# 細胞治療於再生醫學之臨床應用暨
# 2019年台灣再生醫學學會國際學術研討會

## Clinical Application of Cell Therapy
## in Regenerative Medicine
## / 2019 International Annual Meeting of FARM

# 摘要集

2019年3月23日

亞東紀念醫院國際會議廳

主辦單位：亞東紀念醫院骨科部、台灣再生醫學學會

協辦單位：科技部生命科學研究推動中心

贊助單位：衛生福利部

# 目　錄

# Content

# 細胞治療於再生醫學之臨床應用暨 2019 年台灣再生醫學學會國際學術研討會
# Clinical Application of Cell Therapy in Regenerative Medicine / 2019 International Annual Meeting of FARM

## Scientific Program

| Time | Topic | Speakers | Institute | Moderator |
|---|---|---|---|---|
| 08:30 | Registration 報 到 | | | |
| 08:50~10:05 Symposium：**Clinical Application of Regenerative Medicine in Asian-Pacific Region** | | | | |
| **I-01** 08:50~09:15 | Epigenetic Regulation in Mesenchymal Stem Cell Immune Therapies | Songtao Shi | University of Pennsylvania | 陳敏慧教授 張志豪教授 |
| **I-02** 09:15~09:40 | Equivalent 10-year Outcomes after Implantation of Autologous Bone Marrow-Derived Mesenchymal Stem Cells Versus Autologous Chondrocyte Implantation for Chondral Defects of the Knee | James, Hoi Po Hui | Department of Orthopaedic Surgery, Yong Loo Lin School of Medicine, National University Singapore | |
| **I-03** 09:40~10:05 | Advances in Repair of Corneal Endothelium Using Hydrogel Film to Restore Vision- Towards Clinical Trial | Gregory Dusting | Centre for Eye Research Australia, University of Melbourne | 林峯輝教授 |
| 10:05~10:15 Opening Ceremony （大合照）<br>10:05~10:30 Coffee Break | | | | |
| 10:30~12:10 Symposium：**Clinical Application of Cell Therapy in Taiwan** | | | | |
| **I-04** 10:30~10:55 | New Regulation on Cell Therapy in Taiwan: Challenge and Prospect | 石崇良 | 行政院衛生福利部醫事司司長 | 孫瑞昇教授 |
| **I-05** 10:55~11:20 | Allogeneic MSC Therapy: Feasibility Using HLA-Matched Donors ? | 陳耀昌 | 台灣細胞醫療協會理事長 國立台灣大學醫學院名譽教授 | |
| **I-06** 11:20~11:45 | Reprogramming Cellular Identity for Liver Regenerative Medicine | 沈家寧 | 台灣幹細胞學會理事長 中央研究院基因體研究中心 | 張瑞根教授 何美泠教授 |
| **I-07** 11:45~12:10 | Clinical Trial of Cartilage Defect and OA Treatment Using BMMSC and IPFP MSC | 張至宏 | 台灣再生醫學學會理事長 亞東紀念醫院骨科部 | |
| 12:10 會 員 大 會 | | | | |
| 12:10~13:30 Lunch Break | | | | |

| Time | Topic | Speakers | Institute | Moderator |
|---|---|---|---|---|
| 13:30~15:35 Symposium：**Clinical Application of Regenerative Medicine in Korea** | | | | |
| **I-08** 13:30~13:55 | Overview of Korean Regenerative Medicine: Commercial Development and Ecosystem | So Ra Park | Inha University School of Medicine Strategic Center for Regenerative Medicine | 劉華昌教授 胡育誠教授 |
| **I-09** 13:55~14:20 | Current Status of Treatment of Cartilage Defect in OA Knee in Korea | Eun-Kyoo Song | Department of Orthopedic Surgery, Chonnam National University Bitgoeul Hospital | |
| **I-10** 14:20~14:45 | Gene-cell Therapy to Treat Osteoarthritis | Gun-Il Im | Research Institute for Integrative Biomedical Engineering, Dongguk University, Korea | 陳志華教授 黃玲惠教授 |
| **I-11** 14:45~15:10 | Fabrication of an Injectable Engineered Cartilage Using Fetal Chondrogenic Progenitors | Bryan Choi | Inha University School of Medicine | |
| **I-12** 15:10~15:35 | Bioengineering of Vascular Graft | Soo Hyun Kim | Biomaterials Research Center, Korea Institute of Science & Technology | 王兆麟教授 |
| 15:35~16:00 Coffee Break | | | | |
| 16:00~16:50 Symposium：**Clinical Application of Cell Therapy: Regulation and Industry** | | | | |
| **I-13** 16:00~16:25 | Considerations for the Design of Clinical Trials of Cellular Therapy Products | 湯依寧 | Regulatory Science, Center for Drug Evaluation, Taiwan | 詹益聖教授 林泰元教授 |
| **I-14** 16:25~16:50 | Development and Clinical Application of Regenerative Medical Products by Japan Tissue Engineering Co., Ltd. | 篠原力 Chikara Shinohara | Japan Tissue Engineering Co., Ltd. | |
| 16:50~17:20 **產業論壇** | | | | |
| **B-01** 16:50~17:05 | The Clinical Experiences of Fibroblast Cell Therapy | 陳彥聰 | 瑪旺幹細胞醫學生物科技股份有限公司 | 王至弘教授 方旭偉教授 |
| **B-02** 17:05~17:20 | Prospects and Trends of Immune Cell Therapy | 張順浪 (Alarng Chang) | 基亞生物科技股份有限公司 | |
| **壁報競賽頒獎** | | | | |

## 壁報 Poster

評審委員：侯連團教授、曾靖孋教授

壁報論文解說時段：13:00~14:00。

| No. | Topic | Authors | Institute |
|---|---|---|---|
| P-01 | Therapeutic effect of Artificial Tears containing *Bletilla striata* Polysaccharide (BSP) in the Management of Dry Eye Syndrome | Minal Thacker<br>Chih-Yen Chang<br>Feng-Huei Lin[*] | National Taiwan University, Graduate Institute of Biomedical Engineering |
| P-02 | Multilayer Hair Sphere for Epithelium-Mesenchyme Interaction During Hair Neogenesis | 賴正偉 [1*] 黃子婕 [2*]<br>吳佳慶 [1,2,3] | 國立成功大學生物醫學工程學系 [1]<br>國立成功大學基礎醫學研究所 [2]<br>國立成功大學細胞生物與解剖學研究所 [3] |
| P-03 | Tissue-specific Interactions of Human Mesenchymal Stem Cells (hMSCs) in Modulating Peripheral B Lymphocytes Differentiation | 李瑋 [1,2] 王麗姿 [3]<br>徐珮茹 [2] 李雨薇 [2]<br>劉柯俊 [4] 顏伶汝 [2]<br>嚴孟祿 [3] | 國防醫學院生命科學研究所 [1]<br>國家衛生研究院細胞與系統醫學研究所再生醫學研究組 [2]<br>國立台灣大學醫學院婦產科 [3]<br>國家衛生研究院癌症研究所 [4] |
| P-04 | Adipose-derived Stem Cells-Modulated Dendritic Cells tolerogenicityis is Associated with Notch Pathway | 王育婧 陳榮富<br>郭耀仁 | 高雄醫學大學外科部整形外科 |
| P-05 | Ex vivo Expansion of CD34+ Cells from Non-GCSF Mobilized Peripheral Blood Stem Cells | 楊秉恆 [1,2,3]<br>陳德福 [1] 蕭懿 [1]<br>蕭嘉陽 [1] | 國防醫學院醫學科學研究所 [1]<br>三軍總醫院病理部血庫中心 [2]<br>三軍總醫院病理部臨床病理科 [3] |
| P-06 | CRISPR-based Activation of Endogenous Neurotrophic Genes in Adipose Stem Cell Sheet to Stimulate Peripheral Nerve Regeneration | Mu-Nung Hsu[1, §],<br>Han-Tsung Liao[2, §],<br>Vu Anh Truong[1],<br>Kai-Lun Huang[1],<br>Fu-Jen Yu[1],<br>Hwei-Hsien Chen[3],<br>Nguyễn Thị Kiều Nương[1],<br>Yu-Chen Hu[1,4,*] | 國立清華大學化學工程系 [1]<br>桃園長庚紀念醫院整形外科 [2]<br>國家衛生研究院神經及精神醫學研究中心 [3]<br>國立清華大學 前瞻物質基礎與應用科學中心 [4] |
| P-07 | A Single CRISPRai Platform Enabling Simultaneous Gene Activation and Repression for Chondrogenic Differentiation and Calvarial Bone Regeneration | 福安 胡育誠 | 國立清華大學化工所 |
| P-08 | Modulation of Small Molecules for Efficient 3D-Chondrogenic Differentiation of Tissue-specific and Induced Pluripotent Stem Cell (iPSC)-derived Human Mesenchymal Stem Cells (hMSCs) | 謝承展 [1,2] 李雨薇 [2]<br>徐珮茹 [2] 陳令儀 [1]<br>顏伶汝 [2] 嚴孟祿 [3] | 國立清華大學分子醫學研究所 [1]<br>國家衛生研究院細胞及系統醫學研究所 [2]<br>國立台灣大學醫學院附設醫院婦產科 [3] |

| No. | Topic | Authors | Institute |
|---|---|---|---|
| P-09 | The ADSC Product GXHPC1 Facilitated Recovery of Liver Function for Liver Cirrhosis Patient | 蔡侑珍[1] 莊明熙[2] 林怡均[3] 林珀丞[3] 黃奇英[4] | 國立陽明大學醫學生物技術暨檢驗學系[1] 中華大學科技管理研究所[2] 國璽幹細胞應用技術有限公司[3] 國立陽明大學生物藥學研究所[4] |
| P-10 | Parathyroid Hormone (1-34) Ameliorates Human Chondrocyte Apoptosis by Reducing the Expression of Programmed Cell Death 5 | 李智堯[1] 陳崇桓[1,2,3] 林怡珊[1] 張瑞根[1,2] 何美泠[1] | 高雄醫學大學骨科學研究中心[1] 高雄醫學大學附設醫院骨科[2] 高雄市立大同醫院骨科[3] |
| P-11 | The Influence of Fibroblast Growth Factor-2 on Human Adipose-Derived Stem Cells During Long-term *In Vitro* Culture | 鄭穎[1] 林凱旋[1] 鄭乃禎[1,2] | 國立台灣大學附屬醫院外科部[1] 國立台灣大學發育生物學與再生醫學研究中心[2] |
| P-12 | Platelet Lysate Enhanced Adipose-derived Stem Cell Sheet Formation with Improved Angiogenic Capability | 李寧栩[1] 楊台鴻[1] 鄭乃禎[2] | 國立臺灣大學醫學院暨工學院醫學工程所[1] 國立臺灣大學醫學院附設醫院外科部[2] |
| P-13 | Cartilage Regeneration by Autologous Adipose-Derived Mesenchymal Stem Cells for the Treatment of Osteoarthritis | 江宜蓁[1] 磐田振一郎[2] 楊晴棻[1] 白川康一[3] 松岡孝明[1] | STEMCELL 株式會社[1] Riso 診所[2] 京都大學東南亞研究所[3] |
| P-14 | The Helene Medium: A Specialized Stem Cell Culture Medium | 梁安柔[1] 楊晴棻[1] 白川康一[1,2] 松岡孝明[1] | STEMCELL 株式会社[1] 京都大學東南亞研究所[2] |
| P-15 | Can Mesenchymal Stem Cells and Their Conditioned Medium Assist Inflammatory Chondrocytes Recovery? | 陳郁君[1] 張育瑋[2] 陳瑾霈[1] 沈宜珊[1] 王耀宏[3] 張至宏[1] | 亞東紀念醫院骨科部[1] 馬偕紀念醫院外科部[2] 元培醫事科技大學護理系[3] |
| P-16 | Effectiveness Among Hyaluronic Acid, Platelet-Rich Plasma, and Mesenchymal Stem Cells for Knee Osteoarthritis: An *In Vitro* Animal Study on Rabbit | 陳郁君[1] 許元銘[1] 陳瑾霈[1] 方旭偉[2] 張至宏[1] | 亞東紀念醫院骨科部[1] 國立台北科技大學化學工程與生物科技系暨化學工程研究所[2] |

# Invited Lectures

## Songtao Shi Biography

**Songtao Shi, D.D.S., Ph.D.**, is Professor and Department Chair at the University of Pennsylvania School of Dental Medicine. Dr. Shi received his D.D.S. degree and certificate in Pediatric Dentistry from the Peking University School of Stomatology and Ph.D. in Craniofacial Biology from the University of Southern California. Prior to joining the faculty at the University of Pennsylvania, he served as a Principal Investigator and Clinical Fellow for nine years at the National Institute of Dental and Craniofacial Research and a professor for more than eight years at the University of Southern California.

His research program focuses on understanding mechanism of mesenchymal stem cell (MSC)-associated diseases, developing new experimental disease models, and exploring feasibility of translating these bench discoveries to clinical therapies. His group and his collaborators were the first to identify dental pulp stem cells, baby tooth stem cells, periodontal ligament stem cells, root apical papilla stem cells, tendon stem cells, gingiva stem cells, sclera MSCs, and benign tumor MSCs from keloid. These novel and landmark discoveries have opened opportunity for scientists to investigate oral tissues derived stem cells and their use for tissue engineering, disease modeling, and clinical treatment.

In translational study, Dr. Shi's team has used these stem cells to regenerate a variety of tissues, including dentin, pulp, periodontal ligament, tendon, bone, bio-root in preclinical animal models. Dr. Shi collaborated with Dr. Lingyun Sun and Dr. Yan Jin' team to use MSCs to treat systemic lupus erythematosus (SLE) and regenerate dental pulp tissues in patients. Additionally, Dr. Shi and his collaborators were the first to generate bisphosphonate-related osteonecrosis of the jaw-like disease (BRONJ) and keloid disease models in mice and swine.

To understand mechanisms of MSC-based therapies, Dr. Shi's team was the first to reveal that recipient immune cells regulated cell-based bone regeneration. Additionally, Dr. Shi and his collaborators discovered that the interplay between the donor cells and recipient immune cells determined MSC transplantation-mediated immunotherapeutic effect in human and mouse model. Dr. Shi has published more than 190 peer-reviewed articles in a variety of high-impact scientific journals, of which he served as the corresponding author in *Nat Medicine, Cell Stem Cell, Cell Metabolism, Immunity, Lancet, J Clin Invest, Nat Biotechnol, Nature Communication, Science Translational Medicine, Journal of Experimental Medicine, Proc Natl Acad Sci U S A, Cell Research, Blood, EMBO Mol Med, Cell Death Differ*, *J Bone Miner Res, Stem Cells, and J Dent Res.* According to the google scholar, Dr. Shi's publication has been cited over 40,000 times (http://scholar.google.com/citations?user=q1HfzhoAAAAJ&hl=en).

Clinically, Dr. Shi hold Dental Licensure of State of California and had experience working at NIH hospital and private practice section in USA. This background makes Dr. Shi a highly qualified translational researcher to use stem cell for disease treatment. Dr. Shi served on several local and national committees and boards including Scientific Editor for the PLoS ONE and Associate Editor for Journal of Tissue Engineering. He is recipient of the 2013 IADR Distinguished Scientist Award for Pulp Biology & Regeneration. His service has also included: Scientific Advisory Boards for the Journal of Endodontics, the Scientific Committee of Chinese Stomatological Association, and the Scientific Committee of Chinese Military Stomatology Research Institute. Dr. Shi is Changjing Scholar in the Fourth Military Medical University, Distinguished Visiting Professor in Tongji University, Visiting Professor in XiangYa School of Medicine & Stomatology, Central South University (CSU), and distinguished visiting professor in Dankook University, Korea.

