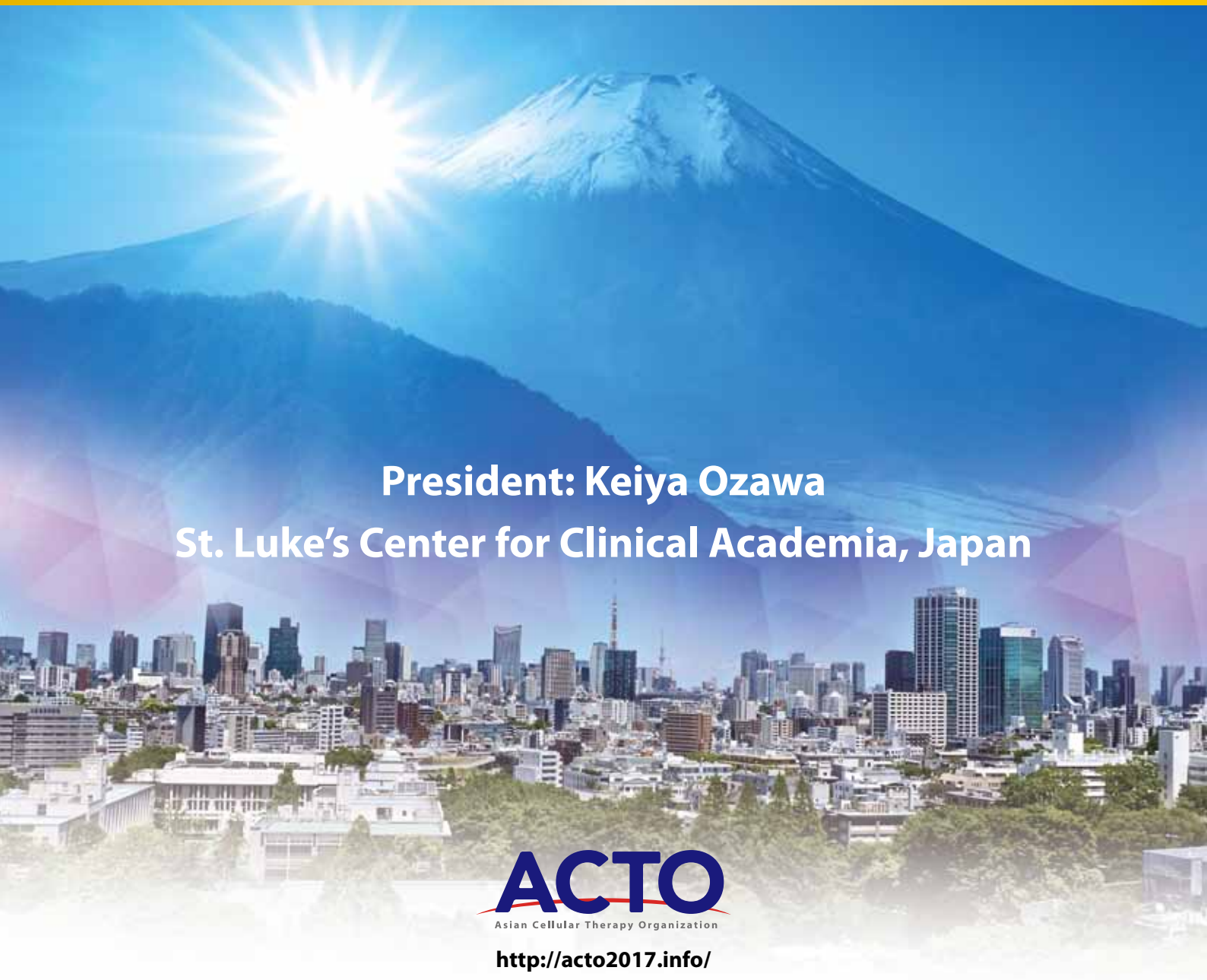
The 8th meeting of ACTO

New Era of Innovative Cell-based Therapy:
Creative Frontier (R&D) and Regulatory Science

Oct.27th(Fri) - 29th(Sun)

Tokyo
2017

Program & Abstracts



President: Keiya Ozawa
St. Luke's Center for Clinical Academia, Japan

ACTO
Asian Cellular Therapy Organization

http://acto2017.info/

Full Compliance with GMP/GCTP

Advanced Regenerative Medicine Cell Processing Systems

Combining our GMP-compliant sterilization processes and aseptic technology attained through the development and manufacturing of pharmaceutical and aseptic food/beverage production lines, we produce systems optimized for researchers and clinicians and of exceptional capability for the production of regenerative medicines and cell-based therapies.

Isolator Cell Processing Systems from Manual to fully Automated

Cell Processing Isolator (CPi)
- manual glove port access.

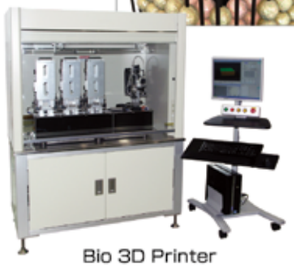
Automated Cell Processing Isolator (CellPROi)
- using Shibuya's sterilized Robotic Systems

Ancillary Equipment for Cell Culture

- Built-in Centrifuge (VPHP Decontamination Available)
- Incubator (Aseptically Connected to Isolator, VPHP Decontamination Available)
- Bio 3D Printer
- Cell Monitoring System (Compatible to the Isolator)
- VAPORIZED Hydrogen Peroxide Decontamination System (Model HYDEC)
- Dispensing and Capping Module

Centrifuge

Incubator



Bio 3D Printer

Fully Configurable Menu Driven Process Control System

- Standard Operating Procedure (SOP) Support System
- Manufacturing Management System
- Process Monitoring System
- Isolator Monitoring System

SOP Support System

Manufacturing Management System

Equipment Maintenance and Management

- Periodic Maintenance
- Validation Support to Ensure Regulatory Compliance as Required

• Contact us

SHIBUYA CORPORATION

Regenerative Medicine Manufacturing Systems Division

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TEL +81-76-262-1202 E-mail rm-info@shibuya.co.jp

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Takeda Pharmaceutical Company Limited

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The 8th meeting of ACTO

New Era of Innovative Cell-based Therapy:
Creative Frontier (R&D) and Regulatory Science

Program & Abstracts

Meeting Infomation

Title of Meeting	**The 8th meeting of Asian Cellular Therapy Organization** New Era of Innovative Cell-based Therapy: Creative Frontier (R&D) and Regulatory Science
Date	**Oct.27th(Fri) - 29th(Sun), 2017**
Venue	**St. Luke's Center for Clinical Academia** 3-6 Tsukiji, Chuo-ku, Tokyo, Japan
President	**Keiya Ozawa, M.D., Ph.D.** Director, IMSUT Hospital Director, Center for Gene & Cell Therapy (CGCT) Professor, Division of Genetic Therapeutics, Advanced Clinical Research Center The Institute of Medical Science, The University of Tokyo (IMSUT)
Chairpearson	**Akihiro Shimosaka Ph.D.** Research Foundation for Community Medicine
Official Language	**English**
Website	**http://acto2017.info/**
Executive Secretary	**Yuji Heike, M.D., Ph.D.** Professor, Division of Biomedical Science、Graduate School of Public Health, St. Luke's International University Chief, Immunotherapy and Cell Therapy Service, St. Luke's International Hospital
Head Office	**The Secretariat of Asian Cellular Therapy Organization** #303 Nakagin-meguro tower,1-5-18, meguro, meguro-ku, Tokyo 153-0063 【Official Site】http://asianct.org/

Contents

Welcome Address

I have been appointed to take on the role of president of the 8th Annual Meeting of Asian Cellular Therapy Organization (ACTO 2017). The meeting is scheduled to take place over a three-day period from October 27 (Fri) to 29 (Sun), 2017, at the OMURA Susumu and Mieko Memorial St. Luke's Center for Clinical Academia in Tsukiji, Tokyo, Japan. The purpose of this meeting is to promote education and research of cell therapy together with standardizing cell therapy and clinical development by organizing international supporting system, cooperating with regulatory authorities and academic societies related to hematopoietic stem cell transplantation, regenerative medicine and gene & cell therapy. Many basic and clinical researchers, clinicians, and agents of regulatory authorities will gather from Asian and other countries and discuss recent progress in the broad field of cell therapy.

The main theme of ACTO 2017 is "New Era of Innovative Cell-based Therapy: Creative Frontier (R&D) and Regulatory Science". Special Lectures will be given by Dr. Willem Fibbe, Dr. Nagahiro Minato and Dr. Hideyuki Okano. Dr. Fibbe is the world-famous leader of MSC (mesenchymal stem/stromal cell) research, Dr. Minato is the distinguished scientist in the field of cancer immunotherapy (immune checkpoint inhibitors), and Dr. Okano is well-known in the field of neuroscience and regenerative medicine. The Plenary Symposium will cover Gene-modified T Cell Therapy (CAR-T and TCR-T cell therapy), that is currently the most exciting topic in cancer gene therapy. I will give an introductory overview of CAR-T cell therapy in the Presidential Lecture. The JSRM (Japanese Society for Regenerative Medicine)-ACTO Joint Symposium will cover Regenerative Medicine, and the ISCT (International Society for Cellular Therapy)-ACTO Joint Symposium will deal with the issue of MSC (mesenchymal stem/stromal cell). We have also sessions on Stem Cell Transplantation and Immuno-regulation & Therapy. In the Regulatory Science session on October 29, Panel Discussion will be held after presentation from many countries. Finally, "Future Direction of ACTO Activities" will be discussed based on reports from each country. As for corporate seminars, you can find many hot topics in Luncheon, Evening, and Technical seminars. The FIRM (Forum for Innovative Regenerative Medicine) session will also be held. Best Abstracts (CHA Award) and Excellent Posters will be selected from the submitted abstracts.

In addition, Satellite session (ACTO-PMDA Special Session on Japanese Regulation) will be held on the afternoon of October 29.

I sincerely hope that we can benefit from the active participation of all delegates and enjoy a convivial and highly significant and meaningful meeting. I also hope that you will have time to enjoy the autumnal beauty of Japan.

Keiya Ozawa, M.D., Ph.D.

President
The 8th Annual meeting of Asian Cellular Therapy Organization (ACTO 2017)
Hospital Director and Professor
The Institute of Medical Science, The University of Tokyo (IMSUT)

Chairperson's Report

It is a great pleasure to be able to organize the 8th ACTO annual meeting for the first time in Tokyo. Prof. Keiya Ozawa and his organizing team worked very hard to make the meeting successful. This year, we are very happy to organize satellite symposium on the Japanese new regulation for cellular therapy together with PMDA. I am sure this symposium will give you good understanding of Japanese new regulation.

I would like to report that ACTO Head Quarter (HQ) office is now legally registered organization. ACTO HQ started as voluntary organization in 2011 and took us some time to change to legal entity. We are able to issue legal document when you need official letters/ document from ACTO HQ.

ACTO collaboration with International Society for Cellular Therapy (ISCT), Japanese Society for Regenerative Medicine (JSRM), Taiwan Association of Cellular Therapy (TACT) as well as Chinese new society organized Prof. Xiao Jun Huang was established and organizing joint meeting/session at ACTO meeting was established. Now joint work became routine event every year. We will continue collaboration with those established society as well as new collaboration with new society in other country. Next ACTO meeting, the 9th annual meeting will be held in Thailand under collaboration with Thailand Hematology Society in Chiang Mai on October 26-28, 2018. Then the 10th Anniversary Meeting will be held in Japan in 2019.

We are planning to have official journal of ACTO soon under collaboration with JSRM and ACTO member will have access to the journal.

Starting from 2018, we will collect membership fee from the members and member will have the right to journal and priority access to the any meetings organized by ACTO.

We do appreciate your registration as a member and continuation of your support for ACTO activity.

I am sure you will enjoy meeting as well as your time in Tokyo. This is a nice season to enjoy Autumn leaves in Japan. Please find time to enjoy your stay in Japan.

Sincerely

Akihiro Shimosaka, Ph.D.

ACTO Chairperson

Committee

President	2017	Keiya Ozawa, The Institute of Medical Science, The University of Tokyo (IMSUT), Japan
President Elect	2018	Wichai Prayoonwiwat, Thailand
Past Presidents	2010	Yoichi Takaue, St. Luke's International University & Hospital, Japan
	2011	Mine Harada, Medical Center, Karatsu Higashimatsuura Medical Association, Japan
	2012	Saengsuree Jootar, Mahidol University, Thailand
	2013	Yao-Chang Chen, National Taiwan University & Hospital,, Taiwan
	2014	Teruo Okano, Tokyo Women's Medical University, Japan
	2015	Hee Young Shin, Seoul National University, Korea
	2016	Xiao-Jun Huang, People's Hospital, Peking University, China

Vice Presidents

Kellathur N. Srinivasan, HSA, Singapore
Hu Chen, 307th Hospital of Chinese People's Liberation Army, Beijing, China
Kai-Yan Liu, People's Hospital, Peking University, China
Khattry Navin, India
Saengsuree Jootar, Mahidol University, Thailand
Yao-Chang Chen, National Taiwan University & Hospital, Taiwan
Il-Hoan Oh, The Catholic University of Korea, Korea
Chi Dung Phu, Vietnam
Abdalla Awidi Abbadi, The University of Jordan, Jordan
Bin Koming Ya'Akop, Malaysia
Mohiuddin Ahmed Khan, Bangladesh
Abbas Ghaderi, Shiraz University, of Medical Sciences, Iran
Ferry Sandra, Trisakti University, Indonesia

The 8th meeting of ACTO

President

Keiya Ozawa, The Institute of Medical Science, The University of Tokyo (IMSUT), Japan

Organizing Committee

Akihiro Shimosaka, Research Foundation for Community Medicine, Japan
Yoichi Takaue, St. Luke's International University & Hospital, Japan
Yuji Heike, St. Luke's International University & Hospital, Japan
Tomomitsu Hotta, National Cancer Research Center, Japan
Shuichi Taniguchi, Toranomon Hospital, Japan

Program Members

Satoshi Takahashi, The Institute of Medical Science, The University of Tokyo
Tokiko Nagamura, The Institute of Medical Science, The University of Tokyo
Makoto Otsu, The Institute of Medical Science, The University of Tokyo
Sumimasa Nagai, The Institute of Medical Science, The University of Tokyo
Yoshinobu Kanda, Jichi Medical University
Ken Ohmine, Jichi Medical University

Guideline

【On-site registration】

On-site registration will be conducted as follows;
Venue: Reception Counter (Entrance hall of Omura Susumu and Mieko Memorial St. Luke's Center for Clinical Academia)
Date & Time: All time available as long as a seat is remained

【On-site registration fee】

Participation fee of main meeting (Oct.27-Oct.29) Member / ¥15,000 Non-member / ¥20,000
Participation fee of satellite session (2pm-6pm Oct.29) Main meeting participant / ¥5,000 Non- participant / ¥20,000

【Admission ticket of dinner session】

The following sessions don't accept on-site registration. Only those who had registered in advance can get the admission ticket at Reception Counter.

- Special Evening Seminar with Tokyo Bay Cruising Dinner (7pm-10pm Oct.28)
- Gala Dinner (7pm-9pm Oct.28)

【Name card】

Name card will be distributed at Reception Counter. When you are in the venue it should be worn at all time.

【Prohibited matter in the venue】

At any place of the venue, smoking (including electronic cigarette) is prohibited.
During the lecture, recording, photography and mobile phone communication are prohibited.
Both eating and drinking at Main Hall (B1 floor) are prohibited.
※ Eating and drinking are permitted at 3rd floor (sponsor's booth lounge) or satellite rooms.

【Poster viewing】

Venue: Satellite Room A (2nd floor)
Date & Time: All time

【Meeting room】

There are 3 meeting rooms all of which need to be booked in advance.
If you would like to book please contact the secretariat (1st floor).

【Breakfast, Lunch】

We serve no meal for breakfast and lunch except the lunch-box distributed at each luncheon seminar.
※ There is a café "TALLY'S COFFEE" at 1st floor. Also a lot of food shops and restaurants are near the venue.

【Luncheon Seminar】

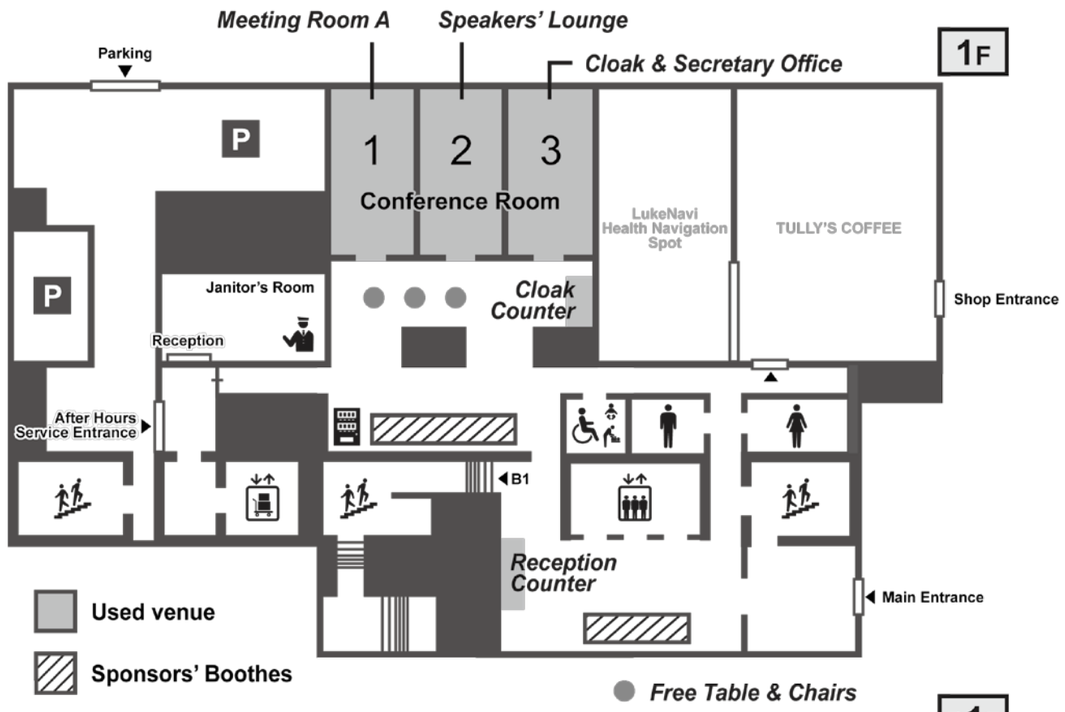
Details are written on the separate sheet.

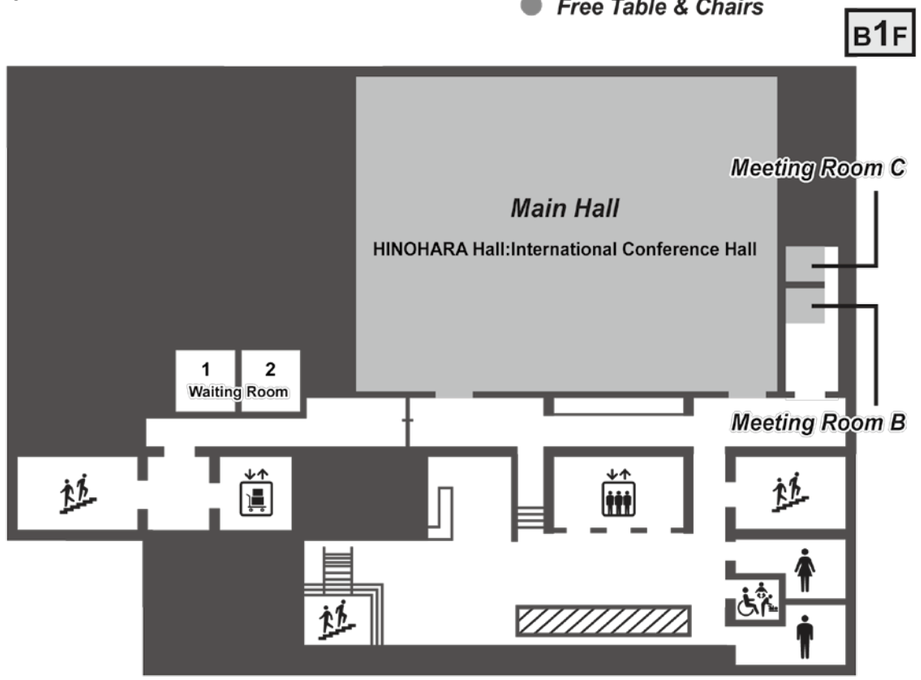
【Free Drink Serving】

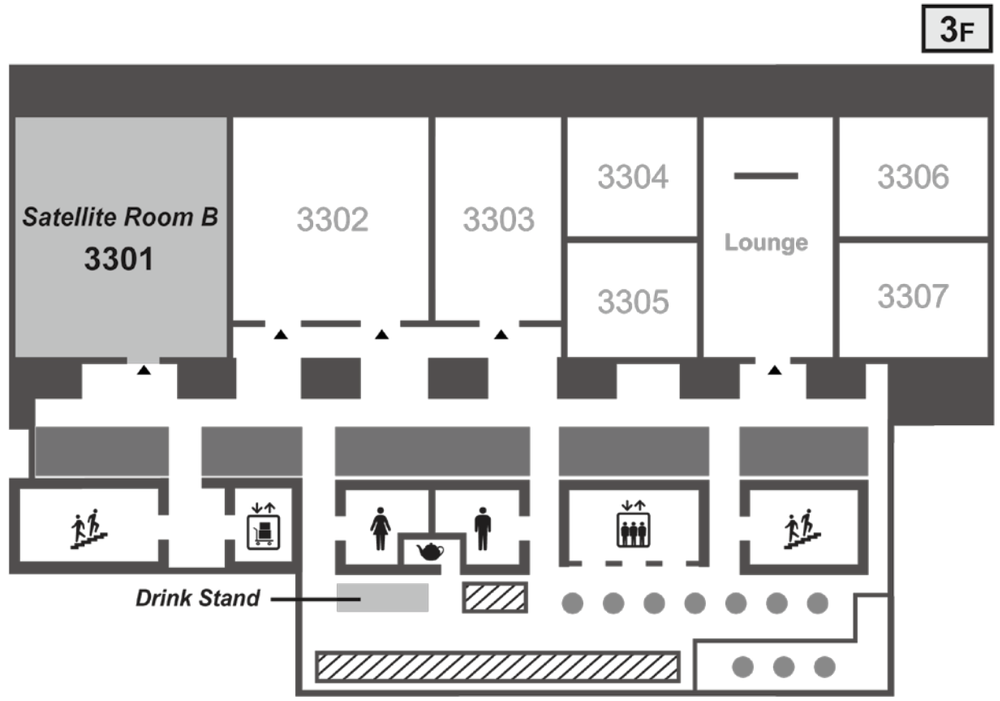
Coffee and tea are prepared at 3rd floor.

