International Society for Cellular Therapy
ISCT

MIYAZAKI
2 0 1 0 JAPAN

The 1st ISCT
Asia-Pacific Regional Meeting

Program & Abstracts

Date **Oct. 17th (Sun.) - 20th (Wed.), 2010**

Venue **PHOENIX SEAGAIA RESORT** World Convention Center SUMMIT

Hamayama, Yamasaki-Cho, Miyazaki City, Miyazaki Prefecture 880-8545
TEL : +81-985-21-1113 FAX : +81-985-21-1239 http://www.seagaia.co.jp/index_en.html

President **Yoichi Takaue, M.D.**
Director, Institute for Research, St. Luke's International Hospital

The 1st ISCT
Asia-Pacific Regional Meeting

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Meeting Information

Title of Meeting	**The 1st ISCT Asia-Pacific Regional Meeting**
Date	**October 17th (Sun.) to 20th (Wed.), 2010**
Venue	**Phoenix Seagaia Resort** World Convention Center Summit Hamayama, Yamasaki-Cho, Miyazaki City, Miyazaki Prefecture 880-8545 TEL: +81-985-21-1113 FAX: +81-985-21-1239 http://www.seagaia.co.jp/index_en.html
President	**Yoichi Takaue, M.D.,** Director, Institute for Research, St. Luke's International Hospital
Vice President	**Yoshihisa Kodera, M.D., Ph. D.,** Professor, Dpartment of Promotion for Blood and Marrow Transplantation (DPBMT), Aichi Medical University School of Medicine **Akihiro Shimosaka, Ph. D.,** Director, The Institute of Medical Science, The University of Tokyo, Scientific Research Advisor
Official Language	English
Website	http://isct-ap2010.jtbcom.co.jp/

Executive Secretary	Yuji Heike, M.D., Ph. D., Department of Medical Oncology, National Cancer Center Hospital
Secretary	Takako Wakeda, M.D., Department of Medical Oncology, National Cancer Center Hospital
Secretariat Office	The 1st ISCT Asia-Pacific Regional Meeting Secretariat c/o JTB Communications, Inc. Tokyo Regional Headquarters, IK Bldg. 3F-2-24-9 Kamiosaki Shinagawa-ku Tokyo 114-8657 TEL: +81-3-5403-7834 FAX: +81-3-5403-7839 E-mail: isct-ap2010@jtbcom.co.jp TEL: +81-985-21-1170 (October 17th (Sun.) to 20th (Wed.))

Sponsored by Miyazaki Convention & Visitors Bureau
Supported by Japan National Tourism Organization
Japanese Society of Hematopoietic Cell Transplantation

Sponsors

Platinum Sponsor	CHUGAI PHARMACEUTICA Co., Ltd. Kyowa Hakko Kirin Co., Ltd. Otsuka Pharmaceutical Co., Ltd.
Gold Sponsor	IRX Therapeutics, Inc. KOHJIN BIO Co., Ltd
Silver Sponsor	MEDINET Co., Ltd

(In alphabetical order)

Contents

Welcome Remarks

It is our great pleasure to hold the first International Society of Cellular Therapy (ISCT) Asian-Pacific Regional Meeting, and I appreciate your participation to make this meeting active and successful. The main purpose of this meeting is for researchers, clinicians, business persons and regulators to share knowledge and expertise regarding the development of equipment and treatments in the field of cellular therapy, i.e. expansion or modification for transplantation, immunotherapy, regenerative medicine and gene therapy. In most Asian countries, expertise in innovative cellular therapy and the development of equipment for clinical use have not been well explored. Additionally, regulatory guidelines for approval processes have not yet been firmly established, although these are essential for the development of new ideas for clinical application. These are serious obstacles for the development of our own research seeds. In this meeting, we expect to have an active discussion in a rather informal atmosphere, and will cover a variety of topics regarding cellular therapy in educational lectures by ISCT members and workshops. We believe that this meeting will help to enhance both communications among Asian professionals and partnerships with Western professionals.

Finally, I am very grateful to Drs. Yuji Heike and Akihiro Shimosaka as Executive Secretaries who prepared this meeting in the mid of world-wide economy crackdown.

Yoichi Takaue,

President of The 1st ISCT Asia-Pacific Regional Meeting

The 1st ISCT Asia-Pacific Regional Meeting Committee

President	Yoichi Takaue (Japan)
Vice President	Akihiro Shimosaka (Japan) Yoshihisa Kodera (Japan)
Executive Secretary	Yuji Heike (Japan)
Secretary	Takako Wakeda (Japan)
International Organizing Committee	Hee Young Shin (Korea) Heinz Zwierzina (Austria) Hyun Ok Kim (Korea) Saengsuree Jootar (Thailand) Yao-Chang Chen (Taiwan)
Scientific Advisory Board	Giovanni Migliaccio (Italy) Karen Edward (USA) Naoto Hirano (USA) Teruhide Yamaguchi (Japan)
Local Organizing Committee	Der-Yuan Wang (Republic of China (Taiwan)) Hack-Ki Kim (Korea) Hyo Seop Ahn (Korea) John Rasko (Australia) Jun Ren (China) Kazutou Takesako (Japan) Kun Soo Lee (Korea) Liu Kaiyan (China) Masaaki Oka (Japan) Mickey Koh (UK) Mitsuo Katano (Japan) Mitsuo Ochi (Japan) Ryuji Maekawa (Japan) Shigetaka Shimodaira (Japan) Shuichi Taniguchi (Japan) Tai Ju Hwang (Korea) Takahito Nakamura (Japan) Teruo Okano (Japan) Yong-Mook Choi (Korea) Yong-Soo Bae (Korea) Yoshifumi Kawano (Japan) Yuichiro Yazaki (Japan)

(In alphabetical order)

Access to the Meeting Site

From Major Cities to Miyazaki

From Major Cities to Miyazaki (Tokyo)

Tokyo	Haneda Airport	Airplane 1 hr 30 min	Miyazaki Airport	Car 20 min	Seagaia
	Tokyo Station	Train 10 hr	Miyazaki Station	Car 15 min	Seagaia
	Kawasaki Harbor	Ship 20 hr 40 min	Hyuga Harbor	Car 1 hr 25 min	Seagaia

From Major Cities to Miyazaki (Fukuoka)

Fukuoka	Fukuoka Airport	Airplane 40 min	Miyazaki Airport	Car 20 min	Seagaia
	Hakata Station	Train 6 hr	Miyazaki Station	Car 15 min	Seagaia
	Hakata Bus Center	Bus 4 hr 10 min	Miyazaki Station	Car 15 min	Seagaia

From Major Cities to Miyazaki (Osaka)

Osaka	Osaka Itami Airport	Airplane 1 hr 5 min	Miyazaki Airport	Car 20 min	Seagaia
	Kansai International Airport	Airplane 1 hr 5 min	Miyazaki Airport	Car 20 min	Seagaia
	Shin Osaka Station	Train 7 hr 20 min	Miyazaki Station	Car 15 min	Seagaia
	Nankang	Ship 16 hr 30 min	Miyazaki Harbor	Car 10 min	Seagaia

From Major Cities to Miyazaki

Area	Round Trip	Miyazaki	Return Journey
Asahikawa	AsahikawaAirport -> Haneda Airport ->	Miyazaki City International Airport	-> Haneda Airport -> AsahikawaAirport
Sapporo	Sapporo Airport -> Nagoya Airport ->		-> Kansai Airport -> Sapporo Airport
Hakodate	Hakodate Airport -> Haneda Airport ->		-> Haneda Airport -> Hakodate Airport
Kushiro	Kushiro Airport -> Haneda Airport ->		-> Haneda Airport -> Kushiro Airport
Aomori	Aomori Airport -> Haneda Airport ->	Miyazaki City International Airport	-> Haneda Airport -> Aomori Airport
Iwate	Akita Airport -> Haneda Airport ->		-> Haneda Airport -> Misawa Airport
Miyagi	Haneda Airport ->		-> Haneda Airport
Akita	Akita Airport -> Haneda Airport ->		-> Haneda Airport -> Akita Airport
Yamagata	Haneda Airport ->		-> Haneda Airport
Fukushima	Haneda Airport ->		-> Haneda Airport
Ibaraki	Haneda Airport ->	Miyazaki City International Airport	-> Haneda Airport
Tochigi	Haneda Airport ->		-> Haneda Airport
Gunma	Haneda Airport ->		-> Haneda Airport
Saitama	Haneda Airport ->		-> Haneda Airport
Chiba	Haneda Airport ->		-> Haneda Airport
Tokyo	Haneda Airport ->		-> Haneda Airport
Kanagawa	Haneda Airport ->		-> Haneda Airport
Niigata	Haneda Airport ->	Miyazaki City International Airport	-> Haneda Airport
Yamanashi	Haneda Airport ->		-> Haneda Airport
Toyama	Toyama Airport -> Haneda Airport ->		-> Haneda Airport -> Toyama Airport
Ishikawa	Komatsu Airport -> Haneda Airport ->		-> Haneda Airport -> Komatsu Airport
Fukui	Komatsu Airport -> Haneda Airport ->		-> Haneda Airport -> Komatsu Airport
Nagano	Haneda Airport ->		-> Haneda Airport
Gifu	Nagoya Airport ->		-> Nagoya Airport
Shizuoka	Nagoya Airport ->		-> Nagoya Airport
Aichi	Nagoya Airport ->		-> Nagoya Airport
Mie	Nagoya Airport ->		-> Nagoya Airport

Area	Round Trip	Miyazaki	Return Journey
Shiga	Itami Airport ->	Miyazaki City International Airport	-> Itami Airport
Kyoto	Itami Airport ->		-> Itami Airport
Osaka	Itami Airport ->		-> Itami Airport
Hyogo	Itami Airport ->		-> Itami Airport
Nara	Itami Airport ->		-> Itami Airport
Wakayama	Kansai Airport ->		-> Kansai Airport
Tottori	Hiroshima West Airport ->	Miyazaki City International Airport	-> Hiroshima West Airport
Shimane	Hiroshima West Airport ->		-> Hiroshima West Airport
Okayama	OkayamaAirport ->		-> OkayamaAirport
Hiroshima	Hiroshima West Airport ->		-> Hiroshima West Airport
Yamaguchi	Fukuoka Airport ->		-> Fukuoka Airport
Tokushima	Itami Airport ->	Miyazaki City International Airport	-> Itami Airport
Kagawa	Itami Airport ->		-> Itami Airport
Ehime	Matsuyama Airport ->		-> Matsuyama Airport
Kouchi	Kouchi Airport ->		-> Kouchi Airport
Fukuoka	Fukuoka Airport ->	Miyazaki City International Airport	-> Fukuoka Airport
Nagasaki	Nagasaki Airport ->		-> Nagasaki Airport
Saga	Fukuoka Airport ->		-> Fukuoka Airport
Okinawa	Naha Airport ->		-> Naha Airport
Seoul	Incheon ->	Miyazaki City International Airport	-> Incheon
Beijing	Beijing ->	Narita Airport ->	Narita Airport -> -> Beijing
Taipei	Taipei ->		-> Taipei
Hong Kong	Hong Kong ->	Kansai Airport ->	Kansai Airport -> -> Hong Kong
Shanghai	Shanghai ->	Fukuoka Airport ->	Fukuoka Airport -> -> Shanghai
Singapore	Singapore ->		-> Singapore

From the Airport, Station, and Port to Seagaia

Miyazaki Airport - Seagaia

		Time (One-Way)	One-Way Fare
Miyazaki Airport - Seagaia	Taxi	20 min	Approx. ¥ 4,500 (mid-size)

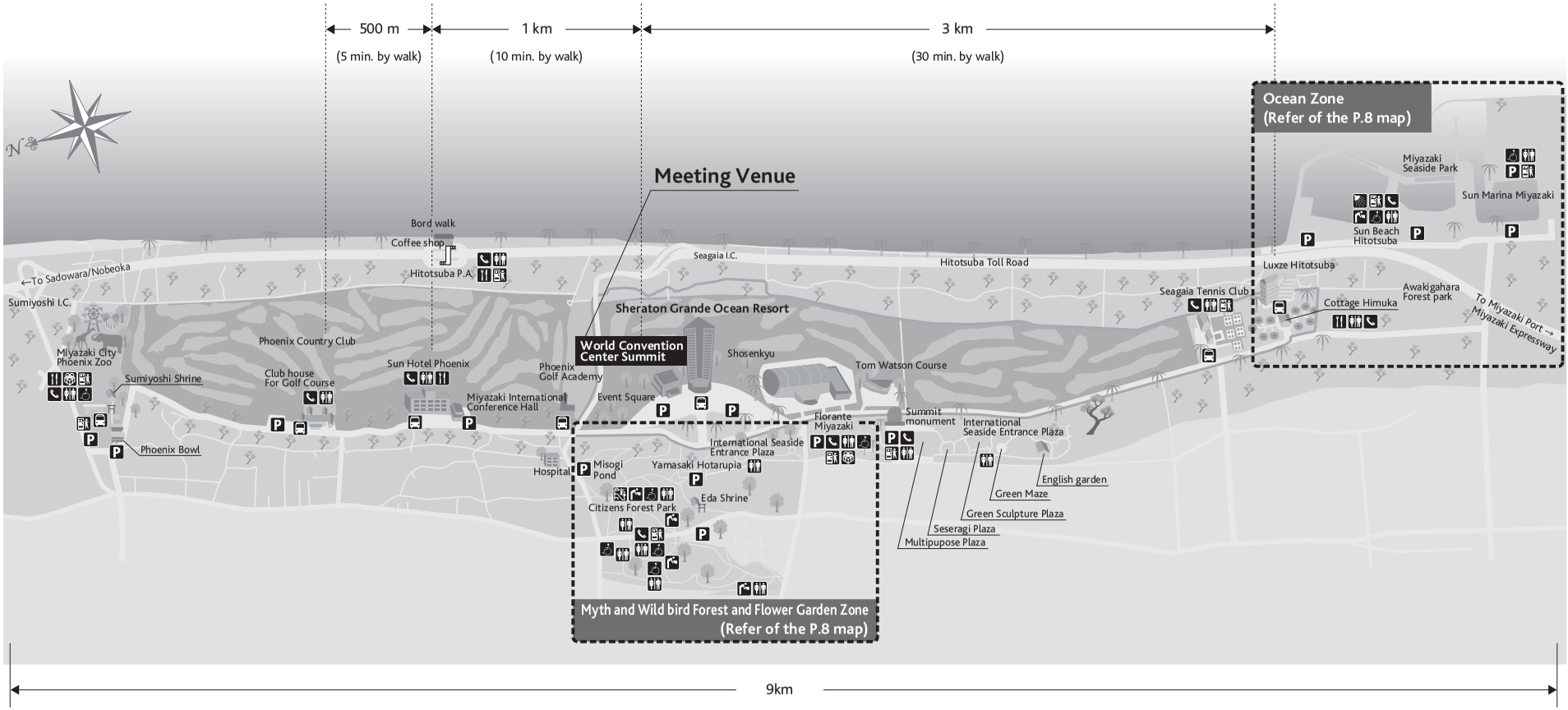
Miyazaki Station - Seagaia

		Time (One-Way)	One-Way Fare
Miyazaki Station - Seagaia	Bus	25 min	¥ 500
	Taxi	15 min	Approx. ¥ 2,500 (mid-size)

Miyazaki Harbor - Seagaia

		Time (One-Way)	One-Way Fare
Miyazaki Harbor - Seagaia	Bus	15 min	¥ 300
	Taxi	10 min	Approx. ¥ 1,800 (mid-size)

Seagaia Map

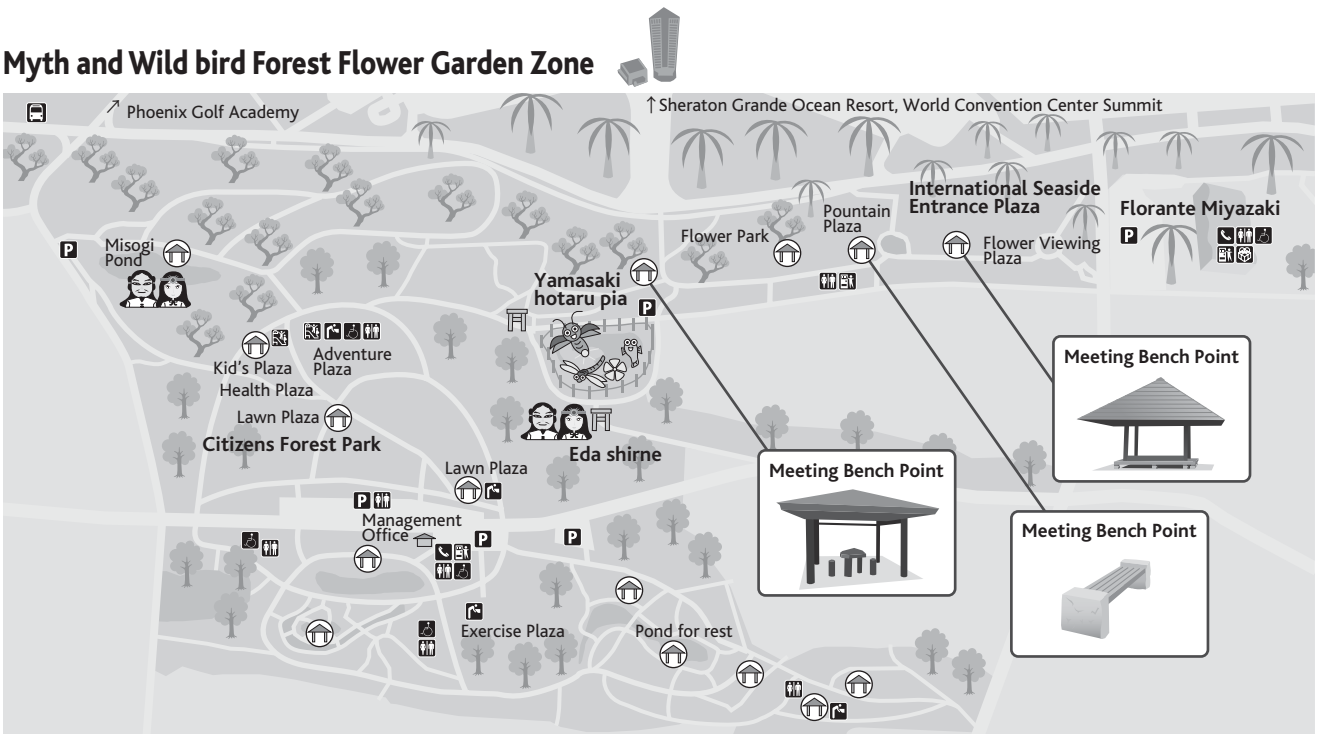


Introductory Remarks

- Telephone
- Parking
- Restroom
- Restroom to meet the needs of the disabled quest
- Drink
- Shopping
- Restaurant
- Watering place
- Play equioment
- Observatory
- Bus Stop
- Rest point
- Shower

Ocean Zone

Myth and Wild bird Forest Flower Garden Zone

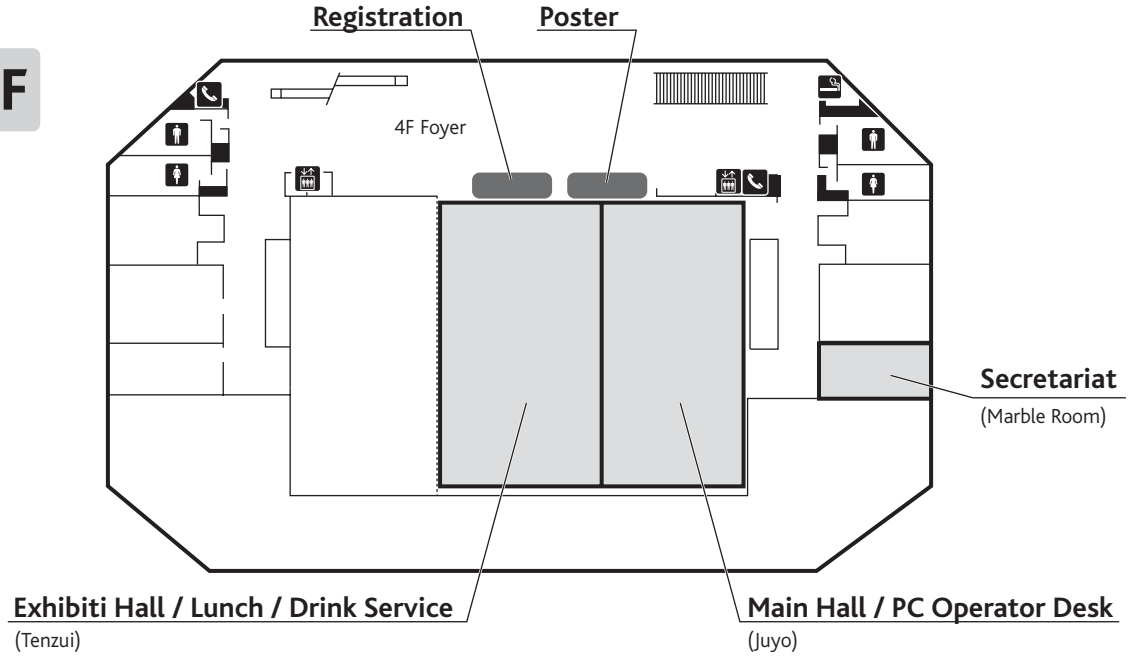


Introductory Remarks

Telephone	Parking	Restroom	Restroom to meet the needs of the disabled quest	
Drink	Shopping	Restaurant	Watering place	Play equiomment
Observatory	Bus Stop	Rest point	Shower	

Floor Guide

4F



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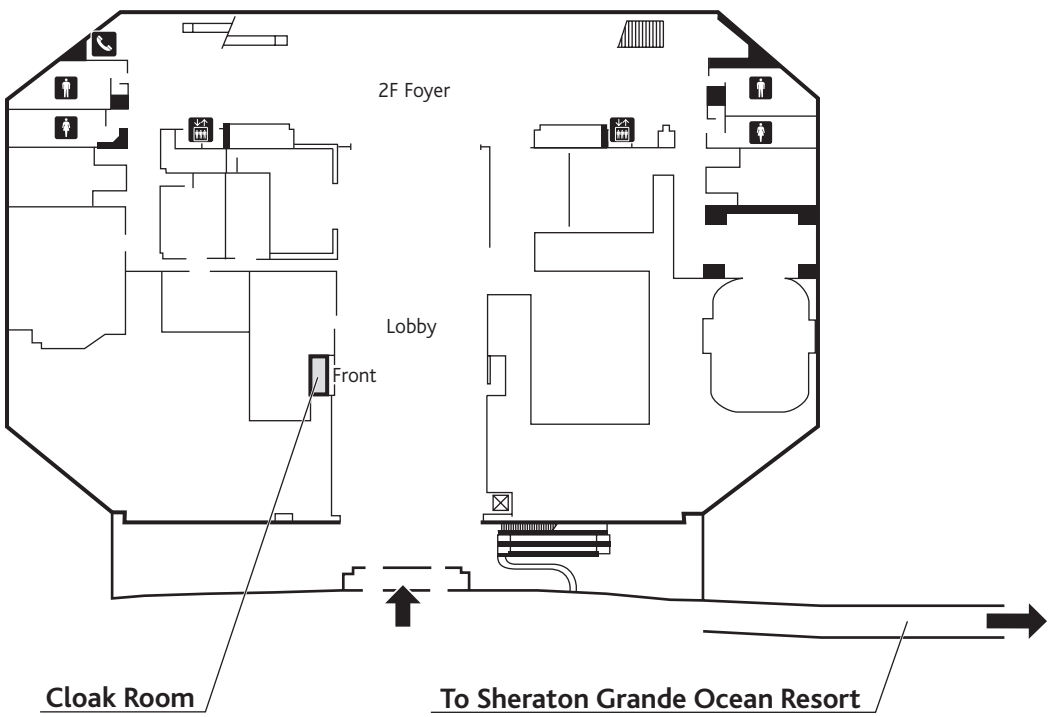

General Information

DUTY FREE IMPORT

Personal effects and professional equipment can be brought into Japan duty free as long as their contents and quantities are deemed reasonable by the customs officer. You can also bring in 400 cigarettes, 500 grams of tobacco or 100 cigars; 3 bottles of alcoholic beverages; 2 ounces of perfume; and gifts and souvenirs whose total market price is less than 200,000 yen or its equivalent. There is no allowance for tobacco or alcoholic beverages for persons aged 19 years or younger. Firearms and other types of weapons, and narcotics are strictly prohibited.

