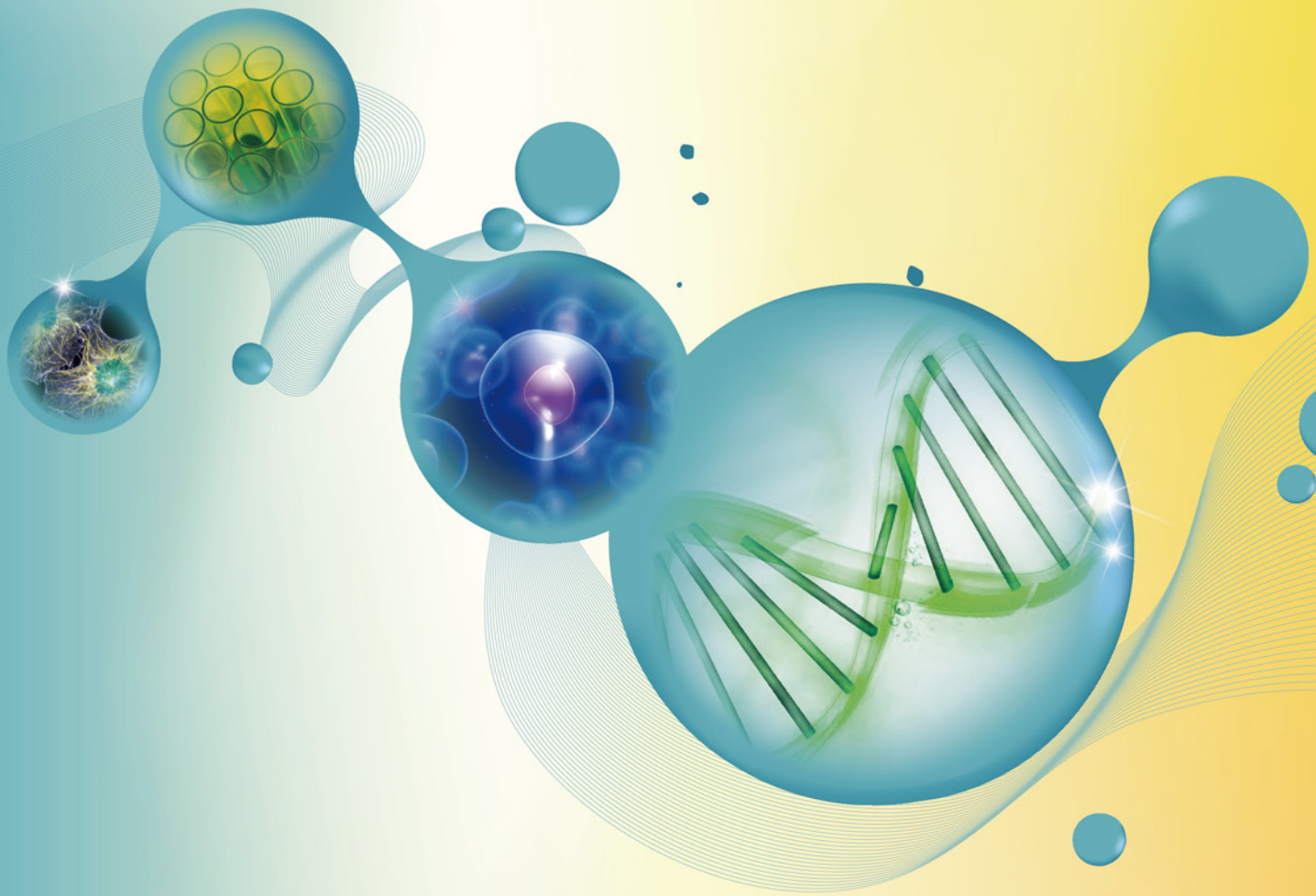
4th 2015 PPSSC
HSINCHU TAIWAN

Pan Pacific Symposium on Stem Cells and Cancer Research

April 11-13, 2015
Sheraton Hsinchu Hotel, Hsinchu, Taiwan

Program Book



Organizers:

Government Units:

It's not just about saving blood... it's about saving lives.

全球臍帶血儲存權威美商永生建構數量龐大公捐臍帶血庫*，協助醫師進行移植，至今已與全球近300家醫學中心建立合作經驗。永生協助移植經驗享譽全球，遠超過其他業者，並吸引多位國際權威一同合作，拓展幹細胞治療新領域的開發。提供消費者國際級臍帶血儲存的美商永生，絕對是您最安心的選擇。

■ 協助移植經驗多 | ■ 公捐血庫數量多 | ■ 幹細胞保留多

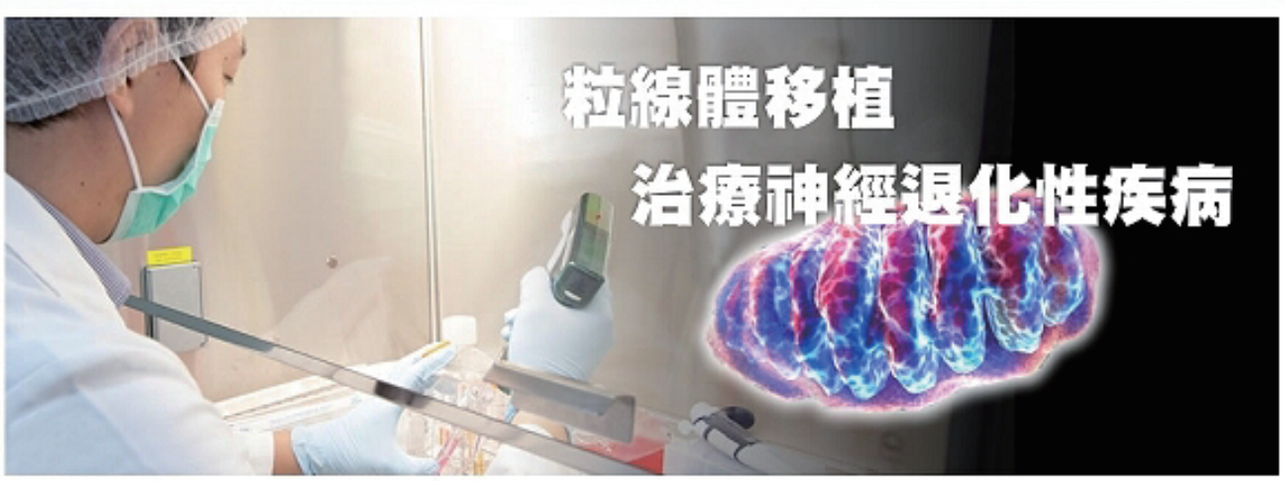
美商永生臍帶血

www.stemcyte.com.tw ☎0800-808080

*包含美國與台灣

台灣粒線體
Taiwan Mitochondrion

粒線體銀行
讓您擁有健康美麗人生



更多訊息請上
http://www.taimito.com

國際認證粒線體檢測能力
製藥規格的粒線體基材
臨床等級粒線體療法

台灣粒線體 (股票代號:7447)
Taiwan Mitochondrion
新竹縣竹北市生醫路二段2號D棟D202室(新竹生醫園區)
電話 03-6579767　傳真 03-6672759

Content

Welcome Message

Dear Colleagues,

Welcome to the 8th Pan Pacific Symposium on Stem Cells and Cancer Research (PPSSC) which take place on 11th to 13th April, 2015 in Hsinchu, the city of wind in Taiwan. On behave of the Board and Members of China Medical University & Healthcare System, I would like to express my gratitude and honor to have everyone's priority to join us in this pioneering event for stem cell and cancer research in the Asian Pacific region.

Pan Pacific Symposium on Stem Cells and Cancer Research (PPSSC) dedicates itself as an open platform in this annual event to facilitate the communication among the researchers and clinical practitioners, to exchange ideas and new research directions, as well as to forge new possibilities for future cooperation. It is a true multi-dimensional occasion for the stem cell and cancer research professionals both in Taiwan and the Asia Pacific region to share knowledge and to seek for inspirations. Based on the past experience in PPSSC, this year we are delighted to have main topics as follows:

1. Frontier in iPS Cell & Epigenetics
2. Targeting Stem Cells: Trials and Translation
3. Emerging Drug Targets in Development and Discovery
4. Cutting Edges of Stem Cell & Immune Modulation
5. Adipose-Derived Stem Cell Plasticity for Regenerative Medicine
6. Stem Cell Technology for Neurodegenerative Diseases

These are the emerging domains we like to emphasize this year. We cordially welcome everyone to join our discussions on the topics above. We encourage everyone to input your thoughts and exchange your experiences so that we can use this short valuable gathering time for mutual stimulation. It is your selfless contribution that strives the success of the conference. We are delightfully to hear from you and looking forward to seeing you this year!

Sincerely yours,

Chang-Hai Tsai, MD., PhD

Honorary Chairman,

The 8th Pan Pacific Symposium on Stem Cells and Cancer Research

Chairman of the Board,

China Medical University & Hospital, Taichung, Taiwan

Dear PPSSC 2015 Attendees,

On behalf of the Organizing Committee, I would like to welcome all of you to come and join us at the 8th Pan Pacific Symposium on Stem Cells and Cancer Research (PPSSC).

China Medical University is a professional university which combines medical science and pharmacology fields. Each department trains experts in all aspects. In regard to stem cell research, we are devoted to connect academic research with clinical trials to benefit more patients and those in need. It is one of the main reasons we keep holding PPSSC incessantly.

It has been 8 years since the beginning of PPSSC in 2008. We are glad to see the continuing development of stem cell and cancer research through this annual conference. This year we have organized a scientific program with width and depth for professionals and students to learn from each other's new findings and exchange information. I must gratefully acknowledge the effort of our Organizing Committee open up an extraordinary conference revealing the best in stem cells, new drug development, and cancer research. I believe this conference will benefit the participants all over the world, and I look forward to meet you as well as share ideas with you at PPSSC 2015.

Wish all of you have a wonderful and memorable conference in Hsinchu this year.

With best regards,

Wen-Hwa Lee,Ph.D.

Organizing Committee,

The 8th Pan Pacific Symposium on Stem Cells and Cancer Research

Chancellor and Academician,

China Medical University, Taichung, Taiwan

Dear Colleagues and Friends,

I am pleased to express my warm welcome to all participants of PPSSC 2015. Thank you for joining the 8th Pan Pacific Symposium on Stem Cells and Cancer Research.

Stem cell transplantation technique, known as one of the most important medical techniques, can repair and update every organ of one's body, and eliminate more than 80 percent of the current diseases. This year we are delighted and honored to have Prof. Mari Dezawa (Japan), Prof. Paolo Fiorina (USA), Prof. Umverto Galderisi (Italy), Prof. Sheng Ding (USA) and Prof. Paul R. Sanberg (USA) as our keynote speakers. In addition, we have invited more than 30 outstanding professionals to share their expertise in penetrating instructional presentation.

The 6th PPSSC was held in Hsinchu City where is toward a global and smart city gradually. Based on a wide range of positive responses in the 6th PPSSC, we decided to host PPSSC in this charming city again. Apart from the scientific program, you can have wonderful experience here. Furthermore, the unique culture and plentiful landscape of Hsinchu will absolutely make incredible memories for you. We recommend that you take some free time to explore this beautiful city during your stay in Taiwan.

We hope all of you will enjoy this scientific meeting and social feast in Hsinchu!

Sincerely yours,

Shinn-Zong Lin, M.D., Ph.D.

Chairman,

2015 the 8th Pan Pacific Symposium on Stem Cells and Cancer Research (PPSSC)

Professor,

Neurosurgery of China Medical University, Taichung, Taiwan

Superintendent,

China Medical University Beigan Hospital, Yunlin, Taiwan

Vice Superintendent,

Center for Neuropsychiatry, China Medical University Hospital, Taichung, Taiwan

Organizing Committee

Organizers

China Medical University Hospital
中國醫藥大學附設醫院

China Medical University Beigang Hospital
中國醫藥大學北港附設醫院

China Medical University
中國醫藥大學

Stem Cell & Regeneration Medicine Foundation
財團法人幹細胞及再生醫學教育基金會

Organizing Committee **Sorted by Last Name*

Honorary Chairman

Chang-Hai Tsai 蔡長海 董事長

Conference Chairman

Shinn-Zong Lin 林欣榮 院長

Organizing Committee

Koji Abe
Yao-Chang Chen 陳耀昌 教授
Shih Hwa Chiou 邱士華 教授
Der-Yang Cho 周德陽 院長
Chung-Y. Hsu 許重義 總執行長
Mien-Chie Hung 洪明奇 院士
Long-Bin Jeng 鄭隆賓 院長
Wen-Hwa Lee 李文華 教授
Ching-Tien Peng 彭慶添 院長
Paul Sanberg
Kwok-Fai So 蘇國輝 院士
Tse-Hua Tan 譚澤華 教授
Fuu-Jen Tsai 蔡輔仁 教授
Jacqueline Whang-Peng 彭汪嘉康 院士
Wise Young 楊詠威 教授

Scientific Committee

Fu-Chou Cheng	陳甫洲 主任
Tzyy-Wen Chiou	邱紫文 教授
Ing-Ming Chiu	邱英明 主任
Horng-Jyh Harn	韓鴻志 主任
Demeral Liu	劉德模 教授
Woei-Cherng Shyu	徐偉成 主任
Hong-Lin Su	蘇鴻麟 副教授
Kang-Hsi Wu	巫康熙 主任

Executive Committee

Yu-Wen Chen	陳郁雯 秘書
Shao-Chih Chiu	邱紹智 博士
Shih-Ping Liu	劉詩平 博士
Ru-Huei Fu	傅如輝 博士

Important Information

Symposium Date

Saturday to Monday, April 11-13, 2015

Symposium Venue

Sheraton Hsinchu Hotel, Hsinchu, Taiwan

Address: No. 265, Dong Sec.1, Guangming 6th Rd., Zhubei City, Hsinchu County, Taiwan

Website: http://www.sheraton-hsinchu.com/

Tel: +886-3-620-6000

Location of Symposium Venue

Registration

The Registration Desk will be open at 3F Lobby of the symposium venue as follows:

07:30-17:00, Saturday, April 11, 2015
08:00-14:30, Sunday, April 12, 2015

Preview Room

Plum Room, 3F

Speakers / presenters are responsible for their presentation functionalities, including the entire data file, the compatibility of data with the congress projection system, and the USB flash drive. Your are advised to check your file at the Preview Room prior to submission to the audio-visual specialist in your session venue to make sure that it could be displayed correctly.

Social Programs

Opening Ceremony

Time: 08:30-08:50, Saturday, April 11, 2015
Venue: 3F, Ballroom I, Sheraton Hsinchu Hotel

Banquet

Time: 18:00-20:00, Saturday, April 11, 2015
Venue: 5F, Chapel Room, Sheraton Hsinchu Hotel
Fee: Invited Speakers for free / Delegates & Accompanying Person: TWD 1,600

Name Badge

All participants will receive the badge upon registration. Please wear and clearly display your name badge to attend all scientific programs and social programs. Access to the congress venue will not be granted without a proper name badge.

Exhibition

A technical and commercial exhibition will be held at 3F, Ballroom III during the Symposium at the following hours:

08:30-17:30, Saturday, April 11, 2015
09:00-15:00, Sunday, April 12, 2015

Instruction for Presenters

Oral Presentation

Speaker	Presentation Time
Keynote Speech	Depends on the program
Invited Speech	30 minutes
Free Paper	12 minutes (10 minutes for presentation and 2 minutes for Q & A)

Poster Presentation

Poster Area: 3F, Ballroom III
Poster Size: 90m WIDTH X 180 cm HEIGHT
Mounting Time: After 08:30, Saturday, April 11, 2015
Presentation Date / Time: 12:40 – 13:00, April 11
Removal Time: Before 15:00, Sunday, April 12, 2015

Language

The official language of the Symposium is English, which will be used in all presentations and printed materials.

Lunch

Lunchbox will be served at 3F, Ballroom I & II.

Internet Access

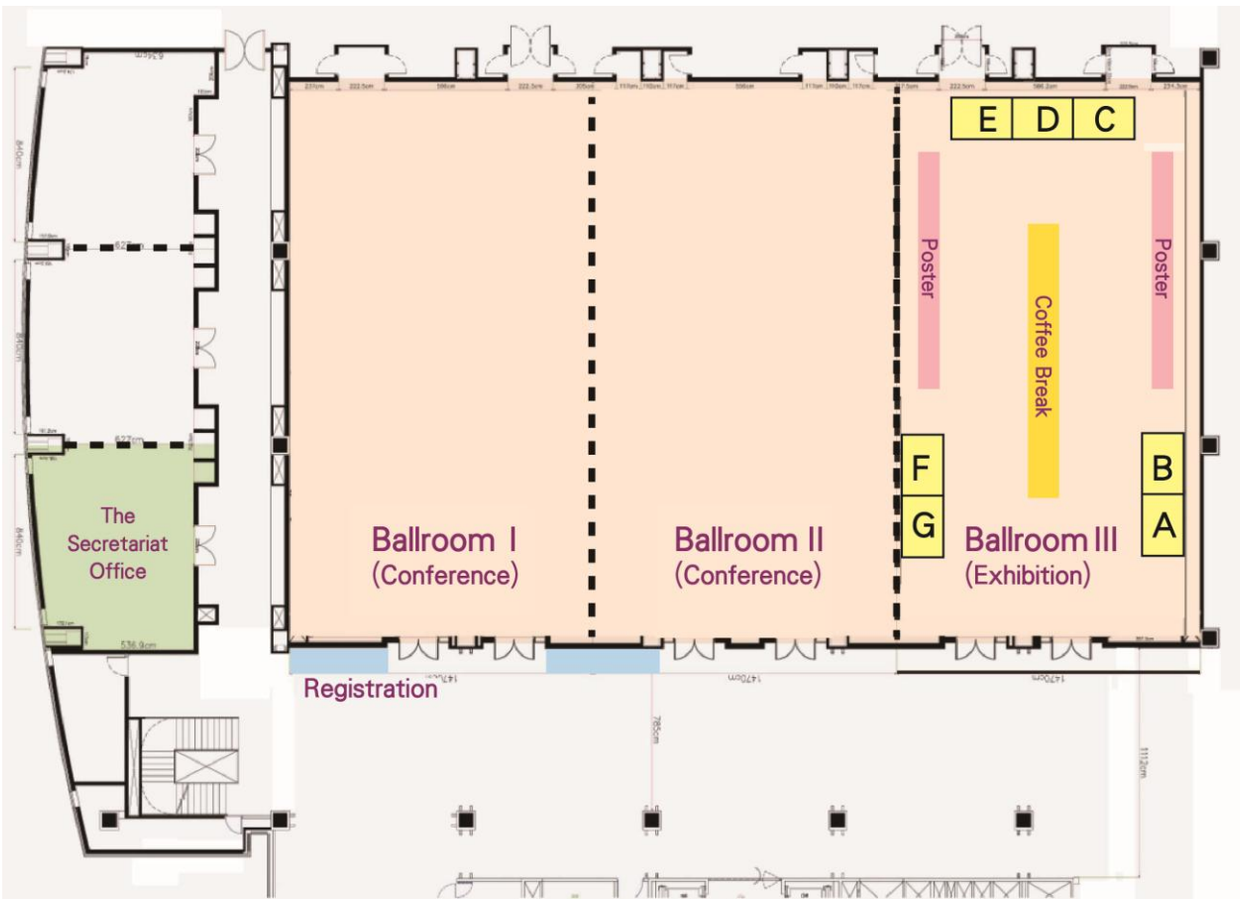
Wireless service is available inside the Splendor Hotel.
Account: Link@Sheraton

Sessions / Changes

Please make sure to be in the session room on time as all sessions will begin per scheduled. The organizing committee reserves the right to adjust or change the program.

Floor Plan

3rd Floor



Exhibitors

A-B	Gwo Xi Stem Cell Applied Technology Co., Ltd. 國璽幹細胞應用技術股份有限公司
C	Level Biotechnology Inc. 進階生物科技(股)公司
D-E	GUANG LI BIOMEDICINE 光麗生醫股份有限公司
F-G	Stem Cyte 美商永生

Date	April 11, 2015 (Saturday)		
Time / Venue		**Ballroom I**	**Ballroom II**
08:30–08:50	Registration (07:30-17:00)	Opening Ceremony	
08:50–10:10		**Keynote Speech [A]**	
10:10–10:30		Coffee Break	
10:30–12:00		**Invited Speech [A1]** Emerging Drug Targets in Development and Discovery	**Invited Speech [A2]** Frontier in iPS cell & Epigenetics
12:00–13:00		**Luncheon Seminar**	
12:40–13:00		**Poster Presentation**	
13:00–14:30		**Invited Speech [B1]** Adipose-derived Stem Cell Plasticity for Regenerative Medicine	**Invited Speech [B2]** Cutting Edges of Stem Cell & Immune Modulation
14:30–14:50		Coffee Break	
14:50–16:20		**Invited Speech [C1]** Stem Cell Technology for Neurodegenerative Diseases	**Invited Speech [C2]** Targeting Stem Cells: Trials and Translation
16:20–16:30		Short Break	
16:30–17:00			**Panel Discussion**
17:00–18:00			
18:00–20:00	**Banquet**		

Date	April 12, 2015 (Sunday)		
Time / Venue		**Ballroom I**	**Ballroom II**
09:00–10:30	**Registration (08:00-14:30)**	**Keynote Speech [B]**	
10:30–10:50		Coffee Break	
10:50–12:20		**Invited Speech [D1]** Stem Cell Technology for Neurodegenerative Diseases	**Invited Speech[D2]** Cutting Edges of Stem Cell & Immune Modulation
12:20–13:20		**Luncheon Seminar**	
13:20–14:50		**Invited Speech [E1]** Cutting Edges of Stem Cell & Immune Modulation	**Invited Speech [E2]** Frontier in iPS Cell& Epigenetics
14:50–15:10		Coffee Break	
15:10–16:40		**Invited Speech [F1]** Targeting Stem Cells: Trials and Translation	**Oral Presentation**
16:40–17:40		**Invited Speech [G1]** Stem Cell Technology for Neurodegenerative Diseases	**Invited Speech [G2]** Emerging Drug Targets in Development and Discovery
17:40-18:00		Short Break	
18:00–20:00		**Presidential Dinner (Invited ONLY)**	

April 11 (Saturday) Ballroom I

Keynote Speech [A]

Moderators: Shinn-Zong Lin 林欣榮 (Taiwan)、Chung-Liang Chien 錢宗良 (Taiwan)

08:50-09:30	K1-I1	Discovery of Muse Cells Shifts the Paradigm of Stem Cell Therapy *Mari Dezawa (Japan)*
09:30-10:10	K1-I2	Hints to Improve the Success Rate of Cellular Therapy Based on Mesenchymal Stromal Cells (Mscs): Secretome of Senescent MSCs Has a Negative Paracrine Effect on Healthy Cells by Reducing the Stemness and Promoting the Senescence *Umberto Galderisi (Italy)*

A1

Emerging Drug Targets in Development and Discovery

Moderator: Kwok Fai So 蘇國輝 (Hong Kong)

10:30-11:00	A1-I1	AC5 Surgical Hemostat™ Is an Effective Hemostatic Agent in Anticoagulated Animals Using a Non-Compressible, Penetrating Liver Wound Model *Rutledge Ellis-Behnke (Germany)*
11:00-11:30	A1-I2	Engineering 3D Hydrogel for Biological Application *Hossein Hosseinkhani (USA)*
11:30-12:00	A1-I3	Emerging Targets Against Drug-Resistance of Lung Cancer via Stemness Pathways *Cheng-Wen Wu 吳成文 (Taiwan)*

Luncheon Seminar

Gwo Xi Stem Cell Applied Technology Co., Ltd. 國璽幹細胞應用技術股份有限公司

12:00-13:00	L1	Sharing Stem Cells Clinical Trial Start-Up Experience in Taiwan *Po-Cheng Lin 林珀丞 (Taiwan)*

B1

Adipose-Derived Stem Cell Plasticity for Regenerative Medicine

Moderator: Wise Young 楊詠威 (USA)

13:00-13:30	B1-I1	Update on MSCs *Paolo Fiorina (USA)*
13:30-14:00	B1-I2	Chondrogenesis from Stem Cells *Gun Il Im (Korea)*
14:00-14:30	B1-I3	Physical Exercise-Induced Hippocampal Neurogenesis and Antidepressant Effects Are Mediated by the Adipocyte Hormone Adiponectin *Kwok Fai So 蘇國輝 (Hong Kong)*

C1

Stem Cell Technology for Neurodegenerative Diseases

Moderator: Jonas Wang (USA)

14:50-15:20	C1-I1	Umbilical Cord Lining Cells-Derived Induced Pluripotent Stem Cells as a Source of Cells for Cell Replacement Therapy in Neurodegenerative Diseases *Chou Chai 蔡兆 (Singapore)*
15:20-15:50	C1-I2	Tissue Engineering and 3D Printing: Seeking for Novel Printing Materials *Shan-Hui Hsu 徐善慧 (Taiwan)*
15:50-16:20	C1-I3	Therapeutic Potential of Amniotic Fluid Stem Cells in Neurogenesis *Shiaw-Min Hwang 黃效民 (Taiwan)*

April 11 (Saturday) Ballroom II

A2

Frontier in iPS Cell & Epigenetics

Moderator: Tomokazu Fukuda (Japan)

10:30-11:00	A2-I1	Feeder-Free Culture and Reprogramming of Human iPSCs on Dishes Grafted with Cell Adhesion Peptides and Having Different Elasticity *Akon Higuchin (Japan)*
11:00-11:30	A2-I2	Development of Cellular Reprogramming and iPSC Technology as Personalized Medicine-Based Platform *Shih-Hwa Chiou 邱士華 (Taiwan)*
11:30-12:00	A2-I3	Human Ipsc-Derived Organ Bud Based Approaches Towards Clinical Application *Takanori Takebe (Japan)*

B2

Cutting Edges of Stem Cell & Immune Modulation

Moderator: Chung Y. Hsu 許重義 (Taiwan)

13:00-13:30	B2-I1	Cell-Based Therapies for Traumatic Brain Injury: Targeting the Secondary Inflammation-Mediated Cell Death *Cesar V. Borlongan (USA)*
13:30-14:00	B2-I2	Stem Cells, Neurokines and Biomaterials in Nerve Injury and Repair *Ing-Ming Chiu 邱英明 (Taiwan)*
14:00-14:30	B2-I3	Induction of Regulatory Macrophage-Like Cells from Mouse Pluripotent Stem Cells that Can Contribute to Suppress Allogeneic Immune Responses *Ken-Ichiro Seino (Japan)*

C2

Targeting Stem Cells: Trials and Translation

Moderator: Paul R. Sanberg (USA)

14:50-15:20	C2-I1	Lumbosacral Spinal Cord Injury *Wise Young 楊詠威 (USA)*
15:20-15:50	C2-I2	Stem Cell Transplantation in Pediatric Malignancies: an Experience from India *Sameer Bakhshi (India)*
15:50-16:20	C2-I3	The Construction and Application of MSC-Based Tissue Engineered Nerve *Xiaosong Gu 顧曉松 (China)*

Panel Discussion

Moderator: Shinn-Zong Lin 林欣榮 (Taiwan)

16:30-17:00	Panelists	*Wise Young 楊詠威 (USA), Paul R. Sanberg (USA), Kwok Fai So 蘇國輝 (Hong Kong), Rutledge Ellis-Behnke (Germany), Winston Town 湯竣鈞 (Taiwan)*