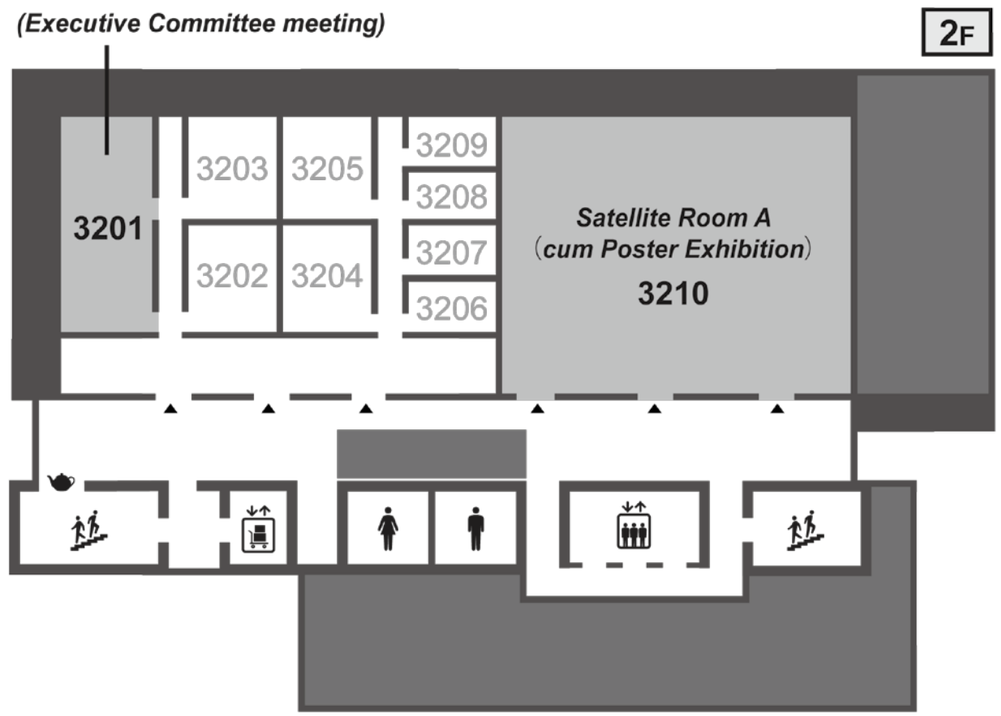
Floor Map

St. Luke's Center for Clinical Academia



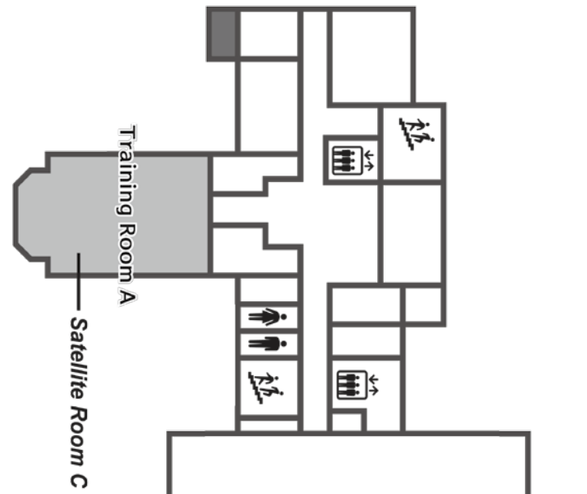




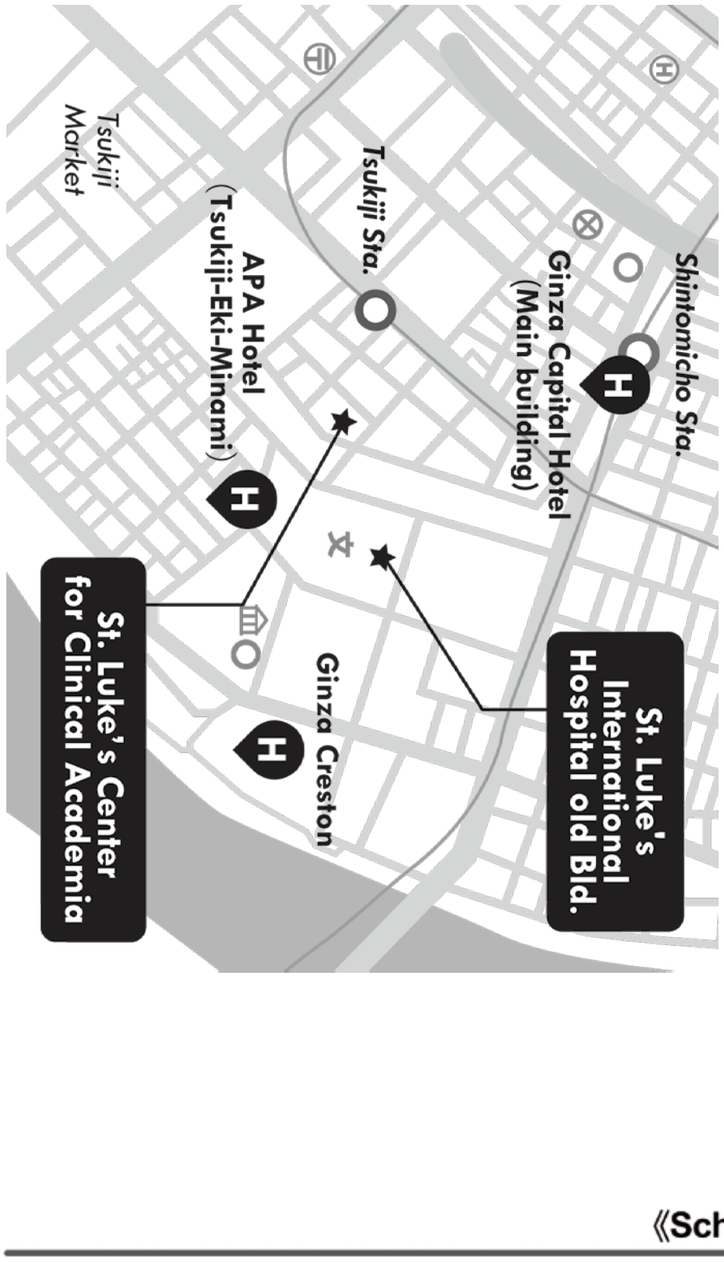


Floor Map

St. Luke's International Hospital old Bld.



Area Map



《Schedule-at-a-Glance》

Date: Oct. 27th (Fri) - 29th (Sun), 2017 **Venue: St.Luke's Center for Clinical Academia**

Day 1 (Friday, October 27)

	9:00–10:00	10:00–11:00	11:00–12:00	12:00–13:00	13:00–14:00	14:00–15:00	15:00–16:00	16:00–17:00	17:00–18:00	18:00–19:00
Main Hall	Opening; Regenerative Medicine (JSRM-ACTO Joint Symposium)		Special Lecture I	Luncheon Seminar II	Stem Cell Transplantation		Technical Seminar		Evening Seminar I-① / Evening Seminar I-②	Best Abstracts (CHA Award)
Satellite Rm A	Poster			Luncheon Seminar I					Evening Seminar II	
Satellite Rm B										
Satellite Rm C										

12:15～13:05 Executive Committee meeting (Rm 3201)

19:30～ Speakers Reception (Invitation-only)

Day 2 (Saturday, October 28)

	9:00–10:00	10:00–11:00	11:00–12:00	12:00–13:00	13:00–14:00	14:00–15:00	15:00–16:00	16:00–17:00	17:00–18:00	18:00–19:00
Main Hall	MSC (ISCT-ACTO Joint Symposium)		Immuno-regulation & Therapy		General Meeting; Presidential Lecture; Special Lecture II; Special Lecture III		Plenary Symposium (Gene-modified T Cell Therapy)		Evening Seminar III	
Satellite Rm A	Poster		FIRM Session	Luncheon Seminar III					Evening Seminar IV	
Satellite Rm B				Luncheon Seminar IV						
Satellite Rm C										

19:00～ Gala Dinner "ESPERANCE"

19:00～ Special Evening Seminar with Cruising Dinner "YAKATABUNE"

Day 3 (Sunday, October 29)

	9:00–10:00	10:00–11:00	11:00–12:00	12:00–13:00	13:00–14:00	14:00–15:00	15:00–16:00	16:00–17:00	17:00–18:00
Main Hall	Regulatory Science: Presentation	Panel Discussion		Future Direction ACTO Activities; Closing	Satellite Session: Opening; Key Lectures	Technical guidance for quality, nonclinical and clinical studies of regenerative medical products			Closing
Satellite Rm A			Luncheon Seminar V						
Satellite Rm B			Luncheon Seminar VI						
Satellite Rm C									

(ACTO-PMDA Special Session on Japanese Regulation)

ACTO
8th ACTO 2017 in Tokyo

Memo

- 1st Day -

Oct. 27th (Fri)

Program & Abstracts

Day 1 Friday, October 27

9:00~9:10 Opening Remarks

Keiya Ozawa
(ACTO 2017 President / The Institute of Medical Science, The University of Tokyo (IMSUT))

9:10~11:15 Regenerative Medicine (**JSRM-ACTO Joint Symposium**)
Chairpersons: Yao-Chang Chen, Yoshiki Sawa

JSRM-1: Yoshiki Sawa (Osaka University, Japan)
"Development of Myoblast Cell-Sheet Transplantation Therapy "Heart Sheet" for Advanced Cardiovascular Disease"

JSRM-2: Hiromi Kojima (The Jikei University School of Medicine, Japan)
"Realization of middle ear mucosal regeneration by cultured nasal mucosal epithelial cell sheet transplantation"

Koichi Nakayama (Saga University, Japan)
"Scaffold-free Bio-3D Printing for Solid organ fabrication"

Jay Lee (Medipost Co., Ltd., Korea)
"Optimized paracrine action of MSC for treatment of alopecia"

Michael Milyavsky (Tel Aviv University, Israel)
"Regulation of DNA Damage Response in Human Normal and Leukemic Hematopoietic Stem Cells"

11:25~12:05 Special Lecture Ⅰ *Chairperson: Tomomitsu Hotta*

Nagahiro Minato (Kyoto University, Japan)
"T cell meets cancer; lesson from checkpoint blockade therapy"

12:15~13:05 Luncheon Seminar Ⅰ sponsored by **ROHTO PHARMACEUTICAL CO., LTD.** (Satellite Room A)
Takahiro Ochiya (National Cancer Center, Japan) *Chairperson: Atsushi Miyajima*
"Generation of Liver Progenitor Cells by Small Molecules"

12:15~13:05 Luncheon Seminar Ⅱ sponsored by **Hitachi Chemical Co., Ltd.** (Main Hall)
Kazuchika Furuishi (Hitachi Chemical Co., Ltd.) *Chairperson: Tomoya Sato*
"Enabling Global Regenerative Medicine Development and Commercialization"

12:15~13:05 Executive Committee meeting (Rm 3201) *Chairperson: Akihiro Shimosaka*

13:15~15:15 Stem Cell Transplantation *Chairpersons: Saengsuree Jootar, Mine Harada*

Kai-Yan Liu (Peking University, China)
"Recent Development of Hematopoietic Stem Cell Transplantation in China"

Jih-Luh Tang (Taiwan University, Taiwan)
"Current Status and Future Perspective of Hematopoietic Stem Cell Transplantation in Taiwan"

Suradej Hongeng (Mahidol University, Thailand)
"Is Haplo-Identical SCT a Feasible and Safe Treatment Option for Patients with Genetic, Non-Malignant Disorders?"

Ho Joon Im (Asan Medical Center Children's Hospital, Korea)
"Graft manipulation in haploidentical hematopoietic cell transplantation"

Yoshinobu Kanda (Jichi Medical University, Japan)
"The effect of HLA-mismatch on transplant outcome in Japan"

Mickey Koh (St. George's Hospital, Singapore)
"The Evolving Roles of Stem Cell Transplants and Cellular Therapy"

15:30~17:10 Technical Seminar *Moderators: Yuji Heike, Il-Hoan Oh*

Sebastian Rodriguez (**Fluidigm Japan K.K.**)
"Robust and sensitive immune monitoring using Helios™ mass cytometry, a CyTOF® system"

Anant Tucker (**Sysmex Corporation**)
"Creating Unique Diagnostic Value"

Setsuko Hashimoto (**CellSeed Inc.**) *Chairperson: Toshihiro Maeda*
"Developing Regenerative Medicine using Cell Sheet Engineering"

Yumi Matsuzaki (Shimane University, Japan / **PuREC Co. Ltd.**)
"Purified human bone marrow derived mesenchymal stem cell "REC""

Taka-aki Sato (Shimadzu Corporation) sponsored by **Kohjin Bio Co., Ltd.**
"The Leading-edge Applications of Mass Spectrometry in the Drug Discovery and Diagnosis"

17:20~17:45 Evening Seminar Ⅰ-① sponsored by **SHIBUYA CORPORATION** (Main Hall)
Mamoru Kokubo (Shibuya Corporation) *Chairperson: Hiroyuki Nayama*
"Shibuya Initiatives and Activities for Regenerative Medicine"

17:45~18:10 Evening Seminar Ⅰ-② sponsored by **Gene Therapy Research Institution Co., Ltd.** (Main Hall)
Shin-ichi Muramatsu (Jichi Medical University, Japan) *Chairperson: Katsuhito Asai*
"Cell therapy for Parkinson disease"

17:20~18:10 Evening Seminar Ⅱ sponsored by **Miltenyi Biotec** (Satellite Room A)
Dirk Balshuesemann (Miltenyi Biotec) *Chairperson: Akihiro Shimosaka*
"Immuno-Oncology – Activities and solutions offered by Miltenyi Biotec"

Yingzi Ge (Miltenyi Biotec)
"Partner in personalized cell and gene therapy from A to Z"

18:10~19:10 Best Abstracts (**CHA Award**) *Chairpersons: Yoichi Takaue, Abbas Ghaderi*

19:30~ Speakers Reception (Invitation-only)

9:10-11:15 **Main Hall**

Regenerative Medicine

(JSRM-ACTO Joint Symposium)

Yoshiki Sawa

Professor and chief,

Department of Cardiovascular Surgery,

Osaka University Graduate School of Medicine, Japan

Development of Myoblast Cell-Sheet Transplantation Therapy “Heart Sheet” for Advanced Cardiovascular Disease

Background: Translational research was launched to test the hypothesis that autologous skeletal muscle-derived cell-sheets transplantation may be feasible, safe and effective for treating severe congestive heart failure.

Methods: Fist study enrolled 4 DCM patients with LVAD and in Second study 7 DCM patients and 7 ICM of NYHA functional class III, who were already treated by maximum medical and/or interventional therapies. Scaffold-free cell-sheets containing 3-9×108 autologous muscle-derived cells were transplanted over the LV free wall via the left thoracotomy without additional interventional treatments.

Results: In the First Study, 2 of 4 patients showed functional recovery and succeeded in bridge to recovery from LVAD. In second study, all patients were discharged from the hospital without mortalities over the follow-up. All patients insisted marked symptomatic improvement post-treatment evaluated by SAS with much decrease of Pulmonary artery pressure and Pulmonary vein resistance. Multi-slice CT scanning revealed that in ICM patients whose LVESVI was between 100 and 130 showed LV reverse remodeling 6 months after sheet implantation compared with pre-value and End systolic share stress (ESS) was decreased in the cell sheet received patients. Survival rate was better after cell sheet implantation compared with estimated value calculated by the Seattle heart failure model.

Conclusions: In this translational research, cell-sheet transplantation was safe and effective with improvement of symptom and survival curve. Thus, it might be a promising regenerative therapy for severe congestive heart failure while further investigation and long term follow-up are needed.

9:10-11:15 **Main Hall**

Regenerative Medicine

(JSRM-ACTO Joint Symposium)

Hiromi Kojima

Professor and Chair of Otorhinolaryngology, The Jikei University School of Medicine

The Oto-Rhino-Laryngological Society of Japan (representative)

Japan Otological Society (director)

Realization of middle ear mucosal regeneration by cultured nasal mucosal epithelial cell sheet transplantation

There is no curative therapy for adhesive otitis media and cholesteatoma other than tympanoplasty. In order for a normal middle ear cavity to form after surgery, regeneration of the middle ear mucosa, recovery of the physiological gas ventilation capacity, and prevention of tympanic membrane adhesion are essential. If regeneration of the damaged middle ear mucosa were possible in the early postoperative period, it would be possible to prevent re-adhesion of the tympanic membrane and recurrence of adhesive otitis media. Additionally, regeneration of middle ear mucosa would prevent recurrence of cholesteatoma. However, achieving early regeneration of the middle ear mucosa has been a major challenge. Therefore, we developed a novel treatment method combining tympanoplasty and autologous nasal mucosal epithelial cell sheet transplantation for postoperative regeneration of the middle ear mucosa. Using a nasal mucosal tissue that we endoscopically harvested, tissue-engineered autologous nasal mucosal epithelial cell sheets were fabricated by culturing the harvested cells in an aseptic environment in a good manufacturing practice-compliant cell processing facility (CPF). The cultivated cell sheets were transplanted, during tympanoplasty, onto the exposed bony surface of the middle ear cavity where the mucosa had been lost. We performed this procedure on four patients with middle ear cholesteatoma and one patient with adhesive otitis media. All patients showed favorable postoperative course with no adverse events or complications.

Moreover, we plan to do new clinical research. The content of new research is collaborative research program of Jikei University School of Medicine and St. Marianna University School of Medicine, and to reveal the fate of the transplanted cells in clinical study. This new co-research program includes transportation of a nasal mucosal tissue and cell sheets between St. Marianna University School of Medicine Hospital and CPF of Jikei University School of Medicine. In addition, utilizing the planned staged surgery of cholesteatoma, it is assumed that we can reveal the fate of the transplanted cells. The planned staged tympanoplasty is conventional method for cholesteatoma. We will transplant the cell sheets to the middle ear and perform the planned staged tympanoplasty in a year after transplantation. We plan to perform a biopsy of tissue from the transplanted site during planned staged tympanoplasty. To reveal the fate of the transplanted cells is our future research issue. We expect to mark the first step toward uncovering the fate of the transplanted cells using the biopsy sample.

This research is the world’s first-in-human study to transplant cultured cells into the human middle ear. This treatment simultaneously preserves the external ear canal morphology, as in standard canal wall up tympanoplasty, and incorporates autologous cell sheet transplantation, which enables prevention of recurrence of cholesteatoma. This study represents a great step forward in the development of a new surgical approach for adhesive otitis media and cholesteatoma.

9:10-11:15 **Main Hall**

Regenerative Medicine

(JSRM-ACTO Joint Symposium)

Koichi Nakayama

Professor and Chairman,
Department of Regenerative Medicine
and Biomedical Engineering,
Faculty of Medicine,
Saga University, Saga City, Japan

Scaffold-free Bio-3D Printing for Solid organ fabrication

Fabrication of transplantable 3D tissue or organ in vitro is one of the major goals in regenerative medicine. Several scaffold-free systems have been developed to avoid potential side effects caused by scaffold mainly used to build three-dimensional tissue construct. They seemed to be still unable to produce fine structures without contamination from exogenous biochemical materials.
Inspired from bone fracture treatments in orthopedic surgery, we established a simple method to fabricate 3D scaffold-free cell construct. This method use spheroids and temporal fixator which enable placement of various types of three-dimensional cells into desired xyz positions without need of hydrogels or biochemical reactive materials. We also developed a robotic system for scaffold-free cell construction.
By using this “Bio 3D printer”, we successfully fabricated cartilage, blood vessels, liver, and so on. In addition, some of pile-lines are already start IN VIVO study.

Near future, we may be able to build living organs for autologous transplantation by using this scaffold free Biofabrication system. This multi-cell construct may be useful research tools for drug development.

9:10-11:15 **Main Hall**

Regenerative Medicine

(JSRM-ACTO Joint Symposium)

Jay Lee

Senior Director, MEDIPOST Co., Ltd.

Optimized paracrine action of MSC for treatment of alopecia

Paracrine action is known to be one of major modalities for therapeutic efficacy of mesenchymal stem cell (MSC) based therapies. We investigated a therapeutic potential of conditioned media of MSC (a collection of trophic factors secreted by MSC) for treatment of alopecia. MSC derived from human umbilical cord blood was first treated with combination of molecules known to be related with hair loss under various conditions before collecting conditioned media in order to prime MSC to secret optimum composition of trophic factors to desired therapeutic action. CM-3 was selected based on the in vitro assay of growth enhancement of human derma papilla (hDP) cells. The selected conditioned media was further tested whether CM-3 influence hair growth of human hair follicles ex vivo, and the result confirmed the priming resulted in significant increase in hair growth compared with control (conditioned media without priming). Toxicity studies have been conducted with CM-3 pursuant to the MFDS guideline for cosmetics products to confirm the conditioned media is safe to use by topical application. A POC clinical study with 30 alopecia patients found that a cosmetic formulation containing CM-3 at 5% (w/w) results in statistically significant superiority in hair density, hair thickness and hair growth rate, respectively, measured at 4, 8 and 16th week after treatment by topical application once daily, compared with placebo control treated with the vehicle formulation without the conditioned media. Further studies are ongoing to elucidate detailed mode of action of the conditioned media in enhancing human hair growth.

9:10-11:15 **Main Hall**

Regenerative Medicine

(JSRM-ACTO Joint Symposium)

Michael Milyavsky

Senior Lecturer, Department of Pathology,
Sackler Faculty of Medicine, Tel Aviv University

Regulation of DNA Damage Response in Human Normal and Leukemic Hematopoietic Stem Cells

Life-long blood regeneration is critically dependent on self-renewing multipotential hematopoietic stem cells (HSCs). HSCs' nearly unlimited self-renewal potential and lifetime persistence in the body, in contrast to the committed blood progenitors (CP), signifies the need for the tight control of HSCs genome integrity. Indeed, accumulation of unrepaired DNA damage in HSCs is associated with bone marrow failure and accelerated leukemogenesis. Our recent findings revealed for the first-time striking differences in DNA Damage Response (DDR) characteristics between HSCs and CPs isolated from umbilical cord blood. Human HSCs exhibited attenuated DNA repair, persistent DDR signaling and increased apoptosis relative to CPs (Milyavsky et al Cell Stem Cell 2012). Although HSPCs are widely considered a target of ionizing radiation (IR)-induced hematopoietic injury, definitive data regarding cell death, DNA repair, and genomic stability in these rare quiescent cells are scarce. We found that irradiated HSCs, but not lineage-committed progenitors (CPs), undergo rapid ATM/p53-dependent apoptosis, which is suppressed upon interaction with bone-marrow stroma cells. Using DNA repair reporters to quantify mutagenic Non-Homologous End Joining (NHEJ) processes, we found that HSPCs exhibit reduced NHEJ activities in comparison with CPs. HSPC-stroma interactions did not affect the NHEJ capacity of HSPCs, emphasizing its cell autonomous regulation. We noted diminished expression of multiple double strand break (DSB) repair transcripts along with more persistent 53BP1 foci in irradiated HSPCs in comparison with CPs, which can account for low NHEJ activity and its distinct control in HSPCs. Finally, we observed an elevated number of clonal chromosomal aberrations in the progeny of IR-surviving HSPCs. Taken together, our results revealed potential mechanisms contributing to the inherent susceptibility of human HSCs to the cytotoxic and mutagenic effects of DNA damage.

Regeneration of normal HSCs as well as leukemia cells after DNA damage relies on cellular pathways that coordinate stress, survival and ultimately preservation of proliferative potential in the subset of viable cells. The molecular determinants governing escape of Acute Myeloid Leukemia (AML) cells from DNA damaging therapy remain poorly defined and account for therapy failures. In an attempt to identify molecular determinants governing the escape of Acute Myeloid Leukemia (AML) cells from DNA damaging therapy, we performed a genome-wide shRNA screen and discovered that SMYD2 lysine methyltransferase (KMT) regulates leukemia cell growth and regeneration after genotoxic stress. We revealed that decreased expression of SMYD2 in AML patients correlated with the reduced sensitivity to therapy and lower probability to achieve complete remission. Interestingly, we found that interplay between SMYD2 and SET7/9 levels shifts leukemia cells from growth to quiescence state that is associated with the higher resistance to DNA damaging agents and rationalized SET7/9 pharmacological targeting in AML (Zipin-Roitman et al., Oncotarget 2017).

Better understanding of normal and malignant stem cells regeneration after genotoxic stress holds the key for the future safe cellular therapies.

11:25-12:05 **Main Hall**

Special Lecture Ⅰ

Nagahiro Minato

Provost of Kyoto University and Project-leading Professor
at Graduate School of Medicine.

T cell meets cancer; lesson from checkpoint blockade therapy

Since the conceptual proposal of cancer immune surveillance by Burnet and Smith more than a half-century ago, a recent clinical success of immune checkpoint blockade therapy in human cancers has provided a breakthrough in cancer immunotherapy. PD-1, originally discovered by Dr. Honjo's group at Kyoto University in 1992, is a TCR-coinhibitory receptor and plays a crucial role in the checkpoint of peripheral T-cell self-tolerance, and in 2002 we reported that the PD-1 checkpoint also takes an important part in restraining endogenous tumor immunity, providing a theoretical basis for current immune checkpoint blockade therapy. Current major effort is directed to the improvement of the efficacy of therapy as well as the search for genetic and other biomarkers predictive of the effectiveness. A main consequence of the clinical success of immune checkpoint blockade therapy has been the reconfirmation of potential importance of host immunity in controlling cancers in general. This was particularly so, because the effects of immunotherapy are often long lasting when it works. Accumulating evidence indicates that major factors influencing the efficacy of immunotherapy are potential immunogenicity of cancer cells and the accessibility of the immune effectors to cancer cells. Although the required cancer immunogenicity may be overcome by adoptive immune cell therapy such as recent CAR-T therapy, the issue of immune accessibility in cancer tissue microenvironment, which may be hampered by many conditions or factors other than PD-Ls, still remains crucial. In this talk, I shall briefly summarize the history and recent advancement in immune checkpoint blockade therapy and stress an importance for ensuring the accessibility of immunity to cancers in tissues by introducing a unique experimental model on chronic myelogenous leukemia.

12:15-13:05 **Satellite Room A**

Luncheon Seminar Ⅰ

Sponsored by ***ROHTO PHARMACEUTICAL CO., LTD.***

Takahiro Ochiya

Chief, Division of Molecular and Cellular Medicine, National Cancer Center Research Institute, Tokyo

Generation of Liver Progenitor Cells by Small Molecules

A challenge for advancing approaches to liver regeneration is loss of functional differentiation capacity when hepatocyte progenitors are maintained in culture. Recent lineage-tracing studies have shown that mature hepatocytes (MHs) convert to an immature stem-like state during chronic liver injury, and we investigated whether this conversion could be recapitulated in vitro and whether such converted cells could represent a source of hepatocytes that can contribute liver regeneration. We report that a cocktail of small molecules can convert rat and mouse MHs in vitro into proliferative bipotent cells, which we term chemically induced liver progenitors (CLiPs) (Katsuda et al., Cell Stem Cell, 2017). CLiPs can differentiate into both MHs and biliary epithelial cells that can form functional ductal structures. CLiPs in long-term culture did not lose their proliferative capacity or their hepatic differentiation ability, and rat CLiPs were shown to extensively repopulate chronically injured liver tissue. Our current progress on generation of human CLiPs (hCLiPs) will be mentioned.

12:15-13:05 **Main Hall**

Luncheon Seminar Ⅱ

Sponsored by ***Hitachi Chemical Co., Ltd.***

Kazuchika Furuishi

General Manager, Regenerative Medicine Business Sector, Hitachi Chemicalt

Enabling Global Regenerative Medicine Development and Commercialization

Kazuchika Furuishi, PhD, Deputy General Manager, Regenerative Medicine Business Sector, Hitachi Chemical, a global contract development and manufacturing organization for the cell therapy industry, will speak on the opportunities and challenges ahead to enable the commercialization of robust, high quality, sustainable, and scalable regenerative medicine products at a reasonable cost of goods. The primary challenges to achieve this future state include achieving a more standardized and automated future state for manufacturing processes, utilizing business models which prepare developers for the costly implications of idle capacity, and developing automated platforms. HCC services include two manufacturing facility in the United States offering almost twenty years of experience in the development and manufacturing of cell therapies, as well as facilities in Yokohama, Japan, as well as efforts to innovate new regenerative medicine delivery platforms.

13:15-15:15 **Main Hall**

Stem Cell Transplantation

Kai-Yan Liu

Professor of Internal Medicine
Deputy Chairman of Peking University Institute of Hematology
Deputy Director of Department of Hematology, Peking University People's Hospital
Deputy Director of Peking University People's Hospital GCP Office
Director of Beijing Cord Blood Bank

Recent Development of Hematopoietic Stem Cell Transplantation in China

During the past decades the total number of hematopoietic stem cell transplantation (HSCTfor both malignant and non-malignant diseases increased continually in China. Total numbers of 21 884 HSCT including 16 631 allo-HSCT (76%) and 5253 auto-HSCT (24%) were performed by 76 centers in China between 1 January 2008 and 30 June 2016. HSCT trends included continued growth in transplant activity, rapid increase in haploidentical donors (HID), and slower growth for unrelated donors(URD), matched-related donors (MRD) and cord blood transplantation (CBT).