**08:50-09:15**

**I-01**

## Epigenetic Regulation in Mesenchymal Stem Cell Immune Therapies

Songtao Shi
University of Pennsylvania

**Abstract:**

Mesenchymal stem cells (MSCs) are multipotent postnatal stem cells capable of regenerating mineralized and non-mineralized tissues and interplaying with various immune cells. MSCs are widely used to treat a variety of autoimmune diseases, such as graft versus host disease, diabetes, rheumatoid arthritis, autoimmune encephalomyelitis, inflammatory bowel disease, systemic lupus erythematosus and multiple sclerosis. However, detailed mechanism by which MSC transplantation (MSCT) offers effective immune therapies is not fully understood. Our recent studies showed that MSCT utilizes multiple mechanisms to interplay with the recipient cellular components to ameliorate disease phenotypes. MSCT is capable of inducing recipient activated T cell apoptosis *via* Fas/Fas ligand pathway to trigger macrophage to take debris of apoptotic T cells, resulting in an elevated TGFbeta level as well as immune tolerance in systemic sclerosis. In addition, exosomes secreted by donor MSCs during MSCT provide functional cell components and miRNA, thereby rescuing recipient impaired MSCs or immune cells *via* a reuse mechanism to regulate DNA methylation and histone modification. Moreover, we found that MSCT is able to directly transfer miRNA to the recipient stem cells to rescue impaired stem cell function. Our findings demonstrate that MSCT use multiple epigenetic regulation to rescue recipient MSC function and ameliorate disease phenotypes..

## Name: Hui Hoi Po, James

**Current Position**:

- Professor, Department of Orthopaedic Surgery, Yong Loo Lin School of Medicine, National University Singapore

**Research Interests:**

- MSC exosomes for treatment of cartilage injuries
- Enhancing self-renewal and therapeutic potential of adult human mesenchymal stem cells through the use of heparan sulfate.
- Repair of Osteochondral Defects using a combination of stem cell and heparan sulfate Device.
- Improving graft bonding at the bone tunnel for Anterior Cruciate Ligament (ACL) reconstruction, using a silk sleeve device.
- Randomized controlled clinical trial to evaluate a novel and minimally-invasive technique of cartilage repair in the human knee using autologous mesenchymal stem cells and Hyaluronic Acid.

**International Refereed Publications in the last 5 years with IF (most recent from over 100 papers)**:

1. Lee JH, Luo X, Ren X, Tan TC, Smith RAA, Swaminathan K, Sekar S, Bhakoo K, Nurcombe V, Hui JH, Cool S. A heparan sulfate device for the regeneration of osteochondral defects. *Tissue Eng Part A*. Oct 23. doi: 10.1089/ten.TEA.2018.0171. [Epub ahead of print] (2018) **IF: 3.508**
2. Lysaght T, Munsie M, Castricum A, Hui JH, Okada K, Sato Y, Sawa Y, Stewart C, Tan LK, Tan LHY, Sugii S. A roundtable on responsible innovation with autologous stem cells in Australia, Japan and Singapore. *Cytotherapy*. Sep;20(9):1103-1109 (2018) **IF: 3.993**
3. Zhang S, Chuah SJ, Lai RC, Hui JH, Lim SK, Toh WS. MSC exosomes mediate cartilage repair by enhancing proliferation, attenuating apoptosis and modulating immune reactivity. *Biomaterials.* Nov 21;156:16-27. (2017) **IF: 8.402**
4. Tan SHS, Ibrahim MM, Lee ZJ, Chee YKM, Hui JH. Patellar tracking should be taken into account when measuring radiographic parameters for recurrent patellar instability. *Knee Surg Sports Traumatol Arthrosc*. Nov 20. (2017) **IF: 3.227**
5. Samsonraj RM, Raghunath M, Nurcombe V, Hui JH, van Wijnen AJ, Cool SM. Concise Review: Multifaceted Characterization of Human Mesenchymal Stem Cells for Use in Regenerative Medicine. *Stem Cells Transl Med. Dec;6(12):2173-2185.* (2017) **IF: 4.929**
6. Parate D, Franco-Obregón A, Fröhlich J, Beyer C, Abbas AA, Kamarul T, Hui JH, Yang Z. Enhancement of mesenchymal stem cell chondrogenesis with short-term low intensity pulsed electromagnetic fields. *Sci Rep*. Aug 25;7(1):9421. (2017) **IF: 4.122**
7. Wijesinghe SJ, Ling L, Murali S, Qing YH, Hinkley SF, Carnachan SM, Bell TJ, Swaminathan K, Hui JH, van Wijnen AJ, Nurcombe V, Cool SM. Affinity selection of FGF2-Binding Heparan Sulfates for Ex Vivo Expansion of Human Mesenchymal Stem Cells. *J Cell Physiol*. 2017 Mar;232(3):566-575 (2017) **IF: 4.080**
8. Toh WS, Brittberg M, Farr J, Foldager CB, Gomoll AH, Hui JH, Richardson JB, Roberts S, Spector M. Cellular senescence in aging and osteoarthritis. *Acta Orthop*. 2016 Sep 23:1-9. **IF: 3.076**

9. Ling L, Camilleri ET, Helledie T, Samsonraj RM, Titmarsh DM, Chua RJ, Dreesen O, Dombrowski C, Rider DA, Galindo M, Lee I, Hong W, Hui JH, Nurcombe V, van Wijnen AJ, Cool SM. Effect of heparin on the biological properties and molecular signature of human mesenchymal stem cells. *Gene*. 15;576(1 Pt 2):292-303. (2016) **IF:2.498**
10. Wong KL, Lee KB, Tai BC, Law P, Lee EH, Hui JH. Injectable cultured bone-marrow derived mesenchymal stem cells in varus knees with cartilage defects undergoing high tibial osteotomy: a prospective, randomized controlled clinical trial with 2 years' follow-up. *Arthroscopy-The Journal of Arthroscopic and Related Surgery* 29(12):2020-8 (2013) **IF: 4.330**

**09:15-09:40**

**I-02**

## Equivalent 10-year Outcomes after Implantation of Autologous Bone Marrow-Derived Mesenchymal Stem Cells Versus Autologous Chondrocyte Implantation for Chondral Defects of the Knee

James, Hoi Po Hui
Department of Orthopaedic Surgery, Yong Loo Lin School of Medicine, National University Singapore

Professor Hui a clinician-scientist who has two decades of experience in treating osteochondral injuries, and is a director of the Cartilage Repair Programme in NUHS. He is dedicated to overcoming the clinical challenges faced in knee repair, through synergistic collaborations with bioengineers and basic research scientists, to strategically improve the replicative capacity and therapeutic efficacy of mesenchymal stem cells.

In collaboration with NUS bioengineers, a novel bone-graft interfacial augmentation (BGIA) device was developed to complement the use of tendon autografts. This followed our research finding that the application of MSCs at the allograft tendon-bone interface during ACL reconstruction led to the formation of an intervening zone of fibrocartilage which enhanced allograft osteointegration and offered the potential of more physiologic and earlier healing. With the submission of a clinical trial application, it is now a step closer to clinical use. Together with collaborators from A*Star, a novel strategy- supplementation of heparan sulfate (HS8) for the ex vivo scale-up of human bone marrow derived mesenchymal stem cells (hMSCs) was established. With increased affinity to fibroblast growth factor (FGF2), HS8 stabilizes and sustains FGF2 bioactivity, resulting in increased proliferation of hMSCs of better quality. The implantation of hMSCs has resulted in improved osteochondral repair in animal models. The team is working to define the full therapeutic potential and applicability of this novel treatment, which has potential to benefit people who suffer from osteochondral lesions or osteoarthritis.

One of the conducted clinical trials compared the long-term clinical outcomes of 72 patients who underwent either ACI or BMSC implantation – matched in terms of age and lesion site. The patients were followed up to a median of at least 10 years. The study shows that BMSC implantation used for treating knee chondral defects resulted in clinical outcomes equivalent to first generation ACI at up to 10 years, with no apparent increased tumor formation risk. This is the only study which has directly compared long-term outcomes of the two procedures.

## Professor Greg Dusting Biographical Summary

**Prof Greg Dusting (*Honorary Professorial Fellow, University of Melbourne*)** is a distinguished pharmacologist who was appointed inaugural Executive Director Research to the *Centre for Eye Research Australia (CERA*) in 2012. This followed 5 years as Professor and Director of Tissue Engineering at the *O'Brien Institute (OBI*) nearby. He was a *NHMRC Principal Research Fellow* of many years standing, and is internationally renowned for his work on the vascular endothelium, tissue engineering and drug mechanisms in cardiovascular and retinal disease. With his team he continues collaborative work at OBI to build cardiac tissue from stem cells, and has been tackling the causes of aberrant corneal and retinal vascularisation in major retinal diseases, and recently also drug-targetable mechanisms of Age-Related Macular Degeneration. He has attracted new recruits to CERA in stem cell biology and cytoprotective strategies in basic pharmacology, who underpin and interact with the world class clinical and genetics researchers in the major retinal diseases at the core of this program. In 2018 CERA was re-affirmed as ranking number 4 of all Eye Research Institutes in the world, based on research output metrics.

Prof Dusting was elected as ***Fellow of the British Pharmacological Society*** in 2005, and in the last 5 years was awarded both the ***Rand Medal for Pharmacology*** by ASCEPT (the most prestigious prize established by this Pharmacological Society), and the ***Heart Foundation Research Medal,*** for distinguished lifetime contributions to cardiovascular research. His additional appointments include Professorial Fellow of University of Melbourne, adjunct Professor of Australian Catholic University, visiting Professor for cardiac regenerative medicine and tissue engineering in the NHC, *SingHealth*; *ChonBuk National University* (2009-2011 BIN Fusion Program), JeonJu, Korea; and the Key Centre for Vascular Re-modelling in *Qilu Hospital, Shandong University*, China. He has been a key instigator of commercial developments from his research, some with established or new biotech companies, and was the major initiator to invention of two cardiovascular drugs now on the market or in clinical trial. The first (treprostinil) now has a worldwide market exceeding $1 billion pa. The second new lead compound to treat heart attack he invented with his team at the Florey Institute. This NCE is in clinical development, and with major Pharma investment is set to conclude in 2018 a Phase 2 clinical trial for *Armaron Bio P/L*, the company which he and colleagues founded with venture capital. He is or has been a member of the Editorial Board of 8 scientific journals including *Pharmacology and Therapeutics* (IF =11) and *Tissue Engineering and Regenerative Medicine* (IF =1.0). He has trained or mentored 10 full professors of Pharmacology or Medicine, now leading distinguished academies in Australia, USA and China

He has published more than 300 original research papers, cited >8,000 times (h-index 50). His major scientific contributions have been discovery of roles of the vascular endothelium in vascular and retinal disease, and invention of new therapeutic approaches based on these mechanisms. He is now helping develop a regenerative approach to repair of damaged cornea and cardiac tissue, and new drugs and delivery materials for retinopathies.

**09:40-10:05**

**I-03**

# Advances in Repair of Corneal Endothelium Using Hydrogel Film to Restore Vision - Towards Clinical Trial

Greg Dusting[1], Karl David Brown[1], Jean-Pierre Scheerlinck[3], Hong Zhang[4], Shereen Tan[2], Greg Qiao[2] Mark Daniell[1]
[1] Ophthalmology, Dept of Surgery, University of Melbourne and Centre for Eye Research Australia, East Melbourne, Victoria, Australia
[2] Department of Chemical and Biomolecular Engineering, University of Melbourne, Parkville, Victoria, Australia
[3] Centre for Animal Biotechnology, University of Melbourne, Parkville,Victoria, Australia
[4]Eye Hospital, The First Affiliated Hospital, Harbin Medical University, China
email: dusting@unimelb.edu.au Tel: +61 403 040532

## Abstract

Our team develops a tissue engineering approach and cell therapy for corneal repair, engaging chemical engineers, cell biologists, and ophthalmologists in integrated activities to cure blinding eye disease. He we focus on the development of a tissue-engineered corneal endothelium (TCE) to replace donor tissue used for corneal endothelial keratoplasties. All Asian countries have a great need for corneal repair technologies because of the non-availability for transplantation of corneas from donors.

A TCE consisting of a polyethylene glycol-based hydrogel film (PHF) and confluent cultured corneal endothelial cells (CEC) was developed. The PHF was selected by the following criteria: the ability to be drawn through a Busin's glide (a funnel used in this surgery), transparency, and optimal proliferation of CEC on its surface. The tensile properties of the selected candidates were tested, whereby films of 1cm$^2$ area were subjected to tensile forces until film breakage. Ultimate stresses and strains were 5.2 +/- 0.2 MPa and 61 +/- 3 % respectively; comparable to donor tissue lenticules widely used in such implantation procedures. Film thickness was determined by scanning electron microscopy and spectral reflectance showed approximately 50µm, compatible with current surgical practice.

Sheep CEC cultured on PHF stained positive for the crucial $Na^+/K^+$-ATPase membrane pump. Cultured CEC density on PHF was 3150 +/- 459 cells/mm$^2$ (n=4). Normal CEC density *in vivo* in sheep was 3150 +/-88 cells/mm$^2$ (n=3). In adult ewes (female sheep) endothelial dystrophy was created by surgically scraping CEC from a 7mm diameter area of the central cornea to assess the TCE for toxicity, immunogenicity and the ability to clear the cornea of oedema. Controls included PHF without CEC and TCE not placed directly over the endothelial wound. Sheep were observed for at least 21 days post-surgery and scored for oedema on a validated scale of 0-4, with 0 being completely thin and 4 being maximally thick. Allogeneic TCE was non-toxic and non-immunogenic for up to 60 days (n=13). When placed over the endothelial wound the implant did indeed abate oedema (by 20 days final score of 0 or 1, 70% n=10 ) . Histology revealed complete degradation of the PHF after 20 days in TCE-transplanted sheep.

*Conclusion*- A tissue-engineered corneal endothelium (TCE) consisting of cultured corneal endothelial cells (CEC) on a hydrogel film might well be suitable to replace donor tissue after corneal injuries or disease causing loss of vision.

## Shih, Chung-Liang 石崇良


Official Title/Position：Director-General （司長）
Institute：
Department of Medical Affairs, Ministry of Health and Welfare, Taiwan （衛生福利部醫事司）

**Biography**

Dr. Shih, Chung-Liang serves as the Director-General of Department of Medical Affairs, MOHW of Taiwan since 2016. From 2008 to 2012, he was the head of Bureau of Medical Affaires that oversees the health care system and leads the health care reform including the programs addressing hospital accreditation, emergency preparedness, postgraduate training, substance abuse, and suicide prevention. Besides, he also initiated a non-fault compensation plan for the childbirth accidents to release the litigation pressure as well as improve patient-physician relationship.

Prior to the appointment as the Director-General in MOHW, Dr. Shih was one of pioneers in Taiwan patient safety campaigns leading the task force in Taiwan Joint Commission on Hospital Accreditation as the deputy executive for 4 years. There were multiple new initiatives or campaigns to improve quality and safety in health care, such as the nation-wide patient safety reporting and learning system, national patient safety goals, patient safety awareness week, and medical teamwork training.

Dr. Shih received M.D. degree from Kaohsiung Medical University in Taiwan. Following the residency training program for internal medicine and emergency medicine in National Taiwan University Hospital (NTUH), he was recruited as a visiting staff in the department of emergency medicine of NTUH in 1998. The interest in addressing medical quality and health issue led him to pursue and earn a Ph.D. in health policy and management from Public Health College of National Taiwan University in 2006.