April 12 (Sunday) Ballroom I

Keynote Speech [B]

Moderators: John Yu 游正博 (Taiwan), Yao-Chang Chen 陳耀昌 (Taiwan)

09:00-09:30	K2-I1	A Chemical Approach to Controlling Cell Fate *Sheng Ding (USA)*
09:30-10:00	K2-I2	Immunological Applications of Stem Cells in Type 1 Diabetes *Paolo Fiorina (USA)*
10:00-10:30	K2-I3	Scientist or Inventor? Entrepreneurship in Regenerative Medicine *Paul R. Sanberg (USA)*

D1

Stem Cell Technology for Neurodegenerative Diseases

Moderator: Horng-Jyh Harn 韓鴻志 (Taiwan)

10:30-11:20	D1-I1	Wnt-3A Signaling Mediated Neuroprotection and Regenerative Activities and Functional Recovery after Brain Injury *Ling Wei (USA)*
11:20-11:50	D1-I2	Aberrant Astrocytes Cause Inflammation and Impair Vascular Reactivity in Huntington's Disease *Yi-Juang Chern 陳儀莊 (Taiwan)*
11:50-12:20	D1-I3	Promoting Adult Neurogenesis as a Strategy to Ameliorate Neurodegenerative Disease *Young-Ji Shiao 蕭永基 (Taiwan)*

Luncheon Seminar

StemCyte Taiwan Co., Ltd. 台灣永生細胞股份有限公司

12:20-13:20	L2	The Clinical Applications and Banking of Human Amniotic Fluid Stem Cells *S.W. Steven Shaw 蕭勝文 (Taiwan)*

E1

Cutting Edges of Stem Cell & Immune Modulation

Moderator: Cesar V. Borlongan (USA)

13:20-13:50	E1-I1	Cancer Immunotherapy in Mice Using Antigen-Specific CTL from Stem Cells *Jianxun Song 宋建勛 (USA)*
13:50-14:20	E1-I2	Strategies to Further Develop the Use of Natural Killer (NK) Cells in Cancer Therapy *Habib Torfi (USA)*
14:20-14:50	E1-I3	Clinical Applications of Intravenous Injection of Adipose Derived Stem Cells *David CP Chen (USA)*

F1

Targeting Stem Cells: Trials and Translation

Moderator: Sheng Ding (USA)

15:10-15:40	F1-I1	Neurorestoration Induced from Endogenous Stem Cells *Sung Rae Cho (Korea)*
15:40-16:10	F1-I2	Application of Hypoxic Mesenchymal Stem Cells for Therapies in Ischemic Limb: From Bench to Bedside *Shih-Chieh Hung 洪士杰 (Taiwan)*
16:10-16:40	F1-I3	Stem Cells Therapy for Stroke *Toru Yamashita (Japan)*

April 12 (Sunday) Ballroom I

G1

Stem Cell Technology for Neurodegenerative Diseases

Moderator: Xiaosong Gu 顧曉松 (China)

16:40-17:10	G1-I1	Optogenetic Stimulation of Striatal Glutamatergic Neurons Enhances Neurogenesis in the Subventricular Zone of Normal and Stroke Mice *Shan Ping Yu (USA)*
17:10-17:40	G1-I2	Neuroprotection and Stem Cell Therapy in Japan *Koji Abe (Japan)*

April 12 (Sunday) Ballroom II

D2

Cutting Edges of Stem Cell & Immune Modulation

Moderator: Umberto Galderisi (Italy)

10:50-11:20	D2-I1	Muse Cells and Their Possible Application to Both Autologous and Allogenic Transplantation Therapy *Mari Dezawa (Japan)*
11:20-11:50	D2-I2	MAP4K Kinases and DUSP Phosphatases in Inflammation and T Cell-Mediated Diseases *Tse-Hua Tan 譚澤華 (Taiwan)*
11:50-12:20	D2-I3	Therapeutic Potential of Human Fetal-Stage Stem Cells *B. Lin-Ju Yen 顏伶汝 (Taiwan)*

E2

Frontier in iPS Cell & Epigenetics

Moderator: Ing-Ming Chiu 邱英明 (Taiwan)

13:20-13:50	E2-I1	Systemic Combined Melatonin-Mitochondria Treatment Improves Rat Acute Respiratory Distress Syndrome *Hong-Lin Su 蘇鴻麟 (Tawian)*
13:50-14:20	E2-I2	Porcine Derived Induced Pluripotent Stem Cells with Six Reprogramming Factors *Tomokazu Fukuda (Japan)*
14:20-14:50	E2-I3	Generation of Pluripotent Stem Cells and Multipotent Neural Progenitors from Somatic Cell Reprogramming *Chia-Ning Shen 沈家寧 (Taiwan)*

Oral Presentation

Moderators: Rutledge Ellis-Behnke (Germany), David CP Chen (USA)

15:10-15:22	O1	Cancer and Stem Cells(NP):Dynamic Equilibrium Prediction *Hsih-Chia Hsieh (Taiwan)*
15:22-15:34	O2	Extracellular Matrix Benefits Peripheral Nerve Reconstruction *Sheng Yi 易晟 (China)*
15:34-15:46	O3	*The Regulatory Mechanisms of Mirnas in Peripheral Nerve Regeneration* *Songlin Zhou 周松林 (China)*
15:46-15:58	O4	*Fluorescent Nanodiamonds Enable in Vivo Tracking of Prospectively Isolated Lung Stem Cells* *Tsai-Jung Wu 吳采蓉 (Taiwan)*
15:58-16:10	O5	*Human Nucleus Pulposus Contains Multilineage-Differentiating Stress-Enduring -Like Progenitor Cells* *Fengjuan Lv 呂鳳娟 (China)*
16:10-16:22	O6	*The Influence of High Glucose Environment on the Stemness and Differentiation Potentials of Adipose-Derived Stem Cells* Nai-Chen Cheng *鄭乃禎 (Taiwan)*
16:22-16:34	O7	*The Role of MSC in the Endometriosis Treatment* Yi-Jen Chen *陳怡仁 (Taiwan)*

G2

Emerging Drug Targets in Development and Discovery

Moderator: Tzyy-Wen Chiou 邱紫文 (Taiwan)

16:40-17:10	G2-I1	Design of Integrin Drugs for Cancer *Woei-Jer Chuang 莊偉哲 (Taiwan)*
17:10-17:40	G2-I2	Polyanhydride, Biodegradable Materials, Bring z-Butylidenephthalide onto Human Glioblastoma Multiforme to Achieve Therapy - A Pre-clinical and Clinical Development *Horng-Jyh Harn 韓鴻志 (Taiwan)*

Profiles & Abstracts of Speakers

Mari Dezawa

Japan

Professor and Chair, Dept. of Stem Cell Biology and Histology &
Dept. of Anatomy and Anthropology,
Tohoku University Graduate School of Medicine, Japan

DISCOVERY OF MUSE CELLS SHIFTS THE PARADIGM OF STEM CELL THERAPY

Mari Dezawa

Department of Stem Cell Biology and Histology, Tohoku University Graduate School of Medicine, Sendai, Japan

Pluripotent stem cells are able to generate all cell types, and are thus considered useful for regenerative medicine in various disease conditions. The well-known pluripotent stem cells, ES and iPS cells, however, carry a risk of tumorigenicity. In contrast, adult stem cells are natural cells that do not exhibit tumorigenic proliferation. Adult stem cells, however, typically generate the cell types of the tissue in which they reside, and thus their differentiation capability is considered limited. A pluripotent stem cell without the risk of tumorigenicity would be ideal for regenerative medicine.

We discovered non-tumorigenic pluripotent stem cells, Multilineage differentiating Stress Enduring (Muse) cells, that reside in the bone marrow, adipose tissue, and dermis, as well as in the connective tissue of nearly every organ (PNAS, 2010; PNAS, 2011; Nat Protocol, 2013). Muse cells correspond to ~0.03% of bone marrow-mononucleated cells and to several percentages of commercially available cultured mesenchymal cells such as fibroblasts. Therefore, ~30 ml of bone marrow aspirate will yield ~1 million Muse cells by 3 day culture, suggesting feasibility of Muse cells for clinical application. They are stress-tolerant, express pluripotent stem cell markers despite low telomerase activity, and are able to self-renew and generate cells of all three germ layers from a single cell. These cells can be identified and collected as cells positive for SSEA-3, pluripotent surface marker.

A unique and highly useful feature that may not be seen in other multipotent/pluripotent stem cells is that Muse cells have a specific receptor to detect damage signals, which allows them to migrate toward and home into damaged tissues only by intravenous injection where they can spontaneously differentiate into cells compatible with the homed-into tissue. These migration and spontaneous differentiation activities of Muse cells were confirmed in models of stroke (both MCAO model and lacuna infarction model), acute myocardial infarction, fulminant hepatitis, and skin ulcer in diabetes mellitus (Stem Cell Transl Med, 2015). These migration and tissue repair effects of Muse cells are not recognized in remainder of mesenchymal cells, namely non-Muse cells.

Muse cells are unique in their high homing rate after intravenous injection, capacity for survival in damaged tissue, stress tolerance, *in vivo* differentiation into cells compatible to the tissue they homed and non-tumorigenicity. Induction prior to transplantation in cell processing center may not be necessary. Thus, they may provide a simple (such as intravenous injection just after collection by SSEA-3), clinically feasible approach cell-based therapy in stroke as well as in other diseases represented by their impressive regenerative performance.

Furthermore, the discovery of Muse cells addresses a longtime question regarding the mechanism of spontaneous recovery in the living body. Muse cells are distributed from the bone marrow to the connective tissue of every organ via the peripheral blood where they contribute to maintaining tissue homeostasis in each region. These cells are highly feasible for clinical therapy because they are non-tumorigenic, and are already components of the human bone marrow. The future of regenerative medicine will depend on the full utilization of the 'laws of nature', taking advantage of the internal regenerative potential already possessed by the living body.

Umberto Galderisi

Italy

- Professor, School of Medicine, Dept. of Medicina Sperimentale, 2nd University of Naples, Italy
- Adjunct Professor, Sbarro Institute for Cancer Research and Molecular Medicine, Temple University, Philadelphia, PA, USA
- Adjunct Professor, Genkök Stem Cell Centre, Erciyes University, Kayseri, Turkey

HINTS TO IMPROVE THE SUCCESS RATE OF CELLULAR THERAPY BASED ON MESENCHYMAL STROMAL CELLS (MSCS): SECRETOME OF SENESCENT MSCS HAS A NEGATIVE PARACRINE EFFECT ON HEALTHY CELLS BY REDUCING THE STEMNESS AND PROMOTING THE SENESCENCE

Nicola Alessio[2], Giovanni Di Bernardo[2], Marilena Cipollaro[2], Gianfranco Peluso3, Umberto Galderisi[1,2,4#]

[1]Sbarro Institute for Cancer Research and Molecular Medicine, Center for Biotechnology, Temple University, Philadelphia, PA, USA

[2]Department of Experimental Medicine, Biotechnology and Molecular Biology Section, Second University of Naples, Naples, Italy

[3]Institute Bioscience and BioResources, CNR, Naples, Italy

[4]Genkök Stem Cell Centre, Erciyes University, Kayseri, Turkey

Cell senescence has been regarded as a strictly intracellular response, with the entire signaling circuitry, which takes place within the cell. Recent findings have demonstrated that several secreted molecules are associated with, and contribute to senescence proliferative arrest.

It is evident that senescence process may greatly affect also the composition of mesenchymal stem cells (MSC) secretome through a shift from a functional paracrine signaling to production of senescent-associated secreted factors that have potent autocrine and paracrine activities. Changes in secretome profiles of MSC may great impair their activities, which depends on the capability to secrete many factors, like cytokines and chemokines.

We performed a comparative analysis of human MSC secretome from young and replicative senescent cultures and evaluate if factors secreted from old MSC cultures may induce senescence, or arrest proliferation, or promote cytotoxic effects in young cells.

Our data strongly evidenced that senescence-associated secretory phenotype (SASP) implements a full senescence response in young cells suggesting that a few senescent cells in the MSC stem cell pool may be a potent trigger for ageing phenomena through a paracrine signaling cascade.

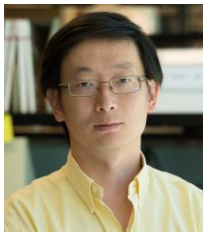
We demonstrated that secretion of IGFBP4 and IGBP7 has a significant senescent paracrine effect on young MSC. Moreover, the inhibition of these factors also reduced the percentage of apoptosis and promoted cell growth suggesting that may have a pleiotropic effect on MSC biology.

In conclusion, we could speculate that our study could pave the way to further investigations aiming to modify, in the near future, the current in vitro MSC expansion protocols for therapeutic purposes to avoid or reduce the occurrence of negative senescence related effects.

Sheng Ding

USA

Professor, Gladstone Institute of Cardiovascular Disease,
Department of Pharmaceutical Chemistry,
University of California San Francisco, USA



A CHEMICAL APPROACH TO CONTROLLING CELL FATE

Sheng Ding

Gladstone Institute of Cardiovascular Disease, Department of Pharmaceutical Chemistry, University of California San Francisco, USA

Recent advances in stem cell biology may make possible new approaches for treatment of a number of diseases. A better understanding of molecular mechanisms that control stem cell fate/function as well as an improved ability to manipulate them are required. Toward these goals, we have developed and implemented high throughput cell-based screens of arrayed chemical libraries to identify and further characterize small molecules that can control stem cell fate in various systems. This talk will provide latest examples of discovery efforts in my lab that have advanced our ability and understanding toward controlling stem cell fate, including self-renewal, survival, differentiation and reprogramming of cells.

Paolo Fiorina

USA

- Assistant Professor, Harvard Medical School, USA
- Staff Scientist, Nephrology Division, Boston Children's Hospital, USA

IMMUNOLOGICAL APPLICATIONS OF STEM CELLS IN TYPE 1 DIABETES

Paolo Fiorina

Nephrology Division, Children's Hospital, Harvard Medical School, Boston, MA, USA

Current approaches aiming to cure type 1 diabetes (T1D) have made a negligible number of patients insulin-independent. The optimal therapeutic approach for T1D should ideally preserve the remaining β-cells, restore β-cell function and protect the replaced insulin-producing cells from autoimmunity. Stem cells possess immunological and regenerative properties that could be harnessed to improve the treatment of T1D; indeed, stem cells may re-establish peripheral tolerance towards β-cells through re-shaping of the immune response and inhibition of autoreactive T-cell function. Furthermore, stem cell-derived insulin-producing cells are capable of engrafting and reversing hyperglycemia in mice. Bone marrow mesenchymal stem cells display a hypo-immunogenic phenotype as well as a broad range of immunomodulatory capabilities, have been shown to cure newly diabetic NOD mice, and are currently undergoing evaluation in two clinical trials. Cord blood stem cells have been shown to facilitate the generation of regulatory T-cells, thereby reverting hyperglycemia in NOD mice. T1D patients treated with cord blood stem cells also did not show any adverse reaction in absence of major effects on glycometabolic control. Although hematopoietic stem cells rarely revert hyperglycemia in NOD mice, they exhibit profound immunomodulatory properties in humans; newly hyperglycemic T1D patients have been successfully reverted to normoglycemia with autologous nonmyeloablative hematopoietic stem cell transplantation. Finally, embryonic stem cells also offer exciting prospects, as they are able to generate glucose-responsive insulin-producing cells. Easy enthusiams should be mitigated mainly because of the potential oncogenicity of stem cells.

Paul R. Sanberg

USA

- Senior Vice President, Research,
  Innovation & Economic Development, USA
- Executive Director, Center of Excellence for Aging & Brain Repair, USA
- Professor, Distinguished University, University of South Florida, USA

SCIENTIST OR INVENTOR? ENTREPRENEURSHIP IN REGENERATIVE MEDICINE

Paul R. Sanberg

Senior Vice President for Research, Innovation & Economic Development, Executive Director, Center of Excellence for Aging & Brain Repair, and Distinguished University Professor, University of South Florida, USA

This presentation will provide an overview of some scientific studies in regenerative medicine that led to the translation of new pharmaceutical and cellular therapeutics utilizing stem cells, including cord blood cells, to clinical trials, patents, and commercialization. As an inventor and founder of several startup companies involved in cell therapy for degenerative disorders, and as a research administrator for a Top 50 U.S. research university, the author has learned to balance these multiple roles and the demands of academic scholarship, institutional research and entrepreneurship. Academics frequently encounter barriers to entrepreneurship within their departments and institutions due to a traditional academic culture that values scholarly publication above invention for tenure and promotion. As government support for academic research decreases, universities must look to industry, foundations, and philanthropies for funding, with relationships that can include intellectual property and return on investment, in order to carry out their studies. Encouraging faculty to translate their discoveries to patents and the marketplace requires a culture change in both the academic institution and the mindset of the faculty member. This has been enhanced through the founding of the National Academy of Inventors (NAI), a non-profit organization which works closely with the U.S. Department of Commerce and the U.S. Patent and Trademark Office to recognize and honor academic invention, and has 3,000 members and Fellows spanning more than 200 academic institutions worldwide. The NAI Fellows program is one of only a handful of honors available to academic inventors and is recognized as a highly prestigious award. The NAI has actively promoted a shift in the academic culture to consider the development of intellectual property and commercialization activity for tenure and promotion through publications in U.S. and international journals. The author also promotes invention in his role as an AAAS-Lemelson Invention Ambassador in the United States.

Rutledge Ellis-Behnke

Germany

Director, Nanomedicine Translational Think Tank,
Medical Faculty Mannheim of the University of Heidelberg, Germany

AC5 SURGICAL HEMOSTAT™ IS AN EFFECTIVE HEMOSTATIC AGENT IN ANTICOAGULATED ANIMALS USING A NON-COMPRESSIBLE, PENETRATING LIVER WOUND MODEL

Domokos Csukas, DVM[1], Rudolf Urbanics, MD, PhD[2,3], Annie Moritz, BSci[4], and Rutledge Ellis-Behnke, PhD[5,6,7]

[1]Dept. of Surgical Research and Techniques, Faculty of Medicine, Semmelweis University, Budapest, Hungary
[2]Nanomedicine Research and Education Center, Semmelweis University, Budapest, Hungary
[3]SeroScience Ltd., Budapest, Hungary
[4]Dept. of Psychology, University of Mannheim, Mannheim, Germany
[5]Dept. of Ophthalmology, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany
[6]Dept. of Brain & Cognitive Sciences, Massachusetts Institute of Technology, Cambridge MA
[7]Center of Excellence for Aging & Brain Repair, University of South Florida Morsani College of Medicine, Tampa FL

Intra-operative and postoperative bleeding is a major concern in surgical procedures for patients taking anticoagulant medications, or where anticoagulants are used to prevent potential life-threatening embolic complications. Heparin and other anticoagulants are used frequently and have an immediate effect on blood clotting, lasting 4 to 6 hours. Although synthetic self-assembling peptides have been shown to achieve rapid hemostasis in small animals, none have adequately addressed the potential for hemostasis in the presence of anticoagulant therapy in-vivo. Our goal was to investigate the hemostatic activity of a known synthetic self-assembling peptide in animals treated and untreated with anticoagulation therapy. Using a rat liver puncture model, animals were treated with known synthetic peptide AC5 Surgical Hemostatic Device™, or saline controls. Time-to-hemostasis and coagulation times were recorded in both anticoagulated and normal animals. Here we show that AC5™ was able to achieve rapid hemostasis equivalently in both anticoagulated and normal animals.

Hossein Hosseinkhani

USA

Professor, Graduate Institute of Biomedical Engineering,
National Taiwan University of Science and Technology, Taipei, Taiwan

ENGINEERING 3D HYDROGEL FOR BIOLOGICAL APPLICATION

H. Hosseinkhani

Graduate Institute of Biomedical Engineering, National Taiwan University of Science and Technology, Taipei, Taiwan

The increasing interest in biomaterials technology has stimulated the researchers to scrutinize biological elements and learn from nature. The ability to generate three-dimensional (3D) *in vitro* living organs that can mimic organ and tissue structure and function is of benefit for a variety of biological applications from basic biology to drug discovery, and will have great impact on the future of science to use human organs and tissues not only as new therapeutic approaches but also as intelligent biological tools for many applications such as early detection of newly formed diseases, next generation of diagnostic tools, and an alternative energy source called "bio-energy" devices. Many 3D models currently in practice, however, require expensive equipment, large sample volumes, long incubation times and/or extensive expertise, and the most disadvantages of them is that they are too far from the nature of human organs. Because of the above problems, research and development on drug discovery, regenerative medicine, biotech and pharmaceutical Industries are very costly and takes several years to bring a single drug/product to the marketing. The goal of our research is to merge biomaterials science, nanotechnology, and biological principles to generate 3D *in vitro* living organs to mimic organ/tissues in order to partially reduce the amount of *in vitro* and *in vivo* animal testing, clinical trials, and to solve the above problems. We propose to do all above costly and timely tests in a rapid and cheap way. At the nanoscale, we play with the chemistry and materials to fabricate novel type of hydrogels that are similar to human organs, infusing the cell-laden hydrogels with extracellular matrix (ECM) molecules and gradients of signaling molecules to influence cell development and aggregation. At microscales, we employ fabrication technologies borrowed from the semiconductor industry, such as photolithography, to mass-produce identical building blocks in a variety of shapes and sizes. These products will have to mimic the physical, chemical, and biological properties of natural organ and tissues at different scales, from molecules to cells to building blocks to organized clusters. In the present seminar, I'll present our new technology on the fabrication new devices for clinical and biological application.

Cheng-Wen Wu (吳成文)

Taiwan

- National Yang-Ming University, Taipei, Taiwan
- Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan
- National Health Research Institutes, Taipei, Taiwan

EMERGING TARGETS AGAINST DRUG-RESISTANCE OF LUNG CANCER VIA STEMNESS PATHWAYS

Cheng-Wen Wu[123]

[1]National Yang-Ming University, Taipei, Taiwan

[2]Academia Sinica:Institute of Biomedical Sciences, Taipei, Taiwan

[3]National Health Research Institutes, Taipei, Taiwan

Lung cancer is the leading cause of cancer-related mortality worldwide. Drug resistance and the highly-metastatic activity are the major reasons of treatment failure. Non-small cell lung cancer (NSCLC) accounts for ~75% of lung cancers, among which the lung adenocarcinoma (LAC) is the most common histological subtype (~40%). LAC is frequently associated with activating mutations in epidermal growth factor receptor (EGFR), and chemotherapy showed limited efficacy on this type of lung cancer. Although the development of EGFR Tyrosine Kinase Inhibitors (TKIs) has offered an improved progression-free survival in LAC patients, drug resistance invariably occurred. In addition, there are still large populations of lung cancers, such as Squamous-Cell Carcinoma (SCC) or LAC with wild-type EGFR, which are insensitive to EGFR-TKI and still lack effective target therapeutics.

Recent evidences have suggested that aberrant regulations of stemness pathways in cancer cells may be responsible for tumor-initiation, metastasis, and drug resistance. Our lab has focused for years on the roles and importance of stemness factors involved in lung cancer, such as OCT4, SOX2, NANOG, BMI-1, SHH/GLI1, miR-134, and miR-630, and the development novel therapeutics targeting these factors to address drug resistance. Our results showed that in lung SCC or LAC harboring wild-type EGFR, SOX2 is frequently highly expressed and associated with poor prognosis. SOX2 formed a positive feed-back loop with EGFR, and promoted chemoresistance through the anti-apoptotic factor BCL2L1. Thiostrepton, a natural cyclic oligopeptide antibiotic, has been identified to efficiently inhibit SOX2 expression and induced robust cell death. Specifically, Thiostrepton showed superior anti-cancer effect in SCC or LAC with high level of SOX2, as compared to other chemotherapy or target therapy drugs currently used in clinic. In lung LAC cells with acquired resistant to EGFR-TKI, we found that Hedgehog (HH) stemness pathway is frequently hyperactive and drives TKI resistance, mainly through inducing HGF expression and AKT phosphorylation. HH inhibitors, such as cyclopamine, significantly inhibited the growth of EGFR-TKI resistant cells.

In summary, our findings suggest that targeting stemness pathways may hold promise to address the current impasse in lung cancer treatment, such as drug resistance. Further studies to elucidate the interaction networks between oncogenic and stemness pathways will be required for designing more efficient target therapeutics.

Akon Higuchi

Japan

Professor, University Chair (Distinguished) Professor,
Department of Chemical & Materials Engineering,
National Central University, Taoyuan, Taiwan

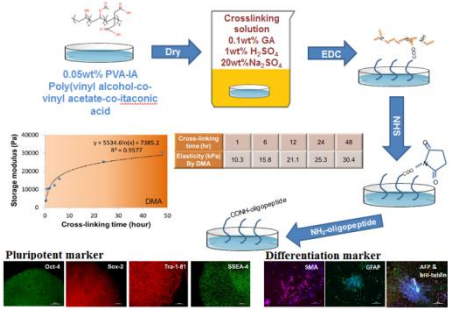
FEEDER-FREE CULTURE AND REPROGRAMMING OF HUMAN IPSCS ON DISHES GRAFTED WITH CELL ADHESION PEPTIDES AND HAVING DIFFERENT ELASTICITY

Akon Higuchi [*1, 2], *Murugan A. Munusamy*[2], *and Abdullah A. Alarfaj*[2]

[1] Department of Chemical and Materials Engineering, National Central University, Jhong-li, Taoyuan, Taiwan

[2] Department of Botany and Microbiology, King Saud University, Riyadh, Saudi Arabia

Human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs) have potentially therapeutic applications in the treatment of many diseases, due to their unique ability to differentiate into any type of somatic cell.1,2 For example, hESCs and hiPSCs have been differentiated into nerve cells that secrete dopamine and β cells that secrete insulin, and these cells can be transplanted for the treatment of Parkinson's disease and diabetes, respectively. The pluripotent nature of these cells could permit the development of a wide range of stem cell-based regenerative therapies and drug discovery platforms. However, the tentative clinical potential of hESCs and hiPSCs is restricted by the use of mouse embryonic fibroblasts (MEFs) as a feeder layer in the culture of these cells. The feeder-free cultures using synthetic biomaterials having nanosegments as stem cell culture materials offer more reproducible culture conditions and lower the cost of production without introducing xenogenic contaminants. Here we report that hiPSCs can be successively cultured without usage of a feeder layer of MEFs. hiPSCs were cultured on polyvinylalcohol-co-itaconic acid (PVA-IA) grafted with several nanosegments (KGGPQVTRGDVFTMP [cell-binding domain derived from vitronectin, oligoVN], GGNGEPRGDTYRAY [cell-binding domain from bone sialoprotein, oligoBSP], and GKKQRFRHRNRKG [heparin-binding domain, oligoHBD]). The hiPSC colony showed alkali phosphatase activity much clearly, and immunohistochemistry suggested that the hiPSCs were generated on PVA-IA dishes grafted with oligoVN and oligoBSP expressing pluripotent protein of SSEA-4. hiPSCs prepared on MEFs as well as PVA-IA dishes having nanosegments generated teratoma and embryonic bodies containing different cell types of the three germ layers. It was found that the optimal elasticity (1000~10,000kPa) and specific nanosegments (oligoVN and oligoBSP) of the cell culture dishes improve to keep pluripotency of hiPSCs on the dishes. Furthermore, we generated hiPSCs by transducing human adipose-derived stem cells (hADSCs) with a retrovirus or Sendai virus containing pluripotency genes, and the hiPSCs were cultured on synthetic dishes grafted with oligoVN (VN-dish). On the fourth day after transduction, the hADSCs transduced with pluripotency genes were transferred to VN-dishes for culture. The hiPSC colonies in the MEF-cultures were clearly observed at day 14 after transduction, whereas hiPSC colonies were detected on the VN-dishes after the cells were passaged. When 105 hADSCs were seeded on the dishes, the number of colonies generated on the MEFs was 120±28, while the number of colonies generated on VN-dishes was 25±8. Thus, the efficiency of hiPSC generation on the VN-dishes under feeder free conditions was lower than hiPSCs cultured on MEFs. However, the hiPSC could be successively generated on VN-dishes under feeder-free conditions.