Among the allo-HSCT, HID-HSCT increased from 29.6%in 2008 to 51.7% in the first half of 2016. The increased numbers of allo-HSCT using HID-HSCT reflect the greater availability of donors and the recognition that HID-HSCT provides equivalent safety to related donor transplantation and URD-HSCT. HID-HSCT can give similar clinical outcomes with MRD-HSCT and URD-HSCT and also the use of HID continues to increase due to its convenience and ready availability without delay.

13:15-15:15 **Main Hall**

Stem Cell Transplantation

Jih-Luh Tang

President, The Hematology Society of Taiwan.
Director, Tai-Cheng Stem Cell Therapy Center, National Taiwan University.
Attending Physician and Associate Professor, Division of Hematology, Department of Internal Medicine, National Taiwan University Hospital and College of Medicine, National Taiwan University Taipei City, Taiwan

Current Status and Future Perspective of Hematopoietic Stem Cell Transplantation in Taiwan

In Taiwan, the first bone marrow transplantation (BMT) was performed in 1983, the total HSCT numbers had accumulated to > 6,200 in 2016 according to the Taiwan BMT Registry (TBMTR) with about 500 HSCT performed annually in 18 BMT centers.

According to the most recent updates of TBMTR outcome registry data of 3,425 cases between 2009-2016, there were 42% auto-HSCT and 58% allo-HSCT (29% from unrelated donors(URD), 23% from matched sibling donors (MSD), and 6% mismatched related donors). The majority of auto-PBSCT was performed for the treatment of lymphoma (25.6%) or multiple myeloma (17.6%), and predominantly using PBSC source. The majority of leukemia and MDS/MPN received allo-HSCT. The top five indications of HSCT were AML (27.6%), non-Hodgkin lymphoma (20.7%), multiple myeloma (17.6%), ALL (13.0%) and Hodgkin lymphoma (4.9%). There were trends for enrolling more elderly patients in recent years, with 37.7% > 50 y/o and 12.1% > 60 years. With a median follow-up of 36 months, the estimated 5-year overall survival (OS) and disease-free survival (DFS) for all patients was 55% and 53% respectively, 62% and 46% for auto-HSCT and 48%, 43% for allo-HSCT. The 5-year OS was comparable between MSD (48%) and URD (52%, p=NS). Currently, 2077 were still alive and 1001 dead. The transplant-related mortality (TRM) was 8.8% at 100 days and 17.5% at 2 years. The main causes of death were disease relapse or progression (55%), followed by infection (26%) and GVHD (9%).

The current and future development of haplo-identical family donor HSCT, incorporation of next-generation molecular testing, the use of sensitive detection of minimal residual disease before and after HSCT, and the use of cell-based immunotherapy in high-risk patients will be discussed briefly.

Stem Cell Transplantation

Suradej Hongeng

Department of Pediatrics, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Is Haplo-Identical SCT a Feasible and Safe Treatment Option for Patients with Genetic, Non-Malignant Disorders?

Background:Allogeneic stem cell transplantation (Allo-SCT) can be curable for debilitating genetic diseases that are marked by significant morbidity, leading to premature death from secondary complications. Among the most commonly recognized genetic diseases is the hemoglobinopathiesy Thalassemia (Thal). Thalassemia-free survival after Allo-SCT is typically at best 80-90% when matched related (MRD) or unrelated (MRD) donors are utilized. Unfortunately, the chance to find a suitable door is only in the range of 40-50%. Therefore, the use of alternative donors has been investigated, but with mostly disappointing results; These patients have an active or even hyperactive immune system, and in addition the standard of care includes frequent blood transfusions, leading to iron overload and, frequently, to HLA-antigen immunization, leading to an excessive risk for both hepatic toxicity from the conditioning regimen and to graft rejection. We hypothesized, that pretransplant iron depletion through chelation, followed by pharmacological pretransplant immunosuppression (PTIS) using two courses of pulse-dexamethasone (Dxm) and fludarabine (Flu) would immunosuppress the patients sufficiently to consistently allow engraftment from either a matched or a mismatched donor after a reduced-toxicity Flu-Busulfan conditioning program, which in the mismatched/haplo-identical graft situation would be followed by post-transplant cyclophosphamide-based (post-Cy) GvHD prophylaxis.

Patients and Methods: Between Jan 2013 and June 2017, 64 patients (pts) with mostly severe, class 3, thalassemia underwent haplo-allo-HSCT. Thirty five subjects were male and 29 were female. The median age was 15 yrs (range; 2-28). Thirty six of 64 received stem cells from mother and 28 from father. Twenty nine of 64 were high risk class 3. They initially received hydroxyurea 20 mg/kg/d for three months, together with chelation to decrease iron overload. All pts received two courses of PTIS with Flu 40 mg/m^2/d and Dxm 25 mg/m^2/d, both for 5 days. After the PTIS, a reduced-toxicity conditioning (RTC) regimen consisting of thymoglobulin 1.5 mg/kg/d (d-11 to d-9), Fludarabine 35 mg/m^2/d i.v. (d-7 to d-2), each dose immediately followed by busulfan (Bu) 130 mg/m^{2}once daily i.v. on d-7 to d-4, which after the first 32 patients was modified to pharmacologically-guided Bu to an average daily AUC of 4,500 µMol-min. GVHD prophylaxis with post-Cy, 50 mg/kg/d was given on d+3 and d+4, and on day+5 we started Tacrolimus or sirolimus to be given for 6-12 months, in addition to mycophenolate mofetil, the latter quickly tapered after 2 months. T-cell replete peripheral blood stem cells were given to all patients, targeting a CD34+ cell-dose of 10 x 10^{6}cells/kg (range, 7-16 x 10^6).

Results: Sixty two of the 64 engrafted with full donor chimerism (100%) while 2 suffered graft failure. These 2 pts received a second transplant on day +30 with minimal added conditioning and additional PBSC after which one achieved full donor chimerism but later developed grade IV aGvHD and died, and one had autologous recovery. Median time to neutrophil engraftment was 18 days (range; 14 -22). Ten pts developed aGVHD gr I, 4 grade II and 1 grade 3. Only one had extensive cGVHD. Median follow-up time is 12 months (range 4-53 mos). Sixty one of 64 pts survive thal-free and have sustained full donor chimerism (100%). One additional patient died of infectious complications. Two-year Event free survival (EFS) and overall survival (OS) are above 95%, and is not different from our results obtained with matched-related or -unrelated donors.

Conclusion: Haploidentical HSCT for high risk thalassemia patients is with our novel approach safe. The EFS rates among MRD, MUD and Haplo-HSCT recipients receiving this regimen, varied only in reference to the choice of matched vs mismatched donor is at least 95%, and we conclude that virtually every patient will now have the option of an allo-SCT regardless of donor compatibility. Therefore, we suggest that all thalassemia patients, even those with high risk class 3 features, should be offered allo-HSCT. We suggest that all thalassemia patients, even those with high risk class 3 features, should be offered allo-HSCT. However, this treatment program is not thalassemia-specific, but it is proof of principle for how to successfully transplant all patients with a genetic disease. The presence of an active or hyperactive immune system in such patients should not prevent their access to allogeneic SCT even if it is necessary to use an alternative donor.

Stem Cell Transplantation

Ho Joon Im

Professor of Pediatrics, Asan Medical Center Children's Hospital, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Graft manipulation in haploidentical hematopoietic cell transplantation

Recent advances in effective ex vivo depletion of T cells or unmanipulated in vivo regulation of T cells, along with better supportive care, and optimal conditioning regimens, have significantly improved the outcome of haploidentical transplant. T cell depletion of donor grafts to prevent fatal GVHD is crucial for successful haploidentical HSCT. The methods of TCD could be carried out in vivo (T cell-replete transplant) or ex vivo (T cell-depleted transplant). The ex vivo techniques to remove T cells have evolved from the selection of CD34+ hematopoietic stem cell progenitors towards the depletion of CD3+ cells and more recently to the depletion of αβ+ T cells. Compared with the positive selection of CD34+ cells, direct depletion of CD3+ cells has the advantage of increased numbers of natural killer cells, monocytes, and other immunomodulating cells. The depletion of CD3+ cells is superior to the selection of CD34+ cells in terms of rapid engraftment and immune reconstitution. Moreover, preliminary reports on αβ+ T cell depletion further showed improved outcomes of T cell-depleted haploidentical transplants. The depletion of αβ+ T cells produces grafts containing many γδ+ lymphocytes and other effector cells. While αβ+ T cells are known to be associated with the initiation of GVHD, γδ+ T cells can enhance immune reconstitution and are not implicated in GVHD. Most recently, a new depletion technique to remove CD45RA+ naïve T cells has been developed to enhance immune function as well as to prevent GVHD after haploidentical HSCT. The selective depletion of CD45RA+ cells can effectively remove alloreactive naïve T cells responsible for GVHD while preserving pathogen-specific immunity. The CD45RA-depleted graft with abundant memory T cells can be used for therapeutic or preemptive antiviral boost after vivo T cell-depleted haploidentical hematopoietic cell transplantation.

In this presentation, I will review the recent progress in graft manipulation in haploidentical hematopoietic cell transplantation and introduce our experience with haploidentical hematopoietic cell transplantation using ex vivo T cell-depleted graft.

13:15-15:15 **Main Hall**

Stem Cell Transplantation

Yoshinobu Kanda

Professor, Division of Hematology, Department of Medicine, Jichi Medical University

The effect of HLA-mismatch on transplant outcome in Japan

The presence of HLA mismatch affects the outcome of allogeneic hematopoietic stem cell transplantation (HSCT). In addition, its impact may differ among different races and different HSCT procedures. Therefore, we have been analyzing the impact of HLA-mismatch in related and unrelated HSCT in Japan using the database of Japan Society of Hematopoietic Stem Cell Transplantation. The presence of one antigen mismatch in related HSCT significantly impaired survival even in the recent era, but the impact was different among HLA-A, -B, and –DR mismatches. In unrelated HSCT, previous analyses showed that HLA mismatches in Class I had greater adverse impact on survival, but recent analysis revealed that the impact was similar among HLA-A, -B, -C, and –DRB1 allele mismatches, with regard to both survival and the incidence of graft-versus-host disease (GVHD). The impact of HLA allele mismatch and antigen mismatch on overall survival was similar. In haploidentical HSCT, the use of post-transplant cyclophosphamide, anti-thymocyte globulin, or alemtuzumab succeeded to decrease the incidence of severe GVHD comparable to that of HLA-matched HSCT, but we still do not have enough data to compare its survival outcome with HLA-matched HSCT.

13:15-15:15 **Main Hall**

Stem Cell Transplantation

Mickey Koh

Dr Mickey Koh is a Consultant Haematologist and Senior Lecturer at St George's Hospital and Medical School, London, UK.
He is the Programme Director of the Stem Cell Transplant Programme at St George's Hospital. He is also the Programme and Medical Director of the Cell Therapy Facility in Singapore.
Dr Koh sits on the board of various transplant and cell therapy organizations including the Worldwide Network for Blood and Marrow Transplantation WBMT) and the International Society of Cellular Therapy (ISCT).

The Evolving Roles of Stem Cell Transplants and Cellular Therapy

Dept of Haematology, St Georges University Hospitals NHS Foundation Trust, London, UK
Cell Therapy Unit, Health Sciences Authority, Singapore

The routine use of both autologous and allogeneic stem cell transplants has been one of the great success stories in modern medicine for the treatment of haematological malignancies. This landscape is changing and will continue to evolve with the development of more potent and targeted drug therapies for such malignancies thus perhaps obviating the need for transplants while balanced against the increasing experience in successfully treating non malignant disorders like haemoglobinopathies with transplants.
The recent major advances in Cellular Therapy like CAR-T cells have also challenged the way transplants are being performed. Immune cells including T cells, Natural Killer (NK) cells and Cytokine Induced Killer (CIK) cells have long been recognised as potentially potent anti-tumour effectors but it has not been easy to fully exploit their potency while trying to minimise any potential toxcicities. The compelling success seen in autologous CAR-T cells has shifted that risk benefit analysis and increasing variations of CAR-T cells are being manufactured for a greater variety of haematological malignancies. There is also an effort to apply these genetic manipulation technologies into NK cells and CIK cells and to move from the autologous into the 3rd party allogenenic setting. The continued advances in in genetic manipulation and editing will only continue to find its way into the clinical cell therapy arena, often using stem cell transplants as a vehicle for the delivery of such genetic modifications.
The Academic Cell Therapy Facility (CTF) in Singapore has an established programme of research and manufacturing production with NK as well as CIK cells and new data including multiple virus specific 3rd party CIK cells will be discussed. The continuing attraction of mesenchymal stromal cells for 3rd party use and easy biobanking will also be discussed.

15:30-17:10 **Main Hall**

Technical Seminar

*Sponsored by **Fluidigm Japan K.K.***

Sebastian Rodriguez

Fluidigm Corporation

Robust and sensitive immune monitoring using Helios™ mass cytometry, a CyTOF® system

Helios™ mass cytometry, a CyTOF® system, is a cytometer that analyzes cells labelled with antibodies conjugated to isotopically purified heavy metal atoms (instead of fluorophores) by using ICP-TOF mass spectrometry technology. Whereas the number of proteins available in conventional flow cytometry is limited by the spectral overlap, Helios™ can simultaneously resolve multiple metal parameters per cell with minimal to non-signal overlap. Nowadays, over 40 isotopic metal probes are available to enable multi-parametric protein analysis, at single-cell resolution, on an accessible, expandable platform designed for breakthrough discoveries.

Even prior to the development of mass cytometry, the need for monitoring features of cell physiology and pathology at the single-cell level has been evident. The advent of mass cytometry allows accounting for complex features that would be much more difficult to study by fluorescent flow cytometry because of the limited number of non-conflicting fluorophore channels per experiment.

In the field of cellular therapy, the advent of mass cytometry has dramatically improved the ability to monitor immunological changes associated with therapeutic intervention and disease activity in, for example, patients treated with high-dose immunosuppressive therapy followed by autologous stem cell transplant.

In this seminar, I will discuss mass cytometry technology and it relevance in the field of cellular therapy.

15:30-17:10 **Main Hall**

Technical Seminar

*Sponsored by **Sysmex Corporation***

Anant Tucker

Sysmex Corporation

Creating Unique Diagnostic Value

This talk describes some of Sysmex's latest testing technologies including Molecular Imaging-Flow Cytometry (MI-FCM) for detecting cell morphology, Super-Resolution Microscopy for imaging biomolecules at nano-scale resolution and BNA-Clamp PCR for high-sensitivity genetic testing. Some open innovation activities with various organizations active in the regenerative medicine field are also introduced.

15:30-17:10 **Main Hall**

Technical Seminar

*Sponsored by **CellSeed Inc.***

Setsuko Hashimoto

President and CEO of CellSeed Inc.

Developing Regenerative Medicine using Cell Sheet Engineering

CellSeed Inc. is a leading company in regenerative medicine in Japan. Employing the cutting edge technology of “cell sheet engineering” as its technological base, we aim to develop regenerative medicine products that can lead to fundamental changes in therapies of severe medical conditions worldwide. The special cultureware features a temperature-responsive polymer that is immobilized on a surface and enables harvesting cell sheets that retain an intact extracellular matrix, leading to the recovery of damage-free cells in sheet form without enzyme treatment. The polymer is able to maintain its hydrophobic surface at 37 degrees C for cell culturing but can be turned hydrophilic by lowering the temperature to around 20 degrees C, leading to the recovery of damage-free cells in sheet form without enzyme treatment.

We develop therapeutic methods with cultured cells in the form of sheets to transplant to patients, and will share our current development status of esophageal epithelium cell sheets and chondrocyte sheets.

Using this technology, research on three-dimensional tissue construction by layering cell sheets is under way. Cell sheet engineering is considered as the future platform for the development of regenerative medicine technology.

15:30-17:10 **Main Hall**

Technical Seminar

*Sponsored by **PuREC Co. Ltd.***

Yumi Matsuzaki

Shimane University, Japan / PuREC Co. Ltd.

Purified human bone marrow derived mesenchymal stem cell “REC”

Mesenchymal stem cells are tissue stem cells that expected to be applied clinically next to hematopoietic stem cells, because fewer ethical problems associated with cell harvesting, and they have a variety of differentiation potential for bone, cartilage and fat. Clinical trials are already being conducted at several domestic facilities and more than 300 clinical trials are conducted in the United States.

For safe and effective cell therapy, it is necessary to guarantee not only the cellular function that MSC should originally possess, that is, the proliferation ability and differentiation ability which have been conventionally used as indicators, but also cell homogeneity and migration ability is there.

We clarified that human MSCs can be selected very efficiently by using the two antibodies LNGFR (CD271) Thy1 (CD90) and developed a technique to separate human MSC directly from bone marrow / peripheral blood / placental chorion / tooth pulp using cell sorter. LNGFR Thy-1 co-positive cells (LT cells) form fibroblast-like colonies at an extremely high frequency of 1 out of 6 cells. About 30 thousand fold colony forming cells are concentrated compared with whole bone marrow mononuclear cells, which is the separation method which achieved the highest enrichment ratio in the world. Comparing the growth rate of each well after separating this LT cell into a 96-well plate after a single cell separation, it was confirmed that Rapidly Expanding Clone (REC), which becomes confluent after 2 weeks, and other (Medium / Slow: MEC / SEC) .

REC compared with MEC / SEC, A) a homogeneous cell population, B) no cell senescence, C) most of the cells are in proliferative phase, D) high differentiation ability (especially fat differentiation ability), E) exhibiting migratory propertie, which clearly shows all the problems that have been a problem until now.

15:30-17:10 **Main Hall**

Technical Seminar

Sponsored by ***Kohjin Bio Co., Ltd.***

Taka-aki Sato

Director of Life Science Research Center, Shimadzu Corporation
Director of R&D Center for Precision Medicine
in Tsukuba University

The Leading-edge Applications of Mass Spectrometry in the Drug Discovery and Diagnosis

Driven by the development of high-end mass spectrometers, proteomic analysis is currently expanding its field beyond conventional quantitative analysis, as demonstrated in biomarker discovery studies, towards in-depth analysis of targeted molecules, such as single-cell imaging and characterization of heterogeneity in post-translational modification.

To illustrate this, the main topics of the present seminar include: (1) visualization of molecular abundance in biological specimens by mass spectrometry imaging (MSI); (2) high-sensitivity detection of diagnostic markers by Immuno-Beads MS technology; and (3) a brief introduction to the development of next-generation mass spectrometry system for contribution in drug discovery and diagnosis field.

We aim to integrate these novel technologies for tackling diseases (primarily cancer and neurodegenerative disease) in a comprehensive fashion; not only by detecting disease-specific biomarkers but also employing molecular imaging strategies for unraveling the molecular basis of pathology, determining the pharmacokinetics and validating the drug delivery system.

17:20-17:45 **Main Hall**

Evening Seminar Ⅰ-①

Sponsored by ***SHIBUYA CORPORATION***

Mamoru Kokubo

Director of the Regenerative Medicine System Division
at Shibuya Corporation in Kanazawa Japan

Shibuya Initiatives and Activities for Regenerative Medicine

Shibuya Corporation is Japan's leading pharmaceutical manufacturing system supplier, and in 1994 became the first company to introduce an isolator system in Japan. Basedon decades of experience in supplying sterile pharmaceutical and biological production equipment and a profound knowledge in aseptic processing, Shibuya began designing and manufacturing equipment and systems for the regenerative medical field in 2004. The following is a list of our current major activities in the field.

1. Public roles and contributions:
Shibuya takes part in many public activities and greatly contributed to establishing various standards for cell processing, including ISO 18362: Manufacture of cell-based health care products. Based on these activities, Shibuya provides the latest information and recommendations to its customers.

2. Equipment and system development:
Shibuya develops and provides exceptional equipment and systems for regenerative medicine using cutting edge technologies to manufacture extremely durable equipment. Shibuya provides cell culture isolators, robotic cell culture systems as well as peripheral equipment such as incubator and observation devices. Shibuya also provides an integrated management system which monitors the production environment, process, and production output.

3. Cell Processing:
Shibuya established an advanced cell processing factory to support cell processing needs for research institutions and their clinical trials. Experience and know-how acquired through the cell processing operations will be utilized for the development of our equipment and systems. Shibuya strives for the progress and growth of regenerative medicine through innovative ideas and cutting edge technologies.

17:45-18:10 **Main Hall**

Evening Seminar Ⅰ-②

Sponsored by ***Gene Therapy Research Institution Co., Ltd.***

Shin-ichi Muramatsu

Professor
Division of Neurology, Department of Medicine,
Jichi Medical University

Project Professor
Center for Gene & Cell Therapy (CGCT)
The Institute of Medical Science, The University of Tokyo (IMSUT)

Cell therapy for Parkinson disease

Parkinson disease (PD) is the second most common neurodegenerative disorder among the elderly, with an estimated 1% of the population over 60 years old suffering from PD. Progressive reduction in the dopamine content of the striatum is closely related the manifestation of motor problems. Cardinal symptoms including resting tremor, muscular rigidity, and bradykinesia become apparent after the 40-50% of the neurons in the substantia nigra are lost and striatal dopamine is reduced to about 20% of normal levels. PD has been the leading target condition for cell therapy since human adrenal gland cells were transplanted into the brain of the patients in1985. Soon after, fetal midbrain cells were used for restoring dopamine production in the striatum. Although initial open-label studies on fetal midbrain cell transplant achieved excellent outcomes, double-blind clinical trials have shown controversial success, and autopsy results have revealed that some of the grafted fetal neurons displayed pathological changes typical of PD. Nevertheless, advances in the field of stem cell research have raised hope for novel cell replacement therapies. Embryonic stem cells or iPS cells may offer a substitute for fetal midbrain cells, because they can proliferate extensively in an undifferentiated state and may provide an unlimited source of dopaminergic neurons. Neurons have been efficiently derived from stem cells, and beneficial effects after transplantation have been demonstrated in animal models of PD. However, some obstacles remain to be overcome before stem cell therapy can be routinely and safely used in humans. Since grafts are ectopically transplanted into the striatum instead of the substantia nigra in most current protocols, surviving dopaminergic neurons are not necessarily of the same subtype as the nigral cells. If the primary mechanism underlying recovery in these cell therapies is restoration of dopaminergic neurotransmission, direct delivery of genes encoding dopamine-synthesizing enzymes into the striatum would be a more straightforward approach. In fact, promising results have been reported in clinical studies of gene therapy using adeno-associated virus vectors. Future targets for cell therapy should include some types of Parkinsonism with degeneration of striatal neurons. To reconstruct local neural network in the basal ganglia, graft cells should be differentiated into GABAergic neurons instead of dopaminergic neurons.

17:20-18:10 **Satellite Room A**

Evening Seminar Ⅱ

Sponsored by ***Miltenyi Biotec***

Dirk Balshuesemann

Ph.D., Miltenyi Biotec, Germany
Dirk Balshuesemann is leading three global marketing teams at Miltenyi Biotec in Germany

Immuno-Oncology – Activities and solutions offered by Miltenyi Biotec

Immuno-oncology is a rapidly growing area of translational and clinical research. Major steps forward have been made over recent years to decrypt the power of the immune system. This improved knowledge of immunological mechanism is helping researchers and clinicians in their efforts to continuously improve and advance concepts for immunotherapies in hematology/oncology.

The introduction of allogeneic bone marrow transplantation more than thirty five years ago pioneered the field, though not much was known at that time about the anti-leukemic potential of donor immune cells. The development of various options for specific graft manipulations has helped to reduce the toxicity of allo transplantation without compromising the anti-leukemic activity. The CliniMACS CD34 System has recently been US FDA approved for use in AML transplants.

T cell depletion / low immunosuppression protocols provide an ideal background for further adoptive cell therapies. CliniMACS-based manufacturing processes have been developed for various cell types which are evaluated in numerous clinical trials: freshly isolated and expanded NK cells, virus-specific T cells, donor memory T cells, monocytes and subsequent generation of dendritic cells, blood-derived dendritic cells and fully automated generation of genetically transduced cells, e.g., CAR T cells. Customized solutions are available for academic and industry partners to allow the establishment of a broad spectrum of cell product manufacturing processes.

17:20-18:10 **Satellite Room A**

Evening Seminar II

*Sponsored by **Miltenyi Biotec***

Yingzi Ge

Program Manager
Clinical Business APAC
Miltenyi Biotec GmbH

Partner in personalized cell and gene therapy from A to Z

Personalized cell and gene therapy is a revolution in medicine. Its powerful benefits are continuously demonstrated by clinical evidence, which has led to a high demand on large-scale clinical trials and market authorization for unmet clinical needs. Although it is similar to biologics-based therapy that standardization of process and quality consistency of final products should be the primal requirements in cell therapy settings, little experience can be adopted from traditional drug production to cell manufacturing. The challenges inherent to manufacturing are unique and being faced by both process developers and regulators today.

Since 2013, the CliniMACS Prodigy platform with its broad applications has provided a revolutionary solution for all sectors. The device itself is a fully integrated and automated cell manufacturing platform. Combined with GMP-compliant software applications, CliniMACS Reagents and MACS GMP raw materials, every patient sample is manipulated in a closed system with operator-independent quality. Thus, this system has the following advantages. First, the final cell product is GMP-compliant. Second, the system greatly mitigates contamination risks which are associated to quality variation. Because of this in some countries a minimization of QC testing before and after individual steps is granted by local authorities. Third, the system maximizes the utilization efficiency of a GMP facility as multiple cell products can be safely manufactured in a single clean room. Last but not least, the system allows an instant scale-up and tech transfer with minimal training requirements, especially when high numbers of patient products are delivered simultaneously. Evidence of comparability is shown across multiple manufacturing sites.

