臺灣幹細胞學會第六屆年會
暨
中山醫大五十週年校慶

會議議程表

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(二樓 0211教室)</td><td>論文發表 (五)
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<tr><td>17:00~17:10</td><td colspan="4">閉幕(理事長致詞)</td></tr>
<tr><td>18:00~20:00</td><td colspan="4">晚宴(主持人：理事長 地點：中港路長榮桂冠)</td></tr>
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臺灣幹細胞學會第六屆年會
暨
中山醫大五十週年校慶

會議時間表

08:30-09:00	**報到**
09:00-09:10	**開幕**：何弘能 理事長 及 王進崑 校長
	Plenary Session I 專題演講 I
09:10-09:50	**Mechanism of Mir-302-Induced Somatic Cell Reprogramming** Shi-Lung Lin (林希龍), Ph.D. 引言人：游正博 教授 及 楊仁宏 教授
09:50-10:30	**Target identification of microRNAs expressed highly and regulated by activin A in human embryonic stem cells** Steven Shoei-Lung Li (李水龍), Ph.D. 引言人：林培正 教授 及 賴德仁 教授
10:30-11:00	**壁報論文及茶點**
	Plenary Session II 專題演講 II 引言人：林欣榮 教授 及 高潘福 教授
11:00-11:30	**Molecular Imaging in the Research of Stem Cells** Ren-Shyan Liu (劉仁賢), MD
11:30-12:00	**Stem cells-molecular imaging and therapeutic implications** Win-Ping Deng (鄧文炳), Ph.D
12:00-12:10	**會員合照**
12:10-13:30	**午餐 / 壁報論文 / Luncheon Symposia**
	Luncheon Symposia
	Sponsor:美商貝克曼庫爾特有限公司 **Advanced Platform for cell therapy research** (0112 教室**)** Mr. Tim Yang (楊人泰), Marketing Manager Sponsor:博克科技有限公司 **MACS® Technology and stem cell research** (0211 教室) Miss Sarah Tseng (曾筱筑), Application Specialist Sponsor:進階生物科技股份有限公司 **Defined chemical culture cystem for stem cell culture** (0212 教室) Miss Shu Ming Wang (王淑明), Product Specialist Sponsor:岑祥股份有限公司 **Eliminate stem cell culture obstacles and barriers using fully closed cell culture system and non enzymatic cell detachment method** (0213 教室) Miss Hyunju Lee, Commercial Product Manager
13:30-14:00	**會員大會**

	Concurrent Session I 論文發表 I: Embryonic Stem Cells and iPS
	引言人：柯俊良 教授
14:00-14:20	**Lentivector applications in stem cell programming and hematopoiesis development**
	Lung-Ji Chang (張隆基), Ph.D.
14:20-14:40	***PiggyBac* transposon jumps in human pluripotent stem cells**
	You-Tzung Chen (陳佑宗), Ph.D.
14:40-15:00	**Study on porcine embryonic stem cells for the therapy of Parkinson's disease in rat model**
	Jenn-Rong Yang (楊鎮榮), Ph.D.
	Concurrent Session II 論文發表 II: Adult Stem Cells
	引言人：顏伶汝 教授
14:00-14:20	**Effect of polyamines on the osteogenic differentiation of human bone marrow-derived mesenchymal stem cells**
	Mon-Juan Lee (李孟娟), PhD
14:20-14:40	**Applications of serum-free expanded hematopoietic stem cells and their differentiated cells**
	Chao-Ling Yao (姚少凌), PhD.
14:40-15:00	**Enrichment of stem cells derived neuron cells by β III-tubulin targeted lineage selection**
	Kowit-Yu Chong (張國友), Ph.D
	Concurrent Session III 論文發表 III: Novel Technology
	引言人：周德陽 教授
14:00-14:20	**Direct reprogramming of cancer cells to cancer stem cells by the cell surface marker CD44**
	Jia-Lin Lee (李佳霖), Ph.D.
14:20-14:40	**Polyurethane-gold nanocomposites promote the maturation of endothelial progenitor cells partially through stromal factor-1 (SCD-1)/CXCR4 signaling pathway in the vascular disease model**
	Huey-Shan Hung (洪慧珊), Ph.D.
14:40-15:00	**Proteomics Study in Stem Cell Research**
	Jue-Liang Hsu (徐睿良), Ph.D.
15:00-15:20	**茶點 / 壁報論文**
	Concurrent Session IV 論文發表 IV: Embryonic Stem Cells and iPS
	引言人：朱志成 教授
15:20-15:40	**Ascorbate activates CD30 expression and causes widespread specific DNA demethylation of the epigenome of serum free cultured human embryonic stem cells**
	Tung-Liang Chung (鐘棟樑), Ph.D.
15:40-16:00	**Stem cells and the left-right asymmetrical control in the sea urchin**
	Yi-Hsien Su (蘇怡璇), Ph.D.
	Concurrent Session V 論文發表 V: Adult Stem Cells

	引言人：潘宏川 教授
15:20-15:40	**Rhodamine-123 efflux activity discriminates different subsets of quiescent lympho-myelopoietic human $CD34^{+}CD38^{-}$ cord blood cells** Min Liu (劉銘), Ph.D.
15:40-16:00	**How Notch regulates airway epithelium cell fate** Po-Nien Tsao (曹伯年), M.D., Ph.D
	Concurrent Session VI 論文發表 VI: Novel Technology
	引言人：劉青山 教授
15:20-15:40	**Neovasculogenic potential of breast cancer stem cells** Wen-Wei Chang (張文瑋), Ph.D.
15:40-16:00	**The roles of Notch signaling in skin homeostasis** Liang-Tung Yang (楊良棟), Ph.D.
16:10-17:00	**壁報論文頒獎及前三名得獎者口頭報告及頒獎**
17:00-17:10	**閉幕** 何弘能 理事長
18:00-20:00	**晚宴** (主持人：理事長 地點：中港路長榮桂冠)

Moderator

Name: John Yu (游正博)
Position: Distinguished Research Fellow and Director
Affiliation: Institute of Cellular and Organismic Biology, Academia Sinica, Taiwan
E-mail: johnyu@gate.sinica.edu.tw

Name: Jen-Hung Yang (楊仁宏)
Position: Director
Affiliation: Medical college, Chung Shan Medical University
E-mail: pblosce@hotmail.com

Name: David Pei-Cheng Lin(林培正)
Position: Director
Affiliation: School of Optometry, Chung Shan Medical University
E-mail:pcl@csmu.edu.tw

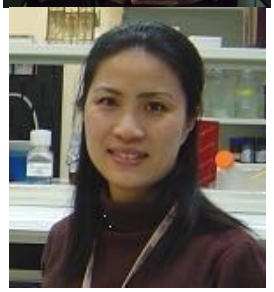
Name: Te-Jen Lai (賴德仁)
Position: Director
Affiliation: Institute of Medicine, Chung Shan Medical University
E-mail: tejenlai@hotmail.com

Name: Shinn-Zong Lin (林欣榮)
Position: President
Affiliation: China Medical University Beigang Hospital
E-mail: shinnzong@yahoo.com.tw

Name: Pan-Fu Kao (高潘福)
Position: Director
Affiliation: Department of Nuclear Medicine, Chung Shan Medical University Hospital
E-mail: pfkao@yahoo.com.tw

Name: Jiunn-Liang Ko (柯俊良)
Position: Director
Affiliation: Research and Development Division, Chung Shan Medical University
E-mail: jlko@csmu.edu.tw

Name: B. Linju Yen (顏伶汝)
Position: Associate Investigator and Attending Physician
Affiliation: Institute of Cellular and System Medicine, Division of Regenerative Medicine, NHRI, Zhunan
E-mail: blyen@nhri.org.tw



Name: Der-Yang Cho (周德陽)
Position: Superintendent
Affiliation: China Medical University Hospital
E-mail: d5057@mail.cmuh.org.tw

Name: Jyh-Cherng Ju (朱志成)
Position: Distinguished Professor
Affiliation: Department of Animal Science College of Agriculture and Natural Resources National Chung Hsing University
E-mail: jcju@dragon.nchu.edu.tw

Name: Hung-Chuan Pan (潘宏川)
Position: Attending Physician
Affiliation: Neurosurgical surgical Taichung Veterans general Hospital.
E-mail: hcpan2003@yahoo.com.tw

Name: Chin-San Liu (劉青山)
Position: Vice-President
Affiliation: Changhua Christian Hospital
E-mail: 26602@cch.org.tw, 128290@cch.org.tw

Plenary Session I

專題演講 I

林希龍 教授

及

李水龍 教授

Shi-Lung Lin, Ph.D.

Director/Assistant Professor
Division of Regenerative Medicine
WJWU & LYNN Institute for Stem Cell Research, USA
Department of Cell & Neurobiology
Keck School of Medicine
University of Southern California, USA
E-mail: shilungl@mirps.org

Education

Ph.D. in Pathology, Keck School of Medicine, University of Southern California, USA (2002)

M.S. in Biochemistry and Molecular Biology, Keck School of Medicine, University of Southern California, USA (1996)

B.S. in Medical Technology, Chung Shan Medical University, Taichung, Taiwan (1989)

Representative Publication

1. **Lin SL**, Chang D, Ying SY, Leu D and Wu DTS; MicroRNA miR-302 inhibits the tumorigenecity of human pluripotent stem cells by coordinate suppression of CDK2 and CDK4/6 cell cycle pathways. Cancer Res. In press, 2010.
2. **Lin SL**, Chang D, Lin CH, Ying SY, Leu D and Wu DTS; Regulation of somatic cell reprogramming through inducible mir-302 expression. Nucleic Acids Res. in press, 2010.
3. Ying SY, Chang CP and **Lin SL**; Intron-mediated RNA interference, intronic microRNAsand applications. Methods Mol Biol. 629: 205-237, 2010.
4. Ying SY and **Lin SL**; Intron-mediated RNA interference and microRNA biogenesis. Methods Mol Biol. 487: 387-413, 2009.
5. Chang SJE, Chang-Lin S, Chang D, Ying SY and **Lin SL**; Repeat-associated microRNA triggers fragile X syndrome in zebrafish. The Open Neuropsycho-pharmacology J. 1: 6-18, 2008.