INSURANCE

The organizer cannot accept responsibility for accidents that might occur.

CLIMATE

The temperature in Miyazaki during the period of the Meeting ranges between 14.9–24 degrees Celsius (59–75 degrees Fahrenheit).

CURRENCY EXCHANGE

Only Japanese yen (JPY) is acceptable at regular stores and restaurants. Certain foreign currencies may be accepted at a limited number of hotels, restaurants and souvenir shops. You can buy yen at foreign exchange banks and other authorized money exchangers on presentation of your passport.

TRAVELER'S CHECKS AND CREDIT CARDS

Traveler's checks are accepted only by leading banks and major hotels in principal cities, and the use of traveler's checks in Japan is not as popular as in some other countries. VISA, MasterCard, Diners Club, and American Express are widely accepted at hotels, department stores, shops, restaurants and nightclubs.

TIPPING

In Japan, tips are not necessary anywhere, even at hotels and restaurants.

ELECTRICITY

Electric current is uniformly 100 volts, AC, throughout Japan, but with two different cycles: 50 in eastern Japan including Funabori and Tokyo, and 60 in western Japan including Kyoto, Osaka and Nagoya. Leading hotels in major cities have two outlets of 100 and 220 volts but their sockets usually accept a two-leg plug only.

SHOPPING

Shops and other sales outlets in Japan are generally open on Saturdays, Sundays and national holidays as well as weekdays from 10:00 to 20:00. Department stores, however, are closed on one weekday, differing by store, and certain specialty shops may not open on Sundays and national holidays.

Guidelines for Participants

On-Site Registration

On-site Registration will be conducted as follows:
Venue: Sheraton Grande Ocean Resort, Front, 1F
Date & Time: Oct. 17th (Sun.) 17:30–21:00
Venue: World Convention Center Summit, Foye, 4F
Date & Time: Oct. 18th (Mon.) 8:00–17:00
Oct. 19th (Tue.) 8:00–17:00
Oct. 20th (Wed.) 7:30–10:00

Registraion Fee

Member: JPY 20,000 Non-member: JPY 30,000 Student: JPY 10,000
All payments must be made in Japanese yen by cash.

Name Card

Name Card will be distributed at Registration Desk. Name Card should be worn at all times. Participants not wearing their badges to the Scientific Session room, Poster, Exhibition and Social Programs will not be granted admittance.

If you produce the Name Card in Sheraton Grande Ocean Resort, you are entitled to below discount.

- Restaurants and Bars (except Ninigi Bakery & Cafe)
- The Ocean Club (Pool, Training Room)
  Ten percent discount
- Shosenkyu (A natural hot spring)
  Normal Fee ¥ 1,500 ⇨ ¥ 1,000 *at one time
- Banyan Tree Spa
  A la carte menu (Facial, Body) = 15% OFF
  More than two hours course = 10% OFF

Cloak Room

Venue: Sheraton Grande Ocean Resort, Cloak Room, 2F
Date & Time: Oct. 17th (Sun.) 17:30–21:30
Venue: World Convention Center Summit, Front, 2F
Date & Time: Oct. 18th (Mon.) 8:00–21:45
Oct. 19th (Tue.) 8:00–19:00
Oct. 20th (Wed.) 7:30–12:00

Lunch

Oct. 18th (Mon.): Buffet lunch will be prepared for luncheon seminar 1.
Oct. 19th (Tue.): Buffet lunch will be prepared for luncheon seminar 2.

Coffee Break

Venue: World Convention Center Summit, Tenzui , 4F

Date & Time: Oct. 18th (Mon.) 16:00–16:15
Oct. 19th (Tue.) 9:45–10:00
15:30–15:45

Communication Onsite

There will be no paging service provided by the venue. Instead, a message board will be setup. Participants are encouraged to check this board regularly.

Social Program

Welcome Dinner

Date & Time: Oct. 17th (Sun.)　Please come to enjoy dinner between 18:00 and 21:00
Venue: Sheraton Grande Ocean Resort, All-day Dinning Pine Terrace, 1F
Style: Buffet
Admission: Free (included in Registration Fee)
Please receive the ticket by the Reception staff at Oct. 17 (Sun.) (Sheraton Grande Ocean Resort, Front, 1F).
* Welcome Dinner is a Buffet-style dinner, not a party.

Presidential Reception

Date & Time: Oct. 18th (Mon.)　19:00–21:30
Venue: World Convention Center Summit, Tenzui , 4F
Style: Buffet
Admission: Free (included in Registration Fee)

Gala Dinner

Date & Time: Oct. 19th (Tue.)　19:00–21:30
Venue: Sheraton Grande Ocean Resort, Shosenkyu Green Garden, 1F
* World Convention Center Summit, Tenzui, 4F (in case of rain)
Style: Buffet
Admission: Free (included in Registration Fee)

Guidelines for Presentation

Guidelines for Oral Presentations

- All oral presentations must be computer based. Presentations using a slide projector will not be accepted. Your own laptop computer or external storage media will be required.
- Please bring your laptop computer and/or media to the PC Operator Desk, 4F Juyo at least 30 minutes prior to your scheduled presentation time so that the PC operator can ensure your computer and/or the presentation media operates correctly.

Presentation Using Your Own Laptop Computer

- Please bring AC power cable together with your laptop computer (Windows or Macintosh).
- If your computer requires conversion cables other than D-SUB15, please bring appropriate connectors.

* Some models of Sony VAIO Note C1/SR/GT/U, Apple iBook G4 , PowerBook G4, AirMac and MacBook may require conversion connectors for screen output.

Presentation Using External Storage Media

- The personal computer that uses it in the hall becomes only Windows.
- Only USB or CD-R are accepted. Please note that MO and other external storage media cannot be accepted.
- Please make the application in Windows version Power Point2003/2007.
- If movie files or other multi-media files are inserted into your presentation material, please bring your laptop computer. The Voice cannot be accepted.
- A monitor, a keyboard and a mouse will be available for your presentation.

Secretariat can only provide connectors compatible with mini-D-Sub15 (see photos below).


Some models of Sony VAIO Note C1/SR/GT/U, Apple iBook C4 and PowerBook G4 may need conversion connectors for screen output.

(e.g.)
VAIO SRX



(e.g.)
iBook



- To avoid trouble during your presentation, please cancel screen saver and power saving functions beforehand.
- Your computer will be returned from PC operator after your presentation.
- All your data will be deleted responsibly after the congress.

Guidelines for Poster Presentation

1) Please find your Poster Number in the Program pages.
2) Placement of Your Poster
   - Please come to the Poster Reception on the date of the Meeting.
   - Poster is to be placed by the presenter within the allotted time below. Pushpins will be prepared on each poster panel.
   - Presentation numbers will be prepared by the Secretariat.
   - Each poster must fit within the dimensions of 90cm width X 190cm height

   * Presentation title, affiliations and names of the authors are to be prepared by the presenter.
3) Posters must be removed after the session within the allotted removal time below. Posters left on the panel after this time will be discarded by the Secretariat.
4) Schedule

Oct. 18th (Mon.)

Poster Placement	8:00– 9:00
Poster Viewing	9:00–18:15
Poster Discussion	18:15–19:00

*Poster Presenters are required to stand in front of their posters during Poster Discussion time.

Oct. 19th (Tue.)

Poster Viewing	9:00–18:45

Oct. 20th (Wed.)

Poster Viewing	9:00–11:00
Poster Removal	11:00–12:00

Program at a Glance

October 17 (Sun.), 2010

	Main Hall (Juyo, 4F)	Exhibiti Hall (Tenzui, 4F)	Poster Corner
8:00			
8:30			
9:00			
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16:00			
16:30			
17:00			
17:30			
18:00	**Welcome Dinner** (Sheraton Grande Ocean Resort, All-day Dining Pine Terrace, 1F)		
18:30			
19:00			
19:30			
20:00			
20:30			
21:00			
21:30			

October 18 (Mon.), 2010

	Main Hall (Juyo, 4F)	Exhibiti Hall (Tenzui, 4F)		Poster Corner
8:00				
8:30				
9:00	Opening Ceremony			
9:30	Plenary Meeting		Exhibition	Poster Viewing
10:00				
10:30	Regenerative Therapy Ⅰ (Cornea, Epidermis, Bone and Cartilage, Teeth)			
11:00				
11:30		Buffet Lunch		
12:00	Lunchon Seminar 1 (Co-Sponsor : CellSeed Inc./Japan Tissue Engineering Co., Ltd.)			
12:30				
13:00	Regenerative Therapy Ⅱ (Blood Vessel, Myocardium)			
13:30				
14:00				
14:30	Regenerative Therapy Ⅲ (Liver, Kidney, Other Organs Including iPS, ES)			
15:00				
15:30				
16:00		Coffee Break		
16:30	Special Session 1 (Co-Sponsor : SANYO Electric Co., Ltd.)	Closed		
17:00				
17:30	Evening Seminar 1 (Co-Sponsor : Kyowa Hakko Kirin Co., Ltd.)			Poster Presenters are required to stand in front of their posters during Poster Discussion time
18:00				
18:30				Discussion
19:00		Presidential Reception		
19:30				
20:00				
20:30				
21:00				
21:30				

October 19 (Tue.), 2010

	Main Hall (Juyo, 4F)	Exhibiti Hall (Tenzui, 4F)		Poster Corner
8:00				
8:30	Hematopoietic Stem Cell Transplantation			
9:00			Exhibition	Poster Viewing
9:30				
10:00		Coffee Break		
10:30	Activated T-cell Therapy			
11:00				
11:30	Special Session 2			
12:00		Buffet Lunch		
12:30				
13:00	Lunchon Seminar 2 (Co-Sponsor : MEDINET Co., Ltd.)			
13:30				
14:00	DC Therapy			
14:30				
15:00	Cell Expansion			
15:30		Coffee Break		
16:00				
16:30	Regulatory Trend			
17:00				
17:30				
18:00	Evening Seminar 2 (Co-Sponsor : CHUGAI PHARMACEUTICAL Co., Ltd.)			
18:30				
19:00				
19:30	GALA Party (Moving to Sheraton Grande Ocean Resort, Shosenkyu Green Garden, 1F)			
20:00				
20:30				
21:00				
21:30				

October 20 (Wed.), 2010

	Main Hall (Juyo, 4F)	Exhibiti Hall (Tenzui, 4F)	Poster Corner
8:00	**Special Session 3** (Immunotherapy) (Co-Sponsor: IRX Therapeutics Inc.)		
8:30			
9:00	**Special Session 4** (Gene Therapy) (Co-Sponsor: KOHJIN BIO Co., Ltd.)	**Exhibition**	**Poster Viewing**
9:30			
10:00	**Special Session 5** (FDA approved DC threrapy)		
10:30			
11:00	**Closing Remark**		**Poster Removal**
11:30			
12:00			
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The 1st ISCT Asia-Pacific Regional Meeting

Program

October 17 (Sun.)

Sheraton Grande Ocean Resort, All-day Dinning Pine Terrace, 1F

18:00-21:00 **Welcome Dinner**

※Welcome Dinner is a Buffet-style dinner, not a party.
Please come to enjoy dinner between 18:00 to 21:00

October 18 (Mon.)

Main Hall (Juyo, 4F)

8:45- 9:00 **Opening Ceremony**

Yoichi Takaue
Institute for Research, St. Luke's International Hospital, Japan

9:00-10:00 **Plenary Meeting**

Chair: **Hee Young Shin** *(Dean for Research Affairs, Seoul National University, Korea)*

PM-1 **Functional Interpretation of Cellular Heterogeneity in Cell Therapy**
Kazuhiro Sakurada
Sony Computer Science Laboratories, Inc., Japan

10:00-11:30 **Regenerative Therapy I**
Cornea, Epidermis, Bone and Cartilage, Teeth

Chair: **Teruo Okano** *(Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University, Japan)*
Wei Liu *(Department of Plastic and Reconstructive Surgery, Shanghai 9th People's Hospital, Shanghai Second Medical University, Shanghai Tissue Engineering Center, China)*

RT I-1 **Osteo-chondreal Regeneration by High Density Mesenchymal Stem Cell Scaffold Free Autologous Constructs**
Koichi Nakayama
Biomedical Engineering Course, Advanced Technology Fusion, Graduate School of Science and Engineering, Saga University, Japan

RT I-2 **Engineering of Various Tissues in Large Animals and Their Potential for Clinical Applications**
Wei Liu
Department of Plastic and Reconstructive Surgery, Shanghai 9th People's Hospital, Shanghai Second Medical University, Shanghai Tissue Engineering Center, China

RT I-3 **Current Status of Clinical Applications of Corneal Regenerative Medicine with Cell Sheet Engineering**
Masayuki Yamato
Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University, Japan

12:00-13:00 **Luncheon Seminar 1**

Co-Sponsor : CellSeed Inc./Japan Tissue Engineering Co., Ltd.

Chair: **Wei Liu** *(Shanghai 9th People's Hospital, Shanghai Second Medical University, China)*

LS1-1 **Cell Sheet Tissue Engineering: Tissue Reconstruction by Layering of Patterned Cell Sheets**
Teruo Okano
Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University, Japan

13:00-14:30 Regenerative Therapy II Blood Vessel, Myocardium

Chair: **Takayuki Asahara** *(Department of Regenerative Medicine Science, Tokai University School of Medicine, Japan / Regenerative Medicine and Research, Kobe Institute of Biomedical Research and Innovation, Japan / Riken Center Of Developmental Biology, Japan)*
Hyo-Soo Kim *(Department of Internal Medicine, Seoul National University College of Medicine, Korea)*

RT II-1 **Endothelial Progenitor Cells for Vascular Regeneration**
Takayuki Asahara
Department of Regenerative Medicine Science, Tokai University School of Medicine, Regenerative Medicine and Research, Kobe Institute of Biomedical Research and Innovation/ RIKEN Center of Developmental Biology, Japan

RT II-2 **Cytokine-based Cell Therapy for Patients with Myocardial Infarction (MAGIC-CELL program) ; Past, Present & Future**
Hyo-Soo Kim
Department of Internal Medicine, Seoul National University College of Medicine, Korea

RT II-3 **Stem Cell Therapy for Severe Heart Failure**
Yoshiki Sawa
Department of Cardiovascular Surgery, Osaka University Graduate School of Medicine, Japan

14:30-16:00 Regenerative Therapy III Liver, Kidney, Other Organs Including iPS, ES

Chair: **Takahiro Ochiya** *(Head, Section for Studies on Metastasis, National Cancer Center Research Institute, Japan)*
Yock Young Dan *(Dept of Medicine, Yong Loo Lin School of Medicine, National University Health System, Singapore/ National University of Singapore, Singapore)*

RT III-1 **Adipose-derived Regenerative Cells - Bench to Bedside -**
Hideki Iwaguro
Clinical Development & Research Planning, Cytori Therapeutics Inc., Japan

RT III-2 **Human Induced Pluripotent Stem Cell-derived Blood Cells toward Clinical Application**
Koji Eto
Stem Cell Bank Section, Center for Stem Cell Biology and Regenerative Medicine, The Institute of Medical Science, The University of Tokyo, Japan

RT III-3 **Long Term Repopulation Potential of Liver Progenitor Cells**
Yock Young Dan
Dept of Medicine, Yong Loo Lin School of Medicine, National University Health System, Singapore / National University of Singapore, Singapore

16:00-16:15 Coffee Break

16:15-17:15 **Special Session 1**
Cell Processing Facility for Advanced Cell Therapy

Co-Sponsor : SANYO Electric Co., Ltd.

Chair: **Taira Maekawa** *(Kyoto University Hospital, Japan)*

SS1-1 **Introduction**
Taira Maekawa
Kyoto University Hospital, Japan

SS1-2 **Practices of Cell Processing Isolator System in Cell Therapy**
Seiichi Yusa
tella, Inc / SANYO Electric Co., Ltd., Japan

SS1-3 **Hitachi Group's Approach to Regenetive Medicine**
Shizu Takeda
Hitachi, Ltd., Japan

SS1-4 **The Introduction of the Advanced Facility for iPS Cell Therapy (FIT)**
Takafumi Kimura
Kyoto University, Japan

17:15-18:15 **Evening Seminar 1**

Co-Sponsor : Kyowa Hakko Kirin Co., Ltd.

Chair: **Yoshihisa Kodera** *(Dpartment of Promotion for Blood and Marrow Transplantation (Dpbmt), Aichi Medical University School of Medicine, Japan)*

ES1-1 **The Use of Haploidentical Stem Cell Transplantation and Alloreactive Donor Lymphocytes for Immunotherapy of Cancer and Using Multi-potent Autologous Stem Cells for Regenerative Medicine**
Shimon Slavin
The International Center for Cell Therapy & Cancer Immunotherapy (Ctci), Weizman Center, Israel

Exhibit Hall (Tenzui, 4F)

19:00-21:30 **Presidential Reception**

Poster Corner

18:15-19:00 **Poster Viewing**

Regenerative Therapy/epidermis, bone

P1 **Cell Administration Technique in Melanocyte Transplantation for Treating Vitiligo**
Bin-Ru She
Biomedical Engineering Lab., Industrial Technology Research Institute, ROC

P2 **Method in Identifying Culture-derived Mixed Skin Cells**
Bin-Ru She
Biomedical Engineering Lab., Industrial Technology Research Institute, ROC

Regenerative Therapy/liver, kidney, other organs

P3 **Human Placenta-Chorion-derived Mesenchymal Cells (pCMCs) May Rescue the Mice From Lethal Total Body Irradiation**
Yin-Kai Chen
Depts. of Laboratory Medicine, Pharmacology, Internal Medicine, Radiotheapy and Pathology, National Taiwan University College of Medicine, ROC

P4 **Isolation and Characterization of a Stem Cell Population from Adult Human Deceased Donor Liver**
Ji-Hyun Lee
Samsung Biomedical Research Institute, Samsung Medical Center, Korea

P5 **Efficacy and Safety Evaluations of a Gel Bead-based Bioartificial Liver Consisting of Gravity Force Perfusion Bioreactor**
Doo-Hoon Lee
Biomedical Research Center, LifeLiver Inc., Korea

P6 **In Vitro Investigation of Interaction between Endothelial Cells and Human Liver Stem Cells.**
In Keun Jang
Biomedical Research Institute, LifeLiver Inc., Korea

P7 **In Vitro-generated Neural Progenitors Mediate Recovery of Dopaminergic Neurons in the Neonatal Hypoxic-ischemic Brain**
Young-Jay Lee
Inst., Maria Biotech Co., Korea

P8 **GD2 Expression is Closely Associated with Neuronal Differentiation of hUCB-derived MSCs**
Yun Kyung Bae
Biomedical Research Institute, MEDIPOST Co, Ltd., Korea

P9 **Identification, Isolation, & Characterization of CD34 Clonogenic Stem Cell (AM-cMSC) in Human Placental Amnion Membrane**
Daniel Tzu Bi Shih
Grad. Inst. Cell & Medical. Sciences, Taipei Medical University, ROC

Regenerative Therapy/others

P10 **Rational Basis for Immune-suppressive Properties of Dedifferentiated Fat Cells in Vitro**
Yuji Iribe
Division of Cell Regeneration and Transplantation, Advanced Medical Research Center, Nihon University School of Medicine, Japan

P11 **Long Term Culture Affects the Cytokine Expression of Hman Umbilcial Cord Blood-mesenchymal Stem Cells**
Hye Jin Jin
MEDIPOST, Korea

P12 **Commercial Scale, Non-viral Platform for Enhancing Potency of Stem & iPS Cell Based Research and Therapeutic Development**
Madhusudan V Peshwa
Executive Vice President, Cellular Therapies, MaxCyte, Inc., USA

P13 **The Novel Cryopreservation and Recovery Media Used in the Research were Formulated, Manufactured and Sponsored by Zenoaq.**
Koh-Ichi Saze
Cell Engineering Team, Research and Development Dept., Nippon Zenyaku Kogyo (Zenoaq) Co. Ltd., Japan

Hematopoetic Stem Cell Transplantation

P14 **Autologous Stem Cells Processing under GMP Management:the Experience in NTUH**
Ming Yao
Cell Therapy Core Lab. Dept.of Medical Research, National Taiwan University Hospital, ROC

P15 **Screening of Immunomodulating Drugs for Graft-versus-host disease by *in vivo* Fluorescence Imaging**
Yoshinori Ikarashi
Host-immune Response, National Cancer Center Res. Inst., Japan

P16 **Antiviral Effect of allo-SCT with RIC for ATLL : Short and Long-term Kinetics of HTLV-1 Proviral Load**
Ilseung Choi
Department of Hematology, National Kyushu Cancer Center, Japan

Immunotherapy/Dendritic cell therapy

P17 **Immunotherapy Utilizing MUC1-mRNA DC and MUC1 CTL with Gemcitabine Targeting Unresectable or Recurrent Pancreatic Cancer**
Yoshinari Maeda
Department of Digestive Surgery & Surgical Oncology (Surgery II), Yamaguchi University Graduate School of Medicine, Japan

P18 **Phase I/IIa Clinical Trials of Dendritic Cell-based Immunotherapy for Acute Myeloid Leukemia in Elderly Patients**
Toshio Kitawaki
Kyoto University Hospital, Japan

P19 **Basic Study on Peptide-pulsed Dendritic Cell-based Immunotherapy for Adult T-cell Leukemia**
Atsuhiko Hasegawa
Dept. of Immunotherapeutics, Tokyo Med. & Dent. Univ., Tokyo, Japan, Japan

P20 **Generation of Clinical Grade Dendritic Cells for Cancer Immunotherapy**
Masahiro Ogasawara
Dept. of Hematology Oncology, Sapporo Hokuyu Hospital, Japan

Cell Expansion

P21 **A Randomized Phase III Trial of NK Cell Therapy for Previously Untreated Diffuse Large B-cell Lymphoma Patients**
Seok-Goo Cho
Department of Hematology, Seoul St. Maryís Hospital, The Catholic University of Korea, Korea

P22 **Ex-vivo Expansion of Lymphocytes from Cord Blood Using Recombinant Human Fibronectin Fragment (CH-296; RETRONECTIN®)**
Yuni Yamaki
Department of Hematology, Oncology and Stem Cell Transplantation, National Cancer Center Hospital, Japan

Regulatory Matters

P23 **The Study of Attitudes and Experiences toward Stem Cells among Researchers in Life Science.**
Heejung Kim
College of Nursing, Catholic University of Daegu, Korea

Immunotherapy/Vaccine

P24 **Two-component Messenger RNA-based Vaccines Generate a Strong Anti-tumor Effect in Combination with Radiation Therapy**
Karl-Josef Kallen
CureVac GmbH, Germany

P25 **The Anti-tumor Effect of Messenger RNA-based Vaccines is Mediated by Inducing Key Immune Response Pathways in the Tumor**
Karl-Josef Kallen
CureVac GmbH, Germany

Immunotherapy/Gene Thearpy

P26 **In Vivo Delivery of Interferon Gene Enhances Antitumor Immunity after Autologous Hematopoietic Stem Cell Transplantation**
Kenta Narumi
Section for Studies on Host-Immunre response, National Cancer Center Research Institute, Japan

P27 **The Next Generation TCR Gene Therapy Using siTCR Vector and RetroNectin Expansion Method**
Junichi Mineno
Center for Cell and Gene Therapy, Takara Bio Inc., Japan

<Late Break Abstract>

P28 **Suicide Gene Modified T Lymphocyte Infusion Therapy Against Relapsed Leukemia After Allogeneic Stem Cell Transplantation**
Shin Kaneko
Division of Stem Cell Therapy, The Institute of Medical Science, The University of Tokyo, Japan

October 19 (Tue.)