In the past 22-years' experience in the clinic, Miltenyi Biotec has developed a comprehensive portfolio of clinical-grade products and regulatory expertise. Recently we extended our capabilities to the next level of support by modeling cell processing facilities for dedicated CliniMACS Prodigy manufacturing protocols. Miltenyi Biotec is committed to be an innovative partner and to enable cell and gene therapies towards commercialization.

Memo

Memo

- 2nd Day -

Oct. 28th (Sat)

Program & Abstracts

Day 2 Saturday, October 28

8:30~10:30 MSC (mesenchymal stem/stromal cell) (**ISCT-ACTO Joint Symposium**)

Chairpersons: Jacques Galipeau, Akihiro Shimosaka

ISCT-1: **Jacques Galipeau** (University of Wisconsin, USA)

"MSC potency assays – An ISCT perspective"

ISCT-2: **Oscar Lee** (National Yang-Ming University, Taiwan)

"Translational Application of Mesenchymal Stem Cells: Treatment of Spinocerebellar Ataxia as an Example"

Shinn-Zong Lin (Tzu Chi University, Taiwan)

"Pilot Trials of Adipose Tissue Derived Stem Cells in Treating ALS"

Abbas Ghaderi (Shiraz Institute for Cancer Research, Iran)

"Adipose-derived stem cells: a friend to be watched out"

Shuji Terai (Niigata University, Japan)

"Stem cell therapy for liver cirrhosis - From autologous cell to allogeneic cell -"

Tokiko Nagamura (IMSUT, Japan)

"Characteristics and clinical applications of umbilical cord-derived mesenchymal stromal cells"

10:30~12:10 Immuno-regulation & Therapy

Chairpersons: Jaeseung Lim, Sumimasa Nagai

Jun Ren (Capital University, China)

"Molecular phenotyping of CD8+PD-1+ T-cells in the adoptive T cell immunotherapy determine the clinical responses"

Seok-Goo Cho (Catholic University of Korea, Korea)

"T cell Immunotherapy for EBV-associated Tumor and CMV Reactivation"

Satoshi Takahashi (IMSUT, Japan)

"Virus-specific T cell therapy in Japan"

Noriko M Tsuji (National Institute of Advanced Industrial Science and Technology: AIST, Japan)

"Double-Stranded RNA in Commensal and Probiotic Lactic Acid Bacteria Boost Protective Immunity via Interferon-β Production"

Troels Jordansen (Glycostem, The Netherlands)

"NK cell based therapy"

10:40~12:10 **FIRM** (Forum for Innovative Regenerative Medicine) Session (Satellite Room A)

[Japanese public-private partnership for standardization of testing methods for the tumorigenicity of pluripotent stem cell-derived cell therapy products]

Chairperson: Keiji Yamamoto

Akihiko Azuma (FUJIFILM Corporation)

"The outcome of discussion on validation test methods of Tumorigenicity for evaluating pluripotent stem cell-derived products"

Hiroto Bando (Takeda Pharmaceutical Company Limited)

"Consideration for ensuring the quality and comparability of pluripotent stem cell-derived products"

Hitoshi Naraoka (Astellas Pharma Inc.)

"Evaluation of biodistribution of pluripotent stem cell-derived products"

12:20~13:10 Luncheon Seminar Ⅲ sponsored by **Takara Bio Inc.** (Satellite Room A)

Ken Ohmine (Jichi Medical University, Japan) *Chairperson: Keiya Ozawa*

"Clinical development of CAR therapy in patients with hematological malignancies: the current enthusiasm for cutting-edge technology"

12:20~13:10 Luncheon Seminar Ⅳ sponsored by **TES Holdings Co., Ltd.** (Satellite Room B)

Yoichi Yamada (TES Holdings Co., Ltd.) *Chairperson: Yusuke Suzumura*

"Clinical practice of bone regeneration by regenerative medicine with mesenchymal stem cells - possibility of various disease application"

13:20~13:40 General Meeting

Akihiro Shimosaka (ACTO Chairperson)

13:40~14:10 Presidential Lecture *Chairperson: Willem Eduard Fibbe*

Keiya Ozawa (IMSUT, Japan)

"Recent development of CAR-T cell therapy and future directions"

14:10~14:50 Special Lecture Ⅱ *Chairperson: Shuichi Taniguchi*

Willem Eduard Fibbe (Leiden University, The Netherlands)

"Dissecting Heterogeneity and Potency of Mesenchymal Stromal Cells"

14:50~15:30 Special Lecture Ⅲ *Chairperson: Shinn-Zong Lin*

Hideyuki Okano (Keio University, Japan)

"iPSCs-based Cell Therapy and Disease Modeling of CNS disorders"

15:45~17:50 Plenary Symposium (Gene-modified T Cell Therapy)

Chairpersons: Keiya Ozawa, Naoto Hirano

Naoto Hirano (Toronto, Canada)

"CAR therapy: Current status and beyond"

Shinich Kageyama (Mie University, Japan)

"Clinical trials of TCR-gene modified T cell therapy for refractory cancer"

Jinming Dai (Genscript Biotech, China)

"LCAR-B38M CAR-T Cells Achieved High Rate of Continuous Complete Remission (CCR) in Refractory or Relapsed Multiple Myeloma Patients"

Koji Tamada (Yamaguchi University and IMSUT, Japan)

"Novel strategy of CAR-T cell therapy for solid tumors"

Yangbing Zhao (University of Pennsylvania, USA)

"Engineering best in class T cells to treat cancers"

18:00~18:50 Evening Seminar Ⅲ sponsored by **AnGes, Inc.** (Main Hall) *Chairperson: Makoto Otsu*

Masafumi Onodera (National Institute of Child Health and Development, Japan)

"Stem cell gene therapy for primary immune deficiencies in Japan"

18:00~18:50 Evening Seminar Ⅳ sponsored by **Life Science Institute, Inc.** (Satellite Room A)

Mari Dezawa (Tohoku University, Japan) *Chairperson: Satoshi Morimoto*

"Endogenous reparative Muse cells may provide novel therapeutic approaches"

19:00~ Gala Dinner (Restaurant "ESPERANCE" in the St. Luke's International Hospital)

19:00~ Special Evening Seminar with Cruising Dinner *Chairperson: Akihiro Shimosaka*

Katsuhito Asai (**Gene Therapy Research Institution Co., Ltd.**)

"Gene Therapy Commercialization Center Plan in King Skyfront, Kawasaki"

8:30-10:30 **Main Hall**

MSC (mesenchymal stem/stromal cell)

(ISCT-ACTO Joint Symposium)

Jacques Galipeau

PROFESSOR,
ASSISTANT DEAN FOR THERAPEUTICS DISCOVER AND DEVELOPMENT
The director of the University of Wisconsin Advanced Cell Therapy Program. The Chair of the ISCT MSC Committee and is a board certified Hematologist with an active clinical practice in consultative benign hematology.

MSC potency assays – An ISCT perspective

Mesenchymal Stromal Cells (MSC) colony forming units (CFU) can be collected from an array of tissue sources, most commonly bone marrow, adipose and umbilical cord. These CFUs can be expanded numerically to generate large numbers of culture-adapted MSCs which can serve as autologous or allogeneic pharmaceuticals to treat acute tissue injury syndromes, chronic inflammatory disease or enhance tissue repair. The therapeutic effect of MSCs reflects their intrinsic biological properties serving as endogenous niche cells and their immune and regenerative responsiveness to tissue injury. Insights on cell biological mechanisms by which MSCs play these roles have been garnered from in vitro and pre-clinical animal studies, and these data provide hypothetical guidance on mechanisms that may be operative in human therapeutic trials. The development of MSC as a pharmaceutical requires defining key elements of their functionality which may correlate and predict for potency in affecting human clinical outcomes. Considering that MSCs are living cells, the biologically plausible therapeutic effects likely arise from the combined action of multiple effector pathways of which a few may serve as robust surrogates of potency. Mapping of these may provide a ruler against which potency of distinct manufacturing runs or lots can be ascertained to meet criteria for release. The ISCT MSC committee has formulated a perspective that functional analysis of MSC potency is best obtained by eliciting a functional response to predetermined biological cues in vitro. This approach was used to specifically interrogate the phenotypic, transciptome and secretome response of MSCs to Interferon-γ as biologically plausible response to inflammation. This reductionist analysis provides for a matrix analysis of pathways which correlate with T-cell suppression in vitro and which may foreshadow the potency of MSCs to mitigate pathogenic inflammation in clinical trials. The published results of this analysis will be presented as well as a future perspective on elements which affect MSC functionality and potency as related to clinical use.

8:30-10:30 **Main Hall**

MSC (mesenchymal stem/stromal cell)

(ISCT-ACTO Joint Symposium)

Oscar Lee

Deputy Superintendent, Taipei City Hospital
Chair Professor, National Yang-Ming University
Director, Stem Cell Research Centre, National Yang-Ming University
Vice President-elect, Asia Region, International Society for Cellular Therapy

Translational Application of Mesenchymal Stem Cells: Treatment of Spinocerebellar Ataxia as an Example

Spinocerebellar ataxias (SCA), are determined rare diseases by the Office of Rare Diseases Research at the National Institutes of Health. SCA causes progressive difficulty with coordination and gait which interferes in performing normal daily functions. SCA patients die from respiratory failure, aspiration pneumonia, or severe infection within 20 years of onset. There are no approved therapeutics for treating SCA (spinocerebellar ataxia). PolyQ SCAs are caused by an extensive CAG sequence repeat which encodes for expanded polyQ residues within the mutated protein. All polyQ SCA patients clinically present limb and gait ataxia because the same ataxia interactome is shared among subgroups. Extensive polyQ in cells, including Purkinje neurons, leads to cell dysfunction and triggers cell apoptosis. Loss of Purkinje cells leads to the symptoms and disease outcomes of SCA. Our pre-clinical research has achieved pre-clinical evidence suggesting adipose tissue-derived mesenchymal stem cell (ADMSC) transplantation ameliorates motor function deterioration of SCA in SCA2 transgenic mice by rescuing cerebellar Purkinje cells (Journal of Biomedical Science 2011, 18:54; Chang, et al). The infusion of ADMSC-derived Stemchymal MSCs into SCA patients may be safe and may demonstrate evidence of ameliorating motor function deterioration by arresting continued loss of Purkinje cells to premature apoptosis caused by oxidative stress from excessive PolyQ expression. Our trial design includes a single 7 x107 Stemchymal cells infusion into seven patients with 12 months follow up. Primary outcome measures for safety include vital signs, clinical lab tests and adverse events. Secondary outcome measures for early evidence of efficacy include changes in the scale for the assessment and rating of ataxia (SARA) score, changes in sensory organization test (SOT) score, changes in adaptation test (ADT) scores and changes in electronystagmogram (ENG). At 10 months, Phase I / II safety and early efficacy data supports the feasibility of using allogeneic Stemchymal (TM) Cell Therapy in the treatment of SCA patients. Longer term follow-up and larger, well-controlled clinical trials will be required to get to reach a definitive conclusion for Stemchymal treatment of SCA.

8:30-10:30 **Main Hall**

MSC (mesenchymal stem/stromal cell)

(ISCT-ACTO Joint Symposium)

Shinn-Zong Lin

President at Bioinnovation Center Buddhist Tzu Chi Medical Foundation The Superintendent at Tzu Chi Hospital, Professor of Neurosurgery at Tzu Chi University, Taiwan.

Pilot Trials of Adipose Tissue Derived Stem Cells in Treating ALS

Background:

Amyotrophic lateral sclerosis (ALS) displays loss of motor neurons in brainstem and spinal cord. Intraspinal neural progenitor cell transplantation in ALS patients stabilized patients' limb function (Riley et al. 2012), but their brain stem functions progressively deteriorated. In order to minimize the surgical trauma to the long length of the spinal cord during the implantation procedures and improve the survival of motor neurons in both brain stem and spinal cord, we proposed that the combined intracerebral (i.c.) and intravenous (i.v.) deliveries of adipose tissue derived mesenchymal stem cells (ADSCs) may slowdown the deterioration of motor neuron loss in brain stem and spinal cord in ALS mice and prolong their life-span. The hypothesis was attested by experiments in animals and an ALS patient. In experiment in the ALS patient after getting official approvals from TFDA and IRB, it was attested in this way and followed-up for one year.

Materials and Methods:

In animal experiment: G93A transgenic mice overexpressing human mutant SOD1 was obtained from Jackson Laboratories. They were randomly distributed into three groups at 60 days of age: (1) untreated group (n=8); (2) riluzole-treated group (n=4), in which the mice were intraperitoneally treated with riluzole 16 mg/kg body weight once daily ; (3) human ADSC treated group (n=8), in which the mice were transplanted with ADSC ($2x10^6$ cells/30 µl PBS,) via i.c. once at 60 days postnatal, and then transplanted with ADSC ($1x10^6$ cells/150 µl PBS, i.v. at 90 days and 104 days postnatal. Immunohistochemical (IHC) staining was performed for BDNF, CXCR4, and motor neurons of the brain stem and spinal cord.

In ALS patient trial: i.c. transplantation once at bilateral peri-cortical spinal tracks with 1.7×10^8 ADSCs in 1.5 ml saline, and i.v. infusion four times per two weeks before and after i.c. transplantation with dosage of $2\pm0.5 \times 10^8$ ADSCs. Taiwan Ministry of Health and Welfare (TFDA) and Institutional Review Board (IRB) of China Medical University Hospital, Taiwan approved this study.

Results:

The life-span of the mice in ADSC-treated group (149.9±4.8 days, $p<0.05$) was much prolonged compared to the untreated (126.4±7.2 days,) and the riluzole treated (133.7±6.4 days) groups. IHC staining showed that ADSC treated group had higher contents of BDNF and CXCR4, as well as volume of motor neurons in comparison to the other two groups.

The ALS patient was treated with the combined i.c. and i.v. deliveries of autologous ADSCs. One year before transplantation, patient's ALSFRS was 17; but one week before trail the score was 7. The post-operative ALSFRS score remained 7-9 points around 6 months follow-up and, the ALSFRS score decreased to around 5 points at 9 and 12 month follow-up.

Conclusions:

The results demonstrate that the combined i.c. and i.v. treatments with ADSCs extend the life-span of ALS mice and slowdown the deterioration rate of motor function in the ALS patient in period of 12 months.

8:30-10:30 **Main Hall**

MSC (mesenchymal stem/stromal cell)

(ISCT-ACTO Joint Symposium)

Abbas Ghaderi

Abbas Ghaderi, Shiraz Institute for Cancer Research, School of Medicine, Shiraz University of Medical Sciences, Shiraz Iran

Adipose-derived stem cells: a friend to be watched out

Mesenchymal stem cell originating from various tissue sources has been widely used in regenerative medicine. There are reports on successful outcome and also limited reports on the side effects and complications associated with use of ASC in tissue engineering. The adipose derived mesenchymal stem cells (ASC) are available in every normal tissue and easily isolate for manipulation and clinical purpose. But the ASC is also regarded as one of the player of the tumor microenvironment (TM). The architecture of tumor microenvironment includes networks of cells and molecular structures plus a complex of enzyme and mediators that collectively participate in tumor spread and invasions. Adipose derived stem cells (ASC), a resident of tumor niche originate from bone marrow, migrated to a wide range of tissues with pleuropotent capacity to differentiate to different cell lineages. ASC is known to produce a large numbers of chemokines and cytokines with anti-inflammatory properties such as IL-10, TGF-β, IDO and PGE2. Production of angiogenic factors such as SDF-1 and matrix metalloproteinases (MMPs) by ASCs is another proposed mechanism for tumor spreading. Role of ASC in tumor niche has been investigated by our group by focusing on breast cancer. The functional differences of ASC from higher stage of breast cancer compare to the lower stages are discussed in term of expression and secretion of mediators and effect on tumor cell in a co-culture system. Our data on co-culture of naïve T cell with ASC indicated a trend of differentiation toward T regulatory response. Moreover, our data support on ASC effect on plasticity of Th0 toward TH2 by augmentation of cytokine release. Our recent data on co-culture of ACS with B cells and NK cells will also be presented. By Producing TGF-β, it is postulated that ASCs might be involved in the regulation of the Epithelial to Mesenchymal Transition (EMT), a process which recently reported to control the tumor metastasis and invasion. Based on our finding, a hypothesis has been generated explaining the contribution of ASC to the cellular basis of the cancer which accordingly we recommend application of ASC for regenerative medicine should be controlled under tight guideline and monitoring.

8:30-10:30 **Main Hall**

MSC (mesenchymal stem/stromal cell)

(ISCT-ACTO Joint Symposium)

Shuji Terai

Chairman & Professor
Division of Gastroenterology & Hepatology,
Graduate School of Medical and Dental Sciences,
Niigata University

Stem Cell therapy for liver cirrhosis
-From autologous cell to allogeneic cell-

In 2003, we started a clinical study using autologous bone marrow cell infusion therapy (ABMi therapy) for decompensated liver cirrhosis. We found the important findings that first induction of recovery of liver fibrosis and sequentially activation of liver regeneration were occurred during this study. By the way, to cure more severe and number liver cirrhosis patient, shift from autologous cell therapy to allogenic cell therapy is needed. We started to elucidate the basic mechanism why ABMi therapy is effective in liver cirrhosis. We analyzed which cell is effective in heterogeneous bone marrow cells to improve liver fibrosis and activate liver regeneration. From basic study, we found mesenchymal stem cell and macrophage interaction is important to induce the improvement of liver fibrosis and liver regeneration effectively. We also confirmed the engraftment of administrated MSCs and macrophages in lung and liver using by live imaging. On the other hands, we also prepare clinical trial: allogeneic adipose tissue derived MSC therapy for liver cirrhosis. The clinical trial was started from July 2017 with Rohto company. In this symposium, we will present current status of stem cell therapy for liver cirrhosis.

8:30-10:30 **Main Hall**

MSC (mesenchymal stem/stromal cell)

(ISCT-ACTO Joint Symposium)

Tokiko Nagamura

Director / Associate Professor, Department of Cell Processing and Transfusion,
Director of IMSUT CORD
The Institute of Medical Science, The University of Tokyo (IMSUT)

Characteristics and Clinical Applications of Umbilical Cord-derived Mesenchymal Stromal Cells

The human umbilical cord (UC) is a rich source of mesenchymal stromal cells (MSCs), which have been reported to possess multi-lineage potential. UC-MSCs to treat various diseases has recently been investigated. UC-derived MSCs (UC-MSCs) have attracted much attention for many reasons, including (1) no adverse events during the collection process, (2) ease of collection even after CB collection or failure to collect CB, (3) minimal ethical controversy, (4) multipotent ability to differentiate into various cell types, including neurogenic cells, (5) low immunogenicity with significant immunosuppressive ability, and (6) facilitating the tissue repair by providing the tissue specific tropic factors. We recently established the UC-MSC banking system, namely IMSUT CORD, to provide UC-MSC to facilitate the clinical and research use. Using UC-MSCs, we are going to start the Physician's initiated clinical trial for the treatment of severe acute graft versus host disease (GVHD) after hematopoietic stem cell transplantation and neonatal encephalopathy, which may develop to a lifelong cerebral palsy. This symposium will be provided a brief review of clinical application potentials of UC-MSC, together with characteristics and our new processing method using serum-free medium and cryoprotectant.

10:30-12:10 **Main Hall**

Immuno-regulation & Therapy

Jun Ren

Jun Ren MD, PhD is the worldwide leading and distinguished onco-immunology researcher and clinical scientist .
The pioneering leader of cancer translational researcher in cancer immunology and clinical application in China with publication 70 SCI cited papers and 200 papers in Chinese core journals.

Molecular phenotyping of CD8+PD-1+ T-cells in the adoptive T cell immunotherapy determine the clinical responses

Purpose: Advanced pancreatic(APC) and gastric cancer(AGC) remain challenging to treat effectively. This study aims to investigate the potential role of CD8+PD-1+ T-cells population on the superiority of immunotherapy with dendritic cells and cytokine induced killer cells (DC-CIK) administered with the chemotherapy(S-1).
Experimental Design: Consecutive patients with advanced pancreatic cancer (n=36) and gastric cancer (n=30) were treated with either DC-CIK or DC-CIK+S-1. CIK cells were expanded with IL-2. Flow Cytometry and ELISPOT were used for sorting and testing the reactivity CD8+PD-1+ T-cells. Survival estimates were calculated according to the Kaplan and Meier methodology.
Results: The median overall survival(OS) and progression free survival(PFS) for DC-CIK plus S-1 were 212 and 136 days which were significantly higher than other groups for treatment of APC($P<0.001$). Similarly, significant differences in PFS and OS were showed in DC-CIK plus S-1 for treatment of AGC($P<0.001$). PD-1- and PD-1+ DC-CIK cells were cocultured with their autologous tumor cell lines, and reactivity was assessed by measuring IFN-γ secretion. We found a clear correlation between the percentage of CD8+PD-1+ T-cells on day 7 of culture and the reactivity of the DC-CIKs after 14 days in culture with IL-2. Moreover, CD8+PD-1+ T-cells showed higher tumor specific IFN-γrelease in ELISPOT, compared to CD8+ PD-1- sorted T-cells or unsorted. Further survival analysis showed that patients with the percentage of CD8+PD-1+ T-cells population enhanced more than 2 times after culture had favorable OS and PFS compared with those having no CD8+PD-1+ T-cells increasing. These results showed that CD8+PD-1+ T-cells population might be an excellent biomarker for tumor or antigen-specific activation of adoptive cell therapy.
Conclusion: CD8+PD-1+ T-cells populations were associated with the superiority of DC/CIK combined S-1 and could be an useful biomarker for enriching tumor specific T-cells for cell immunotherapy of patients with APC and AGC.

10:30-12:10 **Main Hall**

Immuno-regulation & Therapy

Seok-Goo Cho

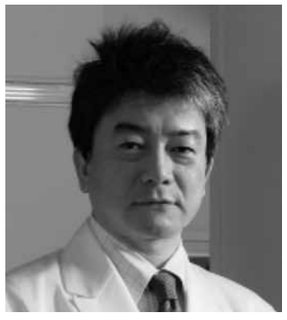
Professor, Department of Hematology, The Catholic University of Korea College of Medicine
Director, Institute of Translational Research and Molecular Imaging, The Catholic University of Korea

T cell Immunotherapy for EBV-associated Tumor and CMV Reactivation

Background: Various T cell immunotherapies, such as tumor-infiltrating lymphocytes (TILs), cytokine-induced killer (CIK) cells, and antigen-specific cytotoxic T lymphocytes (CTLs) have emerged as a method to treat patients with malignant diseases and also viral infection. Initially, clinical studies focused on the use of readily available, easy-to-generate yet non-specific CIK cells; however, more recently with the increasing knowledge of tumor or virus-associated antigens and HLA-restricted epitopes, antigen-specific CTLs have been rapidly developed and have recently been initiated in the clinic.
Methods: We have generated autologous Epstein-Barr virus specific CTLs (EBV-CTLs) from EBV-associated lymphoma patients using EBV latent membrane protein (LMP)-1 and LMP-2a transferred dendritic cells. Ten EBV-associated extranodal natural killer (NK)/T-cell lymphoma (ENKTCL) and two post-transplant lymphoproliferative disorder (PTLD) patients received induction therapy by investigator's choice and achieved complete response. Then, patients received eight doses of 2x10e7 EBV-CTLs/m2 and were evaluated for safety and efficacy. Furthermore, we have applied a simple and robust approach to produce cytomegalovirus (CMV) specific CTLs (CMV-CTLs) by an automatic IFN-γ cytokine capture system using CliniMACs Prodigy and a novel cytokine-based culture system.
Results: Adoptive transfer of EBV-CTLs a safe and effective post-remission therapeutic approach in both ENKTCL and PTLD patients. Following infusion, there were no immediate or delayed toxicities. Clinical outcomes were associated with increased frequencies of LMP-1 and LMP-2a specific T cells in the peripheral blood after CTL infusion and also with the control of plasma EBV DNA levels. In addition, the IFN-γ cytokine capture system (CCS) using the fully automated CliniMACS Prodigy device could rapidly produce CMV-CTLs that may be applicable in clinically urgent CMV-related diseases. Isolated cells revealed functional activity including efficient proliferation, sustained antigen-specific IFN-γ secretion and cytotoxicity effect against pp65 pulsed target cells. Furthermore, our novel approach to expand CMV-CTLs using peptide mixture in the presence of specific cytokines could effectively produce large numbers of virus-specific T cells with dual functional activity expressing both NK cell functions and retained TCR specific cytotoxicity.
Conclusions: T cell immunotherpy may be a highly effective approach to control viral load in virus-associated tumor to promote durable remission and also to control clinically urgent virus infections. In the future, novel methods to produce antigen-specific CTLs may help overcome current manufacturing limitations and help acclerate the application of antigen-specific CTLs world-wide.

10:30-12:10 **Main Hall**

Immuno-regulation & Therapy



Satoshi Takahashi

Dep of Molecular Therapy, IMSUT, Japan

Virus-specific T cell therapy in Japan

Viral infection, especially by reactivated latent viruses is one of most important complications in hematopoietic stem cell transplant (HSCT) recipients. Restoration of virus-specific immunity by virus specific T cells (VSTs) offers an attractive alternative to conventional drugs, and can be highly effective in immunocompromised patients such as HSCT recipients. Several studies has been reported the usefulness of HLA-restricted epitope peptides as antigens to generate VST. While this approach is clinically effective and has a benefit of traceability by tetramer after infusion, a concern was the specificity-restriction of the infused VSTs targeting a single epitope may allow variants to escape. This strategy is also limited in patients with single specific HLA typing. Baylor group has developed a method to generate multi-specific VSTs by direct stimulation of peripheral blood mononuclear cells with overlapping peptide (OLP) libraries recently, and we have adopted the method in serum free culture system. The VST derived from OLP can cover comprehensively viral antigens including unknown epitopes with more diversity. Our group, like Baylor, generated VSTs that targeted 5 viruses (CMV, EBV, AdV, HHV-6 and BKV) in a single line using OLP libraries of those viruses. The phenotype, growth and specificity of multi-specific VSTs produced in serum free medium were equivalent to those generated in conventional serum containing medium. The use of serum free medium allows this approach to be readily introduced to clinical practice with lower cost, greater reproducibility due to the absence of batch-to-batch variability in serum, and without concerns for infectious agents in the serum used. This method could be matched to Japanese regulation above all else. We have now started the clinical study with this simplified and safe approach in patients with severe viral infection after HSCT.