MECHANISM OF MIR-302–INDUCED SOMATIC CELL REPROGRAMMING

Shi-Lung Lin

Global demethylation is required for early zygote development to establish stem cell pluripotency, yet our findings reiterate this epigenetic reprogramming event in somatic cells through ectopic introduction of mir-302 function. Here we report that induced mir-302 expression beyond 1.3 folds of the concentration in human embryonic stem (hES) H1 and H9 cells led to reprogramming of human hair follicle cells (hHFCs) to induced pluripotent stem (iPS) cells. This reprogramming mechanism functioned through mir-302–targeted co-suppression of four epigenetic regulators, AOF2 (also known as KDM1 or LSD1), AOF1, MECP1-p66, and MECP2. Silencing AOF2 also caused DNMT1 deficiency and further enhanced global demethylation during somatic cell reprogramming (SCR) of hHFCs. Re-supplementing AOF2 in iPS cells disrupted such global demethylation and induced cell differentiation. Given that both hES and iPS cells highly express mir-302, our findings suggest a novel link between zygotic and somatic cell reprogramming, providing a regulatory mechanism responsible for global demethylation in both events. As the mechanism of conventional iPS cell induction methods remains largely unknown, understanding this microRNA (miRNA)-mediated SCR mechanism may shed light on the improvements of iPS cell generation.

Steven Shoei-Lung Li, Ph.D.
Professor
Graduate Institute of Medicine
Kaohsiung Medical University, Taiwan
E-mail: lissl@kmu.edu.tw

Education

1964-1968	美國米蘇里大學	哲學（遺傳學）博士
1961-1963	國立台灣大學	農學碩士
1957-1961	國立台灣大學	農學士

Key Experience

2004-present	高雄醫學大學	講座教授
1999-2004	國立中山大學	生物醫學研究所所長
1998-2003	國立中山大學	生物科技中心主任
1996-1999	國立中山大學	學術副校長
1995-1999	國立中山大學	生物科學系講座教授
1987-1995	美國北卡大學及 國立衛生研究院	蛋白質化學研究室主任
1977-1995	美國國立衛生研究院	高級遺傳學家
1974-1977	美國西乃山醫學院	微生物學及免疫學副教授
1970-1974	美國史坦福大學	副研究員(分子生物學)
1968-1970	美國德州大學	博士後研究員(蛋白質化學)

Specialty

遺傳學、蛋白質體學、基礎醫學及幹細胞生物學

Honor and Awards

李遠哲傑出人才講座
美國國家衛生研究院傑出研究獎
高雄醫學大學研究傑出教師獎
世界名人錄
美國名人錄
教育部學術審議委員
Editorial Board: The Open Stem Cell Journal, World Journal of Stem Cells

TARGET IDENTIFICATION OF MICRORNAS EXPRESSED HIGHLY AND REGULATED BY ACTIVIN A IN HUMAN EMBRYONIC STEM CELLS

Steven Shoei-Lung Li

Human embryonic stem (hES) cell lines have been derived from the inner cell mass of blastocysts, and the hESC lines possess remarkable ability of both unlimited self-renewal and pluripotency to generate any cell type differentiated from three germ-layers ectoderm, mesoderm and endoderm. Thus, the hES cell lines have great potentials for cell therapies in regenerative medicine and experimental models for drug discovery and toxicity testing in addition to basic studies on stem cell biology and molecular embryogenesis. Five hES cell lines have been derived with institutional review board approval from preimplantation embryos donated at *in vitro* fertilization clinics in Taiwan, and these lines have since been continuously cultured on mitotically inactivated mouse embryonic fibroblasts (MEF) feeder layer in the hES medium for more than 44 passages and underwent freezing/thawing processes.

Human embryonic stem T3ES cells were spontaneously differentiated into fibroblast-like T3DF cells as feeder with capacity to support the growth of undifferentiated hES cells. The expression of microRNA (miRNA), mRNA and proteins from the undifferentiated T3ES cells and their differentiated T3DF fibroblasts were determined. 206 genes were found to be targets of four hES cell-specific miRNAs miR-302d, miR-372, miR-200c and/or miR-367 by using 2-fold differential expression and inverse expression levels (highly negative correlations) of miRNAs to their target mRNAs. Three common target genes TRPS1, KLF13 and MBNL2 of three highly expressed miRNAs miR-302d, miR-372 and miR-200c were identified, and the target sites of both miR-302d and miR-372 in the 3'UTR of TRPS1, KLF13 and MBNL2 genes were confirmed by the luciferase assay [Li et al. 2009]. YWHAZ (14-3-3 zeta) target of miR-302d and miR-372 was further confirmed by proteomic comparison between T3ES cells and their differentiated T3DF fibroblasts. According to GeneOntology analysis, almost half of these 206 target proteins were located in nucleus and involved in gene transcription.

The hES-T3 cells cultured on either MEF in hES medium (containing 4 ng/ml bFGF) (T3ES) or feeder-free Matrigel in MEF-conditioned medium (supplemented with additional 4 ng/ml bFGF) (T3CM) were found to express very similar profiles of microRNAs and mRNAs. However, the expression profiles, especially microRNAs, of the hES-T3 cells cultured on Matrigel in hES medium supplemented with 4 ng/ml bFGF and 5 ng/ml activin A (T3BA) were found to be different from those of T3ES and T3CM cells. In T3BA cells, four hES cell-specific microRNAs miR-372, miR-302d, miR-367 and miR-200c, as well as three other microRNAs miR-199a, miR-19a and miR-217, were found to be up-regulated, whereas five miRNAs miR-19b, miR-221, miR-222, let-7b and let-7c were down-regulated by activin A. Thirteen abundantly differentially expressed mRNAs, including NR4A2, ERBB4, CXCR4, PCDH9, TMEFF2, CD24 and COX6A1 genes, targeted by seven over-expressed miRNAs were identified by inverse expression levels of these seven microRNAs to their target mRNAs in T3BA and T3CM cells. The NR4A2, ERBB4 and CXCR4 target genes were further found to be regulated by EGF and/or TNF. The 50 abundantly differentially expressed genes targeted by five under-expressed miRNAs were also identified. The abundantly expressed mRNAs in T3BA and T3CM cells were also analyzed for the network and signaling pathways, and roles of activin A in cell proliferation and differentiation were found [Tsai et al. 2010]. These findings will help elucidate the complex signaling network which maintains the self-renewal and pluripotency of hES cells.

Plenary Session II

專題演講 II

劉仁賢 教授

及

鄧文炳 教授

Ren-Shyan Liu, M.D.

Director and Professor
Molecular-Genetic Imaging Core
National Research Program for Genomic Medicine
Division of Nuclear Medicine
National Yang-Ming University Medical School
National PET/Cyclotron Center
Taipei Veterans General Hospital
E-mail: rsliu_0928@yahoo.com.tw

Education

1971-1977 National Defense Medical Center, Taipei, Taiwan

Key Experience

Resident, Department of Nuclear Medicine, Taipei Veterans General Hospital
Fellow, PET Center in KAFA, Julich and Department of Neurology, Köln University Hospital, Germany
Fellow, PET Center in the Institute of Neurology, McGill University, Canada
Fellow, PET Center in Iowa University Hospital, U.S.A.

Field of Interest

Molecular-Genetic Imaging of Small Animal, Nuclear Oncology, Neuronuclear Medicine, Nuclear Endocrinology, Emergency Medical Planning and Management of Radiation Accident

Academic Award and Distinction

Chairman, Post-Congress Symposium of 2010 World Molecular Imaging Congress President, Taiwanese Society for Molecular Imaging (2006~2009)
President, The Chinese Society of Nuclear Medicine (2003~2006)
Chairman, PET Committee, The Society of Nuclear Medicine, R.O.C. (1999~2003)
Secretary-general, The 4th Asia and Oceania Congress of Nuclear Medicine, 1988
Steering Committee, Aug. 30-Sep. 2, 2006 The Fifth Annual Meeting of Hawaii, The Society for Molecular Imaging, U.S.A.
Steering Committee, Sep. 7-10, 2005 The Fourth Annual Meeting of Cologne, Germany, The Society for Molecular Imaging, U.S.A.
The Outstanding Research Award, 1995 (Intra-arterial I-131 lipiodol and histoacryl in treatment of hepatoma), Atomic Energy Council, R.O.C.

MOLECULAR IMAGING IN THE RESEARCH OF STEM CELLS

Ren-Shyan Liu

Monitoring the fate of putative stem cells after transplantation requires cell-labeling and tracing techniques that permit noninvasive whole-body survey. Previous methods used in vitro radiolabeling of cells followed by imaging the transplanted radiolabeled cells in vivo, or labeling of cells with supermagnetic agents followed by magnetic resonance imaging. The ex vivo labeling methods provide excellent short-term results but are not suitable for long-term repetitive imaging because of loss of label owing to radiolabel decay or biological clearance of supermagnetic label. Labeling cells with bioluminescent, fluorescent, and positron emission tomography (PET)-reporter genes for imaging adoptively transplanted cells in vivo has been well developed in recent years. Genetic labeling of cells with different reporter genes allows for long-term, repetitive in vivo imaging using different imaging platforms. These imaging platforms include whole-body fluorescence imaging of green fluorescent protein (GFP) reporter gene expression, bioluminescence imaging of the firefly luciferase (Luc) reporter gene expression using luciferin as reporter probe, PET imaging of HSV1-tk reporter gene using different radiolabeled nucleoside analogs as reporter probes, and PET imaging of human D2 receptor with radiolabeled fluoroethylspiperone as reporter probe. The most developed approaches utilize herpes simplex virus thymidine kinase (HSV1-tk) as a reporter gene, which produces a gene product (an enzyme) that can be identified by phosphorylation of a radiolabeled reporter probe, which is trapped within the gene-labeled cell and can be visualized by PET scanning. This process can be repeated within a short time because of the short half-life of the radiolabeled substrate. This approach has been further developed using a fusion gene between the thymidine kinase gene and a GFP or luciferase genes for multiplatform imaging. Linking the reporter gene to specific promoters allows imaging of different cell types because only the cells activating the promoter will express the reporter gene. Such systems have been used successfully to trace cells expressing p53, T-cells activated to express nuclear factor of activated T-cells, and cells activated to express transforming growth factor-β. Transplanted stem cells may also be followed using a dual-reporter system, which uses a constitutive promoter to image the localization and viability of transplanted cells and an inducible promoter, which is activated when the stem cell commits to a certain differentiation lineage. Noninvasive whole-body imaging of various reporter genes is now being validated in different preclinical models and is expected to play an increasing role in monitoring the fate of transplanted stem cells in human stem cell therapy.