Main Hall (Juyo, 4F)

8:15-9:45 Hematopoietic Stem Cell Transplantation

Chair: **Yao-Chang Chen** *(Laboratory Medicine and Internal Medicine, National Taiwan University Hospital, ROC)*
Saengsuree Jootar *(Faculty of Medicine, Ramathibodi Hospital, Thailand)*

HT-1 **Unmanipulated HLA-mismatched/haploidentical Blood and Marrow Hematopoietic Stem Cell Transplantation**
Xiaojun Huang
Institute of Hematology, People's Hospital, Peking University, China

HT-2 **The Role of HLA Disparity, Pre-engraftment Immune Reaction and Hemophagocytic Syndrome in Engraftment Failure Following Reduced-intensity Cord Blood Transplantation**
Shuichi Taniguchi
Department of Hematology, Toranomon Hospital, Japan

HT-3 **Hematopietic Stem Cell Transplantation in Korea**
Jong Wook Lee
Catholic Blood and Marrow Transplantation Center, Division of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea

10:00-11:00 Activated T-cell Therapy

Chair: **Byoung S Kwon***(Cell and Immunobiology and R&D Center for Cancer Therapeutics, National Cancer Center, Korea)*
Jun Ren *(Dept. of Medical Oncology, Peking University School of Oncology, Beijing Cancer Hospital, China)*

AT-1 **A Randomized Phase III Trial of NK Cell Therapy for Previously Untreated Diffuse Large B-cell Lymphoma Patients**
Seok-Goo Cho
Department of Hematology, Seoul St. Mary's Hospital, The Catholic University of Korea, Korea

AT-2 **Novel Treatment Model of Chemo Plus Activated T Cell Modulations for Metastatic Breast Cancer**
Jun Ren
Dept. of Medical Oncology, Peking University School of Oncology, Beijing Cancer Hospital, China

11:00-12:00 Special Session 2

Chair: **Koji Eto** *(Stem Cell Bank Section, Center for Stem Cell Biology and Regenerative Medicine, The Institute of Medical Science, The University of Tokyo, Japan)*

SS2-1 **Regenerative Medical Research Using Bioimaging Rat and Pig**
Eiji Kobayashi
Centers for Development of Advanced Medical Technology, Jichi Medical University, Japan

12:00-13:30 Luncheon Seminar 2

Co-Sponsor : MEDINET Co., Ltd.

Chair: **Kazuhiro Kakimi** *(Department of Immunotherapeutics (Medinet), Graduate School of Medicine, The University of Tokyo, Japan)*

LS2-1 **Adoptive Tcell Transfer Terapy for HIV and Cancer**
Carl June
University of Pennsylvania, USA

13:30-14:30 DC Therapy

Chair: **Majid Tabesh** *(Dendreon Corporation, USA)*
Naoto Hirano *(Dana-Farber Cancer Institute, Harvard Medical School, USA)*

DC-1 **WT1 and MUC1-pulsed DC Vaccination against Advanced Cancers: Today and Tomorrow**
Shigetaka Shimodaira
Cell Processing Center, Shinshu University Hospital, Japan

DC-2 **Dendritic Cell-based Immunotherapy against Tumors and Autoimmune Disease.**
Yong-Soo Bae
Dept of Biological Science, Sungkyunkwan University, Creagene Research Institute, Korea

14:30-15:30 Cell Expansion

Chair: **Mickey Koh** *(Head-Bone Marrow Transplant, St. George's Hospital and Medical School, UK / Head Cellular Therapy, Health Sciences Authority, Singapore)*

CE-1 **A New Dimension to the Hemopoietic Stem Cell Niche**
John E.J. Rasko
Gene & Stem Cell Therapy Program, Centenary Institute Australia / Sydney Medical School, University of Sydney, Australia / Cell and Molecular Therapies, Sydney Cancer Centre, Royal Prince Alfred Hospital, Australia

CE-2 **Novel Target of Ex Vivo Expansion; Integrin αvβ3 Ligation Enables Regulation of Hematopoietic Stem Cell Division Leading to Maintenance of Reconstitution Potential**
Koji Eto
Stem Cell Bank Section, Center for Stem Cell Biology and Regenerative Medicine, The Institute of Medical Science, The University of Tokyo, Japan

15:30-15:45 Coffee Break

15:45-17:45 Regulatory trend

Chair: **Heinz Zwierzina** *(Biotherapy Development Association, Innsbruck Medical University, Austria)*
Scott R. Burger *(Advanced Cell & Gene Therapy, LLC, USA)*

RTR-1 **Regulatory Perspective of Cell Therapeutic Products in Taiwan - An Alternative Protocol of Mycoplasma Monitoring for Hospitals and Small Enterprises**
Der-Yuan Wang (ROC)
Institute of Biotechnology, National Taipei University of Technology, ROC

RTR-2 **Regulation of Cell Therapy Products in Korea**
Jongwon Kim (Korea)
Advanced Therapy Products Division, Korea Food And Drug Administration, Korea

RTR-3 **Regulation of Cell & Tissue Therapies in Singapore**
Huei-Xin Lou (Singapore)
Pharmaceuticals and Biologics Branch, Pre-Marketing Division, Health Products Regulation Group, Health Sciences Authority, Singapore

RTR-4 **FDA Rules for Human Cells, Tissues, and Cellular and Tissue-Based Products**
Karen J Edward (USA)
Advanced Cell & Gene Therapy, USA

RTR-5 **The Application of the Regulation 1394/2007/EC Regarding the Advanced Therapy Medicinal Products in Europe**
Giovanni Migliaccio (Itary)
Department of Cell Biology and Neuroscience, Istituto Superiore Di Sanitá, Italy

RTR-6 **The Regulation of Cell/tissue-based Medical Products in Japan**
Haruki Shirato (Japan)
Office of Biologics II, Pharmaceuticals and Medical Devices Agensy, Japan

17:45-18:45 **Evening Seminar 2**

Co-Sponsor : CHUGAI PHARMACEUTICAL Co., Ltd.

Chair: **Yoichi Takaue** *(Institute for Research, St. Luke's International Hospital, Japan)*

ES2-1 **Advances in Cellular Immunotherapy for Cancer: From T- Cells to NK Cells**
Richard W. Childs
Capt, U.S. Public Health Service Senior Investigator, Chief Section of Transplantation Immunotherapy Hematology Branch, National Heart, Lung and Blood Institute, National Institutes of Health, USA

Sheraton Grande Ocean Resort, Shosenkyu Green Gerden, 1F

19:00-21:30 **GALA Party**

October 20 (Wed.)

8:00- 9:00

Special Session 3
Immunotherapy

Co-Sponsor : IRX Therapeutics Inc.

Chair: **Haruo Sugiyama** *(Department of Functional Diagnostic Science, Osaka University Graduate School of Medicine, Japan)*

SS3-1 **Developments in Therapeutic Cancer Vaccine Desing**
James E Egan
IRX Therapeutics, Inc, USA

SS3-2 **NY-ESO-1-specific CD8 T-cell Response in NY-ESO-1 Seropositive Metastatic Melanoma Patients Treated with Ipilimumab Correlates with Clinical Benefit**
Jianda Yuan
Ludwig Center for Cancer Immunotherapy, Immunology Program, Memorial Sloan-Kettering Cancer Center, USA

9:00-10:00

Special Session 4
Gene Therapy

Co-Sponsor : KOHJIN BIO Co., Ltd.

Chair: **Keiya Ozawa** *(Division of Hamatology, Department of Medicine, Division of Genetic Therapeutics, Center for Molecular Medicine, Jichi Medical University, Japan)*

SS4-1 **Gene-modified Lymphocytes: Harnessing T Cells for Effective Cancer Treatment**
Hiroaki Ikeda
Department of Immuno-Gene Therapy, Mie University Graduate School of Medicine, Japan

SS4-2 **Immunotherapy Using Retrovirally Engineered T Cells Expressing Chimeric Antigen Receptors Specific to Glioma-Associated Antigens**
Atsushi Natsume
Department of Neurosurgery, Nagoya University School of Medicine, Japan

SS4-3 **Anti-MART1 CTL with a Memory Phenotype Ex Vivo Generated Using a Gene-engineered Artificial APC and IL-15 Can Persist in Melanoma Patients as Memory T cells upon Adoptive Transfer**
Naoto Hirano
Dana-Farber Cancer Institute, Harvard Medical School, USA

10:00-11:00

Special Session 5
FDA approved DC threrapy

Chair: **Akihiro Shimosaka** *(The Institute of Medical Science, The University of Tokyo, Scientific Research Advisor, Japan)*

SS5-1 **Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer**
Majid Tabesh
Dendreon Corporation, USA

11:00-

Closing Remark

Yoichi Takaue
Institute for Research, St. Luke's International Hospital, Japan

MIYAZAKI
2 0 1 0 JAPAN

The 1st ISCT Asia-Pacific Regional Meeting

Abstracts

Plenary Meeting

Kazuhiro Sakurada

Sony Computer Science Laboratories, Inc.

Educational history
Osaka University, School of Science (April 1982 - March 1986)
Osaka University, Graduate School of Science (April 1986 - March 1988)
Ph. D. in Physiology from Osaka University, (October 1993)
M.S. in Physiology from Osaka University, (March 1988)
B.S. in Biology from Osaka University, (March 1986)

Academic Research history
Visiting researcher at Kyoto University, Graduate School of Medicine (April 1991- August 1992)
Visiting scientist at Salk Institute (August 1997 - December 1998)

Job history
Kyowa Hakko Kogyo Co. Ltd. (April 1988 ~ September 2004)
- April 1988 - March 2000
  Researcher of Tokyo Research Laboratories
- April 2000 - September 2004
  Principle investigator of Laboratory of Regenerative Medicine, Tokyo Research Laboratories.
  Nihon Schering KK / Bayer Yakuhin Ltd. (October 2004 ~ December 2007)
- October 2004 - June 2007
  Operating officer of Nihon Schering KK
  Head of Nihon Schering Research Center
  Head of Schering AG Research Center Japan (Member of Corporate Research Management Team)
- July 2007 - December 2007
  Operating officer of Bayer Yakuhin
  Head of Bayer Yakuhin Kobe Research Center
  Head of Bayer Schering Pharma Global Drug Discovery Regenerative Medicine

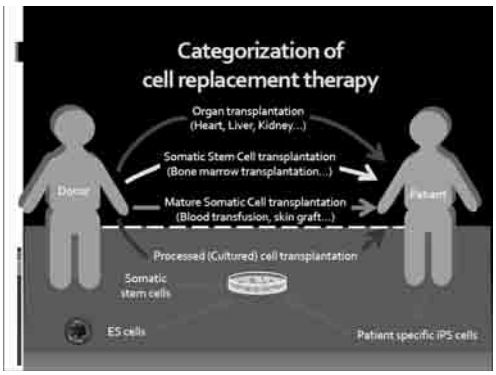
iZumi Bio Inc. (January 2008 ~ August 2008)
  Chief Scientific Officer
Sony Computer Science Laboratories Inc. (September 2008 ~ present)
  Senior Researcher

Functional Interpretation of Cellular Heterogeneity in Cell Therapy

Kazuhiro Sakurada

Sony Computer Science Laboratories, Inc.

By the progress of analyzing the behaviors of single cells, it has become clear that the phenotype of a population cannot represent the phenotype of any individual cell. Cellular heterogeneity in cell therapy products could be the cause of unexpected effects. However, population-average assays should be employed for quality control in cell therapy. Individual cells respond to environmental inputs depends on their gene expression profile. Cell-to-cell differences in gene expression may influence cellular processes to perturbations. To overcome this heterogeneity problem, it is necessary to develop analytical tools to detect the cellular heterogeneity noninvasively. In addition, it is essential to identify which cell-to-cell differences are causes of side effects and which can ignore.



In a series of studies to develop human iPS cell technology, we have identified that human iPS cells are significantly heterogeneous which is caused by leaving epigenetic memory of the tissue of origin. In addition, de novo epigenetic modifications during reprogramming process and in vitro expansion contribute to cellular heterogeneity of human iPS cells. These memories can be categorized into transcriptional, developmental epigenetics and environmental epigenetics. Although transcriptional and developmental epigenetic memories can be reprogrammed by optimization of methods, it is not simple to replace environmental epigenetics. The term “environmental epigenetic modifications” refers to alterations in phenotype triggered by environmental stimuli via epigenetic mechanisms. Epidemiologic and animal model studies show that a subset of such environmental epigenetic marks may affect susceptibility to chronic diseases. A growing body of evidence regarding the culture dependent DNA methylation of housekeeping genes, differentiation genes and behavioral genes indicate that the cellular heterogeneity is the general issue for in vitro culture based cell replacement therapy. I would like to discuss the future direction of human stem cell research for the application in the cell based medicine and the drug discovery based on functional interpretation of environmental epigenetics.

[Reference]

Sakurada, K. Environmental epigenetic modifications and reprogramming- recalcitrant genes. Stem Cell Res 4(3):157-164 2010.

Sakurada, K. et al. Regenerative medicine and stem cell based drug discovery. Angew Chem Int Ed Engl. 47(31):5718-38. 2008.

Masaki, H. et al. Heterogeneity of pluripotent marker gene expression in colonies generated in human iPS cell induction culture. Stem Cell Res. 1(2):105-15. 2008.

Regenerative Therapy I

Koichi Nakayama

Biomedical Engineering Course, Advanced Technology Fusion, Graduate School of Science and Engineering, Saga University, Japan

Professional Experience/Research Experience:

2006 - 2009 Assistant professor
Department of Orthopedic surgery, Kyushu University Hospital

2007 - 2010 Project Leader; Bio-Rapid prototyping project at Japan Science and Technology Agency (JST) Fukuoka

2009 - Current Professor and Chairman, Biomedical Engineering Course Advanced Technology Fusion Graduate School of Science and Engineering, Saga University, Saga City, Japan

EDUCATION

1997 M.D. Kyushu University
2005 Ph.D. Graduate School of Kyushu University.

RT I -1 Osteo-chondreal Regeneration by High Density Mesenchymal Stem Cell Scaffold Free Autologous Constructs

Koichi Nakayama

Biomedical Engineering Course, Advanced Technology Fusion, Graduate School of Science and Engineering, Saga University, Japan

From the era of Hippocrates, it has been well known that repair of damaged articular cartilage is extremely difficult. Surgical techniques such as micro facture, or drilling, could be able to relief injured patients' pain, yet they cannot regenerate normal hyaline cartilage, but fibrous cartilage that is not strong enough as normal hyaline cartilage. After a report about autologous chondrocyte implantation (ACI) in 1994, many new methods and attempts for cartilage regeneration were developed by various researchers, orthopedic surgeons, and companies. At present, more than ten thousands of patients underwent cell transplantation for cartilage repair mostly in US and EU. Most of them showed relatively satisfied clinical results in pain relief and function of the joints. There are several problems, however, still unsolved. One of the issues is the limited indication for these treatments. Most of clinically available treatments for cartilage regenerations are limited to patients those who have only cartilage lesion, and patients who have osteochondral lesion are excluded. Simultaneous osteochondral regeneration is reported to be difficult, due to over-growth of regenerated subchondral bone and subsequent deterioration of the regenerated cartilage. Therefore, number of the patients who receive benefit from these therapies would be relatively small. Another concern is the carrier vehicle to deliver cell into the injured site.

We've been working for the development of scaffold free cell delivery system, named HD MACs (High Density Mesenchymal stem cell scaffold free Autologus ConstructS)

In our presentation, I will introduce our latest data about scaffold free mesenchymal stem cell (MSC) delivery system for osteochondral regeneration. With our system, we achieved excellent hyalin cartilage and subchondral bone regeneration more than 4 years transplantation in rabbit knees. We expect we can perform safer osteochondral regeneration simultaneously by using patient's own MSC without use of any biomaterials. This system is preparing clinical trial in Kyushu university hospital.

Regenerative Therapy I

Wei Liu

Department of Plastic and Reconstructive Surgery, Shanghai 9th People's Hospital, Shanghai Second Medical University, Shanghai Tissue Engineering Center, China

Wei LIU, MD, PhD. Dr. Liu graduated from Shanghai Second Medical University in 1983 with a MD degree and graduated from University of Arkansas for Medical Science in 1998 with a PhD degree followed by two year postdoctoral training at Institute of Reconstructive Plastic Surgery of New York University. He has been a plastic surgeon since 1983 and now is a full time researcher after his return to China in 2000. Currently, Dr. Liu is a Professor of Plastic Surgery of Shanghai Jiao Tong University School of Medicine, and Associate Directors of Shanghai Tissue Engineering Center and Shanghai Institute of Plastic and Reconstructive Surgery, Chief Scientific Officer of National Tissue Engineering Center of China. Dr. Liu is the principle investigator of four national key projects of tissue engineering research sponsored by Chinese Ministry of Science and Technology. Besides more than 50 original articles published in international journals, he has contributed several invited review articles in Tissue Engineering, Biomaterials and Current Gene Therapy, etc. He currently is the editorial board member of Journal of Tissue Engineering and Regenerative Medicine and Biomaterials, Special Issue Editor of Tissue Engineering. Dr. Liu also serves as a peer reviewer for several international journals of Tissue Engineering, Biomaterial and Lancet, etc, and has presented more than 20 invited speeches at various international conferences. Dr. Liu is the organizer of 8th TESI annul meeting and was elected as the Council Member of Tissue Engineering and Regenerative Medicine International Society (TERMIS) Asia-Pacific Chapter. Dr. Liu currently is Asian Liaison of American Plastic Surgery Research Council, Diplomat of European Plastic Surgery Research Council, Chinese delegate of International Union of Societies for Biomaterials Science and Engineering (IUS-BSE).

RT I -2 Engineering of Various Tissues in Large Animals and Their Potential for Clinical Applications

Wei Liu, Yilin Cao

Department of Plastic and Reconstructive Surgery, Shanghai 9th People's Hospital, Shanghai Second Medical University, Shanghai Tissue Engineering Center, China

Tissue engineering is the specialty that applies the techniques of biology and engineering to the generation of new tissues. During the past 15 years, tissue engineering research has advanced so rapidly that generation of human tissue for tissue repair has become a reality.

In our tissue engineering center, most works performed in recent years focused on the construction of different types of tissues in large animal models for tissue repair. These works include tissue engineered bone to repair sheep cranial bone defect and to repair sheep femoral bone defect with successful results. Using isolated autologous chondrocytes, articular cartilage defect was successfully repaired with tissue-engineered hyaline cartilage in a porcine model. Besides, we have also generated tissue-engineered meniscus and successfully repaired the meniscus defects in a porcine model. Tendon construction is another area. Following successful engineering of tendon tissue in a hen model using isolated tenocytes, we now are able to engineer tendon using isolated dermal fibroblasts in a porcine model. In other areas, bilayer living skin has been engineered both in vitro and in vivo; nearly transparent corneal epithelium and stroma were also created; tissue-engineered nerve graft was used to bridge nerve gap and to promote nerve regeneration.

Recently, engineered bone tissue was applied to clinical trial with success. In 20 cases of cranial-maxillofacial bone defects, autologous bone marrow stem cells were isolated and induced to become osteogenic cells. These cells were seeded on demineralized bone graft to form a cell-scaffold construct and was implanted to repair various bone defects. CT scanning demonstrated that bone tissue was developed in patient at 3 months and maintained stable when followed up 1-2 years post-operation. More importantly, the engineered human bone was verified by tissue histology, which provides the direct evidence of engineered bone formation in human being. Our experience in tissue construction and clinical application indicates that tissue engineering has huge potential for tissue repair and tissue regeneration.

Regenerative Therapy I

Masayuki Yamato

Institute for Advanced Biomedical Engineering and Science, Tokyo Women's Medical University

Academic Carrier:

March 1989 B.S., Biochemistry and Cell biology, Department of Arts and Sciences, University of Tokyo
March 1991 M.Sc., Biochemistry and Cell biology, Graduate School of Arts and Sciences, University of Tokyo
March 1994 Ph.D., Biochemistry and Cell biology, Graduate School of Arts and Sciences, University of Tokyo

Carrier:

1994-1997 Research Assistant Professor, Department of Biochemistry, College of Pharmacy, Nihon University
1997-1998 Postdoctoral Fellow of JSPS, Institute of Biomedical Engineering, Tokyo Women's Medical University
1999-2001 Research Assistant Professor, Institute of Biomedical Engineering, Tokyo Women's Medical University
2001-2003 Assistant Professor, Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University
2003-2008 Associate Professor, Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University
2008-Present Professor, Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University

Research Interests:
Tissue Engineering
Stem Cell Biology
Regenerative Medicine

Awards:

1998 The Award for Original Investigation, Japanese Society for Artificial Organs
2000 The Award for Outstanding Paper, Japanese Society for Artificial Organs
2002 The Award for Young Researcher, Japanese Society for Biomaterials
2003 Young Investigator Award, Society for Biomaterials
2003 Good Design Award
2009 Yamazaki Teiichi Award
2009 The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology

Societies:
Japanese Society for Biomaterials
Japanese Society for Regenerative Medicine (board member)
Society for Biomaterials
TERMIS (Tissue Engineering and Regenerative Medicine International Society)

RT I -3 Current Status of Clinical Applications of Corneal Regenerative Medicine with Cell Sheet Engineering

Masayuki Yamato

Institute for Advanced Biomedical Engineering and Science, Tokyo Women's Medical University

Ocular trauma or disease may lead to severe corneal opacification and, consequently, severe loss of vision as a result of complete loss of corneal epithelial stem cells. Transplantation of autologous corneal stem-cell sources is an alternative to allograft transplantation and does not require immunosuppression, but it is not possible in many cases in which bilateral disease produces total corneal stem-cell deficiency in both eyes.