10:30-12:10 **Main Hall**

Immuno-regulation & Therapy

Noriko M Tsuji

Immune Homeostasis Lab
Biomedical Research Institute

National Institute of Advanced Industry and Science Technology (AIST) Japan

Double-Stranded RNA in Commensal and Probiotic Lactic Acid Bacteria Boost Protective Immunity via Interferon-β Production

The small intestine harbors a substantial number of commensal bacteria, which contribute to the maturation of immune system. Here, we elucidate the immune-modulatory effect of double-stranded RNA (dsRNA) from one major commensal species, lactic acid bacteria (LAB) on host-immune cells, and discuss its possibility to become a candidate for oral adjuvant/vaccine for non-communicable diseases (NCDs) including allergy and cancer. We found that dsRNA in LAB triggered IFN-β production from dendritic cells (DCs) via endosomal Toll-like receptors (TLR) 3 activation, which protected mice from experimental colitis. IFN-β secreted in response to LAB further enhanced interleukin-12 secretion by DCs and differentiation of T cells towards IFN-γ-producing Th1 cells. As expected, oral administration of LAB enhances systemic Th1 immunity via TLR3 pathway. These results identify TLR3 as a sensor to small intestinal commensal bacteria, and the mechanism for Th1 polarization due to IFN-β induction in vitro and in vivo may thus confer anti-NCDs activity by commensal and/or probiotic LAB to the host.

10:30-12:10 **Main Hall**

Immuno-regulation & Therapy

Troels Jordansen

Chairman, Glycostem NV, The Netherlands
International healthcare executive with 25+ years experience and two commercial degrees. Special interest in commercialisation, business development, general management, 'turn-around' and 'trouble shooting' projects. Since 2000 has been part of management teams raising in excess of £100 million and has global healthcare network.

NK cell based therapy

"NK-cells show increasing popularity as cancer immunotherapy for several reasons. The safety profile being one, but also the opportunity to use them as allogeneic cellular therapies, which can be delivered "off-the-shelf", is of significant interest for doctors, patients and large pharma. NK-cells can be derived from peripheral and umbilical cord blood but only umbilical cord blood offers truly industrial scale opportunities.

Glycostem is a clinical stage company and at a world leading position in NK cell based therapy supported with strong safety and very interesting efficacy data for the treatment of AML. Glycostem is setting up state-of-the-art closed system GMP manufacturing which offers lowest possible manufacturing costs for NK-cells and other types of cells.

The company's Chairman and CEO, Troels Jordansen, will present about Glycostem, NK-cell manufacturing, clinical results and future prospects for cellular immunotherapy."

10:40-12:10 **Satellite Room A**

FIRM (Forum for Innovative Regenerative Medicine) Session

Japanese public-private partnership for standardization of testing methods for the tumorigenicity of pluripotent stem cell-derived cell therapy products

Akihiko Azuma

2010.9-Present Research Manager, Regenerative Medicine Research Laboratory, FUJIFILM Corporation.
2002.10-2010.8 Research & Development Manager, ArBlast Corporation
2001.4-2002.9 Post Doctor, Molecular Virus Unit, RIKEN

The outcome of discussion on validation test methods of Tumorigenicity for evaluating pluripotent stem cell-derived products

FIRM-MEASURE-CoNCEPT is a committee that aims to standardize and validate evaluation methods of tumorigenicity on pluripotent stem cell-derived products internationally. One of the team in the committee, tumorigenicity evaluation team has focusing and discussing on the evaluation methods that should be standardize and validate. The purpose of the team is to propose the methods that should be conducted multi-center study based on investigation and discussion.
It is said that tumorigenicity of pluripotent stem cell-derived products is relatively higher than that of somatic stem cells. Little experiences were reported about pluripotent stem cell-derived products. So, it is considered that assessment of tumorigenicity is critical for development of the products. Our guidance search indicated that consensus about the methods of tumorigenicity was not built among the world. We have been considering it dividing into three types of risks, that are residual pluripotent stem cells, contamination of transformed cells and transformation in micro environment after implantation. With regards to in vitro methods, some methods based on flow cytometry, PCR technique and cell culture technique were reported for the contaminated transformed cells. Some in vitro methods based on soft agar colony formation and cell culture technique were also reported for contaminated transformed cells. No methods were reported for transformation after implantation. On the other hand, in vivo methods can be used for every purpose. But, it is reported that important parameters such as administration root and period of observation should be applied case by case approach based on the product characterization. We had several discussions focusing on principal and sensibility on the methods.
In this presentation, we will introduce the methods that we plan to conduct multi-center studies to standardize tumorigenicity tests for pluripotent stem cell-derived products.

10:40-12:10 **Satellite Room A**

FIRM (Forum for Innovative Regenerative Medicine) Session

Japanese public-private partnership for standardization of testing methods for the tumorigenicity of pluripotent stem cell-derived cell therapy products

Hiroto Bando

2016.8-Present Global Head of Cell Manufacturing Strategy, Regenerative Medicine Unit
2014.7-2016.7 Research Manager, Innovation Technology Lab., CMC Center
2012.1-2014.6 Senior Director, Finance & Portfolio Management, CMSO Office
2007.4-2011.12 Franchise Coordinator, Strategic Product Planning

Consideration for ensuring the quality and comparability of pluripotent stem cell-derived products

As an activity of the Committee for Non-Clinical Safety Evaluation of Pluripotent Stem Cell (iPSC)-derived Product (CONCEPT) in the Forum for Innovative Regenerative Medicine (FIRM), through collaboration with the National Institute of Health Science, "Multisite Evaluation Study on Analytical Methods for Non-clinical Safety Assessment of human-derived Regenerative Medical Products (AMED-MEASURE) " was initiated in 2016.
Our quality/comparability evaluation team has focused on the iPSC derived products which have high novelty/ expectation, through reviewing the regulatory documents in Japan, US and EU.
In particular, in the case of iPSC derived products, since evaluation of tumorigenicity is the most critical matter from the safety perspective, standardized concept regarding its necessity (why), evaluation items (what), timing/duration (when) and study methods (how) to be evaluated them, is required from pharmaceutical industries who are trying to develop relevant cell products.
On the other hand, taking account of the quality & comparability, since cell products contain living cells with dynamic and complex characteristics, to ensure quality characteristic of cell/tissue products such as identification test (property, cell phenotype, differentiation potency, cell species etc.), purity test (cell phenotype, abnormal growth etc.), manufacturing process-derived impurity test (manufacturing process-derived impurities (serum-derived albumin, antibiotics etc.)), unintended physiologically active impurity test (physiologically active substances etc.), safety assessment (chromosomal aberration, colony formation in soft agar, viruses/ mycoplasma contamination, endotoxin, sterility test), potency test (physiologically active substances secretion, differentiation potency, cell phenotype, cell proliferation, durability etc.) and contents (cell number, cell viability etc.) is required. Thus advanced purification techniques and high sensitive detection methods will also be essential for the removal of transformed cells, undifferentiated iPSC and relevant additives and so on. In addition, different criteria should be considered for autologous and allogenic types of cell products. Since cell amount (dosage) and administration site also have significant impacts on the efficacy and safety, case by case considerations will be applied to each unique product as is now, and a different concept of quality/comparability from previous pharmaceutical products should be discussed.
In this presentation, we will introduce the concept of quality in the evaluation of the tumorigenicity of iPSC derived products, the quality assurance for future manufacturing process etc. based on the KOL's interview after practical discussions with the representatives from relevant companies.

10:40-12:10 **Satellite Room A**

FIRM (Forum for Innovative Regenerative Medicine) Session

Japanese public-private partnership for standardization of testing methods for the tumorigenicity of pluripotent stem cell-derived cell therapy products

Hitoshi Naraoka

Drug Safety Research Labs., Astellas Pharma Inc.
2015 Executive education course, Kellogg school of Management in Northwestern University
2010 MBA; Institute of Business and Accounting, Kwansei Gakuin University Professional Graduated School
2006 Ph.D.; Department of Applied Genetics, University of Tokyo Graduate School of Agricultural and Life sciences

Evaluation of biodistribution of pluripotent stem cell-derived products

Focusing on tumorigenicity assessment of cell therapy products (CTPs), a national institute and private companies work together to provide sound science-based and globally acceptable consensus for safety evaluation policy in the R&D of products.
The subjects of research are as follows: a) organizing the concept of hazards causing tumorigenicity risks and their evaluation considering domestic and international trends, b) establishment of standard protocols and multisite validation for tumorigenicity-associated tests to clarify its usefulness and repeatability, c) organizing and reporting the concept of biodistribution testing for transplanted cells, and d) organizing and reporting the concept of biocomparability evaluation for modification of ingredients and processing. This research project is classified into two steps: step 1, search and discussion on the regulatory policy on tumorigenicity, biocomparability, and biodistribution evaluation; step 2, experimental multi-site joint research for tumorigenicity assessment.
The goal of biodistribution team is to identify the standard methodologies for biodistribution of the implanted cells in preclinical and clinical.
We surveyed guidelines issued by PMDA, FDA, EMA and ISSCR, and summarized their difference in positions of biodistribution testing. The biodistribution testing of CTPs seems to be commonly necessary for confirming efficacy and toxicity/safety of products. We also surveyed testing methods for biodistribution and states of the biodistribution evaluation in clinical research conducted in Japan, US and EU. Interviews with KOLs were performed to obtain information on the meaning of biodistribution testing for product development, handling of results, and testing methods. As qPCR method was quite easy and generally used for biodistribution evaluation of CTPs, preliminary experiments using qPCR were performed to prepare a standard protocol. Based on these results, we are discussing with the study design of qPCR for multi-site validation study.

12:20-13:10 **Satellite Room A**

Luncheon Seminar Ⅲ

*Sponsored by **Takara Bio Inc.***

Ken Ohmine

Division of Hematology, Department of Medicine
Division of Immuno-Gene and Cell Therapy (Takara Bio)
Jichi Medical University

Clinical development of CAR therapy in patients with hematological malignancies: the current enthusiasm for cutting-edge technology

Cancer therapy placed reliance on chemotherapy, surgery, and radiotherapy over the passage of years. Within recent days immunotherapy has been garnering attention as a novel option for a series of cancer therapeutics. The gene-engineered T-cell technology brings out highly efficient and accurate anti-cancer reactivity into effector cells. Chimeric antigen receptor (CAR) is one of the encouraging approaches in this technology, and CAR-T therapy is currently undergoing wide-scale and rapid-growth both in academia and in industry-sponsored clinical trials.

CARs are composed of an extracellular ligand recognition domain, commonly derived from a heavy chain and a light chain of an antibody, linked to an intracellular signaling domain that includes CD3ζ to induce T-cell activation upon antigen binding. Second generation CARs incorporate co-stimulatory domains such as CD28 and 4-1BB, which dramatically improve CAR-T proliferation, cytokine secretion, apoptosis avoidance, and in vivo persistence.

CD19 is a transmembrane glycoprotein expressed in a multitude of B-cell malignancies. CD19-specific CAR therapy has shown substantial benefit in patients with relapsed and refractory acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia and Non-Hodgkin's lymphoma. More than 80% of treated patients reached complete remission as best clinical outcome in ALL clinical trials. On the other hand, life-threatening toxicities have been described related to cytokine release syndrome and neurotoxicity. Recent studies used TALEN gene-editing technology to knock-out TCR αβ expression to overcome the key barriers of the adoptive transfer of healthy donors' CAR-Ts. This manufacturing platform shows potential efficacy as an "off-the-shelf" immune-cell therapy.

In this presentation, I trace the important steps for development of CAR therapy and provide a comprehensive overview of the clinical trials of CD19-CARs have been conducting worldwide.

12:20-13:10 **Satellite Room B**

Luncheon Seminar Ⅳ

*Sponsored by **TES Holdings Co., Ltd.***

Yoichi Yamada

The University of Tokyo, IMSUT hospital

Clinical practice of bone regeneration by regenerative medicine with mesenchymal stem cells - possibility of various disease application

It is facing super-ageing society in the world. People hope youthful happy life improved in quality of life (QOL). Oral function is also important not only for mastication, including nutritional intake, but also for speech, aesthetics, and psychosocial functions such as satisfaction and social well-being. Number of missing teeth increased with age and alveolar bone resorption often occurs following tooth loss. Consequently, bone tissue regeneration represents an important challenge for oral-maxillofacial surgeons and dentists. The gold standard of bone regeneration for severe bone atrophy is autologous bone transplantation, but it requires injuring a healthy region with heavy invasiveness. To overcome these problems, we applied regenerative medicine with bone marrow-derived mesenchymal stem cells (BMMSCs). The safety and effect of the techniques were investigated in preclinical studies. To launch clinical study of bone regeneration with BMMSCs, treatment protocol was designed for patients with conventional problems of masticatory function because of severe alveolar ridge atrophy. The cells obtained from patients were cultured in Cell Processing Center (CPC) and their characteristics were examined for clinical use. The results of clinical application for bone regeneration were good and the long-term prognoses were also stable. In addition, the technique is developed into the TE-BONE™.

Dental pulp obtained from oral tissue appears to be an alternative and more readily available source of stem cells. Dental Pulp Stem Cells (DPSCs) have attracted attention because of the potential for use in cell-based therapy for various systemic disease, such as neurological disease, cardiac disease, and diabetes mellitus. Since DPSCs can be obtained noninvasively and easily from unnecessary teeth such as third molar, this innovative application using DPSCs to regenerate tissue might provide substantial advantages over a conventional technique. We examined characteristics of DPSCs and subsequently carried out pilot trial. In this lecture, we would introduce the good results of clinical cases with MSCs and the future view of stem cell therapy.

13:40-14:10 Main Hall

Presidential Lecture

Keiya Ozawa

Director, IMSUT Hospital
Director, Center for Gene & Cell Therapy (CGCT)
Professor, Division of Genetic Therapeutics, Advanced Clinical Research Center
The Institute of Medical Science, The University of Tokyo (IMSUT)

Visiting Professor, Division of Immuno-Gene & Cell Therapy (Takara Bio)
Jichi Medical University, Tochigi

Recent development of CAR-T cell therapy and future directions

Gene therapy research remained stagnant for many years due to serious side effects. However, clinical gene therapy has been revived in Western countries, because a number of successful clinical trials have been reported recently, including hematopoietic stem cell gene therapy and AAV vector gene therapy mainly for hereditary disorders. Regarding cancer gene therapy, there has been increasing focus on gene-modified T cell therapy, which is divided into CAR (chimeric antigen receptor)-T cell therapy and TCR (T cell receptor)-T cell therapy. These technologies have different characteristics and are used depending on the type of target antigens. CARs are hybrid proteins consisting of an extracelluar single chain fragment of variable region (scFv) fused to intracellular lymphocyte signaling domains CD28 or 4-1BB, coupled with CD3ζ to mediate T cell activation. Recent clinical trials of CD19-targeted CAR-T cell therapy have achieved a great success in the treatment of relapsed/refractory B cell malignancies, including ALL, CLL, and non-Hodgkin lymphoma (NHL). In Japan, we have started clinical study of CD19-CAR-T cell therapy for NHL at Jichi Medical University Hospital, in collaboration with Memorial Sloan Kettering Cancer Center and Takara Bio Inc. Multi-institutional clinical trials of CD19-CAR-T cell therapy for ALL are also being conducted. As for the unique side effects of CAR-T cell therapy, there are cytokine release syndrome (CRS) and neurological toxicities (including cerebral edema). Depletion of normal B cells is called “on-target, off-tumor reaction” and causes immunoglobulin deficiency in the late phase. On August 30, 2017, the U.S. FDA (Food and Drug Administration) approved tisagenlecleucel (KYMRIAH®, Novartis Pharmaceuticals Corp.) for the treatment of pediatric and young adult patients with relapsed/refractory B-ALL. In the near future, CAR-T cell therapy will be expanded to treat the other hematological malignancies and solid tumors. As for solid tumors, the other strategies will be needed to get efficacy in combination with CAR-T. Applications of gene-editing technologies are also exciting topics. Allo (universal) CAR-T cells can be produced by knockout of TCR gene, and PD-1 gene knockout will enhance the efficacy of CAR-T cell therapy by local immune checkpoint blockade.

14:10-14:50 Main Hall

Special Lecture II

Willem Eduard Fibbe

professor of Hematology
and Stem Cell Biology and Head of the Department
of Immunohematology and Blood Transfusion at the LUMC. He studied medicine at the Free University in Amsterdam

Dissecting Heterogeneity and Potency of Mesenchymal Stromal Cells

Mesenchymal stromal cells (MSCs) comprise a heterogeneous population of multipotent cells that can be isolated from various human tissues. Due to the low frequency of MSCs in human tissues, MSC are extensively expanded ex-vivo before being used clinically. The standard conditions for ex-vivo expansion of MSCs are based on the presence of fetal calf serum. However, serum free media that bypass the possible risk associated with the use of animal products have been used with similar results. MSCs are mainly characterized by their multi-lineage differentiation capacity, ability to adhere to plastic surfaces, by their morphology and by immune phenotype by a combination of positive (CD73, CD90, CD105, CD271) and negative (CD14, CD31, CD34, CD45) markers.

MSCs display unique immune modulatory properties that have been first demonstrated in-vitro and subsequently also in-vivo in both animal models and in humans. MSCs constitutively produce IL-6 that induces differentiation of M0 macrophages towards an anti-inflammatory IL-10 producing cell type that shares properties with M2 macrophages. Several reports have indicated that MSCs are not constitutively inhibitory, but need to be activated by an inflammatory environment in order to mediate their immune regulatory effect. In the presence of an inflammatory environment (high levels of TNF-α and IFN-γ), MSC s may become activated and adopt an immune suppressive phenotype by secreting high levels of anti-inflammatory soluble factors, including IDO. In the absence of an inflammatory environment, MSCs may adopt a pro-inflammatory phenotype and enhance T cell responses by the secretion of chemokine’s (CXCL9/ CXCL10/ MIP1α/ MIP1β/ RANTES) that recruit lymphocytes to sites of inflammation. The balance between anti- and pro-inflammatory pathways is critical in controlling host defence and inflammation and in the prevention of excessive tissue damage. Altogether, these data indicate that MSCs play an important role in maintaining tissue homeostasis.

14:50-15:30 **Main Hall**

Special Lecture Ⅲ

Hideyuki Okano

Professor of Physiology,
Keio University School of Medicine, Tokyo, Japan

iPSCs-based Cell Therapy and Disease Modeling of CNS disorders

It is more than 10 years since the first description of iPSCs by Yamanaka group. There is increasing interest in applications of iPSCs technologies for wide variety of biological research fields including cell therapy (regenerative medicine) and disease modeling. Our group has been working cell therapy for spinal cord injury (SCI) and modeling and drug screening for CNS disorders.

In our previous preclinical studies, when neural stem progenitor cells (NS/PCs)-derived from hiPSCs were transplanted into mouse or non-human primate spinal cord injury (SCI) models, long-term restoration of motor function was induced without tumorigenicity, by selecting suitable hiPSCs-lines. However, NS/PCs derived from certain iPSC-lines gave rise to late-onset tumorigenicity after transplantation. Here, to preclude these risks before clinical application, we developed molecular characterization of hiPSCs and hiPSC-derived NS/PCs together with transplantation to injured spinal cord of immune-deficient mice. We investigated global methylation status of tumorigenic hiPSC-NS/PCs and found that aberrant hypermethylation of a tumor suppressor gene was induced along the passage. Based on these findings, we are establishing production and selection method of clinical grade NS/PCs stocks-derived from human iPSC stocks generated from HLA-homozygous super-donors by CiRA. We aim to commence clinical research (Phase I–IIa) trials for treatments of sub-acute phase SCI using hiPSCs-derived NS/PCs in the near future.

In this talk, I will also mention about recent progress on iPSCs-based Modeling and drug screening for neurological and psychiatric disorders, including ALS and Pendred syndrome (a hereditary disease showing a progressive hearing loss).

15:45-17:50 **Main Hall**

Plenary Symposium

(Gene-modified T Cell Therapy**)**

Naoto Hirano

Senior Scientist, Princess Margaret Cancer Centre, Canada
Associate Director for Research, Tumor Immunotherapy Program, Princess Margaret Cancer Centre, Canada
Investigator, Ontario Institute for Cancer Research, Canada

CAR therapy: Current status and beyond

Chimeric Antigen Receptor (CAR)-T cells used in adoptive T cell therapy are ‘living drugs,’ which can grow and persist in the body for years. Many clinical trials have demonstrated that anti-CD19 CAR T cell therapy is impressively effective in B cell malignancies. The anti-CD19 CAR T cell therapy is associated with a different set of adverse events that have not been seen with traditional cancer therapies. In August 2017, the FDA approved Novartis’ Kymriah (tisagenlecleucel), formerly known as CTL019, for relapsing B-cell acute lymphoblastic leukemia (ALL) in children and young adults. The therapy has become the first gene-modified cell therapy approved in North America.

Unfortunately, CAR-T cell therapies targeting solid tumor antigens have not yet achieved the same level of success. This could be due to the immunosuppressive tumor microenvironment often observed with solid tumors and/or due to suboptimal signaling domain(s) encoded by CARs. New strategies to improve the efficacy of CAR-T cell therapies are discussed.

15:45-17:50 **Main Hall**

Plenary Symposium

(Gene-modified T Cell Therapy)

Shinichi Kageyama

Professor, Immuno-gene therapy
Mie University Graduate School of Medicine

Clinical trials of TCR-gene modified T cell therapy for refractory cancer

Adoptive cell transfers of receptor gene-engineered T cells include chimeric antigen receptor-gene transduced T (CAR-T) cell therapy and TCR-gene transduced T (TCR-T) cell therapy. In CD19-CAR-T cell therapy, high incidence of cytokine release syndrome (CRS) is associated with in vivo CAR-T cell proliferation and its clinical efficacy. In human TCR-T cell therapies, there have not been well known about CRS and its association with in vivo T cell kinetics or tumor responses.

We are conducting two clinical trials of MAGE-A4-specfic TCR-gene transduced T (TCR-T) cell transfer (TBI-1201) and NY-ESO-1-TCR-T cells (TBI-1301). MAGE-A4 TCR gene is a wild-type, restricted with HLA-A*24:02, and NY-ESO-1 TCR is mutated for high affinity with replacement of G50A and A51E in CDR2β, with HLA-A*02:01 and A*02:06 restriction. We use original retrovirus vectors that encode siRNA to silence endogenous TCR creation for both TCR-gene transductions. As the NY-ESO-1 TCR is mutated for high affinity, we extensively examined potential cross-reactivities to different antigen-peptides in preclinical studies, and the high-affinity NY-ESO-1 TCR did not recognize analogous peptides. Also, the new generation retroviral TCR-vector provides enhanced expression of transduced tumor-specific TCRs and an inhibition effect of formations of self-reactive TCRs. In the symposium, updated information on the two clinical trials are presented.

In TBI-1301(NY-ESO-1 TCR- T cell), it is the first-in-man clinical trial of the novel NY-ESO-1-specfic TCR-T cell transfer to evaluate the safety, in vivo cell kinetics and clinical responses. It is designed as a cell-dose escalation from 5 x108 to 5 x109 cells. NY-ESO-1-expressing refractory cancer patients were enrolled, with 3+3 cohort design. Cyclophosphamide with/without fludarabine were administered prior to the TCR-T cell transfer as pre-conditioning.

To date, seven patients were treated with the NY-ESO-1 TCR-T cell transfer, and evaluated for the safety and in vivo cell kinetics. The TCR-T cells appeared in peripheral blood with a dose-dependent manner, associated with in vivo proliferation in an early phase. In three patients given 5x108 cells, no toxicities were seen. Two patients receiving 5x109 cells developed early-phase CRS (G2), with elevations of serum IL-6 and IFN-gamma. They were managed the treatment of anti-IL-6 receptor monoclonal antibody, tocilizumab. In a patient who developed CRS, an event of lung injury (G3) occurred, which was associated with marked infiltration of the NY-ESO-1 TCR-T cells. It was successfully treated with steroid.

Two synovial sarcoma patients exhibited tumor responses of PRs. In one patient, progression-free survival lasted more than 8 months.

In summary, the affinity-enhanced NY-ESO-1 TCR-T cell transfer exhibited CRSs in association with in vivo cell proliferation and sequential tumor responses.

15:45 -17:50 **Main Hall**

Plenary Symposium

(Gene-modified T Cell Therapy)

Jinming Dai

Jinming Dai, obtained PhD degree in 2006, has been working in biomedicine industry for more than ten years, which involves in R&D, manufacture, and regulatory in China. He joined Genscript recently, and mainly focusing on investment and strategy collaboration in cell therapy fields.