Win-Ping Deng, Ph.D.

Vice-Dean, Office of Research and Development, Taipei Medical University
Director, Graduate Institute of Biomedical Materials and Engineering and stem cell research center
Taipei Medical University
Professor, Graduate Institute of Biomedical Materials,
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E-mail: youtzungchen@ntu.edu.tw

Education

1994 Postdoctoral training in Genetic recombination of Harvard University
1993 Ph.D. in Cancer Biology of Harvard University
1981 M.S. in Radiation Biology of Tsing Hua University
1979 B.S. in Biology of Tunghai University

Honor and Awards

2010 Steering and Program committee, Chairman, World Molecular Imaging Congress (WMIC) Kyoto, Japan

Representative Publication

1. Chiou, JF,Wu, AT,Wang, WT,Kuo, TS,Gelovani5, JG,Lin, IH, Wu, CH, Chiu, WT and **Deng, WP**.A Preclinical Evaluation of Antrodia Camphorata Alcohol Extracts in the Treatment of Non-small Cell Lung Cancer Using Non-invasive Molecular Imaging..eCAM. 2010.
2. Wei-Hong Chen, Hen-Yu Liu; Wen-Cheng Lo, Shinn-Chih Wu, Chau-Hwa Chi, Hsueh-Yuan Chang; Shih-Hsiang Hsiao; Chih-Hsiung Wu, Wen-Ta Chiu, Bao-Ji Chen, **Win-Ping Deng**. Intervertebral Disc Regeneration in an Ex Vivo Culture System using Mesenchymal Stem Cells and Platelet-rich Plasma. Biomaterials & Tissue Engineering.2009.
3. Wei-Hong Chen, Ming-Tang Lai, Alexander T.H Wu, Chia-Che Wu, Juri G. Gelovani, Che-Tong Lin, Shih-Chieh Hung, Wen-Ta Chiu, and Win-Ping Deng. In Vitro Stage-specific Chondrogenesis of Mesenchymal Stem Cells Committed to Chondrocytes. Arthritis & Rheumatism.2008.
4. Wen-Cheng Lo, Jeng-Fong Chiou, Juri G. Gelovani, Mei-Leng Cheong, Chi-MingLee, Hen-Yu Liu, Chih-Hsiung Wu, Ming-Fu Wang, Che-Tong Lin, **Win-PingDeng**.Transplantation of Embryonic Fibroblast treated with Platelet-Rich Plasma Induces Osteogenesis in SAMP8 Mice Monitored by Molecular Imaging. J Nucl Med. 2008.
5. Lo WC, Hsu CH, Wu AT, Yang LY, Chen WH, Chiu WT, Lai WF, Wu CH, Gelovani JG, **Deng WP**. A Novel Cell-Based Therapy for Contusion Spinal Cord Injury Using GDNF-Delivering NIH3T3 Cells with Dual Reporter Genes Monitored by Molecular Imaging. J Nucl Med. 2008 Aug 14. [Epub ahead of print]

STEM CELLS-MOLECULAR IMAGING AND THERAPEUTIC IMPLICATIONS

Win-Ping Deng

In the current research we integrate stem cell and molecular imaging to study cancer therapy and tissue regeneration.

For cancer therapy, we, the pioneer of molecular imaging study in Taiwan, first applied non-invasive in vivo imaging with radiolabelled FIAU to monitor cancer gene therapy using herpes simplex virus type 1 thymidine kinase (HSV1-tk) and ganciclovir (GCV); and then used stem cell KP-hMSCs to target microscopic tumors and tumor stroma development monitored by noninvasive in vivo positron emission tomography (PET) imaging. A serial in vivo imaging of the lung metastases model and gene therapy using HSV1-tk and GCV; and the molecular imaging with 123I-FIAU, 18F-FUdR, 18F-FET, and 18F-FDG to monitor HSV1-tk and GCV prodrug activating gene therapy of cancer were developed. Based on the models developed above, recently, we combined stem cells and protein vaccine as a novel approach for developing a platform for a potential versatile cancer treatment. Our findings suggest that stem cell KP-hMSCs could be used as a versatile tumor-targeting device and mediate anti-tumor effect of PE(dele-III)-E7-KDEL3. We believe this novel strategy could serve as a platform for developing a universal vaccine for different cancer type. We also showed that the induction of MKP-1, as a potential pharmacological target in non-small cell lung carcinomas assisted by non-invasive molecular imaging, lead to a significant retardation of proliferation and metastasis. MKP-1 could be considered as a potential therapeutic target in NSCLC therapy and PPARg agonists could be explored for combined chemotherapy. Lifelong reporter gene imaging in the lungs of mice following polyethyleneimine-mediated Sleeping Beauty systemic transposon delivery suggests that PEI/SB induces stable transfection specifically in a small population of alveolar progenitor cells. The technique provides a promising platform for future research in distal lung biology and tissue regenerative therapy. In a preclinical evaluation of antrodia camphorata alcohol extracts to treat non-small cell lung cancer, the vivo bioluminescence imaging revealed that tumorigenesis was significantly retarded by oral treatment of ACAE in a dose-dependent fashion. Based on our experimental data, ACAE contains anti-cancer properties and could be considered as a potential CAM agent in future clinical evaluation.

In tissue regeneration, we first developed tissue-engineered intervertebral disc and chondrogenesis using human nucleus pulposus regulated through TGF-b1 in platelet-rich plasma. Currently, we also demonstrated the stage-specific chondrogenesis of stem cell committed to chondrocytic niche; developed intervertebral disc regeneration in an e*x vivo* culture system using mesenchymal stem cells and platelet-rich plasma. Osteoporgenitor cells were applied to prevent the senile ovariectomy-induced osteoporosis in SAMP8 mice by transplantation of refined platelet-rich plasma-treated bona fide NIH3T3-GFP; and a novel cell-based therapy was established for contusion spinal cord injury using gdnf-delivering nih3t3 cells with dual reporter genes monitored by molecular imaging.

Concurrent Session I

論文發表 I

Embryonic Stem Cells and iPS

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陳佑宗 教授
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Education

1986 Ph.D. University of Iowa
1980 B.S. in National Taiwan University, Taiwan

Patents (Issued and Pending)

1. 'Engineered dendritic cells for gene therapy' US filed 2007.
2. 'Materials and methods for control of infections' PCT/US/2007/011519 filed May 2007.
3. 'Production of mature and functional CD4 T cells developed from adult stem cells' US filed 2008**.**

Representive Publications

1. Han, S., Liang, Y., Yang, F., Fu, Y., Wang, Y., Huang, Y., Lien, L. and **Chang, L.-J.** (2009) Phenotype and functional analyses of therapeutic immune cells generated through interferon-gamma or CD137 selection versus dendritic cell activation approaches. Journal of Hematology and Oncoloby 2, 34.
2. Dong L, Gao Z, **Chang L-J**, *et al.* (2009) Adoptive transfer of cytomegalovirus (CMV) /Epstein-Barr virus (EBV)-specific immune effector cells for therapeutic and preventive/preemptive treatment of pediatric allogeneic cell transplant recipients. Journal of Pediatric Hematology/Oncology 32, e31-37.
3. Sengupta N, Caballero S, Sullivan SM, **Chang LJ**, Afzal A, Clazi SL, Kielczewski JL, Prabarakan S, Ellis EA, Moldovan L, Moldovan NI, Boulton ME, Grant MB (2009) Regulation of adult hematopoietic stem cells fate for enhanced tissue-specific repair. Mol. Therapy 17, 1594-1604.
4. Li H, Lu Y, Witek RP, **Chang L-J**, Campbell-Thompson M, Jorgensen M, Petersen B and Song S (2010) Ex vivo transduction and transplantation of bone marrow cells for liver gene delivery of alpha 1 antitrypsin. Mol. Therapy (in press).
5. Brusko TM, Koya RC, Zhu S, Lee MR, Putnam AL, McClymont SA, Nishimura MI, **Han S, **Chang L-J**, Atkinson MA, and Bluestone JA (2010) Generation of engineered antigenspecific human regulatory T cells by T cell receptor gene transfer. PLoS ONE (in press).

LENTIVECTOR APPLICATIONS IN STEM CELL PROGRAMMING AND HEMATOPOIESIS DEVELOPMENT

Lung-Ji Chang

Pluripotent stem cells have been a hot topic in modern medicine but access to sufficient number of such cells and increased understanding of its fundamentals and safety are urgently needed. Many studies have reported reprogramming of differentiated cells into induced pluripotent stem cells (iPSC) with enforced expression of multiple transcription factors. However, the efficiency and safety of this approach and the property of the resulted iPSC require further investigation. We aim to improve the reprogramming efficiency using high titer lentivectors encoding additional cell growth and survival regulatory genes. Lentivectors encoding multiple cell cycle and apoptosis genes in addition to c-Myc, Klf4, Oct4 and Sox2 were used to generate iPSC. The iPSC were extensively characterized by immunohistochemical staining and flow cytometry. Human mesenchymal stem cells were efficiently transduced and reprogrammed into iPSC using lentivectors encoding the four known transcription factors. In addition, siRNA suppressing p53 and cell cycle and survival genes including telomerase and BclxL significantly increased the efficiency and rate of iPSC generation. Therefore, iPSC generation is improved with lentivectors encoding immortalization cellular factors regulating cell cycle progression, senescence and apoptosis. To increase the safety profile of the reprogrammed iPSC, we demonstrated that the integrated lentiviral genomes can be deleted by Cre-loxP recombination. The development of iPSC to hematopoietic stem cells is still under investigation. However, examples of in vitro development of functional T cells and dendritic cells from adult human hematopoietic stem cells (HSC) will be presented. Reprogramming of adult somatic cells to iPSC followed by expansion of iPSC-derived HSC for the purpose of generating functional and safe immune cells will have great potential in clinical applications in the future.