We studied the use of autologous oral mucosal epithelial cells as a source of cells for the reconstruction of the corneal surface. We harvested 3-by-3-mm specimens of patients' own oral mucosal tissue from with bilateral total corneal stem-cell deficiencies.

Tissue-engineered epithelial-cell sheets were fabricated ex vivo by culturing harvested cells for two weeks on temperature-responsive cell-culture surfaces with 3T3 feeder cells or autologous adipose-derived mesenchymal stem cells that had been treated with mitomycin C.

After conjunctival fibrovascular tissue had been surgically removed from the ocular surface, sheets of cultured autologous cells that had been harvested with a simple reduced-temperature treatment were transplanted directly to the denuded corneal surfaces without sutures.

Complete re-epithelialization of the corneal surfaces occurred.

Here, I will show the current status of clinical research and clinical trial performed in Europe.

Regenerative Therapy II

Takayuki Asahara

Department of Regenerative Medicine Science, Tokai University School of Medicine, Regenerative Medicine and Research, Kobe Institute of Biomedical Research and Innovation/ RIKEN Center of Developmental Biology, Japan

Education :

1984 M.D. Tokyo Medical College, Tokyo, Japan

Postdoctoral Training :

1984-1986 Resident in Medicine, Japan Red Cross Hospital, Tokyo, Japan
1986-1988 Resident in Cardiology, Tokyo Medical College Hospital, Tokyo, Japan
1988-1989 Resident in Emergency Unit, Tokyo Medical College Hospital, Tokyo, Japan
1989-1993 Clinical and Research Fellow in Cardiology, Tokyo Medical College Hospital, Tokyo, Japan

Academic Appointment :

1989-1993 Clinical and Research Fellow in Cardiology, Tokyo Medical College Hospital, Tokyo, Japan
1993-1995 Research Fellow in Cardiovascular Research, St. Elizabeth's Hospital, Boston, MA
1995-2003 Assistant Professor of Medicine, Tufts Medical School of Medicine, MA
2000-2002 Associate Professor, Institute of Medical Sciences, Tokai University School of Medicine, Kanagawa Japan
2002- Professor of Department of Regenerative Medicine, Tokai University School of Medicine, Kanagawa Japan
2003-2005 Director of Regenerative Medicine and Research, Institute of Biomedical Research and Innovation Kobe
2003- Team Leader of RIKEN Kobe Institute Center for Developmental Biology
2005- Deputy Research Director of Institute of Biomedical Research and Innovation Kobe
2005- Group Leader of Vascular Regeneration Research Group, Institute of Biomedical Research and Innovation Kobe

RT II-1 Endothelial Progenitor Cells for Vascular Regeneration

Takayuki Asahara

Department of Regenerative Medicine Science, Tokai University School of Medicine, Regenerative Medicine and Research, Kobe Institute of Biomedical Research and Innovation/ RIKEN Center of Developmental Biology, Japan

Recently the regenerative potential of stem cells has been under intense investigation. In vitro, stem and progenitor cells possess the capability of self-renewal and differentiation into organ-specific cell types. In vivo, transplantation of these cells may reconstitute organ systems, as shown in animal models of diseases. In contrast, differentiated cells do not exhibit such characteristics. Human endothelial progenitor cells (EPCs) have been isolated from the peripheral blood of adult individuals, expanded in-vitro and committed into an endothelial lineage in culture. The transplantation of these human EPCs has been shown to facilitate successful salvage of limb vasculature and perfusion in athymic nude mice with severe hindlimb ischemia, while differentiated endothelial cells (human microvascular endothelial cells) failed to accomplish limb-saving neovascularization .

These experimental findings call into question certain fundamental concepts regarding blood vessel growth and development in adult organisms. Postnatal neovascularization has been previously considered synonymous with proliferation and migration of pre-existing, fully differentiated ECs resident within parent vessels, i.e. angiogenesis. The finding that circulating EPCs may home to sites of neovascularization and differentiate into ECs in situ is consistent with "vasculogenesis", a critical paradigm for establishment of the primordial vascular network in the embryo. While the proportional contributions of angiogenesis and vasculogenesis to postnatal neovascularization remain to be clarified, our findings together with the recent reports from other investigators suggest that growth and development of new blood vessels in the adult is not restricted to angiogenesis but encompasses both embryonic mechanisms.

Furthermore, recent studies indicate optional role of EPCs for organ regeneration, including anti-inflammatory and anti-fibrotic effects for the preparation of organ regenerations. I will discuss this issue in the symposium.

Regenerative Therapy II

Hyo-Soo Kim

Professor, Department of Internal Medicine, Seoul National University College of Medicine, Korea

Mar. 1978-Feb. 1984	Seoul National University College of Medicine (M.D.)
Apr. 2006 - present	Professor, Director of National Research Laboratory for Cardiovascular Stem Cell, Seoul National University.

RESEARCH INTERESTS
[1] stem cell biology
[2] gene therapy ; prevention of restenosis by gene therapy using in vivo vascular injury model

RT II-2 Cytokine-based Cell Therapy for Patients with Myocardial Infarction (MAGIC-CELL program) ; Past, Present & Future

Hyo-Soo Kim

Department of Internal Medicine, Seoul National University College of Medicine, Korea

[PAST]

Bone marrow stem cell transplantation has been shown to improve cardiac function in patients with myocardial infarction. But, cytokine-based stem cell therapy for patients with myocardial infarction would be a good alternative option than bone marrow stem cell therapy, because of its noninvasiveness and comparable efficacy. Since 2002, we carried out MAGIC-CELL randomized clinical trial where we tested the efficacy of intracoronary infusion of peripheral blood stem cells (PBSCs) mobilized with Granulocytes-Colony Stimulating Factor (G-CSF) to improve left ventricular function. After a series of RCT from MAGIC CELL-1 to -4, we observed this cytokine-based cell therapy showed mild but definite efficacy to improve LVEF by 5% in patients with AMI although not with OMI. In order to improve the efficacy, we started MAGIC CELL-5-Combicytokine trial where G-CSF and erythropoietin are used since early 2007.

[PRESENT]

G-CSF and erythropoietin are two cytokines that have been demonstrated to improve cardiac function and perfusion in myocardial infarction. G-CSF was initially evaluated as a stem cell mobilizer and EPO as a cytoprotective agent. However both cytokines have direct cytoprotective effects and stem cell mobilizing ability. Direct cytoprotective effects of both cytokines are commonly mediated by Jak-STAT pathway. In preclinical study, G-CSF and erythropoietin improved cardiac function and perfusion by angiomyogenesis and protection of cardiomyocytes in myocardial infarction. However, results from recent clinical trials did not support beneficial effects of cytokine therapy with G-CSF or erythropoietin alone in patients with myocardial infarction. In MAGIC CELL-5-Combicytokine trial employing novel strategies, combicytokine (G-CSF + darbepoetin) is more effective than G-CSF alone in mobilization of PBSCs with angiogenic potentials. Infusion of the mobilized peripheral blood stem cells by G-CSF with/without darbepoetin is effective for reducing infarct size and restoring regional wall motions in patients with acute myocardial infarction. And combicytokine treatment shows potentials to further improve efficacy of PBSC therapy with G-CSF, especially in poor risk patients.

[FUTURE]

As a future strategy, we searched for protein or chemical to enhance the therapeutic efficacy of the mobilized peripheral stem cells by G-CSF with or without erythropoietin. With these new priming agents for PBSC, we prepare to launch MAGIC-CELL-6-PRIMING trial in the near future.

Regenerative Therapy II

Yoshiki Sawa

Department of Cardiovascular Surgery, Osaka University Graduate School of Medicine Japan

Education:	
1980	Graduated from Osaka University Medical School, gained MD
Job history:	
1981~1985	Internship in general, thoracic and cardiovascular surgery
1987	Gained PhD
1989~1991	Research and clinical fellow at Max-Planck Institute in Germany supported by Humboldt Scholarship
1992	Assistant Professor, Department of Cardiovascular Surgery, Osaka University Medical School
1998	Associate Professor, Department of Cardiovascular Surgery, Osaka University Medical School
2002	Associate Professor, Medical Center for Translational Research in Osaka University Graduate School of Medicine
2004	Chief surgeon, Department of Cardiovascular Surgery
2006	Professor and Chief, Department of Cardiovascular Surgery Director, Medical Center for Translational Research in Osaka University Hospital
2008	Director, Heart center in Osaka University Hospital
2009	Visiting Professor, Graduate School of Medicine Kyoto University
2010	Director, The Center for Advanced Medical Engineering And Informatics Osaka University

RT II-3

Yoshiki Sawa

Department of Cardiovascular Surgery, Osaka University Graduate School of Medicine, Japan

Human cardiac regeneration therapy has been performed by using various sources of stem cell. Myoblasts and bone marrow cells have been injected for patients with ischemic cardiomyopathy in our clinical trial and improved cardiac performance. We had examined the efficacy of stem cell therapy using tissue engineered sheet technique compared to needle injection. This technique has advantages such as the ability for treatment to large area, and less invasive for host heart such as lethal arrhythmia. In vivo, implantation of autologous myoblast sheet had improved cardiac function of ischemic or dilated cardiomyopathy models using rat, hamster, canine and porcine models. We also showed that myoblast sheets provided various factors inducing angiogenesis, hematopoietic cell recruitment and anti-apoptosis, following anti-remodeling. Thus, after approved by IRB of our institution, we have started the clinical trial of myoblast sheet implantation for DCM patients, and assessed the feasibility and efficacy for the first patient. In this patient, any sequelae including arrhythmia have not occurred after implantation, and the cardiac function showed recovery.

Furthermore, we have investigated several improvement of this technology for the layered implantation for ischemic heart, for right heart failure, and another cell source to construct the sheet.

Thus, stem cell sheet implantation could be safe and eligible as cardiac regeneration therapy.

Regenerative Therapy III

Hideki Iwaguro

Clinical Development & Research Planning, Cytori Therapeutics Inc., Japan

Education:

March/2003 Ph.D. Tokai University School of Medicine (Kanagawa, Japan)
April/1994 M.D. Graduated Kyorin University School of Medicine (Tokyo, Japan)

Career:

April/2009 - present
Director (Clinical Development & Research Planning)
May/2007 - March/2009
Associate Director (Clinical Development & Research Planning)
April/2003 - April/2007
Instructor (Dept. of Regenerative Medicine, Tokai University School of Medicine)
2000 - 3/2003
Research Fellow (Dept. of Physiology, Tokai University School of Medicine)
1998 - 2000
Research Fellow (Dept. of Vascular Medicine, Tufts University School of Medicine
St. Elizabeth's Medical Center, Boston, USA)
1994 - 1998
Clinical Fellow (Dept. of Cardiology, Kyorin University School of Medicine)
1994 - 1995
Research Assistant (Dept. of Vascular Medicine, Tufts University School of Medicine)

RTIII-1 Adipose-derived Regenerative Cells - Bench to Bedside -

Hideki Iwaguro

Clinical Development & Research Planning, Cytori Therapeutics Inc., Japan

Regenerative medicine, in which lost tissue or organ are regenerated or functionality are restored to damaged tissue that have fallen into functional failure is the most promising field in the 21st century new medicine, and significant development is expected in the near future.

What has been of particular note recently in the field of regenerative medicine are stem cells, which not only have self renewal capacity, but also pluripotency into fat, bone marrow and muscle, and so on. It has been recently demonstrated that there are many stem cells in the adipose tissues, and stem cells have claimed the limelight as the key to tissue regeneration.

Currently, adipose tissue has received great attention as a source of MSCs for cell therapy compared to bone marrow, peripheral blood, cord blood, and the others.

There is an approximate 1300 fold increase in adherent stem cells from adipose tissue compared with bone marrow of approximate equal donor site morbidity.

We have focused their potential and introduced some clinical applications using adipose-derived regenerative cells.

Regenerative Therapy III

Koji Eto

Stem Cell Bank Section, Center for Stem Cell Biology and Regenerative Medicine, The Institute of Medical Science, The University of Tokyo, Japan

1990	Yamanashi Medical School (Currently, University of Yamanashi School of Medicine), Yamanashi, Japan
04/96-05/99	Staff, Cardiologist and Clinical Assistant Professor, Coronary Care Unit, Cardiology Section, Department of Medicine, Teikyo University Hospital, Tokyo, Japan
06/99-12/00	Research Associate, Dept. of Vascular Biology The Scripps Research Institute, La Jolla, CA, U.S.A.
01/01-11/03	Senior Research Associate, Staff Scientist, Dept. of Cell Biology The Scripps Research Institute, La Jolla, CA, U.S.A.
12/03-12/08	Assistant Professor, Laboratory of Stem Cell Therapy The Institute of Medical Science, The University of Tokyo, Tokyo, Japan
01/09-present	Associate Professor, Stem Cell Bank, Center for Stem Cell Biology and Regenerative Medicine, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

Dr. Koji Eto, formerly specialized in cardiovascular medicine (arrhythmia-related potassium channel function, platelet-based atherothrombosis).
He studied platelet biology and integrin signaling at the Scripps Research Institute (supervisor; Dr. Sandy Shattil, M.D.) and started the project to use murine embryonic stem (ES) cells for validating integrin signaling and platelet biology. Since he joined Dr. Hiro Nakauchi's lab at the University of Tokyo, he has been developed in vitro culture system for generating blood cells from human ES cells and iPS cells.

RTIII-2 Human Induced Pluripotent Stem Cell-derived Blood Cells toward Clinical Application

Koji Eto

Stem Cell Bank Section, Center for Stem Cell Biology and Regenerative Medicine, The Institute of Medical Science, The University of Tokyo, Japan

The achievement of "regenerative medicine" needs the global and sophisticated system for translation from the basic science to clinical application. We aim to develop the novel blood transfusion, and gene- and cellular-therapy using human induced pluripotent stem (iPS) cells. We have so far developed the static culture system whereby human iPS cells can be differentiated into the Sac-like structures that concentrate $CD34^+$ hematopoietic progenitors, further generating platelets, erythrocytes, or T lymphocytes in vitro. Our research program eventually aims at the development of safe and stable blood supply for transfusion independently of blood donation or of immune therapy using human iPS cells with an appropriate validation.

In addition, we keep addressing an issue regarding standardization of iPS cells, for example, what clones can be selected as the appropriate hallmarks for efficiency on differentiation potential and/or safety at levels compatible with clinical applications. We propose the future plan based upon iPS cell-derived blood cells toward clinical application.

Regenerative Therapy III

Yock Young Dan

Dept of Medicine, Yong Loo Lin School of Medicine, National University Health System, Singapore / National University of Singapore,Singapore

Current Position
Asst Professor, Department of Medicine Yong Loo Lin School of Medicine National University of Singapore

Consultant, Department of Gastroenterology and Hepatology National University Hospital

Awards

2006-2008	NUS Leadership in Academic Medicine Award
2007	NUH STAR Award
2007	Excellent Service Awards (Silver)
2008	
2009	
2009	
2009	Asia Pacific Association Study of Liver Disease. Best Poster Award
	NHG ASC Best Doctor Award (Gold)
	NHG ASC Best Oral (Health Outcomes and Research)
	Excellent Service Awards (Silver)
	NMRC Clinician Scientist Award

RTIII-3 Long Term Repopulation Potential of Liver Progenitor Cells

Yock Young Dan

Dept of Medicine, Yong Loo Lin School of Medicine, National University Health System, Singapore / National University of Singapore, Singapore

Therapeutic application of hepatocyte transplantation in patients with liver insufficiency is currently limited by the ability to obtain sufficient quantity of high quality hepatocytes and the ability of these cells to engraft and function in injured liver. While much promising progress has been made in transplantation of rat fetal liver cell into the same species, most of the successful models of human cell transplantation have been in models which exert extremely high selection pressures such as the FAH mice or uPA mice. These extreme selection pressures models do not quite reflect real life human liver diseases and thus the key strategy hasbeen to transplant stem progenitor cells that have intrinsically high proliferative potential and may expand to sufficient numbers to be of clinical benefit. Understanding the long term proliferative potential and the safety profile of these cells is critical to their eventual therapeutic use.

We report our follow through of long term transplantation of human fetal liver progenitor cells to gain an in depth understanding of their engraftment and expansion kinetics.

Human fetal liver progenitor cells are unadulterated progenitor cells derived from second trimester human fetal liver and are EPCAM and CD44+. Up to 4 million cells, enriched and expanded in vitro up to 3 months were transplanted into Rag -/- γc mice pretreated with retrorsine and exposed to 3 weeks of intraperitoneal carbon tetrachloride. Mice were sacrificed at 1, 3, 6 and 9 months after transplantation.

Quantitation studies showed that intrasplenic injection of these cells resulted in significant cell trapping in the spleen and portal tributaries of the recipient liver with minimal engraftment within the liver parenchyma up to 2 weeks post-transplant. By 1 month, clusters of cells can be seen engrafting around the portal tracts and demonstrate proliferative activity within the clusters. Even then, the engraftment rate was less than 1% (0.7%). Repopulation of human progenitor cells increased o 2.6% at 3 months but dwindled to 0.8% and 0.2% at 6 and 9 month respectively. This correlated directly with the human albumin mRNA as well as albumin concentration which showed a peak at 3 months and decreased with time. Immunofluorescence and in-situ hybridization confirmed the human lineage of hepatocytes and isolated bile duct cells integrated within the liver parenchyma. These cells are functional, demonstrating tight junction integration with mouse hepatocytes and show no evidence of fusion. Repopulation was patchy but clear correlation was seen where animals with persistently higher fibrosis of the liver demonstrated higher numbers of human cell clusters. qRTPCR of FGF mRNA showed direct correlation between the levels of FGF and persistence of human progenitor cells suggesting stimulatory effect of FGF on these cells. Animals that showed persistent cirrhosis had large macroscopic nodules of functional human cells at 9 months simulating nodular regeneration. No evidence of malignant transformation were seen using chromosome painting for aneuploidy but in the livers of animals with most severe fibrosis at 9 months and highest mRNA for FGF, metaplastic human cell-derived bone spicules and bone marrow cells were seen.

Human hepatocytes derived from fetal livers are able to survive, engraft, integrate as well as function in permissive mouse liver up to 9 months post transplant providing principle of proof of potential long term therapeutic benefit. Proliferation of these cells appears to be driven by pro-fibrotic stimulus in the liver and diminish when liver fibrosis is reversed. In environment of prolonged high growth stimulus, the presence of metaplastic tissues raise concerns on their long term safety potential.

Special Session 1

Taira Maekawa

Kyoto University Hospital, Japan

2003-present	Professor of Medicine and Chairman, Department of Transfusion Medicine and Cell Therapy; Director, Center for Cell and Molecular Therapy, Kyoto University Hospital
2002-2003	Professor of Medicine and Chairman, Department of Transfusion Medicine, Kyoto University Hospital
1997-2001	Associate Professor, Department of Transfusion Medicine The Institute of Medical Science, The University of Tokyo, Tokyo, Japan
1990-1996	Assistant Professor, Department of Hygiene, Kyoto Prefectural University of Medicine, Kyoto, Japan
1988-1990	Research Fellow, Cancer Research Unit, The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia
1986-1988	Assistant Director, Department of Clinical Hematology, Kyoto First Red Cross Hospital, Kyoto, Japan
1982-1986	Senior resident, Department of Internal Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan
1978-1982	Intern, Department of Internal Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan
1978	Graduate from Kyoto Prefectural University of Medicine

Membership of Academic Societies:

- American Society of Hematology
- International Society for Experimental Hematology
- International Society for Cellular Therapy
- Japanese Association of Internal Medicine
- Japanese Society of Hematology
- Japanese Society of Gastroenterology
- Japanese Society of Clinical Hematology
- Japanese Society of Transfusion Medicine
- Japanese Association for Cancer Research
- Japanese Association for Cancer Therapy
- Japanese Society of Gene Therapy
- Japanese Society of Stem Cell Transplantation
- Japanese Society of Antisense RNA/DNA Technology
- Japanese Association for Molecular Target Therapy of Cancer

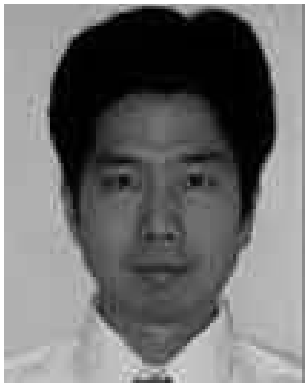
SS1-1 Introduction

Taira Maekawa

Kyoto University Hospital, Japan

Translational research requires high scientific and ethical standards throughout the manufacturing of clinical trial material according to ICH-GCP guidelines. Advanced cell therapy development such as cell transplantation, adoptive immunotherapy, gene therapy and regenerative therapy mandate cGMP (current good manufacturing practices) grade cell processing to assure the safety and quality of manipulated cell products. Successful clinical cell therapy requires regulatory safety and efficacy standards similar to those established for pharmaceutical therapeutics. Cell processing for advanced cell therapy using human tissues, is, however, quite different from the production of conventional pharmaceutical drugs. Manufacturers should be keenly aware that poor cGMP conditions at a manufacturing facility can ultimately pose life-threatening health risks to patients. Therefore, one of the first steps in cGMP conversion from the bench to the clinic is the design of a facility for the preparation of clinical material for use in human trials. To establish and operate an effective cell processing facility, close collaborations with medical doctors and researchers, technicians, pharmacists, engineers, GMP consultants, and government officers are mandatory. Since participants come from different scientific, medical, technological, and political backgrounds, each must try to understand the other's point of view and work with the same purpose of producing novel cell and gene therapies for many patients with incurable diseases. Advanced cell and gene therapies cannot be developed without effective and well thought-out cell processing. Advanced and sophisticated cell-processing system will realize the safe and the cost-effective production of cellular products and in turn bring the successful results in cell therapy. In this special session, these advances of cell processing facility will be discussed.