LCAR-B38M CAR-T Cells Achieved High Rate of Continuous Complete Remission (CCR) in Refractory or Relapsed Multiple Myeloma Patients

Chimeric Antigen Receptor Engineered T cell therapy (CAR-T) is a novel immunotherapy for cancer and has been clinically validated in the treatment of acute lymphoblastic leukemia (ALL) and lymphoma by targeting CD19. Here we report an encouraging breakthrough of treating multiple myeloma (MM) using our proprietary CAR-T modality targeting BCMA. Legend Biotech has developed a unique bispecific CAR-T technology platform, and conducted a single arm phase I/II clinical trial in China using LCAR-B38M to assess the safety and efficacy of the novel technology. A total of 35 patients diagnosed with refractory/relapsed multiple myeloma had been treated. All these patients had experienced previous failure of three or more rounds of first-line therapy. PBMC of the patients were collected by apheresis and LCAR-B38M CAR-T cells were prepared by lentiviral gene transfer. The patients were pretreated with cyclophosphamide (300 mg/m2) 3 days prior to infusion of the LCAR-B38M cells. A split-dose cell infusion schedule was used (day 0, 2 and 6) to enhance the safety. The median number of infused cells was 4.7 (0.6 ~ 7.0) × 106/ kg. Among 30 patients that were followed for longer than 6 months, 21 patients achieved the strict criteria of CR, 9 patients achieved PR. There are 8 patients of more than 12 months post-treatment who have reached the disease-free status. Among all 35 patients treated, the most common adverse event is acute (within 15 days post-treatment) cytokine release syndrome (CRS), which appeared in 29 patients (6 cases free of evident CRS, 17 cases of grade 1, 10 cases of grade 2, 2 cases of grade 3). All 2 grade 3 cases had recovered after treatments with Tocilizumab, vasopressors and diuretic agents. The main chronic (> 30 days) adverse reaction was hypogammaglobulinemia.

In summary, an overwhelmingly positive response (100% ORR) to LCAR-B38M CAR-T cells was observed in refractory/relapsed myeloma patients, and most patients experienced very mild adverse CRS events. Thus, we confidently believe that the outstanding safety and efficacy profile of the innovative LCAR-B38M cell therapy has established itself the best-in-class CAR-T product in treating multiple myeloma.

15:45-17:50 **Main Hall**

Plenary Symposium

(Gene-modified T Cell Therapy)

Koji Tamada

Professor and Chairman, Department of Immunology, Yamaguchi University Graduate School of Medicine
Adjunct Professor, The Institute of Medical Science, University of Tokyo

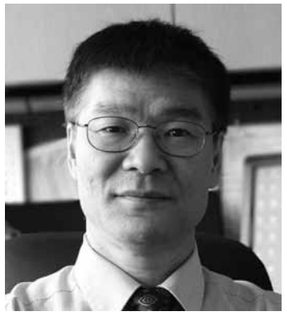
Novel strategy of CAR-T cell therapy for solid tumors

Cancer immunotherapy using chimeric antigen receptor (CAR)-introduced T cells has demonstrated the potent anti-tumor effects, especially in B cell hematological malignancies. At present, FDA approval of CD19 CAR-T cell therapy for B cell acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL) is anticipated without any doubt. On the other hand, CAR-T cell therapy against solid tumors has yet to be fully accomplished, as only a few exceptional cases have been reported to mediate clinical efficacy. In this regard, our group has developed next-generation CAR technology which enables CAR-T cells to simultaneously produce multiple immune-regulatory factors, such as cytokines and chemokines, aiming at efficient accumulation, expansion, and survival of immune cells inside solid tumor tissues. The cytokine/chemokine-producing CAR-T cells demonstrate potent proliferative capacity and trigger active migration of T cells and DC in vitro. Treatment with the cytokine/chemokine-producing CAR-T cells, but not conventional ones, induced rejection of pre-established solid tumors and mouse survival for a long period. Tumor tissues from the mice treated with the cytokine/chemokine-producing CAR-T cells demonstrated massive accumulation of immune cells including the transferred CAR-T cells. Thus, we developed next-generation CAR-T cell technology which confers the enhanced anti-tumor potential against solid tumors. A potential of further application of gene-modified T cells producing cytokines and chemokines will be discussed.

15:45-17:50 **Main Hall**

Plenary Symposium

(Gene-modified T Cell Therapy)



Yangbing Zhao

Director, T Cell Engineering Lab,
Center for Cellular Immunotherapies,
University of Pennsylvania, Philadelphia, PA

Engineering best in class T cells to treat cancers

Despite impressive clinical efficacy of T cells engineered to express chimeric antigen receptors (CAR), the current applications of CAR T cell therapy, especially for treating solid tumors, are limited by some major challenges, such as the lack of cancer specific targets and the interference of tumor microenvironment (TME). We developed a strategy to adjust the affinities of the scFv component of CAR to discriminate tumors that overexpress the target antigen from normal tissues that express it at physiologic levels. Our studies show that the use of affinity-tuned scFvs offers a strategy to empower wider use of CAR T cells against validated targets widely overexpressed on solid tumors, including those considered undruggable by this approach. In addition to express CAR or TCR to re-direct T specificity to the tumors, the T cells can be further modified to avoid TEM suppression by co-introducing PD1-CD28 switch receptors or knocking out PD1 in the T cells using CRISPR. Furthermore, using universal CAR T or CRISPR gene edited TCR T cells to treat cancers holds great promise. Pre-clinical animal studies showed that the anti-tumor activity of the PCRISPR gene edited CAR or TCR T cells was further improved and clinical scale manufacture of CRISPR gene edited CAR or TCR T cells was developed.

18:00-18:50 **Main Hall**

Evening Seminar Ⅲ

*Sponsored by **AnGes, Inc.***

Masafumi Onodera

Department of Human Genetics,
National Institute of Child Health and Development, Japan

Stem cell gene therapy for primary immune deficiencies in Japan

Most of primary immunodeficiencies (PID) are caused by mutations of genes encoding proteins that grant the ability of proliferation or functions to immunocompetent cells. At the moment, there are two clinical approaches toward the diseases, one of which is a transplant of functional hematopoietic stem cells (HSCs) derived from healthy individuals as a replacement therapy (allogeneic stem cell transplantation, HSCT) and the other of which is an infusion of their own HSCs genetically corrected by transduction of functional genes into them (hematopoietic stem cell gene therapy, HSC-GT) using viral vectors. In particular, the latter has proven to be efficacious for X-linked severe combined immunodeficiency (X-SCID), adenosine deaminase (ADA) deficiency, Wiskott-Aldrich syndrome (WAS) and chronic granulomatous disease (CGD), and been conducted as a curative therapeutic option for the diseases.

We have performed HSC-GT for two patients with ADA-SCID and one with CGD in Japan and are now in preparation for WAS. The procedure is that CD34+ cells derived from patients' bone marrow are transduced with functional genes using retroviral vectors and infused back to the patients treated with Busulfan in a CGD case. In contrast, no preconditioning was done for ADA cases. Two patients with ADA-SCID who received HSC-GT 14 years ago have recovered their immune functions and had a life free of severe infections, although both are being treated with enzyme replacement therapy using PEG-ADA because the complete recovery of their immune functions was not attained by HSC-GT due to no preconditions. The CGD patient who received HSC-GT 3 years ago developed MDS at 2 year and half after gene therapy during which time he had spent his life without few admissions by severe infections. Detailed molecular analyses revealed that the blast-like cells had a single provirus integrated in the MECOM IVSII. The patient received HSCT from his father as a donor and has been in remission. HSC-GT for WAS using a lentiviral vector is to start this year for 3 patients.

In this symposium, I would like to introduce the results of our clinical trials above by addition of detailed information and explain the current situation of gene therapy for PID in Japan.

18:00-18:50 **Satellite Room A**

Evening Seminar Ⅳ

*Sponsored by **Life Science Institute, Inc.***

Mari Dezawa

Professor and Chair
Department of Stem Cell Biology and Histology
Tohoku University Graduate School of Medicine

Endogenous reparative Muse cells may provide novel therapeutic approaches

Multilineage-differentiating stress enduring (Muse) cells are naturally existing unique endogenous stem cells that are non-tumorigenic and are pluripotent-like. They express pluripotent markers, can generate cells representative of all three germ layers from a single cell and are able to self-renew. Since they express specific receptor for damage signal, they can preferentially home into damaged site after topical injection or intravenous injection with lower entrapment in the lung and spleen. After integration, they replenish lost cells by spontaneous differentiation into tissue-compatible cells, leading to robust tissue and functional regeneration. The unique reparative functions of Muse cells were demonstrated in animal models of liver cirrhosis, partial hepatectomy, stroke, skin ulcer of diabetes mellitus and chronic kidney disease. They do not have to be "induced," or genetically manipulated, to be pluripotent or be purposive cells before transplantation as required with some other cell varieties.

They can be collected as cells positive for SSEA-3, a surface marker for pluripotent stem cells, from readily accessible sources such as the bone marrow (~0.03% of the total mononucleated cell population), and from cultured fibroblasts (several %), as well as from the dermis and adipose tissue. Recently, Muse cells are shown to circulate in peripheral blood in healthy donors, and the number increases in stroke patients in an acute phase, suggesting that endogenous Muse cells are mobilized into peripheral blood to repair tissues while their number is not sufficient to recover, and that supply of exogenous Muse cells is expected to deliver statistically meaningful functional recovery. Overall, Muse cells are a feasible source for cell-based approaches and may safely provide clinically relevant regenerative effects compatible with the 'body's natural repair systems' by simple cost-effective strategy-collection of Muse cells from sources, large scale expansion and intravenous injection.

Oct. 28th (Sat)

19:00-22:00 **On cruising houseboat "YAKATABUNE"**

Special Evening Seminar with Cruising Dinner

Sponsored by ***Gene Therapy Research Institution Co., Ltd.***

Katsuhito Asai

President, Gene Therapy Research Institution Co., Ltd., Japan

Gene Therapy Research Institution

Gene Therapy Commercialization Center Plan in King Skyfront, Kawasaki

Is GENE THERAPY a dream for the distant future?
Actually, it is already within reach!

Gene therapy is defined as "the administration of a gene or cells with introduced genetic material into the human body to treat diseases", according to the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health Labor and Welfare. Gene therapy research is advancing globally. In Japan, clinical trials have already been conducted for some diseases. The age of gene therapy is about to begin.

In our research, we have observed a unique gene therapy technique that is expected to have great therapeutic effects: an innovative approach using the highly safe adeno-associated virus (AAV) as a vector to carry therapeutic genes. Based on extensive research, we are convinced that we can provide world-leading gene therapies for refractory diseases for which effective therapies are currently lacking.

We initially focused on Parkinson's disease, amyotrophic lateral sclerosis (ALS), and Alzheimer's disease. We established the Gene Therapy Research Institution Co., Ltd. to facilitate innovative basic research that is rapidly translated to clinical studies with the goal of popularizing gene therapy. These gene therapy approaches are expected to have long-term effects by a single procedure; therefore, we believe that they will reduce medical expenses in our super-aged society and confer global competitiveness.

The Gene Therapy Research Institution aims to be the leading gene therapy provider in Japan and makes every effort to pursue safer virus vectors and more effective transgene technology. Our mission is to use globally available knowledge and technology for practical applications and specifically to provide these therapies to patients suffering from refractory diseases worldwide.

(from the company HP)

KING SKYFRONT: the life science & technology innovation hub in Kawasaki

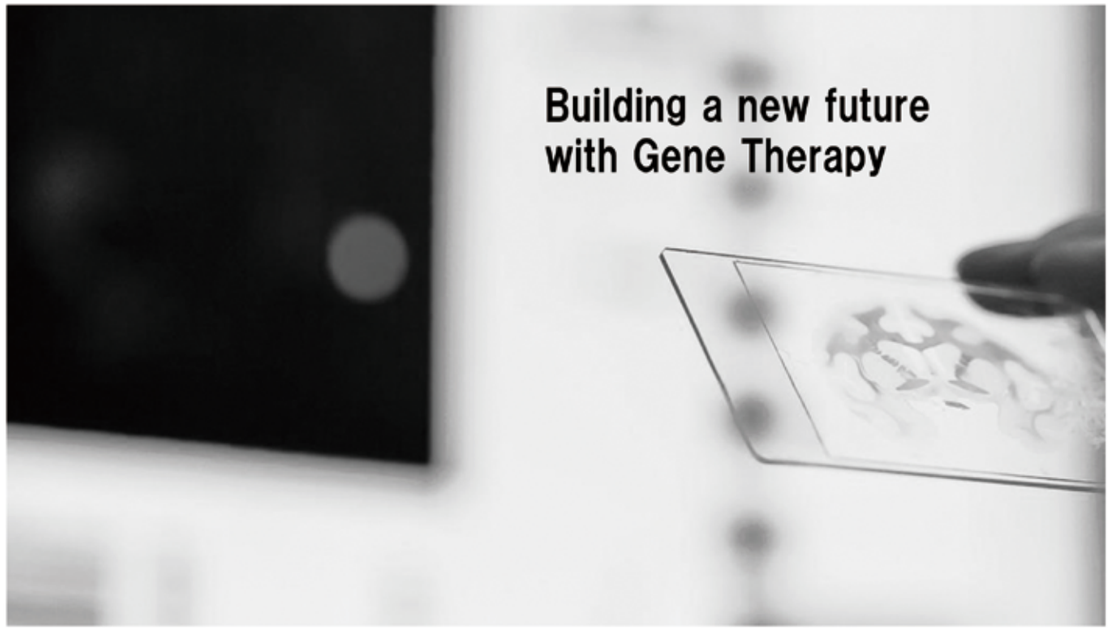
"The Kawasaki INnovation Gateway SKYFRONT is the first important step in establishing the Tonomachi area of Kawasaki City as Asia's Silicon Valley."

The Kawasaki INnovation Gateway (KING) SKYFRONT is the flagship science and technology innovation hub of Kawasaki City. KING SKYFRONT is a 40 hectare area located in the Tonomachi area of Keihin Industrial Region that spans Tokyo and Kanagawa Prefecture and Tokyo International Airport (also often referred to as Haneda Airport).

KING SKYFRONT was launched in 2013 as a base for scholars, industrialists and government administrators to work together to devise real life solutions to global issues in the life science and environment.

(from Kawasaki City HP)

The gateway bridge, now under construction works, will connect Tokyo International Airport Terminal Building and KING SKYFRONT, within a few minutes' walk distance, by 2020, the coming Tokyo Olympic year.



Corporate philosophy

We aim to be the world-leading gene therapy provider, by carrying out innovative gene therapy research, and, by providing the safest and the most efficient therapy worldwide.

Main business

Development and contract manufacturing of gene therapy using adeno-associated virus (AAV) as a vector

Pipeline

Amyotrophic Lateral Sclerosis, AADC Deficiency, Parkinson's Disease, Alzheimer's Disease, Spinocerebellar Degeneration(type 1), Tay-Sachs Disease

Our features

As a contract manufacturing facility for rAAV vector for gene therapy based on GCTP standards, we have the 200 Litter bioreactor, the first in Japan, to support the development of gene therapy as well as our own products.

Gene Therapy Research Institution

Gene Therapy Research Institution Co., Ltd.
Life Innovation Center #414,
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Memo

- 3rd Day -

Oct. 29th (Sun)

Program & Abstracts

Day 3 **Sunday, October 29**

8:30~11:40 Regulatory Science

Chairpersons: Srinivasan N. Kellathur, Yoshiaki Maruyama and Kiyoshi Okada

8:30~10:30 <Presentation>

Morakot Papassiripan (Thailand)
"Regulation of the Advanced Therapy Products in Thailand"

Chung Liang Shih (Taiwan)
"Regulation of Regenerative Medicine in Taiwan"

Shiow-Ing Wu (Taiwan)
"Regulation of Cell Therapy Products in Taiwan"

Huan Yang (China)
"The development of cell therapy and national regulation in China"

Kyoung Suk Choi (Korea)
"Regulation on cell therapy products in Korea"

Maria Cristina Galli (Italy)
"Scientific and Regulatory Issues for Developing Advanced Therapy Medicinal Products: An European Perspective"

Daisaku Sato (Japan)
"Challenges of Japanese Regulations of Regenerative Medical Products"

Masaki Kasai (Japan)
"Regulatory trends in regenerative medicine in Japan"

10:40~11:40 <Panel Discussion>

All presenters

11:50~12:40 Luncheon Seminar Ⅴ sponsored by **Celgene K.K.** (Satellite Room A)

Akihiro Kume (Jichi Medical University) *Chairperson: Tomoko Ohtsu*

"Regulatory issues associated with gene and cell therapy product development in Japan"

11:50~12:40 Luncheon Seminar Ⅵ sponsored by **Nikon CeLL innovation Co., Ltd./ Lonza** (Satellite Room B)

David W. Smith (Lonza) *Chairperson: Takahiro Nakano*

Toshiyuki Nakayama (Nikon CeLL innovation Co., Ltd.)
"Global solution to autologous and allogenic commercial manufacturing of cell therapeutics"

12:50~13:30 Future Direction of ACTO Activities: Reports from Each Asian Country

Chairpersons: Akihiro Shimosaka, Yoichi Takaue

ACTO-Vice Presidents

13:30~13:40 Closing Remarks

Keiya Ozawa (ACTO 2017 President, Japan)
Wichai Prayoonwiwat (ACTO 2018 President, Thailand)
Akihiro Shimosaka (ACTO Chairperson)

8:30-10:30 **Main Hall**

Regulatory Science

Morakot Papassiripan

Pharmacist, Bureau of Drug Control,
Food And Drug Administration,
Thailand

Regulation of the Advanced Therapy Products in Thailand

In Thailand, Advanced Therapy Products (ATPs) include cell therapy product, gene therapy product, stem cell product and other types of both autologous and allogenic cells. ATPs meet the definition of biologic product. In case of, ATPs have manufactured inside the hospital by the minimal manipulation process, they meet the definition of a hospital exemption.

Therefore, Food and Drug Administration of Thailand (Thai-FDA) regulates the ATPs by using the Drug Act. Although, the Drug Act is flexible for regulating the ATPs, but Thai-FDA still keeps the cooperation with the Medical Council of Thailand and Department of Health Service Support for developing the specific regulate system for cell and gene therapy.

For current period, none of ATPs have been approved for sale in Thailand, but 2 cases of Gene therapy products have been approved for using in the clinical studies.

8:30-10:30 **Main Hall**

Regulatory Science

Chung Liang Shih

Director-General, Department of Medical Affairs, MOHW

Regulation of Regenerative Medicine in Taiwan

Along with the significant breakthrough in scientific and medical field, regenerative medicine is a rapidly developing treatment in recent years especially for cancer patients. In Taiwan, cell therapy and gene therapy were regulated as “New Medical Practices“by Department of Medical Affair, however, the cell therapy and gene therapy products are regulated as “medicinal products” in accordance with standards of “Pharmaceutical Affairs Act”. Taiwan’s regulation is more likely to follow the Japan’s regulatory model, but there must be some differences in legislative framework.

From 2017, the regenerative medicine policy in Taiwan focuses not only on stem cell research but also on industry promotion and management mechanism. The main regenerative medicine industries in Taiwan are cell storage and biomaterials, and the development of higher risk products still be promoted by the academia, industries and government.

In order to keep abreast of the international developments, TFDA has released draft “Cell and Gene Therapy Medicinal Product Management Act” to clearly stipulate the cell and gene medicinal products. There are 15 articles in this draft, including registration & market approval, manufacturing standards, obligation of the license holders, advertisement management, measures establishment and penal provisions. As we know, Industries and academia are highly interested in this draft and we got a lot of recommendations and opinions during 60 days of comment period after the draft was issued. In the future, TFDA will continue to work together with regulatory agencies, industries, academic researchers, and medical professionals to create a win-win situation for the development of regenerative medicine.

8:30-10:30 **Main Hall**

Regulatory Science

Shiow-Ing Wu

Deputy Director General,
Food and Drug Administration,
Ministry of Health and Welfare, Taiwan

Regulation of Cell Therapy Products in Taiwan

Along with the significant breakthrough in scientific and medical field, cell therapy is a rapidly developing treatment in recent years especially for cancer patients. Before the inauguration of TFDA in 2010, cell therapy was regulated as “New Medical Practices“by Bureau of Medical Affair, however, after 2010, the cell therapy products are regulated as “medicinal products” in accordance with standards of “Pharmaceutical Affairs Act”.

After the transformation, TFDA face with many controversial Issues such as whether the autologous cells graft used in the same graft procedure are required to submit IND application or not. In order to solve the problems, Taiwan government established two advisory committees within two years for the development of cell therapy products.

In 2015, a Taiwanese with a terminal stage of nasopharyngeal carcinoma was transferred to receive cell therapy treatment in Japan, He urged Taiwan government to accelerate the legalization of cell therapy treatment. This case contributed to the implementation of treatment protocol and legislation of “Cell and Gene Therapy Medicinal Product Management Act (draft)” in 2017.

To facilitate cell therapy product with market authorization in Taiwan, TFDA offers consultation mechanism for the sponsor to identify potential issues and get appropriate way to resolution. In the future, TFDA will continue to work together with industries, academic researchers, and medical professionals to create a win-win situation for the development of cell therapy products.

8:30-10:30 **Main Hall**

Regulatory Science

Huan Yang

Senior clinical reviewer
Center for Drug Evaluation,
China Food and Drug Administration

The development of cell therapy and national regulation in China

In recent years, the cell therapy is developing quickly in China. The presentation will mainly introduce reformatory measures and new policies of drug evaluation in China.
At present, there are two management models for the cell therapy. As to stem cell therapy, The clinical research/study should be performed after the study documents record-filed at NHFPC(previous MoH), and be reviewed by AC meeting quarterly. But for the registry products, the applicants must be submitted to CFDA following drug registration regulations, and the clinical trial could only be performed after approval.
In December 2016,'Technical Guidance for Development and Evaluation of Cell Therapy Products(Draft)'has been released on the website of Center for Drug Evaluation, CFDA to public, and the final version will be issued soon.

NHFPC: China's National Health and Family Planning Commission
CFDA: China Food and Drug Administration
CDE: Center for Drug Evaluation

8:30-10:30 **Main Hall**

Regulatory Science

Kyoung Suk Choi

Ministry of Food and Drug Safety (KFDA prior to April 2013)
Cell and Gene Therapy Products Division
Scientific officer, reviewer
Assessment of quality data for stem cell and gene therapy products
(marketing authorisation and clinical trial applications)

Regulation on cell therapy products in Korea

Cell therapy product is defined as a medicinal product manufactured through physical, chemical, and/or biological manipulation, such as in vitro culture of autologous, allogenic, or xenogeneic cells, and is regulated by the Ministry of Food and Safety (MFDS) under Pharmaceutical Affairs Act in Korea. 14 cell therapy products(including 4 stem cell therapy products) were approved for marketing authorization and more than 100 clinical protocols from commercial sponsors were approved. These cellular products offer great promise for the treatment of many serious medical conditions. However, limited experience on these innovative cellular products, there are many challenges to reliable evaluation of safety and efficacy of these products.
This talk gives an overview on regulation of cell therapy products in Korea including efforts to support the development of this class of products. Regulatory activities and challenges when developing cell therapy products will also be presented.

8:30-10:30 **Main Hall**

Regulatory Science

Maria Cristina Galli

Senior scientist
National Centre for Control and Evaluation of Medicines
Istituto Superiore di Sanità, Roma, Italy

Scientific and Regulatory Issues for Developing Advanced Therapy Medicinal Products: An European Perspective

Advanced Therapies represent a significant tool for efficacious treatments offered to patients.
Recent success in gene and cell therapy fields has resulted into a number of Advanced Therapy Medicinal Products already available on the market, both in EU and worldwide, not only for rare diseases but also in oncology.
Most Regulatory Authorities offer to developers fast procedures for clinical trials and market approval processes, with the aim at fostering the progress of Advanced Therapy Medicinal Products from bench to bedside.
Regulatory expectations for safe and efficacious Advanced Therapy Medicinal Products can be met by developers if they deeply understand their product and carefully plan its development, in continuous and close collaboration with regulatory bodies, taking also advantage of research infrastructures that European Commission has put in place to facilitate an efficient translation of research discoveries into effective ATMP.
This presentation will discuss the scientific and regulatory challenges found when developing Advanced Therapy Medicinal Products and how to overcome them to accelerate translation of a bright research idea into a clinically safe and efficacious Advanced Therapy Medicinal Product, for the benefit of patients.

8:30-10:30 **Main Hall**

Regulatory Science

Daisaku Sato

Daisaku Sato, Ph.D. Director, Pharmaceutical Safety Division, MHLW, Japan

Challenges of Japanese regulations of Regenerative Medical Products

I will first touch upon the story of the regulatory reform, just and regulatory challenges of the last couple of years. The new PMD Act was implemented in 2014, including the regulatory reform of regenerative medicine.

The conditional and time-limited authorization was introduced, which allows product approvals with the clinical data, reasonably likely to predict clinical benefit, before completing the confirmatory trials. However, the PMD Act requires further safety assurance during the post-marketing phase and additional clinical data for confirmation of the evidence. So far, in Japan 4 products have been approved as regenerative medical products, including 1 conditional approval product. The regulatory reform has triggers R&D within Japanese territory so that number of initiated clinical trial protocols have boosted to 68, compared to 4 trials 5 years ago.

Now the forerunner (Sakigake) review designation system has also been in place since 2015. It is a breakthrough therapy type acceleration of review process (rolling submission and shortening review period from 12 to 6 months), for the treatments expecting prominent effectiveness, however, intended to be marketed firstly or simultaneously in Japan. MHLW has designated 6 products so far. We are hoping the first case of the review application derived from Sakigake will be coming early next year. MHLW has started 3rd round public offer of the Sakigake in October 2017.

The products approved under conditional and time limited authorization may be based on the exploratory clinical trial using surrogate endpoints. Then, confirmatory post-marketing study was needed to demonstrate the true endpoint as post-markting commitment. One of the challenges of the conditional approval would be post-marketing observational study using real world evidence and how efficiently you can perform the studies with high quality clinical data. For a solution for the real world evidence collection, PMDA and Japanese Society of Regenerative Medicine have jointly establish clinical registry to collect patient data for clinical trials and post-marketing studies. MHLW has also been developing guidelines and rules to use electronic medical record database for PMS to secure the reliability of the studies and integrity of data within this fiscal year 2017.

