GTPases, EGFR and PTHrP in chondrocytes pathologic changes in vitro as well as in mice OA development. Furthermore, we also integrated biomaterials with bioactive peptide, chemical inhibitors, and metal ion that targeting these signals to facilitate articular cartilage repair and regeneration.
1) It was found that the activity of Rac1, one of Rho GTPases was aberrantly elevated in OA chondrocytes. The down-regulation of OCRL1, one of GTPase-activating proteins (GAPs) accounted for Rac1 activation in OA chondrocytes. Moreover, genetic or pharmaceutical modulation of OCRL1-Rac1 axis affected human chondrocytes hypertrophy and calcification in vitro and osteoarthritis development in vivo. 2) Clinical evidence showed that the level of p-EGFR is elevated whist LC3 and ATG5 are down-regulated in OA cartilage. We demonstrated that gefitinib, a FDA-approved drug for non-small-cell lung cancer to inhibit p-EGFR can not only block cartilage matrix degradation but also promote collagen II synthesis in osteoarthritic joints through modulation of the EGFR-autophagy axis. 3) Li+ ions enhanced the proliferation and osteogenic differentiation of bone BMSCsthrough activation of the Wnt/β-catenin signalling pathway, besides, Li+ ions protecting chondrocytes and cartilage tissues from the inflammatory OA environment through activation of autophagy. We further incorporated Li+ ions into bioactive MBG scaffolds as a viable strategy for fabricating bi-lineageconducive scaffolds that enhanceregeneration of osteochondral defects.
Our studies collectively demonstrate that modulation of important signals in growth plate development in articular cartilage pathologic changes may function as an effective method to develop potential therapeutics for OA and improve cartilage repair efficiency

Brief CV
Prof. Hongwei Ouyang is currently the Professor of Center for Stem Cell and Tissue Engineering, Zhejiang University. From 2011, he has been honored as Qiushi Distinguished Professor of Zhejiang University; National Science Fund for Distinguished Young Scholars of China and National Top-1000 Talent Scholar of China. Prof. Hongwei Ouyang has published many papers with high impact factors (Ann Rheum Dis, Stem Cells Dev, Biomaterial, et al.). His main research interests are arthritis and cartilage regeneration; tendon regeneration and musculoskeletal regenerative medicine.

TECHNOVOLUTION OF CARTILAGE REPAIR: ONE STAGE TECHNOLOGY USING AUTOLOGOUS AND ALLOGENEIC CELLS

Prof. Daniel Saris
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UMC Utrecht University
Netherlands

Background
In the last two decades, the evolution in treatment modalities or "technovolution" in cartilage repair has underlined the progress in regenerative medicine. Where once debridement and microfracture were the only options, we can now provide our highly active and demanding patients with the latest generation of autologous chondrocyte implantation (ACI). However, the high costs of ACI along with the burden of having to undergo two separate procedures have continued to stimulate the technovolution towards single-stage procedures. In recent years, cocultures of two cell types communicating with each other have emerged to achieve this goal. The primary rationale behind this method is that the need for cellular expansion of chondrocytes becomes redundant as these can be replaced by allogeneic mesenchymal stromal cells (MSCs). Indeed, when MSCs are mixed with chondrocytes, reproducible chondrogenesis has been shown.

Cellular communication
Although the coculture approach has been studied extensively, the mechanisms that lead to cartilage regeneration remain difficult to apprehend. This has been highlighted by a recent concise review we have performed that found different papers concluded the differentiation of MSCs is responsible for chondrogenesis in cocultures while there is little evidence to support this hypothesis.2 Meanwhile, more recent studies found MSCs to stimulate chondrocyte proliferation and cartilage production while slowly disappearing from the culture (chondroinduction).4, 5 In a recent laboratory study, using the coculture model in different environments, we have found that direct cell-cell contact as allowed in fibrin scaffolds and cell pellets, to show the highest glycosaminoglycan (GAG) production when cells are in close contact. Indeed, when cultured in alginate beads or in indirect cocultures with separation of the cell types by a membrane insert or MSCs supplemented by chondrogeneic medium could not mimic this effect on cartilage regeneration. Dye transfer tests confirmed that it is most likely that cellular communication works via direct cell-cell contact through gap junctions. A preclinical model that we explored earlier, already found autologous chondrocytes with their pericellular matrix (chondrons) and allogeneic MSCs mixed at a 10:90 ratio capable of regenerating cartilage in both a small and large animal model.6 This has supported he initiation of a first in man study that is currently ongoing (NCT02037204). The rationale behind the use of allogeneic MSCs is that preclinical experience has shown safety and an off the shelve approach has become feasible without having to subject a patient to a bone marrow harvest.

Clinical experience
Current methods to isolate chondrocytes from articular cartilage are based on overnight isolation by collagenase, which is not suitable for a one-stage procedure. However, recent efforts in our lab showed that we can successfully isolate viable chondrons within a timeframe of 40 minutes using the Rapid Digestion Protocol (RDP), which has previously been described by others during 5 hours7. Chondrons are the functional units of healthy articular cartilage consisting of chondrocytes with their surrounding matrix8. Allogeneic MSCs that are used are expanded from bone marrow of human volunteers in the presence of platelet lysate. The MSCs are prepared in a GMP-approved Cell Therapy Facility (CTF) of the UMC Utrecht and are available as an "off the shelf" Advanced Therapy Medicinal Product (ATMP). The current first in man study of Instant MSC Product accompanying Autologous Chondron Transfer (IMPACT) uses this cell combination at a 10:90 ratio in a fibrin glue carrier to treat patients with focal cartilage defects on the femoral condyles and trochlea. Recently the inclusion of all 35 patients has been completed. To date, no serious adverse events have been encountered as monitored by an independent rheumatologist and data safety monitoring board. The first patients that have completed one-year follow-up (n = 4) all have shown significant improvement in clinical outcome scores as well as in MRI evaluated defect fill. Second-look arthroscopy in these patients showed complete defect filling and histology indicated good integration with the subchondral bone and positive proteoglycan staining.

Conclusion
Preliminary findings show that the use of allogeneic MSCs are safe and provides cartilage regeneration and improved clinical outcome by communication with chondrons. These findings are promising as a new road has been opened in terms of safety of single-stage cartilage repair using allogeneic stem cells.

Brief CV
Daniël Saris (Past President of ICRS) is a specialized knee surgeon. He graduated from University of Amsterdam Medical School in 1992. During orthopedic residency dr. Saris did a fellowship at the Mayo Clinic in Rochester MN USA under Prof. Shawn O'Driscoll of the Cartilage and Connective Tissue Research Laboratory and Prof. Kai-Nan An of the orthopaedic biomechanics institute.
Dr. Saris completed a PhD thesis in 2002 at the University of Utrecht in the Netherlands that was titled "Joint Homeostasis in Tissue Engineering for Cartilage Repair". It first introduced the now generally accepted concept of joint homeostasis.
In 2000 Daniël joined as staff member in the department of Orthopaedics at the UMC Utrecht. In March of 2010 dr Saris was appointed as Professor of Reconstructive Medicine at the University of Twente. Prof dr Saris is director of the Biological Joint Reconstruction research program and head of the orthopaedic residency program at the University of Utrecht. As lead investigator he helped establish the first two registered cartilage cell therapy products in Europe and is currently actively pursuing one stage cell based repair in the IMPACT trial and accelerated soft tissue healing for orthopedic sports medicine.

THE CROSSTALK OF THE TOWN! – MACROPHAGES, OSTEOPROGENITORS AND BONE FORMATION

Prof. Stuart B Goodman MD, PhD, FRCSC, FACS, FBSE
Robert L. and Mary Ellenburg Professor of Surgery
Professor, Department of Orthopaedic Surgery and (by courtesy) Bioengineering
Stanford University Medical Center Outpatient Center
USA

Inflammation is generally present in many diseases that involve bone including fractures, bone infections, arthritis, wear particle-induced periprosthetic osteolysis, osteonecrosis and others. Furthermore, increased bone deposition is desirable in spine fusion, joint arthrodesis, and fracture nonunion, clinical scenarios in which inflammation is often prominent. Persisting, dysregulated inflammation is deleterious to bone by increasing bone destruction and diminishing bone formation. However, little is known about the interactions between inflammatory leukocytes, and cells of the mesenchymal stem cell/osteoblast lineage. This is surprising, given that inflammation is recognized to be the first stage of bone healing. Thus, interactions between cells of the monocyte/macrophage lineage, and those of the mesenchymal stem cell (MSC)/osteoblast lineage are crucial to bone health and maintenance. Understanding and modulating the crosstalk between inflammatory cells and osteoprogenitors may provide opportunities for optimizing bone physiology, and suggest important strategies for enhancing tissue engineering of bone.
Our laboratory has studied the effects of monocyte/macrophages on osteoprogenitors using two experimental approaches: 1) the effects of supernatants from cultures of macrophages on subsequent independent cultures of osteoprogenitors and 2) the effects of simultaneous co-cultures of macrophages and osteoprogenitors. The macrophages used in these studies reflect undifferentiated cells (M0), or macrophages polarized into an M1 pro-inflammatory, versus an M2 anti-inflammatory pro-tissue healing state. The bone progenitor cells used in these studies are the murine MC3T3 osteoprogenitor cell line. The culture media used include osteogenic media, versus combined osteogenic and macrophage media.
Our results show that the supernatants from M1 macrophages expressed the highest levels of TNF alpha (TNFa) and Interleukin-1 receptor antagonist (IL-1ra) at 24-48 hours, compared to M0 or M2 macrophages. Furthermore, conditioned media from M1 macrophage cultures produced the greatest bone formation (using Von Kossa staining) by MC3T3 cells after 28 days of culture. Co-cultures of M0, M1 or M2 macrophages with MC3T3 cells in osteogenic or mixed media produced more bone than cultures of MC3T3 cells alone, using Alizarin Red staining. Examining the levels of bone associated proteins and transcription factors at the protein and mRNA levels showed increased alkaline phosphatase protein levels and increased osteocalcin and osteopontin mRNA levels at 2 weeks in the co-cultures containing M1 macrophages in osteogenic media. Interestingly, in the mixed media cultures, the mRNA values for osteocalcin and osteopontin were highest in the M2 co-cultures.
It would appear that in the short term, early inflammation enhances bone formation. Furthermore, the culture conditions have a definite effect on protein and mRNA expression of osteoprogenitors. Future work will examine the mechanisms by which acute and chronic inflammation alter bone formation. This research is directly translational to scenarios that are highly relevant to clinical practice.

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 370 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.

OSTEOARTHRITIS OF THE KNEE- WHAT HAVE WE LEARNT?

Prof. Peter KY Chiu
Li Shu Fan Medical Foundation Professor (Orthopaedic Surgery)
Chief, Division of Joint Replacement Surgery
Department of Orthopaedics and Traumatology
The University of Hong Kong

The joint damage in osteoarthritis (OA) of the knee is caused by systemic factors (age, gender, ethnicity, hormonal status, bone density, nutritional and metabolic) that predispose to the disease, and local mechanical factors (obesity, joint injury, joint deformity, occupational, sports, muscle weakness) that dictate its distribution and severity.

Is OA knee only a problem of the articular cartilage? Our group began to study the role of subchondral bone in the development of OA several years ago. We studied subchondral bone disturbances using spontaneously occurring OA animal model. In Dunkin Hartley (DH) strain guinea pig, subchondral bone was studied with 3-D micro-CT analysis, histology and immunohistochemistry at 1, 2 and 3 months of age. Cartilage degeneration was monitored by histological examination. Microscopic cartilage degeneration was not found, but subchondral bone sclerosis with trabecular ultrastructure turnover was characterized in DH guinea pigs at first 3 months. Subchondral bone ultrastructure change occurred at early stage of OA ahead of microscopic cartilage degeneration. (Wang et al. Osteoarthritis Cartilage 2013).

Is OA knee only a problem of the joint or is it part of a systemic disease? Hypertension and type 2 diabetes mellitus (T2DM) are common comorbidities in elderly patients with knee OA. Approximately 55% of knee OA patients over 65 years old have hypertension and 13% are T2DM (Singh et al. Am J Manag Care 2002). Our group looked at the subchondral bone damages of OA knee osteoarthritis (OA) patients. In the presence of hypertension and T2DM, significant bone loss was observed at the subchondral plate. After adjusting for the age, gender and BMI, hypertension or T2DM was included in a regression model to explain in part the decreased BMD ($r2 = 0.551$, $P = 0.004$) and increased porosity ($r2 = 0.545$, $P = 0.003$) at the subchondral plate in knee OA.

Is OA knee just a wear and tear phenomenon of the cartilage or is it an inflammatory disease? Our group is looking into the roles of inflammatory mediators in knee OA. The first one is Endothelin-1 (ET-1). ET-1 can stimulate the osteoblast-mediated bone formation in both physiological (postnatal growth of trabecular bone) and pathological conditions (bone metastasis of prostate or breast cancer). It contributes to tissue fibrosis in skin, liver, lung, kidney heart and etc., as a consequence of inflammatory or metabolic disorders. Subchondral bone sclerosis shared the similarity with tissue fibrosis in the overproduction of collagen type I. ET-1 was able to stimulate the production of MMP-1 and 13 by articular chondrocytes and synoviocytes, by which it might trigger the enzymatic degradation of articular cartilage in OA. We are working hard to find out the exact role of ET-1 in the subchondral bone sclerosis of OA. The second mediator is Fatty Acid-Binding Protein 4 (FABP4), a novel pro-inflammatory adipokine. We harvested specimens from 39 patients undergone total knee arthroplasty for OA and 26 patients undergone knee arthroscopy (non-OA controls). The FABP4 concentration in synovial fluid (SF), plasma, and medium of explant cultures of infrapatellar fat pad (IFP) & subcutaneous adipose tissue (SAT) was determined using ELISA. FABP4 levels were 9x higher in SF and 3x higher in plasma in OA patients compared to control subjects. In OA patients, FABP4 level was significantly higher in IFP than SAT; and in SF than plasma. Wild type and FABP4 knockout mice were sacrificed at 24 weeks to study the knee cartilage histology. The cartilage in wild type mice showed zonal disorganization and superficial layer fibrillation, while the knockout mice showed no such changes. These suggest FABP4 could be a novel biomarker and potential therapeutic target in managing OA.

Brief CV

CHIU Kwong Yuen Peter is the Li Shu Fan Medical Foundation Professor in Orthopaedic Surgery, The University of Hong Kong. He is Chief of Division of Joint Replacement Surgery, Department of Orthopaedics and Traumatology, Queen Mary Hospital, Pokfulam, Hong Kong. He graduated from the Faculty of Medicine, The University of Hong Kong in 1987. He worked in Department of Orthopaedics and Traumatology, Queen Mary Hospital as a medical officer from 1988 to 1991. He became lecturer in 1991, senior lecturer in 1996, associate professor in 1997 and clinical professor in 2006. Professor Chiu has been invited to lecture in different countries for more than 100 times, and has published more than 180 book chapters and peer-reviewed articles. Apart from clinical management of different arthritic conditions and joint replacement surgery, he also conducts basic research in osteoarthritis. He is very active in educating surgeons in the arts and science of joint replacement surgery. More than 1,300 Chinese surgeons have attended the courses that he organizes at Queen Mary Hospital since 2001. Professor Chiu has been office bearers of many professional bodies, such as Hong Kong Orthopaedic Association, Hong Kong College of Orthopaedic Surgeons and Asia Pacific Orthopaedic Associations. He was elected to the International Hip Society in 2008. He was the founding chapter president of Adult Joint Reconstruction Chapter of Hong Kong Orthopaedic Association in 2011-2. He is the president-elect of the Hong Kong College of Orthopaedic Surgeons in 2013-14.