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Education

1996-2003 Ph.D., Baylor College of Medicine, Houston, USA
1994-1996 M.S., National Taiwan University, Taipei, Taiwan
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Key Experience

2003-2008 Postdoc, University of Texas MD Anderson Cancer Center, Houston, USA

Specialty

Mouse Genetics, Genomics, Stem Cell Biology

Honor and Awards

Clontech-Kenneth Fong - SCBA Travel Award (2001)
ISI Citation Classic Award (2001)
The 4th APOCB Congress Travel Award (2002)

Representive Publications

1. **Chen YT**, Liu P and Bradley A. Inducible gene trapping using drug selectable markers and the Cre/*lox*P system to identify developmentally regulated genes. *Molecular and Cellular Biology* 24(22):9930-9941, 2004.
2. **Chen YT**, Levasseur R, Vaishnav S, Karsenty G and Bradley A. Bigenic Cre/*lox*P, *puDeltatk* conditioal genetic ablation. *Nucleic Acids Research* 32(20): e161, 2004.
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4. Hinoi E, Bialek P, **Chen YT**, Groner Y, Behringer RR, Ornitz DM and Karsenty G. Runx2 inhibits chondrocyte proliferation and hypertrophy through its expression in the perichondrium. *Genes & Development* 20: 2937-2942, 2006
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PIGGYBAC TRANSPOSON JUMPS IN HUMAN PLURIPOTENT STEM CELLS

You-Tzung Chen[1,*], Kenryo Furushima[4], Pei-Shan Hou[2], Amy T. Ku[1], Jian Min Deng[4], Chuan-Wei Jang[4], Haotian Fang[4], Henry P. Adams[4], Min-Liang Kuo[3], Hong-Nerng Ho[1], Chung-Liang Chien[2,*], and Richard R. Behringer[4,*]

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The *piggyBac* transposon from insects is a rising system that mutagenizes and mediates gene transfer into the mammalian genome. It is characterized by its seamless excision so that the genomic integrity of the mutated cell can be restored. Here we use an optimized *piggyBac* transposon system to mediate permanent gene transfer in human embryonic stem (ES) cells. Our inverse PCR product sequencing results provide evidence for transposase-mediated *piggyBac* transposition events in human ES cells. The successful expression of fluorescent reporter genes carried by a *piggybac* vector in human ES cells and their *in vitro* differentiated derivatives further demonstrates that it can mediate permanent gene transfer. We also demonstrate that the integrated *piggyBac* transposon can be removed and an undisrupted insertion site can be restored. In conclusion, the *piggybac* transposon is a convenient system with a great potential to be applied in gene therapy and genetic studies for stem cell researchers.

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Education

2003-2009	Ph.D. Institute of Biomedical Science, National Sun Yat-Sen University
1993-1995	M.S. Graduate Institute of Animal Science, National Taiwan University
1986-1990	B.S. Department of Animal Science, National Chung Hsing University

Key Experience

2001-present	Assistant Researcher, Livestock Research Institute
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1997-2000	Assistant Researcher, Hengchun Branch, Livestock Research Institute
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Representative Publication

1. **Yang, J. R**., C. H. Liao, C. Y. Pang, L. L. H. Huang, Y. T. Lin, Y. L. Chen, Y. L. Shiue, and L. R. Chen. Directed Differentiation into Neural Lineages and Therapeutic Potential of Porcine Embryonic Stem Cells in Rat Parkinson's Disease Model. 2010. Cellular Reprogramming 2010. 12 (4): 447-461.
2. Lin, Y. P., L. R. Chen, C. F. Chen, J. F. Liou, Y. L. Chen, **J. R. Yang**, and Y. L. Shiue. Identification of early transcripts related to male development in chicken embryos. Theriogenology. 2010 Aug 20. [Epub ahead of print]
3. L. R. Chen, S. C. Lee, Y.P. Lin, Y. L. Hsieh, Y. L. Chen, **J. R. Yang**, J. F. Liou, C. F. Chen, Y. P. Lee, and Y. L. Shiue. Prostaglandin-D synthetase induces transcription of the LH beta subunit in the primary culture of chicken anterior pituitary beta subunit in the primary culture of chicken anterior pituitary cells via the PPAR signaling pathway. 2010. Theriogenology 73 (3): 367-382.
4. **Yang, J. R**., Y. L. Shiue, C. H. Liao, S. Z. Lin, and L. R. Chen. Establishment and Characterization of Novel Porcine Embryonic Stem Cell Lines Expressing hrGFP. 2009. Cloning and Stem Cells 11 (2): 235-244.

STUDY ON PORCINE EMBRYONIC STEM CELLS FOR THE THERAPY OF PARKINSON'S DISEASE IN RAT MODEL

Jenn-Rong Yang[1, 2], Chia-Hsin Liao[3, 4], Cheng-Yoong Pang[3, 5], Lynn Ling-Huei Huang[6, 7], Yu-Ting Lin[1], Yi-Ling Chen[1, 2], Yow-Ling Shiue[2] and Lih-Ren Chen[1, 6, 8]

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This study was conducted to direct porcine embryonic stem (pES) cells differentiating into neural lineages and to investigate therapeutic potential of GFP-expressing pES (pES/GFP$^+$) in the rat model of Parkinson's disease (PD). The undifferentiated pES/GFP$^+$ cells and their neuronal differentiation derivatives were transplanted into the Sprague-Dawley (SD) rat's brain, and their survival and development was determined by using live animal fluorescence optical imaging system every 15 days. The results showed that fluorescent signals from the injection site of SD rats' brain could be detected through the experimental period of 3 months. The level of fluorescent signal detected in the treatment group was two folds of that of the control group. The results of behavior analysis showed that PD rats exhibited stably decreased asymmetric rotations after transplantation with pES/GFP$^+$-derived D18 neuronal progenitors. The dopaminergic differentiation of grafted cells in the brain was further confirmed by immunohistochemical staining with anti-TH, anti-DA, and anti-DAT antibodies. These results suggested that the differentiation approach we developed would direct pES cells to differentiate into neural lineages and benefit the development of novel therapeutics involving stem cell transplantation.

Concurrent Session II

論文發表 II

Adult Stem Cells

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Education

2001-2006 Ph. D. in Department of Life Science, National Tsing Hua University

1998-2000 M. S. in Institute of Chemical Engineering, National Tsing Hua University

1994-1998 B. S. in Department of Chemical Engineering, National Tsing Hua University

Key Experience

2007-2008 Joint Appointment Postdoctoral Fellow, Institute of Biomedical Engineering, National Cheng Kung University, and Orthopaedic Research Center, Kaohsiung Medical University

2006-2007 Postdoctoral Fellow, Institute of Medicine, Kaohsiung Medical University

2003.7-10 Internship, Robert Dickson's Lab, Lombardi Cancer Center, Georgetown University, Washington DC, USA

2000-2001 Assistant Researcher, R&D Department, ScinoPharm Taiwan, Ltd.

Research Interest

Mechanisms underlying the osteogenic effect of polyamines in human bone marrow-derived mesenchymal stem cells;

Development of nanobiomaterials as non-viral gene transfection carriers;

Enhancement of the osteogenic potential of stem cells by upregulation of CXCR4 through a highly-efficient non-viral transfection method;

Identification and characterization of physiologically significant proteins from Helicobacter pylori

EFFECT OF POLYAMINES ON THE OSTEOGENIC DIFFERENTIATION OF HUMAN BONE MARROW-DERIVED MESENCHYMAL STEM CELLS

Mon-Juan Lee, Ja-Ruei Hsu, Chi-Yuan Chen and Yu-Jing Wang

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Polyamines are organic polycations that are derived from amino acids. These molecules of low molecular weight are ubiquitous in all organisms, and are essential for cell proliferation and differentiation. Eukaryotes contain the three common polyamines, putrescine, spermidine, and spermine, while in bacteria, the principal polyamines are putrescine, cadaverine and spermidine, but a large range of uncommon polyamines also exists. Polyamines are associated with the growth and development of several tissue types, including embryonic development, and may participate in tissue repair by facilitating tissue remodeling. Several early studies have implicated the relationship of polyamines to the growth and development of bone and cartilage. More recently, polyamines, especially spermine, have been shown to promote the osteogenic differentiation of stem cells. Nevertheless, the mechanisms underlying the osteogenic potential of polyamines remain unclear. In this study, we found that all three of the common eukaryotic polyamines, putrescine, spermidine, and spermine, were capable of promoting the osteogenic differentiation of human bone marrow-derived stem cells (hBMSCs). Extracellular matrix mineralization, a marker for osteoblast maturation, was enhanced in the presence of polyamines. In addition, under the treatment of polyamines, the expression of genes related to osteogenic differentiation was up-regulated in hBMSCs at an earlier stage than the common *in vitro* osteogenic inducers DAG, namely dexamethasone, ascorbic acid, and -glycerolphosphate. These results prompt us to further investigate the relationship between the polyamine metabolic pathways and the osteogenic differentiation pathways. Studies on polyamines as novel osteogenic inducers not only help to explore the function of polyamines and the mechanism of osteogenesis, thus providing an alternative to direct stem cells toward osteogenic differentiation, but also accelerate the development of polyamine-derived new drugs that stimulate bone formation.