**Publications:**

1. Chu HS, Lai CT, Hou YC, Liu HY, Wang IJ, Chen WL, **Shih CL**, Hu FR. Reappraisal of the suitability of corneas from bacteremic donors for use in corneal transplants. Br J Ophthalmol. 2018 Oct 15. pii: bjophthalmol-2018-312816. doi: 10.1136/bjophthalmol-2018-312816.
2. Chuang CC, Rau JY, Lai MK, **Shih CL**. Combining unmanned aerial vehicles and internet protocol cameras to reconstruct 3-D disaster scenes during rescue operations. Prehosp Emerg Care. 2018 Nov 8:1-6. doi: 10.1080/10903127.2018.1528323. [Epub ahead of print]
3. Yeh JZ, Wei CJ, Weng SF, Tsai CY, Shih JH, **Shih CL**, Chiu CH. Disease-specific health literacy, disease knowledge, and adherence behavior among patients with type 2 diabetes in Taiwan. BMC Public Health. 2018 Aug 24;18(1):1062. doi: 10.1186/s12889-018-5972-x.
4. Liao HH, Liang HW, Chen HC, Chang CI, Wang PC, **Shih CL**. Share decision making in Taiwan. Z Evid Fortbild Qual Gesundhwes. 2017 Jun;123-124:95-98. doi: 10.1016/j.zefq.2017.05.009. Epub 2017 May 17. Review.

5. Yang CC, **Shih CL**. A Coordinated Emergency Response: A Color Dust Explosion at a 2015 Concert in Taiwan. Am J Public Health. 2016 Sep;106(9):1582-5. doi: 10.2105/AJPH.2016.303261. Epub 2016 Jul 26.
6. **Shih CL**, Chang TH, Jensen DA, Chiu CH. Development of a health literacy questionnaire for Taiwanese hemodialysis patients. BMC Nephrol. 2016 May 31;17(1):54.
7. Wang CH, **Shih CL**, Chen WJ, Hung SH, Jhang WJ, Chuang LJ, Wang PC. Epidemiology of medical adverse events: perspectives from a single institute in Taiwan. J Formos Med Assoc. 2016 Jun;115(6):434-9.
8. Chen YC, **Shih CL**, Wu CH, Chiu CH. Exploring factors that have caused a decrease in surgical manpower in Taiwan. Surg Innov 2014 21(5):520-7.
9. Chang LC, Wang PX, Chen YY, **Shih CL**. Prospect and vision of the Taiwan Ministry of Health and Welfare. J Formos Med Assoc. 2013 Sep;112(9):505-7.
10. Lin CC, **Shih CL**, Liao HH, Wung CH. Learning from Taiwan patient-safety reporting system. Int J Med Inform. 2012 Dec;81(12):834-41.
11. **Shih CL**. Response to The Biobank-Act as a route to responsible research: a first step for Taiwan? J Formos Med Assoc. 2012 Jan;111(1):53.
12. Wung CH, Yu TH, **Shih CL**, Lin CC, Liao HH, Chung KP. Is it enough to set national patient safety goal? An empirical evaluation in Taiwan. Int J Qual Health Care. 2011 Aug;23(4):420-8.

**10:30-10:55**

**I-04**

## New Regulation on Cell Therapy in Taiwan: Challenge and Prospect

Shih, Chung-Liang （石崇良）
Director-General , Department of Medical Affairs,
Ministry of Health and Welfare, Taiwan

### Abstract

Cell therapy has long been a heated research topic in Taiwan since 1990s. In the past, hospitals in Taiwan could only perform cell therapy by means of clinical study as the safety and efficacy of cell therapy were still under review. Following the development in cell and gene therapy in the world, countries with significant advancement in regenerative medicine have undergone regulatory reform for these types of medicinal product. Taking into account the existing regulatory structure of medicinal products and medical techniques in Taiwan, it is determined that Ministry of Health and Welfare (MoHW) will authorize the application of cell therapy as medical techniques and Taiwan Food and Drug Administration will oversee the marketing authorization for cell therapy products. After a series of discussion with medical professionals, academic researchers, and industrial experts, with the aim to fulfill unmet medical needs for Taiwanese patients, on Sep 6th 2018, MoHW has announced the revision of The Regulation Governing the Application of Specific Medical Technique and Medical Equipment with a new chapter for cell therapy, which includes 6 types of cell therapy that utilize autologous cells to cure specific clinical indications.

The revised regulation stipulates the requirements for hospitals that offer cell therapy to patients with specific indications, including standards of cell processing unit facility, and qualification of medical professional. The cell processing unit will be regulated by TFDA in accordance to the same level of safety control as medicinal product. And doctors who will be performing cell therapies will have to receive certifications on courses of regulation and ethics, cell processing unit management, adverse event report, etc. in addition to experience of relevant medical specialties.

As variation in efficacy of cell therapy is witnessed, to have better evaluation of the safety and efficacy of approved cell therapy, a mandatory review mechanism is added into the newly revised regulation. All hospitals offering approved cell therapy will have to report all cases on an annual basis to the MoHW. MoHW will increase or eliminate items on the list of approved cell therapy based on the reports of efficacy and adverse event submitted by the hospitals.

The revised regulation regarding cell therapy is only a beginning. The future regulatory reform will be aimed to mitigate the gap between medicinal product and medical technique for regenerative medicine, in order to accelerate the development of regenerative medicine in Taiwan.

**YAO-CHANG CHEN, M.D.**
ycchenmd@ntu.edu.tw

Dr. Chen is a renowned professor of Hematology in Taiwan. He is a pioneer of the bone marrow transplantation (BMT) and stem cell research in Taiwan. In 1983 and 1984, he conducted the 1st auto- and allo-BMT in Taiwan respectively. He also facilitated the establishment of Taiwan Marrow Donor Registry in 1990s. During 1993 to 1996, he helped to set up of BMT program at Ho Chi Minh City, Vietnam. He has accomplished many leading clinical works of leukemia therapy and hematopoietic transplantation. He was the founder of Asian-Pacific Blood and Marrow Transplantation (APBMT), and also the president of APBMT (1997-1999).
Dr. Chen's clinical and research interest extended to stem cell research. From 2002 to 2004, he was the Director of the newly established Stem Cell Research Center in the National Health Research Institute. His current research focus is on clinical application of the placenta mesenchymal stem cell. Dr. Chen is the Vice President of Asian Cell Therapy Organization (ACTO) and an active member of the International Society of Cell Therapy (ISCT). In 2014, he became the founder and the President of "Taiwan Association for Cellular Therapy".

**Education and Training**

| | |
|---|---|
| ˙1978-1981 | Hematology Fellow, Rush-Presbyterian-St. Lukes' Medical Center, Rush University, Chicago, U.S.A. |
| ˙1973 | M.D. degree from National Taiwan University. |

**Domestic Appointment**

| | |
|---|---|
| ˙1990-present | Professor of Hematology, National Taiwan University. (Professor Emeritus since 2014) |
| ˙1981-present | Attending Physician, National Taiwan University Hospital. |
| ˙2002-2004 | Director, Stem Cell Research Center, National Health Research Institutes, Taiwan. |
| ˙2014-present | President, Taiwan Association for Cellular Therapy (TACT) |

**International Appointment**

| | |
|---|---|
| ˙1996-1998 | President, Asian-Pacific Bone Marrow Transplantation Group (APBMTG). |
| ˙1992-1995 | Visiting Consultant, Blood Transfusion Hematology Center, Ho Chi Minh City, Vietnam. (helped to set up BMT Center) |
| ˙1990 | Visiting Consultant, King Fahrad Hospital, Jeddah, Kingdom of Saudi Arabia. |
| ˙1989 | Visiting Scholar, The 3rd Department of Internal Medicine, University of Tokyo, Japan. |
| ˙2012-present | Vice President, Asian Cell Therapy Organization (ACTO) |

**10:55-11:20**

**I-05**

## Allogeneic MSC Therapy: feasibility using HLA-matched donors ?

Yao-Chang Chen M.D.
Professor Emeritus
National Taiwan University, College of Medicine, Taipei, Taiwan

### Abstract

Mesenchymal Stem Cells (MSCs) are considered immunoprivileged because they express HLA-Class I but not Class II antigens. Consequently, HLA-matching is considered unnecessarily in clinical applications using allogeneic MSCs, although there have been very few studies to compare the results of matched vs mismatched major histocompatibility complex (MHC) expression.

However, recent human clinical studies often showed that results using allogeneic MSCs seemed not as well as using autologous MSCs. Meanwhile, substantial evidence now exist to prove with multiple studies documenting specific cellular & humoral immunoresponse against donor follow administration of these cells. Industrial allo-MSC product failure analysis also suggested that the role of immunogenesity cannot be neglected.

We propose that the immunoprivilege property of MSCs should be re-evaluated, while the feasibility using HLA-matched allogeneic MSCs should be considered.

## Shen, Chia-Ning 沈家寧

POSITION TITLE
Associate Research Fellow and Deputy Director

| EDUCATION/TRAINING | | | |
|---|---|---|---|
| INSTITUTION AND LOCATION | DEGREE | YEAR(s) | FIELD OF STUDY |
| **National Sun Yat-Sen University, Taiwan** | **B.Sc.** | **1992** | **Biotechnology** |
| **National Yang-Ming University, Taiwan** | **M.Sc.** | **1997** | **Medical Biotechnology** |
| **University of Bath, United Kingdom** | **Ph.D.** | **2002** | **Developmental Biology** |
| **University of Bath, United Kingdom** | **PDF** | **2004** | **Regenerative Medicine** |

**Positions and Employment**

06/13-present Deputy Director, Genomics Research Center, Academia Sinica, Taipei, Taiwan
02/12-present Associate Research Fellow, Genomics Research Center, Academia Sinica, Taipei, Taiwan
08/18-present Acting Executive Director, GRC-affiliated Biotechnology Incubation Center, Academia Sinica, Taiwan
11/17-present President, Taiwan Society for Stem Cell Research
08/18-present Adjunct Associate Professor, Institute of Biopharmaceutical Sciences, National Yang-Ming University, Taiwan
08/14-present Adjunct Associate Professor, Department of Biotechnology & Laboratory Science in Medicine, National Yang-Ming University, Taiwan
08/05-07/14 Adjunct Assistant Professor, Department of Biotechnology & Laboratory Science in Medicine, National Yang-Ming University, Taiwan
07/04-02/12 Assistant Research Fellow, Genomics Research Center, Academia Sinica, Taipei, Taiwan
01/04-02/04 Visiting scholar, Dept. of Pathology and Dept. of Microbiology & Immunology, University of Texas Medical Branch, Galveston, Texas, United States
01/02-07/04 Research officer (postdoctoral scientist), Centre for Regenerative Medicine, University of Bath, United Kingdom

**Selected Recent Publications (selected from ~74)**


- T.L. Chen, Y.W. Lin, Y.B. Chen, J.J. Lin, T.L. Su, C.N. Shen*, T.C. Lee. 2018. A low-toxicity DNA-alkylating N-mustard-quinoline conjugate with preferential sequence specificity exerts potent antitumor activity against colorectal cancer. *Neoplasia* 20(2): 119-130 ( **corresponding author*)

- S.C. Tang, C.N. Shen*, P.Y. Lin, S.J. Peng, H.J. Chien, Y.H. Chou, C. Chamberlain, P. Pasricha. 2018. Pancreatic neuro-insular network in young mice revealed by 3-D panoramic histology. *Diabetologia* 61(1): 158-167 *(*corresponding author).*
- Hsieh, C.C., I.M. Shyr, W.Y. Liao, T.H. Chen, S.E. Wang, P.C. Lu, P.Y. Lin, Y.B. Chen, W.Y. Mao, H.Y. Han, M. Hsiao, W.B. Yang, W.S. Li, Y.P. Sher, and C.N. Shen* 2017. Elevation of beta-galactoside alpha 2,6-sialyltransferase 1 modulated in a fructose-responsive manner promotes pancreatic cancer metastasis. *Oncotarget* 8(5) 7691-7709. *(*corresponding author).*
- P.Y. Lin, S.J. Peng, C.N. Shen*, P. Pasricha and S.C. Tang. 2016. PanIN-associated pericyte, glial, and islet remodeling in mice revealed by 3-D pancreatic duct lesion histology. *American Journal of Physiology - Gastrointestinal and Liver Physiology*. 311(3):G412-G422 *(*corresponding author),*
- Chien, C.Y., H.S. Lee, Candy.H.H. Cho, K.I. Lin, D. Tosh, R.R. Wu, W.Y. Mao, and C.N. Shen*. 2016. Material vitamin A deficiency during pregnancy affects vascularized islet development. *J. Nutritional Biochemistry* 36:51-59 *(*corresponding author),*
- Chang F.P., Candy.H.H. Cho, C.R. Shen, L.W. Ting, and C.N. Shen* 2016. PDGF Facilitate Reprogramming of Hepatocytes to Insulin-Secreting beta-like Cells induced by Pdx1 and Ngn3. *Cell Transplantation.* 25:1893-1909 *(*corresponding author).*

**11:20-11:45**

**I-06**

## Reprogramming cellular identity for liver regenerative medicine

Chia-Ning Shen
Genomics Research Center, Academia Sinica, Taipei 115, Taiwan

**Abstract**

End-stage liver diseases such as liver cirrhosis have become an increasingly prevalent disease. The liver transplantation is the only useful treatment for patients with end-stage liver diseases. However, the shortage of donor liver limit the potential use of liver transplantation to treat patients with end-stage liver diseases. Whether cell reprogramming strategies can be utilized to repair or to rejuvenate injured liver remains to be determined. Human induced pluripotent stem cells (iPSCs) can be generated from patient's skin cells. Recent work has shown that Human iPSC-derived hepatocyte-like cells (iPS-HLCs) have the potential to be used to treat End-stage liver diseases. However, the actual applicability is hampered by the limited availability of metabolically functioning hepatocytes derived from human pluripotent stem cells (hPSCs). In order to generate metabolically functioning hepatocytes, our recent progress has validated the expression of seven hepatic miRNAs including hsa-miR-664a-3p, hsa-miR-194-3p, hsa-miR-29c-5p, hsa-miR-4662a-5p, hsa-miR-885-5p, hsa-miR-126-5p, hsa-miR-122-3p during hepatic differentiation. Among these miRNAs, we revealed transfection of hsa-miR-4662a-5p can enhance metabolic gene expression and/or enzyme activity in HLCs and combination of hsa-miR-4662a-5p together with hsa-miR-126-5p, hsa-miR-122-3p further enhance the maturity of HLCs derived from ESCs and iPSCs. Since the liver is an organ with an enormous capability of regeneration upon injury. Recent progress has further demonstrated hepatocyte reprogramming (dedifferentiation) contributes to regeneration process. We therefore tried to address the potential of reprogramming mature hepatocytes to bipotential progenitors for the purpose of repairing liver injury. Initial efforts had demonstrated that periportal hepatocytes could be reprogrammed into Sox9-expressing progenitor cells in mice treated 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC). The further analysis revealed, in DDC-treated mice, N-methyl-PPIX produced from the breakdown of Cytochrome P450 and transported through ABCG2 could trigger induction of Sox-9 expression in hepatocyte reprogramming. We also confirmed the Sox9-expressing reprogrammed cells can therefore be used to replenish damaged hepatocytes. Collectively, our findings suggest both pluripotent and lineage reprogramming strategies possess the potency to development treatment for patients with end-stage liver diseases.