Shih-Hwa Chiou (邱士華)

Taiwan

- Professor, The Institute of Pharmacology,
  National Yang-Ming University, Taipei, Taiwan
- Physcian Attending, Department of Medical Research and Education,
  Taipei Veterans General Hospital, Taipei, Taiwan

DEVELOPMENT OF CELLULAR REPROGRAMMING AND IPSC TECHNOLOGY AS PERSONALIZED MEDICINE-BASED PLATFORM

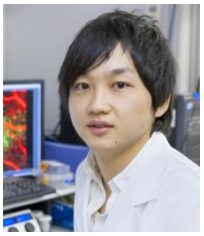
Shih-Hwa Chiou

Institute of Pharmacology, Institute of Clinical medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan
Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan

The development of induced pluripotent stem cells (iPSCs) has opened a new era for stem cell research. Ectopic expression of four key transcription factors (Oct4, Sox2, Klf4, and c-Myc) directly reprograms somatic cells into pluripotent cells, which exhibit similar characteristics as embryonic stem (ES) cells without ethical issues. The generation of induced pluripotent stem cells (iPSCs) is an innovative personalized-regenerative technology, which can transform own-self somatic cells into embryonic stem (ES)-like cells and the potential to differentiate into all cell types of three-dermal lineages. In addition, iPSCs could overcome immunological rejection since autologous patient-specific iPSCs can be easily derived. Moreover, how to quickly, efficiently, and safely produce specific-lineage differentiation from pluripotent-state cells and iPSCs is still an open question. To overcome this critical obstacle, we performed proteomic analysis to find that Parp1, a key factor for DNA repair, plays a crucial role in regulating the efficiency of cellular reprogramming. We show that knockdown of Parp1 and pharmacological inhibition of PARylation both reduced the efficiency of iPSC generation induced by Oct4/Sox2/Klf4/c-Myc. Notably, Parp1 is able to replace Klf4 or c-Myc to enhance the efficiency of iPSC generation. Furthermore, mouse iPSCs generated from Oct4/Sox2/Parp1-overexpressing MEFs formed chimeric offspring, suggesting that Parp1-based cellular reprogramming, not needed c-Myc or Klf-4, provided a more safer platform for generation iPSCs. Moreover, the generation of patient- or disease-specific iPSCs therefore holds promising potential for the drug industry and regenerative medicine. Following this concept with using iPSC technology, we have reprogrammed T cells from patients with dry type AMD into induced pluripotent stem cells (iPSCs) via integration-free episomal vectors and differentiated them into RPE cells that were used as an expandable platform for investigating pathogenesis of the AMD and *in-vitro* drug screening. Therefore, in contrast to cell transplantation therapies, the application of stem cells can further provide a platform for drug discovery and small molecular testing.

Takanori Takebe

Japan



- Associate Professor, Department of Regenerative Medicine, Yokohama City University, Japan
- Visiting Associate Professor, Stanford University Institute for Stem Cell Biology and Regenerative Medicine, USA

HUMAN IPSC-DERIVED ORGAN BUD BASED APPROACHES TOWARDS CLINICAL APPLICATION

Takanori Takebe

[1] Yokohama City University, Japan
[2]PRESTO, Japan Science and Technology Agency, Japan

Over the last decade, numerous publications have described protocols that can induce the cellular differentiation by sequential addition of combinatory factors such as hepatocytes, insulin-producing cells or dopaminergic neurons. However, conventional uni-directional cell induction approach ignores 3-D and chronological multicellular communications, which occur along with physiological cell differentiation during organogenesis. In order to derive therapeutically effective functional cells from stem cells, it is essential to develop a 4-D (spatiotemporal) culture platform, allowing the cells underwent developmental cellular interactions to follow the organogenesis including biophysical stimuli, biochemical and molecular signals and the spatial organization.

To this aim, we have recently showed that specified hepatic cells self-organized into three-dimensional organ buds in a dish by co-cultivated with stromal cell populations; human endothelial and mesenchymal progenitors, which are required for the initiation of hepatogenesis, the budding of the rudimentary liver (liver bud) in the foregut. By transplanting *in vitro* grown organ bud, we have demonstrated the vascularized and functional liver tissues in an immunodeficient animal. Furthermore, we examined the translatability of this principle to the other organ systems using embryonic tissue derived mixed progenitors. Surprisingly, recapitulation of endothelial-mesenchymal interaction in culture was shown to provide a widely conserved morphogenetic force against multiple tissue-derived progenitors, including pancreas, intestine, lung, heart, kidney, brain and even tumor tissue, resulting in the formation of 3D and self-organized tissues. The 3-D organ buds thus generated became immediately vascularized upon transplantation and self-organized into 3-D pancreatic and renal tissue functional architectures that resembled the original one, and exhibited therapeutic potential.

Considering a critical shortage of donor organs for treating end-stage organ failure, manipulation of autologous iPSCs holds great promise for regenerative medicine. However, classic clinical trials of cell transplantation, currently an important target of the stem-cell-based approach, have presented unsatisfactory results. Our proposed concept, *i.e.* organ-bud transplantation, offers an alternative approach to the generation of a three-dimensional, vascularized organ. This will highlight the enormous therapeutic potential using in vitro-grown organ-bud transplantation for treating organ failure. In this talk, I will summarize the state-of-art of these organ bud based approaches, and discuss their future application in regenerative medicine.

Paolo Fiorina

USA

- Assistant Professor-Harvard Medical School, USA
- Staff Scientist, Nephrology Division, Boston Children's Hospital, USA

UPDATE ON MSCS

Paolo Fiorina

Nephrology Division, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

Transplant Medicine, San Raffaele Hospital, Milan, Italy

Mesenchymal stem cells (MSC) are pluripotent stromal cells that have the potential to give rise to cells of diverse lineages. Interestingly, MSC can be found in virtually all postnatal tissues. The main criteria currently used to characterize and identify these cells are the capacity for self-renewal and differentiation into tissues of mesodermal origin, combined with a lack in expression of certain hematopoietic molecules. Due to their developmental plasticity, the notion of MSC-based therapeutic intervention has become an emerging strategy for the replacement of injured tissues. MSC have also been noted to possess the ability to impart profound immunomodulatory effects in vivo. Indeed, some of the initial observations regarding MSC protection from tissue injury once thought mediated by tissue regeneration may, in reality, result from immunomodulation. While the exact mechanisms underlying the immunomodulatory functions of MSC remain largely unknown, these cells have been exploited in a variety of clinical trials aimed at reducing the burden of immune-mediated disease. We are here summarizing the recent advances that have broadened our understanding of the immunomodulatory properties of MSC and provides insights as to their potential for clinical use as a cell based therapy for immune mediated disorders and in particular, type 1 diabetes (T1D).

Gun-Il Im

Korea

Professor, Dept of Orthopaedics,
Dongguk University Ilsan Hospital, Korea

CHONDROGENESIS FROM STEM CELLS

Gun-Il Im

Department of Orthopaedics, Dongguk University Ilsan Hospital, Republic of Korea

Stem cells have drawn attention as an attractive cell source for tissue regeneration. Adult stem cells including mesenchymal stem cells (MSCs) have been widely investigated as a cell source for cartilage tissue engineering. However, chondrogenic differentiation from adult stem cells has posed greater challenges than osteogenic differentiation. TGF-β has been used to induce chondrogenesis from MSCs, but the markers of hypertrophy increase along with chondrogenic markers in this setting. Inhibitor of hypertrophy such as PTHrP can be used to induce chondrogenesis while suppressing hypertrophy from MSCs. Recent advancement in the efficiency of nonviral gene transfer provides a means to induce effective chondrogenesis from adult stem cells. The nonviral gene transfer of SOX trio, the key transcription factors of chondrogenic differentiation, enhances the chondrogenesis from MSCs.

Microporation provides an easier and more efficient method for hard-to-transfect cells with its high transfection efficiency and reproducibility. The chondrogenic differentiation of MSC and adipose stem cells (ASCs) showed significant enhancement when SOX trio were co-transfected using microporation, while subsets with single gene transfer of SOX-5,-6,-or -9 did not show significant elevation. SOX trio co-transfection also decreased the hypertrophic marker type X collagen.

We have also developed a chondrogenic scaffold system in which a plasmid DNA scaffold containing the SOX trio genes was incorporated into a PLGA scaffold and slowly released to transfect ASCs seeded in the scaffold. The pDNA/PEI-PEG complex-incorporated PLGA/Pluronic F127 porous scaffolds were fabricated by a precipitation/particulate leaching method. PLGA scaffolds incorporated with SOX trio pDNA enhanced the chondrogenic differentiation while suppressing hypertrophy of seeded hASCs after 21 days of in vitro culture. Autologous ASCs/SOX trio pDNA-incorporated PLGA scaffolds promoted the healing of osteochondral defects after 8 weeks of in vivo implantation in the rabbit.

We have also tested if the retroviral gene transfer of SOX trio arrests the progression of surgically-induced osteoarthritis in a rat model. SOX trio-co-transduced ASCs in fibrin gel injected into the knee joints of rats with surgically-induced osteoarthritis. ASCs co-transduced with SOX trio significantly promoted the in vivo cartilage healing in osteochondral defect model, and prevented the progression of degenerative changes in surgically-induced osteoarthritis.

Induced pluripotent stem cells (iPSCs), generated from somatic cells by transduction of defined reprogramming transcription factors offer a new path to avoid the ethical controversy of using embryonic stem cells (ESCs). iPSCs function in a manner indistinguishable from ESCs by differentiating into cell types that are characteristic of the three germ layers. The author investigated the chondrogenic features of hiPSCs and examined the differences in the chondrogenesis between hiPSCs and human bone marrow-derived MSCs (hBMMSCs). Embryoid bodies (EBs) were formed from undifferentiated hiPSCs. After EBs were dissociated into single cells, chondrogenic culture was performed in pellets and alginate hydrogel. Chondro-induced hiPSCs were implanted in osteochondral defects created on the patellar groove of immunosuppressed rats and evaluated after 12 weeks. After 21 days of in vitro culture, greater glycosaminoglycan contents and better chondrocytic features including lacuna and abundant matrix formation were observed from chondro-induced hiPSCs compared to chondro-induced hBMMSCs. The expression of chondrogenic markers including SOX-9, type II collagen, and aggrecan in chondro-induced hiPSCs was comparable to or greater than chondro-induced hBMMSCs. A remarkably low level of hypertrophic and osteogenic markers including type X collagen, type I collagen and Runx-2 was noted in chondro-induced hiPSCs compared to chondro-induced hBMMSCs. hiPSCs had significantly greater methylation of several CpG sites in COL10A1 promoter than hBMMSCs in either undifferentiated or chondro-induced state, suggesting an epigenetic cause of the difference in hypertrophy. The defects implanted with chondro-induced hiPSCs showed a significantly better quality of cartilage repair than the control defects. The majority of cells in the regenerated cartilage consisted of implanted hiPSCs. While adult stem cells have been the mainstay cell source in chondrogenesis, iPSCs demonstrates several desirable chondrogenic characteristics. iPSCs may be considered as an alternative cell source for cartilage tissue engineering provided that safety issues are resolved.

Kwok Fai So

Hong Kong

- GHM Institute of CNS Regeneration, Jinan University, Guangzhou, China
- Department of Ophthalmology, Jessie Ho Professor in Neuroscience, The University of Hong Kong, Hong Kong, SAR China

PHYSICAL EXERCISE-INDUCED HIPPOCAMPAL NEUROGENESIS AND ANTIDEPRESSANT EFFECTS ARE MEDIATED BY THE ADIPOCYTE HORMONE ADIPONECTIN

Kwok Fai So

GHM Institute of CNS Regeneration, Jinan University, Guangzhou, China
Department of Ophthalmology, Jessie Ho Professor in Neuroscience, The University of Hong Kong, Hong Kong, SAR China

Adiponectin (ADN) is an adipocyte-secreted protein with insulinsensitizing, antidiabetic, antiinflammatory, and antiatherogenic properties. Evidence is also accumulating that ADN has neuroprotective activities, yet the underlying mechanism remains elusive. Here we show that ADN could pass through the blood–brain barrier, and elevating its levels in the brain increased cell proliferation and decreased depression-like behaviors. ADN deficiency did not reduce the basal hippocampal neurogenesis or neuronal differentiation but diminished the effectiveness of exercise

in increasing hippocampal neurogenesis. Furthermore, exerciseinduced reduction in depression-like behaviors was abrogated in ADN-deficient mice, and this impairment in ADN-deficient mice was accompanied by defective running-induced hosphorylation of AMP-activated protein kinase (AMPK) in the hippocampal tissue.

In vitro analyses indicated that ADN itself could increase cell proliferation of both hippocampal progenitor cells and Neuro2a neuroblastoma cells. The neurogenic effects of ADN were mediated by the ADN receptor 1 (ADNR1), because siRNA targeting ADNR1, but not ADNR2, inhibited the capacity of ADN to enhance cell proliferation. These data suggest that adiponectin may play a significant role in mediating the effects of exercise on hippocampal neurogenesis and depression, possibly by activation of the ADNR1/AMPK signaling pathways, and also raise the possibility that adiponectin and its agonists may represent a promising therapeutic treatment for depression.

Cesar V. Borlongan

USA

Department of Neurosurgery and Brain Repair,
University of South Florida, Morsani College of Medicinee, Tampa, USA

CELL-BASED THERAPIES FOR TRAUMATIC BRAIN INJURY: TARGETING THE SECONDARY INFLAMMATION-MEDIATED CELL DEATH

Cesar V. Borlongan

Department of Neurosurgery and Brain Repair, University of South Florida Morsani College of Medicinee, Tampa, USA

Cell-based therapeutics have emerged as potential treatments for a variety of neurological disorders, including traumatic brain injury (TBI), which is a major cause of death and disability in the United States. A cascade of secondary cell death events, especiialy neuroinflammation, presents as an attractive target for cell-based therapeutics. Here, I will discuss two novel concepts of cell-based therapies that hold promise in abrogating neuroinflammation associated with TBI. First, recent evidence suggests that exogenous Notch-induced bone marrow stem cells form “biobridges” that facilitate the proper migration of endogenous stem cells from the neurogenic niche to the site of cortical injury following the controlled cortical impact model of TBI in adult rats. Such exogenous stem cell-paved biobridges are enriched with extracellular matrix (ECM) stabilizing the structure and organization to the injured tissues and also guiding the migration of and intercellular communication with the endogenous stem cells. Our results, in collaboration with SanBio Inc., indicate that the injured brain not only presents with abnormal composition and structure of the ECM that contributes to the failure of directed endogenous cell migration towards the injured site, but that TBI-mediated disruption of ECM amplifies neuroinflammation ultimately hindering the homing of endogenous stem cells to the damaged tissue. Accordingly, treatments such as the formation of biobridges by Notch-induced bone marrow stem cells designed to stabilize the ECM structure and to harness the ECM’s ability to dampen neuroinflammation stand as potent TBI therapeutics. Second, we advance a paradigm-shifting TBI treatment via a novel mechanism of “nuclear sequestration of inflammatory cell death signals” (i.e., withholding cell death signals in the nucleus to inhibit their propagation to the cytoplasm), which could potentially enhance cell survival and rescue damaged cells in the TBI brain. Building upon the concept that the nucleus is often referred to as the “brain” of the cell, we posit that the cell death signal is communicated to the cell nucleus through the nuclear pore, which serves as a critical gate between the nucleus and cytoplasm, and regulates the entry and exit of most proteins involved in the propagation of cell damage, as well as in mounting a response to the cell injury. The transit of large proteins (>42kD) through the nuclear pore requires carrier proteins, with Exportin 1 (XPO1) identified as a major carrier protein and recently shown to be dramatically upregulated in neural cells

juxtaposed to inflammatory cells following TBI. These interesting data suggest that nuclear export underlies the progressive inflammation-associated pathology of TBI. Here, I discuss our approach designed on the inhibition of XPO1 in an effort to sequester proinflammatory signals in the nucleus after TBI. In collaboration with Karyopharm Therapeutics, we demonstrated that a novel class of potent, small molecule, brain penetrating inhibitors of XPO1, termed Selective Inhibitor of Nuclear Export (SINE) compounds, can sequester cell surviving signals (FOXP1, AKT, among other therapeutic proteins), as well as cell death signals (NFkB) within the nucleus after TBI, resulting in reduced inflammation and improved behavioral recovery in SINE compound-treated TBI animals. Because the SINE compound selinexor is currently being tested in the clinic for cancer patients (i.e., SINE compounds sequester tumor suppressor proteins within the nucleus thereby restoring genomic surveillance and cell checkpoint mechanisms), our proposed lab-to-clinic translational research may expedite the entry of specific SINE compounds, such as KPT-350 that we used in TBI models, as safe and effective drugs, with evidence-based mechanism of action. An in-depth investigation into the nucleus' ability to sequester cell death and cell survival signals will aid in our understanding of how the cell commits to a death or life fate, and may provide insights on how an individual may progress to a neurodegenerative disorder or to a recovery from a pathological injury, such as TBI. Part of this SINE's therapeutic mechanism may be driven by nuclear sequestration of IkB – the inhibitor of NFkB, in that by blocking NFkB transcriptional activity may limit proinflammatory signals thereby protecting the cells in the TBI impacted and peri-impacted areas. In conclusion, cell-based therapies designed to stabilize the ECM or to foster nuclear sequestration of cell death signals represent novel therapies for TBI and other inflammation-plagued neurological disorders.

Ing-Ming Chiu (邱英明)

Taiwan

Distinguished Investigator, Institute of Cellular and System Medicine,
National Health Research Institutes, Miaoli, Taiwan

STEM CELLS, NEUROKINES AND BIOMATERIALS IN NERVE INJURY AND REPAIR

Ing-Ming Chiu

Division of Regenerative Medicine, Institute of Cellular and System Medicine, National Health Research Institutes, Miaoli, Taiwan

Fibroblast growth factor 1 (FGF1) has been shown to regulate cell proliferation, cell division and neurogenesis. We showed that FGF1 gene 1B promoter-driven green fluorescence protein (F1B-GFP) is active in NSCs. We developed a novel approach to isolate neuronal progenitor cells from mouse and human brain tissues using F1B-GFP reporter plasmid. Cells that were double-positive for CD133 and F1B-GFP differentiated more efficiently to the neuronal lineage than $CD133^{+}$/F1B-GFP^{-} cells. We have also shown that F1B-GFP^{+} NSCs, when combined with FGF1 and nerve conduit, could promote the repair of damaged sciatic nerves in mice and rats. These studies could shed light on the role of FGF1 in neurogenesis and neural repair. We further showed that adaptor protein SH2B1, when combined with miRNA124, BRN2 and MYT1L (IBM), can enhance neurite outgrowth of iNs reprogrammed from adult human fibroblasts. These SH2B1-enhanced iNs (S-IBM) showed typical neuronal morphology, expressed canonical neuronal markers and functional proteins for neurotransmitter release. Importantly, SH2B1 accelerated mature process of functional neurons and exhibited action potentials as early as Day 14. Without SH2B1, the IBM iNs do not exhibit proper action potentials until Day 28. Our data demonstrate that SH2B1 can enhance neurite outgrowth and accelerate the maturation of human iNs under defined condition. This reprogramming approach with SH2B1 could facilitate the application of iNs in regenerative medicine, *in vitro* disease modeling, and new drug discovery.

To further identify the function of F1B promoter in the brain, we generated F1B-GFP transgenic mice. Using RT-PCR techniques, we found that GFP was expressed in whole brain of 8-week old mice. Immunohistochemistry (IHC) was conducted to identify the F1B-GFP^{+} cells in mouse brains. The IHC results from brain sections of 12-week old mice showed F1B-GFP^{+} cells were expressed in two distinct populations. One population was ependymal cells of ventricular system, including lateral ventricles (LV), dorsal third ventricle (D3V), third ventricle (3V), aqueduct (Aq) and central canal (CC). The second population of F1B-GFP^{+} cells was neurons throughout the brain. We found that a part of F1B-GFP^{+} cells can express tyrosine hydroxylase, the marker for dopaminergic neurons. In addition, we showed that F1B-Cre transgenic mice, mated with Rosa26 transgenic mice to detect β-galactosidase activity, also exhibited the same expression pattern as F1B-GFP mice. Taken together, we successfully used mouse as an animal model to express human FGF1 gene promoter, F1B, and the F1B-GFP^{+} cells are ependymal and neuronal cells. This F1B-GFP transgenic mouse might provide a novel tool to understand the function of FGF1 in brain development and in related diseases.

Ken-Ichiro Seino

Japan

Division of Immunobiology Institute for Genetic Medicine,
Hokkaido University, Sapporo, Japan

INDUCTION OF REGULATORY MACROPHAGE-LIKE CELLS FROM MOUSE PLURIPOTENT STEM CELLS THAT CAN CONTRIBUTE TO SUPPRESS ALLOGENEIC IMMUNE RESPONSES

Ken-ichiro Seino

Division of immunobiology Institute for Genetic Medicine, Hokkaido University, Sapporo, Japan

Objective: The promise for cell replacement therapy using pluripotent stem cells (PSCs) as a donor source has increased. However, when non-self derived PSCs were used, immune suppression should be required. In this study, we examined a concept that some immunosuppressive cells could be induced from PSCs and those cells could prevent the allogeneic immune rejection of the PSCs-based transplantation.

Materials and methods: We generated iPSCs from mouse fibroblasts by introducing Yamanaka four transcription factors. The iPSCs were differentiated on OP9 feeder cells and with some cytokines including GM-CSF. We could obtain macrophage-like cells which firmly adhered to the bacteriologic petri dish surface by a prolonged culture with IL-4 and addition of LPS. We examined their effect on allogeneic T cell responses.

Results: The differentiated cells expressed molecules such as CD45, CD11b, CD11c, or F4/80, but not Gr-1, MHC class I, nor II. They also expressed some immunosuppressive molecules such as arginase I and Nos2. When added the cells to allogeneic mixed lymphocyte reaction (MLR), they efficiently suppressed allogeneic T cell proliferative response. When the cells injected to recipients of allogeneic transplantation, they significantly prolonged the survival of allogeneic grafts.

Conclusion: We successfully induced regulatory macrophage-like cells from mouse iPSCs that can contribute to suppress allogeneic T cell immune responses. These results suggest a new insight for development of an immune-regulatory strategy in cell replacement therapy using PSCs.

Chou Chai

Singapore

Associate Research Scientist,
National Neuroscience Institute, Singapore

UMBILICAL CORD LINING CELLS-DERIVED INDUCED PLURIPOTENT STEM CELLS AS A SOURCE OF CELLS FOR CELL REPLACEMENT THERAPY IN NEURODEGENERATIVE DISEASES

Chai C.[1], Phan T.T.[3], and Lim K.L[1,2,4]

[1]Department of Research, National Neuroscience Institute, Singapore

[2]Duke-NUS Graduate Medical School, Singapore, Singapore

[3]Department of Surgery, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

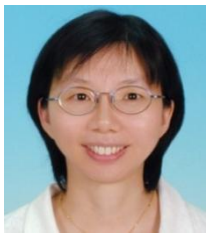
[4]Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Cell replacement therapy holds tremendous promise for the treatment of neurodegenerative diseases such as Parkinson's Disease (PD), Alzheimer's Disease and amyotropic lateral sclerosis. However, at present, the lack of a reliable and suitable source of donor cells has limited the widespread application of this treatment approach in the clinic. The advent of induced pluripotent stem cell (iPS) technology has opened up the possibility of an unlimited source of autologous cells for cell replacement therapy and regenerative medicine. Based on the knowledge that iPS can inherit certain properties from their parental somatic cells via epigenetic transmission, we postulate that iPS derived from tissues that inherently display reduced immunogenicity and that are genetically pristine would present an ideal universal cell source for allogeneic transplantation. The human umbilical cord displays certain degree of immune privilege consistent with its functions in mediating interactions across the feto-maternal interface. Additionally, its relative nascence implies that it has accumulated less de novo somatic mutations compared to adult cells undergoing the aging process. Taking advantage of these beneficial properties, we derived transgene integration- and feeder-free iPS from epithelial and mesenchymal stem cell-like cells isolated from the subamniotic lining of the human umbilical cord. Collectively designated as Cord Lining iPS (CLiPS), these iPS fulfill the morphological, phenotypic and functional criteria for human pluripotent stem cells. When subjected to specific differentiation protocols, CLiPS showed robust differentiation into neurons (ectoderm), cardiomyocytes (mesoderm) and hepatocytes (endoderm). We further demonstrated that CLiPS can be directed to differentiate into dopaminergic neurons, the specific neuronal subpopulation affected in PD. Transplantation of CLiPS-derived neuronal precursors primed towards the dopaminergic fate into the brains of normal adult mice suggest that these cells can survive in an immunocompetent host for up to a month in the absence of pharmacologic immunosuppression. In addition, we showed that CLiPS-derived neuronal precursors can engraft in lesioned brain regions of a 6-hydroxydopamine mouse model of PD. Our results suggest that CLiPS may be a suitable source of donor cells for allogeneic cell replacement therapy for neurodegenerative diseases. Our findings have important implications for the growing trend of umbilical cord tissue banking.

Shan-Hui Hsu (徐善慧)

Taiwan

Distinguished Professor and Director,
Institute of Polymer Science and Engineering,
National Taiwan University, Taipei, Taiwan



TISSUE ENGINEERING AND 3D PRINTING: SEEKING FOR NOVEL PRINTING MATERIALS

Shan-hui Hsu

Distinguished Professor and Director, Institute of Polymer Science and Engineering, National Taiwan University, Taipei, Taiwan

3D printing has many advantages in fabrication of tissue engineering scaffolds and parts for biomedical applications, including fast fabrication, high precision, and customized production. The commercial products available for biomedical 3D printing are still very limited so far. We purpose a new printing material which is water-based polyurethane (PU) nanodispersion based on biodegradable polyesters. The microstructure can be physico-chemically characterized to reveal the possible solidification mechanisms. The dispersion has a low viscosity below room temperature and may undergo solidification by varying the environmental temperatures after printing. We demonstrate that this unique platform can serve as a category of smart elastic biodegradable printing material for 3D printing.