Special Session 1



Seiichi Yusa

tella, Inc. / SANYO Electric Co., Ltd., Japan

1996-1998	PhD student, Basel Institute for Immunology, Switzerland
1996-1999	PhD student, Department of Animal Resource Sciences, The University of Tokyo, Japan
1999-2003	Postdoctoral Fellow, Division of Basic Science, Fox Chase Cancer Center, USA
2003-2007	Senior Scientist, Institute of Neuropathology, University Hospital Zurich, Switzerland
2007-2008	Lecturer, Division of Molecular Biomedicine for Pathogenesis, Center for Disease Biology and Integrative Medicine (CDBIM), Faculty of Medicine, The University of Tokyo, Japan
2008-2010	the general manager, Department of Research & Development, tella Inc (JASDAQ2191), Japan
2010-present	Visiting Professor, Changshu Institute of Technology (National University), China

Academic Societies:

Japanese Society for Immunology
Japanese Cancer Association
Japan Society for Biological Therapy
Japan Association of Cancer Immunology

Research Publications:

PLoS One (2010) 5: e9107
Vet. Immuno. Immunopathol. (2009) 132: 85
J. Immunology (2004) 172: 899
J. Immunology (2003) 172: 7385
Int. J. Hematology (2003) 77: 463
J. Immunology (2003) 171: 3415
Biochem. Biophys. Res. Commun. (2003) 307: 810
J. Immunology (2003) 170: 4539
J. Immunology (2002)168: 5047
J. Biol. Chem. (2001) 276: 22910
etc.

SS1-2 Practices of Cell Processing Isolator System in Cell Therapy

Seiichi Yusa

tella, Inc. / SANYO Electric Co., Ltd., Japan

In order to implement regenerative medicine or cell therapy, the strict aseptic control is required, thus GMP-compliance Cell Processing Center (CPC) needs to be established to provide the required aseptic control. Currently, a number of facilities and institutes have introduced CPCs to perform clinical studies and cell therapy.

SANYO Electric Co.,Ltd, in addition to conventional CPCs, launched Cell Processing Isolator System (Isolator) in 2008 and approximate 50 units were sold so far. One of our customers, Tella Co.,Ltd. has partnered with 17 medical facilities and institutions in Japan to provide innovative immuno-cell therapy to patients, and established 12 facilities that are equipped with SANYO Isolators and as many as 19 units have been installed in total. Additionally, they operate 2 facilities with SANYO CPCs and 2 more facilities with other CPCs.

In 5 years since 2005, approx. 2700 culture practices of dendritic cell therapy (DC therapy), and approx. 7300 culture practices of lymphokine-activated killer therapy (LAK therapy) have been performed in Tella. In comparison of processed practices by facility types, for DC therapy, approx. 1300 cultures in Isolator-equipped facilities and approx. 1400 cultures in CPC facilities. For LAK therapy, approx. 2700 cultures in Isolator-equipped facilities and approx. 4600 cultures in CPC facilities (as of June 2010).

Between CPC and Isolator, there is a big difference in the changeover procedure that affects on productivity which is the CPC's biggest challenge. For Isolator, it is possible to apply the validated hydrogen peroxide decontamination process on each practice basis that allows the handling of different kind of cells continuously. Meanwhile for CPC, the microbiological evaluation needs to be done after every cleaning and decontamination process using chemicals and it takes as long as 2 weeks for culture period to get the test result. Clinical practice that needs to process many cells from many patients has difficulties to perform this evaluation to handle next cells. Isolator can establish high-quality aseptic condition with its closed glove-box design, however, the another challenge attributed to this feature exists, which is the not-so-great workability due to glove work. When using Isolator, the operator has to place his/her hands into the fixed bulky gloves that are much thicker than latex gloves usually used in lab and to perform the culture operation smoothly may require a little efforts and some getting used to.

On this problem, by selecting optimum culture devices, improving its training plan and providing the instruction to carry out the training thoroughly, we have achieved the working efficiency comparable to that of operation time in CPC.

In addition to our expertise and experiences with Isolator, with other information including cost comparison and practical applications, we will give you a report on users and applications of Cell Processing Isolator.

Special Session 1

Shizu Takeda

Hitachi, Ltd., Japan

SS1-3 Hitachi Group's Approach to Regenerative Medicine

Shizu Takeda

Hitachi, Ltd., Japan

Special Session 1

Takafumi Kimura

Kyoto University, Japan

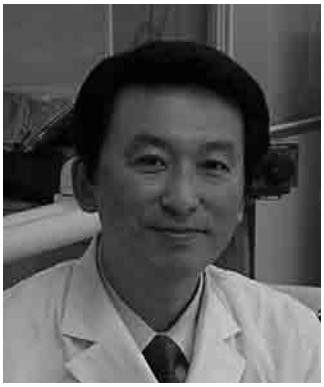
1988	Graduated from Nara Medical University
1988-1989	Resident, Osaka University Hospital (Internal Medicine III)
1989-1990	Department of Internal Medicine, Hannan Chuo Hospital
1990-1993	Department of Internal Medicine, Aizenbashi Hospital
1993-1995	Researcher, Osaka University Hospital (Internal Medicine III)
1995-2000	Assistant, Kyoto Prefectural University of Medicine (Hygieiology)
2000-2001	Research Worker Abroad supported by MEXT, Eberhard Karls University of Tuebingen (Hematology)
2001-2006	Assistant, Kyoto Prefectural University of Medicine (Hygieiology)
2006-2007	Lecturer, Kansai Medical University (Hygieiology)
2007-2008	Section Head, Research Department, Japanese Red Cross Osaka Blood Center
2008-2010	Deputy Director of the Research Department, Japanese Red Cross Osaka Blood Center
2010-	Professor, Center for iPS Cell Therapy, Kyoto University

SS1-4 The Introduction of the Advanced Facility for iPS Cell Therapy (FIT)

Takafumi Kimura

Kyoto University, Japan

Special Session 2



Eiji Kobayashi

Centers for Development of Advanced Medical Technology, Jichi Medical University, Japan,

Dr. Eiji Kobayashi has been working in Translational Research Center during recent 10 years as both Professor positions of Center for Molecular Medicine and Department of Surgery, Jichi Medical University (JMU). He has continuously been a supervisor of more than 140 cases of living-related liver transplantation in the university hospital and made more than 500 research papers. He is also a chief scientific adviser of Otsuka Pharmaceutical Factory, Inc.

Recent advancement of medical sciences and development of high level techniques are far beyond the reach of one surgeon to carry out a challenging innovative therapy. Then, he proposes that the specialists on translational research (TR) play important roles for the clinical application of novel therapeutic strategies developed through experiments in basis sciences. TR is situated at the forefront of real and relevant improvement in the management of some diseases. Surgical innovations or new operative techniques must be investigated and elaborated at a TR center. A new concept of TR on innovative medical treatment includes lots of techniques and knowledge in various fields of science. Practical researchers are required to have high-level surgical skills and knowledge in physiology, immunology, pharmacology, molecular biology, tissue engineering and ethics, and they must be assigned in clinical settings to continuously improve treatments for patients suffering from severe illnesses.

From 2003, he has been a Director of Center for Experimental Medicine, Jichi Medical University and conducted all living animal experiments in this university. He started two big projects of production of transgenic (Tg) rats and biomedical pigs for translational research. For instance of the former project, stem cells isolated from the tg rat and introduced into the disease models at a specific age of development can generate newly-formed. Then, he opened up a new field of bio-imaging study using these colorful variations of Tg rats. They have a great potential utility for cell trafficking after organ transplantation and cell transplantation. Tissue organogenesis and trans-differentiation of stem cells are also targets for the study. The Rat Resource and Research Center (RRRC; www.nrrrc.missouri.edu) in USA and National Bio-Resorce Project for the Rat (NBRP-Rat;nbprat@anim.med.kyoto-u.ac.jp) in Japan are co-working to provide our Tg rats as an academic research tool.

Then, he scaled up pre-clinical approach using a total pig system for human health and disease and built a medical pig center named as Center for Development of Medical Technology (CDAMTec) in 2008. In this center, medical students and residency have used pigs for education of surgical skills and training of emergency treatment. Clinicians also used for development of innovative tool in endo- or laparo- scopical treatment. He succeed in developing clone pigs and focused on an "in vivo bioreactor", where human stem cells can transdifferentiate in their organogenesis.

SS2-1 Regenerative Medical Research Using Bioimaging Rat and Pig

Eiji Kobayashi

Centers for Development of Advanced Medical Technology, Jichi Medical University, Japan

Regenerative medicine is situated in the forefront of translational research. A new concept on innovative medical treatment includes lots of techniques and knowledge in various fields of science. Translational research is also required to efficient experimental animal models that are indispensable for development of innovative medical treatments. For clinical application, the systemic *in vivo* experiment has been required for both scientific and ethical points of view. New technology of *in vivo* imaging is not only scientific but also animal welfare. We have been developing a powerful experimental system from rat to pig using *in vivo* bioimaging. Herein, I will introduce our regenerative medical research using bioimaging rat and pig.

The rat is a perfect animal for medical experiments because its physiology is well understood and because it is large enough for surgical manipulation compared to the mouse. We have developed a transgenic (Tg) technology in rats and succeeded in establishing wide variety of Tg rat strains for biomedical researches. For instance neural stem cells isolated from the Tg rat and introduced into the brain of white matter disease models at a specific age of development can generate newly-formed, functional oligodendrocytes capable of contributing to re-myelination. It is our great honor that our Tg rat is highly evaluated for its brighter expression than any other Tg rats. They have a great potential utility for cell tracking after organ transplantation and cell transplantation. Tissue organogenesis and trans-differentiation of stem cells are also targets for the study. Then, we pay much attention for tissue engineering research using bioimaging rats as the screening before scaling-up to the large animal study.

Recent animal welfare requests 3R for experimental animals. Even where large animal study is essential before moving to clinical phase, we should pay much attention how to reduce the number for experimental animals. I propose `Medical` pigs as the preclinical model system. They will be classified into the two major categories. The one is an experimental animal for pre-clinical large body size. Both spontaneous and genetically-modified pigs have been included. The other is a potential donor for human organ transplantation. The stem cell technology alone could not be still reached to develop the transplantable new organs. The cloned technology will be essential for development of xenoantigen deficient pigs. We opened up a new approach using a total pig system for human health and disease. In our pig center, medical students and residency have used pigs for education of surgical skills and training of emergency treatment. Clinicians also used for development of innovative tool in endo- or laparo- scopic treatment. For the new model, we succeed in developing clone pigs and focused on an "*in vivo bioreactor*". Mesenchymal stromal cell (MSC)s have been established from GPF and RFP Tg pigs for regenerative medical research and tested to transdifferentiate in their organogenesis. Establishment of pig iPS cell is also on going. I would like to show our very resent activities and elaborate the future pig research.

Special Session 3

James E Egan

IRX Therapeutics, Inc., USA

IRX THERAPEUTICS, INC. (www.irxtherapeutics.com)- New York, NY
Director, Business Development-August 2004-present
• Coordinated internal research programs
• Coordinated internal intellectual property estate and generated 10 new patent applications
• Raised $37.5 million in 2 financing rounds
• Evaluate all strategic opportunities to fund clinical programs
• Initiated partnering discussions with multinational pharmaceutical companies
• Evaluated competition and opportunities in the oncology and infectious disease arena
• Assisted in designing 2 Phase 1 studies in prostate cancer and HPV infected women

My responsibilities included fundraising, partnering transaction and intellectual property management reporting directly to the CEO and CFO. Highlights include raising $37.5 million in 2 financing rounds. Prepared fundraising material and presentations. Writing industry reports highlighting unmet need of our market and our intrinsic regulatory and clinical advantages versus potential competition. Identified competing pharmaceutical and biotechnology companies and prepared reports analyzing the risks posed by these firms. Identified potential venture capital partners for the company by extensively analyzing individual investments made by life science based venture capital firms.

Scientist, Functional Genomics:
2001-2004. Cold Spring Harbor Laboratories Directed drug development platform for novel compounds involved in cancer and immune system therapeutics. Assisting in the evaluation of clinical trial protocol and results from ongoing Phase II/III clinical trial. Directed successful collaboration with Cold Spring Harbor Labs Genome Center to determine mechanism of action of several drug candidates by using functional genomics and proteomic techniques. Involved in the regulatory process for the investigative new drug application to the FDA for these compounds.
Consultant, Collaborated with biotechnology analyst of major healthcare mutual fund on a book project that details the future of the biotechnology industry, emphasizing the roles of genomics and proteomics in the diagnosis and treatment of disease. Performed research for a sell-side biotechnology analyst at to determine the pharmacological differences between two competing drugs made by Transkaryotic Therapies and Genzyme.

Post Doctoral Fellow, Stony Brook University, September 2001-May 2002. Research focused on aberrant signaling pathways involved in cancer.

Research Associate, SUNY Stony Brook 1995-2001-Research concentrated on the role of growth factor receptors and oncogenes in the progression of breast and pancreatic cancers. Additionally, collaborated with Schering-Plough on farnesyltransferase inhibitor study to determine mechanism of action.

Academic Honors
Sigma X Travel Award, SUNY at Stony Brook (2000)
National Institutes of Health Pre-Doctoral Fellowship (1996-1998) References: Available upon request

SS3-1 Development in Therapeutic Cancer Vaccine Desing

James E Egan

IRX Therapeutics, Inc., USA

Harnessing the immune system to control cancer has been a challenge for cancer immunotherapists for many years. Recent clinical advances with therapeutic cancer vaccines have shown that immunotherapy can indeed be used to make clinical impact in late-stage disease. The recent approval of sipuleucel-T by the US Food and Drug Administration marks the first antigen-specific immunotherapy approved for cancer treatment. Additionally, several different vaccine approaches in NSCLC, vulvar intraepithelial neoplasia and prostate cancer have shown promising results and are moving into Phase 3 development. Although theses results are encouraging, a major challenge in cancer immunotherapy is the identification of strategies for further enhancing its clinical efficacy. It is becoming apparent that vaccines will need to be combined with other immunomodulatory approaches to mediate useful anti-tumor clinical activity. IRX-2 is a novel adjuvant with multiple active cytokine components, including: interleukin-1β (IL-1β), IL-2, IL-6, IL-8, tumor necrosis factor-α (TNF-α), granulocyte macrophage colony stimulating factor (GM-CSF), and interferon-γ (IFN-γ). IRX-has been shown to act on multiple cell types of the immune system including T cells, dendritic cells and natural killer cells. Additional studies have shown that when combined with various therapeutic cancer vaccine types, IRX-2 is able to increase the immunogenicity of these vaccines. Clinical studies are planned in multiple indications to validate the use of IRX-2 as a critical component of the next generation of therapeutic cancer vaccines.

Special Session 3

Jianda Yuan

Ludwig Center for Cancer Immunotherapy, Immunology Program, Memorial Sloan-Kettering Cancer Center, USA

Dr. Yuan is the Director of Immune Monitoring Core at Ludwig Center for Cancer Immunotherapy (LCCI) at Memorial Sloan-Kettering Cancer Center. His research focuses on cancer immunotherapy and translational research, particularly the investigation of novel immunologic therapies for cancer, such as anti-CTLA-4 and anti-PD-1 antibody therapy.

Development of immune monitoring assays is essential in determining the immune responses in patients receiving novel immune therapies and ultimately transitioning these therapies from the clinical trial phase to standard of care. Working in collaboration with the LCCI committee, Dr. Yuan has produced and validated numerous standard operating procedures (SOPs) with state-of-the-art monitoring capabilities for the past eight years. He serves as a consultant in clinical trial design at MSKCC and assists in immunologic assessments and assay development for innovative approaches to evaluate immune response. He also serves as a Steering Committee Member for Cancer Vaccine Consortium (CVC). Since 2005, he has established solutions to common challenges in cancer vaccine use, development, and commercialization.

The Immune Monitoring Core has participated in a total of 38 clinical trials that have included DNA vaccine, dendritic cell vaccine, anti-4-1BB, anti-CTLA-4, and anti-PD-1 trials. These have implications in the novel immunotherapy approach in melanoma, prostate cancer, hepatocellular carcinoma, multiple myeloma, cororectal cancer, and breast cancer. Eleven trials are now complete and published; the rest are ongoing trials. In 2008, Dr. Yuan introduced the concept of polyfunctional tumor antigen-specific T cell response monitoring into the cancer vaccination and cancer immunotherapy field. Recently, he has been a leader in the immune monitoring studies for the anti-CTLA-4 antibody program at MSKCC. These studies have established an important correlation between, a cancer-testis antigen NY-ESO-1 immunity and clinical outcomes in metastatic melanoma patients treated with ipilimumab.

Selective publications in last two years:

Ginsberg BA, Yuan J, Wolchok JD, et al. Clin Cancer Res. 2010; 16 (15): 4057
Krug LM, Yuan J, Scheinberg DA, et al. Cancer Immunol Immunother. 2010;
Carthon BD, Yuan J, Sharma P, et al. Clin Cancer Res. 2010, 16 (10):2861
Maslak PG, Yuan J, Scheinberg DA, et al. Blood. 2010, 116(2):171
Yuan J, Wolchok JD, et al. Cancer. 2010; 116(7):1767
Yuan J, Wochok JD, et al. 2010 Cancer Immun. 2010
Lin Y, Wolchok JD, Yuan J, et al. Cytotherapy. 2009: 11(7):912
Yuan J. Wolchok JD, et al. PNAS. 2008 105 (51):20410
Perales MA, Yuan J, Wolchok JD, et al. Mol Ther. 2008, 16 (12): 2022

SS3-2 NY-ESO-1-specific CD8 T-cell Response in NY-ESO-1 Seropositive Metastatic Melanoma Patients Treated with Ipilimumab Correlates with Clinical Benefit

Jianda Yuan[1)], Sacha Gnjatic[2)], Lloyd J. Old[2)], James P. Allison[1)], Jedd D. Wolchok[1),2)]

[1)]Ludwig Center for Cancer Immunotherapy, Immunology Program, [2)]Ludwig Institute for Cancer Research; New York Branch; Memorial Sloan-Kettering Cancer Center, USA

Background: Ipilimumab, a monoclonal antibody against cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), has been shown to elicit durable immunologic and clinical responses in patients with metastatic melanoma. Our lab has demonstrated that ipilimumab enhances B- and T-cell immunity to NY-ESO-1, a prototypical cancer-testes antigen expressed in melanoma. Methods: In order to better characterize the association between immune response and clinical outcome, sera from 100 advanced melanoma patients treated with ipilimumab at Memorial Sloan-Kettering Cancer Center were analyzed for NY-ESO-1 seropositivity. In addition, pre- and/or post-therapy peripheral blood mononuclear cells from all NY-ESO-1 seropositive patients without the purification of CD4+ and CD8+ T cells were assayed for NY-ESO-1-specific CD4+ and CD8+ T-cell responses by intracellular cytokine staining following a 10-day in vitro stimulation with NY-ESO-1 overlapping peptides. Results: 20 out of the 100 patients were found to be seropositive at any time-point (6 seroconverted), with a trend toward these patients experiencing more frequent clinical benefit (11/20; 55%) than seronegative patients (25/80; 31%), p=0.067. Within the seropositive subgroup with the availability of suitable specimens, 17/19 (89%) and 13/19 (68%) generated an NY-ESO-1-specific CD4+ and CD8+ T-cell response, respectively. NY-ESO-1 seropositive patients who generated NY-ESO-1-specific interferon-gamma (IFNγ)+ CD8+ T cells experienced significantly more frequent clinical benefit (10/13; 77%) than those who did not mount this immune response (1/7; 14%), p=0.017. No association was found between an NY-ESO-1-specific IFNγ+ CD4+ T-cell responses and clinical outcome (p=0.16). Furthermore, all detectable CD4+ or CD8+ IFNγ+ T-cell responses showed polyfunctionality for TNFα, MIP-1β and/or CD107a. Finally, Being NY-ESO-1 seropositive with a CD8+ T-cell response demonstrated a significant survival advantage compared to the general population (median survival not reached vs. 8 months, p=0.0158). Conclusion: NY-ESO-1 seropositive patients may or may not develop NY-ESO-1 specific CD8+ T cell responses. Those who develop both antibody and CD8+ T-cell responses may be more likely to experience clinical benefit. Further understanding the significance of this association could have prognostic or predictive value and may support future studies in patients previously immune to NY-ESO-1 or other relevant antigens.

Special Session 4

Hiroaki Ikeda

Department of Immuno-Gene Therapy, Mie University Graduate School of Medicine, Japan

EDUCATION:

INSTITUTION AND LOCATION	DEGREE	YEAR	FIELD OF STUDY
Nagasaki University, Nagasaki, Japan	M.D.	1990	Medicine
Nagasaki University, Nagasaki, Japan	Ph.D.	1996	Medical science (Immunology and Oncology)

PROFESSIONAL EXPERIENCE:

Internist of General Internal Medicine

2nd Dept of Internal Medicine, Nagasaki University School of Medicine, Nagasaki University Hospital, Nagasaki, Japan, 1990-1991.

Internist of General Internal Medicine

Sasebo City General Hospittal, Sasabo, Japan, 1991-1992.

Graduate Student

Graduate School of Nagasaki University School of Medicine, working with Professor Hiroshi Shiku on analysis of antigenisity of tumors and identification of tumor antigens on chemically induced-mouse fibrosarcoma system, 1992-1996.

Medical Stuff / Postdoctoral Fellow

2nd Dept of Internal Medicine, Mie University School of Medicine, Mie University Hospital, Mie, Japan, working with Professor Hiroshi Shiku, conducting research and supervising graduate students in tumor immunology, working for clinical service and supervising trainee in hematology/oncology, 1996-1999.

Research Associate / Postdoctoral Fellow

Department of Pathology/Immunology, Washington University School of Medicine, St. Louis, Missouri, USA, working with Professor Robert D. Schreiber on tumor immunosurveillance system and identification of tumor antigens on chemically induced-mouse fibrosarcoma system, conducting research and supervising graduate students, 1999-2004.

Associate Professor

Division of Immunoreguration, Institute for Genetic Medicine, Hokkaido University, Japan. Conducting and organizing cancer vaccine clinical trials with recombinant tumor antigen protein and adjuvant of immunostimulatory activity on innate immunity systems. Conducting research on immunoregulation of Th1/Th2 balance, 2004-2006.

Associate Professor

Department of Cancer Vaccine, Mie University Graduate School of Medicine, Japan. Conducting research on immunotherapy of cancer and on cancer immunoediting hypothesis with mouse model. Conducting and organizing cancer vaccine clinical trials with recombinant tumor antigen protein complexed with nanogels of cholesteryl pullulan, 2006-2009.

Associate Professor

Department of Immuno-Gene Therapy, Mie University Graduate School of Medicine, Japan. Conducting research on immunotherapy of cancer and on cancer immunoediting hypothesis with mouse model. Conducting and organizing adoptive immunotherapy and cancer vaccine clinical trials, 2009-2010 (present).