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Education

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Affiliated Appointments

2010.08-present	Adjunctive Assistant Professor, Graduate School of Biotechnology and Bioengineering, Yuan Ze University, Taiwan
2009.08- present	Assistant Professor, Department of Chemical Engineering and Materials Science, Yuan Ze University, Taiwan
2004.10-2009.07	Research Scientist, Bioresource Collection and Research Center, Food Industry Research and Development Institute, Taiwan

Representative Publication

1. Chen WC, **Yao CL**, Chu IM, Wei YH., "Compare the effects of chondrogenesis by culture of human mesenchymal stem cells with various type of the chondroitin sulfate C." Journal of Bioscience and Bioengineering (revised)
2. Chen WC, **Yao CL**, Wei YH, Chu IM., "Evaluating osteochondral defect repair potential of autologous rabbit bone marrow cells on type II collagen scaffold." Cytotechnology (In press)
3. Hung CJ[1], **Yao CL**[1], Cheng FC, Wu ML, Wang TH, Hwang SM., "Establishment of immortalized mesenchymal stem cells with red fluorescence protein expression for in vivo transplantation and tracing in the rat model with traumatic brain injury." Cytotherpay 2010;12:455-465. ([1]contributed equally as first author)
4. Chang YI, Hua WK, **Yao CL**, Hwang SM, Hung YC, Kuan CJ, Leou JS, Lin WJ., "Protein-arginine methyltransferase 1 suppresses megakaryocytic differentiation via modulation of the p38 MAPA pathway in K562 cells." Journal of Biological Chemistry 2010;285:20595-20606.
5. Chen TW, Hwang SM, Chu IM, Hsu SC, Hsieh TB, **Yao CL***, "Characterization and transplantation of induced megakaryocytes from hematopoietic stem cells for rapid platelet recovery by a two-step serum-free procedure." Experimental Hematology 2009;37:1330-1339. (*corresponding author)

APPLICATIONS OF SERUM-FREE EXPANDED HEMATOPOIETIC STEM CELLS AND THEIR DIFFERENTIATED CELLS

Chao-Ling Yao

Umbilical cord blood (UCB) has been identified as a rich source of hematopoeitic stem cells (HSCs) available for transplantation. Since the first case of Fanconi's anemia patient received successful UCB transplanation in 1988, more than 4,000 patients have been performed. The advantages of using UCB as HSC sources comparing with traditional bone marrow are following: 1) There is no harm to the donor. 2) There is significantly reduced level of graft-verse-host disease. 3) There is low contamination rate/ risk with common viruses, such as CMV and EBV. 4) Mature processing and banking system for storage and management. 5) Cost efficient for transplantation process. However, the limitation of UCB transplantation is the insufficient cell number in the collected UCB unit.

In order to solve the shortage of cell number in UCB, we developed an optimized serum-free medium for ex vivo expansion of $CD34^+$ cells from UCB. Besides, the serum-free expanded $CD34^+$ cells were further to be induced into Natural killer (NK) cells, Megakaryocytes (MKs), macrophage and red blood cells specifically. Here, we would briefly introduce the results of the serum-free expanded $CD34^+$ cells and their differentiated cells according to their future applications, such as HSC transplantation, cell therapy, immunotherapy, cell-based test platform and humanized mice establishment, respectively.

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Education

1999	Ph.D. of Pharmacology Southern Illinois University School of Medicine, Department of Pharmacology Springfield, IL, USA
1984-1988	Bachelor of Science of Medical Technology National Yang-Ming Medical University School of Medical Technology Taipei, Taiwan.

Key Experiences

2004-present	Assistant Professor Graduate Institute of Medical Biotechnology and Laboratory Science, Chang Gung University, Taoyuan, Taiwan
2003-2004	Visiting Assistant Professor. Graduate Institute of Medical Biotechnology, Chang Gung University, Taoyuan, Taiwan
2002-2004	Assistant Investigator Magee-Womens Research Institute, Pittsburgh, PA, USA
2001-2004	Research Instructor Dept Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, PA Pittsburgh Development Center (PDC), Magee Womens Research Institute, Pittsburgh, PA, USA
1999-2001	Post Doctoral Fellow (Sept) Oregon Regional Primate Research Center, Oregon Health Sciences University, Beaverton OR, USA

Honor and Awards

Irene McLenahan Young Investigator Research Award (Dec 2001) Magee-Womens Health Foundation, Pittsburgh, PA

Marine Biological Laboratory Course 2000 Scholarship (May 2000) Frontiers in Reproduction: Molecular and Cellular Concepts and Applications, Marine Biological Laboratory, Woods Hole, MA

ENRICHMENT OF STEM CELLS DERIVED NEURON CELLS BY III-TUBULIN TARGETED LINEAGE SELECTION

Kowit-Yu Chong

The ageing of the baby-boom generation, there has been a dramatic increase in the prevalence of neurodegenerative diseases**.** Parkinson's disease (PD) is characterized by the degeneration of midbrain nigrostriatal dopaminergic neurons resulting in severe motor symptoms. Currently, frontline therapy for PD is the oral administration of dopamine agonists, electrical deep brain stimulation have been reported as a valuable complement the pharmacological treatment for treatment-resistant patients. On the other hand, intrastriatal transplantation of fetal mesencephalic tissue as a promising treatment for Parkinson's has been investigated extensively over past 20 years. Despite of success, the poor availability and ethic issues remains a major obstacle. It was until scientists have successfully grown the embryonic stem cells *in vitro* that has opened-up the whole world regarding the stem cell research. Stem cells are capable of both self renewal and multi-lineage differentiation. Studies indicated that neural stem cell has the potential to proliferate *in vitro* and differentiate into neuronal-like cells with biochemical and electro-physiological properties. Although the neural stem cell provided an unlimited source of neuron, the current differentiation protocol could be difficult to achieve the sufficient amount of homogenous neurons for the therapeutic cell transplantation. Therefore, the main objectives of this study are investigate on the possible use a hybrid approach of "lineage selection" and "forced differentiation" for enriching the stem cell derived neuron with the lineage restricted genes and βIII-tubulin promoter. This study should elucidate the establishment of platform technology for culture and differentiation of neurons derived from mouse neural stem cells. Furthermore, this novel approach may lead a new avenue of cell replacement therapy for neurological degenerative diseases.

Concurrent Session III

論文發表 III

Novel Technology

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洪慧珊 教授
徐睿良 教授

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Education

1999-2004	博士	國立臺灣大學獸醫所
1994-1999	學士	國立臺灣大學獸醫系

Key Experiences

2004-2009	博士後	中央研究院生物醫學研究所
2000-2003	研究助理	中央研究院生物化學研究所
1999-2000	獸醫師	國立臺灣大學農學院附設動物醫院

Specialty

癌症分子生物學、幹細胞生物學、獸醫學(實驗動物)

Representative Publication

1. **Lee J. L.**, Wang M. J., and Chen J. Y. (2009) Acetylation and activation of STAT3 mediated by nuclear translocation of CD44. J. Cell Biol. 185: 949-957.
2. **Lee J. L.**, Wang M. J., Sudhir P. R., and Chen J. Y. (2008) CD44 Engagement Promotes Matrix-derived Survival through CD44-SRC-integrin Axis in Lipid Rafts. Mol. Cell. Biol. 28: 5710-5723.
3. **Lee J. L.**, Wang M. J., Sudhir P. R., Chen G. D., Chi C.W., and Chen J. Y. (2007) Osteopontin promotes integrin activation through outside-in and inside-out mechanisms: OPN-$CD44_V$ interaction enhances survival in gastrointestinal cancer cells. Cancer Res. 67: 2089-2097.
4. **Lee, J. L.**, Chang, C. J., Chueh, L. L., and Lin, C. T. (2006) Secreted Frizzled Related Protein 2 (sFRP2) Decreases Susceptibility to UV-Induced Apoptosis in Primary Culture of Canine Mammary Gland Tumors by NF-kappaB Activation or JNK Suppression. Breast Cancer Res Treat. 100: 49-58.
5. **Lee, J.L.**, Chang, C. J., Wu, S. Y., Sargan, D. R., and Lin, C. T. (2004) Secreted Frizzled-related protein 2 (SFRP2) is highly expressed in canine mammary gland tumors but not in normal mammary glands. Breast Cancer Res. Treat. 84: 139-149.

DIRECT REPROGRAMMING OF CANCER CELLS TO CANCER STEM CELLS BY THE CELL SURFACE MARKER CD44

Hsin-Mei Lai, Chi-Jen Hung, Ying-Jhen Su, Guan-Ying Chen, Yi-Wen Chang and **Jia-Lin Lee**

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Cancers are notorious for their ability to survive treatment and recur. Hopes of understanding how they can do so, however, have grown with the prospective identification of rare populations of cancer stem cells (CSCs) in cancers. Although CD44 is an important marker for a number of different CSC lineages, little has been known about the molecular mechanisms through which CD44 functions as a marker of CSCs. We have previously shown that CD44, once engaged, is internalized and translocated to the nucleus, where it binds to various promoters, including that of *c-myc*, leading to cell fate change through transcriptional reprogramming. In this study, we present evidence that CD44 is required for sphere formation and reprogramming to generate cells with properties of CSCs via the transcriptional reprogramming led by nuclear CD44. We show that a rare subpopulation of $CD44^+$ cells with stem-like characteristics such as increased clonogenic and tumorigenic properties, and the ability to grow as nonadherent spheres in serum-replacement medium. The C-terminal of CD44 leads to an increased resistance to anoikis for sphere formation and nuclear CD44/STAT3 is required for self-renewal *in vitro* in sphere-forming cells. Such outgrowth triggers reprogramming to generate cells with properties of CSCs and then exhibits attributes of cells that have undergone an EMT (the epithelial-mesenchymal transition). We propose that nuclear CD44/STAT3 performs an unexpected tumor progressing function by enhancing cell outgrowth into structures where cells with properties of CSCs can be generated from differentiated somatic cells in advancing cancers. These results indicate that CD44 is a robust marker and is of functional importance for CSCs for cancer initiation.

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Education

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Specialty

Cell Biology and Signal Transduction, Stem Cell Biology and Tissue Engineering, Vascular Nanotechnology, Biomaterial Application

Research Interest

My research interests focus on tissue engineering, stem cell biology and development of new nano-biomaterials on vascular diseases. My main research projects include: (1) to investigate the correlation of blood stem cells in cellular molecular information; (2) cells and biomaterials in vascular tissue engineering applications; (3) the development of new nano-biomaterials potential of vascular repair. The main objective of our research on the vascular disease hope to provide an effective treatment strategy.