# Curriculum Vitae

## PERSONAL INFORMATION

**Name：** **Chih-Hung, Chang 張至宏**
**Tel:** **+886 289667000 ext 2888**
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**Specialties:** **Orthopedic Surgery, Biomedical Engineering, Regenerative Medicine**

## EDUCATION

| | | | | |
|---|---|---|---|---|
| ■ | 2000~2005 | PhD | Institute of Biomedical Engineering | National Taiwan University |
| ■ | 1985~1992 | MD | Department of Medicine, Medical College | National Taiwan University |

## POSITIONS HELD

- ■ 2018~present **President**, Formosa Association of Regenerative Medicine
- ■ 2014~present **Professor**, Yuan Ze University
- ■ 2005~present **Chief**, Department of Orthopedics, Far Eastern Memorial Hospital
- ■ 2016~2018 **The Secretary-General**, Taiwan Orthopaedic Association
- ■ 2016~2018 **The Secretary-General**, Formosa Association of Regenerative Medicine
- ■ 2010~2014 **Associate Professor**, Yuan Ze University
- ■ 2007~2010 **Assistant Professor**, Yuan Ze University
- ■ 2006~2007 **Chief of Department**, Department of Surgery, Far Eastern Memorial Hospital
- ■ 2005~present **Collateral Assistant Professor**, Department of Orthopedics, Medical College, National Taiwan University
- ■ 2001~present **F.I.C.S.**, International College of Surgeon
- ■ 2000 **Visiting Clinician**, Mayo Clinic, Rochester, Minnesota, U.S.A. with Dr. Morrey

## REPRESENTATIVE HONORS AND AWARDS

- ■ 2008 5th National Innovation Award
- ■ 2010 8th Y. Z. Hsu Scientific Award: Outstanding Professor Award
- ■ 2011 8th National Innovation Award
- ■ 2014 3rd New Taipei Medical Charity Award : Educational Research Award

## INDIVIDUAL SPECIALTY

- Orthopedic surgery, Elbow surgery, Traumatology, Arthroplasty
- Biomedical engineering
- Tissue engineering &Regenerative medicine

- **SCI PUBLICATIONS:**

1. Yu-Chun Chen, Yu-Wei Chang, Kinn Poay Tan, Yi-Shan Shen, Yao- Horng Wang, **Chih-Hung Chang***.(2018, Nov) Can mesenchymal stem cells and their conditioned medium assist inflammatory chondrocytes recovery? *PLoS ONE 13(11): 0205563.*
2. Yu-Chun Chen, Yuan-Ming Hsu, Kinn Poay Tan, Hsu-Wei Fang, **Chih-Hung Chang***. (2018, Oct) Intraarticular injection for rabbit knee osteoarthritis: effectiveness among hyaluronic acid, platelet-rich plasma, and mesenchymal stem cells. *Journal of the Taiwan Institute of Chemical Engineers*. 91, 138-145
3. Yeong-Jang Chen., Jwo-luen Pao., Chiang Sang Chen., Yu-Chun Chen., Chun-Chien Chang., Fang-Ming Hung., **Chih-Hung Chang***.(2017, Feb). Evaluation of New Biphasic Calcium Phosphate Bone Substitute: Rabbit Femur Defect Model and Preliminary Clinical Results. *Journal of Medical and Biological Engineering*, 37(1), 85-93.
4. Karl Wu, Yu-Chun Chen, Yuan-Ming Hsu, **Chih-Hung Chang*.** 2016, March. Enhancing Drug Release from Antibiotic-loaded Bone Cement Using Porogens. *Journal of the American Academy of Orthopaedic Surgeons*, 24(3): 188–195.
5. Yuan-Ming Hsu, Chun-Hsing Liao, Yu-Hong Wei, Hsu-Wei Fang, Hsiang-Huan Hou, Chia-Chun Chen and **Chih-Hung Chang*** (2014, Oct). Daptomycin-loaded polymethylmethacrylate bone cement for joint arthroplasty surgery. *Artificial Organs*, 38(6): 484-492.
6. **Chih-Hung Chang***, Chia-Chun Chen, Cheng-Hao Liao, Feng-Huei Lin, Yuan-Ming Hsu and Hsu-Wei Fang (2014, Jul). Human acellular cartilage matrix powders as a biological scaffold for cartilage tissue engineering with synovium-derived mesenchymal stem cells. *Journal of Biomedical Materials Research: Part A*, 102A: 2248-2257.
7. **Chih-Hung Chang***, Yuan-Ming Hsu, Yu-Chun Chen, Feng-Huei Lin, Subramaniam Sadhasivam, Siow-Tung Loo, Sivasubramanian Savitha. (2014, Apr). Anti-Inflammatory effects of hydrophilic and lipophilic statins with hyaluronic acid against LPS-induced inflammation in porcine articular chondrocytes. *Journal of Orthopaedic Research*, 32(4): 557-65.
8. **Chih-Hung Chang**, Yuan-Ming Hsu, Chun-Ni Hsiao, Ming-Huang Chang, Tzong-Fu Kuo* (2014, Feb). Critical-sized Osteochondral Defects of Young Miniatrure Pigs as A Preclinical Model for Articular Cartilage Repair. *Biomedical Engineering-Applications Basis Communications 2014*, 26(1):140003-1--140003-8.

**11:45-12:10**

**I-07**

# Clinical Trial of Cartilage Defects and Osteoarthritis Treatment Using Bone Marrow Mesenchymal Stem Cells and Infrapatellar Fat Pad Mesenchymal Stem Cells

Chih-Hung Chang[1,2]
Department of Orthopedics, Far Eastern Memorial Hospital, New Taipei City, Taiwan[1]
Graduate School of Biotechnology and Bioengineering, Yuan Ze University, Taoyuan, Taiwan[2]

## Abstract

Osteoarthritis (OA), one of the most common joint disease, affects more than 80% of the population aged 70 or over. Non-operative treatment for OA, despite NSAIDs, hyaluronic acid (HA) or platelet-rich plasma (PRP) injection, had also developed in Taiwan. Mesenchymal stem cells (MSCs) show multi-potent differentiation and self-renewal capability, and, after exposure to an inflammatory environment, also exhibit immunosuppressive properties. Currently, we cooperated with EMO Corp. to conduct a phase I clinical trial study of infrapatellar fat pad MSC (IPFP-MSC) for OA treatment. Twelve subjects were enrolled in the study. Results showed that the IPFP-MSC can express CD73, CD90 and CD105, and they do not express CD11b, CD19, CD34, CD45 and HLA-DR. They have highly proliferative and differentiate capability. Importantly, they possess anti-inflammatory ability to inhibit peripheral blood mononuclear cell proliferation and TNF-α production. Preliminary phase I clinical outcome indicated that there is an improvement with time in keen pain (VAS score) and knee function (IKDC, KOOS score).

For the treatment of cartilage defect, mosaicplasty and microfracture surgeries are the most common treatment method in Taiwan. Engineered cartilage Kartigen© is an MSC-derived pre-chondrocyte bio-product. This technique is developed by Dr. Hwa-Chang Liu, Prof. Feng-Huei Lin and Dr. Chih-Hung Chang. It is derived from bone marrow MSC, and there is no need to harvest autologous cartilage. After 5 years, clinical results showed significant improvement of the knee function in IKDC scoring. The new generation of Kartigen© techniques had been modified by fixation with fibrin glue without the use of periosteum.

Recently, Taiwan's government had launched regulations "Specific Medical Management Regulation" for the autogenous cell therapy, the draft of regulations for regenerative medicine also had been announced. Medical care institution could draft a proposal and submit to the central competent for specific autologous cell therapy technics. We believe these polices will be very encouraging to the Taiwan's regenerative medicine industries.

Keywords: osteoarthritis, cartilage defects, mesenchymal stem cells, cell-therapy, clinical study

# Curriculum Vitae

## So Ra Park, M.D., PhD.

Dean/Professor, School of Medical Inha University
Director, Strategic Center for Regenerative Medicine

**Contact Information**

Address: **S**trategic **C**enter for **R**egenerative **M**edicine(as known as GSRAC)
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**Personal Information**

Date of Birth: Aug. 19, 1960
Marital Status: Married
Sex: Female

**Education and Degree**

1989 – 1993 Ph.D., Physiology, Graduate School of Medicine, Yonsei University, Korea
1987 – 1989 M.S., Physiology, Graduate School of Medicine, Yonsei University, Korea
1985 – 1986 Internship, Yonsei University Medical Center, Korea
1981 – 1985 M.D., College of Medicine, Yonsei University, Korea
1979 – 1981 B.A., College of Liberal Art and Science, Yonsei University, Korea

**Major Professional Experience**

1991 – Present Professor, School of Medicine, Inha University
2017 – Present Dean, School of Medicine, Inha University
2018– Present Director, Strategic Center for Regenerative Medicine
2011 – 2018 Director, Global Stem Cell & Regenerative Medicine Acceleration Center (GSRAC)
2018– Present Member, Civilian Committee, Regulatory Reform Committee, Korea
2018– Present Member, Self-Evaluation Committee, Korea Centers for Disease Control and Prevention(KCDC), Korea
2017 – Present Member, Health Technology &Policy Deliberative Committee, Ministry of Health and Welfare, Korea
2016 – Present Secretary General, Council for Advanced Regenerative Medicine (CARM), Korea
2014– Present Member, Pharmaceutical Industry Development Practice Support Committee, Ministry of Health and Welfare, Korea
2017 – 2017 Member, Healthcare Medical R&D Future Strategy working group, Korea Health Industry Development Institute
2017 – 2017 Member, R&D Division, Pharmaceutical Industry Long-term Strategic planning working group, Ministry of Health and Welfare, Korea
2013 – 2017 Member, Assessment of Medical Service Benefits Committee, Korean Health Insurance Review and Assessment Service, Ministry of Health & Welfare, Korea

| | |
|---|---|
| 2010 – 2017 | Member, Steering Committee, National Center for Standard Reference Data, Ministry of Knowledge Economy, Korea |
| 2011 – 2012 | Member, Advisory Committee, Executive Office of the President (Secretary Office of Health & Welfare), Korea |
| 2008 – 2010 | Director, New Technology Development Group, R&D Promotion Headquarter, Korean Health Industry Development Institute, Korea |
| 2008 – 2009 | Member, Advisory Committee for Future Strategies for Science and Technology R&D projects, Ministry of Education, Science and Technology, Korea |
| 1996 – 1998 | Visiting Fellow, Bone Research Lab, Medical Research Council, Oxford University, U.K. |

**Research Interest**

Stem Cell Biology & Tissue Engineering
Biological Effects and Cellular Mechanism of Low Intensity Ultrasound Stimulation

**13:30-13:55**

**I-08**

## Overview of Korean Regenerative Medicine: Commercial Development and Ecosystem

So Ra Park
Dean/Professor, School of Medical Inha University
Director, Strategic Center for Regenerative Medicine

### Abstract

Korea approved the first stem cell therapy product in the world and currently has the largest number of approved products, which is predominantly due to the favorable government support with the great funding, reasonable regulatory pathway and excellent ecosystem.

The RM sector in Korea obtains strong government support not only for basic research but also for translation and commercialization of technologies. Currently, six ministries of Korea are investing the R&D funds into stem cell and RM. Korea also makes efforts in improving regulatory environment of RM to accelerate the commercialization and clinical adoption of RM products. The Bill on the Support and Safety Management of Advanced Regenerative Medicine (hereinafter referred to as ARM Act) was first proposed by the Congress in November 2016 with the support of the MOHW, which consists of the two pillars of the safety control on the medical practice and non-commercial trials and the promotion of the RM industry. It is currently under review in Congress and waiting for a final decision.

## Eun- Kyoo, Song MD, PhD

1972.3-1978.2; chonnam national university medical school
1979.3-1983.2; PhD degree, graduate school chonnam national university
1986.3 - present; professor and chairman of knee surgery,
department of orthopedic surgery
chonnam national univ. bitgoeul hospital

2010.10-2011.10; president of korean arthroscopy association
2010.11-present; natioal delegate of asia-pacific knee society
2011.3-2012.2; president of CAOS -asia
2011.6-2012.6; president of CAOS-international
2011.11-2012.11; president of korean orthopedic society of sports medicine
2012.5-2013.5; president of korean knee society
2018.11-- president of APKS

2010.3.-2011.2; president of chonnam national univ. hwasun hospital
2011.3-2014.2; president of chonnam national university hospital

2014.6; poster award 2014 AOSSM
201310; grand prix scientific award,fall annual meeting,KOA
2009.2 ; first place award of poster,2009 AAOS
2009.6; first place award of poster,2009 CAOS-internatioal

**13:55-14:20**

**I-09**

## Current Status of treatment of cartilage defect in OA Knee in Korea

E K Song,MD PhD
Department of Orthopedic Surgery
Chonnam National University Bitgoeul Hospital Korea

### Abstract

A cartilage defect of the osteoarthritic knee was frequently combined with varus deformity of the knee and its treatment should be combined with correction of varus deformity.
If varus deformity was not adequately corrected, treatment of cartilaginous defect was not able to be successful or recurrence could be developed.
The treatment methods of cartilage defect were microfracture, augmented microfracture, chondrocyte transplantation and stem cell treatment. Each treatment methods has its adventage and disadvantages.
During the last 15 years over 500 cases of high tibial osteotomy with repair of cartilage defect were performed. The old age, high-grade cartilage injury on medial and lateral compartment, under-correction of varus deformity appeared to be significant factors associated with the failure after medial open wedge high tibial osteotomy.

Recently augmented microfracture, cartistem(allogenic umbilical cord blood derived MSC), gene-transfected chondrocyte(invossa) and adipos tissue drived MSC have been used for treatment of cartilage defect of OA knee in Korea. Those methods and its clinical results will be introduced and discussed.

Comparison analysis study showed clinical outcomes were improved regardless of augmentation for microfracture. However, Augmented microfracture was more effective for cartilage regeneration than microfracture alone in medial unicompartmental OA.
Another comparison study suggested Cartistem may be better in cartilage regeneration in 2nd look A/S finding when compared with augmented microfracture for the treatment of so called “kissing lesion” of the OA Knee.

## Gun-Il Im, M.D., Ph.D.

**Affiliation:**
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E-mail: imgunil@hanmail.net

**RESEARCH FIELDS AND INTERESTS**

1. Stem cell and tissue regeneration of musculoskeletal system
2. Adult reconstruction

**AFFILIATION TO SOCIETIES**

**National**

1. President, Korean Society for Cartilage and Osteoarthritis
2. Vice-President, Korean Society for Tissue Engineering and Regenerative Medicine
3. President Elect, Korean Society for Biomaterials
4. Chairman of By-Law Committee, Korean Society for Bone and Mineral Research
5. Council Board Member, Korean Orthopaedic Research Society
6. Council Board Member, Korean College of Rheumatology

**International**

1. President Elect, International Combined Orthopaedic Research Society
2. Member at large, Board of Directors, Osteoarthritis Research Society International
3. Council Board Member, Tissue Engineering and Regenerative Medicine International Society Asia-Pacific Chapter (2013-2016).