SS4-1 Gene-modified Lymphocytes: Harnessing T Cells for Effective Cancer Treatment

Hiroaki Ikeda[1)], Sachiko Okamoto[2)], Junichi Mineno[2)], Naoko Imai[1)], Shinichi Kageyama[1)], Mamoru Ito[3)], Masaki Yasukawa[4)], Kazutoh Takesako[2)], Hiroshi Shiku[1)]

[1)]Department of Immuno-Gene Therapy, Mie University Graduate School of Medicine, Japan, [2)]Center for Cell and Gene Therapy, Takara Bio Inc., Japan, [3)]The Central Institute for Experimental Animals, Japan, [4)]Department. of Bioregulatory Medicine, Ehime University Graduate School of Medicine, Japan

It is becoming increasingly evident that adoptive transfer of tumor-specific T cells has a potential to induce tumor regression in patients with advanced malignancies, sometimes with high rate of clinical response. T cell receptor (TCR) gene transfer is an attractive strategy for redirecting the antigen specificity of polyclonal T cells to create tumor-specific lymphocytes. This approach, TCR gene therapy, has a potential to extend the application of adoptive T cell therapy by overcoming the limitation in the isolation and expansion of antigen-specific lymphocytes that preexists in the patient.

A TCR transgenic mouse model in which $CD8^+$ T cells express the TCR specific for a mouse fibrosarcoma tumor antigen, mutated ERK2, was utilized to analyze immunological response and regulatory factors in adoptive T cell therapy. We found that tumor progression limits the multifunctionality of transferred T cells. However, $CD4^+$ T cell help, GITR stimulation, vaccination with antigen peptide, or depletion of Treg induced high multifunctionality in the transferred cells even in hosts with progressing tumor resulting in efficient anti-tumor performance of the therapy.

Based on these results, we plan a clinical trial using lymphocytes engineered to express TCR specific for a tumor antigen, MAGE-A4. Human PBMC were efficiently transduced with MAGE-A4-specific TCR and lysed the antigen-expressing tumor cells. Adoptive transfer of the engineered cells inhibited the growth of antigen-expressing human tumor in immunodeficint NOD/SCID/$c\gamma^{-/-}$ (NOG) mice. When combined with MAGE-A4 peptide vaccination, transferred cells acquired high multifunctionality and memory phenotype *in vivo*, and induced enhanced tumor eradication. Approved by the Japanese Ministry of Health, Labour and Welfare, we have started a clinical trial to treat esophageal cancer patients with MAGE-A4-specific TCR-engineered T cells.

The existence of endogenous TCR has been reported to be associated with the inefficient expression of transduced TCRs in T lymphocytes. Endogenous TCR competes with introduced TCR for CD3 molecules. In addition, the introduced TCR α and β chains mispair with endogenous TCR subunits. Mispairing of endogenous and transduced TCRs not only reduce the expression of transduced TCR, but also can cause the generation of T cells with unexpected specificities including self-reactivity. To resolve these obstacles in TCR engineering, we developed novel retroviral vectors encoding both siRNA that down-regulate the endogenous TCR and a siRNA-resistant TCR specific for MAGE-A4. These vectors efficiently suppressed the endogenous TCR and enhanced the expression of transduced MAGE-A4-specific TCR resulting in the enhanced tumor cytotoxicity. These findings help us to design improved T cell therapy overcoming the immunosuppression in tumor-bearing hosts.

Special Session 4

Atsushi Natsume

Department of Neurosurgery, Nagoya University School of Medicine, Japan

Positions and Employment

1995-1997	Internship and Residency, Dept. of Neurosurgery, Okazaki Municipal Hospital, Aichi, Japan
1999-2002	Research Associate, Dept. of Molecular Genetics and Biochemistry, Univ. of Pittsburgh, U.S.A.
2002-2003	Kariya Toyota General Hospital, Aichi, Japan
2003-2006	Assistant Professor, Center for Genetic and Regenerative Medicine, Nagoya Univ. Hospital
2007-	Associate Professor, Department of Neurosurgery, Nagoya Univ., School of Medicine

Selected Honors & Awards

1995	Medical licensure, Ministry of Health and Welfare of Japan; Physicians License
2003	Board-certified Neurosurgeon, Japan Neurosurgical Society
2006	Japan Neurosurgical Society, Research Award

Selected Activities in Professional Organizations

2006	Committee Member, Japan Society of Gene Therapy

SS4-2 Immunotherapy Using Retrovirally Engineered T Cells Expressing Chimeric Antigen Receptors Specific to Glioma-Associated Antigens

Atsushi Natsume[1)], Masasuke Ohno[1)], Hidetaka Iwamizu[1)], Ken-ichiro Iwami[1)], Kazuhiro Yoshikawa[2)], Toshihiko Wakabayashi[1)]

[1)]Department of Neurosurgery, Nagoya University School of Medicine, Japan, [2)]Center for Cell Therapy, Aichi Medical University, Japan

Induction of tumor-specific effecter T-cells are efficient for the eradication of bulky solid tumors, and it is the final goal of cancer immunological approaches. Tumor-specific cytotoxic T-lymphocytes (CTLs) can be genetically engineered to express altered or totally artificial T-cell antigen receptors (TCR). Many of the restrictions associated with immunotherapy can be circumvented by arming polyclonal CTLs with tumor-specific chimeric TCRs, the so-called "T-body" approach. Chimeric TCRs typically consist of a tumor antigen-specific recognition single-chain variable fragment (scFv) element derived from a monoclonal antibody (mAb) and components of TCRs that mediate the signal transduction into the CTL. The T-body approach has the potential to recognize specific antigens in a major histocompatibility complex (MHC)-independent manner; the applicability of this approach has been demonstrated both in vitro and in vivo.

We have cloned the genes of heavy and light chains with variable domain from hybridomas producing a mAb specific for glioma-associated antigens, such as EGFR variant III. After successful construction of the specific chimeric scFv/ TCR cDNA sequence, the cDNA was transduced by retroviral vector. The expression of the chimeric TCR on the T body was observed by using western blotting and flow cytometory, and the specificity of T body to target cells was evaluated by the interferon-gamma ELISpot assay and a standard Cr-releasing cytotoxic assay. Furthermore, we demonstrated that the systemic delivery of T-body into intrabrain tumor-bearing mice significantly delayed tumor growth.

In conclusion, T-body-based immunotherapy appears to be a promising approach for the treatment of glioma.

Special Session 4

Naoto Hirano

Dana-Farber Cancer Institute, Harvard Medical School, USA

Naoto Hirano, MD, PhD is an Assistant Professor at the Harvard Medical School. He attended medical and graduate schools at the University of Tokyo, receiving both M.D. and Ph.D. Dr. Hirano completed a residency in internal medicine at the University of Tokyo Hospital and the Jichi Medical University Hospital. After completing a fellowship in Hematology/Oncology at the University of Tokyo Hospital, he served as an Attending Physician at the International Medical Center of Japan in Tokyo. Dr. Hirano received his postdoctoral training in the laboratory of Dr. Lee Nadler at the Dana-Farber Cancer Institute, Harvard Medical School. Dr. Hirano's research has been focusing on the development of novel cancer immunotherapy and the elucidation of the pathogenesis of immune-mediated aplastic anemia. As a translational researcher, he has always conducted his scientific inquiries with an eye towards translation to the clinic.

SS4-3 Anti-MART1 CTL with a Memory Phenotype Ex Vivo Generated Using a Gene-engineered Artificial APC and IL-15 Can Persist in Melanoma Patients as Memory T cells upon Adoptive Transfer

Naoto Hirano

Dana-Farber Cancer Institute, Harvard Medical School, USA

An important goal of cancer immunotherapy is to build long-lasting anti-tumor immunologic "memory" in patients that can reject tumors for a lifetime. We and others demonstrated that CD83 and IL-15 deliver signals which promote the development of effective memory T cells with the capacity to persist. CD83 delivers a CD80-dependent T cell stimulatory signal that allows T cells to be long-lived. Unlike IL-2, which can bring activation-induced cell death, IL-15 is an anti-apoptotic factor that promotes the proliferation of central memory T cells rather than effector memory T cells in vivo. Supported by these observations, we developed a human cell-based artificial antigen-presenting cell (aAPC) by transducing the human erythroleukemia cell line, K562, with HLA-A*0201 (A2), CD80, and CD83. This aAPC can naturally process and present class I peptides and can, in the presence of low dose IL-2 and IL-15, uniquely support the priming and prolonged expansion of large numbers of antigen-specific $CD8^+$ T cells with a memory phenotype. Cytotoxic T lymphocytes (CTL) specific for a wide array of HLA-A2 restricted peptides derived from multiple tumor-associated antigens are readily established from A2 positive donors. Antigen-specific CTL display a central memory~effector memory phenotype consistent with in vivo persistence, possess potent effector function, and specifically recognize tumor cell lines. Furthermore, CTL can be maintained in vitro for a prolonged period of time, up to >1 year without any feeder cells or cloning. Importantly, these long-lived CTL did not express CTLA-4 or PD-1, lacking an exhausted phenotype.

Based on these findings, we hypothesized that aAPC-generated CTL with a memory phenotype will persist in vivo as memory T cells, traffic to the lymph node and tumors, and induce effective anti-tumor responses in patients when adoptively transferred. We produced a clinical grade aAPC, $aAPC^{33}$, under cGMP guidelines and fulfilled all regulatory requirements including review by the NIH, FDA and IRB. We have conducted a "proof of concept" clinical trial in which large numbers of $MART1_{27\text{-}35}$ peptide specific CTL generated ex vivo using $aAPC^{33}$, IL-2, and IL-15 are infused into patients with metastatic melanoma (ClinicalTrials.gov number NCT00512889). Autologous $CD8^+$ T cells are stimulated weekly with peptide-pulsed $aAPC^{33}$ and expanded with low dose IL-2 and IL-15. After three weeks, polyclonal MART1 CTL are infused without lymphodepletion, adjuvants, or cytokine administration. Two infusions are scheduled per subject where the 2nd graft is produced from $CD8^+$ T cells harvested 14 days after the 1st infusion. With 9 patients treated, objective clinical responses were observed. Notably, over 16 months after reinfusion, adoptively transferred MART1 CTL were still detectable in periphery at greater than 6% by HLA/peptide multimer and displayed a central memory~effector memory phenotype. This is surprising, since patients received no lymphodepletion, adjuvants, or cytokine. Moreover, freshly isolated $CD8^+$ T cells showed robust anti-MART1 memory responses without any ex vivo sensitization and recognized $MART1^+$ tumor cells. We also found that infused CTL can traffic and localize to sites of disease. Intriguingly, we were able to identify MART1 CTL clonotypes that were not detectable in the CTL grafts but possibly emerged after CTL infusion, indicating that adoptive transfer of MART1-specific CTL may provoke a de novo anti-tumor response. These results suggest that anti-tumor T cells with a memory phenotype generated ex vivo using our aAPC, IL-2, and IL-15 can persist as memory T cells and establish long-lasting anti-tumor immunological memory in humans when adoptively transferred. Our aAPC-based system may serve as a platform for further improvements in a T cell culture system dedicated to anti-cancer adoptive cell therapy.

Special Session 5

Majid Tabesh

Dendreon Corporation, USA

Career Highlights Urology, Oncology and Immunotherapy Research:
1. Vice President of Medical affairs at Dendreon, in charge of: a. All Medical Affairs activities such as Global Life Cycle Planning (LCP) for Provenge, Medical Education, Publications, Key Opinion Leader Development, Medical Information and etc at Dendreon Corporation.
2. Pfizer Global Medical Director for Genitourinary Oncology, in charge of : a. All Clinical Trial implementation and LCP for pipeline agents as well as Medical responsibilities for Sutent and Market evaluation for incoming pipeline products within the GU BU.
b. Oncology Global Medical Affairs lead for Business development. Evaluating all external products suitable for GU Franchise.
3. Medical Director, Sanofi Aventis in charge of :
a. Docetaxel Clinical trial and Supporting programs in GU Oncology.
b. Docetaxel clinical LCP&M design in Prostate Cancer.
c. Eligard, clinical Trial support for LHRH therapy in Prostate Cancer Patients.

Training and Education
Rush Presbyterian St. Luke's Medical Center.
Rush University School of Medicine. Department of Immunology/Rheumatology.
Chicago, Illinois.
Fellowship Immunology and Rheumatology

Cleveland Clinic
Cleveland, OH
Internal Medicine Residency

Medical college of Ohio (MCO)
Toledo, Ohio
Doctor of Medicine (M.D.).

The University of Illinois
Chicago, IL, U.S.A.
Doctor of Philosophy (Ph.D.). Immune Pathology.

The University of Iowa
Iowa City, Iowa, U.S.A.
Bachelor of Science with an Honor in Chemistry.

Professional Associations/Board Certifications and Awards
■ American College of Rheumatology (ACR).
■ American Society of Clinical Oncology (ASCO).
■ European Society of Medical Oncology (ESMO)
■ American Urological Association (AUA).
■ American Society for Investigative Pathology (ASIP).
■ Association of Clinical Research Professionals (ACRP).
■ Alpha Chi Sigma (ΑΧΣ) Fraternity.
■ The University of Iowa Honor House.

SS5-1 Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer

Majid Tabesh, Philip W. Kantoff, Celestia S. Higano, Neal D. Shore, E. Roy Berger, Eric J. Small, David F. Penson, Charles H. Redfern, Anna C. Ferrari, Robert Dreicer, Robert B. Sims, Yi Xu, Ph.D., Mark W. Frohlich, Paul F. Schellhammer

Dendreon Corporation, USA

Background

Sipuleucel-T, an autologous active cellular immunotherapy, has shown evidence of efficacy in reducing the risk of death among men with metastatic castration-resistant prostate cancer.

Methods

In this double-blind, placebo-controlled, multicenter phase 3 trial, we randomly assigned 512 patients in a 2:1 ratio to receive either sipuleucel-T (341 patients) or placebo (171 patients) administered intravenously every 2 weeks, for a total of three infusions. The primary end point was overall survival, analyzed by means of a stratified Cox regression model adjusted for baseline levels of serum prostate-specific antigen (PSA) and lactate dehydrogenase.

Results

In the sipuleucel-T group, there was a relative reduction of 22% in the risk of death as compared with the placebo group (hazard ratio, 0.78; 95% confidence interval [CI], 0.61 to 0.98; P = 0.03). This reduction represented a 4.1-month improvement in median survival (25.8 months in the sipuleucel-T group vs. 21.7 months in the placebo group). The 36-month survival probability was 31.7% in the sipuleucel-T group versus 23.0% in the placebo group. The treatment effect was also observed with the use of an unadjusted Cox model and a log-rank test (hazard ratio, 0.77; 95% CI, 0.61 to 0.97; P = 0.02) and after adjustment for use of docetaxel after the study therapy (hazard ratio, 0.78; 95% CI, 0.62 to 0.98; P = 0.03). The time to objective disease progression was similar in the two study groups. Immune responses to the immunizing antigen were observed in patients who received sipuleucel-T. Adverse events that were more frequently reported in the sipuleucel-T group than in the placebo group included chills, fever, and headache.

Conclusions

The use of sipuleucel-T prolonged overall survival among men with metastatic castration-resistant prostate cancer. No effect on the time to disease progression was observed. (Funded by Dendreon; ClinicalTrials.gov number, NCT00065442.)

*Principal investigators in the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) study are listed in the Appendix of the Paper.

Luncheon Seminar 1

Teruo Okano

Institute of Advanced Biomedical Engineering and Science Tokyo Women's Medical University, Japan

Teruo Okano is currently the Professor and Director of the Institute of Advanced Biomedical Engineering and Science (ABMES) at Tokyo Women's Medical University (TWMU) in Tokyo, Japan. He received his Ph.D. in polymer chemistry from the Department of Applied Chemistry at Waseda University in Tokyo, Japan, in 1979. After several years as an Assistant Professor at TWMU, he joined the University of Utah in Salt Lake City, UT, USA, as a Research Assistant Professor from 1984-1986 and later served as a Research Associate Professor in the prominent Department of Pharmaceutics from 1986-1988. He returned to TWMU in 1988 as an Associate Professor and became a Full Professor in 1994, one of the first non-M.D. full professors in any medical schools in Japan. Prof. Okano then became the Director of the Institute of Biomedical Engineering in 1999 and initiated the present institute, ABMES, in 2001. Currently, he is also an Adjunct Professor at the Department of Pharmaceutics and Center for Controlled Chemical Delivery at the University of Utah since 1994 as well as a Visiting Professor of Consolidate Research Institute for Advanced Science and Medical Care at Waseda University since 2004. He has been a Fellow of the American Institute of Medical and Biological Engineering since 1997 and also a Fellow of the International Union of Societies for Biomaterials Science and Engineering since 2000.

Prof. Okano's research interests currently involve the use of intelligent biomaterials for biomedical research applications such as microdomain structured polymers, stimuli-responsive polymers, hydrogels, polymeric micelles, modulated drug release, targetable drug carriers, blood compatible polymers, cell engineering, tissue engineering, and artificial organs as well as others. His research group has succeeded in harvesting cultured cells as viable and confluent cell layers by modifying temperature-responsive polymer, poly (N-isopropylacrylamide) (PIPAAm) onto ordinary polystyrene tissue culture dish surfaces. Based on this temperature-responsive surface, they have proposed a new concept of "Cell Sheet Engineering" which introduces an alternate path for tissue and organ regeneration, using only manipulated cell sheets.

Prof. Okano is the author or co-author of more than 500 peer-reviewed journal articles as well as over 250 books and book chapters. He currently serves as an Associate Editor and Editorial Board for a number of journals, including *Tissue Engineering*, *J. of Biomedical Materials Research* and *Biomaterials*. He was the recipient of the Science News Award (1983) and awarded with the 48th and 49th Noteworthy Inventions (1989 and 1990), given by the Science and Technology Agency of Japan. He also received the Outstanding Paper Award (1990, 1995, and 1996), given by the Controlled Release Society, and the Award of the Japanese Society for Biomaterials in 1992; the Outstanding Pharmaceutical Paper Award (1997) from the Controlled Release Society and the Clemson Award for Basic Research (1997) given by the Society for Biomaterials (USA). More recently, he has also received the Award of the Society Polymer Science, Japan (1998), the Founders Award (2000) from the Controlled Release Society, Leona Esaki Prize (2005) and Nagai Innovation Award from Controlled Release Society (2006). The latest additions are the Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology (2009), the Emperor's Medal with Purple Ribbon (National Meritorious Achievement Award) (2009), and the Yamazaki-Teiichi Prize (2009).

LS1-1 Cell Sheet Tissue Engineering: Tissue Reconstruction by Layering of Patterned Cell Sheets

Teruo Okano

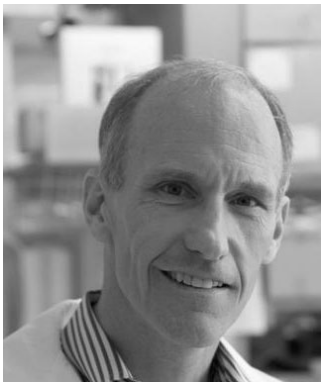
Institute of Advanced Biomedical Engineering and Science Tokyo Women's Medical University, Japan

Our research has been focused on constructing a novel form of co-culture consisting layered tissue structure. For our goal, we first developed unique tissue culture dishes which equipped their inner-bottom surface coated with the temperature-responsive polymer poly (N-isopropyl acrylamide) (PIPAAm). The "intelligent surface" of these dishes possessed the hydrophobicity similar to regular tissue culture polystyrene dishes at 37℃. However, the surface reversibly became hydrophilic at a lower temperature and spontaneously released the cultured cells as a single layer without the need for trypsin or EDTA, thus leaving the cell layer with extracellular matrix (ECM) intact. All the cultured confluent cells were harvested as a single contiguous cell sheet from the temperature-responsive culture dishes and readily applied to other biological and non-biological surfaces, thanks to the intact ECM. We here propose this novel system of cells and cell-layers arrangement called "cell sheet engineering."

We initiated human clinical studies of cell sheet engineering therapy using oral mucosal cell sheet for treatment of cornea epithelium deficient disease and recovery from endoscopic submucosal dissension surgery for esophageal epithelial cancer, and we also succeeded in treating cardio-myopathy using myoblast cell sheet. However, these applications only required primarily two dimensional manipulations of the cultured cells without prevascularized networks, which would be essential for the development of biological structures to treat or replace dysfunctional organs and tissues in human patients, the next stage of cell sheet tissue engineering. While they were vital, there were no known feasible methods to introduce effective vascular networks to sustain the fundamental functions of the regenerated organs and tissues, e.g., the liver and capillary blood vessels. Therefore, a new strategy was required, and the construction of cell sheets which had more than one type of cells became necessary in attempt to create the desired prevascular networks in three dimensional biological constructs.

In order to overcome the challenges of developing crucial and functional prevascular networks, first the copolymers with different phase transition temperatures were coated on the surface of culture dishes to produce a patterned dual phase thermo-responsive cell culture surface using electron beam polymerization method and porous metal masks. On the patterned surface of the dishes, site-selective adhesion and growth of hepatocytes and endothelial cells yielded a patterned co-culture layer based on the hydrophobic-hydrophilic surface chemistry regulated by simple temperature change. In addition, the recovered co-cultured cell sheets could be modified and multilayered, and other types of cells could even be inserted between the cell sheets. The experimental results demonstrated that this method could provide a new approach for the development of organ-like structures with the essential vascular networks found in normal human organs. Therefore, cell sheet engineering with the intelligent surface is a highly promising tool for tissue engineering and regenerative medicine.

Luncheon Seminar 2



Carl H. June

University of Pennsylvania, USA

1978-1979	Research Fellow, World Health Organization Immunology Research and Training Center, Geneva, Switzerland
1979-1980	Internship: Basic Medicine, National Naval Medical Center, Bethesda, Maryland
1980-1982	Teaching Fellow, Department of Medicine, Uniformed Services, University of the Health Sciences, Bethesda, MD
1980-1982	Residency: Internal Medicine, National Naval Medical Center, Bethesda, Maryland
1982-1983	Instructor, Department of Medicine, Uniformed Services University
1982-1983	Chief Resident: Internal Medicine, National Naval Medical Center, Bethesda, Maryland
1983-1985	Fellow in Oncology, University of Washington and Fred Hutchinson Cancer Research Center, Seattle, Washington
1986-1990	Assistant Professor, Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland
1990-1995	Associate Professor, Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland
1995-1999	Professor, Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland
1999-2001	Professor of Molecular and Cellular Engineering, University of Pennsylvania School of Medicine
2001-present	Professor of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine
2004-present	Professor of Medicine, University of Pennsylvania School of Medicine

LS2-1 Adoptive T cell Transfer Therapy for HIV and Cancer

Carl H. June

University of Pennsylvania, USA

While there are exciting examples of successful clinical strategies to mobilize the immune system to attack cancer cells, overall the results have been disappointing in randomized clinical trials. We are exploring the use of engineered T cells bearing chimeric receptors and strategies to augment their antitumor efficacy in adoptive transfer settings for cancer and HIV. HIV therapy with antiretroviral drugs is effective to control viremia, however it has not shown promise to eradicate the viral reservoir, leading to the necessity for lifelong therapy. The unique observation that allogeneic stem cell transplantation with a CCR5 deficient stem cell preparation led to eradication replication competent HIV raises the question as to whether autologous T cells or stem cells rendered CCR5 deficient could lead to a similar reduction in the HIV reservoir. We are testing the feasibility of zinc finger nucleases to create CCR5 deficient CD4 T cells in an ongoing clinical trial.