Dr. Lui Che Woo Distinguished Professor Public Lecture

NEW ERA OF MEDICINE WITH iPS CELLS

Prof. Shinya Yamanaka, MD, PhD
Nobel Laureate in Physiology or Medicine 2012
Shaw Laureate in Life Science and Medicine 2008
Director of the Center for iPS cell Research and Application
Kyoto University
Japan

Induced pluripotent stem cells (iPSCs) were originally generated from mouse and human skin fibroblasts by introducing four specific transcription factor genes. Because iPSCs have the ability to proliferate almost indefinitely and differentiate into multiple lineages, they are thought to have great potential for medical and pharmaceutical applications. Another attractive feature of iPSCs is that they can be generated from any individual including patients. These iPSCs and the subsequently differentiated target cells/tissues could provide unprecedented opportunities in regenerative medicine, disease modelling, drug screening, and personalized medicine.

We are aiming to standardize iPSC technology for the preparation of clinical grade iPSCs by providing clear guidelines for cell sources and induction factors, along with reliable methods for quality control. Many improvements have already been achieved in iPSC production with regards to both safety and efficacy.

This year, the world's first clinical study using iPSCs was initiated to transplant iPSC-derived RPE (retinal pigment epithelium) sheets for treatment of age-related macular degeneration. In addition, iPSC studies have recently shown major progress in other conditions, including corneal diseases, blood diseases and Parkinson's disease, suggesting more iPSC-based regenerative medicine in the near future. From a broader perspective, we are proceeding with an iPSC stock project in which iPSC clones are being established from donors with a homologous HLA (human leukocyte antigen) haplotype, which is associated with a decreased immune response, in order to provide quality-assured iPSCs for future cell transplantation.

Brief CV
Shinya Yamanaka received his M.D. from Kobe University in 1987 and a Ph.D. from Osaka City University in 1993. From 1987 to 1989 he was a resident at the National Osaka Hospital. He spent the period from 1993 to 1996 as a postdoctoral fellow at the Gladstone Institute of Cardiovascular Disease, San Francisco. He returned to Osaka City University Medical School to take an assistant professor position in 1996, and was appointed as an associate professor at Nara Institute of Science and Technology in 1999, where he became a full professor in 2003. He moved on to take up his current position as a professor in Kyoto University in 2004. His research team announced the successful generation of mouse iPS cells in 2006 and of human iPS cells in 2007. With the breakthrough technology, he was appointed as a senior investigator at Gladstone in 2007. Since 2008, he serves as the director of the Center for iPS cell Research and Application (CiRA), Kyoto University.

Owing to his prominent deeds and discoveries, he has received many awards including 2008 The Shaw Prize in Life Science and Medicine (Hong Kong), 2009 Albert Lasker Basic Medical Research Award (U.S.), 100th Imperial Prize and Japan Academy Prize (Japan) in 2010, 26th Annual Kyoto Prize in Advanced Technology in 2010, 2011 Wolf Prize in Medicine (Israel), order of Cultural Merit in 2012 (Japan) and the Nobel Prize in Physiology or Medicine 2012. He was also selected as a foreign associate of the National Academy of Sciences (U.S.) in 2011.

Session 8: Muscle Highlights Symposium

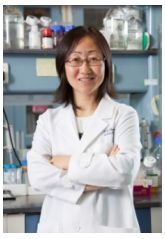
MOLECULAR REGULATION OF STEM CELL QUIESCENCE

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

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

Brief CV
Prof. Tom Cheung obtained his bachelor in University of Colorado, USA with the major of Biochemistry and Minor in Computer Science in 2001, and received his Ph.D degree in the major of Biochemistry in 2006 in University of Colorado, USA. After post-doctoral training in Stanford University School of Medicine (2006-2011), he then became a Research Associate in Stanford University School of Medicine (2011-2013). Prof. Tom Cheung is currently an Assistant Professor in the Division of Life Science, The Hong Kong University of Science and Technology. His main research interests are Stem cell biology; Stem cell quiescence; Post-transcriptional Regulation; Biology of Ageing. He also owned a provisional US patent of Activation of Quiescent Stem Cells (61/768,161). Prof. Tom Cheung has published many papers with high impact factors (Nature, Stem Cells, PNAS, JBC, Nature Review Molecular Cell Biology, Cell Stem Cell, Cell Reports, et al.)

FUNCTIONAL CHARACTERIZATION OF MALAT1 IN SKELETAL MYOGENIC DIFFERENTIATION AND MUSCLE REGENERATION



Prof. Huating Wang
Department of Orthopaedics and Traumatology
The Chinese University of Hong Kong
Hong Kong, China

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. Here we also discuss our findings on the roles of lncRNA Malat1 in skeletal muscle cell and muscle regeneration.

Brief CV
Dr. Wang is currently an Assistant Professor at Li Ka Shing Institute of Health Sciences, Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong. She received her B.S degree from Nanjing University, China and PhD at the Ohio State University (OSU), USA. Since joining Dr. Denis Guttridge's lab as a Postdoctoral researcher at OSU in 2004, she has been working on dissecting gene 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.

THE ROLE OF STAT3 IN ADULT MUSCLE STEM CELLS

Prof. Zhenguo Wu
Division of Life Science
Hong Kong University of Science & Technology
Hong Kong, China

We previous showed that the JAK1/STAT1/STAT3 pathway inhibits myogenic differentiation in cell culture models. It remains unclear whether this pathway plays a role in adult muscle satellite cells (MuSC) in vivo. When STAT3 was conditionally deleted in MuSC, the adult MuSC was not affected during normal muscle development. Upon repeated muscle injuries, the number of the quiescent MuSC in the STAT3-null mice decreased and the regeneration was delayed, suggesting defective MuSC maintenance. Consistently, when we conditionally deleted STAT3 in the MuSC of the dystrophin-null mice, a mouse model for human Duchenne muscular dystrophy, the double knockout (dKO) mice had decreased number of MuSC, enhanced inflammation and fibrosis. Mechanistically, the loss of STAT3 in the dystrophin-null MuSC resulted in downregulation of several key myogenic genes including Pax7 and MyoD and upregulation of many pro-inflammatory and pro-fibrotic genes, which collectively contributed to the defective MuSC maintenance and aggravated inflammation and fibrosis.

Brief CV
Dr. Zhenguo Wu obtained his BSc from Nanjing University in China in 1986 and his PhD degree from the University of Western Ontario in Canada in 1995. He did his postdoctoral training in Dr. Michael Karin's lab in the University of California, San Diego from 1996-1999. He set up his own lab in the Hong Kong University of Science & Technology in 1999 as an assistant professor and was promoted to professor in 2010. His group is interested in studying molecules and signaling pathways involved in regulation of adult muscle stem cells, muscle differentiation, and muscle regeneration.

TARGETING THE PGC-1α SYSTEM TO REGULATE SKELETAL MUSCLE FUNCTION AND ASSOCIATED DISEASES

Prof. Jorge Ruas
Department of Physiology and Pharmacology
Karolinska Institutet
Assistant Professor at the Molecular & Cellular Exercise Physiology Group
Swedish Research Council
Sweden

Although the benefits of physical exercise for the prevention and treatment of depression are well documented, the mechanisms that mediate these effects remain largely unknown. It is also unclear which components of the exercise program confer the therapeutic effect (i.e. skeletal muscle conditioning, cardiovascular effects, or even psychosocial influences). Proteins of the PGC-1α family of transcriptional coactivators mediate many of the changes in skeletal muscle associated with exercise training. While some PGC-1α variants respond to endurance exercise and mediate changes in muscle oxidative metabolism, others regulate muscle mass maintenance. We have used these genetic tools to isolate muscle conditioning from other exercise components and have uncovered a mechanism by which skeletal muscle PGC-1α changes local kynurenine metabolism and protects from stress-induced depression. Activation of the PGC-1αPPARα/ δ pathway increases skeletal muscle expression of kynurenine aminotransferases, thus enhancing the conversion of kynurenine into kynurenic acid, a metabolite unable to cross the blood-brain barrier. Reducing plasma kynurenine protects the brain from stress-induced changes associated with depression and renders skeletal muscle-specific PGC-1α1 transgenic mice resistant to depression induced by chronic mild stress or direct kynurenine administration. This study suggests that targeting the PGC-1α-PPAR axis in skeletal muscle could offer a novel therapeutic strategy for the treatment of stress-induced depression.

Brief CV
Dr. Jorge Ruas received his Pharm.D. degree from the University of Lisbon, Portugal, after which he initiated pre-doctoral work at the Karolinska Institutet. During his doctoral studies he investigated how cellular oxygen levels can regulate gene expression, and in 2005 received his Ph.D. in Cell and Molecular Biology. In 2006 he moved to Boston to pursue postdoctoral studies at the Division of Metabolism and Chronic Disease at the Dana-Farber Cancer Institute and Harvard Medical School. During this period he focused on the study of transcriptional networks that control skeletal muscle physiology with focus on regulation of muscle mass and associated pathologies. Dr. Ruas started his laboratory at the Department of Physiology and Pharmacology at the Karolinska Institutet in July 2011. He is appointed assistant professor by the Swedish Research Council. Research at the Molecular & Cellular Exercise Physiology Group (www.ki.se/research/jorgeruas) is aimed at understanding the molecular mechanisms that mediate local and systemic adaptations to physical exercise, and to the translation of these lessons to therapies against muscle atrophy, diabetes, obesity and associated diseases.

THE LONG NONCODING RNA LINC-RAM REGULATES MUSCLE DIFFERENTIATION AND REGENERATION BY FACILITATING MYOD-BAF60C-BRG1 COMPLEX ASSEMBLY

Prof. Dahai Zhu
Institute of Basic Medical Science, Chinese Academy of Medical Sciences
School of Basic Medical Sciences, Peking Union Medical College
China

Regulation of cellular differentiation by long ncRNAs (lncRNAs) is an emerging topic of outstanding interest that promises to shed light on the complex relationship between coding and non-coding epigenome in cell fate determination and functional specialization. Previous studies have reported on the identification of lncRNAs that contribute to the regulation of development and differentiation of several cell types, including skeletal muscle. However, for most of them there are key mechanistic aspects that remain unexplored, including selective expression in specific cell types, definition of the upstream regulatory signals and downstream targets, as well as the evaluation of their ability to regulate in vivo process.

In this study, we report on the identification, functional and molecular characterization of a muscle-specific intergenic long ncRNA - linc-RAM (Linc-RNA Activator of Myogenesis) - that is selectively expressed in satellite cells and promotes skeletal muscle regeneration in vivo and differentiation of cultured myoblasts in vitro. Most notably, linc-RAM is necessary for MyoD-mediated reprogramming of fibroblasts into skeletal muscle cells, which for the first time provides a direct evidence for a role of the cell-type specific lncRNAs in establishing cell lineage.

We have identified two key components of the upstream signaling that promotes linc-RAM. One is the muscle-specific transcriptional activator MyoD, which directly activates linc-RAM transcription, via binding to upstream regulatory elements, and accounts for the muscle selective expression. The other is the bFGF-activated RAS-RAF-ERK pathway, which suggests an unprecedented link between cues from the regeneration environment and the regulation of the non-coding epigenome in muscle progenitors.

Next, we have determined the linc-RAM downstream targets and molecular mechanism by which linc-RAM acts as a coactivator of MyoD, using an integrated biological and bio-informatic approach. This analysis shows that linc-RAM binds MyoD and promotes the expression of MyoD target genes during myogenic differentiation, by directing the recruitment of the SWI/SNF complex. Specifically, linc-RAM appears to mediate interactions between pre-assembled MyoD/Baf60c complex and Brg1-based SWI/SNF complex on regulatory elements of muscle genes.

Taken together, our findings engender a keener appreciation of the profound functions of cell-type specific lncRNAs in establishing cell lineage and controlling terminal differentiation of myogenic progenitors, and expand our knowledge on the mechanism that links the coding and non-coding epigenome of muscle progenitors in response to environmental cues.

Brief CV

Prof. Zhu Dahai received his Ph.D degree in the Department of Genetics, North Carolina State University with the research field of molecular genetics in 1994. After post-doctoral training in the Howard Hughes Medical Institute, Duke University Medical Center, he then became the senior fellow in Laboratory of Reproductive and Developmental Toxicology (1995-1998), and then Research Assistant Professor in NCSU (1998-1999). He is currently the Professor of Peking Union Medical College Beijing (in National Laboratory of Medical Molecular Biology, Department of Biochemistry and Molecular Biology and Institute of Basic Medical Science), and also Professor in the Molecular and Cellular Developmental Biology Laboratory of Harbin Institute of Technology. Prof. Zhu Dahai also obtained the Award of NIH intramural Research and training grant (1995-1998), Fellow Award for Research Excellence of NIH (1997), and NIH Merit Award (1997). His main research interests are Muscle stem Cell and Muscle Regeneration and Muscle function as an endocrine organ during disease (type II diabetes) development. His major publications involved the following journals, PNAS, Development, Cancer Research, Nucleic Acids Res., Cell Research, Oncogene, Cell Death and Disease, BMC Genomics, Genetics, J. Biol. Chem., Cellular and Molecular Life Sciences, Molecular Pharmacology, Cellular Signaling, Free Radical Biology and Medicine.

Session 9: Regulatory Factors in Development and Diseases

CALCIUM PHOSPHATE-BEARING MATRICES INDUCE OSTEOGENIC DIFFERENTIATION OF MESENCHYMAL STEM CELLS THROUGH ADENOSINE SIGNALING

Prof. Oscar Lee
Deputy Superintendent
Taipei City Hospital
China

Synthetic matrices emulating the physicochemical properties of tissue-specific ECMs are being developed at a rapid pace to regulate stem cell fate. Biomaterials containing calcium phosphate (CaP) moieties have been shown to support osteogenic differentiation of stem and progenitor cells and bone tissue formation. By using a mineralized synthetic matrix mimicking a CaP-rich bone microenvironment, we examine a molecular mechanism through which CaP minerals induce osteogenesis of human mesenchymal stem cells with an emphasis on phosphate metabolism. Our studies show that extracellular phosphate uptake through solute carrier family 20 (phosphate transporter), member 1 (SLC20a1) supports osteogenic differentiation of human mesenchymal stem cells via adenosine, an ATP metabolite, which acts as an autocrine/paracrine signaling molecule through A2b adenosine receptor. Perturbation of SLC20a1 abrogates osteogenic differentiation by decreasing intramitochondrial phosphate and ATP synthesis. Collectively, this study offers the demonstration of a previously unknown mechanism for the beneficial role of CaP biomaterials in bone repair and the role of phosphate ions in bone physiology and regeneration. These findings also begin to shed light on the role of ATP metabolism in bone homeostasis, which may be exploited to treat bone metabolic diseases.