**EDITORIAL BOARD ACTIVITIES**

1. Associate Editor, Tissue Engineering and Regenerative Medicine
2. Editorial Board, Journal of Orthopaedic Research.
3. Editorial Board, Korean Orthopaedic Association
4. Editorial Board, Clinics in Orthopaedic Surgery
5. Editorial Board, Korean Hip Society

**14:20-14:45**

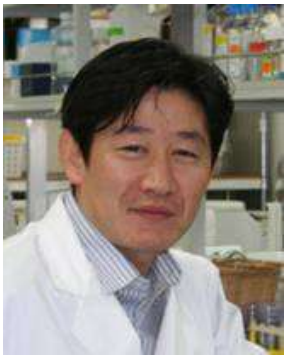
**I-10**

## Gene-cell therapy to treat osteoarthritis

Gun-Il Im, M.D., Ph.D.
Research Instute for Integrative Biomedical Engineering
Dongguk University, Siksa-Dong, Goyang 410-773, Korea

### Abstract

Gun-IL IM Research Instiute for Intergrative Regenerative Medical Engineering, Dongguk University Gene transfer has been used experimentally to promote cartilage regeneration and treat osteoarthritis. While it is controversial to apply gene therapy for nonlethal conditions, there is a possibility that the transfer of therapeutic transgenes may dramatically increase the effectiveness of cell therapy. Single or combination of growth factors and transcription factors has been transferred to mesenchymal stem cells using both nonviral and viral approaches. The current challenge for the clinical applications of genetically modified cells is ensuring the safety of gene therapy while guaranteeing effectiveness. Viral gene delivery methods have been mainstays currently with enhanced safety features being recently refined. On the other hand, nonviral delivery which is inherently safer than viral delivery has been greatly improved in transfection efficiency. Our group has been using microporation of SOX trio genes to enhance chondrogenesis from stem cells. We have recently developed SOX-6, 9-transfected human adipose stem cells (SOX-6, 9 ASCs) to treat OA and tested their effectiveness in arresting OA progression when injected intra-articularly (IA) in a surgically-induced OA caprine model. SOX-6, 9-transfection led to in vitro chondrogenesis of ASCs comparable to that achieved by growth factor treatment. IA injection of SOX-6, 9 ASCs arrested the progression of surgically-induced OA in goats. We suggest that SOX-6, 9 ASCs offer a novel potential strategy to treat OA.



**Byung Hyune Choi, Ph.D. (Bryan Choi)**
Professor, Inha University College of Medicine
Vice-director, Strategic Center for Regenerative Medicine (SCRM)

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**1. EDUCATION:**
Mar. 1987 – Feb. 1991 Bachelor of Science
Department of Molecular Biology, Seoul National University, Seoul, Korea
Mar. 1991 – Feb. 1993 Master of Science
Department of Molecular Biology, Seoul National University, Seoul, Korea
Mar. 1993 – Feb. 1999 Ph. D. in Molecular Genetics
Department of Molecular Biology, Seoul National University, Seoul, Korea

**2. PORFESSIONAL EXPERIENCES AND EMPLOYMENTS:**
Apr. 1996 – Jun. 1996 Visiting Student, National Heart, Lung and Blood Institute, National Institute of Health, USA
Feb. 1999 – Mar. 2000 Postdoctoral Fellow, Research Center for Cell Differentiation, Department of Molecular Biology, Seoul National University, Korea
Apr. 2000 – Jan. 2002 Postdoctoral Fellow, Institute of Chemistry and Cell Biology (ICCB), Harvard Medical School, USA
Feb. 2002 – Dec. 2002 Research Scientist, Target Validation Team, LG Biomedical Institute in San Diego, USA
Jan. 2003 – May. 2004 Research Professor, Catholic Neuroscience Center, Catholic University, Korea
Jul. 2004 – Feb. 2007 Research Professor, Inha Research Institute for Medical Sciences, College of Medicine, Inha University, Korea
Mar. 2007 – Aug. 2008 Research Professor, Cell Therapy Center, School of Medicine, Ajou University, Korea
Sep. 2008 – Present Professor, Department of Biomedical Sciences, College of Medicine, Inha University, Korea
Nov. 2011 – Present Vice-director, Strategic Center for Regenerative Medicine (SCRM), Korea
May. 2016 – Apr. 2017 Vice-president & CSO, CureCell Inc., Korea
Apr. 2017 – Mar. 2018 Visiting Scholar, Parker H. Petit Institute for Bioengineering and Bioscience, Georgia Institute of Technology, Atlanta, GA, USA
Jan. 2018 – Present Director of R&D Center, ATEMs Inc., Korea

**3. RESEARCH SOCIETY**

Jan. 2006 – Present Committee Member & Associate Editor, Korean Tissue Engineering and Regenerative Medicine Society

Mar. 2007 – Present Committee Member, Korean Society of Cartilage and Osteoarthritis (KSCO)

**4. RESEARCH INTEREST**

My research covers relatively broad area of cell therapy and regenerative medicine. I am working on basic research on stem cell biology and translational research to develop regenerative medicine. The translational research on regenerative medicine is based on mesenchymal stem cells (MSCs) and cartilage progenitors from human donors, and utilized various technologies incorporating gene modification of cells, biomaterials and tissue engineering. Target indications include the cartilage defect, osteoarthritis, fibrosis and spinal cord injury.

Since 2011, I have been working for Strategic Center for Regenerative Medicine (SCRM). It is a non-profit center commissioned by Ministry of Health and Welfare, Korea and plays a think-tank for the government and related stakeholders in the RM field in Korea.

**14:45-15:10**

**I-11**

## Fabrication of an Injectable Engineered Cartilage Using Fetal Chondrogenic Progenitors

Byung Hyune Choi
Department of Biomedical Sciences, Inha University College of Medicine
(bryan@inha.ac.kr)

### Abstract

Regeneration of cartilage defect remains an unmet medical need despite extensive studies in the world for long time. It is generally regarded that a high-quality engineered cartilage tissue is required for efficient regeneration of hyaline cartilages but suffers from many technical limitations. We utilized human fetal cartilage-derived progenitor cells (hFCPCs) as a source of cartilage tissue engineering. Fetal cartilage tissue was obtained from fetus of GA12-16 with the IRB approval and written consent from donors. hFCPCs were isolated at very high yield and expanded for more than 20 passages without a significant growth delay or senescence. They also showed stem cell properties in the colony forming assays, gene expression pattern and multi-potent differentiation ability. Then, we developed a propriety scaffold-free protocol from hFCPCs to fabricate a high quality and injectable artificial cartilage tissue with a pliable mechanical property. We have proven its pre-clinical safety and efficacy for cartilage regeneration in several animal models of cartilage defect. We believe our technology could be the most advanced allogeneic regenerative therapy to treat cartilage defect.

Acknowledgement: This study was supported by a grant of the Korea Health Technology R&D Project (HI17C2191) funded by the Ministry of Health & Welfare, Republic of Korea.

**SOO HYUN KIM**
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- Education

1988-1992 : Ph.D. in Department of Polymer and Textile Engineering, Seoul National University, Seoul, Korea
1978-1984 : B.S. & M,S. in Department of Polymer and Textile Engineering, Seoul National University, Seoul, Korea

- Experience

2011 - present : Tenure Research Scientist, KIST
2012 - present : Professor, KU-KIST Graduate School, Korea Univ.
2006 - present : Adjunct Prof., North Carolina State Univ., USA
2003 - present : Professor, KIST International R&D Academy
2018 - present : President, Korean Tissue Eng. and Regenerative Medicine Society
2007 - present : Vice President, Korean Biodegradable Plastics Association
1992 - present : Principal Research Scientist Biomaterial Research Center, KIST
2002 - 2011 : Head, Biomaterial Research Center, KIST
2005 - 2011 : Head, Cardiovascular & Neural Bioorgan Research Center, MOHW
1994 - 1995 : Visiting Scientist, U. of Connecticut, USA
1984 - 1992 : Researcher in Polymer Chemistry Laboratory, KIST

- Professional Activity :

President, Biomaterials Division, The Polymer Society of Korea (2009 - 2011)
President, Korean Tissue Eng. and Regenerative Medicine Society (2018 – present) :
Vice President, Korean Biodegradable Plastics Association, (2008 - )
Editorial Board, Journal of Biomedical Materials Research: Applied Biomaterials (2014 ~ )
Editorial Board, Journal of Regenerative Medicine and Tissue Engineering (2012 ~ )
Editorial Board, Biomatter (2011 ~ )
Asia Editor, Editorial Board, Journal of Biomaterials and Tissue Engineering (2010 ~ )
Editorial Board, Journal of Clinical Rehabilitative Tissue Engineering Research (2006 ~ )
Editorial Board, Biomedical Materials (2006 ~ )

- Research Activity : Publications 227, Patents 59

- Research Interest

1. Biomedical Polymer
2. Biodegradable Polymer for Medical Application
3. Biodegradable Polymer for Environmental Application
4. Tissue Engineering

**15:10-15:35**

**I-12**

## Bioengineering of Vascular Graft

Soo Hyun Kim

Biomaterials Research Center, Korea Institute of Science and Technology,
P.O. Box 131, Cheongryang, Seoul 130-650, Korea

## Abstract

Cardio-vascular disease remains as the leading cause of mortality each year. Although new therapies are actively being developed and used for cardiovascular pathologies, these attempts have not significantly decreased the mortality rates. Recent advances in tissue engineering and regenerative medicine have offered new therapeutic opportunities for repairing damaged tissues and organs.

There is a clinical need for a tissue-engineered vascular graft(TEVG). We checked possibility for bioengineering of vascular graft through a tubular double-layered scaffold using a gel spinning technique from an elastic biodegradable polymer (Polylactide-caprolactone, PLCL). The implanted scaffolds in to the abdominal aortas of dogs kept their patency more than 1 year after operation. There were some problems like uniformity. We made woven type and knitted type scaffolds, which have fiber structure using Polylactide(PLLA) or Polydioxanone(PDO), to solve this problem. PLLA woven scaffold have very thin layer. It has similar structure like Dacron vascular prostheses. PLLA or PDO knitted scaffold coated by PLCL for improve compliance. We expected more developed bioengineering of vascular graft through scaffold of fiber structure like woven fabric and knit.

For small diameter vascular graft, we used neuropeptide substance P (SP) to accelerate tissue repair by endogenous cell mobilization and recruitment. PCL/SP-conjugated poly(L-lactide-co-ε-caprolactone) (PLCL-SP) vascular grafts were implanted as rat abdominal aorta substitutes for up to 2 weeks and 4 weeks. Ex vivo results delineate that SP can recruit mesenchymal stem cells. SP grafts also exhibit more numbers of α-smooth muscle actin-positive cells and laminin+ blood vessels than that of the control group. These results indicate that SP can induce endogenous tissue regeneration in cell-free grafts, which may be of great interest for regenerative medicine and tissue engineering applications.

## TANG, I-Ning

**Position:** Section Chief, Regulatory Science

**Affiliation:** Center for Drug Evaluation, Taiwan

**Current Position**
Section Chief, Regulatory Science, Center for Drug Evaluation (CDE), Taiwan.

**Education**
Ph.D. candidate. National Taiwan University. Graduate Institute of Biomedical Electronics and Bioinformatics, College of Electrical Engineering and Computer Science.
Master of Science. Chang Gung University. Graduate Institute of Rehabilitation Science.
Medical Doctor. National Cheng Kung University. Department of Medicine, College of Medicine.

**Professional Experience**
- Team Leader. Center for Drug Evaluation (CDE), Taiwan.
- Medical reviewer. Center for Drug Evaluation (CDE), Taiwan.
- Senior reviewer. Division of Medical Devices, Food and Drug Administration (FDA), Taiwan.
- Attending physician. Metropolitan and community teaching hospitals.
- Research fellow. Taipei Medical University Hospital.
- Resident and Chief resident. Department of Physical Medicine and Rehabilitation, National Cheng-Kung University Hospital.

**Specialty**
Regulatory science, Rehabilitation science, Neuroimaging

**Honors and Awards**

| | |
|---|---|
| 2017, 2018 | Invited speaker, International society of cell and gene therapy (ISCT) |
| 2016-now | Board member, Taipei Medical University JIRB. |
| 2016-now | International pharmaceutical regulators programme (IPRP) gene therapy working group (GTWG) member. |
| 2014 | Visiting expert, European Medicines Agency (EMA). |

**Autobiography :**
Dr. Tang is currently the Team Leader of Regulatory Science in Center of Drug Evaluation (CDE), Taiwan. She has worked as a medical reviewer since 2010 after years of clinical practice. Since joining in the regulatory science filed, Dr. Tang has been involved in various projects. She is an experienced reviewer in evaluating market authorization and clinical trial application of medical devices, drugs, and advanced therapy medicinal products. A major part of her work at present is to provide scientific advice to domestic biotech companies, pharmaceutical companies, non-government organization and research institutes, assist

government agencies such as the Ministry of Economic Affairs in evaluating biopharmaceutical industry development programs and budget, and give advice to government agencies for formulating policy and laws related to biopharmaceutical industry and trade. She is also a frequent invited speaker in various international conferences to introduce the regulatory environment in Taiwan.

**16:00-16:25**

**I-13**

## 細胞治療臨床試驗審查重點
## Considerations for the design of clinical trials of cellular therapy products

TANG, I-Ning (湯依寧)
Section Chief, Regulatory Science, Center for Drug Evaluation, Taiwan

### Abstract

目前國內細胞治療以產品及醫療技術併行管理. 本次演講, 將依照查驗中心針對細胞治療臨床試驗案件技術性資料的審查經驗, 分享臨床試驗計畫書的撰寫要素, 以及審查重點.

In this presentation, I will talk about key issues regarding clinical trial design of cellular therapy product, and I will also share review experiences in Taiwan.

# Curriculum Vitae

## Chikara Shinohara, Ph.D.

Japan Tissue Engineering Co., Ltd.
6-209-1 Miyakitadori, Gamagori, Aichi 443-0022, Japan
E-mail: chikara_shinohara@jpte.co.jp

**EXPERIENCE**

| | |
|---|---|
| 1999 – Present | Japan Tissue Engineering Co., Ltd.<br>Gamagori, Aichi, Japan<br>Senior Manager<br>Custom Development & Manufacturing Department<br>Sales & Marketing Promotion Division |
| 1996 – 1999 | Sagami Chemical Research Institute<br>Sagamihara, Kanagawa, Japan<br>Post Doctoral Fellow |

**EDUCATION**

| | |
|---|---|
| 1996 | Ph. D., Tokyo University of Agriculture and Technology<br>Fuchu, Tokyo, Japan |

**16:25-16:50**

**I-14**

# Development and Clinical Application of Regenerative Medical Products by Japan Tissue Engineering Co., Ltd.

Chikara Shinohara, Ph.D.
Japan Tissue Engineering Co., Ltd.

## Abstract

Japan Tissue Engineering Co., Ltd. (J-TEC) was founded in February 1999, and our is "To develop a basic tissue regeneration medical treatment based on the science of tissue engineering, which will bring a qualitative change in medical treatment practices, and thus develop into a business that will transform 21st century medical treatment itself".

J-TEC develops three businesses. A first business is called "Regenerative Medicine Business", with developing, manufacturing and selling tissue-engineered medical products based on the Pharmaceutical and Medical Device Act. A second business group called the "R&D Support Business", which is not subject to this law. We also develop a third business group named the "Custom Development & Manufacturing Business" as a Contract Development and Manufacturing Organization (CDMO), and as a Contract Research Organization (CRO).

Tissue-engineered medical products are subject to the Pharmaceutical and Medical Device Act which requires the approval of the Welfare, Health and Labor Ministry in Japan in order to sell these products. J-TEC has 2 product lines, autologous cultured epidermis (JACE®) and autologous cultured cartilage (JACC®).

JACE® was approved for the severe burn patients as the first regenerative medicine product in Japan in October 2007. National health insurance has been applied since January 2009. A congenital giant pigmented nevus was added as another indication of JACE® in September 2016. In December 2018, epidermolysis bullosa was also added as 3rd indication.

JACC® was approved for relief of symptoms of traumatic cartilage defects and osteochondritis dissecans (excluding osteoarthritis) in July 2012. National health insurance has been applied since April 2013.

In Japan, the "Pharmaceutical and Medical Device Act" and the "Act on the Safety of Regenerative Medicine" came into effect in November 2014, for further promoting product development and clinical application of regenerative medicine.