POLYURETHANE-GOLD NANOCOMPOSITES PROMOTE THE MATURATION OF ENDOTHELIAL PROGENITOR CELLS PARTIALLY THROUGH STROMAL FACTOR-1 (SCD-1)/CXCR4 SIGNALING PATHWAY IN THE VASCULAR DISEASE MODEL

Huey-Shan Hung

Endothelial cell layer formed on the cavity with the surface of vascular medical devices, particularly vascular bypass surgery, is an important attribute in order to enhance the effectiveness of implantation of artificial blood vessels. Blood endothelial progenitor cells (Endothelial progenitor cells, EPCs) physiological function, now known to have been by the endothelium of (endothelializtion) process, the implantation of artificial blood vessels and repair damaged tissue has an important capacity.

Previously, we have developed a new polyurethane gold nanoparticles composite (polyurethane-gold nanocomposites, PU-Au) as a model system, using optimal little amount of gold nanoparticle (≈ 43.5 ppm) in the material surface because of the uniform distribution of the substrate surface induced phase separation of the phenomenon, the promotion of endothelial cells (ECs) produce proliferation effect and the migration effect, to change the behavior of endothelial cells. Moreover, the study confirmed that this effect is also through NO-dependent (PI3K/Akt/eNOS) and NO-independent (FAK / Rho-GTPase / Rac/Cdc42) regulated by two signaling pathways. Vascular tissue damage triggered by the process of repair effects, usually through the EPCs for secretion of factors related to the message, for example, chemical chemotaxis and the homing effect caused by physiological changes produced by micro-environment. Stromal derived factor-1α (SDF-1α) can return the message corresponding to the release of endothelial precursor cells, homologous receptor expression. Importantly, the regulation of this return message, this can increase the production of endogenous EPCs to help improve the clinical treatment of cardiovascular diseases and application potential.

We assume that this novel gold nanoparticles composite material, can be established graft luminal micro-environment, and promote the differentiation of EPCs, support, and endothelial progenitor cell adhesion and migration, effectively improve the response capacity of vascular tissue damage.

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Education

Ph.D. in 2001, Chemistry department, National Taiwan University
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Key Experiences

2009-present	Assistant professor in Graduate Institute of Biotechnology in National Pingtung University of Science and Technology
2007-2009	R&D manager in Life Science BU in C SUN MFG. LTD.
2005-2007	R&D manager in Life Science Dept. in ProSys Technology integration, Inc.
2001-2005	Postdoctoral associate in National Cheng-Kung University
1997-1998	Teaching assistant in National Taiwan University

Honor and Awards

Young Scientist Award (*HUPO* 3rd Annual World Congress, 2004). (HUPO: Human Proteome Organization)

Representative Publication

1. Chun-Che Lin, **Jue-Liang Hsu**, Gwo-Bin Lee, "Sample preconcentration in microfluidic devices" Accepted for publication in Microfluid Nanofluid 2010.
2. Chin-Jen Wu, **Jue-Liang Hsu**, Sheng-Yu Huang, Shu-Hui Chen, "Mapping N-Terminus Phosphorylation Sites and Quantitation by Stable Isotope Dimethyl Labeling". Journal of the American Society for Mass Spectrometry 2010, 21, 460471.
3. Chun-Yen Chen, Chin-Yang Chang, Hung-Jen Liu, Ming-Huei Liao, Chi-I Chang, **Jue-Liang Hsu**, Wen-Ling Shih, "Apoptosis induction in BEFV-infected Vero and MDBK cells through Src-dependent JNK activation regulates caspase-3 and mitochondria pathways". Veterinary Research, 2010, 41, 15.
4. Shu-Hui Chen, Yi-Wen Wang, **Jue-Liang Hsu**, Chi-Yun Wang, Po-Tsun Shen, Jing-Jing Chuang, Hung-Wen Tsai, Chi-Wu Chiang, Chung-Ta Lee, Fang-Chih Chang, Hsiao-Sheng Liu, Nan-Haw Chow, "Nucleophosmin in the Pathogenesis of Arsenic-related Bladder Carcinogenesis Revealed by Quantitative Proteomics". Toxicology and Applied Pharmacology 2010, 242, 126135.

PROTEOMICS STUDY IN STEM CELL RESEARCH

Jue-Liang Hsu

Proteomics is an emerging area of molecular biology that is concerned with the systematic, large-scale analysis of proteins, particularly their structures and functions. It encompasses four applications: the mining of protein identities, mapping of protein post-translational modifications (PTMs), protein-expression profiling and protein-network mapping. Currently, the proteome analytical platforms have been widely applied to stem cells (SCs) researches including the discovery of cell surface markers involved in stage- and lineage-specific expression, differential expression analysis at different stages (or under stimulations), mapping of PTMs involved in signal transduction, and so on. This discovery-driven approach has produced large data sets of proteins involved in mechanisms and pathways regulate SCs proliferation and differentiation.

According to the previous report, the pluripotency of mouse germline stem cells with strong alkaline phosphatase activity (AP^+GSCs) can be maintained by insulin-like growth factor-1 (IGF-1)-dependent pathway. Interestingly, the AP activity, cell proliferation, IGF-1/IGF-1R protein expression, and pluripotent gene expression were simultaneously increased when AP^+GSCs cultured under hypoxia condition (5 % O_2) comparing those with the normoxia (21 % O_2). In order to comprehensively study the proteins regulated by the niche stress, the shotgun approach was utilized to investigate the protein expression of AP^+GSCs under hypoxia stimulation. In the present work, we mainly focused on the large-scale identification of proteins distributed in cytosolic fraction as well as those in membrane fraction. The profiling of membrane proteins was achieved by the tube-gel assisted digestion protocol followed by the analysis of liquid chromatography—tandem mass spectrometry (LC-MS/MS) and database matching on Mascot search engine. The preliminary result and other details will be presented in the lecture.

Concurrent Session IV

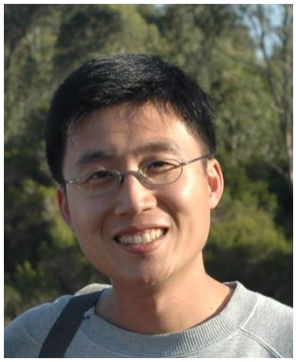
論文發表 IV

Embryonic Stem Cells and iPS

鐘棟樑 教授

及

蘇怡璇 教授



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Education

2005-2009 Ph.D. in Human Biology of Monash University, Australia
1996-1998 M.S. in Biological Sciences of National Sun Yat–Sen University, Taiwan ROC
1992-1996 B. S. in Biology of National Sun Yat–Sen University, Taiwan ROC

Key Experience

2009-present	Postdoctoral Research Fellow in Australian Institute for Bioegineering and Nanotechnology, university of Queensland, Australia
2008-2009	Research Assistant in Australian Institute for Bioegineering and Nanotechnology, university of Queensland, Australia
2002-2005	Research Assistant in the Faculty of Biotechnology Kaohsiung Medical University, Taiwan ROC
2000-2002	Full-Time Missionary Service for The Church of Jesus Christ of Latter–Day Saints in Toronto (Missionary Training for two months in Provo. UT USA)

Representative Publication

1 Chou SY, **Chung TL**, Chen RJ, Ro LH, Tsui PI, Shiuan D: Molecular cloning and analysis of a HSP (heat shock protein)-like 42 kDa antigen gene of Mycoplasma hyopneumoniae. Biochem Mol Biol Int. 41:821-831, 1997.

2 **Chung TL**, Farh L, Chen YL, Shiuan D: Molecular cloning and characterization of a unique 60 kDa/72 kDa antigen gene encoding enzyme I of the phosphoenolpyruvate: sugar phosphotransferase system (PTS) of Mycoplasma hyopneumoniae. J Biochem (Tokyo) 128:261-269, 2000.

3 **Chung TL**, Hsiao HH, Yeh YY, Shia HL, Chen YL, Liang PH, Wang AH, Khoo KH, Shoei-Lung Li S: *In vitro* modification of human centromere protein CENP-C fragments by small ubiquitin-like modifier (SUMO) protein: definitive identification of the modification sites by tandem mass spectrometry analysis of the isopeptides. J Biol Chem. 279:39653-39662, 2004.

4 Shoei-Lung Li S, Liu YH, Tseng CN, **Chung TL**, Lee TY, Singh S : Characterization and gene expression profiling of five new human embryonic stem cell lines derived in Taiwan. Stem Cells Dev 15, 532-55 (2006).

5 Herszfeld D, Wolvetang E, Bunker EL, **Chung TL**, Filipczyk AA, Houssami S, Koh K, Laslett AL, Michalska A, Nguyen L, Reubinoff BE, Tellis I, Auerbach JM, Ording CJ, Looijenga LH, Pera MF : CD30 is a survival factor and a biomarker for transformed human pluripotent stem cells. Nat Biotechnol 24, 351-7 (2006).

ASCORBATE ACTIVATES CD30 EXPRESSION AND CAUSES WIDESPREAD SPECIFIC DNA DEMETHYLATION OF THE EPIGENOME OF SERUM FREE CULTURED HUMAN EMBRYONIC STEM CELLS

Tung-Liang Chung[1], Romulo M. Brena[2], Gabriel Kolle[3], Sean M Grimmond[3], Benjamin P. Berman[2], Peter W. Laird[2],Martin F. Pera[4], Ernst Wolvetang[1]

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The genetic and epigenetic integrity of human embryonic stem cells (hESCs) is critical to their future application in research and medicine. hESCs cultured in serum free media can accumulate point mutations, aneuploidy, and progressive epigenetic changes over prolonged culture *in vitro*. We have identified ascorbate as the only molecule in the very widely used Knock-out serum replacement medium that is sufficient to induced expression of CD30, a member of the tumour necrosis factor receptor superfamily and a biomarker for embryonal carcinoma cells. Our data further show that this activation of CD30 is epigenetically regulated in hESCs. Strikingly, we discover that hESCs cultured in the presence of ascorbate for 20 passages not only display DNA demethylation at CD30 locus, , but exhibit widespread and remarkably specific and consistent DNA demethylation of 1,847 genes in both HES2 and HES3 cells, with a clear bias towards demethylation at CpG island boundaries. The underlying biochemistry and the significance of the gene changes mediated by ascorbate remain to be determined. The specific ascorbate-induced DNA demethylation changes in the hESC epigenome, of which 86% are shared between the two lines, identify a subset of genes in hESCs, including CD30, that are sensitive to serum free culture medium induced epigenetic changes.