Brief CV
Prof. Oscar Lee obtained his M.D. degree in National Yang-Ming University (1986-1993), and received his Ph.D degree in University College London (1999-2002). Prof. Oscar Lee is also an EMBA in National Chengchi University (2008). He is currently a Deputy Superintendent in Taipei City Hospital, Professor of Institute of Clinical Medicine and Director of Stem Cell Research Center of National Yang-Ming University, Professor of Department of Orthopaedics and Traumatology in Taipei Veterans General Hospital and Clinical Professor at School of Medicine of National Defense Medical Center. Prof. Oscar Lee is also a Joint Appointed Professor in Institute of Biophotonics and Institute of Biomedical Engineering of National Yang-Ming University. He is also the Honorary Senior Research Fellow in Institute of Orthopaedics and Musculo-skeletal Science of University College London, and Jointly Appointed Investigator in Institute of Cellular and System Medicine of National Health Research Institutes of Taiwan.

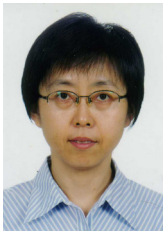
THE ROLE OF INFECTION AND DEVELOPMENT OF CHRONIC TENDON INJURIES AND FAILED HEALING

Prof. Christer Rolf
Division of Orthopaedics
Karolinska Institutet
Sweden

Introduction : Tendon ruptures are common causes of morbidity both in sports and leisure and pose a significant health burden on society. Histologic analyses show that most Achilles tendon and Rotator cuff ruptures have an underlying deteriorated collagen, often asymptomatic, prior to rupture. There are parallel evidences in other collagen structures to suggest that subclinical infections may cause “similar” collagen pathology in a range of cardiovascular diseases such as valve disease and chronic myocarditis. We speculate that some pathogens can trigger and control an active “non-healing” process via hampering collagen regeneration and increasing risk of chronic pain conditions and rupture. In this pilot study, we explored the role of infection in tendon injuries and failing to heal.
Materials and Methods: We collect intraoperative tissue samples under sterile conditions and serum from consecutive patients with surgically treated tendon rupture. Using polymerase chain reaction (PCR) technique we aim to identify the presence of 16s ribosomal RNA (16s rRNA) gene, the most common housekeeping genetic marker used to identify genus and species of bacteria.
Results and Discussion: We have set up a detection platform for human 16s rRNA gene in tendon tissue which will now be used for testing our clinical samples. Methods for characterization of microbes and elucidation of potential underlying injury mechanisms are under development.

Brief CV
Prof. Christer Rolf received his M.D. in the Umeå University in 1983, and then obtained his Full Medical License to practice, Board of Health in Sweden in 1986. He received his Ph.D in Orthopedics och Rehabilitation of Umeå University in 1987. From 1991 to 1993, Prof. Christer Rolf worked as Specialist Orthopedic Surgery in Karolinska University Hospital, and then Consultant Orthopedic Surgeon in Karolinska University Hospital (1993-1997). Prof. Christer Rolf used to be the Visiting Clinical Professor of Sports Medicine Department Orthopedics in Prince Of Wales Hospital, The Chinese University of Hong Kong (1997-2000). From 2000-2010, he was appointed as the Founding Clinical Chair in Sports Medicine in the University of Sheffield. Meantime, he was also the Foreign Adjunct Professor of Sports Medicine of Karolinska Institutet (2008-2014). Prof. Christer Rolf also served as the Chairman of FIMS International Federation of Sports Medicine Scientific and Education Committee (1998-2002) and European Federation of Sports Medicine Associations Scientific and Education Committee (2000-2010). He is currently the Consultant Orthopedic Surgeon in the Head Arthroscopy and Sport Injury Section in the Department of Orthopedics of Karolinska Universitetssjukhuset, and also the Clinical Head Karolinska University Hospital Multidisciplinary Day Case Centre, and the Professor of Sports Medicine in Clintec of Karolinska Institutet. He is also the honorary Visiting Professor in Department Orthopedics, Prince of Wales Hospital, Chinese University of Hong Kong (2013-present). In 2013, he became the Joint Coordinator and Principal Investigator (KI) with Prof KM Chan (CUHK) of an MOU and Joint Research Program in Musculoskeletal Regenerative Medicine between Karolinska Institutet and Chinese University of Hong Kong (2013-2018). Prof. Christer Rolf is 125 peer reviewed articles in international Journals, 23 books, 6 book chapters.

MODULATING STEM CELL GENES USING ENGINEERED TALE AND CAS9 TRANSCRIPTION FACTORS



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

The newly developed TALE and CRISPR/Cas9 transcription factors (TF) offered a powerful and precise approach for modulating gene expression. In this study, we systematically investigated the potential of these new tools in activating the stringently silenced pluripotency gene Oct4 (Pou5f1) in mouse and human somatic cells. First, with a number of TALEs and sgRNAs targeting various regions in the mouse and human Oct4 promoters, we found that the most efficient TALE-VP64s bound around −120 to −80 bp, while highly effective sgRNAs targeted −147 to −89 bp upstream of the transcription start sites (TSS) to induce high activity of luciferase reporters. In addition, we observed significant transcriptional synergy when multiple TFs were applied simultaneously. Although individual TFs exhibited marginal activity to up-regulate endogenous gene expression, optimized combinations of TALE-VP64s could enhance endogenous Oct4 transcription up to 30-fold in mouse NIH3T3 cells and 20-fold in human HEK293T cells. More importantly, the enhancement of OCT4 transcription ultimately generated OCT4 proteins. Furthermore, examination of different epigenetic modifiers showed that histone acetyltransferase p300 could enhance both TALE-VP64 and sgRNA/dCas9-VP64 induced transcription of endogenous OCT4. Taken together, our study suggested that engineered TALE-TF and dCas9-TF are useful tools for modulating gene expression in mammalian cells.

Brief CV
Dr. Bo Feng is currently an Assistant Professor in the School of Biomedical Sciences. Dr. Feng obtained her Ph.D. from National University of Singapore in 2016, and received her postdoc training in Genome Institute of Singapore, where she started stem cell research. By setting up a platform to study the cellular reprogramming, she identified Esrrb, Nr5a2 and PRDM14 as novel factors that promote the generation of iPSCs from mouse and human fibroblasts. Her works have been published in Nature Cell Biology, Cell Stem Cell and Nature, respectively. In Nov 2010, Dr Feng joined the School of Biomedical Sciences, CUHK, and her current research interest lies within the molecular mechanism that controls pluripotency and differentiation of stem cells.

CARDIAC TELOCYTES SYNERGIZED ADULT STEM CELL THERAPY FOR MYOCARDIAL INFARCTION

Prof. Dongqing Cai
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 Development and Regenerative Biology, Ji Nan University
China

Stem cell therapy has shed light to regenerate the Myocardial Infarction (MI). However, low survival rate of transplanted stem cells and very low terminal differentiation of transplanted stem cells limit therapeutic effects of stem cell to achieve functional and structural regeneration of MI. In addition the discrepancies and poor long term effect in clinical studies further suggest that we need to develop novel strategy to establish cell therapy for functional regeneration of infarct myocardium. Recently our lab reveals that a novel interstitial cell in myocardium, named as cardiac telocytes (CTs), play an important role in regeneration of myocardium. We found that cardiac telocyte network in myocardium was impaired during 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 finding further revealed that the therapeutic effects of CTs transplantation for MI were better than that of transplantation of bone marrow derived stem cells (MSCs) and endogenous cardiac stem cells (CSCs) respectively. In addition, CTs synergized with adult stem cell therapy for MI was able to mediate better therapy effects than CTs or adult stem cells alone. Our finding suggested that CTs might be considered as novel cell types for cell mediated therapy to regenerate MI used alone or tandem stem cells.

ACKNOWLEDGEMENTS
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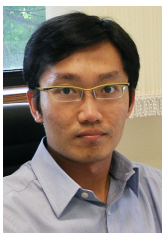
Brief CV
Professor Cai Dong-qing: Education: M.D. (Guangzhou Medical College; 1987), Ph.D. (The Chinese University of Hong Kong; 2000), Postdoctoral Associate (Weill Medical College of Cornell University [U.S.A.]; 2000-2003). Employment: Professor and Director, Key Laboratory for Regenerative Medicine, 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: 36 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)

YAP1 INHIBITS THE INITIATION OF FRACTURE HEALING BY CONTROLLING CHONDROCYTE DIFFERENTIATION



Prof. Kingston Mak
School of Biomedical Science
The Chinese University of Hong Kong
Hong Kong, China

Bone possesses intrinsic repair capacity for regeneration in response to fracture injury. Although many signaling activities in endochondral and intramembranous ossifications are recapitulated during the repairing process, osteogenesis is less efficient suggesting that additional signaling cues are employed for regeneration. Hippo signaling controls organ size and tissue regeneration in many organs, but its roles in bone repair remain elusive. Here, we demonstrate that Yap1, an effector of Hippo pathway, governs the initiation of fracture repair by regulating cartilage maturation. Yap1 activation in mice shows severely impaired cartilaginous callus formation after fracture injury, but skeletal development of these mice is relatively normal. Mechanistically, Yap1 regulates chondrocyte differentiation at multiple steps during bone repair. First, Yap1 is required for mesenchymal stem cell maintenance. It also promotes early chondrocyte proliferation but inhibits further chondrocyte maturation. Our results identify Hippo pathway as a specific regulator responsible for the initiation of endogenous bone repair and it could be a potential therapeutic target for treatment of fracture injury.

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.

Session 10: Cartilage Regeneration and Osteoarthritis

EPIGENETIC DYSFUNCTION IN OSTEOARTHRITIS

Prof. Nidhi Bhutani
Assistant Professor
Department of Orthopaedic Surgery
Stanford University School of Medicine
USA

Osteoarthritis (OA) is an age-associated multifactorial disease characterized by joint dysfunction and cartilage degeneration that affects as much as 40% of the elderly population. Clinical management of this widely prevalent disorder is largely limited to pain management or an eventual total joint replacement. Various genes render susceptibility to OA, however there is not a single consensus genetic basis for the disease. Insight into the early epigenetic changes leading to the altered gene expression in OA can provide a novel target axis for OA pathology. Our long-term goal is to identify the epigenetic mechanisms underlying OA pathogenesis that are largely unknown, and to evaluate their therapeutic potential with a focus on DNA methylation (5mC) and demethylation. Our recent studies have elucidated that DNA methylation patterns are greatly altered in cartilage from OA patients thereby regulating the aberrant gene expression. The goal now is to elucidate the precise target genes regulated by DNA hydroxymethylation in order to devise strategies to prevent or reverse these changes for a potential therapeutic benefit. In addition, mapping early epigenetic changes in OA can potentially lead to early biomarkers for OA. Early detection of OA has remained challenging and overcoming this difficulty can help devise early interventions for the disease before the widespread joint damage takes over. Our epigenetic studies therefore have the potential to provide novel insights into OA pathogenesis as well as therapeutic strategies.

Brief CV
Dr. Bhutani is an Assistant Professor in the Department of Orthopaedic Surgery at Stanford University and is affiliated with the Cancer Biology Program, the BioX program and the Children Health Research Institute at Stanford. Her research interests broadly encompass the molecular mechanisms regulating regeneration and repair of the musculoskeleton, with a focus on epigenetic regulation by DNA methylation and demethylation. Another main focus area for her laboratory is application of stem cell and reprogramming based approaches towards musculoskeletal tissue engineering and for understanding the molecular basis of developmental disorders.

TISSUE-SPECIFIC EXTRACELLULAR MATRIX CONTROLS THE FATE OF BONE MARROW-DERIVED MESENCHYMAL STEM CELL DIFFERENTIATION

Prof. Xiaodong Chen
The University of Texas Health Science Center at San Antonio
USA

Mesenchymal stem cells (MSCs) differentiate into many distinct cell lineages depending upon the local microenvironment that is mainly constituted by extracellular matrix (ECM) proteins and associated growth factors. However, it has been challenging to dissect the key components that direct the differentiation of MSCs because of the limited availability of in vitro models. Previously, we reported that in both mice and humans, cell-free ECM prepared from marrow stromal cells (BM-ECM) significantly promoted proliferation of MSCs and preserved their stem cell properties. Here, we wanted to investigate whether the BM-ECM was unique in its ability to preserve MSC properties by comparing to ECM made by fibroblasts derived from different tissues such as skin and fat. Cell-free bone marrow-, skin-, and adipose-derived ECMs were prepared by cultured bone marrow cells, skin fibroblasts and adipose stem cells (ASCs), respectively. Human marrow stromal cells (hMSCs,

passage 1 to 3) were cultured on the various ECMs, or tissue culture plastic (TCP) in expansion medium until confluence (~7 days), then maintained under conditions known to induce commitment to a specific cell lineage including osteoblasts and adipocytes. The lineage specific transcripts were measured by TaqMan PCR at day 7, 14, 21 and 28 post-confluence. We found that hMSCs maintained on BM-ECM expressed much higher levels of alkaline phosphatases (ALP), type I collagen and bone sialoprotein than cells maintained on adipose-ECM and skin-ECM after treatment with osteoblast differentiation medium. The cells maintained on skin-ECM did not respond to the treatment of osteoblast differentiation medium, showing no increased expression of these osteoblast markers compared to the untreated cells. In contrast, hMSCs maintained on adipose-derived ECM in both the expansion and adipose differentiation media expressed significantly higher levels of PPARγ2, and C/EBPα (a key regulator of adipogenesis) than the cells maintained on TCP, BM-ECM or skin-ECM. Interestingly, only hMSCs cultured on skin-ECM in the expansion medium expressed a considerable high level of keratin 6A (an early differentiation marker of epithelial cells). We conclude that the differentiation of hMSCs can be directed by exposure to tissue-specific ECM. The unique protein profiles for these ECMs will be further determined using proteomic analysis.

Brief CV

Dr. Xiao-Dong Chen has more than 20 years of experience in stem cell biology and regenerative medicine and is the author of over 45 peer-reviewed scientific publications and four patents. Dr. Chen has served as a Professor (tenured) at University of Texas Health Science Center at San Antonio and a VA Research Health Scientist at South Texas Veterans Health Care System. The major focus of his research is to study how extracellular matrix (ECM), as part of the microenvironment or niche, retains the ability of mesenchymal stem cells (MSCs) to both self-renew and respond appropriately to pro-differentiating signals. His group was the first to establish cell-free native ECM made by bone marrow stromal cells. This system have been using for growing large numbers of high-quality non-hematopoietic stem cells from different sources including bone marrow and umbilical cord blood for the purposes of either basic research or cell-based therapies. During the past seven years, as a principal investigator, he has doggedly pursued his research toward "bench to clinic" applications and established numbers of interdisciplinary research projects including: 1) Rejuvenation of aged MSCs; 2) Isolation and characterization of MSCs from human umbilical cord blood (UCB); 3) Evaluation of the efficacy of UCB-derived MSCs for heart repair after myocardial infarction (MI) and anti-diabetes; and 4) Development of an in vitro tissue-specific MSC niche.

In November 2010, Dr. Chen co-founded StemBioSys, Inc. (www.stembiosys.com) to license, develop and commercialize innovative stem cell technologies developed by his laboratory. The goal of the company is to develop proprietary, disruptive technology platforms that will fundamentally change the methods, efficiency and cost of isolating, growing and delivering robust stem cells for therapeutic applications.

IDENTIFICATION OF ALPHA 2 MACROGLOBULIN (A2M) AS A MASTER INHIBITOR TO ATTENUATE OSTEOARTHRITIS CARTILAGE DEGENERATION

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

Objective: To determine if supplemental intra-articular alpha-2 macroglobulin (A2M) has a chondroprotective effect in anterior cruciate ligament-transected (ACLT) knees.