Shiaw-Min Hwang (黃效民)

Taiwan

Senior Scientist and Associate Head,
Bioresource Collection and Research Center (BCRC)/
Food Industry Research and Development Institute, Hsinchu, Taiwan

THERAPEUTIC POTENTIAL OF AMNIOTIC FLUID STEM CELLS IN NEUROGENESIS

Ming-Song Tsai[1], Yu-Jen Chang[2], Li-Feng Hsu[2], Tzyy-Wen Chiou[3], and Shiaw-Min Hwang[2]

[1]Prenatal Diagnosis Center, Cathay General Hospital, Taipei, Taiwan
[2]Bioresource Collection and Research Center, Food Industry Research and Development Institute, Hsinchu, Taiwan
[3]Department of Life science, National Dong Hwa University, Hualien, Taiwan

Mesenchymal stem cells (MSCs) are a population of multipotent cells with the capacity of self-renewal and differentiation potentials into various tissue lineages including osteoblasts, chondrocytes, adipocytes, smooth muscle cells, even neurons and hepatocytes etc. MSCs can be isolated from many tissues. Recent findings extend our understanding of the remarkable plasticity of MSCs. This has raised the new strategies for cell therapy and regeneration medicine. However, it is well accepted that the frequency and functionality of stem cells are decreased along with ages. Considering accessibility and the youngest sources, we have developed a two-stage culture protocol to isolate amniotic fluid stem cells (AF-SCs) from amniocentesis. AFSCs exhibit similar phenotypes of surface antigens with bone marrow MSCs. AFSCs can differentiate into osteoblasts, chondrocytes, and adipocytes efficiently. Surprised but not unexpected that AFSCs express Oct-4, Sox-2 and Nanog, which are embryonic stem cell markers for pluripotency. AFSC At the level of single clonal analysis, AFSCs could also be induced into neuron-like cells with dopamine-releasing capability. AFSCs do not express HLA-II even under gamma-interferon stimulation. When transplanted, AFSCs show behavior improvement in Parkinsonism rat model. Considering the proliferation capability, genomic stability and non-tumorigenesis, AFSCs is recognized as a unique and promising cell source for the study of neurogenesis and therapeutic application.

(Acknowledgement: MOST 103-2325-B-080-001)

Wise Young

USA

- Founding Director and Professor,
  W.M. Keck Center for Collaborative Neuroscience,
  Rutgers University, New Jersey, USA
- Distinguished Visiting Professor, The University of Hong Kong,
  Hong Kong

LUMBOSACRAL SPINAL CORD INJURY

Wise Young, Dongming Sun, Sam Wen

W. M. Keck Center for Collaborative Neuroscience, Rutgers State University of New Jersey, Piscataway, New Jersey, USA

If one were to examine the statistics of spinal cord injury, one would never suspect that lumbosacral spinal cord injuries (SCI) account for about a third of human SCI. In the United States, about 40% of SCI are cervical, 45% are thoracic, and 15% are lumbar. Injuries to the spine below L1 vertebra usually cause cauda equina injuries, since the spinal cord ends just below L1. Based on this information, one would think that lumbosacral spinal cord injury is relatively rare. Actually, lumbosacral SCI are quite common because the lumbosacral enlargement is located from T11 through L1. Injuries to T10, T11, T12, and L1 spine injure the lumbosacral spinal cord. Lumbosacral SCI is devastating, not only because it paralyzes leg muscles and pelvic organs but because it damages motor centers for crucial functions, including locomotion (L2), micturition (S1), ejaculation (S2-3), and defecation (S4-5). Regeneration of long tracts alone will not restore function. Replacement and regeneration of interneurons and motoneurons is necessary. Unfortunately, there is no standardized animal model of lumbosacral SCI available. We therefore created the first standardized rat lumbosacral SCI model and quantitative outcome measures to assess regeneration and recovery in the model. Using retrograde labelling of the anterior tibial and gastrocnemius branches of the sciatic nerves, we were able to quantify the number of motoneurons damaged by a 10-gram weight dropped 12.5 or 25 mm onto L3-4 spinal cord exposed by a T12-T13 laminectomy of the rat. These two contusions result in consistent graded losses of motoneurons that result in atrophy of the anterior tibial and gastrocnemius muscles, as well as loss of foot function that could be readily quantified from footprint changes. New therapeutic approaches to treating this model will be discussed.

Sameer Bakhshi

India

Professor, Department of Medical Oncology,
Dr. B. R. A. Institute Rotary Cancer Hospital,
All India Institute of Medical Sciences, New Delhi, India

STEM CELL TRANSPLANTATION IN PEDIATRIC MALIGNANCIES: AN EXPERIENCE FROM INDIA

Prof. Sameer Bakhshi

Department of Medical Oncology, Dr. B. R. A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India

Stem cells are used in malignancies for treatment mostly in relapse and refractory malignancies. Allogenic transplantation is used wherein primarily the malignancy involves the stem cells. Autologous transplantation on the other hand is utilized as a rescue wherein high doses of chemotherapy are administered to patients in a relapse setting.

Stem cell transplantation was initiated in India in 1983. The department of Medical Oncology at the cancer center of AIIMS, which is the premier medical institution of India, performed the first stem cell transplant in early 1990s. The department is credited with performing the **first peripheral blood stem cell transplantation** as also the **first whole blood transplant** in India. Since then the cancer center of AIIMS, namely, Dr. BRA Institute Rotary Cancer Hospital, has emerged as perhaps the largest transplant center in the country for malignant disorders and is currently performing more than 8-9 transplants every month.

Although pediatric stem cell transplants were also performed in the initial period but they have been routinely performed since 2005. The center has performed more than 160 stem cell transplants for various pediatric malignancies since 2005. Further, the center has also been performing cord blood stem cell transplants since last 3 years. In this presentation, the various indications, challenges and results of pediatric autologous, matched related and cord blood stem cell transplantation at AIIMS is discussed.

Notably only 30% of patients who require an allogenic transplantation have a matched sibling donor. Thus in these situations, the alternatives include matched unrelated donor and/or cord blood stem cell transplantation. Specifically the challenges faced by India are also highlighted with respect to stem cell transplantation; further, the presentation also brings out the potential sources for cord blood banking and the emerging role of cord blood transplantation in India.

Xiaosong Gu

China

- Director, Jiangsu Key Laboratory of Neuroregeneration of Nantong University, China
- Honorary President, Chinese Society, Anatomical Sciences (CSAS), China
- Chief, Regenerative Medicine Branch, CSAS, China

THE APPLICATION OF BIODEGRADABLE MATERIALS-BASED TISSUE ENGINEERED NERVE IN NERVE REPAIR

Xiaosong Gu

Jiangsu Key Laboratory of Neuroregeneration, Co-innovation Center of Neuroregeneration, Nantong University, China

Peripheral nerve defect leads to a high disability rate. The functional reconstruction of injured nerve is an important issue in regenerative medicine.

Based on the mechanisms underlying peripheral nerve regeneration and the properties of biomaterials, we have developed a natural chitosan nerve graft that biodegrades at a controlled speed, for repairing injured peripheral nerve. Chitosan conduit satisfies the biological and physicochemical requirements of physical scaffold of tissue engineered nerve graft, such as biocompatibility, biodegradability, permeability, biomechanical properties, surface properties, and low immunogenicity, and thus is used in our laboratory as an ideal neural scaffold. The application of chitosan conduit allows sufficient exchange of nutrient and gas, benefits the growth of blood vessel, and promotes and guides the oriented growth of nerve fibers. The biodegradation product of chitosan, chitooligosaccharide, promotes the adhesion and growth of neural cells as well as the proliferation and migration of Schwann cells. Our recent studies demonstrated that its neuroregenerative effect is through the regulation of microRNAs.

Based on dog experiments, the results were observed that the sciatic nerve truck had been reconstructed with restoration of nerve continuity, functional recovery for conducting electrical impulses and transporting materials, and re-innervations of target skeletal muscle, which improved the locomotion activities of the operated limb.

With the approval from the Chinese State Food and Drug Administration (SFDA) into clinical trials, we have launched a prospective randomized controlled multicenter study for the clinical use of chitosan-based nerve grafts, getting satisfying functional recovery.

Ling Wei

USA

Professor and Chair, John E. Steinhaus,
Emory University School of Medicine, USA

WNT-3A SIGNALING MEDIATED NEUROPROTECTION AND REGENERATIVE ACTIVITIES AND FUNCTIONAL RECOVERY AFTER BRAIN INJURY

Ling Wei

Departments of Anesthesiology and Neurology, Emory University School of Medicine, Atlanta, GA, USA

Wnt signaling is a conserved pathway for neuronal identity and expansion of neuronal progenitors during neural development. However, the role of Wnt signaling in brain repairs after stroke and traumatic brain injury has been largely unknown. We hypothesized that Wnt-3a would play an important role for neurogenesis and brain repair following brain injury. Animals were subjected to a focal ischemic stroke or controlled cortical impact targeting the sensorimotor cortex. The Wnt-3a recombinant protein was intranasally delivered for 3 to 7 days after injury. Functional behavior assessments were performed 1 month later. We observed that Wnt-3a protected neurons and reduced infarct/contusion volume through the poly-ADP-ribosylating tankyrases regulation. In addition, Wnt-3a protected neural stem cells, stimulated endogenous neurogenic activity through Wnt/beta-catenin cannonical pathway to promote neuroblast migration from the SVZ. In a combination with physical therapy of whisker stimulation, Wnt-3a showed reinforced regenerative effects via beta-catenin-mediated transcription and BDNF-mediated regenerative activities. As a result of a series of regeneratic activities including neurogenesis, angiogenesis, and neurovascular unit remodeling, Wnt-3a treatment promoted local cerebral blood flow and sensorimotor functional recovery. The therapy also attenuated the sleep disorder following cerebral injury. In neonatal stroke models, the social activity impaiment developed after stroke was improved after Wnt-3a administration. Many of these benefits were blocked by selectively inhibiting Wnt signaling using Dkk-1 and/or XAV939. It is concluded that the Wnt-3a signaling is a critical contributor to neuroprotection and endogenous neural regeneration leading to functional recovery after brain injury.

Yi-Juang Chern (陳儀莊)

Taiwan

Distinguished Research Fellow, Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan

ABERRANT ASTROCYTES CAUSE INFLAMMATION AND IMPAIR VASCULAR REACTIVITY IN HUNTINGTON'S DISEASE

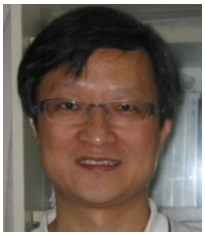
Yijuang Chern

Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan

Huntington's disease (HD) is an inherited neurodegenerative disease caused by the mutant *Huntingtin* gene (mHTT), which harbors expanded CAG repeats. We previously reported that the brain vessel density is higher in mice and patients with HD than in controls. The present study determines whether the vascular function is altered in HD and characterizes the underlying mechanism. The brain vessel density and vascular reactivity (VR) to carbogen challenge of HD mice were monitored by 3D ΔR_2-mMRA and BOLD/FAIR MRI, respectively. The amount of vascular endothelial growth factor (VEGF)-A and the pericyte coverage were determined by immunohistochemistry and ELISA in human and mouse brain sections, primary mouse astrocytes and pericytes, and human astrocytes derived from iPSC. Expression of mHTT in astrocytes and neurons are sufficient to increase the brain vessel density in HD mice. BOLD and FAIR MRI revealed gradually impaired VR to carbogen in HD mice. Astrocytes from HD mice and patients contained more VEGF-A, which triggers proliferation of endothelial cells and may be responsible for the augmented neurovascular changes. Moreover, an astrocytic inflammatory response, which reduces the survival of pericytes through an IκB kinase- dependent pathway, mediate the low pericyte coverage of blood vessels in HD brains. Our findings suggest that the inflammatory-prone HD astrocytes provide less pericyte coverage by promoting angiogenesis and reducing the number of pericytes and that these changes can explain the inferior VR in HD mice. The resultant impaired VR might hinder cerebral hemodynamics and increase brain atrophy during HD progression.

Young-Ji Shiao (蕭永基)

Taiwan



- Associate Investigator, National Research Institute of Chinese Medicine, Ministry of Health and Welfare, Taipei, Taiwan
- Part-time Associate Professor, Institute of Biopharmaceutical Science, National Yang-Ming University, Taipei, Taiwan

---

PROMOTING ADULT NEUROGENESIS AS A STRATEGY TO AMELIORATE NEURODEGENERATIVE DISEASE

Tsai-Teng Tzeng[1] and Young-Ji Shiao[1,2]

[1] Institute of Biopharmaceutical Science, National Yang-Ming University; Taipei, Taiwan
[2] Division of Basic Chinese Medicine, National Research Institute of Chinese Medicine, Taipei, Taiwan

Adult neurogenesis is a lifelong process with a decreasing rate of stem cell proliferation and differentiation in aging that result in cognition impairment. In AD patients, the presence of amyloid-β (Aβ) peptide in the brain inhibits this process. *Hericium erinaceus* is an edible and medicinal mushroom with various pharmacological activities. Compounds isolated from its fruiting bodies and mycelia exhibit a potent activity to stimulate nerve growth factor expression and secretion *in vitro* and *in vivo*. Recent studies demonstrated anti-dementia activity of its fruiting bodies in mice with cognitive deficits induced by Aβ and in people with mild cognitive impairment. However, the effect and mechanism of *H. erinaceus* mycelia on Alzheimer's disease are remained unclear. In this study, we examined the effect of *H. erinaceus* mycelia (HE-My) and its components, the ethanol extract (HE-Et) and isolated pure compound erinacine A (HE-A) on Aβ-related pathologies in APPSWE/PS1ΔE9 transgenic mice. Female mice (21-23 weeks old) were fed with HE-My, HE-Et or HE-A for 30 days. The Aβ accumulation was detected by immunohistochemistry, thioflavin S staining and enzyme-linked immunosorbent assay. The inflammatory cells were detected by GFAP- and Iba-1immunohistochemistry. The results showed that HE-A significantly attenuated both the Aβ plaque loading in cerebral cortex and hippocampus and the level of insoluble Aβ in the homogenized cerebral cortex. The effects may mediated by microglial clearance. On the other hand, the aberrant neurogenesis in APPSWE/PS1ΔE9 transgenic mice was not significantly ameliorated by the administration of HE-A, despite which promoted neurogenesis in the wild type mice, elevated the level of neuroplasticity, and protected neurons against Aβ-mediated neurotoxicity. Interestingly, HE-Et may promote the maturation of newborn neurons and HE-My may reduce the level of insoluble and soluble Aβ in the homogenized cerebral cortex. Our present data highlighted the potentials of *H. erinaceus* mycelia on the therapy of Alzheimer's disease and on pro-neurogenic and nootropic activities.

Mari Dezawa

Japan

Professor and Chair,
Dept. of Stem Cell Biology and Histology &
Dept. of Anatomy and Anthropology,
Tohoku University Graduate School of Medicine, Japan

MUSE CELLS AND THEIR POSSIBLE APPLICATION TO BOTH AUTOLOGOUS AND ALLOGENIC TRANSPLANTATION THERAPY

Mari Dezawa

Department of Stem Cell Biology and Histology, Tohoku University Graduate School of Medicine, Sendai, Japan

We discovered non-tumorigenic pluripotent stem cells, Multilineage differentiating Stress Enduring (Muse) cells, that reside in the bone marrow and adipose tissue, and are collectable as SSEA-3(+) cells. They correspond to several percent of mesenchymal stem cells collected from these tissues. They are stress-tolerant, express pluripotency markers despite low telomerase activity, and are able to self-renew and generate cells of all three germ layers from a single cell. A highly useful feature of Muse cells is their specific ability to detect damage signals, which allows them to migrate toward and home into damaged tissues when infused into the peripheral blood stream where they can spontaneously differentiate into cells compatible with the homed-into tissue. These activities were confirmed in models of stroke, fulminant hepatitis, and skin injury. In contrast, these effects are not recognized in remainder of mesenchymal cells, namely non-Muse cells.

While Muse cells have a lot of strong points, the possibility of Muse cells will extend extensively if they are able to apply to allo-transplantation as well as to autologous transplantation. Mesenchymal stem cells (MSCs) are already applied to allo-transplantation in graft-versus-host disease because of their strong immunosuppression activity. Here we evaluated immunosuppressive activity of Muse cells. Human bone marrow-Muse cells demonstrated substantial suppression activities for monocytes-denderitic cell differentiation, and suggested to stimulate regulatory and helper T cells. Furthermore, xenotransplantation of human Muse cells into mouse chronic kidney disease model demonstrated renal function recovery and integration and differentiation of human Muse cells in the glomerulus for up to 7 weeks. Therefore, Muse cells are suggested to have immunosuppression activity, and thus are able to be applied to allo-transplantation.

Tse-Hua Tan (譚澤華)

Taiwan

Distinguished Investigator / Director,
Immunology Research Center,
National Health Research Institutes, Miaoli, Taiwan

MAP4K KINASES AND DUSP PHOSPHATASES IN INFLAMMATION AND T CELL-MEDIATED DISEASES

Tse-Hua Tan

Immunology Research Center, National Health Research Institutes, Miaoli, Taiwan

The c-Jun N-terminal kinases (JNKs) belong to the mitogen-activated protein kinase (MAPK) superfamily. JNKs play crucial roles in cell proliferation, differentiation, stress responses, and apoptosis. JNK kinase activity can be activated by diverse stimuli, including growth factors, cytokines, environmental stresses, and apoptotic stimuli. MAPKs are regulated by various MAP kinase phosphatases (MKPs), which belong to a subfamily of dual-specificity phosphatases (DUSPs). We discovered that DUSP22/JKAP and DUSP14/MKP6 are negative regulators of T cell signaling by inhibiting Lck tyrosine kinase and TAB1/TAK1 kinase complex, respectively. DUSP22 knockout mice spontaneously develop systemic inflammation and autoimmunity.

MAP kinase kinase kinase kinases (MAP4Ks) are a subfamily of mammalian Ste20-like serine/threonine protein kinases that activate the JNK-MAPK kinase cascade. We have cloned and characterized the roles of three MAP4Ks, namely HPK1 (MAP4K1), GLK (MAP4K3) and HGK (MAP4K4) in T-cell signaling pathways and immune regulation. HPK1 (MAP4K1) is a negative regulator of T-cell signaling by phosphorylating the T-cell adaptor SLP-76, leading to SLP-76 degradation and attenuation of T-cell signaling. We also discovered that conditional knockout of HGK (MAP4K4) in T cells results in TRAF2 upregulation and subsequent induction of inflammatory IL-6/IL-17-producing T cells in adipose tissue, leading to type 2 diabetes and systemic inflammation. This reveals a novel pathogenesis mechanism of T helper 17 (Th17) cell-mediated type 2 diabetes.

GLK (MAP4K3) activates PKC-θ/IKK/NF-κB during TCR signaling. Autoimmune systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) patients show significantly increased GLK levels and PKC-θ/IKK/NF-κB activation in inflammatory Th17 cells, and the percentage of GLK-overexpressing T cells is correlated with autoimmune disease severity. We propose that GLK (MAP4K3) is a novel diagnostic biomarker and therapeutic target for various pro-inflammatory IL-17-mediated diseases.

B. Lin-Ju Yen (顏伶汝)

Taiwan

Investigator & Attending Physician,
Regenerative Medicine Research Group (RMRG),
Institute of Cellular and System Medicine (ICSM),
National Health Research Institutes (NHRI), Miaoli, Taiwan

THERAPEUTIC POTENTIAL OF HUMAN FETAL-STAGE STEM CELLS

B. Lin-Ju Yen

Investigator & Attending Physician, Regenerative Medicine Research Group (RMRG), Institute of Cellular and System Medicine (ICSM), National Health Research Institutes (NHRI), Miaoli, Taiwan

Despite the isolation of human embryonic stem cells (hESCs) and the more recently discovered induced pluripotent stem cells (iPS), many critical issues still surround these cells in terms of prevalent clinical use, the most important likely being the ethical concerns of hESC derivation, and tumorigenic potential of both these pluripotent stem cells.

Increasing reports of plasticity for many adult stem cells (ASCs) have brought excitement and hope for broad therapeutic application, but these are rare cells and require invasive procedures for procurement. Thus, the search continues for ethically conducive, easily accessible, and high-yielding source of human stem cells for clinical application. We have isolated and studied the immunobiology of novel sources of fetal-stage mesenchymal stem cells (MSCs), including placenta-derived multipotent cells (PDMCs) and hESC-derived mesenchymal progenitors. Fetal extraembryonic tissues are developmentally and immunologically more naïve than adult tissue, and are discarded after the birth of the neonate, making this source ideal for isolation of progenitor cells for therapeutic use. We have found that these fetal-stage MSCs exhibit many markers common to adult bone marrow (BM) MSCs including CD105 and CD73, as well as hESC markers such as SSEA-4, demonstrating the earlier developmental origin of these MSCs. Highly proliferative compared with adult BMMSCs, fetal-stage MSCs possess broader differentiation capacity than adult BMMSCs based on our recent data, and are strongly immunomodulatory towards allogeneic leukocytes. Mechanistically, suppression of allogeneic leukocytes by fetal-stage MSCs is largely due to secreted factors, and can be surprisingly enhanced with interferon-**γ**, a proinflammatory cytokine. The immunomodulation of fetal-stage MSCs extend to both innate and adaptive leukocytes, via mechanisms which we are interested in delineating for optimization of clinical application using these versatile stem cells. With such broad immunosuppressive properties and multilineage differentiation capacity, fetal-stage MSCs may represent a potential cell source for therapeutic use.

Jianxun Song

USA

Professor, Department of Microbiology and Immunology,
The Pennsylvania State University College of Medicine, USA

CANCER IMMUNOTHERAPY IN MICE USING ANTIGEN-SPECIFIC CTL FROM STEM CELLS

Jianxun Song

Department of Microbiology and Immunology, The Pennsylvania State University College of Medicine, Hershey, USA

T lymphocytes (T cells) are essential for normal immune surveillance systems, and their dysfunction leads to the development of fatal diseases, such as cancers. Naive tumor-reactive T cells are activated through encounters with tumor-specific/associated antigen (Ag) that are presented by specialized Ag-presenting cells, such as dendritic cells; while activating T cells are capable of directly recognizing Ags that are presented on the surfaces of tumor cells. Tumor-specific T cells recognize cognate Ags expressed on tumor cells through engagement of T cell receptor (TCR), resulting in migration into the tumor areas and the production of cytokines (*e.g.*, IFN-γ, TNF), chemokines (*e.g.*, CC chemokine receptor 1), and anti-angiogenic factors (*e.g.*, IL-12) that affect tumor growth. In addition, T cells also directly mediate cytotoxic responses against tumor cells, either through their expression of apoptosis-inducing molecules or through the release of cytotoxic granules. Recent advances demonstrate that immunotherapy based on the adoptive cell transfer of naturally occurring or gene-engineered T cells can mediate tumor regression in patients with metastatic cancers.

Under the right circumstance, pluripotent stem cells (PSC) can produce almost all of the cells in the body, including $CD8^+$ cytotoxic T lymphocytes (CTL), *i.e.*, PSC-CTL. PSC provide a chance to obtain a renewable source of healthy T cells to treat a wide array of diseases. However, the right circumstance for development of T cells from PSC has not been defined. Previously we have reported the successful generation of PSC-CTL by using a well-established *in vitro* system. Our follow-up study demonstrated that induce PSC (iPSC) could be reprogrammed into functional Ag-specific CTL, which enhance the tumor immunosurveillance in the tumor-challenged mice. Here we show that a combination of *in vitro* differentiation and *in vivo* development induces generation of tumor Ag-specific iPSC-CTL that suppresses tumor growth. Murine iPSC genetically transduced with H-$2K^b$-restricted tyrosinase related protein 2 (TRP2)-specific T cell receptor (TCR) were co-cultured on the bone marrow stromal cell line OP9 expressing Notch ligand Delta-like 1 and 4 (OP9-DL1/DL4 cell) for a week, then adoptively transferred into recipient mice. Four weeks later, TRP2-specific CTL developed in the lymph nodes and spleen and responded to TCR-mediated stimulation *in vitro*. In addition, TRP2-specific CTL infiltrated melanoma tissue in mice subcutaneously injected with B16 melanoma cells in the flank region. Moreover, inhibition of tumor growth and improved survival occurred in mice that received the adoptive transfer of iPSC transduced with TRP2-specific TCR combined with the *in vitro* differentiation. These results support a new approach to generate Ag-specific PSC-CTL for cancer immunotherapy.

Isolation of embryonic stem cells from patients is not feasible, and in addition, the alternative hematopoietic stem cells have reduced differentiation and proliferative capacities. As a result, iPSC have high potential for advancing the field of cell-based therapies. Our studies provide a foundation for generating tumor-associated PSC-T cells and in so doing drive forward the use of therapeutic PSC-T cells for cancer immunotherapy.

Habib Torfi

USA

Founder, Chairman and CEO of Invitrx Inc., USA

STRATEGIES TO FURTHER DEVELOP THE USE OF NATURAL KILLER (NK) CELLS IN CANCER THERAPY

Habib Torfi

Founder, Chairman and CEO of Invitrx Inc., USA

Natural killer (NK) cell therapy has been enjoying a renewed interest in cancer treatments; specifically in hematopoietic malignancies. The role of NK cells in cancer therapy has long been established as one of the many autologous routes in personalized medicine. Here we will review different approaches on purifying a subset of freshly isolated NK cells for use in cell-based immunotherapy. The in-vitro expansion of purified NK cells may advance the arsenal of personalized medicine in the war against viruses and cancer.

David CP Chen

USA

- Associate Professor, University of Southern California, USA
- Medical Director, Advanced Anti Aging Center, City of Industry, USA

CLINICAL APPLICATIONS OF INTRAVENOUS INJECTION OF ADIPOSE DERIVED STEM CELLS

David CP Chen, MD., MPH.

University of Southern California, USA

Stem cells (SC) can improve health through regeneration of multiple cells, tissues or organs. They can be directly injected to the injured tissue such as tendon, joint, or bone fracture. They can also be injected intravenously to improve organ functions. SC can differentiate to mature cells of many tissues to repair and stimulate them to regenerate. They can produce many cell growth factors to adjust the growth, structure and function. Theologically, stem cells can help a lot of diseases. It will be hope for these so called “Non-curable disease”.

The sources of adult SC are blood SC and adipose derived SC (ADSC). ADSC are superior to blood SC because they are easy to get with a large number of stem cells isolated and no needed for cell expansion. They can differentiate into multiple organs such as liver, pancreas, kidney, heart, and brain. Homing is unique function for ADSC. With chemotaxis, ADSC will migrate to the site of tissue, which was injured and needed to be repaired. Studies showed through intravenous (IV) injection, stem cells will migrate to the site of bone fracture. For patients with stroke, they will migrate to the injured brain tissue and reduce the size of stroke.

It is safe of IV administration of ADSC because they are non-differentiated cells. Surface antigenicity is very weak. A lot of studies show no severe adverse reaction. Only mild fever, or headache is noted.

Clinical applications of IV of include diabetes(mainly type-2), respiratory diseases such as COPD, asthma, cardio-vascular disease, stroke, Parkinson’s and Alzheimer’s diseases, renal failure, liver cirrhosis, visual problems(macular degeneration, optic nerve injuries), tinnitus (ear problem), spinal cord injury, rheumatoid arthritis, joint pain, low back pain, and others. The main mechanisms of ADSC to help the above diseases are anti-inflammation, immuno-modulation and differentiation into injured cells.