PMDA has compiled question and answers often raised during the R&D consultations for the ease of sponsors to study regulatory strategy. The technical guidance was elaborated in collaboration with academic societies and industry last year. We would like to contribute to the world’s regenerative medicine in cooperation with other regulatory agencies in the world. We actively continue to participate in international regulatory dialogues to exchange scientific information and make scientific alignment with other agencies, such as IPRF, ATMP cluster teleconference with USFDA, Health Canada and EMA.

8:30-10:30 **Main Hall**

Regulatory Science

Masaki Kasai

Pharmaceuticals and Medical Devices Agency

Regulatory trends in regenerative medicine in Japan

In Japan, regulatory reform was carried out to accelerate the practical use of regenerative medicine while maintaining safety for patients. Regenerative medical products were newly defined and conditional and time-limited approval system was provided in the Pharmaceuticals and Medical Devices Act (PMD Act), which was enacted on 25 November 2014. Two regenerative medical products were approved on 18 September 2015 in Japan under PMD Act.

Since we started pharmaceutical affairs consultation on R&D strategy in 2011, the number of the IND submission of regenerative medical products has been increasing especially after the implementation of PMD Act. The development of regenerative medical products is rapidly progressing. On the other hand, we have some challenges with regard to overall developmental plan including clinical evaluation in post-marketing phase and CMC strategy under the new regulation.

I will introduce regulatory trends in regenerative medicine in Japan and share our challenges to achieve early access to regenerative medical products.

11:50-12:40 **Satellite Room A**

Luncheon Seminar Ⅴ

Sponsored by ***Celgene K.K.***

Akihiro Kume

Jichi Medical University

Regulatory issues associated with gene and cell therapy product development in Japan

Recent progress in stem cell research has raised much anticipation of realizing regenerative medicine products (RMPs) to meet many unmet medical needs. Because of such ‘niche’ applications and their inherent complexity, RMPs challenge distinct issues in quality control and non-clinical safety testing, as well as specific designing of clinical trials. Therefore, a new legislative framework on regenerative medicine has been built in Japan. In line with the Regenerative Medicine Promotion Law, the Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD Act; formerly the Pharmaceutical Affairs Law) and the Act on the Safety of Regenerative Medicine were enacted in 2014. In PMD Act, RMPs are separately categorized from drugs and medical devices, and ‘conditional and time-limited approval’ was introduced. This new, and somewhat challenging authorization schema is based on the intrinsic variability of RMPs, the limited number of patients available for clinical trials, and other specific problems with regenerative medicine. Herein a conditional and time-limited approval is considered when the safety of an RMP is confirmed and its probable benefit is demonstrated in the clinical trials. A probable benefit can be demonstrated with the data that predicts efficacy through surrogate end points in a relatively small exploratory study. After conditional and time-limited approval, vendors can market such RMPs, but they must confirm safety and efficacy further before the approval expires (maximum 7 years). This seminar will be trying to give some basic ideas and points to consider in developing RMPs in Japan. Regarding extraordinary complexity of RMPs, discussion with Pharmaceuticals and Medical Devices Agency from an early stage of product development would be very helpful. Hence, companies and academic institutions are encouraged to take advantage of ‘Pharmaceutical Affairs Consultation on R&D Strategy’.

11:50-12:40 **Satellite Room B**

Luncheon Seminar VI

*Sponsored by **Nikon CeLL innovation Co., Ltd./ Lonza***

David W. Smith

VP, Global Business Development, Emerging Technologies, Lonza group

Global solution to autologous and allogenic commercial manufacturing of cell therapeutics

Companies are choosing a strategy of pursuing orphan indications and regulatory agencies across the world are embracing fewer clinical trials/patients for regenerative medicine products. As a result, it will be possible to get approval with as few as two clinical trials. This rapid approval process is challenging other portions of the regulatory filing, especially the CMC section. Lonza will discuss the need for better product characterization and requirement for locking down a commercial manufacturing process sooner, in light of these changes. Nikon CeLL innovation Co., Ltd. will introduce GCTP/GMP compliant CDMO/CMO facility and its services located in Tokyo, under Nikon-Lonza Partnership.

11:50-12:40 **Satellite Room B**

Luncheon Seminar VI

*Sponsored by **Nikon CeLL innovation Co., Ltd./ Lonza***

Toshiyuki Nakayama

President, Nikon CeLL innovation Co., Ltd.

Global solution to autologous and allogenic commercial manufacturing of cell therapeutics

Companies are choosing a strategy of pursuing orphan indications and regulatory agencies across the world are embracing fewer clinical trials/patients for regenerative medicine products. As a result, it will be possible to get approval with as few as two clinical trials. This rapid approval process is challenging other portions of the regulatory filing, especially the CMC section. Lonza will discuss the need for better product characterization and requirement for locking down a commercial manufacturing process sooner, in light of these changes. Nikon CeLL innovation Co., Ltd. will introduce GCTP/GMP compliant CDMO/CMO facility and its services located in Tokyo, under Nikon-Lonza Partnership.

Memo

- Poster -

Abstracts

~ Winners ~

★ **Best Abstracts –CHA Award (100,000JPY & Trophy)**

Xiaoli Wang (China)
Ryota Tamura (Japan)
Takeo Mukai (Japan)
Sung Han Kang (Korea)
Alvin Chua (Singapore)

★ **Excellent Poster Award (30,000JPY)**

Guoliang Qiao (China)
Masahito Kawabori (Japan)
Lefu Huang (China)
Takayasu Ohtake (Japan)
Mahboobeh Razmkhah (Iran)

★ **Travel Award –sponsored by CHA (50,000JPY)**

Alireza Shoae-Hassani, Amir Ali Hamidieh (Iran)
Nasrollah Erfani (Iran)

1 Autologous NK-cell-enriched cell therapy in breast cancer: preclinical setting phase, Shiraz experience

Nasrollah Erfani

Shiraz University of Medical Sciences, Shiraz, Iran

Introduction: NK cell therapy has proven to be a promising approach for treatment of hematological malignancies and solid tumors. Obtaining the large numbers of functional NK cells using ex-vivo culture was always a challenging issue. Masuyama et al. have recently introduced a new method for ex-vivo autologous NK cell expansion; resulting in the production of ample active NK cells for a promising cell therapy regimen. In collaboration with Masuyama clinic and St. Luck's International University Hospital we are about to start phase I clinical trial of this immune cell therapy approach in refractory breast cancer. Accordingly, and as a prerequisite for clinical trial phase I, preclinical setting of the protocols was carried out in GMP facilities in Ghadir Hospital affiliated to Shiraz University of Medical Sciences, Shiraz, Iran. The aim of preclinical setting was to evaluate the proliferative efficacy of the method, the activation status of the expanded autologous NK cells and the likely unwanted contamination of the final cell product. **Subjects and Methods:** PBMCs were isolated from 30 ml of 5 healthy-individuals' peripheral blood; transferring directly to the specified initial culture bag containing antibodies for CD3, CD52 as well as IL-2 cytokine. A part of the sample was separated for phenotyping and functional analysis before expansion. The cells were cultured for 14-17 days in incubators; during which the cell received condition media, and underwent several passages into bigger culture bags. Final cell product was assessed for both phenotyping as well as functional analysis and unwanted contamination including HCV, HBV, HIV, Mycoplasma and endotoxin. The whole procedure was carried out in the clean room and associated facilities. **Result:** Our results indicated that NK cells were expanded 600-fold in average (range 200-1100 fold) and the purity of NK cells per whole lymphocytes exceed 68%. The expanded cells were highly lytic as indicated by in vitro cytotoxic assay; with strong expression of NKG2D and CD16. The cytotoxic (CD11b+ CD27-) and regulatory (CD11b-/+ CD27+) subsets of NK cells consisted about 85% and 10% of the expanded NK cells, respectively. The tolerant subset of NK cells (CD11b- CD27-) consisted less than 6% of the expanded NK cells. The prepared final cell products were negative for HCV, HBV, HIV, Mycoplasma and endotoxin. **Conclusion:** In the preclinical setting phase, large numbers of activated and uncontaminated NK cells from 30 ml of peripheral blood were successfully generated. The procedure seems to provide ample clean cell product with no contamination; suitable to be infused back to the patients. Proposal for the clinical phase I in refractory breast cancer is under final assessment in ethics committee of the Shiraz University of Medical Sciences.

2 Does B cell play a role in T cell-mesenchymal stem cell crosstalk?

Fereshteh Mehdipour

Shiraz Institute for Cancer Research, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

Introduction: Adipose derived mesenchymal stem cells (ASCs) have immunomodulatory effects on T cells. Recently, it is suggested that B cells are able to induce or expand FoxP3$^+$ T regulatory (Treg) cells. In the present study, immunomodulatory effects of ASCs derived from breast fat of breast cancer patients or mesenchymal stromal cells derived from their tumors (TSCs) on T cells in the presence or absence of B cells were investigated.
Materials and methods: Mononuclear cells were isolated from tumor draining lymph nodes (TDLNs) of breast cancer patients using Ficoll-Hypaque gradient centrifugation. B cells were depleted from mononuclear cells using anti-CD19 microbeads. ASCs or TSCs were co-cultured with either intact mononuclear cells or B cell depleted mononuclear cells (BDMNCs) for 72 hours. Frequencies of CD25$^+$FoxP3$^+$ Tregs, IL-10$^+$ or IFN-γ$^+$ cells were assessed among CD4$^+$ T cells in different conditions and compared.
Results: The frequencies of CD25$^+$FoxP3$^+$, CD25$^-$FoxP3$^+$, CD25$^+$FoxP3$^-$, IL-10$^+$ and IFN-γ$^+$ cells among CD4$^+$ T cells in either intact mononuclear cells or BDMNCs did not show significant changes in co-culture with ASCs or TSCs in comparison with the control groups (intact mononuclear cells or BDMNCs alone). However, the mean frequency of CD25$^+$FoxP3$^+$CD4$^+$ Treg cells in either intact mononuclear cells or BDMNCs showed about 1.5 folds increases in the presence of ASCs or TSCs in comparison with the control groups. The frequencies of IL-10 producing T cells in both intact mononuclear cells and BDMNCs had non-significant increasing trends when cultured with TSCs.
Conclusion: The presence or absence of B cells did not significantly affect the interaction of TDLNs' T cells with ASCs or TSCs.

3 Role of Herbal Extract in Stem Cell Development

Ferry Sandra

Department of Biochemistry and Molecular Biology, Division of Oral Biology, Faculty of Dentistry, Trisakti University, Jakarta, Indonesia

To meet a successful stem cell treatment, several factors need to be considered, including cell number. Therefore optimal cell number should be achieved. Meanwhile, in some circumstances, isolated cell number is not enough, therefore cell number should be enriched in an in vitro stem cell culture setting. The addition of growth factors is a part of the strategies to reach a better enrichment. This strategy was then pursued by the scientist involved in herbal medicine. Herbal extract has been shown to be useful in inducing proliferation and differentiation of stem cell/progenitor cells. For instance, it was found that epigallocatechin gallate (EGCG), epicatechin gallate (ECG), epigallocatechin (EGC) and catechin of tea extract could induce differentiation of peripheral blood mononuclear cells (PB-MNCs) into peripheral blood-derived endothelial progenitor cells (PB-EPCs). Not only proliferation and differentiation, the extract can be useful for a specific role, such as inhibiting osteoclastogenesis. Caffeic acid inhibited osteoclastogenesis induced by receptor activator nuclear factor (NF)-κB ligand (RANKL) and tumor necrosis factor alpha (TNFα) through the NF-κB underlying mechanism. This shows that some extracts might have different specific roles. Hence, depending on their activities, the extract can be beneficial for future use in medicine. Therefore, other potential herbal extracts should be further explored.

4 Combination of DC/CIK adoptive T cell immunotherapy with adjuvant chemotherapy in advanced non-small-cell lung cancer (NSCLC) patients: a Prospective Patients' Preference-based Study (PPPS)

Guoliang Qiao

Department of Medical Oncology, Beijing Key Laboratory for Therapeutic Cancer Vaccines, Capital Medical University Cancer Center, Beijing Shijitan Hospital, Capital Medical University

Objectives: Advanced non-small cell lung cancer (NSCLC) has remained challenging to treat effectively. This study aimed to investigate the clinical effects and safety of immunotherapy with dendritic cells and cytokine-induced killer cells (DC-CIK) administered with chemotherapy (CT) in this malignancy.
Materials and Methods: We have introduced the new clinical trial design termed as the prospective patient's preference-based study (PPPS). Consecutive patients (n=135) with advanced NSCLC were treated with DC-CIK administered with CT or mono-therapy (CT or DC-CIK alone).
Results: For all the patients, the median PFS was 5.7 months and the median OS was 17.5 months. The 1-year PFS and OS rates were 29.4% and 58.2%, respectively. The 1-year PFS and OS rates for DC-CIK plus CT were significantly higher than that in the group of patients who received DC-CIK alone and CT alone ($P<0.05$). The number of adoptively infused DC-CIK cells was associated with clinical efficacy. After adjusting for competing risk factors, DC-CIK combined with CT and infused number of CIKs remained independent predictors of PFS and OS. Phenotypic analysis of peripheral blood mononuclear cells showed that CD8+CD28+, and CD8+CD28- T cells, changed significantly in all groups ($P<0.01$). The CD3+ T cells increased in the chemotherapy plus immunotherapy and the immunotherapy alone group ($P<0.01$), while CD3-CD16+CD56 T cells decreased in the chemotherapy plus immunotherapy and the immunotherapy alone group ($p<0.01$).
Conclusions: For advanced NSCLC patients, DC-CIK immunotherapy alone achieved similar 1-year PFS and OS rates compared with chemotherapy alone. DC-CIK combined with chemotherapy administration resulted in numerically superior PFS and OS compared with monotherapy.

5 Development of Serum-Free Culture Conditions for CAR T Cell Expansion

Hsin-Lin Lu

Development Center for Biotechnology

Expansion of T cells was a critical step for preparing chimeric antigen receptor (CAR) T cells for therapy. Although serum was widely applied in the culture or expansion of T cells, the quality of serum could be varied from batch to batch, leading to the variation of T cell expansion and quality. In addition, the safety of pathogens from serum was required to be considered. To overcome the disadvantages of serum application in T cell culture, serum-free and xeno-free culture conditions were required. Here, we developed a rapid serum-free culture condition for the expansion of immune T cells ex vivo. Human T cells were isolated from the PBMCs of healthy donor using a density gradient medium followed by CD3+ magnetic cell separation. The isolated CD3+ T cells were applied into serum-free medium supplied with IL-2. After a 2-week culture, T cells could expand more than 100-3,000 folds, and the cell viability in all samples was above 90%. The T cell pollutions could be controlled at averagely about 40% of CD8+ T cells and averagely about 55% of CD4+ T cells after culture. These conditions could be applied in the expansion of CAR T cells for cell therapy to support the minimum requirement of blood or cell samples from patients.

6 Shift of EMT gradient in 3D spheroid mesenchymal cells for activated microenvironment

Il-Hoan Oh

Catholic High-Performance Cell Therapy Center, The Catholic University of Korea, College of Medicine

Mesenchymal stromal cells (MSCs) have been widely employed in cell therapy for paracrine support in clinical trials, but their variable and heterogeneous clinical outcome pose major challenges. While three-dimensional (3D) MSC cultures are emerging as alternative approaches, key changes in cellular characteristics during 3D-spheroid formation remain unclear. Here, we show that MSCs in 3D spheroids undergo further progression towards the epithelial-mesenchymal transition (EMT), driven by upregulation of EMT-promoting microRNAs and suppression of EMT-inhibitory miRNAs. The shift of EMT in MSCs is associated with widespread histone modifications mimicking the epigenetic reprogramming towards enhanced chromatin dynamics and stem cell-like properties, but without changes in their canonical surface phenotype. Notably, these molecular shifts towards EMT in 3D MSCs caused enhanced stem cell niche activity, resulting in higher stimulation of hematopoietic progenitor self-renewal and cancer stem cell metastasis. Moreover, miRNA-mediated induction of EMT in 2D MSCs were sufficient to mimic the enhanced niche activity of 3D spheroid MSCs. Thus, the molecular hierarchy in the EMT gradient among phenotypically indistinguishable MSCs revealed the previously unrecognized functional parameters in MSCs, and the EMT-enhanced “naïve” mesenchymal state represents an ‘activated mesenchymal niche’ in 3D spheroid MSCs. These findings should provide a key functional parameter for MSC-based cell therapy for more reproducible and efficient cell therapeutic trials.

7 CD8+PD-1+ T cells predicts higher tumor-reactivity and Favorable Prognostic in advanced pancreatic carcinoma and gastric cancer patients receiving dendritic cells-cytokine induced killer cells immunotherapy

Huang Lefu

Beijing Key Lab for Therapeutic Cancer Vaccines, Capital Medical University
Cancer Center, Beijing Shijitan Hospital

Background: Adoptive T cell therapy was proved to be potentially effective when combined with chemotherapy for advanced malignancies, including gastric cancer and pancreatic cancer. Dendritic cell/cytokine induced killer(DC-CIK) cell immunotherapy has been widely used in China. The present study aims to investigate the prognostic effects of CD8+ PD-1+ T cells in cultured DC-CIKs for both advanced pancreatic carcinoma(APC) and gastric cancer(AGC) patients.
Design: From 2013 to 2016, 30 patients with AGC and 35 patients with APC treated with multicycle cell immunotherapy were enrolled into this study. The percentages of T lymphocyte subpopulations of cultured CIK cells, including CD3+, CD3CD4+, CD3+CD8+, CD4+PD-1+, CD8+PD-1+, were measured every week. IFN- enzyme-linked immunospot (ELISPOT) and CCK-8 cytolytic assays were used to measure the infused CIK cells avidity. Survival estimates were calculated according to the Kaplan and Meier methodology.
Results: In present study, we found the number of CIK cells increased as time went by and CIK cells had the strongest ability to proliferate when cultured at 15 days. Meanwhile, the percents of CD3CD4+, CD3+CD8+, CD4+PD-1+, CD8+PD-1+ T cell also reached to the highest. we sorted high purity of CD8+PD-1+ T cell by flow cytometry. Moreover, We found CD8+PD-1+ T-cells showed higher tumor specific IFN-γ releasing detected by ELISPOT and stronger gastric and pancreatic cell cytotoxicity detected by CCK-8 compared to CD8+PD-1-. Survival analysis showed that patients with the percentage of CD8+PD-1+ T-cells population enhanced more than 2 times after culture had favorable overall survival(OS) in both APC(P=0.014) and AGC(P=0.036). Moreover, T-cells population enhanced more than 2 times after culture had favorable progressive-free survival (PFS) in both APC(P=0.035) and AGC(P=0.003).
Conclusions: Our study demonstrated the PD-1 receptor could be a useful biomarker for enriching tumor specific T cells. CD8+PD-1+ T-cells showed much higher avidity after cultured in IL-2, and could effectively improve the prognosis of patients with APC and AGC after receiving DC-CIK treatment.

8 Adipose tissue-derived mesenchymal stem cells (ASCs) and alleviation of radiation-induced xerostomia

Mahboobeh Razmkhah

Shiraz Institute for Cancer Research, School of Medicine, Shiraz University of Medical Sciences, Shiraz-Iran

Background. Salivary hypo function and xerostomia may be the main complaints of head and neck cancer patients treated with radiotherapy. Stem cell transplantation has been widely proposed as a potential treatment for radiation-induced xerostomia. Here we investigated the effect of ASCs on radiotherapy induced xerostomia.
Material and methods. We examined 40 Sprague dawley rats in 4 groups, group A did not received radiation, group B received 18 Gy single dose radiation and were injected with culture medium without ASCs, group C received 18 Gy single dose radiation and were injected once with 1×10^6 ASCs in their submandibular gland 24 hours post radiation and group D received 18 Gy single dose radiation and were injected with 1×10^6 ASCs in submandibular gland under guide of sonography two times, 24 hours and one week after radiotherapy. Salivary secretory function was determined by measuring salivary flow rates (SFRs) and lag time and salivary glands were pathologically assessed 6 weeks after irradiation.
Results. Groups C and D had statistically significant lower lag time compared to group B. SFRs showed statistically significant increase in groups C and D compared to group B. SFRs in group C was 82% of normal group. Tissue staining showed infiltration of lymphocytes with atrophy of acini, mild decrease in mucin acini and fibrosis of salivary gland tissue in sections of salivary glands isolated from group B. Sections of salivary gland from other groups showed mixed population of serous and mucinous acini with no fibrosis, inflammation, atrophy or alteration in mucine content. No statistically significant difference was found between groups C and D in lag time, SFRs and pathological findings.
Conclusion. ASCs transplantation may represent a promising venue for targeting radiation-induced xerostomia and salivary gland dysfunction in head and neck cancer patients.

9 Variation of the manufacturing reproducibility depends on transit time of collected blood in an autologous NK cells expansion

Manabu Mizutani

Graduate School of Engineering, Osaka University

When an autologous cell-based product is prepared in a cell processing facility, the raw material, which is collected from a patient, is transported from a medical institution located in unspecified area. A group of medical institutions with different locations, which have a medical cooperation, sometimes request cell-based products of the same manufacturing method to a licensed manufacturing company under the Act on the Safety of Regenerative Medicine in Japan. The Biotherapy Institute of Japan (BIJ) is one of the licensed manufacturing companies. A manufacturing method of the natural killer, NK cells product was adopted by several medical institutions, which have a medical cooperation, in a cell processing facility of BIJ. In this study, an analysis of manufacturing reproducibility was carried out on the experienced batches for two clinics by evaluating the apparent specific growth rate, μ. In the early phase of the culture, the variability of μ containing influences of the transit time was observed, meanwhile it was presumed that the transit time for one day at room temperature was an acceptable transport condition for peripheral blood in this manufacturing method. The μ in the later phase was equally distributed and the standard deviations, SDs were similar, hence it was considered the manufacturing reproducibility containing individual difference of raw materials was estimated.

10 Comparative analysis of mesenchymal stem cells markers originated from cerebrospinal fluid (CSF) and brain tissue

Nooshafarin Chenari

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Mesenchymal stem cells (MSCs) can be found in almost all body tissues including heart, lung, umbilical cord blood, Wharton's jelly, peripheral blood, adipose tissue, muscle, cartilage, dental pulp, bone marrow, brain and CSF. These cells have numerous characteristics including well-defined plastic adherence, self-renewal capacity, an ability to differentiate to adipocytes, chondrocytes and osteocytes and expression of a specific panel of CD markers. In this study we scrutinized the surface markers of MSCs isolated from high and low grade gliomas along with MSCs isolated from CSF of meningioma patients. **Methods:** CSF from 2 meningioma patients was transferred into a sterile tube which contained complete media (DMEM 10% FBS), and was centrifuged. Subsequently, the pellet was transferred to a flask and after 3 passages, the expression of some mesenchymal stem cell markers including CD44, CD166, CD73, CD105, CD10, CD146, CD106, CD29 CD14, CD45, CD34 and CD90 by flow cytometry were examined. Additionally, brain sample tissues from 3 low and high grade gliomas patients were transferred in sterile condition to the lab, and tissues were washed with phosphate buffered saline (PBS), minced and digested by 0.2% collagenase type I. Then the single cells were cultured in DMEM containing 10% FBS for three passages. Afterward the cultured cells were evaluated for the expression of mesenchymal stem cell markers. **Results:** MSCs isolated from brain tumors and CSF fluid demonstrated the same expression of some markers, including CD44, CD166, CD73, and CD105. In contrast, the amount of CD10, CD146, CD106, CD90 and CD29 showed divergent percentages among the cells isolated. **Conclusion:** MSCs may play identical roles regarding their location in the body and differential expression of specific markers.

11 Suicide gene therapy for malignant glioma using neural stem/progenitor cells derived from human induced pluripotent stem cells

Ryota Tamura

Keio university school of medicine

Introduction: Suicide gene therapy using herpes simplex virus thymidine kinase (HSVtk)/ganciclovir (GCV) system is an attractive treatment for malignant glioma. However, clinical trials using viral vectors for suicide gene delivery have not been successful due to the limited transduction efficiency. We evaluated the efficacy of suicide gene therapy using human induced pluripotent stem cell (hiPSC)-derived neural stem/progenitor cells (NS/PCs) expressing HSVtk through the bystander effect.
Materials and methods: hiPSC-derived NS/PCs were transduced with the lentiviral vector expressing the HSVtk (therapeutic stem cell 1 (TSC1)). Since constitutive expression of the HSVtk in iPSCs is cytotoxic, hiPSCs were transduced with the lentiviral vector containing the tetracycline-inducible HSVtk expression system and were differentiated into NS/PCs (TSC2). TSC1 or TSC2 was transplanted into a mouse model of human glioma using a luciferase-expressing U87 cell line, and GCV or GCV/doxycycline was administered. The tumor growth was monitored by bioluminescence signals of U87 cells, and the tumor volume was evaluated at three weeks after transplantation. In addition, live-cell imaging of brain slice cultures was performed. Survival rates were compared with control groups.
Results: Time-lapse imaging of slice cultures could visualize the migration of TSCs and bystander killing of glioma cells. In both TSC 1 and TCS 2 transplanted groups, bioluminescence signals and tumor volume were dramatically decreased at three weeks after transplantation, and TSCs were not identified in brain sections. Survival rates were significantly increased.
Conclusions: hiPSC-derived NS/PCs with HSVtk/GCV system showed a significant therapeutic effect on a human malignant glioma xenograft mouse model.

12 Efficient clinical-scale expansion of adipose tissue-derived mesenchymal stem/stromal cells in a closed and automated hollow-fiber bioreactor under xeno-free culture conditions

Gary Shen

AventaCell BioMedical Corp., Ltd.