Methods: A2M was identified as a potential therapeutic agent by comparing A2M concentrations in serum, synovial fluid (SF), and cartilage from normal and osteoarthritic (OA) patients by Western blotting, mass spectrometry, ELISA, and immunohistochemistry (IHC). The effects of A2M on IL-1-induced cartilage catabolic enzymes were evaluated by Luminex and ELISA in cultured chondrocytes and cartilage organ cultures. In vivo effects were evaluated in male rats (N=120) randomized to four treatments: (1) ACLT + saline, (2) ACLT + A2M (1IU/kg), (3) ACLT + A2M (2IU/kg) or (4) sham surgery + saline. Intra-articular injections were given immediately and 3 days after surgery, then once weekly for 6 weeks. Catabolic enzymes were monitored in vivo via Fluorescence Molecular Tomography (FMT) using murine partial medial meniscectomy (PMM). Histological analyses and IHC were performed to assess cartilage damage. The concentration of MMP-13 in SF lavages was measured using ELISA. Gene expression was quantified by RT-qPCR.

Results: The levels of A2M were 7-fold lower, while the levels of MMP-13 were 2.8-fold higher in SF compared with serum from OA patients. Supplementation with exogenous A2M inhibited cartilage catabolic enzymes in a dose-dependent manner in human chondrocytes. Catabolic enzymes in PMM mice peaked 2 days after surgery. Early supplemental intra-articular injection of A2M reduced the concentration of MMP-13 in SF and attenuated OA pathogenesis in the rat ACLT model.

Conclusion: A2M is a plasma protease inhibitor that is not present in sufficient concentrations to inactivate the high concentrations of catabolic enzymes found in OA SF. Our findings suggest that supplemental intra-articular A2M could provide chondral protection for post traumatic OA.

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, HDAC4 and A2M proteins.

Cbfβ PROMOTES OSTEOGENESIS AND CHONDROGENESIS BY SUPPRESSING ADIPOCYTE REGULATOR EXPRESSION AND ACTIVATING Wnt/β-CATENIN SIGNALING

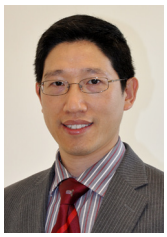
Prof. Yiping Li
Department of Pathology
University of Alabama at Birmingham
USA

How osteoblast (OB) lineage commitment and chondrocyte lineage commitment are achieved is a fundamental question in bone biology. Despite recent insights gained from the effects of targeted deletion of OB regulator genes, the mechanism of OB lineage commitment from multipote¬nt mesenchymal stem cells (MSCs) remains unclear. Core-binding factor, beta (Cbfβ) plays an important role in skeletal development. However, the role of Cbfβ in MSC lineage determination has not been clarified yet. To determine its role, we generated Cbfβ conditional knockout mice using skeletal lineage-specific Cre-loxP systems. Oil red O staining showed that Cbfβf/fPrx1-Cre, Cbfβf/fCol2α1-Cre, and Cbfβf/fOsx-Cre mice, but not Cbfβf/fCol1α1-Cre mice, have dramatically decreased bone density and a pronounced accumulation of bone marrow adipocytes, which resembles osteoporosis in aging humans. Our findings indicate that the regulation of Cbfβ in OB lineage commitment is cell lineage-specific. Calvarial cells derived from Cbfβf/fOsx-Cre mice maintained strong adipogenic tendencies despite being cultured in osteogenic medium. qPCR and Western blot data demonstrated that compared to wild-type (WT) OBs, Cbfβf/fOsx-Cre and Cbfβf/fPrx1-Cre OBs highly expressed adipocyte regulator genes and marker genes (e.g. C/ebpα, PPARγ, FABP4). Using chromosome immonoprecipitation (ChIP) analysis, we determined that Cbfβ binds to both C/ebpα and PPARγ promoters at the Cbfβ/Runx binding sites near their transcription start sites. Promoter analysis data showed that Cbfβ and Runx2 co-transfection, but not Cbfβ or Runx2 alone, highly inhibited C/ebpα promoter activity, indicating that inhibition functioned through the Cbfβ/Runx2 complex. We also wondered how Cbfβ promotes OB lineage commitment. Our data showed that although β-catenin mRNA expression was similar between WT and Cbfβf/fOsx-Cre cells, non-phosphorylated β-catenin protein and β-catenin cell nucleus translocation were dramatically increased in Cbfβf/fOsx-Cre cells, indicating that Cbfβ may promote MSC lineage commitment through Wnt/β-catenin signaling. In summary, we demonstrated that Cbfβ regulates MSC differentiation toward osteoblastogenesis by inhibiting both C/ebpα and PPARγ expression at the transcriptional level and by activating Wnt/β-catenin signaling. This is the first report of the role of Cbfβ in MSC lineage determination. Our data also demonstrated that cbfβ deficiency resulted in spontaneous osteoarthritis and AAV mediated cbfβ overexpression promoted chondrogenesis for cartilage regeneration in mouse osteoarthritis model. Our study indicates that Cbfβ can be a new therapeutic target of aging-related bone diseases (e.g. human age-related osteoporosis and osteoarthritis).

Brief CV
Prof. LI Yiping received his bachelor degree in Zhejiang University in Chemistry in 1979 and obtained his Ph.D in Shanghai Institute of Biochemistry, Chinese Academy of Sciences in 1988 with the research field of Molecular Genetics. He then began his postdoc training in Ctr. Biomedical Res, Rockefeller University, NY (1989-1990) and The Forsyth Institute; Harvard School of Dental Medicine, Boston (1990-1993), in the field of Molecular Biology and Bone and Cell Biology respectively. From 1990, Prof. LI Yiping has worked in Cytokine Biology Department, The Forsyth Institute, Harvard School of Dental Medicine for more than 20 years from being a Staff Associate to the Senior Member of the Staff (equivalent to Tenured Professor). He is currently the Adjunct Senior Research Investigator of Cytokine Biology Department, The Forsyth Institute, Harvard School of Dental Medicine, the Jay M. McDonald Endowed Professor in Bone Biology of University of Alabama at Birmingham (2010-present), Senior Vice Director for Research at the Center for Metabolic Bone Disease of the University of Alabama at Birmingham (2010-present), and also the Professor in UAB Dental School Secondary Appointment (2013-present).

Session 11: Musculoskeletal Tissue Engineering

ERYTHROPOIETIN/ERYTHROPOIETIN RECEPTOR IN SKELETAL REGENERATION



Prof. Chao Wan
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Hong Kong, China

Erythropoietin (EPO)/erythropoietin receptor (EPOR) signaling is involved in the development and regeneration of several non-hematopoietic tissues including the skeleton. EPO is identified as a downstream target of the hypoxia inducible factor-α (HIF-α) pathway. It is shown that EPO exerts a positive role in bone repair, however, the underlying cellular and molecular mechanisms remain unclear. In the present study we show that EPO and EPOR are expressed in the proliferating, pre-hypertrophic and hypertrophic zone of the developing mouse growth plates as well as in the cartilaginous callus of the healing bone. The proliferation rate of chondrocytes is increased under EPO treatment, while this effect is decreased following siRNA mediated knockdown of EPOR in chondrocytes. EPO treatment increases biosynthesis of proteoglycan, accompanied by up-regulation of chondrogenic marker genes including SOX9, SOX5, SOX6, collagen type 2, and aggrecan. The effects are inhibited by knockdown of EPOR. Blockage of the endogenous EPO in chondrocytes also impaired the chondrogenic differentiation. In addition, EPO promotes metatarsal endothelial sprouting in vitro. This coincides with the in vivo data that local delivery of EPO increases vascularity at the mid-stage of bone healing (day 14). In a mouse femoral fracture model, EPO promotes cartilaginous callus formation at days 7 and 14, and enhances bone healing at day 28 indexed by improved X-ray score and micro-CT analysis of microstructure of new bone regenerates, which results in improved biomechanical properties. Our results indicate that EPO enhances chondrogenic and angiogenic responses during bone repair. EPO's function on chondrocyte proliferation and differentiation is at least partially mediated by its receptor EPOR. EPO may serve as a therapeutic agent to facilitate skeletal 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, School of Medicine, The 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 Department of Trauma and Orthopaedic Surgery, School of Medicine, The Queen's University of Belfast, UK, and in Department of Pathology, School of Medicine, 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.

REPAIR AND RECONSTRUCTION OF ARTICULAR CARTILAGE AND SUBCHONDRAL BONE WITH SOX 9 GENE THERAPY AND BIPHASIC SCAFFOLD

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Although Sox9 is essential for chondrogenic differentiation and matrix production, its application in cartilage tissue engineering has been rarely reported. We firstly evaluated the chondrogenic effect of Sox9 on bone marrow mesenchymal stem cells (BMSCs) in vitro. Rabbit BMSCs were transduced with adenoviral vector containing Sox9. Toluidine blue, safranin O staining and real-time PCR were performed to check chondrogenic differentiation. The results showed that Sox9 could induce chondrogenesis of BMSCs both in monolayer and on PGA scaffold effectively. The rabbit model with full-thickness cartilage defects was then established and then repaired by PGA scaffold and rabbit BMSCs with or without Sox9 transduction. HE, safranin O staining and immunohistochemistry were used to assess the repair of defects by the complex. Better repair, including more newly-

formed cartilage tissue and hyaline cartilage-specific extracellular matrix and greater expression of several chondrogenesis marker genes were observed in PGA scaffold and BMSCs with Sox9 transduction, compared to that without transduction.
We also try to reconstructed both articular cartilage and subchondral bone with biphasic scaffold fabricated using CAD/CAM technology. The poly-ε-caprolactone/ hydroxyapatite (PCL/HA) scaffold and mold of the polylactic acid-coated polyglycolic acid (PGA/PLA) scaffold were fabricated by fused deposition modeling (FDM) controlled by computer-aided manufacturing (CAM) software, then the PGA/PLA scaffold was fabricated. Together, the PGA/PLA scaffold and PCL/HA scaffold formed biphasic scaffold. The content of PLA and HA was optimized to a proper ratio, thus the scaffolds could achieve appropriate stiffness which was more conducive to articular cartilage and bone regeneration respectively. Furthermore, computer-aided design and manufacturing (CAD/CAM) technology was employed to fabricate the biphasic scaffolds into the desired shape and structure. The biphasic scaffolds with fine cell biocompatibility matched perfectly. Chondrocytes and bone marrow stromal cells (BMSCs) were seeded into the scaffolds for cartilage and bone regeneration respectively. After 10 weeks of implantation in nude mice subcutaneously, the cell-scaffold constructs successfully regenerated goat femoral heads. The regenerated femoral heads presented a precise appearance in shape and size similar to that of native goat femoral heads with a smooth, continuous, avascular, and homogeneous cartilage layer on the surface and stiff bone-like tissue in the microchannels of PCL/HA scaffold. Additionally, histological examination of the regenerated cartilage and bone showed typical histological structures and biophysical properties similar to that of native ones with specific matrix deposition and a well-integrated osteochondral interface. The strategy established in the study provides a promising approach for regenerating a biological joint which could be used to reconstruct the impaired joint.

Brief CV
Ting-ting Tang, MD, PhD. is professor, doctoral supervisor, director of Shanghai Key Laboratory of Orthopeadic Implants, vice Director of Orthopedic Department of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. He got his Bachelor degree in Anhui College of Traditional Chinese Medicine in 1988, Master degree in Heilongjiang College of Traditional Chinese Medicine in 1993 and Doctor degree in Shanghai Second Medical University in 1996. Later on, he has received advanced training (1-3 months) in Washington University in St Louis in USA, University du Littoral in France, and AO Research Institute in Switzerland. His main research interests include stem cell research and musculoskeletal regeneration, cancer and bone disease, orthopedic implants and biomaterials. He have over 100 peer-reviewed international publications and had been awarded as candidate of New Century Excellent Talent Program of Ministry of Education, New Century Hundred, Thousand and Ten Thousand Talent Program in China. Currently he also serves as 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 15 international and Chinese journals including Journal of Orthopaedic Translation, Bone Research, Chinese Journal of Orthopaedic Trauma, et al.

EXOSOMES SECRETED BY HUMAN-INDUCED PLURIPOTENT STEM CELL-DERIVED MESENCHYMAL STEM CELLS ATTENUATE ISCHEMIC INJURY BY PROMOTING ANGIOGENESIS

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China

Introduction: "Patient-specific" induced pluripotent stem cells (iPSCs) are attractive because they can generate abundant cell source without immune rejection for cell therapy. Though iPSCs- derived mesenchymal stem cells (iMSCs) exhibited powerful proliferation, differentiation, and therapeutic effects, they bear a similar risk as other MSCs of tumor formation. Recently, most studies indicate that paracrine mechanism of stem cells plays an important role in cellular therapeutics, and exosomes are important paracrine factor. The objective of this study was to evaluate whether exosomes derived from iMSCs(iMSCs-Exo) possess the ability to attenuate limb ischemia and promote angiogenesis after transplantation into limbs of mice suffering from femoral artery excision.
Methods: Human iPSCs (iPS-S-01, C1P33, and PCKDSF001C1) were used to differentiate into iMSCs using a simple method. iMSCs were characterized by flow cytometry and multipotent differentiation potential analysis. Ultrafiltration combined purification method was used to isolate iMSCs-Exo; Transmission Electron Microscopy (TEM) and Western Blotting were used to identify iMSCs-Exo. After establishment of mice hind-limb ischemia with excision of femoral artery and iMSCs-Exo injection, blood perfusion was monitored at day 0, 7, 14, and 21; microvessel density in ischemic muscles was also analyzed. In vitro migration, proliferation, and tube formation experiment were used to analyze the ability of pro-angiogenesis in iMSCs-Exo; Quantitative Reverse-Transcriptase polymerase chain reaction (qRT-PCR) and Enzyme-linked immunosorbent assay (ELISA) were used to identify expression level of angiogenesis-related molecules in human umbilical vein endothelial cells (HUVECs) after cultured with iMSCs-Exo.

Results: iPSCs were efficiently induced into iMSCs with MSCs positive and negative surface antigens and has osteogenesis, adipogenesis, and chondrogenesis differentiation potential. iMSCs-Exo with a diameter of 70.93±6.06 nm and expressed CD63, CD81, and CD9. Intramuscular injection of iMSCs-Exo markedly enhanced microvessel density and blood perfusion in mice ischemic limb, consistent with an attenuation of ischemic injury. In addition, iMSCs-Exo could activate angiogenesis-related molecules expression and promote HUVECs migration, proliferation and tube formation.
Conclusion: Implanted iMSCs-Exo were able to protect limb from ischemic injury via the promotion of angiogenesis, which indicated that iMSCs-Exo may be a novel therapeutic approach in the treatment of ischemic disease.

Brief CV
Wang Yang, Ph.D., is professor at Institute of Microsurgery on Extremities, Shanghai Jiaotong University Affiliated Sixth People's Hospital. She received her degree of BS(1986) in clinical medicine, MS(1991) in Microbiology and Immunology and Ph.D(2002) in Surgery Science at the same university(Nanchang University). From 2008 to 2009, Dr. Wang visited Australian Stem Cell Centre.
The research of her group are focus on stem cells biology and tissue engineering including specific differentiation and regulation of embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), culture technique of tissue specific stem cells, application of stem cells in tissue regeneration. Professor Wang has published more than thirty refereed papers in international journals.