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Education

2005-2007. Postdoctoral research fellow, Division of Biology, California Institute of Technology, Pasadena, California, USA

2005. Ph.D. in Marine Biology, Scripps Institution of Oceanography, University of California, San Diego, La Jolla, California, USA

1997. M.S., Division of Biomedical Science, Department of Life Science, National Tsing Hua University, Hsinchu, Taiwan

1995. B.S., Department of Zoology, National Taiwan University, Taipei, Taiwan

Representative Publication

1. Pai C.Y., Chen J.H., Liao C.H., Chen Y.C., **Su Y.H.** (2010) Fgf signaling connects the aboral and oral ectoderm gene regulatory networks in the sea urchin embryo. In preparation.
2. Chen J.H., Luo YJ, **Su Y.H.** (2010) Dynamic gene expression patterns of transcription factors constituting the sea urchin aboral ectoderm gene regulatory network. *Dev Dyn*., in revision.
3. **Su Y.H.**, Li E., Geiss G.K., Longabaugh W.J., Kramer A, Davidson E.H. (2009) A perturbation model of the gene regulatory network for oral and aboral ectoderm specification in the sea urchin embryo. *Dev Biol*., 329, 410-421.
4. **Su Y.H.** (2009) Gene regulatory networks for ectoderm specification in sea urchin embryos. *Biochimica et Biophysica Acta - Gene Regulatory Mechanisms*, 1789, 261-267.
5. Nam J, **Su Y.H.**, Lee P.Y., Robertson A.J., Coffman J.A., Davidson E.H. (2007) Cis-regulatory control of the nodal gene, initiator of the sea urchin oral ectoderm gene network. *Dev Biol*., 306, 860-869**.**

STEM CELLS AND THE LEFT-RIGHT ASYMMETRICAL CONTROL IN THE SEA URCHIN

Yi-Jyun Luo and **Yi-Hsien Su**

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Adult sea urchins are penta-symmetric, and they develop from the bilaterally symmetric embryos. This transition relies on a left-right asymmetrical control that results in the formation of the rudiment on the left side of the larva. The adult rudiment develops from the left larval coelomic pouch that is contributed partly by the small micromere lineage. The small micromeres are originated from two asymmetric cell divisions early in embryogenesis and subsequently set aside for constructing the adult. Therefore, small micromeres are thought to be multipotent stem cells and contribute to several cell types in the adult sea urchin. Past studies have shown that the Nodal signals emitted from the right side of the larva prevent the right coelomic pouch from forming the adult rudiment. However, a positive regulator at the left side of the larva for rudiment formation has never been found. Here we discover that Smad-dependent BMP signaling is detected initially in both the left and right coelomic pouches then the signal at the right pouch fades away. The nuclearization of the phospho-Smad1/5/8 retains in the left pouch and its derived tube-like structure, the hydroporic canal. Inhibition of BMP signaling prevents the formation of the coelomic pouches and the hydroporic canal, suggesting that BMP signaling is required for the initiation of the rudiment formation at the left side of the larva. We also show that an antibody that recognized a dual specificity phosphatase, PRL (phosphatase for regenerating liver), labels all the nuclei in the first few cleavage stages. After the formation of the small micromeres, PRL specifically localizes to the nuclei of the small micromeres. This transition correlates with the activation of transcription in all cells except the small micromeres during embryogenesis. We therefore hypothesize that the function of PRL in the small micromeres is to repress the transcriptional activity. This idea is supported by the complementary staining of the phopho-Ser2 residues in the carboxy-terminal domain of RNA polymerase II. Therefore, we propose that PRL silences the transcriptional activity in the small micromere lineage and sets these multipotent stem cells aside before they start to proliferate in the left coelomic pouch. The proliferated small micromeres, together with the BMP signaling receiving cells in the left coelomic pouch, construct the penta-symmetrical adult rudiment at the left side of the larva.

Concurrent Session V

論文發表 V

Adult Stem Cells

劉銘 教授

及

曹伯年 教授

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Education

1996-2004	University of California, Riverside, Ph.D. Molecular, Cell and Developmental Biology
1991-1995	University of California, Berkeley, B.S. Integrative Biology

Key Experience

2004-2007	Postdoctoral Fellow	BC Cancer Agency / Terry Fox Laboratory (Vancouver, British Columbia Canada): characterization of transplantable hematopoietic stem cells in human cord blood cells and development of an in vitro system suitable for investigating the self-renewal of normal and leukemic toti-potent human hematopoietic cells and their differentiation into all lymphoid and myeloid lineages
1995-1996	Research Assistance	Smith-Kettlewell Eye Research Institute (San Francisco, California USA): study of smooth pursuit eye movements which are used to follow moving objects and how neurons in the brain process visual information in order to direct the eyes towards an object of interest
1994-1995	Research Student	University of California Berkeley Botanical Research Center (Berkeley, California USA): systematic data analysis and database entry

RHODAMINE-123 EFFLUX ACTIVITY DISCRIMINATES DIFFERENT SUBSETS OF QUIESCENT LYMPHO-MYELOPOIETIC HUMAN $CD34^+CD38^-$ CORD BLOOD CELLS

Min Liu

In vitro assays offer powerful approaches to dissecting events that regulate hematopoietic stem cell (HSC) functions but suitable systems and endpoints that can be practically applied to human HSCs still await definition. Here we demonstrate the heterogeneity in their functional features of primitive human cord blood (CB) cells using a newly developed in vitro assay. Our study shows that Rhodamine-123 efflux activity (Rho^- cells) discriminates a subset of lineage marker-negative (lin^-) $CD34^+$ CB cells with phenotypic ($CD38^-$, $CD133^+$, KIT^+, Thy-1^+, and $CD49f^+$) and a cell population of highly enriched HSC with functional features that produce lymphoid and myeloid progeny in vivo. We also show that Rho efflux activity discriminates between $lin^-CD34^+CD38^-$ cells with lympho-myeloid differentiation activity in cultures containing stromal cells engineered to produce human growth factors that support the generation of clonal populations of varying combinations of human B, NK, pre-T and multiple myeloid cell lineages. Assessment of their respective clonal progeny outputs in cultures containing genetically engineered stromal cells showed several patterns of differentiation after 6 and 12 weeks. These findings reveal extensive variation in the behavior of different subsets of primitive human CB cells suggestive of some dissociation in the mechanisms controlling their self-renewal and lineage determination

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Education

2006-2008	Postdoctor Research Training, Pulmonary Center Boston, University School of Medicine, Boston, U.S.A
2000-2004	Ph.D., Graduate Institute of Clinical Medicine, National Taiwan University, Taipei, Taiwan
1985-1992	M.D., College of Medicine, Chung-Shan Medical University, Taichung, Taiwan

Key Experiences

1999-present	Attending physician in Neonatology & Medical Genetics, National Taiwan University Hospital
2005-present	Clinical Assistant Professor of Neonatology Division, Department of Pediatrics, National Taiwan University Hospital

Representative Publication

1. **Tsao PN**, Vasconcelos M, Izvolsky1 KI, Qian J, Stanley P, Lu J, and Cardoso1 WV. Notch signaling controls the balance of ciliated and secretory cell fates in developing airways. Development 2009 Jul;136(13):2297-307.
2. **Tsao PN**, Chen F, Izvolsky KI, Walker J, Kukuruzinska MA Lu J, Cardoso WV. Gamma-secretase activation of notch signaling regulates the balance of proximal and distal fates in progenitor cells of the developing lung. J Biol Chem. 2008 Oct 283(43):29532-44.
3. Lee MC, Wei SC, Tsai-Wu JJ, Wu CH, **Tsao PN**. Novel PKC signaling is required for LPS-induced soluble Flt-1 expression in macrophages. J Leukoc Biol. 2008 Sep;84(3):835-41.
4. **Tsao PN**, Chan FT, Wei SC, Hsieh WS, Chou HC, Su YN, Chen CY, Hsieh FJ, Hsu SM. Soluble Vascular Endothelial Growth Factor Receptor-1 Protects Mice in Sepsis. Crit Care Med 2007 Aug;35(8):1955-60.
5. **Tsao PN**, Su YN, Li H, Huang PH, Chien CT, Lai YL, Lee CN, Chen CA, Cheng WF, Wei SC, Yu CJ, Hsieh FJ*, Hsu SM. Overexpression of placenta growth factor contributes to the pathogenesis of pulmonary emphysema. Am J Respir Crit Care Med 2004 169(4):505-11.

HOW NOTCH REGULATES AIRWAY EPITHELIUM CELL FATE

Po-Nien Tsao

In the respiratory system, airways are lined by a well-balanced population of ciliated, secretory, neuroendocrine and goblet cells which perform functions as diverse as air humidification, detoxification and clearance of environmental particles. How these different cell types emerge in the developing and adult airways, remains an open question. Our studies focused on how disruption of Notch signaling affects lung progenitor cell fate and differentiation events in the airway epithelium. Here we provided evidence that, in the developing airways, Notch signaling is used to silence the ciliated program in the cells that will continue to expand and differentiate into secretory cells (Clara cells). Our results support a major role for Notch in establishing the balance between ciliated and secretory cell fates during airway differentiation.

Goblet cell hyperplasia and mucus production contribute to the pathogenesis of chronic lung diseases including asthma, chronic obstructive pulmonary disease. In the intestine Notch signaling plays opposing roles in goblet cell differentiation depending on the stage and location. However it is unclear whether Notch influences goblet cell differentiation from Clara cells postnatally. To address this issue, we inactivated Notch signaling conditionally in the epithelium of trachea and proximal airway using a *TGFβ3-Cre* deleter mouse line and mice carrying floxed alleles of the *Pofut1* gene, which encodes an O-fucosyltransferase essential for Notch-ligand binding. *TGFβ3-Cre* targets the airway epithelium in a mosaic fashion. Preliminary analysis of these lungs postnatally revealed decreased Clara cell number and a dramatic goblet cell hyperplasia in the proximal respiratory epithelium. Our data suggest that during postnatal life Notch signaling is required to maintain conducting airway homeostasis. Notch may be required to prevent goblet cell differentiation presumably by maintaining the Clara cell phenotype in proximal airways. Notch signaling may be critical in the response of the lung to environmental injurants or allergens that results in goblet cell hyperplasia.