Hong-Lin Su (蘇鴻麟)

Taiwan

- Professor, Department of Life Sciences, National Chung-Hsing University, Taichung, Taiwan
- Research fellow, Center for Developmental Biology, RIKEN, Japan

SYSTEMIC COMBINED MELATONIN-MITOCHONDRIA TREATMENT IMPROVES RAT ACUTE RESPIRATORY DISTRESS SYNDROME

Hong-Lin Su

Department of Life Sciences, National Chung-Hsing University, Taichung, Taiwan

Background: Despite high in-hospital mortality associated with acute respiratory distress syndrome (ARDS), there is no effective therapeutic strategy. We tested the hypothesis that combined melatonin-mitochondria treatment ameliorates 100% oxygen-induced ARDS in rats.

Methods: Adult male Sprague-Dawley rats (n=40) were equally categorized into normal controls, ARDS, ARDS-melatonin, ARDS with intravenous liver-derived mitochondria (1500 μg/rat) 6h after ARDS induction, and ARDS receiving combined melatonin-mitochondria.

Results: Seventy-two hours after ARDS induction, oxygen saturation (SaO2) was lowest in ARDS group and highest in normal controls, significantly lower in ARDS-melatonin and ARDS-mitochondria than in combined melatonin-mitochondria group, and significantly lower in ARDS-mitochondria than in ARDS-melatonin group, whereas right ventricular systolic blood pressure and lung weight showed an opposite pattern compared with SaO2 among all groups (all $p<0.001$). Histological integrity of alveolar sacs showed a pattern identical to SaO2, whereas lung crowded score exhibited an opposite pattern (all $p<0.001$). Albumin level and inflammatory cells (MPO+, CD40+,

CD11b/c+) from broncho-alveolar lavage fluid showed a pattern opposite to SaO2 (all $p<0.001$). Protein expressions of indices of inflammation (MMP-9, TNF-α, NF-κB), oxidative-stress (oxidized protein, NO-1, NOX-2, NOX-4), apoptosis (mitochondrial Bax, cleaved caspase-3 and PARP), fibrosis (Smad3, TGF-β), mitochondrial-damage (cytochrome-C), and DNA damage (γ-H2AX+) exhibited an opposite pattern compared to SaO2 in all groups, whereas protein (HO-1, NQO-1, GR, GPx) and cellular (HO-1+) expressions of antioxidants showed a progressively increased pattern from normal controls to ARDS combined melatonin-mitochondria group (all $p<0.001$).

Conclusion: Combined melatonin-mitochondrial was superior to either alone in attenuating ARDS in a rat model.

Fukuda Tomokazu

Japan

Research Associate, Tohoku University,
Graduate School of Agriculture, Sendai, Japan

PORCINE DERIVED INDUCED PLURIPOTENT STEM CELLS WITH SIX REPROGRAMMING FACTORS

Tomokazu FUKUDA, Ph.D.

University, Graduate School of Agriculture, Sendai, Japan

We created porcine induced pluripotent stem (iPS) cells using six reprogramming factors (OCT3/4, KLF4, SOX2, C-MYC, LIN28, and NANOG). The resulting cells showed growth dependent on LIF (leukemia inhibitory factor) and expression of multiple stem cell markers. Furthermore, the iPS cells caused teratoma formation with three layers of differentiation and had both active X chromosomes (XaXa). Our iPS cells are the first cell line showing both important properties of stem cells: teratoma formation and activation of both X chromosomes. Injection of these iPS cells into morula stage embryos showed that these cells participate in the early stage of porcine embryogenesis. We can conclude that the expression of six reprogramming factors enables the creation of porcine iPS cells, which is partially close to naive iPS state.

Chia-Ning Shen (沈家寧)

Taiwan

Genomics Research Center, Academia Sinica,
Taipei, Taiwan

GENERATION OF PLURIPOTENT STEM CELLS AND MULTIPOTENT NEURAL PROGENITORS FROM SOMATIC CELL REPROGRAMMING

Chia-Ning Shen, Ph.D.

Genomics Research Center, Academia Sinica, Taipei, Taiwan

Pluripotent reprogramming achieved by introducing the Yamanaka factors Oct4, Sox2, c-Myc and Klf4 into a variety of somatic cells provides experimentally accessible opportunities for investigating the regulatory mechanisms underlying pluripotency, disease pathophysiology, and novel drug targets. We and others' recent findings have demonstrated that Yamanaka factor-mediated fibroblast reprogramming can not only generate induced pluripotent stem cells (iPSCs), but can also generate cells that possess features of multipotent neural stem cells (iNSCs). However, the crucial factors controlling the commitment of cells undergoing reprogramming toward either pluripotent or multipotent neural cell fates has not been clearly determined.

Since cell-cycle control is modulated for meeting the requirements of cell fate commitment during development. For example, pluripotent cells exhibit a shortened G1 phase, while neural stem/progenitor cells (NPCs) have tightly regulated lengthened G1 phase. We therefore dissect the crucial factors controlling the commitment of reprogramming cell via examining how reestablishment of the fidelity of cell-cycle control is linked to cell-fate decision during Yamanaka factor-mediated reprogramming by applying RNA-seq analysis and cell-cycle profiling to reprogramming fibroblasts that transgenically expressed Oct4-EGFP reporter. Low levels of cyclin D1 were initially found to associate with an atypical cell-cycle profile that resembles that of embryonic stem cells. In contrast, NPC-like cells expressed higher levels of cyclin D1 and several G1-phase regulators linked to a cell-cycle featuring a lengthened G1 phase. In addition to the well-established role of cyclin D1 as a G1-phase regulator, cyclin D1 was found to transcriptionally upregulate Pax6 which promoted commitment of reprogramming cells to neural progenitors instead of pluripotent cells. We demonstrate overexpression of Pax6 together with Yamanaka factors was able to efficiently reprogram fibroblasts to neural progenitor cells. In contrast, knockdown of cyclin D1 or treatment reprogramming cells with CDK4/6 inhibitor counteracted neural progenitor fate commitment but enhanced generation of iPSCs. The findings explain the importance of reestablishment of G1-phase restriction in pluripotent reprogramming and lead to a new strategy to controllably generate either iPSCs or iNSCs using Yamanaka factors.

Sung Rae Cho

Korea

Associate Professor, Dept of Rehabilitation Medicine,
Yonsei University College of Medicine, Korea

NEURORESTORATION INDUCED FROM ENDOGENOUS STEM CELLS

Sung-Rae Cho M.D.,Ph.D.

Department and Research Institute of Rehabilitation Medicine, Yonsei University College of Medicine, Seoul, Korea
Yonsei Stem Cell Research Center, Avison Biomedical Research Center, Korea

Multipotential neural stem cells, which are capable of giving rise to both neurons and glia, in subventricular zone (SVZ) lining the cerebral ventricles of all adult animals, including humans. These cells may be mobilized and induced to undergo neuronal differentiation in vivo, by stimulating resident stem/progenitor cells with neurotrophic/growth factors by overexpression using viral vectors, chronic infusion using osmotic pump, paracrine actions by transplanted stem cells, magnetic stimulation or rehabilitation exercise. The fate and survival of neural-lineage cells arising from adult progenitors is dictated by both the availability of a permissive pathway for migration and the environment into which migration occurs. In both rodents and humans, the differentiation and survival of neurons arising from the postnatal SVZ may be regulated by access to postmitotic trophic factors. Indeed, overexpression of fibroblast growth factor-2 (FGF-2) or brain-derived neurotrophic factor (BDNF) has allowed the generation and maintenance of neurons from the adult human SVZ.

This suggests the feasibility of inducing neurogenesis, and this strategy may be particularly efficacious in striatal neurodegenerative conditions such as Huntington's disease, in which lost medium spiny striatal neurons may be replenished through directed induction of progenitor cells lining the striatal ventricular wall, as well as cerebrovascular diseases such as ischemic stroke and cerebral palsy which have widely been met in the clinics of neurorehabilitation. More broadly, our increasing understanding of the molecular control of progenitor cell mobilization and differentiation will likely afford many new opportunities for using induced neuronal replacement as a therapeutic strategy for neurodegenerative diseases or cerebrovascular diseases. Taken together, these findings give hope that functional brain repair through induced neurogenesis will soon be a clinical reality.

Shih-Chieh Hung (洪士杰)

Taiwan

Professor, Institute of Clinical Medicine, Faculty of Medicine,
National Yang-Ming University, Taipei, Taiwan

APPLICATION OF HYPOXIC MESENCHYMAL STEM CELLS FOR THERAPIES IN ISCHEMIC LIMB: FROM BENCH TO BEDSIDE

Shih-Chieh Hung, M.D. Ph.D

Institute of Clinical Medicine, Institute of Pharmacology, Faculty of Medicine, National Yang-Ming University, Taipei, Taiwan
Stem Cell Laboratory, Department of Medical Research and Education, Orthopaedics and Traumatology,
Taipei Veterans General Hospital, Taipei, Taiwan

The effects of hypoxia on mesenchymal stem cells (MSCs) have been investigated. In a long term culture, hypoxia can inhibit senescence, increase the proliferation rate and enhance differentiation potential along the different mesenchymal lineages. More importantly, hypoxic culture increases the expression of pluripotency transcription factors in MSCs, which in turn upregulate Dnmt1, thereby inhibiting the expression of p16 or p21, and the developmental markers or lineage genes. Hypoxia also modulates the paracrine effects of MSCs, causing upregulation of various secretable factors, including the vascular endothelial growth factor and IL-6, and thereby enhances wound healing and fracture repair. Hypoxia also plays an important role in mobilization and homing of MSCs, primarily by its ability to induce SDF-1-CXCR4.

Recently, we demonstrated that hypoxic MSCs from B6 mice ameliorate limb ischemia of Balb/c mice compared with normoxic MSCs. We also demonstrated that hypoxic MSCs have an increased ability to engraft in allogeneic recipients by reducing natural killer (NK) cytotoxicity and decrease the accumulation of host-derived NK cells when transplanted in vivo. These allogeneic hypoxic MSCs gave rise to CD31+ endothelial cells and α-smooth muscle actin (SMA)+ and desmin+ muscle cells, thereby enhancing angiogenesis and restoring muscle structure. Moreover, application of anti-NK antibodies together with normoxic MSCs enhanced angiogenesis and prevented limb amputation in allogeneic recipients with limb ischemia. These results strongly suggest that hypoxic MSCs are intrinsically immunoprivileged and can serve as a 'universal donor cell' for treating cardiovascular diseases. We are currently applying these results in future cellular therapy in patients with ischemic limbs.

Toru Yamashita

Japan

Lecturer, Department of Neurology,
Okayama University Medical School, Japan

DIRECT REPROGRAMMED NEURONAL CELLS AS A NOVEL RESOURCE FOR CELL TRANSPLANTATION THERAPY

Toru Yamashita, Kosuke Matsuzono, Koji Abe

Department of Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Cell transplantation/replacement therapy is attractive as a novel strategy for neurological diseases such as Parkinson's disease, Alzheimer's disease, and stroke. To realize this therapy, safer and more therapeutic effective cell resources are now required. Since induced pluripotent stem cells (iPSCs) can retain high replication competence and pluripotency when they differentiate into various kinds of cells, they are regarded as a promising cell source for cell transplantation therapy. However, high tumorigenesis of iPSCs has to be overcome for clinical applications. Recent progress includes the combination of novel transcriptional factors that can convert somatic cells to various kinds of mature neuronal cells and neural stem cells without requiring iPSC fate. Some evidence indicates that these directly induced neuronal cells have little tumorigenic potential.

In this symposium, we would like to discuss the advantage, issues, and possibility of clinical application of these cells for cell transplantation therapy, especially for post-stroke patient.

Shan Ping Yu

USA

Professor and Chair, Department of Anesthesiology,
Emory University School of Medicine, USA

OPTOGENETIC STIMULATION OF STRIATAL GLUTAMATERGIC NEURONS ENHANCES NEUROGENESIS IN THE SUBVENTRICULAR ZONE OF NORMAL AND STROKE MICE

Shan Ping Yu

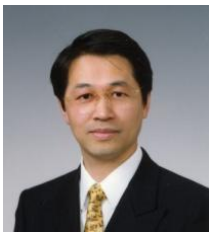
Department of Anesthesiology, Emory University School of Medicine, USA

Neurogenesis in the subventricular zone (SVZ) of the adult brain is an endogenous mechanism in potential regenerative treatments of brain diseases. Using the transgenic mouse expressing the light-sensitive channelrhodopsin-2 (ChR2) channel in glutamatergic neurons, we show that optogenetic stimulation of the striatum triggered glutamate release and increased cell proliferation of neuroblasts in the SVZ, mediated by selective activation of AMPA receptors in these cells. This regulatory mechanism was demonstrated in neuroblast cultures, the normal mouse brain and in a focal ischemic stroke mouse model. The novel striatum-SVZ glutamatergic connection favored brain repair by driving more neuroblasts to migrate to and survive in the peri-infarct cortex and differentiate into glutamatergic neurons. Stroke animals treated with the optogenetic stimulation showed improved sensorimotor functional recovery. This investigation provides the first direct evidence that the activity of the striatum-SVZ excitatory pathwayregulates SVZ neurogenesis. This neuronal and functional connection may be a therapeutic target for promoting neurogenesis, brain tissue repair and functional recovery after ischemic stroke.

Koji Abe

Japan

- Professor and Chairman, Department of Neurology, Graduate School of Medicine, Dentistry and Pharmacological Sciences, Okayama University, Japan
- President, International Society of Cerebral Blood Flow and Metabolism, USA



NEUROPROTECTION AND STEM CELL THERAPY IN JAPAN

Koji Abe, MD, PhD

Department of Neurology, Graduate School of Medicine and Dentistry, Okayama University, Shikatacho, Okayama, Japan

Neuroprotection is essential for therapy in acute stage of stroke. Both NTFs and free radical scavenger can be such neuroprotective reagents with inhibiting death signals and potentiating survival signals under cerebral ischemia. For example, topical application of GDNF greatly reduced the infarct size and brain edema after middle cerebral artery (MCA) occlusion in rats. Edaravone, a free radical scavenger, is the first clinical drug for neuroprotection in the world which has been used from 2001 in most ischemic stroke patients in Japan. Edaravone scavenges hydroxyl radicals both in hydrophilic and hydrophobic conditions, and is especially useful in thrombolytic therapy with tissue plasminogen activator (tPA). Combination therapy of Edaravone with tPA greatly increased survival of stroke animals, reduced infarct size, and inhibited molecular markers of oxidative damage in lipid, protein and DNA. Use of Edaravone greatly reduced hemorrhagic transformation accompanied by tPA treatment,and may also extend therapeutic time window with tPA therapy for more than 3 hr in human stroke patients.

It is important for regenerative therapy that the neural stem cells which are intrinsically activated or exogenously transplanted. To support stem cell migration, an artificial scaffold can be implanted to injured brain for promoting ischemic brain repair. Addition of NTFs greatly enhanced an intrinsic migration or invasion of stem cells into the scaffold, which could provide a future regenerative potential against ischemic brain damage at chronic stage. G-CSF may promote bone marrow cell migration into ischemic brain to reduce such a damage. In vivo optical imaging is a recent technology to detect ischemic and other neurologic disorders without killing subjects, which make able time-dependent monitoring of the disease conditions such as MMP9 activation and macroautophagy. Transient increase of such in vivo optical images were detected from living mice brain after ischemic stroke and the spinal cord in ALS model mice. Macroautophagy image was also obtained in mice model of motor neuron disease ALS from the back of the animal. We report a cell therapy for both ischemic stroke and ALS model mice.

Woei-Jer Chuang (莊偉哲)

Taiwan

Chairman and Distinguished Professor,
Department of Biochemistry and Molecular Biology,
National Cheng Kung University College of Medicine,
Tainan, Taiwan

DESIGN OF INTEGRIN-SPECIFIC DRUGS FOR CANCER

Woei-Jer Chuang

Department of Biochemistry and Molecular Biology, National Cheng Kung University College of Medicine, Tainan, Taiwan

Venoms from snakes, cone snails, scorpions, spiders, sea anemone, and other species provide an immense reservoir of potent bioactive peptides that target specific receptors, enzymes, and ion channels. They represent major sources of lead compounds for novel drugs. Integrins are αβ heterodimers that are expressed on virtual all cells with adhesive capacity. They are involved in fundamental cellular processes such as attachment, migration, proliferation, differentiation, and survival. Disintegrins are a family of RGD-containing proteins found in snake venoms that contain 47 to 84 amino acids with 4-7 disulfide bonds. Rhodostomin (Rho) is obtained from *Calloselasma rhodostoma* venom and belongs to the family of disintegrins. Our study showed that Rho expressed in *Pichia pastoris* possesses the same function and structure as native protein. In order to design integrin-specific disintegrins, we expressed >400 Rho mutants in *Pichia pastoris* and used platelet aggregation and cell adhesion assays to identify the mutant proteins that can selectively inhibit integrins αIIbβ3, αvβ3, and α5β1. We found that the mutant proteins containing the AKGDWN and ARLDDL motifs can selectively inhibit integrins αIIbβ3 and αvβ3, respectively. We also determined 3D structures and backbone dynamics of integrin-specific disintegrins using NMR spectroscopy and X-ray crystallography. According to the results of animal disease models, we found that integrins-specific disintegrins can be used for the treatment of integrins-related diseases, such as osteoporosis, age-related macular degeneration, and metastatic tumors. We also design various disintegrin variants to avoid its immunogenicity and to increase its half-life. This drug candidate will be in clinical trial for the treatment of age-related macular degeneration.

Horng-Jyh Harn (韓鴻志)

Taiwan

Professor, Department of Pathology,
China Medical University,
Taichung, Taiwan

POLYANHYDRIDE, BIODEGRADABLE MATERIALS, BRING Z-BUTYLIDENEPHTHALIDE ONTO HUMAN GLIOBLASTOMA MULTIFORME TO ACHIEVE THERAPY A PRE-CLINICAL AND CLINICAL DEVELOPMENT

Horng-Jyh Harn MD PhD, Tzyy-Wen Chiou PhD, Shinn-Zong Lin, MD. PhD

Department of Pathology, China Medical University Hospital, Taichung, Taiwan
Department of Life Science and Graduate Institute of Biotechnology, National Dong Hwa University, Hualien, Taiwan
Center for Neuropsychiatry, China Medical University Hospital, Taichung, Taiwan

In terms of human malignant brain tumors the global market about 10 billion U.S. dollars, and estimated up to 21 billion in 2017. There are rarely types of drugs and the effect is limited for the treatment of human malignant brain tumors. Thus, we developed a more effective and non-toxic drug for clinical application. Our products Cerebraca Wafer mainly implanted into the brain when surgery removing cancer, and local delivery active substance z-Butylidenephthalide onto human glioblastoma multiforme. We have been awarded patents, including the "z-Butylidenephthalide against human glioblastoma multiforme", " the delivery device of polyanhydrides p (CPP-SA) with Z-type Butylidenephthalide, which could against human glioblastoma multiforme" and "treatment of brain cancer or to reduce the resistance of temozolomide pharmaceutical composition and its applications". Such technologies and patents are exclusive license, and relevant published in 20 SCI papers. This project intends to conduct biomedical materials polyanhydride with Z-type Butylidenephthalide treatment in early clinical development plan. Further, we will complete the project in a chemical manufacturing and control, preclinical efficacy and preclinical safety assessment and other tests. The purposes of those plans are achieve the U.S. and Taiwan experimental new drug (IND) registration, and following speed up entering clinical trials and subsequent marketing.

Regarding to our project, there are six distinctive implementation advantages:

(A) Physician initiation, which is a Taiwan's first indigenous development of orphan drugs.
(B) Our teams have completed an exclusive license to the relevant patents and technology transfer.
(C)Polyanhydrides with Z-type Butylidenephthalide delivery device was significantly better than the effectiveness of existing products on the market.
(D) Z-type Butylidenephthalide found no side effects.
(E) Development of orphan drugs can save a lot of cost and time.
(F) Our teams have completed three aspects of integration, involving the industry, academia and medicine.

Besides, this project has following expected benefits:

(A) The implementation of the pre-clinical phase, which is an important basis for clinical trials.
(B) To promote the development of biotechnology in the medical field, and downstream alliances related industries.
(C) Development of new drugs related practice nurturing talent.
(D) Provide the actual production technology and complete innovative biomedical technology industry experience in Taiwan.

Gwo Xi Stem Cell Applied Technology Co., Ltd.
(國璽幹細胞應用技術股份有限公司)

Po-Cheng Lin

Taiwan

Vice President,
Gwo Xi Stem Cell Applied Technology Co., Ltd., Hsinchu, Taiwan

SHARING STEM CELLS CLINICAL TRIAL START-UP EXPERIENCE IN TAIWAN

Po Cheng Lin

Vice President. Gwo Xi Stem Cell Applied Technology Co., Ltd., Hsinchu, Taiwan

Gwo Xi is established on the 31th of March 2004. As a biotech pharmaceutical company, utilizing autologous adipose derived stem cells (ADSCs) on liver fibrosis treatment is the one of our prospective projects. Excitingly, this ADSCs project has been shown many positive results in animal models and further we continually carry on this study to clinical trial.

Gwo Xi's customized ADSC processes, including cell isolation, culture and expansion also cryopreservation, are all conformed to the Good Tissue Practice (GTP) requirements. In Taiwan, the GTP requirements can be referred to the Code of Federal Regulation, Title 21, part1271 which is established by the U.S Food and Drug Administration (FDA) and the GTP guideline which is established by Taiwan Food and Drug Administration (TFDA). Follow the process control, these ADSCs have been proven that they share the same characters of mesenchymal stem cells. Most of all, they present genetic stability at least within 12 passages in culture. In order to ensure the safety and efficacy of our customized ADSCs in liver cirrhosis patients, we have proposed a clinical trial to TFDA in July 2013.

After strict scrutiny, this proposal has been approved by the China Medical University & Hospital Research Ethics Committee and TFDA in August 2014. Also, we have registered at Clinical.gov and the register number is NCT02297867.

StemCyte
(美商永生臍帶血)

Sheng-Wen Steven Shaw

Taiwan

Department of Obstetrics and Gynecology,
Chang Gung Memorial Hospital, Linkou, New Taipei, Taiwan

THE CLINICAL APPLICATIONS AND BANKING OF HUMAN AMNIOTIC FLUID STEM CELLS

S.W. Steven Shaw, MD, PhD

Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Linkou, Taiwan

Human amniotic fluid is a promising resource of pluripotent stem cells and it makes fetal therapy using autologous transplantation possible. Human amniotic fluid stem (AFS) cells are a unique subgroup of human AF-derived stem cells that express pluripotent stem cell markers, and which possess amazing capability of self-renewal and potential to differentiate. These AFS cells also have the mesenchymal stem cells (MSC) characteristics showing MSC surface markers. Here we presented the standard procedure of banking AFS from collection, primary culture, expansion, and frozen down. The fresh amniotic fluid will be collected clinically during amniocentesis. Only small amount of amniotic fluid can be expanded up to 10^8 cells within few weeks. The AFS cells could be defrosted with good recovery rate, and preserve the same stem cell potential. For the clinical purpose, these cells could be obtained prenatally for autologous cell fetal therapy, or storage the cells for postnatally tissue engendering in the future.

Moderator Profiles

**Sorted by Program*

Shinn-Zong Lin（林欣榮）

Chairman, the 8th Pan Pacific Symposium on Stem Cells and Cancer Research (PPSSC)
Professor, Graduate Institute of Immunology, China Medical University, Taichung
Superintendent, China Medical University Beigan Hospital, Yunlin
Vice Superintendent, Center for Neuropsychiatry, China Medical University Hospital, Taichung
Taiwan

Chung-Liang Chien (錢宗良)

Professor, Department of Anatomy and Cell Biology, College of Medicine, National Taiwan University
Taiwan

Chung Y. Hsu (許重義)

Professor, Graduate Institute of Clinical Medical Science, China Medical University
Taiwan

Jonas Wang

Chairman, StemCyte International, Ltd.
USA

Yao-Chang Chen (陳耀昌)

Professor, Division of Hematology-Oncology, College of Medicine, National Taiwan University
Attending Physician, Department of Laboratory and Internal Medicine, National Taiwan University Hospital
Taiwan

John Yu (游正博)

Distinguished Visiting Fellow, Institute of Cellular and Organismic Biology, Academia Sinica
Taiwan

Tzyy-Wen Chiou (邱紫文)

Professor, Department of Life Science and the Institute of Biotechnology, National Dong Hwa University
Taiwan

O1

CANCER AND STEM CELLS (NP): WHY IS DYNAMIC EQUILIBRIUM A PREDICTION WITHOUT PARAMETERS?

Hsieh Hsih-Chia[1], *Pei-Gin Hsieh*[2]

[1]Hsing-Kuo University, Tainan, Taiwan
[2]National Chung-cheng University, Chiayi, Taiwan

The prediction without parameters is dynamic general equilibrium, which is a shape angle of regulatory standard, a drug and policy threshold, and a common grazing boundary of response and incentive. Non-deterministic polynomials (NP) compute the dynamic equilibrium for a large-scale production of economy, for drug doses and for species and school choices. Results of policy shift the Moore law and the Weibulian distribution. Predictions without parameters reduce the recurrent infection, and blow-up of risk or cancer viruses.

O2

EXTRACELLULAR MATRIX BENEFITS PERIPHERAL NERVE RECONSTRUCTION

Sheng Yi, Yun Gu, Leilei Gong, Haihong Jiang, Yongjun Wang, Xiaosong Gu

Jiangsu Key Laboratory of Neuroregeneration, Co-innovation Center of Neuroregeneration, Nantong University, China

Extracellular matrix (ECM) establishes and maintains an ideal microenvironment for tissue regeneration and thus has been applied in tissue engineering. Schwann cell (SC)-derived ECM assists the organization of peripheral nerve tissue, enhances the adhesion, growth, and differentiation of SCs, and regulates axonal growth. Therefore, in the current study, we have constructed tissue engineered nerve scaffold composed of SC-derived ECM, applied it to sciatic nerve transected rats, and evaluated its repairing effect. SCs were co-cultured with chitosan and silk fibroin (SF) for ECM deposition and then subjected to decellularization. Immunochemical staining identified the presence of two ECM components, fibronectin and laminin, suggesting the maintenance of bioactive ECM assembled scaffold. *In vivo* outcomes from morphological analysis as well as electrophysiological examination suggested that the repairing function of SC-derived ECM-modified scaffold was as good as an acellular nerve graft, but superior to those by a plain chitosan/SF scaffold, in supporting axonal outgrowth from the proximal stump at an early regenerative stage and in the morphological and electrophysiological properties in the long term. Moreover, the safety evaluation using blood routine, biochemical examination, and thrombosis assay, indicated that no adverse effects were observed. Taken together, these outcomes suggested that the joint use of ECM and biomaterials represents a promising approach to nerve tissue engineering.