3D PRINTING TECHNIQUE BASED BONE TISSUE REGENERATION STRATEGY

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National Tissue Engineering Center of China
Shanghai Key Laboratory of Tissue Engineering
Department of Plastic and Reconstructive Surgery
Shanghai 9th People's Hospital
School of Medicine, Shanghai Jiao Tong University
China

Rapid prototyping technique (or generally known as 3D printing technique recently) is an emerging fabrication technique with the capacity to manufacture complex structure which cannot been achieved by traditional techniques and has been highly regarded as the third industrial revolution. With many unique features and advantages, 3D printing technique possess great potential for biomedical application, especially as porous implant to promote bone defect healing and regeneration. We have previously developed a novel three dimensional porous biodegradable scaffolds using fused deposition modeling technique and demonstrated its efficacy for different bone defects treatment including craniofacial bone defect, long bone defect, dental defect and spinal fusion application with or without the use of stem cells. More recently, we have utilized the cutting-edge Electronic beam melting technique to fabricate porous Titanium scaffold with stronger and favorable mechanical properties for load bearing application and prove its capacity for the early stage talar osteonecrosis treatment in a preclinical sheep model. Furthermore, in this talk, I would like share with your our preliminary research work on exploring and investigating the influence of 3D architecture of scaffold design and pathological condition such diabetes on the regenerative capacity of 3D printed porous scaffold.

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 the database of Pubmed and Clinicaltrial.gov. He has filed 6 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.

Session 12: Stem Cells Manipulation

DEDIFFERENTIATION-REPROGRAMMED MSCS IN REGENERATIVE MEDICINE

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Hong Kong, China

In mammals, the differentiation process was thought to be irreversible. However, recent studies have demonstrated that dedifferentiation may take place during wound repair or functions as an alternative mechanism to stem-cell-based pathways to achieve tissue regeneration in mammals. In addition, recent studies show that terminally differentiated mammalian cells can be manipulated in vitro to undergo dedifferentiation into induced pluripotent stem cells (iPS) through reprogramming by transfecting just a few genes. These groundbreaking findings indicate that dedifferentiation-mediated regeneration is an evolutionary trait conserved inter-species. While silenced or inactivated in mammals, it can be re-activated under certain conditions, such as tissue injury. Thus, inducing dedifferentiation appears as a logical strategy to promote regeneration in mammals.

Can we induce dedifferentiation readily in culture without gene manipulation and obtain reprogrammed stem cells with improved therapeutic potential? It took us a series of work to provide a positive answer. We came to notice the phenomena of dedifferentiation in vitro when we studied the plasticity of adult rat bone marrow MSCs. After in vitro induction and differentiation into 5 hydroxytryptamine (5-HT)-sensitive neurons, these cells could revert back, or dedifferentiate, to a morphological and phenotypical state similar to that of MSCs. The dedifferentiated MSCs (DeMSCs) could undergo further proliferation, or in vitro expansion, and be induced to redifferentiate into 5-HT sensitive neurons again, indicating that these adult stem cells are more plastic than we previously thought. This notion is further supported by our later studies demonstrating that monoclonally derived MSCs could be reprogrammed in vitro via neuronal differentiation and dedifferentiation with enhanced therapeutic efficacy in a rat model with ischemic brain damage.

Apart from neural lineage, we have found that after in vitro induction of osteogenic differentiation, MSCs can also be reverted to a primitive stem cell population (dedifferentiated osteogenic MSCs) with enhanced stem cell potency as demonstrated by improved cell survival, colony formation, osteogenic potential, migratory capacity and increased expression of pluripotency genes. In addition, we demonstrate that Nanog plays critical role in maintaining the dedifferentiation phenotype, since Nanog-knockdown in MSCs completely reverses the enhanced cell survival and differentiation in De-Os-MSCs. More interestingly, we reveal that the increased expression of Nanog and Oct4 is attributed to the epigenetic activation involving both DNA methylation and histone modifications, as evidence by decreased methylation and promoter accrual of activating histone marks, such as H3K4me3 and H4ac on gene promoters.

Our findings indicate that dedifferentiation can be achieved after different lineage commitment in MSCs and reinforce the potential therapeutic benefit of in vitro dedifferentiation strategy, which could have broad impact on the application of MSCs in regenerative medicine.

Brief CV

Dr. Jiang Cynthia Xiaohua graduated from Shanghai Second Medical University (currently School of Medicine, Shanghai JiaoTong University), and completed her internship and residency at RuiJin Hospital in Shanghai. She obtained her PhD degree 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 biological mechanisms underlying the regulation of stem cell function and application of adult stem cells in tissue regeneration and cancer targeting. Dr. Jiang has published fifty papers in peer-reviewed journals, including Nature Medicine, Stem Cells, Cell Research, Cancer Research, Gastroenterology and Oncogenes.

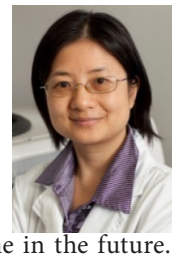
LARGE SCALE EXPANSION OF WHARTON'S JELLY-DERIVED MESENCHYMAL STEM CELLS WHILE RETAINING SELF-RENEWAL AND MULTIPOTENCY CHARACTERISTICS AND THEIR CAPACITY FOR ENHANCING SKIN WOUND HEALING

Prof. Jinyu Liu
Department of Pathobiology
College of Basic Medicine
Jilin University
China

Successful stem cell therapy relies on large-scale generation of stem cells and their maintenance in a proliferative multipotent state. Wharton's jelly is readily available, rich source of mesenchymal stem cells, offering an attractive cell source in stem cell-based regenerative medicine. This study aimed to establish a 3D culture system for large-scale generation of human Wharton's jelly-derived mesenchymal stem cells (hWJ-MSCs) and investigated the self-renewal activity, multi-lineage differentiation potential, biological efficacy and related mechanism in enhancing skin wound healing.
hWJ-MSCs were seeded on gelatin microbeads and cultured in spinning bottles (3D cultures). Cell proliferation, surface marker expression, multipotent differentiation (adipogenic, chondrogenic, and osteogenic potentials), and expression of core transcription factors (OCT4, SOX2, NANOG, and C-MYC), as well as their efficacy and related mechanism in accelerating skin wound healing, were investigated and compared with that of hWJ-MSCs derived from 2D cultures, in in vivo and in vitro experiments.
hWJ-MSCs attached to and proliferated on gelatin microbeads in 3D cultures, reaching a maximum of 1.1–1.30 × 107 cells on 1 g of microbeads by days 8–14; in contrast, hWJ-MSCs derived from 2D cultures reached a maximum of 6.5–11.5 × 105 cells per well in a 24-well plate by days 6–10. hWJ-MSCs derived by 3D culture incorporated significantly more EdU ($P < 0.05$; 0.24% ± 0.02% [2D] vs. 0.21% ± 0.01% [3D]) and had a significantly higher proliferation index ($P < 0.05$; 0.40 ± 0.001 [2D] vs. 0.28 ± 0.011 [3D]) than those derived from 2D culture. Immunofluorescence staining, real-time PCR, flow cytometry analysis, and multipotency assays showed that hWJ-MSCs derived from 3D culture retained MSC surface markers and multipotency potential for differentiation toward adipocytes, chondrocytes, and osteoblasts, similar to 2D culture-derived cells. 3D culture-derived hWJ-MSCs also retained the expression of core transcription factors at levels comparable to their 2D culture counterparts. Direct injection of hWJ-MSCs derived from 3D or 2D cultures into animals exhibited similar efficacy in enhancing skin wound healing. Mechanistic study showed exosome derived hWJ-MSCs significantly suppressed Cytochrom C and AIF-mediated apoptosis in keratinocytes treated with hydrogen peroxide.
Thus, hWJ-MSCs can be expanded markedly in gelatin microbeads, while retaining MSC surface marker expression, multipotent differential potential, expressing core transcription factors, and enhancing skin wound healing, in a manner comparable to hWJ-MSCs obtained from 2D cultures.

Brief CV
Dr. Jin Yu Liu received his MD and PhD from Norman Bethune University of Medical Sciences. From 1999 to 2004 he worked as postdoctoral with Professor Gunter Burg on skin tissue engineering and wound healing at the Department of Dermatology, Zurich University hospital, Switzerland. From 2005-2009 he worked as research assistant professor with Dr. Stelios Andreadis on stem cell-based vascular tissue engineering at the Department of Chemical and Biological Engineering, State University of New York at Buffalo, USA. Since 2009 he was appointed as vice director and professor at the Department of Pathobiology, Key Lab of Ministry of Education, Jilin University. Dr. Jin Yu Liu's research focuses on stem cell biology and stem cell-based regenerative medicine, with particular interests in stem cell self-renewal, tissue engineering, in situ tissue repair and regeneration and gene therapy. Dr. Jin Yu Liu is the author of more than 20 peer-reviewed research articles, including Cell Transplantation, Wound Repair and Regeneration, Tissue Engineering, Cardiovascular Research, PLoS ONE, Dermatology, Biochemical and Biophysical Research Communications, Stem cell Review and Report, International Journal of Molecular Medicine, Annals of Biomedical Engineering.

THE ROLE OF RIF1 IN PLURIPOTENT STEM CELL STABILITY



Prof. Ping Yuan
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Pluripotent stem cells such as embryonic stem cells have great potential to be used as regenerative medicine in the future. However, prolonged culture of embryonic stem (ES) cells leads them to adopt embryonal carcinoma cell features, introducing enormous dangers to their further applications. We previously reported that Smad3 plays an important role in maintaining mouse ES cell fidelity, as depletion of Smad3 results in cancer cell like properties in ES cells and Smad3-/- ES cells are prone to grow big and malignant teratomas. In this study, we further investigate the underlying mechanism. We find that Rif1, a factor involved in DNA damage repair, DNA replication timing control, telomere homeostasis and ES cell pluripotency, is a direct target of Smad3 and plays a critical role in maintaining ES cell fidelity. Rif1 level needs to be tightly controlled in ES cells, as low level of Rif1 is associated with ES cell differentiation, but high level of Rif1 is linked to ES cell transformation. In ES cells, Oct4 and Smad3 co-bind to Rif1 but play opposite role on Rif1. Oct4 activates Rif1 expression, while Smad3 represses Rif1 expression. Oct4 recruits Smad3 to bind to Rif1 promoter, but Smad3 facilitates the loading of polycomb complex to generate repressive epigenetic modification on Rif1 promoter, and hence keep Rif1 to express at a proper level in ES cells. Interestingly, Rif1 knockdown can partially rescue the malignant phenotype of Smad3-/- ES cells, suggesting it is worthwhile investigating whether control of Rif1 levels by drugs could benefit the teratocarcinoma treatment.

Brief CV
I obtained my Ph.D. degree from The National University of Singapore in 2004. During my Ph.D. training, I was appointed as a Visiting Research Fellow and worked in the Department of Pathology in Brigham & Women's Hospital, Harvard Medical School, USA in 2001. Thereafter, I was a Research Associate in the Department of Molecular Biology in Princeton University from 2004 to 2006 and a Postdoctoral Research Fellow in Genome Institute of Singapore from 2006 to 2010. In 2010, I was appointed as an Assistant Professor in the Department of Chemical Pathology and Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong.
Research Interests:
My research interests lie in the mechanism studies and practical applications of stem cells, especially pluripotent stem cells. My research topics include:
1. Discover novel interplays between the transcription factors and epigenetic modifiers in stem cells with functional genomics and molecular biology methods;
2. Identify genes that drive lineage specific differentiation in pluripotent stem cells; and
3. Derive the disease specific induced pluripotent stem cells (iPS cells) and exploit their applications on drug screening and cell therapy.

INVOLVEMENT OF FOXO3A IN SENESCENCE OF CARDIAC MICROVASCULAR ENDOTHELIAL CELLS

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Key Laboratory for Regenerative Medicine of Ministry of Education
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Cardiac microvascular endothelial cells (CMECs) play important roles in cardiovascular disease. FoxO3a plays important roles in aging processes and decreases with aging. However, the involvement of FoxO3a in senescent CMECs proliferation and angiogenesis as well as the underlying mechanism are still not elucidated.
This study investigated the activation of FoxO3a, cell proliferation and angiogenesis using a senescent model of rat CMECs. Our data showed that FoxO3a was greatly deactivated in senescent CMECs in parallel with the inhibition of both proliferation and tube formation. Following deactivation of FoxO3a in senescent CMECs, activation of antioxidant enzymes (catalase and Mn-SOD), the downstream targets of FoxO3a, was significantly decreased, thereby leading to cell cycle arrest in G1-phase by activating p27Kip1 pathway. However, constitutive activation of FoxO3a by lentivirus infection could block ROS generation and p27Kip1 activation by increasing antioxidant activation in senescent CMECs.
In conclusion, FoxO3a deactivation in senescent rat CMECs can promote ROS generation through decreasing activation of catalase and Mn-SOD, thereby increasing p27Kip1 activation and cell cycle arrest, ultimately suppresses CMECs proliferation and angiogenesis. Thus, FoxO3a might be developed as a potential therapeutic target to promote the angiogenic ability of senescent CMECs by mediating cell cycle progress.

Brief CV
Dr. Qi got his Ph.D. degree from Yonsei University in Korea and subsequently joined in the Key Laboratory for Regenerative Medicine of Ministry of Education, Ji Nan University, Guangzhou, China. The research interests include the inflammatory microenvironment and regeneration of infarcted myocardium, ROS signaling and myocardial infarction, and reprogramming of fibroblast into cardiomyocyte. Until now, we already published more than 30 research papers which include 20 SCI papers such as Cell Death Dis, Br J Pharmacol, J Cell Physiol, Mol Immunol, Toxicol Lett, J Ethnopharmacol, Evid Based Complement Alternat Med, J Cell Mol Med, Food Chem Toxicol and Mol Cell Toxicol. Our research have been supported by the National Natural Science Foundation of China (81100079, 81270183, 81211140351),Guangdong Province Natural Science Fund (S2013010013598, S2011040003230), the New Star of Pearl River on Science and Technology of Guangzhou (2014J2200002) and the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry (2013-693).

Session 13: Biomaterials and Regenerative Medicine

GRADIENT BIOACTIVE SCAFFOLD FOR IN VIVO RECONSTRUCTION OF ARTICULAR CARTILAGE/SUBCHONDRAL BONE

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Natural total articular cartilage is constituted by a multilayer structure, including cartilage layer, calcified cartilage layer and subchondral bone layer. Therefore, simulation and fabrication of such a biocompatible multilayer structural scaffolds are a key premise for its reconstruction. In this work, a bioactive composite scaffold consisted of PCL/HAp gradient contents was designed to repair complex defect of articular cartilage/subchondral bone. The fabrication of scaffolds was realized by a modified SLS technique. The resulting bioactive multilayer scaffold possessed interconnected porous structure. After in vivo implantation for 4w and 12w, the composite multilayer scaffold demonstrated a favourable reconstruction of full articular cartilage which was based on general observation, micro-CT, histological staining and related gene expression testing.

Acknowledgements
The work was supported by the National Basic Research Program of China (No:2012CB933601) and the National Natural Science Foundation of China (No.30870624; No.81071263).