A major limitation of cancer therapy is that tolerance to self antigens leads to a poor repertoire of T cells. The surface membrane glycoprotein mesothelin is a promising target for the immunotherapy of mesothelioma, ovarian, and pancreatic tumors due to the uniform overexpression of mesothelin and the benign phenotype of mesothelin null mice. Our preclinical data indicates that use of lentiviral engineered T cells with chimeric receptors that incorporate a 'tumor resistance genotype' should have improved function for cancer immunotherapy. We have tested mesothelin redirected T cells in humanized mouse models bearing tumor xenografts. The T cells are able to eradicate large, well established tumors at an in vivo E:T ratio of at least 1:70. As a complementary strategy, we have engineered artificial antigen presenting cells (aAPC) to express ligands for either CD28 or ICOS. These aAPC appear to be useful to reprogram T cells, and increase the antitumor efficacy of adoptively transferred T cells. In ongoing clinical trials testing adoptive transfer of T cells after retroviral or lentiviral gene transfer we find that the T cells engraft and persist at high levels for 10 years or more, indicating that central memory T cells with "stem cell like qualities" can be transduced.

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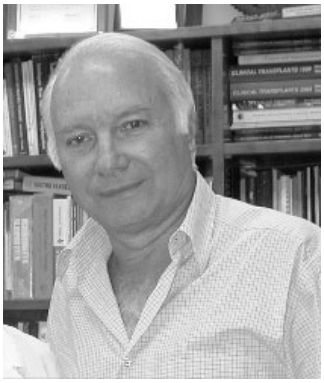
Evening Seminar 1



Shimon Slavin

The International Center for Cell Therapy & Cancer Immunotherapy (Ctci), Weizman Center, Israel

Shimon Slavin graduated at the Hadassah Hebrew University School of Medicine in Jerusalem and got his degree in 1967. He served as the doctor of the Frogman Unit in the Israeli Navy until 1970. He specialized in internal medicine (1970-1975) and subsequently specialized in clinical immunology and rheumatology at Stanford University, Palo Alto, California USA and Seattle's Bone Marrow Transplant Center at the Fred Hutchinson's Cancer Research Center, Seattle, Washington USA for three years. Upon returning to Israel in 1978, he opened the first bone marrow transplantation (BMT) unit, officially recognized as Israel's National Bone Marrow Transplantation Center and for the past 30 years Slavin served as the Director of The Department of Stem Cell Transplantation & Cancer Immunotherapy of the Hadassah Medical Center in Jerusalem. Dr Slavin was a visiting professor at SouthWestern University of Dallas at Texas and The University of Minneapolis at Minnesota and helped establish many transplant centers worldwide. Slavin is an honorary member of the Argentinean Academy of Science and was awarded many international awards for medical achievements.

Baxter Healthcare Corporation based in Chicago recognized the potential of Cell Therapy and signed an agreement which resulted in major investment with Dr. Slavin while he was at Hadassah for further development of new approaches based on cell therapy for the treatment of cancer, autoimmune disorders, genetic diseases and immune deficiency including development of new approaches for bone marrow and organ transplantation, based on new methods for regulation of the immune system. Slavin and his team are committed to clinically related basic science and pre-clinical research of human diseases, resulting in pioneering clinical application of innovative procedures focusing on immunotherapy and cellular therapies, aiming to develop user friendly personalized cost-effective modalities towards cure of otherwise incurable diseases for a larger number of patients in need, pioneering clinical application of cutting edge basic science and proprietary biotechnology.

More recently, stem cells are being developed at Slavin's laboratory for tissue repair including new production and repair of bone and cartilage as well as the use of bone marrow and adipose tissue derived mesenchymal stromal stem cells (MSC) for the treatment of neurological and autoimmune disorders. Successful clinical application of procedures involving the use of multi-potential MSCs for various additional indications aiming for tissue repair and regenerative medicine are currently underway.

Slavin served until recently as the Medical Director of Cancer Immunotherapy at the Cancer Treatment Centers of America (CTCA) based in Chicago. Currently, teaming with American companies involved in biotechnology, Slavin serves as the Medical & Scientific Director of the newly established International center for Cell Therapy & Cancer Immunotherapy (CTCI). The center, which operates in full cooperation with satellites abroad, attracts patients with cancer and other diseases treatable by personalized procedures involving the use of stem cells, immunotherapy and targeted anti-cancer modalities from all over the world.

Slavin serves on many Editorial boards, National and International committees and Advisory Boards. He authors >650 scientific publications and 4 books.

ES1-1 The Use of Haploidentical Stem Cell Transplantation and Alloreactive Donor Lymphocytes for Immunotherapy of Cancer and Using Multi-Potent Autologous Stem Cells for Regenerative Medicine

Shimon Slavin[1], Chaya Brodie[2]

[1]International Center for Cell Therapy & Cancer Immunotherapy (CTCI), Weizman Center, Israel, [2]Mina & Everard Goodman Faculty of Life-Sciences, Bar-Ilan University, Ramat-Gan, Israel, Hermelin Brain Tumor Center, Department of Neurosurgery, Henry Ford Hospital, USA

The large majority of patients in need of allogeneic stem cell transplantation (SCT) have no matched donor available. The therapeutic benefits of SCTs from fully matched related or unrelated donors are limited by the risks associated with graft-versus-host disease (GVHD) and inadequate graft-versus-malignancy (GVM) effects. Furthermore, although GVM effect following allogeneic SCT is a well-established procedure for induction of anti-cancer effects, procedure related toxicity and mortality may be unavoidable and occasionally prohibitive especially in elderly patients or patients with poor performance status. Accordingly, we designed a protocol for safer transplantation of haploidentically mismatched donors using non-T cell depleted stem cell allografts based on preferential deletion of host-vs-graft and graft-vs-host alloreactive T cells, using reduced intensity conditioning with engraftment facilitated by short lived immunocompetent T cells. Deletion of host-vs-graft alloreactive T cells was obtained by alloantigen-primed lymphocyte depletion (APLD) by cyclophosphamide 200mg/kg or lower dose cyclophosphamide 100mg/kg in conjunction with non-specific immunosuppressive agent to delete the pool of alloreactive T cells. Similarly, graft-versus-host alloreactivity that could result in GVHD was accomplished by post transplant administration of cyclophosphamide. Graft-vs-tumor effect was accomplished by administration of rIL-2 activated donor NK cells. Using this new approach for induction of bilateral transplantation tolerance of host-vs-graft and graft-vs-host, treatment of patients with fully resistant leukemia could be accomplished while avoiding acute or chronic GVHD. In contrast, the feasibility and safety of immunotherapy of minimal residual disease mediated by short-lived intentionally mismatched rIL-2 activated killer lymphocytes (IMAK) with no prior stem cells engraftment was also investigated in patients with advanced chemotherapy-resistant hematological malignancies and metastatic solid tumors. Based on successful experiments in mice and man we can conclude that treatment with short-lived IMAK can be effective for elimination of minimal residual disease while elimination of bulky disease requires durable engraftment of donor lymphocytes. In contrast to the preferred use of allogeneic stem cells, autologous bone marrow and adipose tissue derived mesenchymal stromal stem cells (MSC) that can be prepared from liposuction seem to be preferable for regenerative medicine for durable engraftment with no prior conditioning. MSCs are mesoderm-derived cells that typically reside in adult bone marrow and adipose tissue at very low concentrations. In addition to their well-known ability to differentiate to fat, bone and cartilage, MSCs have been also reported to differentiate into cells with various neural phenotypes. We studied the role of MSCs in experimental autoimmune encephalitis as a model of human multiple sclerosis (MS) and found that treatment of mice with bone marrow derived MSCs resulted in significant suppression of anti-self reactivity and improved disease manifestations. We have also demonstrated that in addition to down regulation of autoimmunity, neural differentiation of these cells may occur in vivo. These observations suggested that treatment with MSCs might be used for immune regulation of anti-self reactivity and for neuroprotection. Supported by the murine data, we pioneered a phase I/II open clinical trial in patients with inflammatory and degenerative neurological disorders to evaluate the feasibility and safety of intrathecal and intravenous administration of autologous bone marrow derived MSCs and more recently also adipose tissue derived mesenchymal stromal stem cells (ADSC) which can be prepared from liposuction. Our ongoing pilot study in patients with severe multiple sclerosis (MS) failing conventional modalities and some with amyotrophic lateral sclerosis (ALS) suggests that treatment with mesenchymal stromal cells is feasible, safe and potentially effective. No major side effects were noticed during a follow up period of up to 4 years. More recently, we have discovered a new procedure capable of inducing differentiation of both bone marrow and adipose tissue derived MSCs that can be differentiated into neural stem cells, motor neurons, astrocytes and myelin producing oligodendrocytes that in principle may induce remyelination. These results further emphasize the potential role of autologous MSCs for treatment of autoimmune, neuroinflammatory and neurodegenerative disorders.

Evening Seminar 2

Richard W. Childs

Capt, U.S. Public Health Service Senior Investigator, Chief Section of Transplantation Immunotherapy Hematology Branch, National Heart, Lung and Blood Institute, National Institutes of Health, USA

Dr. Richard Childs is a Captain in the United States Public Health Service and is the Chief of the *Section of Transplantation Immunotherapy* in the Hematology Branch of The National Heart Lung and Blood Institute (NHLBI) at the National Institutes of Health (NIH). Dr. Childs graduated from Georgetown University in Washington, D.C., in 1987 and Georgetown University Medical School in 1991. He completed his internship, residency, and a Chief Residency in internal medicine at the University of Florida in Gainesville followed by fellowships in medical oncology at the National Cancer Institute (NCI) and hematology at the National Heart Lung, and Blood Institute (NHLBI), at the National Institutes of Health (NIH).

Dr Childs was appointed as a tenure-track investigator in the Hematology Branch of the NHLBI in 1999 and received tenure in at the NIH in 2006, when he was appointed Chief of the Section of Transplantation Immunotherapy.

Dr Childs'research has focused on tumor immunology and allogeneic immunotherapy to treat nonmalignant hematological disorders, hematological malignancies, and solid tumors. He was the first to establish the existence of a graft-vs-solid tumor effect mediated by transplanted donor T-cells that could cure patients with metastatic renal cell carcinoma. This seminal observation published in the New England Journal of Medicine defined a new therapeutic application for allogeneic immunotherapy. Subsequently, his group characterized the immune mechanisms mediating this graft-vs-solid tumor effect and in novel experiments using allogeneic T-cells from responding patients identified a solid tumor antigen derived from an endogenous retrovirus that is immunogenic in vivo. Translational research conducted in Dr. Childs'laboratory has focused on targeting the human immune system against kidney cancer and as well as to develop novel NK cell-based strategies to prevent GVHD and to treat advanced cancers. Information gleaned from this research has been translated into several novel clinical immunotherapy trials to treat humans with cancer. Dr Childs has published over 150 papers in peer reviewed journals and has won numerous awards including the NIH Director's Scientific Medal Award, The NIH Distinguished Clinical Teacher Award, and in 2010 he received the Distinguished Service Medal from The United States Surgeon General, which is the United States Commissioned Corps highest honor award, for research that has improved the field of hematopoietic stem cell transplantation.

ES2-1 Advances in Cellular Immunotherapy for Cancer: From T- Cells to NK Cells

Richard W. Childs

Capt, U.S. Public Health Service Senior Investigator, Chief Section of Transplantation Immunotherapy Hematology Branch, National Heart, Lung and Blood Institute, National Institutes of Health, USA

Over the past few decades, cancer immunotherapy has focused primarily on methods to target T-cells against tumors. The 3 main approaches to T-cell-based cancer immunotherapy that have been explored to date have included the a) Nonspecific stimulation of T-cell immune effectors (i.e. high-dose IL-2 therapy) b) Active T-cell immunization to enhance anti-tumor reactions through the use of cancer vaccines and c) The passive transfer of activated T-cells with anti-tumor immunity. In the non-conditioned host, adoptively transferred tumor reactive T-cells expand only minimally in vivo. Recently, investigators have shown that highly immunosuppressive preconditioning can eradicate regulatory T-cells and other immune populations which might either suppress the proliferation of adoptively transferred tumor reactive T-cells in vivo or compete for homeostatic cytokines which are vital for T-cell survival. More recently, investigators have attempted to improve cell transfer therapy using T-cell receptor gene modified cells. Viral vector encoding T-cell receptors (TCRs) with high affinity for a variety of tumor antigens have also been developed and are currently being explored in pilot clinical cancer trials to transduce autologous PBL to express tumor reactive TCRs for subsequent adoptive transfer in cancer patients. Optimal T-cell based immunotherapy for cancer requires targeting an antigen that is both highly expressed and restricted to the tumor. Unfortunately, at present, most tumor antigens do not meet these criteria, which potentially may account for the failure of conventional T-cell based immunotherapy to improve survival in the majority of patients with advanced solid tumors.

Recently, increasing research has focused on the potential of natural killer (NK) cells to treat cancer. The ability of NK cells to kill tumor cells without the need to recognize a tumor-specific antigen provides advantages over T cells and makes them appealing to investigate as effectors for immunotherapy. The mechanism by which an NK cell recognizes a target cell, with subsequent activation or inhibition of killing, is complex. Under physiological circumstances, NK cell recognition of target cells is predominantly mediated by paired inhibitory and activating signals through NK receptors, as well as various adhesion and co-stimulatory molecules.

The most compelling evidence in humans to support the activity of NK cells against cancer comes in patients with acute myeloid leukemia undergoing mismatched allogeneic hematopoietic stem cell transplantation. In a report by Ruggeri et al. on 112 haploidentical T cell-depleted transplants for high-risk AML, there was a highly statistically significant event free and overall survival advantage for patients receiving haploidentical transplants where NK alloreactivity existed in the graft-versus-leukemia direction (n=34; 60% event free survival at 5 years) compared with transplants without alloreactivity (n=58; 5% event free survival at 5 years; $P<0.0005$). Remarkably, graft rejection and GVHD were not observed in any recipients receiving NK alloreactive transplants. These seminal findings showed that in the setting of an HLA mismatched hematopoietic cell transplant, NK cells can serve as both GVL effectors and can facilitate engraftment independent of T-cell-mediated GVH reactions.

NK cell based therapy outside the context of an allogeneic HCT is just now being explored and may open new avenues for the treatment of AML relapse and other malignant diseases. Manipulating the balance between inhibitory and activating NK receptor signals, discoveries in NK-cell receptor biology and the recent advent of novel approaches to expand ex vivo large numbers of NK cells have fueled enthusiasm for clinical trials investigating a number of novel methods to potentiate NK cytotoxicity against human malignancies. An alternative strategy to offset KIR ligand inhibition that augments NK cell tumor killing would be to render tumor cells more susceptible to NK cell tumor attack. Recently, investigators have shown that histone deacetylase (HDAC) inhibitors and proteosome inhibitors can be used to sensitize tumors to NK cell killing via TRAIL and perforin granzyme. Drug-induced tumor sensitization is now being explored as a novel strategy to potentiate anticancer effects of adoptively infused NK cells in patients with cancer. Although NK cell based cancer immunotherapy is still in its infancy, preliminary reports of tumor regression occurring after adoptive NK cell infusions clearly define the potential of NK cell based immunotherapy for treating malignancies.

Poster

P1 Cell Administration Technique in Melanocyte Transplantation for Treating Vitiligo

Hui-Ti Lin, Yi-Chen Chen, Pei-Ju Lin, Bin-Ru She

Biomedical Engineering Lab., Industrial Technology Research Institute, ROC

Vitiligo is an epidermal depigmentation disease characterized by the loss of melanocytes in the affected skin. This common disorder imposing serious psychological burden to the patients affects 1-2% of total population worldwide. Clinical studies indicate that autologous transplantation of melanocytes to the vitiligo lesion is a viable alternative to the current phototherapy and drug therapy. We had previously established the manufacture process of melanocytes in the GTP/GMP Cell Manufacture Facility of Industrial Technology Research Institute. Results of the phase I/II IND of autologous melanocyte transplantation to treat vitiligo showed a positive profile in safety/tolerability and efficacy. However, uneven repigmentation occurred to the treated retroacuricular lesion, probably attributing to the uneven delivery and run-off of the cell suspension. In additions, our laboratory simulation indicated that a significant amount of cells might have been lost due to the absorption by the gauze dressing. To solve these problems, we established a new cell administration technique with gel and membrane dressings. In this technique, the melanocyte suspension is mixed with the gel for a thick texture, and spread evenly on the membrane which is then applied on the denuded vitiligenous lesion. We evaluated several commercially available wound gels and membrane dressings for the maneuverability and compatibility with the melanocytes. Several factors were examined, including the ratio of the gel and melanocyte suspension, mixing method, uniformity of the gel on the membrane. Viability, tyrosinase activity, and the re-attachment ability of the melanocytes were examined for this technique. The best results were obtained by using a hydrocolloid gel and a polyurethane membrane. Melanocytes were able to retain the tyrosinase activity and viability of 90% or above after mixing with the gel. In a simulation of the gel and membrane administration process, about 70% of the cells were able to re-attach and distribute evenly onto the culture dishes *in vitro*. There are several potential advantages by using this technique: cells do not run-off; cells are distributed more evenly; cell density per area can be better controlled; no absorption of cells by the gauze; the membrane can be easily attached onto the curved or bend lesion; transparency of the gel and the membrane allows convenient observation of the treated lesions. A clinical study is necessary to check further whether this cell administration technique allows effective cell engraftment *in vivo*.

P2 Method in Identifying Culture-derived Mixed Skin Cells

Hsiang-Chun Hsu, Jun-Jae Huang, Bin-Ru She, Su-Yo Lin, Chih-Ching Liao, Ying-Jung Yang, Shu-Fen Yeh, Yi-Ping Wu

Biomedical Engineering Lab., Industrial Technology Research Institute, ROC

Culture-derived skin cells are often mixtures of keratinocytes, fibroblasts and melanocytes. For skin cell therapy it is important to assess the percentage of each type of cells. In this study, we used DOPA staining, immunostaining and flowcytometry to analyze homo- and mixed skin cell populations in order to establish reliable method for this purpose. The results showed DOPA staining clearly distinguished melanocytes from fibroblasts. However, for a culture containing both melanocytes and fibroblasts the percentage of the latter was often underestimated, probably due to the poor visibility of fibroblasts under microscope. Adding a nuclear staining to the procedure greatly improved the accuracy. Immunostaining and flowcytometry using tyrosinase antibody for identifying melanocytes and CK14 antibody for keratinocytes resulted in high sensitivity and specificity for homo- and mixed cell populations. Immunostaining with FSP1 antibody showed good staining for fibroblasts, negligible staining for keratinocytes, and some staining for the nucleus, but not the cytoplasm, of melanocytes. With flowcytometry, FSP1 antibody could not clearly differentiate melanocytes and fibroblasts. CD73, CD29, and CD90 were detected on both melanocytes and fibroblasts through flowcytometry. Interestingly, although CD90 was clearly detected in adult melanocytes, it was not detected in newborn melanocytes. Although detection by specific antibody was always correlated with the isotypic antibody, source and amount of antibody used can create aberrant results. It is suggested that with each lot of antibody, specific antibody and isotypic antibody should be titrated against each other using positive and negative control cell population. In conclusion, while we have not identified an antibody which could specifically stain fibroblasts but not melanocytes in flowcytometry, we have found tyrosinase, CK14 and FSP1 antibodies to be reliable in assessing the percentage of melanocytes, keratinocytes and fibroblasts, respectively, in a mixed culture using immunostaining method. An improved DOPA staining is also reliable for assessing the percentage of melanocytes in a mixed skin cell culture. The procedures established here are useful for the quality control in skin cell manufacturing for clinical application.

P3 Human Placenta-Chorion-derived Mesenchymal Cells (pCMCs) May Rescue the Mice From Lethal Total Body Irradiation

Yao-Chang Chen[1)], Thai-Yen Lin[1)], Chia-Hsien Cheng[1)], Yin-Kai Chen[1),2)], Shih-Yi Lin[1)], Meng-Shiue Wu[1)], Shu-Yi Lu[1)], Jie-Yang Jhuang[1)], Chia-Tung Shun[1)], Yen-Hua Huang[2)]

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Background:

We have successfully isolated and expanded human placenta-derived mesenchymal cells (DMCs) from a source without ethical concern *(Stem Cells. 2005; 23: 3~9)*, and now modified into a placenta-chorion-mesenchymal cells (pCMCs) in serum free culture.

Acute radiation syndrome is a challenging complication of radiotherapy for patients with malignancies. Effective treatment is currently seldom available. Mesenchymal stem cells (MSCs) derived from a variety of human tissues have been considered to have repair property to various types of tissue injury. The aim of this study was to evaluate the effects of human pCMCs on mice receiving lethal total body irradiation (TBI).

Methods:

B6 mice received TBI on day 0 with doses of 600~900 cGy from ^{137}Cs source. Different scehdules of pCMCs infusion were applied after TBI. Mice were monitored for survival, weight loss and hemogram change. Sections of lung, liver and spleen were compared histopathologically between groups.

Results:

In the group of mice with TBI 800 cGy, the survival rates on day 14 and day 21 were 16% and 5% respectively. When pCMCs were added right after TBI on day 0, the survival rates were improved to 37% and 20% respectively. When 2 doses of pCMCs were given on day 0 and day 7, the survival rates were 71% and 29% respectively. Survival advantage was clearly shown in the pCMCs-treated mice.

Histopathologically, radiation injury of lung epithelium was more evident in mice without pCMCs as compared to mice with pCMC therapy.

Conclusions:

Our results suggested that human pCMCs may exert cell protective effects in TBI treated mice through amelioration of TBI induced tissue necrosis especially lung epithelium. Whether culture medium may replace pCMCs will be the next challenge.

P4 Isolation and Characterization of a Stem Cell Population from Adult Human Deceased Donor Liver

Ji-Hyun Lee[1)], Hey-Jung Park[1)], Young-A Kim[1)], Doo-Hoon Lee[2)], Jeong-Kwon Noh[2)], Jong-Gab Jung[2)], Eun-Mi Jang[2)], Soo-Min Jung[3)], Suk-Bae Moon[3)], Suk-Koo Lee[3)]

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Liver transplantation is the only effective treatment for end-stage liver disease. Because of limited donor availability, attention has been focused on the possibility to restore liver mass and function through cell transplantation. Stem cells are a promising source for liver repopulation after cell transplantation, but whether or not the adult liver contains hepatic stem cells is highly controversial.

Several studies suggested the presence of stem cells in the adult normal human liver; however, a population with stem cell properties has not yet been isolated. The purpose of this study was to identify and characterize progenitor cells in normal adult human liver. By stringent conditions of liver cell cultures, we isolated and characterized a population of human liver stem cells (HLSCs). HLSCs expressed the mesenchymal stem cell markers CD29, CD73, CD44, CD90, CD105, and CD166 but not the hematopoietic stem cell markers CD34, CD45, and CD117. HLSCs were also positive for vimentin and nestin, a stem cell marker. The absence of staining for cytokeratin-19, CD117, and CD34 indicated that HLSCs were not oval stem cells. In addition, HLSCs expressed CD26, and in a small percentage of cells, cytokeratin-8 and cytokeratin-18, indicating a partial commitment to hepatic cells. HLSCs not differentiated in mature hepatocytes when cultured in the presence of hepatocyte growth factor and fibroblast growth factor 4. But, HLSCs were able to undergo osteogenic, chondrogenic, and adipogenic differentiation when cultured in the appropriated differentiation media.