O3

THE REGULATORY MECHANISMS OF MIRNAS IN PERIPHERAL NERVE REGENERATION

*Songlin Zhou, Sheng Yi, Leilei Gong, Haihong Jiang, Bin Yu, Yongjun Wang, Fei Ding, Xiaosong Gu**

Jiangsu Key Laboratory of Neuroregeneration, Nantong University, Co-innovation Center of Neuroregeneration, Nantong JS, PR China

When peripheral nerve injury occurs in adult animals, mature differentiated Schwann cells undergo profound phenotypic modulation, dedifferentiating to a progenitor or stem-cell-like state. Using microarray analysis, we investigated time-dependent expression patterns of miRNAs in rat models of sciatic nerve injury, and identified 77 known miRNAs that showed significant changes during the phenotypic modulation. Specifically, miR-221/222 promote Schwann cell proliferation and migration by targeting longevity assurance homologue 2 (LASS2), a suppressor of cell growth or metastasis and might increasing intracellular H^+ through the interaction with subunit c of vacuolar type H^+-ATPase (V-ATPase). Collagen triple helix repeat containing protein 1 (Cthrc1) has been shown to be overexpressed in injured tissues, and Cthrc1 increases cellular motility to repair the injury by promoting cell migration. miR-9 was identified as an important functional regulator of Schwann cell migration by directly targeting Cthrc1, which in turn inactivated downstream Rac1 GTPase. In vivo, high expression of miR-9 reduced Schwann cell migration within a regenerative nerve microenvironment. It generally takes at least a few days after nerve injury, known as 'the initial delay period', for Schwann cells to start proliferation and migration in the proximal stump. We found that miR-182 inhibited Schwann cell proliferation and migration by targeting fibroblast growth factor 9 (FGF9) and neurotrimin (NTM), respectively at this stage following sciatic nerve injury. Collectively, our systematic research confirmed the role of miRNAs in regulating peripheral nerve injury and regeneration, thus offering a new approach to peripheral nerve repair.

O4

FLUORESCENT NANODIAMONDS ENABLE IN VIVO TRACKING OF PROSPECTIVELY ISOLATED LUNG STEM CELLS

John Yu, M.D., Ph.D.

Institute of Stem Cell and Translational Cancer Research, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan
Institute of Cellular & Organismic Biology, Academia Sinica, Taipei, Taiwan

Lung stem/progenitor cells are potentially useful for regenerative therapy, for example in repairing damaged lung tissue in patients. Several optical imaging methods and probes have been used to track how stem cells incorporate and regenerate themselves *in vivo* over time. However, these approaches are limited by photobleaching, toxicity and interference from background tissue autofluorescence. Here we show that fluorescent nanodiamonds, in combination with fluorescence-activated cell sorting, fluorescence lifetime imaging microscopy and immunostaining, can identify transplanted $CD45^{-}CD54^{+}CD157^{+}$ lung stem/progenitor cells *in vivo*, and track their engraftment and regenerative capabilities with single-cell resolution. Fluorescent nanodiamond labelling did not eliminate the cells' properties of self renewal and differentiation into type I and type II pneumocytes. Time-gated fluorescence imaging of tissue sections of naphthalene-injured mice indicates that the fluorescent nanodiamond-labelled lung stem/progenitor cells preferentially reside at terminal bronchioles of the lungs for 7 days after intravenous transplantation. Our results demonstrate not only the remarkable homing capacity and regenerative potential of the isolated LSCs, but also the ability of finding rare LSCs *in vivo* using FNDs and time-gated imaging technologies. This technology may offer insights into the factors that determine the acceptance of transplanted stem cells and their ability to regenerate within a host.

O5

HUMAN NUCLEUS PULPOSUS CONTAINS MULTILINEAGE-DIFFERENTIATING STRESS-ENDURING -LIKE PROGENITOR CELLS

Feng-Juan Lv[1,2], Yan Peng[1], Kenneth M.C. Cheung[1] , Victor Y.L. Leung[1,2]

[1]Department of Orthopaedics and Traumatology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, China
[2]HKU Shenzhen Institute of Research and Innovation, China

Background: Recently, it is reported that mesenchymal stem cell (MSC)-like progenitor cells have been found in the IVD. As multilineage-differentiating stress-enduring (MUSE) cells is a type of progenitor cells more primitive than MSCs and is able to gives rise to induced pluripotent stem (iPS) cells, in this study, we aim to investigate whether human IVDs contain MUSE-like cells, and whether this would be affected by degeneration process.

Methods: Human IVDs were collected from patients with severe disc degeneration (graded IV-V at the Schneiderman scale) undergoing discectomy, and from patients undergoing corrective scoliosis surgery in the Duchess of Kent Children's Hospital in Hong Kong with informed patient consent and corresponding approval from institutional review board (IRB). Nucleus pulposus (NP) Cells were isolated by enzymatic digestion and cultured in monolayer in DMEM medium in a 37^{o}C incubator. Expression of MSC markers (CD105, CD146 and CD90), and MUSE markers (Oct3/4, Nanog, SSEA-3) were investigated by immunofluorescent stain.

Results: Interestingly, a few spheroid-like clusters were spontaneously formed in both human degenerated and scoliotic NP cells cultured in monolayer, though the occurrence of spheroid clusters was lower in degenerated NP cells. Immunofluorescent staining demonstrated that the spheroids in the degenerated and scoliotic NP cell culture possessed progenitor marker expression profile. They positively expressed MSC markers, including CD105, CD146 and CD90, and they were also positive for MUSE cell markers, including Nanog, Oct3/4, and SSEA-3.

Conclusion: This is the first report on the detection of MUSE-like progenitor cells in the IVD. The MUSE markers are also embryonic stem cell markers. The expression of MUSE markers by human NP cells elucidated that there is a primitive subpopulation in the disc, which might be responsible for natural IVD repair and remodeling. More importantly, IVD degeneration did not totally attenuate the existence of this subpopulation. Our finding brings novel light on IVD homeostasis and allow future IVD regeneration therapy development.

Acknowledgements: This work was supported by General Funding from National Science Foundation of China (NSFC, No. 81371993), and Small Project Funding of The University of Hong Kong (201209176179).

O6

THE INFLUENCE OF HIGH GLUCOSE ENVIRONMENT ON THE STEMNESS AND DIFFERENTIATION POTENTIALS OF ADIPOSE-DERIVED STEM CELLS

Nai-Chen Cheng[1], *Tsung-Yu Hsieh*[2], *Tai-Horng Young*[2]

[1] Department of Surgery, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan
[2] Institute of Biomedical Engineering, College of Medicine and College of Engineering, National Taiwan University, Taipei, Taiwan

Adipose-derived stem cells (ASCs) represent an important source of mesenchymal stem cells for clinical application. However, several reports revealed that a diabetic milieu damage many cellular functions, thus raising a concern that ASCs from diabetic patients may not fulfill therapeutic purposes. In this study, we aimed to investigate how high glucose (HG) alter the regenerative capabilities of ASCs in diabetic patients. We obtained human ASCs from subcutaneous adipose tissue of diabetic (dASCs) and non-diabetic donors (nASCs), and their stem cell properties were evaluated. Then nASCs were cultured under prolonged high glucose (4.5 g/L glucose) or low glucose (1.0 g/L glucose) conditions to investigate the effect of a diabetic milieu on the proliferation, senescence, stemness and differentiation capabilities of ASCs. Compared with nASCs, enhanced expression of pluripotent markers Sox-2, Oct-4 and Nanog was noted in dASCs. Under HG culture condition, nASCs generated significantly more reactive oxygen species (ROS) than the LG counterpart. Although we found decreased cell proliferation, migration with enhanced senescence in nASC under high glucose culture condition, HG treatment significantly enhanced expression of Sox-2, Oct-4 and Nanog. However, treating HG-conditioned ASCs with an antioxidant revealed no stemness enhancement. These findings suggested that HG enhances stemness of ASCs through ROS production. Moreover, by culturing ASCs in proper induction medium, HG-pretreated ASC transdifferentiation capabilities into neuron-like cells were significantly enhanced, while adipogenic and osteogenic differentiation capacities were still maintained. Our data suggested that proliferative activity of ASCs is impaired with more senescence in a diabetic milieu. However, prolonged HG culture also enhanced ASC stemness and transdifferentiation capabilities. The information may be important for future ASC-based cell therapy for diabetic patients.

O7

THE ROLE OF MSC IN THE ENDOMETRIOSIS TREATMENT

Yi-Jen Chen [12], Hsiao-Wen Tsai[12], Peng-Hui Wang[12], Ming-Shyen Yen[12]*

[1] Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan
[2] National Yang-Ming University, Taipei, Taiwan

Endometriosis is a common condition that affects 10% to 15% of reproductive-aged women. Endometriosis might cause pelvic inflammation, adhesions, chronic pain, and infertility. This endometriosis tissue development is dependent on oestrogen produced primarily by the ovaries and, therefore, traditional management has focused on suppression of ovarian function. Their side effects are caused by hypoestrogenism and include hot flashes, vaginal dryness, reduced libido, and osteoporosis.

Endometriosis is also a chronic inflammatory disease. Mounting evidence shows that altered immune function plays a crucial role in the development of endometriosis. Thus the modulation of the inflammation as an alternative approach for endometriosis treatment. Mesenchymal stem cells (MSCs) are suggested to be immune modulators. Therapeutic approaches using multipotent MSCs are advancing in regenerative medicine, transplantation, and autoimmune diseases. The mechanisms behind MSC immune modulation are still poorly understood. The goals of this project are to investigate the role of adipose-derived MSC (ADSC) in the endometriosis treatment.

We establish an in vivo endometriosis animal model using autologous transplantation of mouse endometrial tissue in the peritoneal cavity. The ectopic lesion was assessed in two groups of animals (ADSC and vehicle control). Adipose-derived MSC was injected weekly. Control groups included a vehicle control where animals received PBS alone. Finally, tumor volumes were decreased in ADSC treatment group. Furthermore, we also evaluate the macrophage (M1 and M2) expression in the different group. ADSCs will be an immune modulator to regulate various macrophage to inhibit the development of endometriosis.

Poster Session

12:40-13:00, Saturday, April 11, 2015 Location: 3F, Ballroom III

Frontier in iPS Cell & Epigenetics	
PA-1	IDENTIFICATION OF A NOVEL OXIDATION-RELATED GENE MEDIATED HESC RENEWAL FROM A HIGH-THROUGHPUT SCREEN ***Cheng-Kai Wang , Shang-Chih Yang, Wei-Kai Huang, Bei-Chia Yang, John Yu, Jean Lu***
Targeting Stem Cells: Trials and Translation	
PB-1	DISRUPTION OF NME6 AFFECTS GASTRULATION AND LEADS TO EMBRYONIC LETHALITY DUE TO APOPTOSIS ***Yu-Ting Kao, Chun-Yu Chen, I-Shing Yu, Shu-Wha Lin, Jean Lu***
PB-2	MESENCHYMAL STEM CELLS AND DERIVED CYTOKINES PROMOTE WOUND HEALING AND SKIN REGENERATION ***Martin Sieber, Huan-Ting Lu***
Emerging Drug Targets in Development and Discovery	
PC-1	PROTECTIVE EFFECT OF TELMISARTAN ON NEUROVASCULAR UNIT AND INFLAMMASOME IN STROKE-RESISTANT SPONTANEOUSLY HYPERTENSIVE RATS ***Wentao Liu, Toru Yamashita, Nozomi Hishikawa, Yasuyuki Ohta, Koji Abe***
PC-2	EF-004 RECEPTORS IN PANCREATIC CANCER: EXPRESSION AND ITS ROLE IN REGULATING THE ORPHAN NUCLEAR RECEPTOR ***Yi-Wen Chou, Mao-Hsuan Huang, Shinn-Zong Lin, Horng-Jyh Harn***
PC-3	EFFECT OF RIBOFLAVIN CONCENTRATION ON THE DEVELOPMENT OF PHOTO-CROSS-LINKED AMNIOTIC MEMBRANES FOR CULTIVATION OF LIMBAL EPITHELIAL CELLS ***Li-Jyuan Luo, Jui-Yang La***
PC-4	STABILIZATION OF COLLAGEN NANOFIBERS WITH L-LYSINE IMPROVES THE ABILITY OF CARBODIIMIDE CROSS-LINKED AMNIOTIC MEMBRANES TO PRESERVE LIMBAL EPITHELIAL PROGENITOR CELLS ***Si-Tan Chen, Jui-Yang Lai***
PC-5	HK-001 DOWN-REGULATION AUTOPHAGY IN SPINAL CORD PROLONGS THE SURVIVAL OF ALS MICE ***Kuo-Wei Hsueh, Shinn-Zong Lin, Horng-Jyh Harn***
PC-6	EF-001 RE-EXPRESSES TUMOR SUPPRESSOR GENE THOUGHT DNA METHYLTRANSFERASE INHIBITION IN GLIOBLASTOMA CELL LINES ***Mao-Hsuan Huang, Shinn-Zong Lin, Tzyy-Wen Chiou, Horng-Jyh Harn***
PC-7	DEVELOPING A NEW DRUG THAT PREFERENTIALLY TARGET BRAIN CANCER STEM CELLS - CANDIDATES TARGETING EZH2 AND AXL-1 ***Ssu-Yin Yen, Shinn-Zong Lin, Horng-Jyh Harn, Tzyy-Wen Chiou***
PC-8	ISOCHAIHULACTONE INDUCES APOPTOSIS OF HUMAN GLIOBLASTOMA MULTIFORME CELLS THROUGH THE ENDOPLASMIC RETICULUM STRESS RELATED PROTEIN DDIT3 MODULATED NAG-1 ***Sheng-Fong Tsai, Mao-Hsuan Huang, Hong-Meng Chuang, Yi-Wen Chou, Ssu-Yin Yen, Horng-Jyh Harn***

PC-9	TO EXPLORE THE EFFECT OF MIR-21 IN HUMAN MELANOMA A375.S2 CELL FROM UV RAYS INDUCED MELANIN PIGMENTATION ***Kuan-Yu Lin, Woei-Cherng Shyu, Lian Chiu, Cheng-You Lu***
Cutting Edges of Stem Cell & Immune Modulation	
PD-1	GENETIC ENGINEERED MESENCHYMAL STEM CELLS EXPRESSING INTERLEUKIN-12 AND/ OR INTERLEUKIN-18 ACTIVATED UNPRIMED T LYMPHOCYTES ***Fei Ling Yap, Chooi Fun Leong, Ammu Radhakrishnan, Soon Keng Cheong***
Adipose-Derived Stem Cell Plasticity for Regenerative Medicine	
PE-1	EFFECT OF ADIPOSE-DERIVED STEM CELL THERAPY ON PERIODONTAL REGENERATION IN SURGICALLY-CREATED DEFECT IN RAT ***Hsiao-Pei Tu, Min-Wen Fu, Chieh Wang, Earl Fu***
PE-2	INTRACEREBRAL IMPLANTATION OF HUMAN ADIPOSE-DERIVED STEM CELLS AMELIORATES IMPAIRED SYNAPTIC PLASTICITY IN BETA-AMYLOID INFUSED RATS ***Sheng-Tzung Tsai, Guo-Fang Tseng, Horng-Jyh Harn, Po-Cheng Lin, Pi-Chun Huang, Shinn-Zong Lin***
PE-3	DEVELOP THE TEARING OF ROTATOR CUFF IN THE RAT MODEL BY SURGERY: PRELIMINARY EXPERIMENT OF A NOVEL TECHNIQUE ***Hsin-Shui Chen, Yu-Ting Su, Tzu-Min Chen, Horng-Jyh Harn, Shinn-Zong Lin, Yun-Chain Yau, Shao-Chih Chiu***
PE-4	THERAPEUTIC EFFECT OF ADSC STIMULATED BY HK-002 IN MOUSE THROMBOEMBOLIC STROKE MODEL ***Kang Chi, Po Cheng Lin, Horng-Jyh Harn, Shih-Ping Liu, Ru-Huei Fu, Shinn-Zong Lin***
PE-5	HK002 INDUCE EXPRESSION OF TENDON RELATED GENES IN HUMAN ADIPOSE-DERIVED STEM CELLS AND ENHANCE THE RESTORATION OF TENSILE STRENGTH OF TENDON IN THE ROTATOR CUFF INJURY MODEL ***Yi-Tung Jiang, Yu-Ting Su, Wan-Sin Syu, Shao-Chih Chiu***
PE-6	THE ANTI-SENESCENCE EFFECT OF TRANS-CINNAMALDEHYDE ON ADIPOSE-DERIVED STEM CELLS ***Karthyayani Rajamani, Yi-Chun Lin, Tung-Chou Wen, Jeanne Hsieh, Yi-Maun Subeq, Jen-Wei Liu, Po-Cheng Lin, Horng-Jyh Harn, Shinn-Zong Lin, Tzyy-Wen Chiou***
Stem Cell Technology for Neurodegenerative Diseases	
PF-1	ESTABLISH A SHRNA FUNCTIONAL SCREEN IN HESCS AND REVEAL A NOVEL METHOD TO GENERATE NSCS ***Shang-Chih Yang, Cheng-Kai Wang, Wei-Ju Chen, Wei-Kai Huang, Bei-Chia Yang, John Yu Jean Lu***
PF-2	TRANSFER OF HUMAN NEURAL STEM CELL SHEETS ENHANCES NEURONAL DIFFERENTIATION ***Chung-Hsing Chou***

PA-1

IDENTIFICATION OF A NOVEL OXIDATION-RELATED GENE MEDIATED HESC RENEWAL FROM A HIGH-THROUGHPUT SCREEN

Cheng-Kai Wang[1,2], Shang-Chih Yang [1,2], Wei-Kai Huang[2], Bei-Chia Yang[2], John Yu[2], Jean Lu[2]

[1] Institute of Biochemistry and Molecular Biology, National Yang-Ming University, Taipei, Taiwan
[2] Genomics Research Center, Academia Sinica, Taipei, Taiwan

Human embryonic stem cells (hESCs) derived from the inner cell mass of the early embryo and is characterized by its pluripotency, unlimited proliferation ability, and oncogenicity. hESCs can differentiate into embryoid body which composed by ectoderm, endoderm, and mesoderm cells. In addition, the oxidation stress can force ESC differentiation, but the direct molecular mechanism is unknown. By a high throughput screen with 517 shRNA, we pinpoint that 21 genes are essential for the ESC renewal. Among them, hESC-A is one of the most promising hits since it can efficiently affect both ES cell expansion and pluripotency to a level comparable to the knockdown of c-Myc. The hESC-A is a novel gene that its function and signals have never been reported. Thus we are the first group to demonstrate hESC-A gene functions. We found (1) hESC-A expression is enriched in undifferentiated hESCs, but not in differentiated ESCs and human fibroblasts. (2) hESC-A is essential for the expression of critical stem cell transcriptional factor such as Sox2 and Nanog, and the downregulation of hESC-A upregulate the expression level of p27. (3)In addition, the expression of shRNA of hESC-A (sh-hESC-A) forced hESC differentiated into endomesoderm and expressed the master regulator Brachyury. (4)Moreover, hESC-A is crucial for the maintenance of reduction/oxidation status of glutathione/Glutathione disulfide and preventing of oxidative apoptosis. Thus for the first time, we proposed a novel gene, hESC-A, can bridge the pluripotency signal with the oxidation pathway. This will contribute to our understanding in stem cell biology and the reduction pathway.

Keywords: human embryonic stem cells, differentiation, Sox2, reduction, oxidation

PB-1

DISRUPTION OF NME6 AFFECTS GASTRULATION AND LEADS TO EMBRYONIC LETHALITY DUE TO APOPTOSIS

Yu-Ting Kao[1], Chun-Yu Chen[2], I-Shing Yu[2], Shu-Wha Lin[2], Jean Lu[1]*

[1]Genomics Research Center, Academia Sinica, Taipei, Taiwan
[2]Department of Clinical Laboratory Sciences and Medical Biotechnology, National Taiwan University, Taipei, Taiwan

Nme6 plays a critical role in embryonic stem cells (ESCs) renewal by regulating Oct4, Nanog, Klf4, c-Myc, telomerase, Dnmt3B, Sox2, and ERas expression. However, the in vivo physiological function of Nme6 remains uncharacterized. To address the biological function of Nme6, we generate Nme6 knockout mice. Interestingly, no viable Nme6$^{-/-}$ could be obtained from the intercross of Nme6 heterozygote. We found that Nme6$^{-/-}$ embryos showed severe abnormalities between E6.5 and E7.5. During this stage, the Nme6$^{-/-}$ embryos displayed increasing apoptosis compared to wild-type embryos. The failure of DNA synthesis, essential for initiating gastrulation beginning around E6.5, is likely the cause of the embryonic lethality at E7.5 due to Nme6 disruption. Thus, these results demonstrate that Nme6 is essential for early development of mouse embryos.

PB-2

MESENCHYMAL STEM CELLS AND DERIVED CYTOKINES PROMOTE WOUND HEALING AND SKIN REGENERATION

Martin Sieber, Huan-Ting Lu

Technical department, BIONET Corp., Taipei, Taiwan

Background: Mesenchymal Stem Cells (MSC) are multipotent stem cells that have been isolated from various tissues. They are characterized as being able to multiply in vitro to large numbers, differentiate into many different cell types, and secrete growth factors and cytokines. MSC have been investigated in the fields of cell therapy, regenerative medicine, or tissue engineering; and also in wound healing. It has been reported that MSC promote wound healing through secretion of cytokines and growth factors. Here we test the capability of MSC from umbilical cord and dental pulp and MSC derived cytokines alone in mouse wound healing models.

Methods: Artificial full thickness wounds on normal mice were treated with MSC from umbilical cord or dental pulp. Cells were applied directly onto the wound every 2 days for 6 days. The same experiment was then performed on diabetic mice to show MSC can promote wound closure also on bad healing wounds. To show the effectiveness of MSC derived cytokines alone, cytokines were applied in a diabetic full thickness wound model, applied every 2 days. Increasing doses were tested. Further we investigated the effect of MSC derived cytokines on partial wounds, which were inflicted using laser.

Results: Both MSC from umbilical cord and dental pulp decreased the closure time of full thickness wounds in about 12 days, where the control needed 16 days for complete wound closure. In the diabetic model, wound closure occurred within 14 days and 16 days for treatment group and control, respectively. For this diabetic model, MSC derived cytokines alone could increase the healing speed. The concentration of cytokines was dose dependent, with a higher cytokine concentration closing the wound quicker. For the partial wounds, MSC derived cytokines had an enormous impact on the healing speed, with a size reduction of 80% within 5 days compared to 40% in the control group. Complete healing time was 16 days for the treatment group and 18 days for the control.

Conclusion: Mesenchymal Stem Cells from umbilical cord as well as dental pulp promote wound closure in normal and diabetic full thickness wounds, making those cells very useful in regenerative medicine, and will be of importance especially in the treatment of chronic and bad healing wounds, which have extended healing times. The MSC derived cytokines alone can enhance wound healing and may be an alternative to the cells. As they can also be used for lighter wounds as they occur at laser abrasions, the cytokines may therefore extend their use into the field of cosmetics.

PC-1

PROTECTIVE EFFECT OF TELMISARTAN ON NEUROVASCULAR UNIT AND INFLAMMASOME IN STROKE-RESISTANT SPONTANEOUSLY HYPERTENSIVE RATS

Wentao Liu, Toru Yamashita, Nozomi Hishikawa, Ohta Yasuyuki, Koji Abe

Department of Neurology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Japan

Objectives: Hypertension is a crucial risk factor both for stroke and dementia, including Alzheimer's disease (AD). We inspected the effect of telmisartan on the neurovascular unit (NVU) and related inflammatory responses in spontaneously hypertensive rat stroke resistant (SHR-SR) by observing the components of NVU such as N-acetyl glucosamine oligomer (NAGO), collagen IV, astrocytes, and matrix metalloproteinase-9 (MMP-9), as well as inflammasome NOD-like receptors family protein 3 (NLRP3).

Methods: In the present study, we examined the effect of a highly selective angiotensin type 1 (AT-1) antagonist of angiotensin 2 receptor with high lipid solubility, telmisartan, on NVU and related inflammatory responses in SHR-SR with a low dose (0.3 mg/kg/day) only for improving metabolic syndrome, and a high dose (3 mg/kg/day) for improving both metabolic syndrome and SHR-SR hypertension.

Results: Compared to normotensive Wistar rats, long-lasting hypertension in SHR-SR disrupted NVU by changing immunohistological components such as NAGO, collagen IV, astrocytes, and MMP-9. SHR-SR also strongly induced AD-related inflammasome NLRP3 in neuronal cells with age. However, such NVU disruption and inflammasome activation were greatly improved with dose-dependent telmisartan treatments.

Discussion: These results suggest that telmisartan comprehensively protected the NVU components by reducing inflammatory reactions relative to AD in hypertensive rats, which could also preclude the risk of AD under hypertension.

PC-2

EF-004 RECEPTORS IN PANCREATIC CANCER :EXPRESSION AND ITS ROLE IN REGULATING THE ORPHAN NUCLEAR RECEPTOR

Yi-Wen Chou[1], *Mao-Hsuan Huang*[2], *Shinn-Zong Lin*[1,3,4] *and Horng-Jyh Harn*[3,4]

[1] Center for Neuropsychiatry, China Medical University Hospital, Taichung, Taiwan
[2] Department of Life Sciences, National Chung Hsing University, Taichung, Taiwan
[3] Department of Pathology, China Medical University Hospital, Taichung, Taiwan
[4] Department of Medicine, China Medical University, Taichung, Taiwan

BACKGROUND

Pancreatic cancer is highly treatment-resistant and has one of the highest fatality rates of all cancers

and is the fourth highest cancer killer worldwide. The 5-year survival rate remains <5%. New treatment methods to improve survival and quality of life in patients with urgent needs PC. In this study, we developed a novel compound EF-004 and determined that it inhibits cancer cell growth. Furthermore, we found that all three members of the NR4A1, NR4A2 and NR4A3 orphan nuclear hormone receptor subfamily were transcription factors that exert their functions through activation and subsequent induction of the downstream pathways. . They have been shown to play a role in complex pathways of cell survival and apoptosis.

METHODS

Pancreatic cancer cells line Mia-PACA2 was treated with EF-004 and MTT assay was determined the cell survival. To determine the mechanism of EF-004-induced growth arrest and apoptosis. Using an orthotopic animal model,the orthotopic mouse model of human pancreatic cancer was established by injecting GFP-expressing MiaPaCa-2 human pancreatic cancer cells into the pancreas of 6-week-old female athymic mice.

RESULTS

The human pancreatic cancer cell line, MiaPaCa-2, was used for the orthotopic model. EF-004 significantly inhibited pancreatic cancer tumor growth and metastasis, as measured by imaging, with no overt toxicity. Survival of tumor-bearing mice was also prolonged by EF-004 treatment.

CONCLUSION

The results indicate that EF-004 can have non-toxic efficacy against metastatic pancreatic cancer and that EF-004 can have an important role in the treatment of pancreatic cancer.

PC-3

EFFECT OF RIBOFLAVIN CONCENTRATION ON THE DEVELOPMENT OF PHOTO-CROSS-LINKED AMNIOTIC MEMBRANES FOR CULTIVATION OF LIMBAL EPITHELIAL CELLS

Li-Jyuan Luo [1], Jui-Yang Lai [1]

[1] Institute of Biochemical and Biomedical Engineering, Chang Gung University, Kwei-Shan, Taoyuan, Taiwan

The amniotic membrane (AM) is featured with low immunogenicity, anti-inflammatory, anti-angiogenic, and anti-scarring properties. Although the AM has been clinically shown to help management of ocular surface diseases, the matrix material itself appears to be limited by rapid degradation and resorption in vivo. The photo-cross-linking-mediated alterations in AM ultrastructure and nanotopography were confirmed by transmission electron and atomic force microscopy studies. The in vitro biocompatibility of photo-cross-linked AM materials was assessed by measuring the viability of human corneal epithelial cells, and analyzing the anti-inflammatory activity of test samples. Irrespective of the riboflavin concentration, the test samples were fully biocompatible and retained anti-inflammatory activities. Results of quantitative real-time reverse transcription polymerase chain reaction and Western blot analyses showed that the LECs cultured on the AM substrates with different cross-linking densities had varying levels of enhanced stemness. Given that the cell differentiation ability strongly depends on matrix stiffness, the mechanical properties of photo-cross-linked AM correlated with the photoinitiator concentration may also contribute to the maintenance of stemness in LEC cultures. In the future, taking the advantages of photo-cross-linking-mediated surface nanotopographical features, the behaviors of LECs cultured on the UV-irradiated biological tissues can be adequately controlled through the design of the stable AM scaffolds with tunable cross-linking densities. For the first time, here we demonstrate that the riboflavin concentration may play an important role in the modulation of properties of photo-cross-linked AM as a new LEC carrier.