Brief CV
Dr. Shengmin Zhang received his Ph.D. in Biomedical Materials from Wuhan University of Technology, China. Starting in 2003 he was the Chair Professor and Director of the Advanced Biomaterials and Tissue Engineering Center at Huazhong University of Science and Technology in Wuhan, China. His previous academic positions were Professor (2000-2003), Associate Professor (1996-2000) and Assistant Professor (1992-1996) in Materials Science at the Wuhan University of Technology. He is the Founding Chair of the China-Korea Center for Biomaterials and Nano-Biotechnology (NSFC-KOSEF). Prof. Zhang has over 20-year experience in biomaterials and tissue engineering fields and has authored more than 100 peer-reviewed papers, 5 books and given about 50 keynote or invited speeches in various conferences. He co-chaired the International Conference on Regenerative Biomedical Materials (ICRBM 2013,website: www.icrbm2013.com) and a series of China-Korea Bilateral Symposium. He also is the inventor of more than 30 patents, which have led to 2 Product Certificates of Registration authorized by CFDA. Prof. Zhang is an Executive Director of Chinese Biomanufacturing Society (CBMS) and the Vice Director of Biomaterials Committee, CBMS. He serves on the editorial boards of Tissue Engineering (Part A, B and C, USA), Biomedical Materials (IOP, UK), Frontiers of Materials Science, etc. Main research interests: New Concept (Future) biomaterials; Materials for Regenerative Medicine; Molecular, Nano-biomaterials; 3-D Printing and Biofabrication; Cell/gene-active Materials; Product and Technique Standard for Biomedical Material and Tissue Engineering Device.

TISSUE-ENGINEERING A VASCULARIZED B-TCP SCAFFOLD USING BIOMEMITIC PERIOSTEUM FOR BONE REGENERATION

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Florida Atlantic University
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The efficacy of large bone reconstructions using synthetic scaffolds is limited due to insufficent vascularization. This study is to engineer a vascularized bone graft by integrating a biomimetic cell-sheet-engineered periosteum-like membrane (CSEP) and a biodegradable macroporous beta-tricalcium phosphate (β-TCP) scaffold, and to evaluate its vascularization and osteogenesis. The biomimetic CSEP contains a highly prevascularized cell sheet outer layer and an osteogenic cell sheet inner layer. The prevaculairzed cell sheet was formed by seeding human umbilical vein endothelial cells (HUVECs) on an undifferentiated human mesenchymal stem cells (hMSCs) sheet, and the osteogenic layer was formed by inducing undifferentiated hMSCs to osteogenic cells. The two cell sheets were sequentially wrapped onto β-TCP scaffolds to fabricate CSEP/β-TCP grafts. Non-CSEP cell sheet/β-TCP and plain β-TCP were used as controls. In vitro studies indicate that the hMSCs sheet facilitated endothelial cells to form rich capillary-like networks. In vivo studies indicate that CSEP enhanced angiogenesis and functional anastomosis between the in vitro preformed human endothelial capillary networks and the mouse host vasculature. MicroCT analysis and osteocalcin staining show that the CSEP/β-TCP group formed more bone matrix compared to the other groups. These results suggest that the CSEP that mimics the cellular components and spatial configuration of periosteum plays a critical role in vascularization and osteogenesis. Our studies also suggest that the combination of a CSEP and a rigid macroporous scaffold is a promising approach for tissue-engineering bone grafts.

Brief CV
Prof. Kang Yunqing received his bachelor degree in the major of Materials Science and Engineering in Sichuan University (1997-2001), and Master degree in Biomedical Engineering in Sichuan University (2003-2005), and then obtained his Ph.D in in Biomedical Engineering in Sichuan University (2005-2008). He took his postdoc training in the Restorative Dentistry & Biomaterials Department, the University of Texas Dental Branch at Houston (2009-2011) and in the Department of Orthopedic Surgery, Stanford University (2011-2014). He is currently the Assistant Professor in the College of Engineering, Florida Atlantic University.

FUNCTIONAL BIOMATERIALS FOR CARTILAGE REPAIR

Prof. Liming Bian
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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. Furthermore, studies have revealed that the survival, maintenance and differentiation of stem cells are tightly regulated by mechanical, biochemical, intercellular and neural signals from their local microenvironment. This talk focuses on the design and development of biologically and physically functional biomaterials to mimic microenvironmental signals 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 hMSCs. These findings provide important insights into clinical translation of stem cell therapy for cartilage repair.

Brief CV
Dr. Bian received his Ph.D. degree in Biomedical Engineering under the advisory of Dr. Clark T. Hung and Dr. Gerard A. Ateshian at Columbia University in 2009. After three years of postdoctoral research with Dr. Jason Burdick and Dr. Robert Mauck in the Department of Bioengineering at the University of Pennsylvania, Dr. Bian joined CUHK as an Assistant Professor in the Department of Mechanical and Automation Engineering in August 2012. His research focuses on stem cell tissue engineering of cartilage and the development of functional biomaterials for cartilage regeneration. Dr. Bian's reseach work has been published in a number of journals including "PNAS", "Biomaterials", "Acta Biomaterialia", "PLoS ONE", "Osteoarthritis and Cartilage", "Tissue Engineering", etc. Dr. Bian is a member of the Orthopedic Research Society, American Society of Mechanical Engineers and Society for Biomaterials.

MAGNESIUM AS BIOACTIVE AND BIOCORROSIVE ORTHOPAEDIC IMPLANTS

Prof. Ling Qin
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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 good 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), SMART Program of Lui Che Woo Institute of Innovative Medicine, Faculty of Medicine, the Chinese University of Hong Kong supported by Lui Che Woo Foundation Limited, and CAS-Croucher Founding Scheme for Joint Laboratories (Ref. CAS 14303).

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 Experimental Morphology 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 past President of the International Chinese Musculoskeletal Research Society (ICMRS) (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) and International Journal of Sports Medicine (http://www.thieme.de/sportsmed) . He holds memberships in several international and national orthopaedic and related research organizations, including collage fellow of American Institute of Medical and Biological Engineering (http://www.aimbe.org). He has received over 30 Research Awards and holds 4 patents. Dr. Qin published 7 monographs as editor or associate editor, 3 conference proceedings, 80 book chapters, over 300 journal papers in English, German, and Chinese, including 220 SCI articles published in Nat Med, JBMR, Osteoporosis Int, Bone, A&R, Biomaterials, Acta Biomateralia, Am J Sports Med, etc. with citation over 4000 and a H-index of 37.

Session 14: Free Paper and Award Paper

INVITED FREE PAPER 1
THEMOREVERSIBLE HYALURONAN HYDROGEL INDUCES DISC PHENOTYPE IN HUMAN MESENCHYMAL STROMAL CELLS

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AO Research Institute Davos
Switzerland

Human Mesenchymal Stromal Cells (hMSCs) hold great potential for intervertebral disc (IVD) regeneration, but their fate after injection can be negatively affected by the adverse environment of the degenerating IVD. Pre-differentiation prior to injection and use of a suitable injectable matrix may improve hMSC survival and yield upon injection in a compromised IVD. Thus, the goals of this project were to develop a thermoreversible hyaluronan hydrogel (HpN) for the three dimensional in vitro culture of hMSCs, to evaluate the supplementation of hMSCs in combination with the hydrogel and assess if preconditioning in the hydrogel contributes to a better hMSC response in a whole organ culture.
Hydrogel was synthesized by chemically grafting thermoresponsive poly(N-isopropylacrylamide) (pNIPAM) to hyaluronan. hMSC encapsulated in HpN were cultured in for 1 week under hypoxia in chondropermissive medium alone and with the supplementation of transforming growth factor β1 (TGF-β1) or growth and differentiation factor 5 (GDF-5). Ex-vivo, hMSCs were either suspended in HpN and directly supplied to bovine IVDs in organ culture, or pre-differentiated with GDF-5 for 1 week in HpN and then supplied to the IVDs. Cell viability was evaluated by Live-Dead assay and DNA, while GAG and gene expression were used to assess hMSC differentiation toward the disc phenotype.
The HpN produced in solution had a gelling temperature of 30°C allowing injection, encapsulation and culture of hMSCs. It induced hMSC differentiation toward the disc phenotype more effectively than alginate gel. In vitro, higher GAG/DNA ratio and higher COL2, SOX9, KRT19, CD24 and FOXF1 expression were found for hMSCs cultured in HpN compared to alginate, regardless of the addition of growth factors. Following one week of culture in a nucleotomized IVD, the differentiation toward the disc-like phenotype was stronger in undifferentiated hMSCs than in pre-cultured hMSCs.
In conclusion, thermoreversible hayluronan hydrogel supports hMSC differentiation toward the disc phenotype without the need for growth factor supplementation both in vitro and ex-vivo. This thermoreversible hydrogel may provide a safe and effective injectable hMSCs carrier for the treatment of intervertebral disc degeneration.

Brief CV
David Eglin is a Principal Investigator and leader of the Polymers and Surfaces team in the Musculoskeletal Regeneration Program (Prof. Mauro Alini) at the AO Research Institute Davos in Switzerland. Upon completion of Biology and Chemistry studies at the University of Science and Technology in Lille, France, he relocated to Cardiff, Wales, to start an industrial career at the Dow Corning Research & Development Center. Following doctoral studies in Chemistry at Nottingham Trent University, England, in 2002 he joined Prof. Jacques Livage group at the laboratory of Chemistry of Condensed Matter, Collège de France, Paris, as a post-doctoral researcher. In 2006, he became the leader of the Polymer team at the AO Research Institute Davos, Switzerland. Dr Eglin's research interests lie in macromolecular chemistry and material science, focusing on polymers for medical devices, tissue engineering and regenerative medicine. He develops scaffolds, membranes and hydrogels for both the understanding of cell-material interactions and for translational research in the orthopaedic field. He has published over 40 articles, as well as book chapters and patents, and given over 50 national and international invited lectures. He is the recipient of the European Society for Biomaterials Jean Leray Award 2011.

AWARD PAPER 1
YAP1 INHIBITS THE INITIATION OF FRACTURE HEALING BY CONTROLLING CHONDROCYTE DIFFERENTIATION

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Stem Cell and Regeneration Thematic Research Program, School of Biomedical Sciences
The Chinese University of Hong Kong
Shatin, HKSAR

Bone possesses intrinsic repair capacity for regeneration in response to fracture injury. Although many signaling activities in endochondral and intramembranous ossifications are recapitulated during the repairing process, bone regeneration is less efficient suggesting that additional signaling cues are employed during the healing process. Hippo signaling controls organ size and tissue regeneration in many organs, but its roles in bone repair remain elusive. Here, we demonstrate that Yap1, an effector

of Hippo pathway, governs the initiation of fracture repair by regulating cartilage maturation. Both transgenic and genetically modified mice with Yap1 activation in chondrocytes show severely impaired cartilaginous callus formation after fracture injury, but skeletal development of these mice are largely normal. Mechanistically, Yap1 regulates chondrocyte differentiation at multiple steps during bone repair. Yap1 is required for mesenchymal stem cell maintenance and promotes early chondroblast proliferation through direct regulation of the expression of Sox6. However, it inhibits further chondrocyte maturation by direct suppression of Col10a1 expression. Consequently, most of the cells are maintained as immature chondrocytes, which impairs endochondral ossification during fracture healing. We identify Yap1 as a specific regulator responsible for the initiation of endogenous bone repair and it could be a potential therapeutic target for treatment of fracture injury.

AWARD PAPER 2
STEPWISE DIFFERENTIATION OF HUMAN INDUCED PLURIPOTENT STEM CELLS FOR ACHILLES TENDON REGENERATION BY CHANGE OF PHYSICAL SUBSTRATE

Can Zhang[1], Huihua Yuan[2],Huanhuan Liu[1], Xiao Chen[1],Zi Yin[1], Hongwei Ouyang[1]
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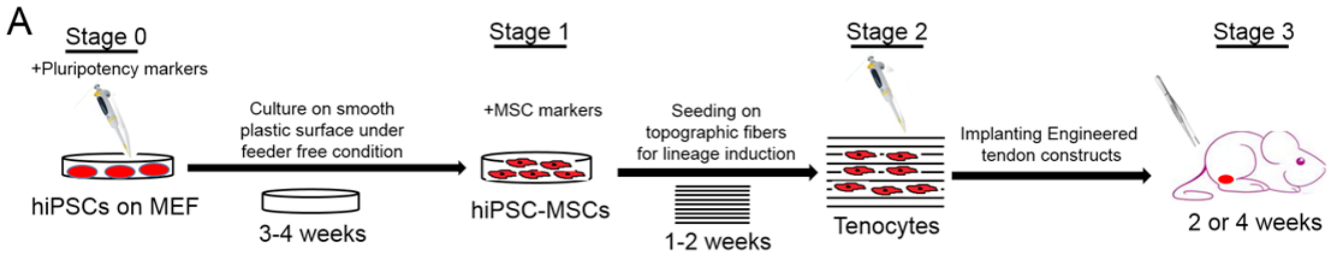
[2]College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, Shanghai, PR China

Physical properties of substrates such as stiffness and topography have been reported to induce mesenchymal stem cells differentiation into bone, muscle and neuron lineages [1]. Human-induced pluripotent stem cells (hiPSCs) are highly promising cell source for realizing personalized treatments and applications in regenerative medicine. Nevertheless, the induction and utility of hiPSCs for tendon repair have not been adequately explored yet. Here we developed a robust, stepwise topographic strategy to induce hiPSCs differentiate into teno-lineage. hiPSCs were first differentiated into MSCs on smooth plastic surface through an EMT (Epithelial-Mesenchymal Transition) process. Subsequently, the hiPSC derived MSCs were seeded onto well-aligned nanoscale fibers to differentiate into tenocyte-like cells through activating mechanic-signal pathway. The in situ Achilles tendon repair model further confirmed that AC-treated (i.e., aligned fiber scaffold with hiPSC-MSCs) tendon had much better structural and mechanical properties than RC-treated (i.e., random fiber scaffold with hiPSC-MSCs) tendon and induced matrix synthesis. Moreover, no teratoma was found in any samples. These findings present an efficient physical strategy that enabled hiPSC differentiation into functional tenocytes through stepwise manner. The in situ repair results suggests that well-aligned fiber scaffold with iPSC-MSCs for tendon regeneration may assist in clinical regenerative medicine to treat tendon diseases.



AWARD PAPER 3
RECOVERY OF SYSTOLIC SYNCHRONY IN ACUTE MYOCARDIAL ISCHEMIA WITH TREATMENT OF AUTOLOGOUS-BONE-MARROW-MESENCHYMAL STEM CELL TRANSPLANTATION IN COMBINATION OF TRANSMYOCARDIAL LASER REVASCULARIZATION IN RABBIT MODEL

Fang Fang[1,2], Guang-Long Sun[2], Zheng Qu[2], Zhi-an Li[2], Yu-jie Zhou[2], Cheuk-man Yu[1]
[1]IVM; LiHS; Institute of Innovative Medicine; S.H. Ho CDSC & Division of Cardiology; HEART Center, Dept of M&T, PWH, CUHK, Hong Kong, Hong Kong SAR, People's Republic of China
[2]Beijing Anzhen Hospital, Capital Medical University.

Objectives: Although stem cell therapy is an optional treatment for myocardial infarction, it remains unclear whether the differentiated myocardium by stem cell can contract coordinately with auto-myocardium. This study is aimed to evaluate the left ventricular systolic dyssynchrony after stem cell therapy in myocardial infarction rabbit model.
Methods: Acute myocardial infarction (AMI) model was built up in 32 rabbits by the ligation of proximal segment of left anterior descending artery and then randomly divided into 4 groups: control group, bone-marrow-derived mesenchymal stem cells group (MSc group), transmyocardial laser revascularization (TMLR) group and the combination (MSc+ TMLR) group.