The potential of mesenchymal stem/stromal cell (MSC)-based therapies has been extensively studied over the years with many clinical trials worldwide for a broad range of diseases. However, the highly demanding cell doses used in clinical trials (up to millions of cells/kg patient) require a scalable, efficient and GMP-compliant manufacturing process. The main goal of this work was to evaluate the feasibility of using a closed, automated and disposable hollow fiber bioreactor (Quantum cell expansion system - Terumo BCT) under xeno(xeno)geneic-free culture conditions for the successful expansion and recovery of adipose tissue (AT)-derived MSC, preserving their intrinsic features for cellular therapy applications. For this purpose, AT-MSC (n=2, two different donors) were inoculated at initial cell density of 30x106 cells in the hollow fiber bioreactor using low-glucose DMEM culture medium supplemented with a human platelet lysate (HPL)-based supplement (UltraGROTM-PURE, a xeno-free, fibrinogen-depleted product, AventaCell BioMedical Corp., Ltd) (5%(v/v)). After 5 days of culture, 240 (± 0.42) x106 total cells were harvested, representing a fold increase in total cell number of 11.4 (± 2.02). During the expansion process, there was no depletion of nutrients (glucose and glutamine) and neither lactate nor ammonia by-product reached inhibitory concentrations. Expanded MSC retained their differentiation potential into adipogenic, osteogenic and chondrogenic lineages. The results of immunophenotypic analysis revealed that the expanded cells maintained the characteristic identity proposed by ISCT1,2, and no significant differences were observed before and after cell expansion ($p>0.05$). The results presented herein represent a major breakthrough towards the establishment of MSC manufacturing in an automated GMP-compliant bioreactor system, using a xeno-free culture medium, allowing the generation of clinically meaningful cell numbers in a time- and cost-effective way.

13 CD45RA-depleted donor lymphocyte infusion for refractory CMV infection after haploidentical HSCT

Sung Han Kang

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Although preemptive antiviral therapy is highly effective to prevent CMV disease, patients unresponsive to antiviral therapy have an increased morbidity and mortality in hematopoietic stem cell transplant (HSCT). Recently, cellular adoptive immunotherapy has been used to treat CMV infections that are unresponsive to antiviral therapy. Here, we report our experience with CD45RO+ T cell enriched donor lymphocyte infusion (DLI) in children with refractory CMV infection after ex vivo T cell-depleted haploidentical HSCT.

A 13-year old girl diagnosed as very severe aplastic anemia received allogeneic HSCT from haploidentical family donor using αβ T cell-depleted graft without additional graft-versus-host-disease (GVHD) prophylaxis. She achieved complete chimerism on day 14 post-transplant without acute GVHD. CMV reactivation was detected on 34 days after HSCT using CMV PCR. Ganciclovir was used for initial management of CMV reactivation.

However, due to increasing level of PCR titer and combined cytopenia, ganciclovir was switched to foscarnet. Despite continuous use of foscarnet, CMV viremia was persistent at a high level. Furthermore, resistant study using genomic analysis revealed mutations in V787Lwhich is a known mutation conferring resistances on both ganciclovir and foscarnet.

Consequently, she received CD45RA-depleted graft from the same donor which would be enriched for CD3+ CD45RO+ memory T cells. Three times of DLI at 2-week interval were given at the dose of CD3+ CD45RO+ cells of $2.5x10^4$/kg, $5x10^4$/kg, and $5x10^4$/kg, respectively. Following the DLIs, CMV PCR titer decreased to undetectable level, and cell mediated immunity against CMV became positive which was confirmed by ELISPOT technique. There was no GVHD at the time of report.

In the haploidentical HSCT setting, CD45RA-depleted DLIs can be safely administered for efficient enhancement of viral immunity with low risk of GVHD. We demonstrate the successful use of this approach in refractory CMV infection in haploidentical HSCT recipients.

14 Co-delivery of HER2 antigen and TRICOM by adenovirus enhance antigen-specific responses and anti-tumor effect

Suya Wang

Capital Medical University Cancer Center, the Ninth Clinical Medical College of Peking University, Beijing Shijitan Hospital

Despite the improvement in screening, diagnosis and treatments of HER2 positive breast cancer, the death toll resulting from HER-2 positive breast cancer is still very high. This calls for novel and effective therapies and combinations. Because HER2 is strongly expressed in this subtype of breast cancer, vaccine targeting HER2 could be an effective approach. Considering wild type HER2 is a potential oncogene, full-length HER2 with inactivated for kinase function is recombined with adenovirus (Ad-HER2-ki). We further designed a recombinant adenovirus expressing co-stimulater factors, ICAM-1, B7, LFA-3 (Ad-TRICOM). 6-8 weeks old female BALB/C mice with normal immune system were immunized with Ad-HER2-ki alone or combined with Ad-TRICOM to evaluate the vaccine safety and immunogenicity. Anti-tumor effect of vaccines is assessed in HER2 positive wild-type BALB/C mice model. HER2 specific T cells and antibody responses were mearsured by Elispot and Elisa assay. Ad-TRICOM induced persistent express of co-stimulater factor, and significantly increased number of HER2-specific T cells when combined with Ad-HER2 compared with Ad-HER2 alone. And the combination of Ad-HER2 and Ad-TRICOM showed more anti-tumor effect than Ad-HER2 alone. This study provided preliminary preclinical data for the application of targeting HER2 adenovirus as vaccine in anti-tumor immunotherapy.

15 Human peripheral blood mononuclear cells incubated in vasculogenic conditioning medium dramatically improve ischemia/reperfusion acute kidney injury in mice.

Takayasu Ohtake

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Acute kidney injury (AKI) is a major clinical problem that still has no established treatment. We investigated the efficacy of cultured human peripheral blood mononuclear cells (PBMNCs) for AKI. Ischemia/reperfusion injury (IRI) was used to induce AKI in male non-obese diabetic (NOD/SCID) mice aged 7-8 weeks. PBMNCs were isolated from healthy volunteers and were subjected to quality and quantity controlled (QQc) culture for 7 days in medium containing stem cell factor, thrombopoietin, Flt-3 ligand, vascular endothelial growth factor, and interleukin-6. IRI-induced mice were divided into 3 groups and administered 1) $1×10^6$ PBMNCs after QQc culture (QQc PBMNCs group), 2) $1×10^6$ PBMNCs without QQc culture (non-QQc PBMNCs group), or 3) vehicle without PBMNCs (IRI control group). PBMNCs were injected via the tail vein 24 hours after induction of IRI, followed by assessment of renal function, histological changes, and homing of injected cells. Blood urea nitrogen and serum creatinine 72 hours after induction of IRI in the QQc PBMNCs group dramatically improved compared with those in the IRI control and the non-QQc PBMNCs groups, accompanied by the improvement of tubular damages. Interstitial fibrosis 14 days after induction of IRI was also significantly improved in the QQc PBMNCs group compared with the other groups. The renoprotective effect noted in the QQc PBMNCs group was accompanied by reduction of peritubular capillary loss.

The change of PBMNCs' population (increase of CD34+ cells, CD133+ cells, and CD206+ cells) and increased endothelial progenitor cell-colony forming potential by QQc culture might be one of the beneficial mechanisms for restoring AKI. In conclusion, an injection of human QQc PBMNCs 24 hours after induction of IRI dramatically improved AKI in mice.

16 The superiority of autologous dendritic cell-cytokine induced killer cell immunotherapy combined with S-1 plus cisplatin in patients with advanced gastric cancer: A prospective phase II trial

Xiaoli Wang

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Background: Advanced gastric cancer remains lethal despite multiagent chemotherapy. Dendritic cell-cytokine induced killer cell immunotherapy is a promising, broadly applicable strategy under evaluation in multiple malignancies. In this multi-arm phase II study, we assessed the combination of DC-CIK with S-1 and cisplatin chemotherapy in AGC and the role of mutational analysis of cell free DNA (cfDNA) in predicting clinical outcome.

Methods: We did this investigator-initiated, open-label, single center, multiple arm, phase II study of DC-CIK and chemotherapy as follows: Consecutive patients (n=63) with advanced gastric cancer were allocated to treatment with with DC-CIK combined with S-1 plus cisplatin, S-1 plus cisplatin, DC-CIK combined with S-1 and S-1 alone. Circulating cfDNA of patients who received DC-CIK was analyzed by next generation sequencing.

Findings: The disease control rates were 5.6%, 33.3%, 47.1% and 76.9% in S-1 alone, S-1 plus cisplatin, DC-CIK combined with S-1 and DC-CIK combined with S-1 plus cisplatin groups respectively (P=0.001). There were significant differences in PFS and OS among the four groups (P<0.001). After adjusting for competing risk factors, the therapeutic modality of DC-CIK combined with S-1 plus cisplatin was confirmed to be an independent predictor of overall survival and PFS. (HR : 0.336, 95% CI : 0.261-0.752 : P =0.001 and HR : 0.458, 95% CI : 0.335-0.766 : P =0.001). The $CD3^+$, $CD3^+/CD4^+$ and $CD8^+/CD28^+$ T lymphocytes proportions were elevated (P <0.05), while the $CD8^+/CD28^-$, $CD4^+/CD25^+$ and NKT cell were significantly decreased in peripheral blood after DC-CIK cell immunotherapy (P <0.05). 19 patients (63.3%) had a decrease in the frequency and number of cfDNA mutations after treatment with DC-CIK infusion, which was associated with favorable PFS and OS.

Interpretation: DC-CIK combined with S-1 plus cisplatin resulted in a favorable PFS and OS. Clinical benefit was predicted by changes in cfDNA mutational profiles and mutational frequency.

17 Exosomes from NKs Previously Exposed to Neuroblastoma Cells can educate Naïve NKs to eradicate neuroblastoma tumors in vivo

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Background: Immune cell-derived exosomes can increase immunity against tumors. On the other hand, tumor-derived exosomes can reduce the immunity and can change the tumor microenvironment to further develop and provide metastasis. These effects take place by an alteration in the innate and adoptive immune cell functions. In this experiment, we have studied the NK cell (NKs) effectiveness on tumor cells after expansion and then incubation it with exosomes.
Methods: The exosomes were derived from two populations of NKs: 1) Naïve NKs and, 2) NKs previously exposed to neuroblastoma cells. Also, we have studied the neuroblastoma derived exosomes (NB-Ex) on NK function. The molecular load of the characterized
exosomes (by means of nanoparticle tracking analysis, flow cytometry, scanning electron microscopy and western blot) from NKs exposed to the neuroblastoma cell was revealed their expression of NCRs in addition to CD56, NKG2D, and KIR2DL2 receptors. These exosomes were used to treat NKs and then administered to NB tumor cells both in vitro and in vivo.
Results: Our results showed some kind of NK education by the exosomes. This education from NKs previously exposed to neuroblastoma cell-derived exosomes caused efficient and greater cytotoxicity against NB tumors, but NB-Ex act as tumor promoters by providing a tumor supporting niche.
Conclusion: This method of preparing the exosomes has a dramatic effect on activation of anti- NKs against neuroblastoma cells.

Keywords: Cancer Therapy, Exosome, Immune Cell Therapy, Natural Killer Cell, Neuroblastoma

18 Culturing Human Epidermal Keratinocytes in Chemically Defined and Xenogeneic-free system

Alvin Chua

Singapore General Hospital

The gold standard method to culture human epidermal keratinocytes for severe burn treatment involves the use of both murine 3T3 fibroblasts as feeder cells as well as bovine serum. This system carries a risk of exposing human cell culture to animal pathogens and therefore questions on its safety have been raised by regulators, especially in a Good Manufacturing Practice (GMP) setting. We have developed a system for culturing human epidermal keratinocytes under a completely xeno-free and fully human conditions. By using pure laminin matrices, chemically defined, and serum-free medium, this method supports autologous keratinocyte survival in vitro without the aid of feeder cells for up to 30 population doublings on adult patients. Normal expression of basal cell markers and differentiation markers of these cells over increasing passages are shown in qRT-PCR as well as immunostaining and FACS analysis. Through an in-vitro functional assay (organotypic culture), keratinocytes cultured in our fully human method system show normal stratification and expression of keratinocytes markers and transcription factor. In addition, our in-vivo assay of xeno-free keratinocyte culture grafted on nude mice also demonstrated positive take. As our culture system is xeno-free and fully defined, this new technology shows potential for cultured cell products to be used even in the management of less severe burns and chronic wounds.

19 Contribution to neurogenesis of brain-derived neurotrophic factor and hepatocyte growth factor secreted from umbilical cord-derived mesenchymal stromal cells

Takeo Mukai

The Institute of Medical Science, The University of Tokyo (IMSUT)

Recently human umbilical cord-derived mesenchymal stromal cells (UC-MSCs) have been used in regenerative medicine to treat various neurological disorders including intraventricular hemorrhage (IVH). The objectives of this study are to evaluate the neuroprotective effect of UC-MSCs in a neonatal model of IVH and to investigate key factors of neuroprotective effect.
UC-MSCs were intravenously administered two days after IVH, and brain MRI and neurological behavioral measurements were performed, accompanied by histopathological analysis, cytokine beads assays of serum and cerebrospinal fluid, in vivo imaging, and human Alu-PCR for tracking of transplanted UC-MSCs. After that, in vitro co-culture of primary mouse neuron after oxygen glucose depletion (OGD) and UC-MSCs was performed in order to investigate the neurotrophic factors secreted from UC-MSCs. Concentration of neurotrophic factors in supernatant were calculated, and neurogenesis effect by these neurotrophic factors were also confirmed by adding neutralizing antibodies.
UC-MSCs administered group exhibited significant behavioral improvement compared to the control group. Histopathological analysis revealed UC-MSCs significantly attenuated periventricular reactive gliosis, hypomyelination, and periventricular cell death observed after IVH. Furthermore, human brain-derived neurotrophic factor (BDNF) and hepatocyte growth factor (HGF) were elevated in the serum of neonatal IVH model mice. However, transplanted UC-MSCs detected in the brain and lung of IVH mice were eliminated 3 weeks after injection.
In vitro experiment, BDNF and HGF secreted from UC-MSCs co-cultured with mouse neuron after OGD were elevated. In addition, neurogenesis effect indicated by BrdU incorporation and immunochemistry of GAP43 and Histon H3 was attenuated by addition of neutralizing antibodies of BDNF and HGF.
These results suggest that amelioration of neuronal injury followed by functional improvement might result from secretion of trophic factors such as BDNF and HGF rather than neuronal differentiation and eternal cell replacement by UC-MSCs, and that these neurotrophic factors secreted from UC-MSCs contribute to neurogenesis in injured nerve system.

20 Phase I clinical trial of intracerebral transplantation using bone marrow stromal cell (BMSC) against acute ischemic stroke (RAINBOW project)

Masahito Kawabori

Department of Neurosurgery, Hokkaido University

Background: Recent breakthrough in cell therapy is expected to reverse the neurological sequelae of stroke. Prior studies have demonstrated that bone marrow stromal cells (BMSCs) have therapeutic potential against stroke, however, there are several problems remain unsolved. In this study, we investigated the use of autologous BMSC transplantation for acute ischemic stroke with several new aspects as a next-generation cell therapy for treating stroke. This study is called the Research on Advanced Intervention using Novel Bone marrOW stem cell (RAINBOW, UNIN ID: UMIN000026130).
Methods/Design: RAINBOW is a phase 1, open-label, uncontrolled, dose-response study, with the primary aim to determine the safety of the autologous BMSC administered to the patients with acute ischemic stroke. Estimated enrollment is 6–10 patients suffering from moderate to severe neurological deficits. Approximately 50 mL of the bone marrow is extracted from the iliac bone of each patient 15 days or later from the onset, and BMSCs are cultured with allogeneic human platelet lysate (PL) as a substitute for fetal calf serum and are labeled with superparamagnetic iron oxide for cell tracking using magnetic resonance imaging (MRI). BMSCs are stereotactically administered around the area of infarction in the subacute phase. Each patient will be administered a dose of 20 or 50 million cells. Neurological scoring, MRI for cell tracking, 18F-fuorodeoxyglucose positron emission tomography, and 123I-Iomazenil singlephoton emission computed tomography will be performed throughout 1 year after the administration.
Discussion: This is a first-in-human trial to use labelled BMSC to the patients with acute ischemic stroke. We expect that intraparenchymal injection can be a more favorable method for cell delivery to the lesion and improvement of the motor function. Moreover, it is expected that the bio-imaging techniques can clarify the therapeutic mechanisms.

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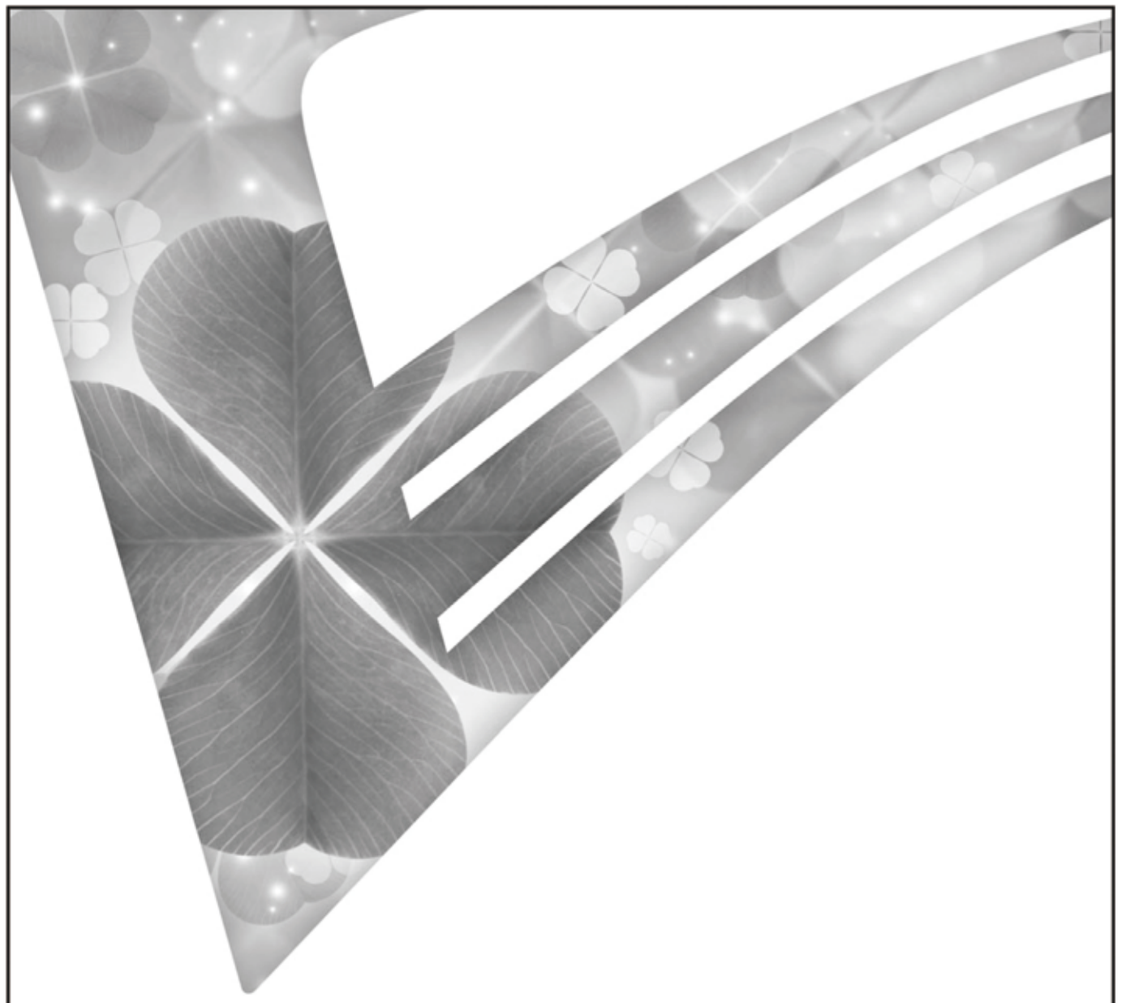

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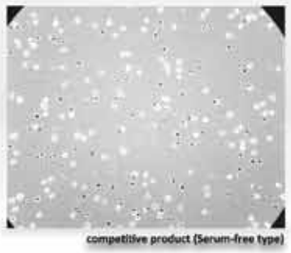
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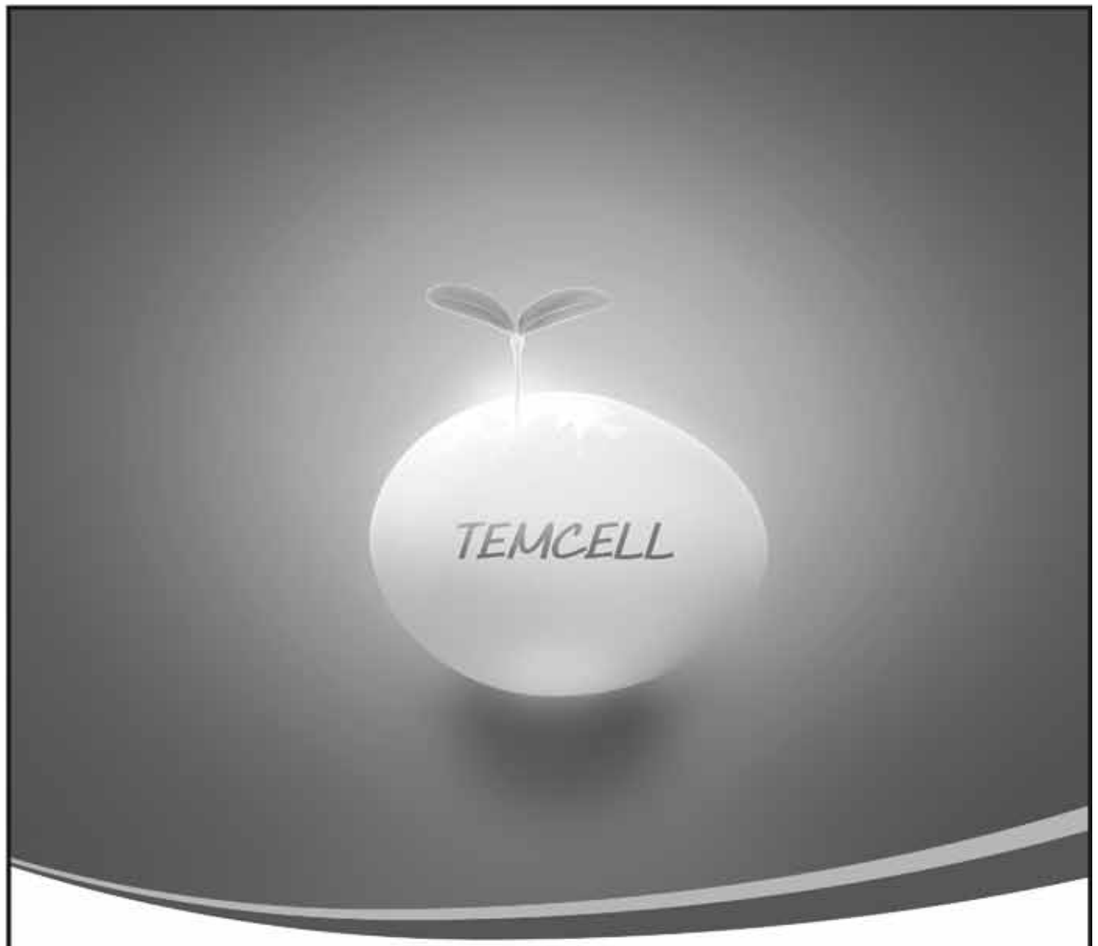

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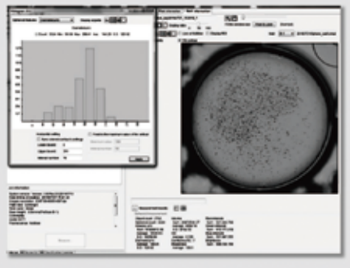

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ヒストグラム表示が可能。

- 細胞数、細胞塊数
- 死細胞、死細胞塊の数
- 生死細胞以外の検出数
- ウェル内の生細胞、生細胞塊 面積・体積合計、平均、SD
- Confluence
- 光学濃度値　平均、SD
- 真円度　平均、SD
- 直径　平均、SD
- 輪郭鮮明度　平均
- 明視野撮像細胞塊ごとでの蛍光発光平均

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シングルセル細胞タンパク解析の革命児 フローサイトメトリーを超えた新しい研究の世界

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40種類以上のパラメーターで解析可能

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Eメール：info-japan@fluidigm.com
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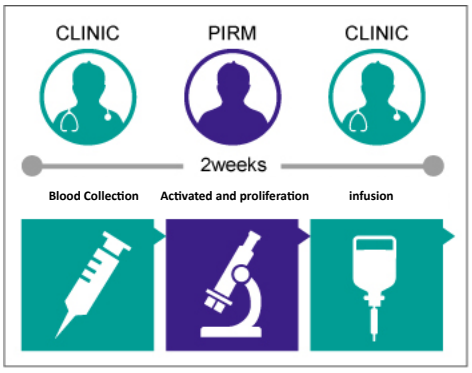
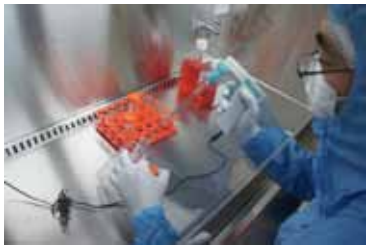
Kohjin Bio has 20 years experience for medium manufacturing.
Kohjin Bio succeed to supply of a high-quality products firmly by having kept the joint development of research laboratories and the enterprise constantly, and studying technology.
Kohjin Bio has been approved as a GMP compliant facility and would like to provide the best service to our customers with full effort.

Tissue Culture Media
Manufacturing Process

Pyrogen-Free Water
Producing System

PIRM aims at becoming a pioneer in the regenerative medicine.
PIRM obtained license for the manufacture of specified cell products in July, 2015. (Authorization number: FA3150006)
PIRM provide cell processing service at the highest level for the demanders involuntarily generated by the new act, building on our cell culture techniques amassed through the development of various kinds of medium, and a new cell processing center in conformity with the relevant GMP-guidelines.





We will offer the state-of-the-art products that are needed just now by using our plenty of experience.

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