PC-4

STABILIZATION OF COLLAGEN NANOFIBERS WITH L-LYSINE IMPROVES THE ABILITY OF CARBODIIMIDE CROSS-LINKED AMNIOTIC MEMBRANES TO PRESERVE LIMBAL EPITHELIAL PROGENITOR CELLS

Si-Tan Chen [1], *Jui-Yang Lai* [1]

[1] Institute of Biochemical and Biomedical Engineering, Chang Gung University, Kwei-Shan, Taoyuan, Taiwan

To overcome the drawbacks associated with limited cross-linking efficiency of carbodiimide modified amniotic membrane, this study investigated the use of L-lysine as an additional amino acid bridge to enhance the stability of a nanofibrous tissue matrix for a limbal epithelial cell culture platform. Results of ninhydrin assays and zeta potential measurements showed that the amount of positively charged amino acid residues incorporated into the tissue collagen chains is highly correlated with the L-lysine-pretreated concentration. The cross-linked structure and hydrophilicity of amniotic membrane scaffolding materials affected by the lysine molecular bridging effects were determined. With an increase in the L-lysine-pretreated concentration from 1 to 30 mM, the cross-linking density was significantly increased and water content was markedly decreased. The variations in resistance to thermal denaturation and enzymatic degradation were in accordance with the number of cross-links per unit mass of amniotic membrane, indicating L-lysine-modulated stabilization of collagen molecules. It was also noteworthy that the carbodiimide cross-linked tissue samples prepared using a relatively high L-lysine-pretreated concentration (ie, 30 mM) appeared to have decreased light transmittance and biocompatibility, probably due to the influence of a large nanofiber size and a high charge density. The rise in stemness gene and protein expression levels was dependent on improved cross-link formation, suggesting the crucial role of amino acid bridges in constructing suitable scaffolds to preserve limbal progenitor cells. It is concluded that mild to moderate pretreatment conditions (ie, 3–10 mM L-lysine) can provide a useful strategy to assist in the development of carbodiimide cross-linked amniotic membrane as a stable stem cell niche for corneal epithelial tissue engineering.

PC-5

HK-001 DOWN-REGULATION AUTOPHAGY IN SPINAL CORD PROLONGS THE SURVIVAL OF ALS MICE

Kuo-Wei Hsueh[1,2], Shinn-Zong Lin[2,3,4], Horng-Jyh Harn[5,6]

[1]Ph.D. Program for Aging, Dep. of Medicine, China Medical University, Taichung, Taiwan
[2]Center for Neuropsychiatry, China Medical University Hospital, Taichung, Taiwan
[3]Department of Neurosurgery, China Medical University Beigan Hospital, Yunlin, Taiwan
[4]Graduate Institute of Immunology, China Medical University, Taichung, Taiwan
[5]Department of Pathology, China Medical University Hospital, Taichung, Taiwan
[6]Department of Medicine, China Medical University, Taichung, Taiwan

Background：

Amyotrophic lateral sclerosis (ALS) is a lethal degenerating disease, characterized by progressive muscular atrophy without any effective treatment. Here, we demonstrated the efficacy of abrograting autophagy in motor neurons (MN) by treatment with HK-001 in ALS transgenic mice ($SOD1^{G93A}$). In this study, we found HK-001 may pose as a therapeutic regimen for ALS and relevant neurodegenerative diseases.

Methods：

Animals were randomly distributed into three groups at 60 days of age: (1) vehicle, (2) HK-001 (100)-treated, given 100 mg HK-001/Kg/qd body weight, (3) HK-001 (500)-treated, given 500 mg HK-001/Kg/qd body weight, and (4) 250 mg HK-001/Kg/bid body weight. HK-001 was dissolved in olive oil (HK-001; Lancaster Synthesis Ltd., Newgate, Morecambe, UK), and administered by oral gavages once daily beginning at 60 days of age. The end-point was determined as the inability of the mouse to roll over within 30 s after being placed on its side (Gurney et al., 1996).

Results：

Pre-symptomatic oral administration of 250 mg/kg/bid HK-001 significantly prolonged the survival period (203.9 ± 18.3 days), improved motor function, and attenuated MN loss compared to vehicle control (126.4 ± 7.2 days). This prolonged survival of ALS mice is much more robust than that reported with riluzole (133.7 ± 6.4 days), which is an approved clinical therapy for ALS. The therapeutic mechanism targeted by HK-001 involved the autophagic pathway as evidenced by decreased LC3-II expression (a biomarker of autophagy), enhanced mTOR levels, and attenuated autophagic activity, altogether increasing MN survival in a dose-dependent manner. This result was also confirmed by double transgenic mice ($SOD1^{G93A}$::LC3-GFP) which showed that oral administration of HK-001 reduced GFP density and decreased caspase-3 expression. In addition, electron microscopy revealed that HK-001 administration not only decreased autophagosome number but also reduced morphological dysfunction of mitochondria. In summary, these results indicate that down-regulation of autophagy activation via HK-001 may as potential compound for testing therapeutic effect in ALS symptoms.

PC-6

EF-001 RE-EXPRESSES TUMOR SUPPRESSOR GENE THOUGHT DNA METHYLTRANSFERASE INHIBITION IN GLIOBLASTOMA CELL LINES

Mao-Hsuan Huang[1], *Shinn-Zong Lin*[2, 3, 4], *Tzyy-Wen Chiou*[5], *Horng-Jyh Harn*[6, 7]

[1]Department of Life Sciences, National Chung Hsing University, Taichung, Taiwan
[2]Center for Neuropsychiatry, China Medical University and Hospital, Taichung, Taiwan
[3]Department of Neurosurgery, China Medical University Beigan Hospital, Yunlin, Taiwan
[4]Graduate Institute of Immunology, China Medical University, Taichung, Taiwan
[5]Department of Life Sciences and Graduate Institute of Biotechnology, National Dong Hwa University, Hualien, Taiwan
[6]Department of Medicine, China Medical University, Taichung, Taiwan
[7]Department of Pathology, China Medical University Hospital, Taichung, Taiwan

Background

Recent studies have shown some important genes are silence due to hypermethylation of promoter regions in cancer. DNA methyltransferases (DNMT) regulation provides novel opportunities for the therapy of cancers. Here we report that EF-001, a small molecular from traditional Chinese herb can inhibit DNMT activity and rescue tumor suppressor gene in glioblastoma cells.

Methods

GBM cell lines GMB22 were treated with EF-001. Then cell survival, promoter methylation, DNMT activity and tumor suppressor gene expression were measured.

Results

We treated human glioblastoma cells with EF-001 and growth reduction was observed within 48 hr. DNMT1 and DNMT3a expression was decreased after exposure to EF-001 as detected by RT-PCR and Western blot. In addition, tumor suppressor gene p53, p16, p21 and p27 expression was rescued. Then we analyze p16 promoter region by Methylation-specific PCR. The result show methylation ratio of CpG islands decrease in dose-dependent. In order to determined tumor suppressor gene re-expression mediated by DNMT, we restored the DNMT by exogenous overexpression. The p16 expression didn't increase after EF-001 treatment.

Conclusions

Those results suggest that EF-001 block DNMT might be involved tumor suppressor gene re-expression in glioblastoma cells.

PC-7

DEVELOPING A NEW DRUG THAT PREFERENTIALLY TARGET BRAIN CANCER STEM CELLS-CANDIDATES TARGETING EZH2 AND AXL-1

Ssu-Yin, Yen[1], Shinn-Zong Lin[2, 3,4,5], Horng-Jyh Harn[6,7], Tzyy-Wen Chiou[1]

[1]Department of Life Science and Graduate Institute of Biotechnology, National Dong Hwa University, Hualien, Taiwan
[2]Center for Neuropsychiatry, China Medical University Hospital, Taichung, Taiwan,
[3]Department of Neurosurgery, China Medical University Beigan Hospital, Yunlin, Taiwan
[4]Department of Neurosurgery, China Medical University An-Nan Hospital, Tainan, Taiwan
[5]Graduate Institute of Immunology, China Medical University, Taichung, Taiwan
[6]Department of Pathology, China Medical University Hospital, Taichung, Taiwan
[7]Department of Medicine, China Medical University, Taichung, Taiwan

Glioblastoma multiforme (GBM) is the most common and aggressive brain tumors. It has high recurrence rate and high mortality rate. The main cause of tumor recurrence is twofold: one, highly vascularized malignant brain tumors and invasive, diffuse growth characteristics, and normal brain tissue and tumor margin has been difficult to define, making it impossible to completely remove the tumor in surgery. Second, the cause of cancer recurrence or chemotherapy for cancer treatment, radiation therapy for cancer, one of the reasons that cancer is not valid exist in cancer stem cells(CSCs). Therefore, the treatment of malignant glioma remains an important challenge to the medical profession, to understand the mechanism of brain tumor and invasion of GBM CSCs is one of the new therapeutic strategies to develop essential. EZH2 is highly expressed in a wide range of cancer types, including breast, prostate, colon, lung, brain, pancreatic cancer. Overexpression of EZH2 is often correlated with advanced stages of human cancer progression and poor prognosis. Also, EZH2 is essential for GBM CSCs self-renewal and tumorigenicity. Axl-1 has been shown to be involved in tumor invasiveness and metastases in multiple tumors including GBM. In our study, we found that cell-cycle *arrest* at $G2/M$ and growth inhibition by EF-001 in human GBM CSCs. Beside, EF-001 can regulate EZH2 and Axl-1 expression in GBM CSCs, and it also influences the GBM CSCs stemness. Furthermore, EF-001 can reduce the migratory and invasive capabilities of GBM CSCs, and Axl is a crucial target in the inhibition of GBM CSCs EMT, migration, and invasion. These results will contribute to understand the mechanism of EZH2 and Axl on CSCs and the development of a new drug for treating GBM high recurrence rate and high mortality rate and increasing survival in clinical.

PC-8

ISOCHAIHULACTONE INDUCES APOPTOSIS OF HUMAN GLIOBLASTOMA MULTIFORME CELLS THROUGH THE ENDOPLASMIC RETICULUM STRESS RELATED PROTEIN DDIT3 MODULATED NAG-1

Sheng-Fong Tsai[1] , Mao-Hsuan Huang[1] , Hong-Meng Chuang[1] , Yi-Wen Chou[2] , Ssu-Yin Yen[3] , Horng-Jyh Harn[4,5]

[1]Department of Life Sciences, National Chung Hsing University, Taichung, Taiwan
[2]Center for Neuropsychiatry, China Medical University Hospital, Taichung, Taiwan
[3]Department of Life Science and Graduate Institute of Biotechnology, National Dong Hwa University, Hualien, Taiwan
[4]Department of Pathology, China Medical University and Hospital, Taichung, Taiwan
[5]Department of Medicine, China Medical University, Taichung, Taiwan

Glioblastoma multiforme (GBM) is the most malignant brain tumor characterized, most aggressive, poor prognosis and untreatable. There is urgent need to identify novel drugs targeting GBM and to develop more effective therapeutic strategies. Isochaihulactone, which extracted from Chinese traditional herb NAN CHAI HU, have proved dramatic anti-tumor ability to against prostate cancer and lung cancer. In this study, we find that isochaihulactone decrease GBM cell line cell viability, cause GBM cell lines apoptosis and cell cycle arrest in G2/M stage in dose-dependent treatment. The endoplasmic reticulum stress always inactivate in normal cell but overexpressed in several cancer. DDIT3 (DNA damage induced transcriptional factor 3) is a apoptotic factor that is activated at multiple levels during ER stress. We found that isochaihulactone can induced DDIT3 in GBM cell line. Many anti-cancer drugs and chemicals induce NAG-1 expression, but the mechanisms are not fully understood between DDIT3 and NAG1. We demonstrated that isochaihulactone induced DDIT3 expression to up-regulate NAG-1 expression leading glioblastoma cell death. And we use siRNA to knockdown DDIT3 in transcription level, the NAG1 mRNA expression level depression as well. In vivo study, we use the xenograft animal model to demonstrate isochaihulactone did inhibit the GBM tumor growth. In summary, this result support isochaihulactone cause glioblastoma cell apoptosis via DDIT3 and NAG1 tumor suppressor pathway.

PC-9

TO EXPLORE THE EFFECT OF MIR-21 IN HUMAN MELANOMA A375.S2 CELL FROM UV RAYS INDUCED MELANIN PIGMENTATION

Kuan-Yu Lin[1], Woei-Cherng Shyu[2, 3], Lian Chiu[4], Cheng-You Lu[2, 3]*

[1]Dermatology, Feng Yuan Hospital, Ministry of Health and Welfare, Taichung, Taiwan
[2]Center for Neuropsychiatry and Translational Medicine Research Center, China Medical University Hospital, Taichung, Taiwan
[3]Graduate Institute of Immunology, China Medical University, Taichung, Taiwan
[4]Department of Nursing, College of Medicine and Nursing, Hungkuang University, Taichung, Taiwan

The excessive environmental ultraviolet (UV) radiation produces genetic mutations that can lead to skin cancer. The present study was designed to assess the potential inhibitory activity of microRNA-21 (miR-21) on the UV irradiation- stimulated melanogenesis signal pathway in melanoma cells. The molecular mechanism of miR-21-induced inhibitory activity on the UV-stimulated melanogenesis-regulating proteins was examined in A375.S2 cells. UV irradiation induced melanogenesis signal pathway by increasing melanin production and A375.S2 cell number. Similarly, UV radiation increased α-melanocyte-stimulating hormone (α-MSH) protein expression and decreased melanogenesis-regulating signal such as EGFR and Akt phosphorylation. Notably, miR-21overexpression in UV stimulated A375.S2 cells decreased α-MSH expression, and increased EGFR and Akt phosphorylation levels. Furthermore, miR-21 on UV induced melanogenesis was down-regulated by Akt inhibitor and EGFR inhibitor (Gefitinib). Our results suggest that the activity of miR-21 on UV-stimulated melanogenesis may involve the down-regulation of α-MSH and the activation in both of EGFR and Akt.

PD-1

GENETIC ENGINEERED MESENCHYMAL STEM CELLS EXPRESSING INTERLEUKIN-12 AND/ OR INTERLEUKIN-18 ACTIVATED UNPRIMED T LYMPHOCYTES

Yap Fei-Ling[1], Leong Chooi-Fun[2], Ammu Radhakrishnan[1] and Cheong Soon-Keng[3]

[1] Pathology Division, International Medical University, Kuala Lumpur, Malaysia
[2] Blood Bank, Hospital Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia
[3] Faculty of Medicine and Health Sciences, Universiti Tunku Abdul Rahman, Sungai Long, Malaysia

Activation and proliferation of appropriate immune competent cells are one measure of a successful immune response. Multiple proteins include CD69, CD71, CD25 and HLA-DR are known to be up-regulated during the immune activation process. As an activation inducer molecule (AIM), CD69 is one of the most commonly studied activation marker owing to its early expression in activated T, B or NK cells. In the study, peripheral blood mononuclear cells (PBMCs) from healthy donors were stimulated with genetic engineered mesenchymal stem cells (GE-MSCs) expressing IL-12 and/ or IL-18 or their conditioned media, respectively and were analyzed for the expression of CD69 using flow cytometer. Daily kinetic experiments were performed to compare responsiveness from day 1 to day 4. Activated T lymphocyte subsets ($CD69^+$) in helper T lymphocytes ($CD3^+/CD4^+$) and cytotoxic T lymphocytes ($CD3^+/CD8^+$) in PBMCs were identified and enumerated. From the study, GE-MSCs expressing IL-12 and/ or IL-18 as well as their conditioned media were able to up-regulate the expression of CD69. In fact, a gradual increase in CD69 expression was observed in activated T cells from day 1 until day 4. There was no significant difference in the CD69 expression in PBMCs that were co-cultured with the GE-MSCs compared to PBMCs that was stimulated with their respective conditioned media, suggesting that GE-MSCs did not interfere with the expression of CD69. It was also noted that only the activated T cells expressed CD69 but not the resting T lymphocytes. In conclusion, GE-MSCs expressing IL-12 and/ or IL-18 do not prevent priming of T cell activation but capable of activating the unprimed T lymphocytes by up-regulating CD69. Thus, the GE-MSCs generated were able to act as T lymphocytes activator rather than suppress the immunological response.

PE-1

EFFECT OF ADIPOSE-DERIVED STEM CELL THERAPY ON PERIODONTAL REGENERATION IN SURGICALLY-CREATED DEFECT IN RAT

Hsiao-Pei Tu[1,2], Min-Wen Fu[1], Chieh Wang[1], Earl Fu[1]

[1] Department of Periodontology, School of Dentistry, National Defense Medical Center and Tri-Service General Hospital, Taipei, Taiwan, ROC Affiliation

[2] Department of Dental Hygiene, China Medical University, Taichung, Taiwan

Background: Aim of study was to evaluate the regenerative ability of the adipose stem cells (ADSCs) in the surgically created periodontal defect of rat.

Materials and methods: Twenty four male SD rats were divided into four groups, including control, defect, ADSC, and ADSC-plus-Ligustilide (LIG) groups. Under the general anesthesia, the sham operation of gingival flapping was performed on the region mesial to the first maxillary molar in control rats. In defect group, the bony defect was surgically created and a collagen sponge with saline was inserted into the defect, whereas the collagen sponge soaked with stem cells (ADSCs, approximately 2 × 106) without and with LIG (10 ug/ml) was inserted into the defect for the ADSC, and ADSC-plus-LIG groups, respectively. Ten weeks later, all animals were sacrificed and the maxillary specimens were obtained for dental radiography and microcomputed tomography (micro-CT).

Results: The radiographic distance from CEJ to bone increased in animals of defect group if compared that of control group; however, the distance of ADSC-plus-LIG group was significantly reduced if compared with that of defect group but similar to that of control group. Opposite findings were observed for the radiographic PBSr measurements. By micro-CT, the similar findings were repeatedly observed as that by radiography, except that the distance from CEJ to bone and PBSr in ADSC group were also significantly reduced if compared with that in defect group. We therefore suggested that the ADSC-pluse-LIG might have a potential to regenerate the lost periodontal tissue, at least in this surgically created periodontal defect animal model. Further detailed investigation is needed.

PE-2

INTRACEREBRAL IMPLANTATION OF HUMAN ADIPOSE-DERIVED STEM CELLS AMELIORATES IMPAIRED SYNAPTIC PLASTICITY IN BETA-AMYLOID INFUSED RATS

Sheng-Tzung Tsai[1], Guo-Fang Tseng[2], Horng-Jyh Harn[3], Po-Cheng Lin[4], Pi-Chun Huang[4], Shinn-Zong Lin[3]

[1]Department of Neurosurgery, College of Medicine, Tzu Chi University, Hualien, Taiwan
[2]Department of Anatomy, College of Medicine, Tzu Chi University, Hualien, Taiwan
[3]Department of Neurosurgery, China Medical University Beigang Hospital, Yunlin, Taiwan
[4]Gwo Xi Stem Cell Applied Technology Co., Ltd, Hsinchu, Taiwan

Background: Alzheimer's dementia (AD) involves declines in memory and cognition and results from β-amyloid (Aβ) deposition and dysfunctional cognitive circuits from the hippocampus to the cerebral cortex. The aim of this study is to evaluate the feasibility and therapeutic potentials of human adipose-derived stem cells (ADSC) for Aβ infused AD rats.

Methods: Intraventricular Aβ protein infusion in rats was used as the model of dementia. The spatial memory acquisition of the rats was evaluated with the Morris water maze task (WMT). Expression levels of the glutamatergic post-synaptic density protein 95 (PSD95) in the medial prefrontal cortex (mPF) and CA1 hippocampus were examined to assess excitatory connectivity. Additionally, the dendritic spines of the pyramidal neurons in the studied areas were revealed with intracellular dye injection and analyzed accordingly.

Results: We confirmed that human ADSC successfully survived in brain at four weeks after intracerebral implantation. Intracerebral implantation of ADSC significantly improved the escape latency in WMT of Aβ infusion rats to a level comparable to that in the normal control rats. In addition, ADSC reversed the reduction in PSD95 in the mPF and CA1 hippocampus that were observed in Aβ infusion rats, restoring PDS95 expression to levels comparable to those of the normal controls. Morphologically, ADSC also increased the densities of dendritic spines on the pyramidal neurons in the mPF and hippocampal CA1 of the Aβ infusion rats to levels comparable to those of the normal controls.

Conclusions: Human ADSC may be used as a treatment for AD through it's improvement in structural synaptic plasticity.

PE-3

DEVELOP THE TEARING OF ROTATOR CUFF IN THE RAT MODEL BY SURGERY: PRELIMINARY EXPERIMENT OF A NOVEL TECHNIQUE

Hsin-Shui Chen[1,2,3], Yu-Ting Su[1], Tzu-Min Chan[4], Horng-Jyh Harn[6], Shinn-Zong Lin[6,7,8,9], Yun-Chain Yau[3], Shao-Chih Chiu[6,7]

[1] Department of Physical Medicine and Rehabilitation, China Medical University Beigang Hospital, Yunlin, Taiwan
[2] College of Medicine, School of Medicine, China Medical University, Taichung, Taiwan
[3] PH.D. Program of Aging, School of Medicine, China Medical University, Taichung, Taiwan
[4] Department of Medical Education and Research, China Medical University Beigang Hospital, Yunlin, Taiwan
[5] Department of Pathology, China Medical University Hospital, Taichung, Taiwan
[6] Graduate Institute of Immunology, China Medical University, Taichung, Taiwan
[7] Center for Neuropsychiatry, China Medical University Hospital, Taichung, Taiwan
[8] Department of Neurosurgery, Tainan Municipal An-Nan Hospital, Tainan, Taiwan
[9] Department of Neurosurgery, China Medical University Beigang Hospital, Yunlin, Taiwan

Background: Rotator cuff tear is a common issue in shoulder tendon injury. It is easily caused by improper lifting or pulling, repetitive stress and the impinge by acromion spur. Not only the elders, people who stretches their muscles all the time, such as the baseball pitcher or construction worker, are the main candidates in this type of injury. The rotator cuff repair is an often procedure to treat rotator cuff tear and improved the shoulder pain and function. No acceptable rat model to rotator cuff full thickness tear was developing for study. Therefore, we develop a new concept to induce rotator cuff tendon full-thickness tear rat model.

Methods: We open the bilateral SD rat skins and use the ear punch to induce a small full thickness hole (5/64 inch) at one side supraspinatus tendon then close the skin bilateral and follow up 21 days .We sacrificed the rat and separated the bilateral supraspinatus tendon. The tension tensile test, which we develop to define the strengthening of bilateral supraspinatus tendon, is used to figure the tenacity.

Results: Three days after the manual tearing, supraspinatus tendon is showing a significant bleeding in area when compared with control group, and the tendon tensile strengths are significantly decreased to 15.33±4.61N. At day seven, the translucent milky white new tissues-form is surrounded on the surface of tendon, this phenomenon will gradually reduce as the day pass, and fully disappear after twenty-one days. The tendon tensile strength is recovered to 19.49±1.54N at day seven. At fourteen and twenty-one days, the tendon tensile strength will significantly increase to 30.06±0.49N and 31.91±0.46N, respectively.

Conclusions: The results confirm that new technique in rotator cuff tear reduces tendon strength. Therefore, the research direction of rotator cuff tendon repair in future will be focusing on adipose stem cells, which has the ability to differentiate into tendon cells in vitro and in vivo. This idea will also be developed with animal model.

PE-4

THERAPEUTIC EFFECT OF ADSC STIMULATED BY HK-002 IN MOUSE THROMBOEMBOLIC STROKE MODEL

Kang Chi[1], Po Cheng Lin[2], Horng-Jyh Harn[1], Shih-Ping Liu[1], Ru-Huei Fu[1], Shinn-Zong Lin[1]

[1] Center for Neuropsychiatry, China Medical University Hosipital, Taichung, Taiwan
[2] GWOXI Stem Cell Applied Technology Co., Ltd, Hsinchu, Taiwan

Stroke is caused by cerebral ischemia which triggers a cascade of both physiological and biochemical events and it has no effective therapeutic method. For this reason, stem cells may become a powerful material to rescue stroke. Adipose-derived stem cells (ADSCs) are abundant adult stem cells source for future regenerative medicine. However, the therapeutic efficiency of ADSC transplanted into stroke mouse model requires further improvement. HK-002 isolated from *Angelica sinesis* has been shown to have neuronal protective effect. We also demonstrated that HK-002 treatment increase expression level of homing factors such as SDF-1 and CXCR4. In this study we investigated the therapeutic effect of ADSC transplantation combined with HK-002 treatment in mouse thromboembolic stroke model by behavior tests including Beam Walking, Locomotor Activity and Rotarod. ADSCs with pretreatment of HK-002 were transplanted into the brain of stroke mice. The results showed that the therapeutic effect of ADSCs pretreated with HK-002 is better compared to those without pretreatment. Interestingly, mice with ADSCs transplantation combined with HK-002 S.C. treatment showed no better recovery result than those with only ADSCs transplantation. The TUNEL assay showed that apoptosis cells in mice transplanted with ADSCs pretreated both with and without HK-002 are fewer than those in control group. In summary, ADSCs pretreated with HK-002 improve the therapeutic efficiency in transplantation treatment. The results will help to provide an improved stem cell therapeutic strategy in the future clinical application.

PE-5

HK002 INDUCE EXPRESSION OF TENDON RELATED GENES IN HUMAN ADIPOSE-DERIVED STEM CELLS AND ENHANCE THE RESTORATION OF TENSILE STRENGTH OF TENDON IN THE ROTATOR CUFF INJURY MODEL

*Yi-Tung Jiang[1], Yu-Ting Su[1], Wan-Sin Syu[2], Shao-Chih Chiu[1,3]**

[1] Graduate Institute of Immunology, China Medical University, Taichung, Taiwan
[2] Gwo Xi Stem Cell Applied Technology Co., Ltd, Hsinchu, Taiwan
[3] Center for Neuropsychiatry, China Medical University Hospital, Taichung, Taiwan

The prevalence of tendinopathy is increasing in the world as the average age of the population and life expectancy increases. Adult stem cell therapy for the treatment of tendon injuries is a growing area of research. Human adipose-derived stem cells (hADSCs) are multipotent cells that can differentiate into tenocyte-like cells under appropriate induction *in vitro*. In the present study, we examined the effect of HK002 on human adipose-derived stem cell (hADSC) and also evaluated whether the effects of hADSC application can be further fine-tuned by pre-conditioning treatment using HK002 or growth factors. It had been shown over 2-fold changes in expression levels of tendon related genes (EGR1: 2.7 fold, SCX: 2.5 fold, DCN: 2.8 fold, TNC: 3.6 fold and COL1a1: 2.3 fold) after pretreating hADSC with HK002 by real-time RT-PCR analysis. Furthermore, injection of preconditioned hADSC in the site of rotator cuff injury had indicated the enhancement of restoration of tensile strength at day-7. It was also observed the over expression of tendon related proteins (SCX, TNC and COL1a1) in tendon tissues by use of immunohistochemistry staining. Taken together, these findings demonstrate that the recovery processes in damaged tendons can be potentially facilitated *via* pretreatment of hADSC. The finding of present study provided fresh insights into the tendon healing and a new therapeutic manner for tendon cure.