Serial echocardiography with tissue Doppler imaging were performed at baseline, post AMI and after treatment. Systolic dyssynchrony was assessed by the time difference of septal-to-lateral segment. Immunohistochemistry staining used to evaluate MSCs survival and capillary density of the treated myocardium.
Results: Left ventricular systolic function deteriorated as evident by the decreased ejection fraction and increased septal-to-lateral delay after AMI when compared to baseline in all groups (all $p<0.05$). After treatment, the improvement of ejection fraction and systolic dyssynchrony was only found in MSc group and combination group relative to the corresponding post-AMI values (both $p<0.05$) but remained unchanged in the other 2 groups. In addition, positive cells were found only in MSc group and combination group. Moreover, myocardial capillary vessels density in combination group was significantly more than other groups; and this was higher in MSc group and TMLR group than control group. Delta septal-to-lateral delay (between post-AMI and after therapy) was inversely correlated to myocardial capillary vessels density.

INVITED FREE PAPER 2:
INTERVENTION THE CELL ENERGY METABOLISM – A POSSIBLE ROUTE TO PREVENT OSTEOPOROSIS?

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The accelerated marrow adipogenesis in aging might reflect an unbalanced mesenchymal stem cell differentiation scheme. However, how aging makes the preferential shift from osteogenesis to adipogenesis is largely unknown. Sirt1 has been shown to regulate lifespan in lower organisms and affect age-related diseases in mammals. We previously showed that Sirt1 activity affected the lineage fate determination between osteogenesis and adipogenesis of MSCs. Since Sirt1 activity is largely dependent on the availability of NAD+ and influenced by the intracellular concentration of nicotinamide we supposed that MSC differentiation could be affected by enzymes involved in the NAD+ salvaging pathway.
The present study showed that the bone marrow stromal cells derived from 15-month-old C57BL/6 mice developed fewer bone nodules (as shown by von Kossa and alizarin red staining) and more adipocytes (as shown by oil red O staining) than cells derived from 4-week-old mice. The cells derived from aged mice had significantly lower intracellular NAD+ concentration and lower Sirt1 activity. However, the expression of Sirt1 protein was not reduced by aging. We also found that the potent and specific Nampt inhibitor, FK866 significantly increased the adipocyte formation in mesenchymal stem cell line C3H10 cells. In addition, adipocyte formation was significantly increased in cells tranfected by Nampt shRNA Lentiviral transduction particles. Q-PCR analysis showed that the expression of the adipocyte specific transcription factor PPARγ was significantly higher in Nampt deficient cells while the osteoblast key transcription factor Runx2, as well as the osteoblast marker genes, osteocalcin and OPG, were significantly downregulated. A significant reduction of Sirt1 activity was found in Nampt deficient cells, which had significantly lower NAD+ and higher intracellular concentration of NAM.
In conclusion, the present study showed that the lineage fate determination of MSCs could be affected by the activity of Nampt, the enzyme catalyzing NAD+ resynthesis from nicotinamide, possible through affecting Sirt1 function. Therefore, senile osteoporosis might occur with a deregulation of cell energy metabolism in mesenchymal stem cells.

Brief CV
I was born in 1977 in Changchun, Jilin Province, China. In 1996, I started my medical education with the 7-year clinical program at Peking University, Health Science Center. In 2003, after two years of junior resident training at the Department of Neurosurgery, Peking University First Hospital I moved to Stockholm, Sweden with a Ph.D. offer from the Department of Clinical Intervention and Technology (CLINTEC), Karolinska Institute.
My Ph.D. project is about the osteoblast differentiation from mesenchymam stem cells and I finished the doctoral thesis in 2008. This research experience helped me later established in the research field – the fat-bone balance with skeletal aging. My Ph.D. supervisor is Prof. Urban Lindgren, the Chairman of the Orthopedic Department, Karolinska University Hospital Huddinge, who, as a mentor, guided me to choose orthopedic as my career and continue the academic activities in Sweden.
I got a resident position in the Department of Orthopedics, Karolinska University Hospital in 2009 and will become a specialist orthopedic surgeon in 2015. I continued my academic career at CLINTEC, Karolinska Institute and have so far published 13 peer-reviewed articles.

AWARD PAPER 4
REPAIR OF OSTEOCHONDRAL DEFECTS WITH BIODEGRADABLE HYDROGEL ENCAPSULATING MANIPULATED MESENCHYMAL STEM CELLS IN AN ANIMAL MODEL

Sien Lin, Liangliang Xu, Yuk Wai Lee, Ling Qin, Kaiming Chan, Gang Li
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Introduction: Tissue engineering strategies combining stem cells, scaffolds and bioactive factors were believed to be a potential break-though for cartilage defect. Previous studies demonstrated that dedifferentiated reprogrammed mesenchymal stem cells (De-MSCs) showed advantages both in cell viability and lineage differentiation commitment. This study hypothesized that the combined delivery of De-MSCs and hydrogel under mechanical stimulation would enhance the quality of new cartilage formation in a rat osteochondral defect model.
Methods: Bone marrow-derived mesenchymal stem cells from a GFP-trangenic rat were cultured in either α-MEM (MSCs) or chondrogenic induction medium for 10 days followed by α-MEM for another 10 days (De-MSCs). Potentials for osteogenic, adipogenic, and chondrognenic differentiation were compared using standard assays. 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. Lineage differentiation-related markers were measured by qRT-PCR. Cell pellets were sectioned for histological assay. 2% methacrylated hyaluronic acid (MeHA) hydrogel constructs laden with MSCs (n=18) or De-MSCs (n=18) after photoencapsulated were cultured in defined chondrogenic medium. Then the constructs laden with MSCs and De-MSCs were subjected to compressive loading in a CartiGen bioreactor, or subjected to loading-free condition for 15 days. The constructs were implanted subcutaneously at dorsal side of nude mice (n=6) for another 30 days. Mechanical loading test, biochemistric assay, and histology were conducted in this study. The constructs including cell-free ones (Gel, n=6) were also implanted into the osteochondral defects in the femoral trochlear groove of rats (n=30, with 6 rats per group) under anesthesia. After 2 months, the rats were sacrificed and the distal femurs were collected for histological analysis.
Results: De-MSCs exhibited higher clonogenicity, faster proliferation, and higher cell survival rate than MSCs. De-MSCs also expressed higher chondrogenic markers in vitro. Nude mice study indicated MeHA hydrogel laden with De-MSCs under mechanical stimulation showed advantages in mechanical properties and glycosaminoglycan production. Data also showed beneficial effects on new cartilage formation and tissue integration in osteochondral defect models by the combined delivery of De-MSCs and hydrogel under mechanical stimulation.
Conclusion: De-MSCs took advantages in proliferation, cell survival and chondrogenesis of MSCs. The combined delivery of De-MSCs and hydrogel under mechanical stimulation enhanced the quality of new cartilage formation both in the nude mice model and osteochondral defect rat model.

AWARD PAPER 5
PIGGYBAC MEDIATED MULTIPLEX GENE TRANSFER IN MOUSE EMBRYONIC STEM CELLS

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South University of Science and Technology of China

PiggyBac system has been shown to have a high efficiency to mediate gene transfer. However, there are no reports on its efficiency to mediate multiplex transgenes in mouse embryonic stem cells (ESCs). Here we first established an immortalized feeder cell line by introducing four antibiotic resistance genes simultaneously into the original SNL 76/7 feeder cell line utilizing the PiggyBac system. This is the feeder cell line with the most diverse types of antibiotic resistance genes reported so far, which will enable researchers to perform simultaneous multiplex gene transfer or gene targeting experiments in ES cells. With such feeder cell line, we were able to quantitatively characterize the transposition efficiency of PiggyBac system in mouse ES cells using five transposons carrying different inducible fluorescence proteins and antibiotic resistance genes, and the efficiency ranged from about 2% for one transposon to 0.5% for five transposons. Based on this system, we can easily establish multiple ES cell reporters labeling different core transcription factors (TFs). In addition, we introduced different cassettes to introduce inducible overexpression and knockdown of the key genes so that we can alter the differentiation preferences. The highly efficient multiplex gene transfer mediated by PiggyBac will no doubt provide researchers with more choices in biomedical research and development.

AWARD PAPER 6
MIR-21 OVEREXPRESSING MESENCHYMAL STEM CELLS ACCELERATE FRACTURE HEALING IN A RAT CLOSED FEMUR FRACTURE MODEL

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Department of Orthopaedics and Traumatology
The Chinese University of Hong Kong

MicroRNAs (miRs) are small noncoding RNAs involved in numerous biological processes. Emerging evidence suggests that microRNAs play important roles in osteogenesis and skeletal homeostasis. Recent studies indicated the significate regulation function of mir-21 in osteogenesis in vitro, but little information is known about its veritable functions in vivo. In the present study, we aimed to investigate the effect of mir-21 intervention on osteogenic differentiation of rats bone marrow derived mesenchymal stem cells (rBMSCs) and repair capacity in rats closed femur fracture model with internal fixation. The results showed that the up-regulation of mir-21 not only increased the expression of osteopontin and ALP in rBMSCs but also promoted mineralization under osteogenic induction condition. Furthermore, the bone healing properties was also improved in fracture healing model according to the results of microCT, mechanical test and histological analysis. The current study confirms that the over expression of mir-21 promotes osteogenesis, and accelerates bone fracture healing, which may contribute to a new therapeutic way for fracture repair.

MOHAWK CONTRIBUTES TO TENDONGENIC LINAGE DIFFERENTIATION OF MESENCHYMAL STEM CELLS THROUGH TGFβ SIGNALING PATHWAY

Huanhuan Liu, Hong Wei Ouyang
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Hangzhou, China

More recently, Mohawk (Mkx) has been found essential for tendon development. Nevertheless, no published data are available regarding the roles of Mkx in tendinopathy and its application to tendon regeneration so far. Here, we found that Mkx expression level was dramatically lower in human tendinopathy tissue by using gene expression omnibus datasets and immunofluorescence assays. Moreover, Mkx is highly expressed in tendon progenitor cells and forced Mkx expression in mesenchymal stem cells (MSCs) strikingly promoted tenogenesis with higher tenogenic gene expression and greater collagen fibril growth, even more efficiently than Scleraxis (Scx), a master transcription factor of tendon. Interestingly, we also demonstrated that Mkx dramatically up-regulated Scx expression through binding to the Tgfb2 promoter. Additionally, the transplantation of Mkx expressing-MSC sheets promoted tendon repair in a mouse model of Achilles-tendon defect. Taken together, these data defined the crucial roles of Mkx in tendon pathology and tendon repair, as well as demonstrated that tenogenesis of mouse MSCs can be induced by modulating the expression of Scx and tenogenic ECM molecules in vitro and in vivo.

U0126 PROMOTES OSTEOGENESIS OF RAT BONE MARROW-DERIVED MESENCHYMAL STEM CELLS BY ACTIVATING BMP/SMAD SIGNALING PATHWAY

Yang Liu, Liangliang Xu, Gang Li
Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong

U0126 has been reported as a specific inhibitor for the ERK1/2 signaling pathway which plays a vital role during osteogenic differentiation of mesenchymal stem cells (MSCs). In the present study, we reported a positive effect of U0126 on osteogenesis of rat MSCs. We found that U0126 promoted the osteogenic differentiation of rat MSCs as demonstrated by quantitative real time PCR of osteogenic markers, ALP (alkaline phosphatase) activity and calcium nodule formation. Our study showed that this was due to U0126 enhanced BMP/Smad signaling pathway in rat MSCs, while inhibiting the ERK1/2 signaling pathway. Furthmore, the western blot result demonstrated that U0126 could increase Smad1/5/8 phosphorylation synergistically with β-glycerophosphate. In addition, we found U0126 significantly increased the expression of BMP2 during the process of osteogenesis in rat MSCs. And the level of phosphorylated Smad1/5/8 was significantly decreased by BMP2 antibody, suggesting that U0126 could also promote the expression of BMP2 to enhance Smad proteins phosphorylation. Taken together, we have demonstrated a novel function of U0126 in promoting osteogenic differentiation of rat MSCs by activating the BMP/Smad signaling pathway.

THE ANTI-SENESCENCE EFFECT OF HUMAN FETAL MESENCHYMAL STEM CELL DERIVED SECRETION

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Cellular senescence, in tissue remodeling, usually acts during embryonic development or tissue damage repair. In pathological site, accumulation of senescent cell will induced by insufficient clearance and then the regeneration of functional cell. Besides the tissue repairing process, senescence also involved in organismal aging process. There are adequate evidence indicate that anti-senescent therapy may help the recovery of tissue function by get rid of the senescent cell. For aging research, embryonic development study could give us hints. By comparing fetal and adult, we may open a new avenue in stem cell treatment. Although adult stem cell, such as Mesenchymal stem cell (MSC), have been widely investigated. In autologous transplantation, adult MSC still have the problems in expansion because in vitro culture of MSC will induce the cellular senescence of MSC. On the contrary, fetal derived MSC have higher proliferation rate, also have or even more advantage than its counterpart, such as higher differentiation potential and low immunogenicity. Then here comes the question, can we cure the aging by learn from fetal or embryonic development. However, in human there is no research report that if the factors secreted by fetal MSC can reverse aging phenotype of adult MSC. Our pilot study have shown that, after training the adult MSC of secreted factors (secretion) comes from fetal MSC, the proliferation rate, ontogenesis ability of adult MSC can be enhanced, and beta-galactosidase activity is reduced. Furthermore, the expressions of longevity genes, such as SIRT1, FOX3A, are increase. These data show us a new angle of view that fetal tissue may have the ability to help us on anti-aging research.