# 產業論壇

# 陳彥聰 Yen-Chung Chen

## EDUCATION

2003 - 2007 Ph.D. in Biochemistry & Molecular Biology
National Yang Ming University, Taipei, Taiwan
國立陽明大學**生化暨分子生物研究所** 博士

2000 - 2003 M.S. in Biochemistry
National Chung Hsing University, Taichung, Taiwan
國立中興大學生物化學研究所 碩士

## POSITIONS HELD

2016 – present R&D Director
Maria Von Med-Biotechnology Co., LTD, Taiwan
瑪旺幹細胞醫學生物科技股份有限公司 研發協理

2013 - 2016 Research Fellowship
Taiwan Advance Bio-Pharmaceutical Incorporation, Taiwan
台灣尖端先進生技醫藥股份有限公司 資深研究員

2008 - 2013 Postdoctoral Fellowship
National Health Research Institutes, Taiwan
國家衛生研究院 博士後研究員

## EXPERTISE

Molecular Biology; Cell Biology; Cancer Biology; Stem Cell Biology; Hematopoiesis; R&D of iPSCs, HSCs and MSCs.

## PUBLICTION

1. Chang TC*, **Chen YC***, Yang MH, Chen CH, Hsing EW, Ko BS, Liou JY, Wu KK. Rho kinases regulate the renewal and neural differentiation of embryonic stem cells in a cell plating density-dependent manner. *PLoS One.* 2010 Feb; 5(2):e9187. (***Co-first author**)
2. Wang JQ, Chen JH, **Chen YC**, Chen MY, Hsieh CY, Teng SC, Wu KJ. Interaction between NBS1 and the mTOR/Rictor/SIN1 complex through specific domains. *PLoS One*. 2013 Jun 6;8(6):e65586.
3. **Chen YC**, Yang SF, Chen HL, Yet SF, Wu KK. Prostacyclin and PPARα Agonists Control Vascular Smooth Muscle Cell Apoptosis and Phenotypic Switch Through Distinct 14-3-3 Isoforms. *PLoS One.* 2013 Jul 3;8(7):e69702.
4. Chan TM, Harn HJ, Lin HP, Chou PW, Chen JY, Ho TJ, Chiou TW, Chuang HM, Chiu SC, **Chen YC**, Yen SY, Huang MH, Liang BC, Lin SZ. Improved human mesenchymal stem cell isolation. *Cell Transplant*. 2014;23(4-5):399-406.

**16:50-17:05**

**B-01**

# 纖維母細胞治療臨床經驗分享
# The Clinical Experiences of Fibroblast Cell Therapy

陳彥聰
瑪旺幹細胞醫學生物科技股份有限公司

## Abstract

The normal skin is composed mainly by three components: epidermis, dermis and hypodermis. Among them the dermis layer contains a large number of collagens and elastic tissues secreted by fibroblast. When dermal proteins and fibers are damaged, the skin can self repair through dermal fibroblast regeneration capability. However, in many times this repair was insufficient due to severe damage of fibroblasts, causing depressed scars. With the influence of various deleterious environmental factors and natural aging process, the function of fibroblasts will gradually deteriorate, reducing its collagen production, and causing the skin to wither, lose its natural softness, elasticity and form the wrinkle and wounded scars by trauma, diseases such as acne vulgaris, folliculitis, or burns etc.

The skin biopsy from each participant will be collected and delivered to MariaVon GTP (Good Tissue Practice) facility for cell culture. Fibroblasts will be developed, expanded and stored for clinical use. The therapy with 3 times of treatment will be arranged and the interval of each treatment is 2 weeks, and subsequent 1, 3, and 6 months of observation period is necessary for the following up and record.

Skin defects from the volunteers such as open wounds, post-traumatic scars, depressive scars or wrinkles can be improved by autologous fibroblast injection since the collagen fibers will be rearranged, producing a young, healthy and organized collagen. Filling the skin defects and improving the overall quality and smoothness of the skin.

This technology of autologous cultured cell transplantation using patient's self material, therefore, there is no risk of allergic reactions, rejection or transmission of infectious diseases. Comparing with allogeneic filling materials (as hyaluronic acid or animal collagen), its safety is much higher and less likely to lose its function by being absorbed or rejected. This technology can be useful not only on the clinical treatments of depressive scars, but also on the burns, post traumatic wounds, diabetic ulcers and congenital or acquired atrophic skin disorders.

## 張順浪 Alarng Chang

【學歷】
1. 美國 Genentech 公司博士後研究（細胞激素/腫瘤免疫學）(1990~1993)
2. 美國密西根州立大學（分子免疫學博士）(1984~1990)
3. 臺灣大學農業化學系（微生物學碩士）(1982~1984 )
4. 臺灣大學農業化學系（學士）(1976~1980)

【現任】
1. 基亞生技公司　總經理暨研發長 (2016/3~迄今)
2. 臺北醫學大學　兼任副教授 (2000~迄今)

【曾任】
1. 長春藤公司生命科學公司　總經理 (2004/4~2015/11)
2. 基亞生技公司研發部　副總經理 (2000~2005)
3. 鴻亞生技公司　總經理 (2001~2005)
4. 部經濟法人科技專案計畫　審查委員 (2004~2015)
5. 慈濟醫學院免疫學科　代理科主任 (1995~2000)
6. 中法學術交流協會　交換學者 (1995~1996)
7. 慈濟醫學院免疫學科　副教授 (1993~2000)

【國內外演講/學術交流】
1. 2010/12/10 廣東中山大學（第五屆全國生物治療學術大會）：
   細胞治療的法規與現況/台灣經驗
2. 2009/02/18 北京 301 醫院：
   免疫殺手細胞簡介及細胞治療之前景
3. 2009/03/25 雲南昆明第二醫學院：
   免疫殺手細胞簡介及前景
4. 2008/09/11 山西太原（中國第十屆全國腫瘤生物治療學術會議）
5. 2007/07/12 廈門醫學院：免疫殺手細胞抗癌醫療技術說明

【主要專長】
細胞治療、免疫學、案件評估、新藥開發、臨床試驗設計

【專利發明】
免疫殺手細胞培養方法及配方（台灣、中國、美國）

**17:05-17:20**

**B-02**

# 免疫細胞治療之前景與趨勢
# Prospects and Trends of Immune Cell Therapy

張順浪
基亞生物科技股份有限公司

## Abstract

以 CAR-T 細胞治療 B 細胞相關之血液癌症已有兩產品於 2017 年獲得美國 FDA 核准上市，但以 CAR-T 細胞治療非 B 細胞系列之癌症或實體腫瘤則效果仍然非常有限。針對 CAR-T 細胞之缺點，現已有研究走向 universal 之 CAR-T 細胞或以 NK 細胞取代 T 細胞做成各種 CAR-NK 細胞，希望能得到更好的治療效果、降低副作用甚至減少生產所需之成本。此外，細胞生產的自動化以及導入精準醫療之概念來篩選合適之病人都是未來的趨勢之一。

# Poster Paper

**P-01**

# 含白芨多糖（BSP）人工淚液治療乾眼綜合症的療效觀察

# Therapeutic effect of Artificial Tears containing *Bletilla striata* Polysaccharide (BSP) in the Management of Dry Eye Syndrome

Minal Thacker, Chih-Yen Chang, Feng-Huei Lin*
National Taiwan University, Graduate Institute of Biomedical Engineering

**Introduction**：DES is defined as a multifactorial disease of the tear and ocular surface resulting in tear film instability with potential damage to the ocular surface. BSP is a plant-based polysaccharide possessing anti-inflammatory, antioxidant, anti-tumorous properties as well as excellent moisturizing effect along with great biocompatibility. The aim of this study is to develop an artificial tear solution with anti-inflammatory effect for dry eye syndrome treatment.

**Materials and Methods**：*Bletilla Striata* was purchased from Sheng Chang Company (Taoyuan, Taiwan), WST-1 Cell Proliferation Assay Kit was purchased from Takara Bio USA, Inc. All other chemicals were purchased from Sigma-Aldrich (USA). The extracted BSP was tested for its antioxidant and anti-inflammatory properties followed by the test for biocompatibility. The solution was injected in the DES induced rabbit eyes and were examined for the change in ocular surface, cornea thickness, tear production followed by histological evaluation.

**Results**：In this research, we successfully developed artificial tears containing BSP and evaluated its efficacy for the treatment of dry eye. Compared with control group, treatment with artificial tears containing BSP promoted corneal recovery, suppressed inflammation and increased corneal thickness. WST-1 and live and dead assay using HCEC cell lines showed good cell viabilities when treated with different concentration of BSP. It is also shown that BSP reduces inflammation in DES induced rabbit eyes significantly and effectively promoted recovery. Additionally, our study provided the values of refractive index, pH value, viscosity, and osmolality of artificial tears which further exhibited its efficacy as they are all very close to real human tears

**Discussion**：BSP artificial tears provides the affirmation of efficacy and biocompatibility for the treatment of dry eye syndrome. BSP has the functions of anti-oxidant, anti-inflammation and anti-tumor and therefore has been widely used in traditional Chinese medicine. Remedies that promptly and productively suppresses inflammation are crucial for the treatment of DES. Hence, BSP has proven to be suitable candidate.

**Conclusions**：This study possesses a potential treatment effect for the dry eye syndrome which is the most prevalent ocular surface disease in the whole world affecting 8-14% of the population. BSP containing artificial tears represents a promising candidate for the treatment of DES.

## P-02

# 運用多層毛囊細胞球來探討於毛髮新生過程的上皮與間質的交互作用
# Multilayer hair sphere for epithelium-mesenchyme interaction during hair neogenesis

賴正偉 [1*] 黃子婕 [2*] 吳佳慶 [1,2,3]
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**Introduction**：Regenerative medicine has been developed for treating hair loss recently. The hair follicle (HF) inductive capacities require not only the dermal papilla (DP) but also the interactions between epithelium and mesenchyme cells. In this study, we established the 3D co-culture system to create multilayer cell spheres for investigating the cell-cell interactions between DP, keratinocytes (KCs) and adipose-derived stem cells (ASCs).
**Materials and Methods**：The DP cells, KCs and ASCs were isolated from C57BL/6 mice. The multilayer spheres were created by sequential seeding of different cells into a chitosan-coated 96 well plate. This 3D co-culture system can mimic the HF structure with providing physical interactions in different arrangement of layer-by-layer cells. The chemical effect on HF induction was also evaluated by applying the conditional medium isolated from KCs and/or ASCs for DP cells. The functional assay was performed by using patch assay to demonstrate the HF regeneration on nude mice.
**Results**：The DP cells, KCs, and ASCs were sequentially seeded to form diverse multi-layer cell spheres with different orders in 6 days. From the core to the outer layer were DP/KC/ASC sphere, DP/ASC/KC sphere, and a mixed outer layer was DP/ASC+KC sphere. We showed that the expression of hair-inductive DP markers in multi-layer spheres with this DP/KC/ASC arrangement were raised the most significantly. Interestingly, the expression of hair-inductive DP markers under the physical contact effect of DP/KC sphere was promoted more in comparison with the chemical delivery effect from any conditional medium which suggested the close contact between DP cells and KCs was more beneficial in inducing DP cells features. We also found that DP/KC/ASC spheres among other heterotypic spheres were more effective and successful in inducing hair regeneration in vivo.
**Discussion/Conclusion**：Our 3D culture system provided the individual environment for each sphere that allowed us to give hair inducing gene-amplified treatments. This study demonstrated that the chitosan-coated 96 well plates could create a multilayer sphere to mimic the structure of hair for HF induction. The sphere with the DP core, KCs in the mid-layer, and ASCs in the outer-layer showed the best functional performance on promoting hair regeneration in vivo.

## P-03

# 人類間質幹細胞在調控周邊 B 淋巴細胞分化上的組織特異性
# Tissue-specific interactions of human mesenchymal stem cells (hMSCs) in modulating peripheral B lymphocytes differentiation

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**Introduction**：B lymphocytes, also called B cells, are a type of white blood cell within the immune system. Circulating in the blood and activated by pathogens/antigens, peripheral B cells play an important role in both physiological and pathological conditions, being responsible for the humoral immunity of the adaptive immune system as well as acting as professional antigen-presenting cells (APCs) to critically orchestrate T cell responses. Despite the importance of B cells, surprisingly little is known about their interactions with mesenchymal stem cells (MSCs), a type of multilineage somatic progenitor cell with strong immunomodulatory properties. First isolated from the bone marrow (BM), MSCs have since been found to exist in numerous adult as well as fetal-derived tissues/organs. Given that the BM is the site for B lymphocyte development, interactions between B cells and MSCs from this source are likely to be different from MSCs derived from other sources. We therefore were interested in the interactions of B cells to BM-MSCs and term placenta-derived MSCs (P-MSCs).
**Materials and Methods**：Human isolated B cells were stimulated via anti-Ig, CD40L, CpG and IL-2 for 6 days in co-culture system with MSCs. After co-culture, we assay the B cells percentage and proliferation in each subsets B cells populations. For in vivo mouse model, lipopolysaccharide (LPS) was injected intraperitoneally into 7-week-old mice followed 2 hours later by transfer of human MSCs (1x105 cells/mouse). Mice were sacrificed on day 3 with excision of spleen and harvesting of splenocytes for analysis of B cell subpopulations.
**Results**：We found that P-MSCs but not BM-MSCs affect the maturation of activated B cell at several stages. Moreover, similar findings were seen in an in vivo mouse model of B cell activation.
**Conclusions**：Our preliminary findings demonstrate that B cell interactions with MSCs can differ significantly depending on the source of MSCs. Studies are ongoing to elucidate the mechanisms mediating tissue-specific MSCs interactions with this important population of the adaptive immune system.

(APOLOGY STATEMENT: We are going of writing a patent, since abstracts get published all the time, we think it is better to be vague in the abstract until we have applied for the patent.)

**P-04**

# Notch路徑參與脂肪間質幹細胞調節樹突細胞免疫耐受之作用
# Adipose-derived Stem Cells-Modulated Dendritic Cells tolerogenicityis is Associated with Notch Pathway

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**Introduction**：Adipose-derived stem cells (ASCs) are potential immunomodulators and prolong the survival of vascularized composite allotransplantation (VCA). Maturated dendritic cells (DCs) present the alloantigen to effector T cells and induce the immune rejection or inflammation. Studies showed that the Notch ligand, Jagged-1, was presented on bone marrow-derived stromal cells, which induced the accumulation of DC precursors and prevented their transition to terminally differentiated DCs. The aim of this study is to investigate the role of Notch pathway in ASC-modulated DC tolerogenicity and the effect on regulation of immune response.

**Materials and Methods**：ASCs, myeloid DCs and $CD4^+$ T cells were isolated from Lewis (LEW) rats' groin fat pad, femur bone marrow and spleen, respectively. DCs were directly co-cultured with ASCs to evaluate the suppressive effect of ASCs. $CD4^+$ T cells were co-cultured with DCs pretreated with or without ASCs. Notch inhibitor, DAPT, was used for blocking the Notch signaling. The maturation of DCs and regulatory T cells were analyzed by flow cytometry. The expressions of Notch1, Jagged1 in DCs and ASCs were detected by real-time PCR, Western blotting and immunofluorescence. Cytokine expressions in different treatments were measured by ELISA.

**Results**：Notch 1 and Jagged 1 were highly expressed on ASC-treated DCs and ASCs, respectively. The percentages of CD80, CD86 and MHC II of DCs in the ASC-treated group were significantly reduced as compared to that in mature DCs without ASC treatment. Inhibition of Notch pathway by DAPT could restore the dedifferentiation effects in the ASC-treated DCs. The percentage of $CD25^+/FOXP3^+/CD4^+$ regulatory T cell (Treg) population were significantly increased in ASC-treated DC group, but reduced with the administration of DAPT.