Concurrent Session VI

論文發表 VI

Novel Technology

張文瑋 教授

及

楊良棟 教授

Wen-Wei Chang, Ph.D.

Assistant Professor
School of Biomedical Sciences
Chung Shan Medical University, Taichung, Taiwan
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Education

1999-2006	Ph. D. in Institute of Basic Medical Sciences, National Cheng Kung University, Tainan, Taiwan
1995-1999	B. S. in Department of Biology, National Cheng Kung University, Tainan, Taiwan

Key Experiences

2006-2006	International exchange in Institut de Pharmacologie et de Biologie Structurale, Toulouse, France. Laboratory of Dr. Isabelle Maridonneau-Parini.
2006-2009	Post-doctoral fellow in Dr. Alice L. Yu's laboratory, Genomics Research Center, Academia Sinica, Taipei, Taiwan.

Representative Publication

1. *Cheng TL, ***Chang WW**, Su IJ, Lai MD, Huang W, Lei HY, and Chang WT. 2005. Therapeutic inhibition of hepatitis B virus surface antigen expression by RNA interference. Biochem. Biophys. Res. Commun. 336: 820-830. * Contributed equally.
2. **Chang WW**, Su IJ, Lai MD, Chang WT, Huang W, and Lei HY. 2005. Toll-like receptor-4 plays an anti-HBV role in a murine of acute hepatitis B virus expression. World J. Gastroenterol. 11:6631-6637.
3. Hsieh YH, Su IJ, Wang HC, Tsai JH, Huang YJ, **Chang WW**, Lai MD, Lei HY, Huang W. 2007. Hepatitis B virus pre-S2 mutant surface antigen induces degradation of cyclin-dependent kinase inhibitor p27Kip1 through c-Jun activation domain-binding protein 1. Mol Cancer Res. 5:1063-72.
4. **Chang WW**, Su IJ, Lai MD, Chang WT, Huang W, and Lei HY. 2008. Suppression of p38 mitogen-activated protein kinase inhibits hepatitis B virus replication in human hepatoma cell the antiviral role of nitric oxide. J. Viral Hepat. 15(7):490-7.
5. **Chang WW***, Lee CH*, Lee PS, Lin JW, Hsu CW, Hung JT, Lin JJ, Yu J, Yu JC, Shao LE, Wong CH, and Yu AL. 2008. Expression of Globo H and SSEA3 in breast cancer stem cells and the involvement of fucosyl transferases 1 & 2 in Globo H synthesis. Proc Natl Acad Sci U S A. 105(33):11667-11672. * Contributed equally.

NEOVASCULOGENIC POTENTIAL OF BREAST CANCER STEM CELLS

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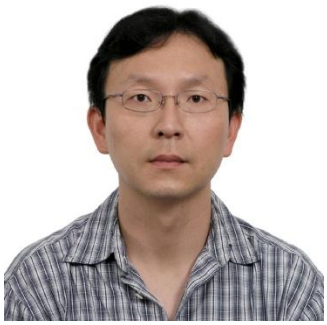
Neovascularization is a natural process to form vascular networks during embryogenesis and development via angiogenesis and vasculogenesis and it is also necessary for tumor maintenance and progression. Breast cancer stem cells (BCSCs) have been identified as a subpopulation of breast cancer cells with markers of $CD24^{-}CD44^{+}$ or high aldehyde dehydrogenase activity (ALDH+) and have been proved to be associated with radiation resistance and metastasis. In the view of differentiation capacity of cancer stem cells, it has been reported that ovarian cancer stem-like cells could transdifferentiation into CD34+ endothelial progenitor cells and contribute to neovascularization of ovarian cancer. In glioblastoma study, the stem-like glioma cells could release vascular endothelial growth factor (VEGF) to stimulate angiogenesis within tumor. It is unclear that whether BCSCs play any role in neovascularization of breast cancer. We have established two xenograft human breast cancer cells from patients in immunocompromised NOD/SCID mice and the BCSC population within these cells has been identified by surface markers $CD24^{-}CD44^{+}$ and high intracellular ALDH activity. Using these powerful xenograft breast cancer cell lines, we investigate the role of BCSCs in tumor neovascularization. In the matrigel-based tube formation assay, only ALDH+ BCSCs but not ALDH- non-BCSCs formed vessel-like structure, as similar as HMEC-1, a human microvascular endothelial cell line. Enrichment of BCSCs by mammopshere culture also increases the tube formation capacity. With comparison of different culture media, several factors, such as EGF, bFGF or heparin, might contribute to the neovasculogenic activity of BCSCs. We also find that BCSCs express several angiogenic factors, receptors and endothelial cell markers, such as VEGFA, VEGFR2, SDF-1, CXCR4, CD31, and CD34. With small molecule inhibitors, inhibition of VEFGR2 or CXCR4 did not suppress the tube formation capacity and it suggests that VEGFR2 or CXCR4 signaling pathway might not involve in the neovasculogenic potential of BCSCs. Further investigations the molecular mechanisms of neovasculogenic potential of BCSC will provide a new insight in CSC biology and CSC-based targeting therapy.



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Education

Ph.D. in Basic Biomedical Science, Graduate School of Arts and Science, New York University, New York, USA

M.S. in Pharmacology, Graduate School of Arts and Science, New York University, New York, USA

B.S. in Agricultural Chemistry, Department of Agriculture Chemistry, National Taiwan University, Taipei, Taiwan

Key Experience

2007 -present	Assistant Investigator, Stem Cell Research Center, National Health Research Institutes, Taiwan
2004-2007	Research Associate, Department of Pathology, Childrens Hospital Los Angeles, University of Southern California, USA
1999-2004	Postdoctoral fellow, Department of Biological Chemistry, School of Medicine, University of California Los Angeles (UCLA), Los Angeles, USA

Honor and Awards

Postdoctoral fellowship, California Institute of Regenerative Medicine, USA, 2006

Representative Publication

1. Rajasekaran, S; Kao,Y-Y; Chen,M-R; **Yang, LT**; Hsu;C-H; Chen;C-T; Lin, M-C. Detection of experimentally induced pulmonary granuloma inflammation in monocyte chemoattractant protein-1 reporter mice. Mol. Imaging and Biol.: article in press, 2009
2. **Liang-Tung Yang**, Wai-Yee Li, and Vesa Kaartinen. Tissue-specific expression of Cre recombinase from the *Tgfb3* locus. *Genesis.* 46(2):112-8, 2008.
3. **Liang-Tung Yang** and Vesa Kaartinen. *Tgfb1* expressed in the *Tgfb3* locus partially rescues the cleft palate phenotype of *Tgfb3* null mutants. *Developmental Biology*, 312(1):384-95, 2007.
4. Marek Dudas, Wai-Yee Li, Jieun Kim, **Liang-Tung A. Yang**, and Vesa Kaartinen. Palatal fusion - Where do the midline cells go? A review on cleft palate, a major human birth defect. *Acta Histochem*, 109(1):1-14, 2007.
5. Ena Ladi, James T. Nichols, Weihong Ge, Alison Miyamoto, Christine Yao, **Liang-Tung Yang**, Jim Boulter, Yi E. Sun, Chris Kintner, and Gerry Weinmaster. The divergent DSL ligand Dll3 does not activate Notch signaling but cell autonomously attenuates signaling induced by other DSL ligands. *Journal of Cell Biology,* 170(6):983-92, 2005.

THE ROLES OF NOTCH SIGNALING IN SKIN HOMEOSTASIS

Hsien-Yi Lin, Cheng-Heng Kao, Kurt Ming-Chao Lin, Vesa Kaartinen and **Liang-Tung Yang**

Mammalian Notch receptors and ligands are single transmembrane proteins, and Notch signaling involves a cell-cell contact between receptor-bearing cells and ligand-presenting cells. Notch signaling regulates a variety of processes such as differentiation, proliferation, apoptosis, and cell fate choice. Ligand binding leads to conformational changes in the Notch receptor and facilitates its sequential proteolysis to generate the active Notch intracellular domain (NICD). NICD translocates into the nucleus and binds to Rbpj and Mastermind, thereby activating the transcription of target genes, e.g. members of the *Hes* and *Hey* family. Notch signaling is modulated by glycosylation of the extracellular domain of Notch receptors and O-fucose modification of mammalian Notch receptors by Protein O-fucose transferase-1 (*Pofut1*) is required for efficient ligand-receptor binding and subsequent signal transduction. Multiple Notch receptors and ligands are expressed in the epidermis and hair follicle during embryonic development and adult stage. Although Notch signaling has been demonstrated to play an essential role in regulating differentiation of the epidermis and hair follicles, it remains unclear how Notch signaling participates in late-stage epidermal differentiation and postnatal hair cycle homeostasis.

Here, we conditionally inactivated Notch signaling by individual deletion of *Rbpj* and *Pofut1* using *Tgfb3*-Cre which induces gene recombination in the hair follicle epithelium and suprabasal layer of the epidermis. *Rbpj* conditional knockout (*Rbpj*cKO) mice displayed an early onset of epidermis and hair follicle phenotypes than *Pofut1* conditional knock (*Pofut1*cKO) mice. *Rbpj*cKO mice exhibited granular parakeratosis early in life and *Pofut1*cKO mice developed defects in granular layer differentiation later in life. Compared with *Rbpj*cKO mice which did not develop pelage after birth, *Pofut1*cKO mice displayed epidermal hyperplasia, progressive hair loss, and epidermal cysts in the second hair cycle. Abrogation of Notch signaling in follicular lineages by deletion of *Pofut1* resulted in fewer bulge stem cells and a concomitant increase of K14-positive keratinocytes in the isthmus. Interestingly, *Pofut1*cKO hair follicles had abnormalities in hair germs and hair bulbs, and displayed dysregulation of proliferation and apoptosis during the hair cycle transition. Taken together, our data demonstrate that Notch signaling has roles in maintaining tissue homeostasis of the skin.