PE-6

THE ANTI-SENESCENCE EFFECT OF TRANS-CINNAMALDEHYDE ON ADIPOSE-DERIVED STEM CELLS

Karthyayani Rajamani[1], Yi-Chun Lin[2], Tung-Chou Wen[1], Jeanne Hsieh[3], Yi-Maun Subeq[4], Jen-Wei Liu[1], Po-Cheng Lin[2], Horng-Jyh Harn[5], Shinn-Zong Lin[6-9], Tzyy-Wen Chiou*[1]*

[1]Department of Life Science and Graduate Institute of Biotechnology, National Dong Hwa University, Hualien, Taiwan
[2]Gwoxi Stem Cell Applied Technology Co., Ltd., Hsinchu, Taiwan
[3]Molecular Medicine Program, National Taiwan University, Taipei, Taiwan
[4]Department of Nursing, Tzu Chi University, Hualien, Taiwan
[5]Department of Pathology, China Medical University and Hospital, Taichung, Taiwan
[6]Graduate Institute of Immunology, China Medical University, Taichung, Taiwan
[7]Center for Neuropsychiatry, China Medical University Hospital, Taichung, Taiwan
[8]Department of Neurosurgery, China Medical University Beigang Hospital, Yunlin, Taiwan
[9]Department of Neurosurgery, China Medical University- An-Nan Hospital, Tainan, Taiwan

As assuring cell quality is an essential parameter for the success of stem cell therapy, the impact of various senescence-inducing stress signals, and strategies to circumvent them, has been an important area of focus in stem cell research. The aim of this study was to demonstrate the capacity of trans-cinnamaldehyde (TC) to reverse stress-induced senescence and maintain the quality of stem cells in a chemically (H_2O_2)-induced cell senescence model. Because of the availability and the promising application potential in regenerative medicine, adipose-derived stem cells (ADSCs) were chosen for the study. We found that H_2O_2 treatment resulted in the expression of senescence characteristics in the ADSCs, including decreased proliferation rate, increased senescence associated-β-galactosidase (SA-β-gal) activity, decreased *SIRT1* (silent mating type information regulation 2 homolog) expression and decreased telomerase activity. However, TC treatment was sufficient to rescue or reduce the effects of H_2O_2 induction, ultimately leading to an increased proliferation rate, a decrease in the percentage of SA-β-gal positive cells, upregulation of *SIRT1* expression, and increased telomerase activity of the senescent ADSCs at the cellular level. Moreover, a chemically induced liver fibrosis animal model was used to evaluate the functionality of these rescued cells in vivo. Liver dysfunction was established by injecting 200 mg/kg thioacetamide (TAA) intraperitoneally into Wistar rats every third day for 60 days. The experimental rats were separated into groups; normal group (rats without TAA induction), sham group (without ADSC transplantation), positive control group (transplanted with normal ADSCs); H_2O_2 group (transplanted with H_2O_2 -induced senescent ADSCs), and H_2O_2+TC group (transplanted with ADSCs pretreated with H_2O_2 and then further treated with TC). In the transplantation group, 1×10^6 human ADSCs were introduced into each rat via direct liver injection. Based on the biochemical analysis and immunohistochemical staining results, it was determined that the therapeutic effects on liver fibrosis by the induced senescent ADSCs (H_2O_2 group) were not as significant as those exerted by the normal ADSCs (the positive control group). However, the H_2O_2+TC group showed significant reversal of liver damage when compared to the H_2O_2 group 1 week post transplantation. These data confirmed that the TC treatment had the potential to reduce the effects of H_2O_2-induced senescence and to restore the in vivo functionality of the induced-senescent ADSCs. It is therefore suggested that TC has potential applications in maintaining stem cell quality and could possibly aid in the treatment of senescence-related disorders.

PF-1

ESTABLISH A SHRNA FUNCTIONAL SCREEN IN HESCS AND REVEAL A NOVEL METHOD TO GENERATE NSCS

Shang-Chih Yang[1], Cheng-Kai Wang [1], Wei-Ju Chen[3], Wei-Kai Huang[2], Bei-Chia Yang[4], John Yu[4], Jean Lu[1, 2]

[1] Institute of Biochemistry and Molecular Biology, National Yang-Ming University, Taipei, Taiwan
[2] Genomics Research Center, Academia Sinica, Taipei, Taiwan
[3] Genome and Systems Biology Degree Program, National Taiwan University, Taipei, Taiwan
[4] Institute of Stem Cell and Translational Cancer Research, Chang Gung University, Taoyuan, Taiwan

Human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSC) are characterized by their robust expansion ability and pluripotency. However, the application of ESCs or iPSCs derived cells is hampered by the low efficiency of differentiation. To reveal genes inhibit ESC differentiation, a shRNA functional screen is performed with 517 shRNA targets 121 genes. Based on the results of ESC undifferentiated marker alkaline phosphatase activity assay and the relative cell number alamar blue assays, 21 genes altered ESC pluripotency were identified.

Among these hits, the downregulation of one candidate gene, hESC-B, can promote ectoderm differentiation by the upregulation of early neuroectoderm genes SOX2 and PAX6 within 3days with nearly 100% efficiency. Of note, conventional differentiation methods required 1-2 weeks to differentiate hESCs into neural stem cells. Thus we identify an efficient method to derive ESCs to neural stem cells. Consistently, the overexpression of hESC-B inhibited the upregulation of SOX2, which is required for neuron induction. We also found that hESC-B can bind to the promoter regions of SOX2 and PAX6 by CHIP-PCR assay. This suggest hESC-B may serve as a suppressor by directly binding to Sox2 and Pax6 promoters.

We will further reveal the molecular mechanisms of how hESC-B inhibits neuroectoderm differentiation by the regulating SOX2 and PAX6. The downregulation of hESC-B with shRNA or siRNA provide an efficient method to generate neural lineage cells that might be useful for drug screening and regenerate medicine in the future.

PF-2

TRANSFER OF HUMAN NEURAL STEM CELL SHEETS ENHANCES NEURONAL DIFFERENTIATION

Chung-Hsing Chou

Department of Neurology, Tri-Service General Hospital, Taipei, Taiwan

Reconstruction of lost brain tissue with functional restoration poses a major challenge to the researchers in the field of tissue engineering. Tissue regeneration of human brain and restoration of lost brain functions is a main goal of clinical neurology. Neural stem cells (NSCs) have the potential of differentiating to neural lineage cells, including neurons, astrocytes, and oligodendrocytes. In addition to neural lineage cells, vascular endothelial cells (ECs), as well as extracellular matrix (ECM), are essential compositions of the neurovascular unit (NVU). Using a currently developed *in vitro* model of the neurovascular environment, human NSC sheets can be constructed by coculturing NSCs with ECs. ECM molecules were demonstrated by immunocytochemistry in the human NSC sheets for transplantation in both *in vitro* and *in vivo* models. Notably, the proportion of cells positive for a neuronal marker, MAP2, in the cell sheet was as twice as that in the NSC monoculture. Furthermore, the proportion of cells positive for MAP2 was doubled, when the cell sheet was transferred to a new surface coated with collagen, with the same duration of differentiation. Here we show that the technique of NSC sheet transfer would be a novel application guiding NSC differentiation. The ongoing study of NSC sheet transplantation in animal models of neurodegenerative diseases and traumatic brain injuries will reveal more evidence of the therapeutic effects of the cell sheet construct.

Everfront Award

Everfront Award for Stem Cells and Cancer Research

Everfront Award will be presented by the committee of the Pan Pacific Symposium on Stem Cells and Cancer Research (PPSSC) to an individual on the basis of world class research contributions in the field of stem cell and cancer researches. The contributions can be preclinical, clinical or translational work. The award consists of monetary value (including travel expenses and accommodation) and a plaque to be given at the annual meeting of PPSSC.

The Winner of 2011 Everfront Award

Paul R. Sanberg
Senior Vice President, Office of Research and Innovation
Distinguished University Professor
Executive Director, Center of Excellence for Aging and Brain Repair
Vice Chairman, Department of Neurosurgery and Brain Repair University of South Florida
U.S.A.

The Winner of 2012 Everfront Award

Kwok-Fai So
Chair of Anatomy, Department of Ophthalmology, and Jessie Ho Professor in Neuroscience,
Honorary Professor , Department of Anatomy
The University of Hong Kong
Hong Kong

The Winner of 2013 Everfront Award

Wise Young
Founding Director, W.M. Keck Center for Collaborative Neuroscience at Rutgers
Richard H. Shindell Chair in Neuroscience, Rutgers University, Piscataway, NJ
CEO and Co-Chair of the Board, China Spinal Cord Injury Network, Hong Kong
Distinguished Professor of Cell Biology & Neuroscience, Rutgers University
USA

The Winner of 2014 Everfront Award

Koji Abe
Professor and Chairman,
Department of Neurology, Graduate School of Medicine, Dentistry
and Pharmacological Sciences, Okayama University, Japan
President, International Society of Cerebral Blood Flow and Metabolism, USA

The Winner of 2015 Everfront Award

Mari Dezawa

Japan

CURRENT POSITION

Professor and Chair, Dept. of Stem Cell Biology and Histology & Dept. of Anatomy and Anthropology, Tohoku University Graduate School of Medicine

EDUCATION AND PAST POSITION

- 1983-1989 Undergraduate, School of Medicine Chiba University, Chiba, Japan.
- 1991-1995 Graduate, Dept. of Anatomy, Graduate School of Medicine, Chiba University

RESEARCH AND PROFESSIONAL EXPERIENCE

- 1983-1989 Dept. of the Internal Medicine and Cardiology, School of Medicine Chiba University. Resident.
- 1995-1997 Dept. of Anatomy, School of Medicine Chiba University. Research Associate
- 1997-2000 Dept of Ophthalmology、School of Medicine Chiba University. Research Associate
- 2000-2003 Dept. of Anatomy, Yokohama City University School of Medicine. Assistant Professor
- 2003-2008 Dept. of Anatomy and Neurobiology, Kyoto University Graduate School of Medicine, Associate Professor
- 2008-present Dept. of Stem Cell Biology and Histology & Dept. of Anatomy and Anthropology (Interlocking Professor), Tohoku University Graduate School of Medicine, Professor and Chairperson
- 2012-present Cellular and Structural Physiology Institute, Nagoya University Graduate School of Pharmaceutical Sciences, Visiting Professor

MEMBERSHIP OF ACADEMIC SOCIETIES

- American Association of Anatomist
- Society for Neuroscience
- Japanese Association of Anatomists
- Japanese Society of Microscopy
- The Japanese Society of Regenerative Medicine

ACADEMIC AWARDS

- 1997: Research Aid of Inoue Foundation for Science
- 1999: Incitement Award of the Japanese Association of Anatomists
- 2003: Incitement Award of the Japanese Society of Microscopy
- 2011: Prizes for Science and Technology, The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology, Japan Government

Acknowledgements

The Organizing Committee gratefully acknowledges the financial contribution from the following sponsors.

Government Units

	Bureau of Foreign Trade 經濟部國際貿易局
	Department of Health, Executive Yuan, R.O.C. 衛生福利部
	Ministry of Foreign Affairs, Republic of China (TAIWAN) 外交部
科技部	Ministry of Science and Technology 科技部
	Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (DOH102-TD-B-111-004)
	Ministry of Health and Welfare, China Medical University Hospital Cancer Research Center of Excellence (MOHW103-TD-B-111-03, Taiwan)

Corporate Sponsorship

Platinum Members

	Gwo Xi Stem Cell Applied Technology Co., Ltd. 國璽幹細胞應用技術股份有限公司
	Guang Li Biomedicine 光麗生醫股份有限公司 (在確定一次是要放光麗還是長弘)
	StemCyte Taiwan Co., Ltd. 台灣永生細胞股份有限公司
Taiwan Mitochondrion 台灣粒線體	Taiwan Mitochondrion Applied Technology Co.,Ltd 台灣粒線體應用技術股份有限公司

Others

Level Biotechnology Inc.
進階生物科技(股)公司

成漢教育基金會

Upwards Biosystems, LTD.
日龍儀器股份有限公司

Hsinchu City Tour

April 13, 08:00-18:30

Pick-up: AM 08:00-18:30
Date: April 13, 2015
At: Lobby of Sheraton Hsinchu Hotel
Duration: 10.5hr
Fare: NTD 3,000

Itinerary

1. Mawudo Exploration Forest
2. Nei Wen traditional Hakka restaurant
3. Nei Wen Old Street
4. HsiuChu Du Cheng Huang Temple

Mawudo Exploration Forest

Mawudo Exploration Forest is near the north part of Taiwan. The forest has many natural features and creates an environment for a diversity of animal species. It is much loved by tourists for a rich diversity of plants and animals living in this well-planned leisure park. If you come here, don't forget to take a photo with the 500-year-old waxberry tree in the park and take some sweet memories with you.

Nei Wen Traditional Hakka Restaurant

Within all the attractions, Nei Wen cinema is one of the most popular spots. The cinema has been restored into a traditional Hakka restaurant which offers great food, where old classic movies are played for free for dining guests, providing the experience of travelling through time, back to the old days.

Nei Wen Old Street

In Nei Wen, there are many scenery spots such as Nei Wen suspension bridge and Nei Wen old street; Nei Wen train station is also a well known spot which many tourists like to stay. Nei Wen suspension bridge is a key traffic way across Lo-Sie and Nan-pin. On the bridge, you can outlook all scenes of Lo-Sie river valley. Nei Wen old bridge is beyond the Nei Wen train station and many gourmet foods are available, such as Hakka food, traditional shaved ice, curd and cake.

HsiuChu Du Cheng Huang Temple

For millenniums, Taoism has been the most popular and influential religion among the Chinese people. It is unique to China, as no similar belief has ever been found in other countries. "Tao" in Chinese means "way" or "path". The religion encourages the human mind to strive towards the path of purification

About Taiwan

Welcome to Taiwan


Taiwan is an island on the western edge of the Pacific Ocean. Many airlines fly to Taiwan, making it the perfect travel destination. We have established 7 national parks and 13 national scenic areas to preserve Taiwan's best natural ecological environment and cultural sites. The blending of Hakka, Taiwanese, indigenous people and mainland Chinese cultures has produced a rich plethora of cultural and social color. Food is the best representative of this cultural mixing and matching. Aside from cuisines from different parts of the mainland, there is also Taiwanese cuisine as well as local delicacies from each area on the island.

Language

Mandarin is the official language in Taiwan, and Taiwanese (Min-Nan) is also widely spoken. The most commonly used foreign language is English. However, to be on the safe side, when taking a taxi in Taiwan, it is advisable to prepare a note with your place of destination written in Chinese to show to the Taxi drivers.

Climate

Situated off the east coast of Asia and in the path of warm ocean currents, Taiwan has an oceanic and subtropical monsoon climate that is conspicuously influenced by its topography. Summers are long and accompanied by high humidity, while winters are short and usually mild. Late September and early October is probably the most pleasant for a visit to Taiwan. The mean temperature in Taipei during the conference should be around 20~25 degree Celsius.

Currency

The Taiwan currency is the New Taiwan Dollars (TWD). Major credit cards are widely accepted in Taiwan.

Time Zone

In relation to Greenwich Mean Time, Taiwan is +8 hours.

Electricity

Electricity current in Taiwan is 110 Volt AC, 60 Hz.

Business Hours

Bank: Banks are open from 09:00 to 15:30 from Monday through Friday. Almost every bank has 24-hour ATM machine.

Shops: Shops, shopping malls, restaurants, etc. are mostly open from 10:00 to 21:00

Safety

Although we are proud of the low rate of crime in Taiwan, it is our responsibility to remind you that burglary, pick-pockets, and robbery are not unknown. It is wise to take some precautionary measures during your stay in Taiwan, especially when you are in a crowded area or when you are alone in a remote area. Be prepared by keeping photocopies of your passport, other identification, and credit cards. You should exercise caution when crossing streets because some drivers might not respect your right of way.

Emergencies

In case of emergency, call 110 for polices; 119 for ambulance. No coin is required in using public telephone for these two numbers.

Useful Phone Numbers

Overseas Operator		100
Chinese Local Directory Assistance		104
Chinese Long Distance Directory Assistance		105
English-Language Directory Assistance		106
Telephone Repair		112
Time		117
Weather		166
Tourist Information Hotline		+886-2-2717-3737
24-Hour Toll-Free Travel Information Call Center		0800-011-765
Taiwan Taoyuan International	Passenger Terminal Building I	+886-3-383-2194
Airport Tourist Service Center	Passenger Terminal Building II	+886-3-398-3341
Tourist Service Center, Kaohsiung International Airport, Tourist Bureau		+886-7-805-7888
Government Information Office		+886-2-3356-8888
International Community Service Hotline		0800-024-111
Board of Foreign Trade		+886-2-2351-0271
China External Trade Development Council (CETRA)		+886-2-2725-5200

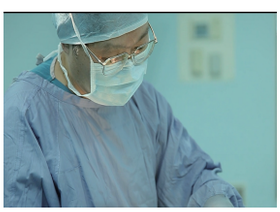
國璽幹細胞公司是以幹細胞技術為平臺的生技新藥公司，目的為將幹細胞技術應用於再生醫學與保健醫學以開發創新的幹細胞新藥與保健產品。由於幹細胞是新生細胞的來源，能提供疾病的治癒契機，因此國璽長期投入此領域技術的研發，並結合產、官、學、研、醫，希望以幹細胞再生技術造福人類。

國璽脂肪幹細胞儲存優勢

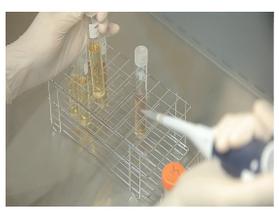
1. 創新研發平台---以幹細胞技術創造優質生命與健康人生
2. 科學臨床實證---透過客觀科學檢驗及臨床實證評估分析
3. 卓越品質保證---導入國際優良製造標準並落實品質把關
4. 顧客信賴服務---以人為本使顧客信賴進而達到善的循環
5. 跨界團隊整合---產官學研醫跨界合作實現人類再生夢想

脂肪幹細胞儲存服務流程


完整的健康評估及術前諮詢


安全、快速的微創手術，切取脂肪組織


以100多道標準作業程序進行脂肪幹細胞純化


由檢測實驗室進行品質鑑定


24小時不間斷監控的超低溫凍存設施


完善的培養及製劑技術

國璽幹細胞應用技術股份有限公司
Gwo Xi Stem Cell Applied Technology Co.,Ltd.
30261新竹縣竹北市生醫路二段22號3樓
TEL:03-6585959 FAX:03-6579922
http://www.gwoxi.com
Email:service@gwoxi.com

光麗生醫
GUANG LI BIOMEDICINE

及時儲存
無限未來

讓這雙手不再皺褶

全國第一家全方位幹細胞銀行

光麗生醫為國內第一間同時擁有脂肪、周邊血、新生兒臍帶、臍帶血幹細胞與免疫細胞之研究與儲存中心。為強化幹細胞研發實力、提供全面且高品質的客戶服務，購併臍帶血銀行「祈福生物科技股份有限公司」，整併臍帶血幹細胞儲存業務，成為國內最具規模的專業幹細胞儲存與服務公司之一。

光麗致力於提升差異化優勢，博碩士級團隊帶領之實驗中心，陸續通過 ISO-9001 國際品質認證與 TFDA「人體器官保存庫」之「臍帶血」項目審查核可，並陸續於國內外發表幹細胞研究成果與進行多項專利技術之申請。

產品與服務

周邊血、新生兒臍帶血儲存

新生兒臍帶血與成人的周邊血液中含有豐富的造血幹細胞，相較於骨髓，不但取得容易，且有著移植後免疫排斥反應低的優勢。

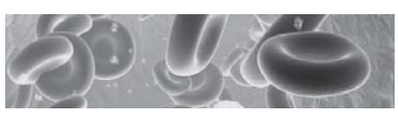
光麗生醫分離臍帶血或周邊血液中之富含有核細胞層並依國內衛生主管機關現行規範標準，長期妥善儲存，成為寶寶未來最珍貴的健康保障。

脂肪幹細胞、新生兒臍帶儲存

近年來，自脂肪中萃取幹細胞在國際上之研究發展，為民眾開啟健康的希望之窗。2011 年獲美《時代雜誌》評選為年度最佳 50 大發明之一。

光麗導入國際領先的間質幹細胞分離、純化、培養與儲存技術。將珍貴、有限的幹細胞進行妥善儲存，鎖住年輕菁華，未來在自身的健康上將有極佳的發展潛力。

免疫細胞儲存



癌症高居國人十大死因之首，平均每 6 分鐘就有一人罹癌，癌症醫療儼然成為現代醫學最重要的課題。

免疫細胞群為具備完整免疫能力之細胞群，可由成人血液分離純化得到，包含樹突細胞、CIK 細胞及 T 細胞等多種免疫細胞，目前已有大量臨床研究顯示免疫細胞可用於癌症輔助細胞治療，未來醫療應用潛力極高。

光麗生醫股份有限公司
新北市汐止區康寧街169巷31號11樓之1　電話：02-2694-9880　免付費客服專線：0809-009299　www.guangli.com.tw

B-A-02-1503-05

美商永生 StemCyte Inc.

美商永生(StemCyte)於 1997 年成立於美國加州，分別於美國、台灣及印度分別建立臍帶血技術中心，並以「致力於協助全球的醫師，提供高品質、安全、有效的幹細胞移植及治療給需要的病人，以救治更多的性命」為公司使命。

臍帶血是珍貴醫療資源

臍帶血因富含幹細胞而使得其醫療潛力受到重視，全球第一例臍帶血移植於 1988 年在法國，治療一名 Fanconi's anemia 病童。迄今，全球臍帶血移植案例數超過 30,000 個，可用來治療 80 種以上血液及免疫方面疾病。

美商永生參與締造台灣臍帶血移植記錄

美商永生目前已提供超過 2,000 單位的臍帶血，給全球 300 家以上移植醫學中心進行治療，其中超過 300 單位臍帶血，即由台灣臍帶血技術中心提供。

美商永生有幸參與締造台灣臍帶血移植的歷史，協助建立很多台灣第一例經驗的，如：首例臍帶血移植成功治療重症海洋性貧血、首例雙單元臍帶血移植成功治療慢性白血病、首例臍帶血移植成功治療重症複合免疫不全症、首例臍帶血移植成功治療骨質石化症(大理石寶寶)、首利私存臍帶血「弟弟救哥哥」移植成功案例等。

專利的「紅血球不分離處理流程」

臍帶血移植的研究證實，移植時臍帶血內幹細胞數目多寡會影響移植成敗。美商永生發展出一個獨特的「紅血球不分離處理流程」，包含超過 400 項標準作業流程及品質作業監控，經由這套處理流程，可保留較多幹細胞，此優異結果已於重要學術研討會及學術期刊中發表。

最大華人公捐血庫之一

美商永生美國與台灣兩地公捐血庫合計超過 30,000 單位，登錄於 BMDW(Bone Marrow Donors Worldwide)，是全球最大華人公捐臍帶血血庫之一。目前華人若需要臍帶血，在美商永生公捐血庫配對成功率高達 99% 以上。

以醫學中心認可的專業流程提供私人儲存服務

經成功移值經驗驗證儲存流程及品質後，美商永生將此儲存流程提供給父母，來儲存寶寶珍貴臍帶血；2003 年於美國、2004 年於台灣開始提供臍帶血私存服務，讓父母儲存寶寶臍帶血時，有最安心的選擇。

美商永生免費諮詢專線：**0800-808080**

台灣粒線體
Taiwan Mitochondrion

（股票代號：7447）

- 保健食品開發 MitoFood
- 粒線體製劑開發 MitoBio
- 幹細胞製劑開發 MitoCell
- 粒線體檢測服務

以粒線體應用技術為發展主軸，藉由粒線體修復或替換身體內，
因老化、生病、受損之粒線體，進而讓器官與組織再生。
主要應用於神經退化性疾病，如帕金森氏症與多發性系統退化症，
達到一般藥物無法完成的恢復神經元活性。

更多訊息請上
http://www.taimito.com

台灣粒線體
Taiwan Mitochondrion
新竹縣竹北市生醫路二段2號D棟D202室（新竹生醫園區）
電話 03-6579767　傳真 03-6672759

光麗生醫
GUANG LI BIOMEDICINE

及時儲存。無限未來

讓這雙手不再皺褶

癌症、慢性疾病長期佔據國人十大死因；高齡化社會的發展趨勢，人們更得面臨老化疾病威脅。醫學科技的發展，幹細胞成為一種得以長遠留藏的珍稀之物。及早存下年輕健康的細胞，在未來需要時，都是真正的瑰寶。

二〇一一年脂肪幹細胞獲《時代雜誌》評選為全球五十大最佳發明、二〇一二年諾貝爾醫學獎授予幹細胞科學家、二〇一三年免疫細胞登《科學》期刊封面，國際上大量的研究亦證實幹細胞與免疫細胞在臨床醫學應用之潛力。

光麗生醫GTP等級實驗研發中心與細胞儲存中心，為您珍藏獨有的細胞精髓，守護來自自體的健康與青春契機。

光麗生醫股份有限公司
新北市汐止區康寧街169巷31號11樓之1　電話：02-2694-9880　免付費客服專線：0809-009299　www.guangli.com.tw

B-A-02-1503-05

GWOXI
Stem Cell

國璽幹細胞應用技術股份有限公司

Gwo Xi Stem Cell Applied Technology Co., Ltd.

1好 品質管理 通過國際認證

2好 創新研發 在幹細胞應用

3好 最多優勢的 幹細胞公司

脂肪幹細胞儲存第一品牌
要存　就找品質最好的

新藥發展

- 「幹細胞治療肝損傷的新藥製劑」進入人體臨床第一期。
- 「幹細胞治療腦中風的新藥製劑」申請進入人體臨床第一期。
- 未來預計會開發幹細胞治療「心肌梗塞」、「糖尿病」、「肌腱．韌帶損傷」的新藥製劑。

認證

- 2013年通過ISO 9001、ISO 17025認證。
- 獲得「SNQ國家品質標章」認證。
- 2013年通過衛生福利部審查符合GTP規範實驗室。

獎項

- 『具觀察視窗之生物產品儲藏裝置』發明專利獲得新竹科學園區頒發「創新研究獎」。
- 治療肝硬化/纖維化之幹細胞新藥 (GXHPC1) 獲得103年新竹科學園區創新產品獎。

專利論文

- 已有多篇脂肪幹細胞研究論文發表在SCI國際學術期刊上。
- 幹細胞修復肝損傷治療技術已獲得美國、台灣 、中國專利核准。

政府支持

- 全國第一家通過國科會核准，以幹細胞技術進駐新竹生物醫學園區的公司。
- 全國第一家通過經濟部審定，以幹細胞製劑符合「生技新藥產業發展條例」的生技新藥公司。

專業技術．守護健康

Health

Stem Cell

以高規格標準 為客戶把關

依『人體細胞組織優良操作規範（GTP）』進行操作

Professional