**Discussion**：Our previous studies have provided evidence that both immature and tolerogenic features of DCs induced by ASCs *in vitro*. In addition, our rodent hind-limb allotransplantation model showed that the recipient immature tolerogenic DCs, which was alloantigen-pulsed by donor cells, could prolong allograft survival by increasing the population of regulatory T cells. Moreover, *in vitro* studies reported that DCs pulsed with ovalbumin in the presence of MSCs are less proficient in promoting CD4+ T cell proliferation, and this effect is reversed by addition of gamma-secretase inhibitor, which inhibits the Notch activation. These results are compatible with our findings that ASCs regulate the immune modulation by inducing tolerogenic DCs via activating Notch signaling.

**Conclusions**：The results indicated that ASC induced of DC tolerogencity and the down-stream immune responses is associated with the activation of Notch pathway. Our study suggests ASC-induced tolerogenic DCs as a potential immunomodulatory tool for clinical application.

## P-05

# 體外培養未經白血球生成激素驅動之周邊血 CD34+幹細胞
# Ex vivo Expansion of CD34+ Cells from Non-GCSF Mobilized Peripheral Blood Stem Cells

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**Introduction**：Cell therapy has been considered as a promising way in treating different diseases. The Ministry of Health and Welfare loosen up the regulation regarding cell therapy in September 2018, enabling six stem cell therapy technology practices. Stem cell-based therapy has shown its potential to mitigate damages after stroke. Peripheral blood hematopoietic stem cells (PBSCs) are used increasingly as a source for cell transplantation due to its faster hematological recovery. Previous reports also suggested the therapeutic potential of $CD34^+$ cells in PBSC in treating cerebrovascular diseases by promoting new vessels formation. Therefore, it is critical to have a sufficient amount of $CD34^+$ cells to reach therapeutic effect. In this study, we aim to perform ex vivo expansion of $CD34^+$ cells from non-Granulocyte Colony-Stimulating Factor (G-CSF) mobilized PBSCs, and to establish a method to suggest a potential therapeutic regimen for treating chronic ischemic stroke in the future.

**Materials and Methods**：SD rats were randomized to non-G-CSF and G-CSF groups, and G-CSF group was administered G-CSF intravenously with concentration of 5μg/kg. Peripheral blood samples of both groups were obtained by cardiac puncture with spray-dried $K_2$EDTA vacuum tube. Phosphate-buffered saline and whole blood were mixed with the proportion to 1:1. The mixture was slowly added into Ficoll-Paque™ Premium and centrifuge to isolate buffy coat from whole blood, and the middle layer liquid was collected for culture. Cell was cultured in $CD34^+$ selective medium (unpublished formulation) at 37°C, 5% $CO_2$. $CD34^+$ antibody was used to validate cell identity by flow cytometry.

**Results**：The primary culture of peripheral blood included different cell types. FACS analysis showed that G-CSF group have a higher percentage of monocytes and granulocytes compared with the non-G-CSF group. Moreover, the percentage of $CD34^+$ cells showed small difference between G-CSF and non-G-CSF group. Both groups of cells cultured were monitored and microscopy images were captured on Day2, Day6, Day11, Day14, and Day18. It showed a slower expansion rate at the beginning, and revealed clustering in both groups on day14, about 80% confluency at day 18.

**Discussion**：After culturing for 18 days, our results showed the growth of $CD34^+$ cells from both G-CSF and non-G-CSF mobilized PBSCs, indicating it is doable to expand $CD34^+$ cells without the mobilization of G-CSF. In addition, non-G-CSF group showed various cell types in morphology, whereas the G-CSF group showed a monotonous cell population after culturing, suggesting that the non-G-CSF mobilized $CD34^+$ cells may have higher potential in promoting vessels formation.

**Conclusions**：Indicated by the results of this study, ex vivo expansion of $CD34^+$ cells without the mobilization of G-CSF is performed. This selective medium can form part of regimen in performing cell therapy. Based on the potential therapeutic effects of $CD34^+$ in treating different diseases according to the previous reports, our intended study will focus on evaluating the therapeutic potential of human PBSCs for chronic ischemic stroke using this ex vivo expansion regimen.

## P-06

# CRISPR-based Activation of Endogenous Neurotrophic Genes in Adipose Stem Cell Sheet to Stimulate Peripheral Nerve Regeneration

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**Introduction**：Peripheral nerve regeneration is a complex and delicate process that requires coordinated functions of neurotrophic factors and neuronal cells to promote the development, survival, proliferation, differentiation and regeneration of injury neurons. We adapted the CRISPR activation (CRISPRa) system with baculovirus to exploit the new CRISPRa-based BV vector for genetic modulation of rat ASCs sheets for neurotrophic factors (BDNF, GDNF and NGF) expression and peripheral nerve regeneration.
**Materials and Methods**：For sciatic nerve regeneration, we developed simple procedure to fabricate adipose stem cells sheets. Rat ASCs were seeded 6-well plates $2\times10^6$ cells/well and cultured with α-MEM containing 20% FBS. After 24 h, ASCs sheets were formed and BV transduction was performed with virus diluent in different M.O.I. for 6 h, followed by removing the transduction mixture and culture with α-MEM medium containing 3 mM sodium butyrate. At 48 h post-seeding, briefly trypsinized using 0.05% trypsin-EDTA for 10s, washed twice and incubated in PBS. The transparent ASCs sheets spontaneously detached from the well and shrank. The detached ASCs sheets were handled with a forceps for ensuing implantation.
**Results**：We demonstrated that the expression of CRISPRa system in rat adipose-derived stem cells (ASC) enabled robust activation of neurogenesis-related genes (e.g. BDNF, GDNF and NGF). The CRISPRa-mediated enhanced expression of neurotrophic factors stimulated the migration of Schwann cell and neurite extension, and guided the remyelination process in vitro. Importantly, implantation of the hybrid BV-engineered ASCs into sciatic nerve transection site in rats significantly improved the nerve regeneration as judged from the enhanced functional recovery, integrity of nerve conduction, electrophysiological functionality, axon regeneration and remyelination.
**Discussion**：These data and features implicate the potentials of CRISPRa hybrid BV incorporate with ASCs sheets for peripheral nerve regeneration.
**Conclusions**：We exploited the newly developed tools, CRISPRa system, for multiplex genomic modulation in rat ASCs and established a new platform for nerve regeneration research.

**P-07**

# 利用 CRISPRai 系統同時執行基因活化與抑制以促軟骨細胞分化及顱骨再生
# A Single CRISPRai platform enabling simultaneous gene activation and repression for chondrogenic differentiation and calvarial bone regeneration

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**Introduction**：Calvarial bone healing has seen an imminent delay in clinical settings. Studies have shown such conundrum might be addressed by stimulating implanted stem cells towards chondrogenic lineage in lieu of conventional osteogenic induction. Here, we demonstrated for the first time the development of an all-in-one platform termed CRISPRai that facilitates simultaneous, bidirectional, and multiplexing gene manipulation to induce chondrogenic and inhibit adipogenic commitment in stem cells.

**Materials and Methods**：Adipose derived and bone marrow derived stem cells (rASC and rBMSC) were maintained and expanded in α-MEM (Gibco) supplemented with FBS, penicillin, streptomycin, and bFGF. ASC or BMSC was singly transduced with baculovirus encoding the CRISPRai cassette and the sgRNA array activation the master regulator of chondrogenesis (Sox9) and repressing that of adipogenesis (PPAR-γ) or co-transduced along with a second virus carrying Cre recombinase (Cre/loxP system). The transduced cells were subsequently cultured in 2D or 3D format for further analysis.

**Results**：In this study, we achieved simultaneous activation of *Sox9* (17.1-fold) and repression of *PPAR-γ* (to 30.3%) using the CRISPRai platform. The *Sox9* activation effect was further extended to 107.9-fold with the Cre/loxP system. These resulted in an upregulation of chondrogenic (*Col2a1, Acan*) and downregulation of adipogenic (*C/ebpα, Fabp4*) markers. Such effect was extensively confirmed by Alcian Blue/Safranin O (GAG accumulation) and Oil Red O (lipid droplet formation) staining. Implantation of the CRISPRai-engineered rBMSC into calvarial defects facilitated bone regeneration and quality as evident by micro CT imaging and immunohistochemical assay.

**Discussion**：CRISPR/Cas9 had been repurposed into a sequence-specific DNA-binding RNA-guided complex for gene activation (CRISPRa) and interference (CRISPRi). Nonetheless, they were utilized in two separate vectors due to limitation in capacity (e.g. AAV) while none has been applied to yield a medical outcome in tissue engineering. Our study, therefore, developed a single 12.6-kb platform (CRISPRai) enabling simultaneous gene activation and manipulation carried by baculovirus. CRISPRai allows orthogonal and selective gene switching on (*Sox9*) and off (*PPAR-γ*) and paves the way to translate such powerful tool to clinical settings for tissue regeneration.

**Conclusions**：The all-in-one CRISPRai is able to orthogonally activate *Sox9* and repress *PPAR-γ* leading to subsequent enhancement of chondrogenesis and inhibition of adipogenesis in 2D and 3D culture and ultimately promotes calvarial bone healing capability of rBMSCs.

**P-08**

# 運用小分子藥物調節增進人類成體與誘導性多能幹細胞衍伸間葉幹細胞之軟骨分化能力
# Modulation of Small Molecules for Efficient 3D-Chondrogenic Differentiation of Tissue-specific and Induced Pluripotent Stem Cell (iPSC)-derived Human Mesenchymal Stem Cells (hMSCs)

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**Introduction**：Human mesenchymal stem cells (MSCs) are post-natal stem cells considered as excellent cell sources for tissue engineering of cartilage, a tissue without the capacity for regeneration or repair but often injured in activity and with aging. Among them, induced pluripotent stem cell (iPSC)-derived MSCs (iMSCs) are a novel source of MSCs which are strongly proliferative and can be designed to be patient-specific. We therefore studied the use of iMSCs for therapeutic use in cartilage-related diseases and investigate how 3D culture conditions mechanistically modulate MSC chondrogenesis for discovery of novel small-molecular targets by which the efficiency of the process can be enhanced.

**Materials and Methods**：MSCs were differentiated from human iPSCs, with subsequent chondrogenic differentiation of iMSCs was performed by 3D pellet culture and verified by Alcian Blue staining for glucosaminoglycan expression. Real-time quantitative PCR was performed for analysis of gene expression and immunofluorescence staining of 3D pellets was performed for analysis of protein expression and localization.

**Results**：We found one pair of small-molecule agonist/antagonist X and Y, respectively, which resulted in opposing effects on iMSC chondrogenic differentiation. Furthermore, drug Y was able to induce MSC chondrogenesis in the absence of TGF-β, which upregulated $\alpha$-SMA expression, a marker of fibrosis as well as smooth muscle lineage.

**Discussion**：Traditionally, TGF-β has been applied to induce MSC chondrogenic differentiation, but we found that TGF-β-mediated chondrogenic induction—which is the current standard protocol—in MSCs was associated with upregulation of $\alpha$-SMA expression, a lineage marker for smooth muscle and also a marker for fibrosis, and may interfere with achieving chondrogenic end-differentiation. Interestingly, drug Y was able to induce MSC chondrogenesis in the absence of TGF-β. Our data demonstrate the strong chondrogenic effect of drug Y on MSCs from diverse sources without induction of $\alpha$-SMA, implicating this small molecule as a novel and highly efficient inducer of MSC chondrogenesis.

**Conclusions**：Our preliminary data demonstrate that use of small molecules affecting chondrogenic pathways can more efficiently modulate iMSCs toward a chondrogenic fate as compared to standard differentiation methods which including using TGF-β. We are continuing to elucidating the mechanisms involved, as well as expanding the investigation towards tissue-derived MSCs from diverse sources for broader therapeutic application.

**P-09**

# 脂肪幹細胞製劑 GXHPC1：具有肝硬化病患肝功能恢復能力
# The ADSC product GXHPC1 facilitated recovery of liver function for liver cirrhosis patient

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**Introduction**：Currently, the only effective therapy for cirrhosis of the liver is liver transplantation. However, finding a compatible liver is difficult due to the low supply of healthy livers and the ever-increasing demand. Stem-cell therapy may offer a solution for liver cirrhosis.
**Materials and Methods**：Adipose tissue (2–5 g) was harvested from the subcutaneous fat of each patient's abdominal wall during gynecologic surgery. All tissue were manufactured in a good tissue practice (GTP) lab (Gwo Xi Stem Cell Applied Technology Co., Ltd.). On the day of injection, adipose-derived mesenchymal stem cells (AD-MSCs) were harvested and washed three times with sterile saline. AD-MSCs were resuspended in physiological saline at a final concentration of $1 \times 10^8$ cells/ml (ie. GXHPC1). The health of patients was continuously monitored according to the visit schedule and study procedures. A 21G hepatobiliary needle (21 gauge, 200 mm) was used to pierce the right anterior leaf of the liver from the seventh and eighth ribs on the right side of each patient. Once the hepatobiliary needle was positioned, the prepared GXHPC1 was injected. The health of patients was continuously monitored according to the visit schedule and study procedures.
**Results**：Intrahepatic injection of GXHPC1 did not cause any safety issues in the analysis of adverse drug reactions and suspected unexpected serious adverse reactions and showed a tendency for improvement of liver function, METAVIR score, Child-Pugh score, MELD score, and quality of life for subjects with liver cirrhosis.
**Discussion**：Recent clinical trials have demonstrated that MSC transplantation has been beneficial to patients with liver failure. However, MSCs from bone marrow procurement may be distressing to patients, and indeed it has proven difficult to obtain a sufficient amount of autologous adult stem cells. GXHPC1 is a cell product that contains autologous AD-MSCs and was developed for the treatment of liver cirrhosis. In this study, we successfully manufactured each patient's GXHPC1 and used for direct administration into the liver parenchymal tissue to restore liver function and to ameliorate liver fibrosis.
**Conclusions**：This study showed that intrahepatic injection of GXHPC1 could be considered as a safe and feasible for the treatment of liver cirrhosis.

**P-10**

# 副甲狀腺素 1-34 藉由抑制 PDCD5 的表現緩解軟骨細胞的細胞凋亡
# Parathyroid Hormone (1-34) Ameliorates Human Chondrocyte Apoptosis by reducing the Expression of Programmed Cell Death 5

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**Introduction**：The chondrocyte in osteoarthritis (OA) cartilage undergo apoptotic features and hypertrophic change compared with that of normal health cartilage. Parathyroid hormone 1–34 (PTH [1–34]) ameliorates OA progression by reducing apoptosis of human articular chondrocyte. Programmed cell death 5 (PDCD5, PD-5), a novel apoptosis-related gene, was found enhanced expression and nuclear accumulation in cells undergoing apoptosis. To clarify the mechanisms of PTH (1–34), we evaluated the roles of PDCD5 in the apoptosis of human articular chondrocyte in the pathogenesis compared with treatment of PTH (1–34) in OA.

**Materials and Methods**：We used quantitative real-time PCR and Western blot to evaluate the expression level of PDCD5 in azacytidine (Aza-C) and Interleukin1β (IL-1β)-induced OA phenotypes and investigated the treatment effect of PTH(1–34) on human articular chondrocytes. Four groups were control, PTH treatment alone, terminal differentiation induction alone, and terminal differentiation induction with PTH. We further investigated the protein expression levels of PDCD5 by in vivo animal model on aging related OA model in guinea pigs with different degree of aging including 4 months, 5 months, 7 months, and 11 months compared with PTH(1–34) treatment by immunohistochemistry and quantified by Image-Pro Plus software.