LncRNA DUM INTERACTS WITH DNMTS TO REGULATE DPPA2 EXPRESSION DURING MYOGENIC DIFFERENTIATION AND MUSCLE REGENERATION

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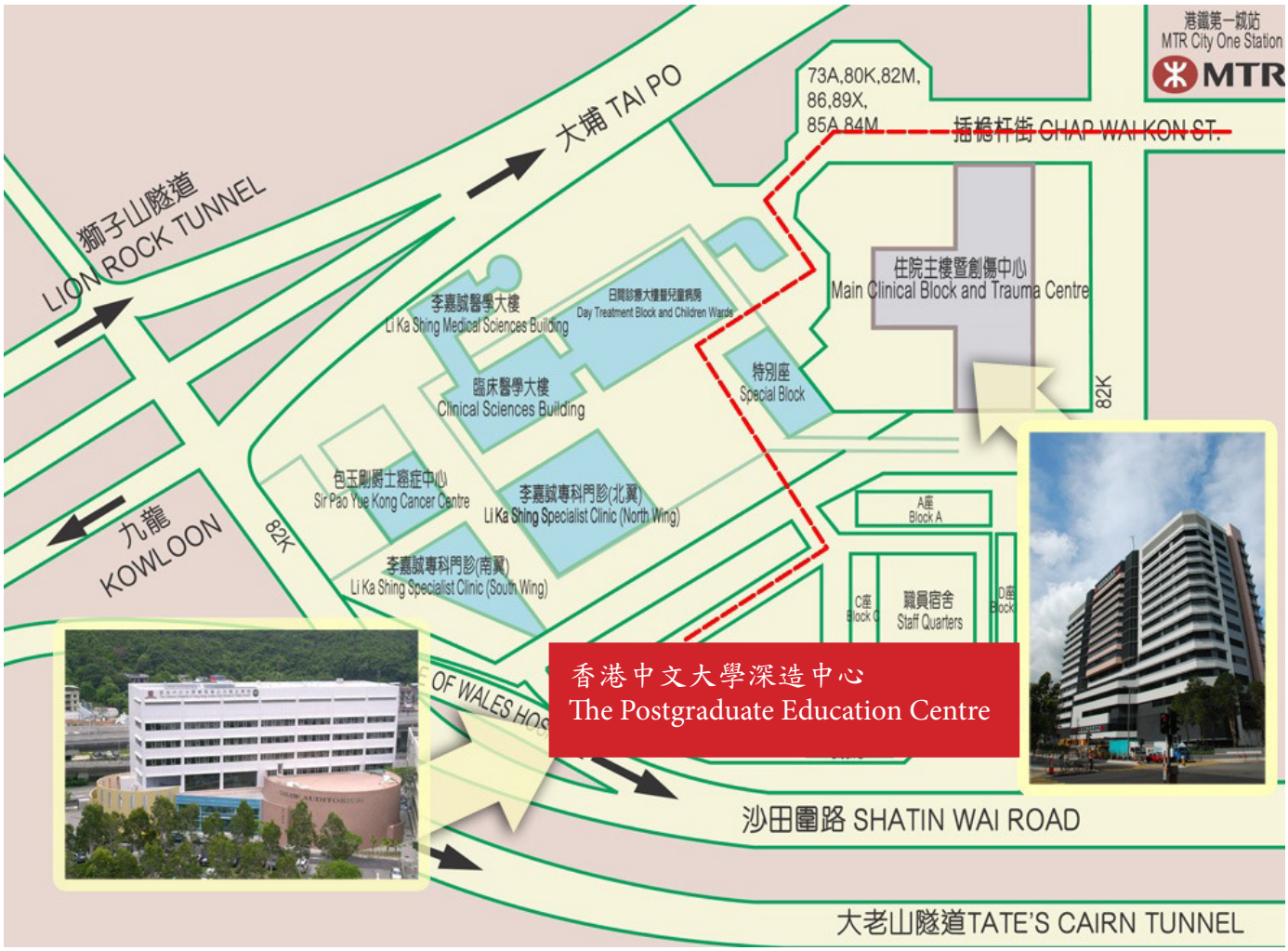
Emerging studies document the roles of long non-coding RNAs (LncRNAs) in regulating gene expression at chromatin level but relatively less is known how they regulate DNA methylation. Here we identify an lncRNA, Dum in skeletal myoblast cells. The expression of Dum is dynamically regulated during myogenesis in vitro and in vivo. It is also transcriptionally induced by MyoD binding upon myoblast differentiation. Functional analyses show it promotes myoblast differentiation and damage induced muscle regeneration. Mechanistically Dum was found to silence its neighboring gene, Dppa2 in cis through recruiting Dnmt1, Dnmt3a and Dnmt3b. Furthermore intrachromosomal looping between Dum locus and Dppa2 promoter is necessary for Dum/Dppa2 interaction. Collectively we have identified a novel lncRNA that interacts with Dnmts to regulated myogenesis.

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



Programme Rundown

Day 1 November 17, 2014 (Monday)

	Time	Key Event	Speaker
Venue: PEC Shaw Auditorium			
Session 1: Stem Cells in Tendon and Intervertebral Regeneration Moderators: **Prof. Mauro Alini** **Prof. Gang Li**	08:30-08:50	Tendon stem cell aging and rejuvenation	**Prof. Herb Sun, MD, PhD** *Albert Einstein College of Medicine, USA*
	08:50-09:10	Tenogenic differentiation of MSCs and their applications	**Prof. Gang Li, MD, PhD** *The Chinese University Hong Kong*
	09:10-09:30	Stem cells for intervertebral disc regeneration: Which cells? At which time? And how to deliver them?	**Prof. Mauro Alini** *AO Research Institute Davos, Switzerland*
	09:30-09:50	Notch signaling in development and disease	**Prof. Urban Lendahl** *Karolinska Institutet, Sweden*
	09:50-10:00	Panel discussion	
	10:00-10:30	Tea break and exhibitions	
Session 2: Conference Ceremony Moderator: **Prof. KM Chan**	10:30-10:45	Welcome address Group photo	**Prof. Francis Chan** *Dean, Faculty of Medicine* *The Chinese University Hong Kong*
Session 3: Musculoskeletal Regeneration Research Network (MRN) Moderator: **Prof. KM Chan**	10:45-10:55	Musculoskeletal Regeneration Research Network (MRN)	**Prof. KM Chan** *The Chinese University Hong Kong*
	10:55-11:05	UMC Utrecht and CUHK	**Prof. Wouter Dhert** *Utrecht University, Netherlands*
	11:05-11:15	Karolinska Institute and CUHK	**Prof. Christer Rolf** *Karolinska Institute, Sweden*
	11:15-11:23	Stanford University and CUHK	**Prof. Gang Li** *The Chinese University Hong Kong* **Prof. Stuart Goodman** *Stanford University*
	11:23-11:30	ACC and OUH-Danish Technological Institute & CUHK	**Prof. Ling Qin** *The Chinese University Hong Kong*
	11:30-11:40	CUHK Institute of Innovative Medicine - SMART	**Prof. KM Chan** *The Chinese University Hong Kong*
	11:40-11:50	2015 Karolinska Institute MRN meeting, Stockholm, June 2-4, 2015	**Prof. Li Felländer-Tsai** *Karolinska Institute, Sweden*
Session 4: Keynote Speech 1 Moderator: **Prof. Wai Yee Chan**	12:00-13:00	Application of iPS cell technologies to cartilage regeneration	**Prof. Noriyuki Tsumaki, M.D., Ph. D.** *Kyoto University, Japan*
	13:00-14:00	Lunch break and exhibitions Buffet lunch in foyer	
Session 5: New Technologies and Advancements Moderators: **Prof. Stuart Goodman** **Prof. Wouter Dhert**	14:00-14:20	3D printing technology and applications in orthopaedics	**Prof. Jos Malda** *Utrecht University, Netherlands*
	14:20-14:40	MiR-204 suppresses skeletal neoplasia through inhibition of Runx2-Activated AKT signaling in mesenchymal stem cells	**Prof. Di Chen** *Rush University, USA*
	14:40-15:00	Towards intraoperative cell repair	**Prof. Geoff Richards** *AO Foundation Research Institute, Switzerland*
	15:00-15:15	Panel discussion	
Session 6: Keynote Speech 2 Moderator: **Prof. Jack Cheng**	15:15-15:50	Regenerative applications of adult stem cells: repair, renovate, and re-create	**Prof. Rocky Tuan** *University of Pittsburg, USA*
	15:50-16:05	Tea break and exhibitions	
Session 7: Clinical Perspectives of Regenerative Medicine: The Reality and Challenges Moderators: **Prof. Jack Cheng** **Prof. Li Felländer-Tsai**	16:05-16:25	From development to osteoarthritis (OA) treatment	**Prof. Hongwei Ouyang** *Zhejiang University, China*
	16:25-16:45	Technovolution of cartilage repair: one stage technology using autologous and allogeneic cells	**Prof. Daniel Saris** *Utrecht University, Netherlands*
	16:45-17:05	The crosstalk of the town! – macrophages, osteoprogenitors and bone formation	**Prof. Stuart Goodman** *Stanford University, USA*
	17:05-17:25	Osteoarthritis of the knee: What have we learnt?	**Prof. Peter KY Chiu** *The University of Hong Kong*
	17:25-17:40	Panel discussion	
	18:00-19:00	Dr. Lui Che Woo Distinguished Professor Public Lecture New Era of Medicine with iPS Cells	**Prof. Shinya Yamanaka, MD, PhD** *Nobel Laureate in Physiology or Medicine 2012* *Shaw Laureate in Life Science and Medicine 2008*
	19:20	Meeting adjourns and bus transport to dinner venue at Shatin centre for invited guests and speakers	
	19:45	Conference Welcome dinner for invited guests and speakers	

Day 2 November 18, 2014 (Tueseday)

Time\Venue	PEC Kai Chong Tong		PEC Seminar Room 2-3	
	Session 8: Muscle Highlights Symposium	Moderators: **Prof. Huating Wang** **Prof. Jorge Ruas**	Session 9: Regulatory Factors in Development and Diseases	Moderators: **Prof. Yiping Li** **Prof. Kenneth Lee**
08:30-08:50	**Prof. Tom Cheung** *The Hong Kong University of Science and Technology* Molecular regulation of stem cell quiescence		**Prof. Oscar Lee** *Yangming University, Taiwan* Calcium phosphate-bearing matrices induce osteogenic differentiation of mesenchymal stem cells through adenosine signaling	
08:50-09:10	**Prof. Huating Wang** *The Chinese University of Hong Kong* Functional characterization of Malat1 in skeletal myogenic differentiation and muscle regeneration		**Prof. Christer Rolf** *Karolinska Institute, Sweden* The role of infection and genetic predisposition of failed healing in chronic tendon injuries and failed healing	
09:10-09:30	**Prof. Zhenguo Wu** *The Hong Kong University of Science and Technology* The role of STAT3 in adult muscle stem cells		**Prof. Bo Feng** *The Chinese University of Hong Kong* Modulating stem cell genes using engineered TALE and Cas9 transcription factors	
09:30-09:50	**Prof. Jorge Ruas** *Karolinska Institute, Sweden* Targeting the PGC-1α system to regulate skeletal muscle function and associated diseases		**Prof. Dongqing Cai** *Jinan University, China* Cardiac telocytes synergized adult stem cell therapy for myocardial infarction	
09:50-10:10	**Prof. Dahai Zhu** *Beijing Union Hospital, China* The long noncoding RNA linc-RNA regulates muscle differentiation and regeneration by facilitating myoD-baf60c-brg1 complex assembly		**Prof. Kingston Mak** *The Chinese University of Hong Kong* Yap1 inhibits the initiation of fracture healing by controlling chondrocyte differentiation	
10:00-10:20	Panel discussion			
10:20-10:40	Tea break and exhibitions			
	Session 10: Cartilage Regeneration and Osteoarthritis	Moderators: **Prof. Xiaodong Chen** **Prof. Lei Wei**	Session 11: Musculoskeletal Tissue Engineering	Moderators: **Prof. Tingting Tang** **Prof. Kevin Ho**
10:40-10:55	**Prof. Nidhi Bhutani** *Stanford University, USA* Epigenetic dysfunction in Osteoarthritis		**Prof. Chao Wan** *The Chinese University of Hong Kong* Erythropoietin/erythropoietin receptor in skeletal regeneration	
10:55-11:10	**Prof. Xiaodong Chen** *Texas University, USA* Tissue-specific Extracellular Matrix Controls the Fate of Bone Marrow-derived Mesenchymal Stem Cell Differentiation		**Prof. Tingting Tang** *Shanghai Jiaotong University, China* Repair and reconstruction of articular cartilage and subchondral bone with Sox 9 gene therapy and biphasic scaffold	
11:10-11:25	**Prof. Lei Wei** *Brown University, USA* Identification of Alpha 2 Macroglobulin (A2M) as a master inhibitor to attenuate osteoarthritis cartilage degeneration		**Prof. Yang Wang** *Shanghai Jiaotong University, China* Exosomes secreted by human-induced pluripotent stem cell-derived mesenchymal stem cells attenuate ischemic injury by promoting angiogenesis	
11:25-11:40	**Prof. Yiping Li** *University of Alabama, USA* Cbfβ promotes osteogenesis and chondrogenesis by suppressing adipocyte regulator expression and activating Wnt/β-catenin signaling		**Prof. Zhiyong Zhang** *Shanghai Jiaotong University, China* 3D printing technique based bone tissue regeneration strategy	
11:40-12:00	Panel discussion			
12:00-13:00	Lunch break and exhibitions Buffet lunch in foyer			
	Session 12: Stem Cells Manipulation	Moderators: **Prof. Ping Yuan** **Prof. Herb Sun**	Session 13: Biomaterials and Regenerative Medicine	Moderator: **Prof. Barbara Chan** **Prof. Li-ming Bian**
13:00-13:15	**Prof. Cynthia Jiang** *The Chinese University of Hong Kong* Dedifferentiation-reprogrammed MSCs in regenerative medicine		**Prof. Shengmin Zhang** *Huazhong University of Science and Technology, China* Gradient bioactive scaffold for in vivo reconstruction of articular cartilage/ subchondral bone	
13:15-13:30	**Prof. Jinyu Liu** *Jilin University, China* Large scale expansion of Wharton's jelly-derived mesenchymal stem cells while retaining self-renewal and multipotency characteristics and their capacity for enhancing skin wound healing		**Prof. Yunqing Kang, Kevin** *Florida Atlantic University, USA* Tissue-engineering a vascularized β-TCP scaffold using biomimetic periosteum for bone regeneration	
13:30-13:45	**Prof. Ping Yuan** *The Chinese University of Hong Kong* The role of Rif1 in pluripotent stem cell stability		**Prof. Liming Bian** *The Chinese University of Hong Kong* Functional biomaterials for cartilage repair	
13:45-14:00	**Prof. Xufeng Qi** *Jinan University, China* Involvement of Foxo3a in senescence of cardiac microvascular endothelial cells		**Prof. Ling Qin** *The Chinese University of Hong Kong* Magnesium as bioactive and biocorrosive orthopaedic implants	
14:00-14:20	Panel discussion			
14:20-14:40	Tea break			

Day 2 November 18, 2014 (Tueseday)

	Time	Key Event	Speaker
Venue: PEC Kai Chong Tong			
Session 14: Invited Free Paper 15 min Award Paper 7 min presentation & 3 min questions Judges and commentators: **Prof. Stuart Goodman** **Prof. Yiping Li** **Prof. Kingston Mak** **Prof. Tingting Tang**	14:40-14:55	Themoreversible hyaluronan hydrogel induces disc phenotype in human mesenchymal stromal cells	**Dr. David Eglin** *AO Foundation, Switzerland*
	14:55-15:05	Yap1 inhibits the initiation of fracture healing by controlling chondrocyte differentiation	**Yujie Deng** *School of Biomedical Sciences, CUHK*
	15:05-15:15	Stepwise differentiation of human induced pluripotent stem cells for Achilles tendon regeneration by change of physical substrate	**Can Zhang** *Zhejiang University*
	15:15-15:25	Recovery of systolic synchrony in acute myocardial ischemia with treatment of autologous bone marrow mesenchymal stem cell transplantation in combination of transmyocardial laser revascularization in rabbit model	**Fang Fang** *Cardiology, CUHK*
	15:25-15:40	Intervention the cell energy metabolism – a possible route to prevent osteoporosis?	**Dr. Yan Li** *Karolinska Institute, Sweden*
	15:40-15:50	Repair of osteochondral defects with biodegradable hydrogel encapsulating manipulated mesenchymal stem cells in an animal model	**Sien Lin** *Orthopaedics and Traumatology, CUHK*
	15:50-16:00	PiggyBac mediated multiplex gene transfer in mouse embryonic stem cells	**Xibin Lu** *South University of Science and Technology of China*
	16:00-16:10	Mir-21 overexpressing mesenchymal stem cells accelerate fracture healing in a rat closed femur fracture model	**Yuxin Sun** *Orthopaedics and Traumatology, CUHK*
	16:10-16:20	Comments and questions	**Judge panel members**
		Free paper awards ceremony	**Prof. Gang Li** **Prof. Stuart Goodman**
	16:20-16:30	Conclusion remarks	**Prof. KM Chan** **Prof. Gang Li**
	16:30	Meeting adjourns	

Special Thanks To:

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

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

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

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