**Results**：AzaC and IL-1β-induced OA phenotypes of chondrocyte, including upregulation of Collagen X and MMP-13, increased the mRNA expression level of PDCD5. PTH(1–34) treatment inhibited the OA markers as well as the mRNA expression level of PDCD5. In addition, IL-1β-induced apoptosis of chondrocyte induced early apoptotic signal, PDCD5, was ameliorated by PTH(1–34) treatment. Immunohistochemical staining showed the expression levels of immunolocalized PDCD5 were higher at more aging and severe OA, and PTH (1-34) treatment ameliorates OA progression and eliminates the expression of PDCD5.

**Discussion**：Chondrocyte apoptosis is one of the important causes of OA. PDCD5 was previously identified as an early signal molecule upregulated in cells undergo apoptosis. Our analysis demonstrated that the chondrocytes underwent OA change and aging of articular cartilage were prone to express more PDCD5. PTH(1–34) ameliorated chondrocyte apoptosis and OA progression, at least in part, were by suppressing the expression and activation of PDCD5.

**Conclusions**：We thus conclude that PTH(1–34) inhibited the expression of early apoptotic signal, PDCD5, and then prohibited the downstream death signal to ameliorated chondrocyte apoptosis and OA progression. However, further studies are still needed to elucidate the functional roles of PDCD5 in the signaling pathways of OA amelioration after PTH (1-34) treatment.

**P-11**

# 第二型纖維母細胞生長因子在人類脂肪幹細胞於長期體外培養時之影響
# The influence of fibroblast growth factor-2 on human adipose-derived stem cells during long-term *in vitro* culture

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**Introduction**：Adipose-derived stem cells (ASCs) exhibit great potentials in regenerative medicine, and *in vitro* expansion is frequently necessary to obtain sufficient ASCs for clinical use. Fibroblast growth factor (FGF)-2 is a common supplement in the ASC culture medium to enhance ASC proliferation. However, the effect of FGF2 on ACS culture during prolonged culture has not been determined before.

**Materials and Methods**：In the experimental group, 1 ng/mL FGF2 was added to the basal medium for hASC culture. Further comparisons at different passages were conducted about cell size, senescence, cumulative population doubling, colony forming unit-fibroblast (CFU-F) assay, cell cycle, presentation of fibroblast growth factor receptors and specific proteins, and tumorigenicity *in vivo* and *in vitro*.

**Results**：Our study showed that FGF2 maintained small cellular morphology and expedited proliferation kinetics in the early passages of ASCs. However, after prolonged *in vitro* expansion, FGF2-treated ASCs exhibited increased cell size, proliferation arrest and increased senescence relative to the control ASCs. We observed upregulation of *FGFR1c* and enhanced expression of the downstream STAT3 in the initial passages of FGF2-treated ASCs. Application of FGFR1 or STST3 inhibitor effectively blocked the enhanced proliferation of ASCs resulting from FGF2 treatment. *FGFR1c* upregulation and enhanced STAT3 expression disappeared in the later passages of FGF2-treated ASCs, suggesting the continuous stimulation of FGF2 became ineffective to ASCs because of the refractory downstream FGFR1 and the STAT3 signaling pathway. Moreover, no evidence of malignant transformation *in vitro* and *in vivo* was noted in prolonged FGF2-cultured ASCs,

**Discussion**：FGF2 exerts positive effects in the early passages of ASC culture, resulting in the maintenance of cellular morphology and expedited proliferation kinetics. However, after prolonged *in vitro* expansion of ASCs with FGF2, increased cell size, proliferation arrest, and increased senescence were noted in the later passages. This phenomenon may be mediated through FGFR1c and the downstream STAT3 signaling pathway.

**Conclusions**：FGF2 supplementation for ASC expansion is desirable for limited passages to obtain ASCs with optimal quality and quantity for therapeutic purposes. This indicates that FGF2-treated ASCs can be a safe source of stem cell-based therapy, though the expansion-stimulating effect is limited to the early passages.

**P-12**

# 人體血小板裂解液對於脂肪幹細胞薄片增生及其促進血管新生潛力之探討
# Platelet lysate enhanced adipose-derived stem cell sheet formation with improved angiogenic capability

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**Introduction**：Adipose-derived stem cells (ASCs) holds a valuable future in regenerative medicine. ASC sheet has been suggested to promote tissue healing and has been applied as possible treatment in a variety of disease models. However, the use of animal-derived serum supplemented growth media may lead to concerns regarding to clinical complication. In recent years, human platelet lysate (PL) provides an attractive alternative to fetal bovine serum (FBS) for the *ex vivo* expansion of mesenchymal stem cells for clinical use. In this study, we compare ASC sheets that have been cultured in growth media supplemented with either FBS or PL.
**Materials and Methods**：ASCs were cultured in Dulbecco's modified Eagle's medium (DMEM)-high glucose supplemented with either FBS or PL. Cell sheet formation was further induced by the addition of ascorbic acid 2-phosphate. We performed quantitative PCR, western blotting, ELISA and proteomic analysis to further compare ASC sheets culture with FBS and PL. HUVEC tube formation was used as an *in vitro* angiogenesis assay.
**Results**：In this study, we found that ASC sheet cultured with PL acquired a higher population doubling and better osteogenic differentiation, though adipogenic differentiation was reduced relative to ASC sheet cultured with FBS. Proteomic analysis of sheet extracellular matrix showed a much more abundant extracellular matrix deposition. PL-supplemented culture media significantly enhanced expression of hepatocyte growth factor (HGF) and chemokine (C-C motif) ligand 5, which have been shown to play important roles in angiogenesis. ASC sheets induced by PL-supplemented growth media also promoted endothelial cell migration and vessel formation. Conditioned medium collected from ASC sheets cultured in PL- supplemented media showed significantly more tube formation in *in vitro* HUVEC angiogenesis assay.
**Discussion**：Supplementation of PL promoted a faster and more robust ASC sheet formation, and the secretion of angiogenic paracrine factors from ASC sheets was also enhanced. ASC sheet cultured with PL has been shown to promote *in vitro* tube formation. The use of PL for ASC sheet formation circumvented the untoward side effects for using FBS for cell culture, and our *in vitro* data demonstrated a potential **angiogenic** capability of PL-cultured ASC sheet.
**Conclusions**：ASC sheet cultured in PL-supplemented media expressed enhanced proliferation, matrix formation and angiogenic capacity *in vitro*. Therefore, as PL-cultured ASC sheet exhibits great potential in future clinical application to treat ischemic diseases.

## P-013

# 軟骨再生: 脂肪組織獲取之間質幹細胞治療退化性關節炎
# Cartilage regeneration by autologous adipose-derived mesenchymal stem cells for the treatment of osteoarthritis

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**Introduction**：Osteoarthritis (OA) is a degenerative joint disease mainly caused by wear and tear of the cartilage cushion between joints. Millions of people, especially the aged population, are suffering chronic pain and limited movement due to osteoarthritis around the world. Current treatment of osteoarthritis generally focuses on medication and knee replacement surgery depending on the deterioration level of the knee joint. However, medication has a limited effect on the symptoms and the patients who take the knee replacement surgery may suffer persistent pain around the replaced joint. In view of these limitations, numerous efforts have been made to find a more effective treatment, such as cell therapy to prevent the cartilage from deteriorating and reverse the course of arthritis.

**Materials and Methods**：The adipose-derived MSCs from the patients are cultured and expanded to a specific amount with the optimized stem cell culture medium, the HELENE MEDIUM. After that, the cultured MSCs are directly injected into the injured knee joints of patients.

**Results**：Here we show that in twelve clinical cases, the cartilage was observed successfully regenerating and covering the defect region in knees after the intra-articular injection with adipose-derived mesenchymal stem cells (MSCs) in six months after treatment. Moreover, these patients showed improvement in clinical outcomes by measurements of the WOMAC Osteoarthritis index and Harris Hip Score.

**Discussion**：Based on the preclinical and clinical reports, except for replacement as chondrocytes, MSCs are able to secrete paracrine factors which take effects in modulating the microenvironment of the damaged sites, leading to an optimal condition for tissue regeneration. Also, further research will focus on determining co-injection of MSCs with differential factors could facilitate the cartilage regeneration.

**Conclusions**：In summary, our results demonstrate the success in MSCs treatment of osteoarthritis by cartilage regeneration in clinical cases. We expect our findings of MSCs for osteoarthritis treatment could be a starting point in the field of regenerative therapy to more cartilage diseases and unsolved diseases.

## P-014

# 幹細胞培養專用培養液：Helene 培養液
# The Helene Medium: A Specialized Stem Cell Culture Medium

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**Introduction**：Expansion of stem cells require delicate environment control of the culture methods, the serum concentration and the culture medium. Stem cells for medical usages demand even finer care. Our medical center in Japan, the Helene clinic, provides autologous adipose-derived mesenchymal stem cell therapy for various illness. In light of effectiveness as well as safety, we developed a specialized stem cell culture medium for primary stem cell culture, the Helene medium, aiming for excelling growth rate, more stable cell growth, and disinclination to differentiation.
**Method**：In this study, we tested the Helene medium and two other commercial mediums through investigating their growth rates, cell morphology, and passage number. As the usage of serum might induce cell differentiation, we also examined the quality and potency of cells cultured in all three mediums with autologous serum added.
**Result**：Stem cells cultured without serum grew slower than those with serum. Yet in either case, growth rate of the cells cultured in Helene medium exceeded all the others. Within Helene medium, cells also showed retained phenotypic and differentiation. Others, however, underwent conspicuous morphology change.
**Discussion**：Although the advantage of Helene medium was phenotypically revealed, detailed analysis of the genotypic difference, e.g. oligonucleotide microarray, is further needed for stronger supportive results.
**Conclusion**：The Helene medium outstands the commercial mediums in terms of better cell growth, more stable morphology, and maintained potency under both serum-free and serum-containing condition.

## P-015

# 是否間質幹細胞與間質幹細胞條件培養基具備幫助已受損發炎軟骨細胞恢復健康之能力?
# Can Mesenchymal Stem Cells and Their Conditioned Medium Assist Inflammatory Chondrocytes Recovery?

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**Introduction**：Osteoarthritis (OA), one of the most common joint disease, affects more than 80% of the population aged 70 or over. Mesenchymal stem cells (MSCs) show multi-potent differentiation and self-renewal capability, and, after exposure to an inflammatory environment, also exhibit immunosuppressive properties. Thus, in this study, we would like to examine whether the cartilage repair induced by MSC therapy was due to MSC-chondrocyte direct contact, paracrine effects, or a combination of the two. Moreover, a cytokine-only culture system: MSC-conditioned medium (CM) system was also been set up for inflammatory chondrocyte recovery evaluation.

**Materials and Methods**：In this study, we have used a model of lipopolysaccharide (LPS)-stimulated chondrocytes to evaluate MSC anti-inflammatory efficacy. The anti-inflammatory mechanism was tested in two cell-contained culture systems: (i) MSC-chondrocyte indirect contact system and (ii) MSC-chondrocyte direct contact system, and one cytokine-only culture system: MSC-conditioned medium (CM) system.

**Results**：The inflammation-associated, and free-radical-related genes were down-regulated significantly in the direct contact system on 24 h, however, the TNF-$\alpha$. IL-6 were upregulated and aggrecan, COLII were downregulated on 72 h in direct contact system. We found CM produced by MSC possess well therapeutic effect on inflammatory chondorcyte, and the 10-fold concentrated MSC-conditioned medium could down-regulated chondorcyte synthesis inflammation-associated, and free-radical-related genes, such as TNF-$\alpha$, IL-1$\beta$, IL-6 and iNOS even treated for 72 h.

**Discussion**：Results showed that MSCs reduced chondrocyte inflammation through both paracrine secretion and cell-to-cell contact. But the anti-inflammation ability of MSC would decrease with incubation time increase, especially in direct cell contact co-culture system. However, treatment with MSC-CM for a longer period (72 h) did not result in upregulation of the expression of inflammation-related genes, especially in the group of CM10X.

**Conclusions**：In conclusion, MSC-CM has multiple beneficial effects on inflammatory chondrocytes, including an anti-inflammatory effect and an increase in chondrocyte numbers. Besides, it can be freeze-dried, packaged, and transported, and mass production in the future. MSC-CM showed great potential for MSC-based therapy for OA.

## P-016

# 以動物實驗評估玻尿酸、血小板濃縮液與間質幹細胞對膝關節炎治療之療效

# Effectiveness Among Hyaluronic Acid, Platelet-Rich Plasma, and Mesenchymal Stem Cells for Knee Osteoarthritis: An *In Vitro* Animal Study on Rabbit.

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**Introduction**：Both hyaluronic acid (HA) and platelet-rich plasma (PRP) injection are the common prescribed treatments for osteoarthritis (OA) patients. HA can serve as a good lubricant to reduce the fraction force of cartilage surface while PRP provide several growth factors to assist tissue repair. Considering the efficiency of tissue regeneration, mesenchymal stem cells (MSCs) injections becomes an attractive method because of their self-renewal and multi-differentiation potential. Thus, in the study, we compared the treatment effect of PRP and HA with/without MSCs.

**Materials and Methods**：Eighteen rabbits weighing from 1.8 to 2.2 kg underwent anterior cruciate ligament transection for OA knee induction, and then injected with saline, PRP, HA, HA+PRP, PRP+MSCs or HA+MSCs intra-articularly. Half of the animals were sacrificed after 1 month, and the remaining animals received second injections then sacrificed after 3 months for treatment effect evaluation.

**Results**：Compared with the results of HA group, the cartilage treated with HA+PRP and PRP+MSCs showed better repair results in micromorphology and glycosaminoglycan synthesis. We also found that the Osteoarthritis Research Society International (OASRI) scores in HA+PRP and PRP+MSC groups were significantly lower than that of the others at month 1 and month 3, separately.

**Discussion**：We found that a combination of HA and PRP was more effective than HA or PRP alone, but only in the medial compartment at month 1. This result indicates that the cushioning effect provided by the combination of HA and PRP might have a short-term growth-factor effect. However, the viscoelastic properties of HA might decrease, leading to the loss of its lubricating ability after long-term use. Moreover, results of macro- and microscopic observation and OARSI scores showed that PRP+MSC treatment could repair the OA knee for a longer time. We hypothesize that PRP released various growth factors gradually; and these proteins may not only assist in tissue repair but also promote MSC differentiation for matrix synthesis.

**Conclusions**：These indicates that the combination of HA and PRP could provide short-term tissue protection effect while PRP and MSC could provide a long-term tissue regeneration effect. PRP+MSC could be considered as a promising biological method for OA treatment.

# 台灣再生醫學學會 （個人、贊助、準）會員入會申請書

| 姓名 | | 性別 | | 出生年月日 | | 出生地 | | 身分證 ID or 統編 | |
|---|---|---|---|---|---|---|---|---|---|
| 學歷 | 民國　年　月畢業於 | | | | | | | | |
| 戶籍住址 | | | | | | | | | |
| 現任職務 | 醫院或單位： | | | 科部： | | 職稱： | | | |
| 通訊地址 | | | | | | 專科醫師證書字號：<br>(無者免填) | | | |
| 電話 | (公) | | (宅) | | | 傳真： | | | |
| 其他連絡方式 | (e-mail)： | | | | | 行動電話： | | | |
| 審查結果<br>(由學會填寫) | | | 會員類別<br>(由學會填寫) | | | | 會員證號碼<br>(由學會填寫) | | |
| 本人贊同貴會宗旨，擬加入為會員，嗣後並願意遵守會章，共圖發展<br><br>此致　台灣再生醫學學會　申請人：　(簽章)<br><br>中華民國　年　月　日 | | | | | | | | | |