In conclusion, HLSCs expressed several mesenchymal but not hematopoietic stem cell markers and CD26, CK18, indicating a partial commitment to hepatic cells. But HLSCs not differentiated in mature hepatocytes. We here identified in the adult human liver a cell population that fulfils criteria for stem cell definition such as the capacity for self-renewal and multi-potent differentiation.

P5 Efficacy and Safety Evaluations of a Gel Bead-based Bioartificial Liver Consisting of Gravity Force Perfusion Bioreactor

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Various extracorporeal bioartificial liver (BAL) support systems have been developed. Most BAL utilize porcine primary hepatocytes as a biological component. The performance of a BAL depends on the functional activities of the hepatocytes immobilized in the system. We designed the stable gravity force perfusion system that does not induce any damages to the gel beads in the bioreactor of the system. A packed-bed bioreactor with gel beads has higher surface area to volume ratio and cell capacity than those of a hollow fiber bioreactor. Therefore, the type of bioreactor may be a better alternative for hollow fiber-based BAL systems. In regards to flow direction, upward flow direction has been applied to most packed-bed bioreactor. However, the packed-bed bioreactor with upward flow could result in bead disruptions or channeling, in case that it was under the high pressure caused by excessive flux or clogging. So, we designed the stable gravity force perfusion system that does not induce any damages to the gel beads. In the gravity perfusion system the flow direction through the bioreactor is downward. The perfusion flow was generated by media level difference between the reservoir and outlet chamber placed before and after the bioreactor respectively. As results, our packed-bed bioreactor with gel beads showed stable liver functions for 12 hrs and no physical damage detected at the beads even after the 60 hours operation.

The preclinical safety studies were performed to investigate systemic adverse events and the effect on the immune responses when applying repeatedly to healthy beagle dogs. Various kinds of toxicity indices were monitored including general symptoms, vitals, ophthalmic observation, urine analysis, hematologic & biochemical analysis, immunotoxicity, autopsy findings, and histopathologic finding, ect. Any specific adverse events were not observed during the safety study.

The efficacy was evaluated using 50 kg pigs with ischemic liver failure by portocaval shunt and ligation of hepatic artery. The pigs were divided into three groups: 1) anhepatic control group (n=4), 2) Blank(without cell) group (n=4), and 3) BAL (with hepatocytes) group (n=4). As results, specific adverse events were not observed during preclinical safety studies. The survival time of pigs with FHF was significantly prolonged by 50% with BAL treatment as compared to blank group(blank: 19.25+/-1.38h, BAL: 29+/-1.22h; P=0.002). In addition, intracranial pressure, blood ammonia, creatinine levels were lower in the BAL group than in control and blank group. This spheroid-based BAL system will be a good candidate for the treatment of fulminant hepatic failure patients. The first clinical trials of our BAL system for acute liver failure patients are underway at Samsung Medical Center, Seoul, Korea.

P6 In Vitro Investigation of Interaction between Endothelial Cells and Human Liver Stem Cells

In Keun Jang[1)], Hee Hoon Yoon[4)], Doo-Hoon Lee[1)], Ji-Hyun Lee[2)], Mal Sook Yang[1)], Jong Eun Lee[1)], Hyo Eun Kim[1)], Suk-Koo Lee[3)]

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Hepatocyte transplantation is severely limited by organ shortage despite of advance in transplantation methodology. So the alternative hepatocyte source is needed. Recently we isolated and expanded human liver stem cell (HLSC) from partial liver tissue.

However the successful transplantation of HLSC into liver must be conducted by basic research on transplantation mechanism.

In general, stem cells including HSLC for liver therapy are transplanted into portal vein. Firstly the transplanted cells must adhere to the endothelium and transmigrate across the endothelium. Secondly these cells must engraft into liver tissue. Finally the differentiation to mature hepatocytes must be performed in vivo.

In this study, we investigated the interaction between HSLC and endothelial cells in vitro during adhesion, transmigration quantitatively as well as qualitatively. For this experiment, we adopted some models such as monolayer, flow-based monolayer and transwell model.

To examine the morphology and the time course of the interaction of HLSC with endothelial cells, HLSC labeled with DiI (Red colour). In the human umbilical vein endothelial cells (HUVEC) or rat sinusoidal endothelial cells (RSEC) monolayer model, the first contact and adhesion of HLSC were observed within 15 min and increased time-dependently. Later, HLSC integrated into the endothelial monolayer. The contact, adhesion and spreading of HLSC in flow-based RSEC monolayer model were visually observed with the video. In the transwell model, the invasion and transmigration of HLSC were observed with rat hepatocyte and cytokine mixture at lower compartment of multiple well plate.

Further studies will provide some important information how HSLC is transplanted to liver tissue and also which factors play a critical role in the transplantation.

P7 In Vitro-generated Neural Progenitors Mediate Recovery of Dopaminergic Neurons in the Neonatal Hypoxic-ischemic Brain

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Dopaminergic neurons in the developing rodent brain appear approximately 11.5 days post coitum and the number is roughly fixed throughout the life. Recent studies claimed that this is due to a dopaminergic neurogenesis after birth, although neurogenesis is believed to be restricted into two areas: subventricular zone (SVZ) and subgranular zone (SGZ). In this report, we showed that neural progenitors differentiated from the hPLC (first-trimester human placenta cell) can restore the dopaminergic system from HI insult. The established hPLCs proliferated for 90~150 days in vitro. Approximately 30% of the undifferentiated hPLCs expressed nestin and upon enhanced cell-cell interaction, all of the hPLCs became nestin-expressing neural progenitor cells (hP+) with inductions of Dcx, Sox1, and HuD. The effects of hP+ on the dopaminergic neurogenesis were examined using hypoxia-ischemia (HI) animals where the dopaminergic neurons in the substantia nigra pars compacta (SNc) were almost completely degenerated in 2 weeks. The insult further caused destructure of nigrostriatal circuit and severely damaged the locomotor activity. Transplantation of hP+ into bilateral striatum at 2 weeks after the insult recovered locomotor activity. Immunohistochemical examinations revealed that the implanted hP+ differentiated into several different types of neuroectodermal cells in the recipient striatum including tyrosine hydroxylase-expressing (TH+) cells. Further analyses showed a near complete recovery of SNc in terms of TH+ neurons. 5-bromodeoxyuridine (BrdU) was incorporated into several of the new TH+ neurons manifesting the occurrence of dopaminergic neurogenesis. Infusion of fluorogold (FG) into striatum confirmed that these newborn neurons have successfully restored the nigrostriatal circuit that was disrupted by the HI insult. Relevance of these results to other dopaminergic degenerative disease needs to be confirmed, however, we propose that progenitors and/or stem cells can induce regeneration of the diseased tissues by stimulating the resident tissue-specific progenitors as well as supplementing the lost tissues.

P8 GD2 Expression is Closely Associated with Neuronal Differentiation of hUCB-derived MSCs

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GD2 ganglioside has been identified as a key determinant of adipose cells and bone marrow-derived mesenchymal stem cells (BM-MSCs). Here, we characterized GD2 ganglioside expression and its implications in umbilical cord blood-derived MSCs (UCB-MSCs). Usingimmune-selection analysis, we showed that both GD2-positive and GD2-negative UCB-MSCs expressed general stem cell markers and possessed mesodermal lineage differentiation potential. Although the fraction of GD2-expressing cells was lower in UCB-MSC than in BM-MSC populations, inhibition of GD2 synthesis in UCB-MSCs suppressed neuronal differentiation and down-regulated basic helix-loop-helix (bHLH) transcription factors, which are involved in early stage neuronal differentiation. In addition, the levels of bHLH factors in neuronally induced UCB-MSCs were significantly higher in GD2-positive than GD2-negative cells. Our data demonstrate that GD2 ganglioside expression is associated with regulation of bHLH factors and identify neurogenic-capable UCB-MSCs, providing new insights into the potential clinical applications of MSC-based therapy.

P9 Identification, Isolation, & Characterization of CD34 Clonogenic Stem Cell (AM-cMSC) in Human Placental Amnion Membrane

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Introduction & Background: In regenerative medicine, identifying a source of pluri-potent or multi-potent stem cells are of high safety and efficacy in repairing and renewing damaged and defective tissues has extensively been investigating and much work is needed to fulfill.

One hypothesis is that ontologically, neonatal placenta is the only tissue supporting the neonatal development from embryo and fetus that should consists with various superior functioning stromal stem/progenitor cells with greater proliferation ability and the immune safety.

By a systemic screening of mesenchymal stromal stem/progenitor cells isolated from the placenta tissue, we have identifed a subset of CD34+ clonogenic mesenchymal stem cells (AM-cMSC) from the placenta amnion membrane stromal cells (Am-MSCs), by a CD34 cell antigen FACS sorting. We found the isolated AM-cMSCs exhibited sphere-like clonogenicty in early passages and expresses pluripotent embryogenic stem cell (ESCs) like characteristics in vitro. Specifically, we found nearly 1/3 (25-45 %) of CD34+ AM-cMSCs in the p3 cultured Am-MSCs, by a flow cytometry analysis of eight placenta donors. We further examined the morphology, phenotype, and the differentiation potentials of the purified AM-cMSCs in culture. The isolated AM-cMSC subpopulation can be expanded, while maintaining the stemness genes and the phenotype marker expressions in culture over a month. These cells homogenously expressed embryogenic (e.g. Oct-4, Nanog, Rex-1, Sox-2), stemness (e.g. CD117, CD34, CD44) surface antigens, in addition to present various lineage markers including: MSC (e.g. CD29, CD90, CD73, CD105, CD106), hem-angiogenic (e.g. AC133, CD34), myo-nurogenic (e.g. CD54, nestin, NSE). AM-cMSCs exhibits trans-dermal differentiation potentials in vitro, at least including adipogenesis, osteogenesis, chondrogenesis, nurogenesis, vasculogenesis, & myogenesis, tested to date.

The above study provides a better insight into the ESCs like clonogenic stem cells can be derived from non-embryonic neonatal placental tissue. The proliferative and differentiation potentials found from this study indicates that a great potential of AM-cMSCs to be used for clinical regenerative therapies. More in vivo animal studies as well the in vitro molecular profiling characterization in gene expression and protein synthesis are under going.

Acknowledgement: The study is supported by an internal collaboration project among the Graduate Institute of Medical Sciences, Taipei Medical University, and OBGYN research Center, Cathy General Hospital, and Genomic Research Center, Academia Sinica. A partly support financially of this study is obtained from Sino Health Bank, Taiwan.

P10 Rational Basis for Immune-suppressive Properties of Dedifferentiated Fat Cells in Vitro

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Dedifferentiated fat (DFAT) cells, established from mature adipocytes have mesenchymal stromal/stem cell (MSCs) properties such as ability to differentiate into multiple mesenchymal lineages. Since MSCs have also been noticed to possess the capability of immunomodulation, human DFAT cells were examined for their immunomodulating ability.

Flow cytometry analysis showed that DFAT cells were negative for CD80, CD86 and HLA-DR, whereas CD54 and CD58 were positive. DFAT cells readily responded to interferon gamma, which consequently led to the upregulation of CIITA gene and HLA-DR cell surface expression. Interferon gamma also induced cell surface expression of CD274 and expression of the following genes: IDO1, PTGS2, NOS2, HGF, TNFSF10 and HLA-E. DFAT cells significantly suppressed CD3/CD28 stimulated T cell proliferation. DFAT cells inhibited maturation of naive CD4 positive T lymphocytes into Th1, Th17 effectors, whereas augmented induction of $CD25^{bright}/FoxP3^{bright}$ cells.

These data indicate that DFAT cells are capable of modulating immune response in the same way that MSCs derived from various tissues are.

P11 Long Term Culture Affects the Cytokine Expression of Hman Umbilcial Cord Blood-mesenchymal Stem Cells

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MEDIPOST, Korea

Mesenchymal stem cells (MSCs) are of great therapeutic potential Mesenchymal stem cells (MSCs) are of great therapeutic potential because of their ability to self-renew and differentiate into multiple tissue. The low frequency of this cell population in umbilical cord blood (UCB) necessitates their in vitro expansion prior to clinical use. We analyzed the effects of long-term serial passage on the characteristics of UCB-MSCs. UCB-MSCs examined was found to maintain a stable phenotype through 11-13 passages as assessed by morphological appearance and surface antigen. We observed that while osteogenic and chondrogenic differentiation potentials of UCB-MSCs dropped in relatively late passages (11-13th passages), some cytokines such as IL-6, NT-4 and CXCL16 are expressed higher in late passage MSCs culture medium. Further investigation is required to evaluate the higher expression of cytokine profiles in late passage MSCs culture.

P12 Commercial Scale, Non-viral Platform for Enhancing Potency of Stem & iPS Cell Based Research and Therapeutic Development

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The ability to specifically enhance biological function and control cell fate decisions without genetic modification represents a desired approach for generation of enhanced potency stem cells and pharmaceutical grade iPS cells for therapeutic and drug screening applications.

We have developed a rapid, automated, scalable platform to process 200 billion cells in under 30 minutes by loading them with small molecule, protein, siRNA, miRNA, mRNA or plasmid DNA; singly or in combination. The platform technology utilizes a cGMP compliant closed system for transient, non-viral approaches to modulation of intracellular signaling pathways and is supported by an FDA Master File and a CE Mark.

Our experiences in enabling development and clinical-commercial delivery of a patient-specific encompass an autologous cellular vaccine commercially marketed as an Oncology therapy in Japan, an endothelial stem cell product for treatment of pulmonary arterial hypertension (PAH) in phase IIA trials in Canada, and multiple other engineered cell therapies is various stages of clinical and pre-clinical development. For the PAH product, endothelial progenitor cells were modified to enhance secretion of endothelial nitric oxide synthetase. The resulting engineered stem cell product uses the stem cells to deliver pharmacological levels of nitric oxide into pulmonary vasculature and enhances their ability to regenerate new vasculature in the lungs, resulting in reduction of ventricular systolic pressure and improved overall survival.

This platform technology is also used in pharmaceutical drug discovery applications wherein large number of cells loaded with target or reporter molecules are used in cell based assays, and is under evaluation for generation of iPS cells and iPS cell derivatives using non-viral approaches to delivery of re-programming factors.

We will present data on modulation of biological activity leading to enhanced potency of engineered stem & iPS cells for clinical or commercial cellular therapy delivery and drug discovery applications.

P13 The Novel Cryopreservation and Recovery Media Used in the Research were Formulated, Manufactured and Sponsored by Zenoaq.

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An effective serum and xeno free chemically defined freezing procedure for human embryonic and induced pluripotent stem cells.

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Background: Both human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) bear a great potential in regenerative medicine. In addition to optimized clinical grade culture conditions, efficient clinical grade cryopreseravation methods for these cells are needed. Obtaining good survival after thawing has been problematic.

Methods: We used a novel, chemically defined effective xeno free cryopreservation system for cryostorage and banking of hESCs and iPSCs. The earlier established slow freezing protocols have, even after recent improvements, resulted in low viability and thawed cells had a high tendency to differentiate. The medium is a completely serum and animal substance free product contining dimethylsulfoxide, anhydrousdextrose and a polymer as cryoprotectants. The cells were directly frozen at -70 degree, without a programmed freezer.

Results. The number of frozen colonies versus the number of survining colonies differed significantly for both HS293 and HS306. After thawing, the cells had a high viability (90% - 96%) without any impact on proliferation and differentiation, compared with the standard freezing procedure where viability was much lower (49%). The frozen thawed hESCs and iPSCs had normal karyotype and maintained properties of pluripotent cells with corresponding morphological characteristics, and expressed pluripotency markers after 10 passages in culture. They formed teratomas containing tissue components of the three germ layers.

Conclusion: The defined freezing thawing system descried here offfers an excellent simple option for banking of hESCs and iPSCs

Key words: human embryonic stem cells/defined/cryopreservation/survival/differentiation

P14 Autologous Stem Cells Processing under GMP Management:the Experience in NTUH

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CD34 positive cell purging in the autologous transplantation setting may be used for removing autoreactive cells or contaminating tumor cells from peripheral blood stem cell graft. Development of selected stem cell transplantation needs a support from a GMP grade cell processing and pass authority GTP regulation in Taiwan. We used magnetic labeling cell selection system and sterile tubing welder to establish a closed cell process system. From peripheral blood stem cell harvest, CD34 positive cell purge, cell product cryopreservation, final product cryo-transportation, to cell thawing and graft transplant, all of these steps have established standard operating procedure and passed quality validation. The final cell products also have to determine the target cell number, viability, sterility and the presence of endotoxin. All the characters of final cell product have passed the release criteria then arrangement of conditioning regimen could be commence. Standard approaches outlined here are used in National Taiwan University Hospital cell therapy core laboratory as the field continues to evolve.

P15 Screening of Immunomodulating Drugs for Graft-versus-host disease by *in vivo* Fluorescence Imaging

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Allogeneic hematopoietic stem cell transplantation (allo HSCT) is an effective therapy for various malignancies. However, a major cause of morbidity and mortality in allo HSCT is graft-versus-host disease (GVHD), which is triggered by donor T cells. It is known that donor T cells are activated in secondary lymphoid organs and migrate into target organs. Therefore, tracking of donor cell is useful for exploring the pathogenesis of GVHD and developing effective drugs for its control. We have reported that the combination of *in vivo* fluorescence imaging system with EGFP transgenic mice as donors to visualize donor cells at single cell level and localization in whole body. Here, we examined whether our system could evaluate the effect of immunomodulating reagents against GVHD by monitoring noninvasively the donor cell infiltration into ear skin. After the transplantation, croton oil as stimulator of inflammation or dexamethasone as suppressor of inflammation was painted on the ears to alter the donor infiltration in the skin. Semiquantitative and noninvasive imaging analysis revealed that croton oil treatment rapidly promoted donor cell infiltration, and that treatment with dexamethasone suppressed it. This noninvasive *in vivo* imaging system is a powerful tool for exploring immunomodulating reagents for skin GVHD.

P16 Antiviral Effect of allo-SCT with RIC for ATLL : Short and Long-term Kinetics of HTLV-1 Proviral Load

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Adult T-cell leukemia/lymphoma (ATLL) develops in older individuals who have been infected with the human T-cell leukemia virus type 1 (HTLV-1), and the prognosis for such patients (pts) has so far been extremely poor.

Objectives: We evaluated the safety and feasibility of allogeneic hematopoietic stem cell transplantation with reduced-intensity conditioning regimen (RIC) for ATLL pts using a conditioning regimen consisting of fludarabine and busulfan. Low-dose antithymocyte globulin was added in the 1st study (NST-1), while it was omitted for the 2nd study (NST-2). Here we report the results of the longitudinal patterns of changes in HTLV-1 proviral load after RIC.

Patients and Methods: Between Apr, 2001 and Feb, 2006, 30 pts ranged from 50 to 67 years of age were enrolled in NST-1 (16 pts) and NST-2 (14 pts). After undergoing the conditioning regimen, they received G-CSF-mobilized peripheral blood (PB)stem cells from HLA-matched sibling donors. Half of the donors were HTLV-1 carriers. The primary end points in both studies were achievement of complete donor chimerism before day 90, and absence of early transplant-related mortality (TRM) before day100. The HTLV-1 proviral load was estimated using PB samples serially after RIC. HTLV-1 proviral DNA was measured by the quantitative PCR amplification of HTLV-1 pX DNA. The detection limit of the HTLV-1 proviral load was 0.5 copies/1000 cells.

Results: The results have been already published elsewhere. The two studies were considered as successful according to the primary end points. Ten of the 29 pts have survived for a median of 93 months (range, 63-108 months) after RIC. Overall and progression free survival rates at 5 years for the studies were 36% (95% IC, 21 to 51%) and 31% (95% IC, 17 to 45%), respectively.

Kinetics of HTLV-1 Proviral Load: In 28 pts who could be examined serially for HTLV-1 proviral load in the PB, this value decreased and reached an undetectable levelwithin 6 months after RIC in 16 of 28 pts (57%). It became undetectable in 8 of 15pts in NST-1 and 8 of 13 pts in NST-2, respectively. In 11 of 14 pts who were transplanted from an HTLV-1 negative donor and 5 of 14 pts who were transplanted from an HTLV-1 carrier donor, proviral load became undetectable level. Serial changes in the HTLV-1 proviral load after RIC in the 10 long-term survivors are heterogeneous but can be roughly classified into 3 patterns. In the first pattern, seen in 3 pts, the proviral load became undetectable after RIC and continued to remain so. In the second pattern, seen in 3 pts who had received RIC from HTLV-1 negative donors, the proviral load had become undetectable but returned to detectable levels thereafter. Lastly, in the third pattern, seen in 4 pts who had received the grafts from HTLV-1-carrier donors, the proviral load had remained at the carrier level. All the 10 survivors continue to show complete donor chimera during the observation period regardless of the HTLV-1 proviral load level. In 28 pts who could be examined serially, the clinical outcome, namely disease recurrence, did not correlate with the level of HTLV-1 proviral load.

Summaries: We have observed the heterogenous patterns of post-RIC changes in HTLV-1 proviral load among the pts. This is the first prospective observation on the long-term anti HTLV-1 effects of RIC for ATLL pts.

Other coauthors:Masao Tomonaga, Mine Harada, Takeharu Yamanaka, Mari Kannagi and the ATLL allo-HSCT study group.

P17 Immunotherapy Utilizing MUC1-mRNA DC and MUC1 CTL with Gemcitabine Targeting Unresectable or Recurrent Pancreatic Cancer

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Background
Mucin 1 (MUC 1) is known as a mucin core protein expressing in invasive ductal carcinomas of the pancreas. MUC 1 specific cytotoxic T lymphocytes (CTLs) recognize MUC 1 molecules in a HLA unrestricted manner. We have previously reported that the adoptive immunotherapy (AIT) utilizing MUC 1 CTLs stimulated with a MUC 1 expressing human pancreatic cancer cell line, named YPK 1, was useful and safe. We also reported the development of an AIT of MUC 1 CTLs in combination with dendritic cells (DCs) pulsed with MUC 1 peptide as well.
Here we report that the therapy using DC encoding MUC 1 mRNA and MUC 1 CTLs targeting unresectable or recurrent pancreatic cancer is safe and effective.
Purpose
Data were assessed whether this immunotherapy is safe and effective.
Objective and Methods
Twenty patients with unresectable or recurrent pancreatic cancer had the therapy what we planned. Gemcitabine (1000mg square meter), Administrating for 3 weeks off a week) was administrated followed by leukapheresis one week later of the first shot of Gemcitabine. Peripheral blood mononuclear cells (PBMC) were harvested by leukapheresis and were separated to induce DCs and CTLs. Matured DCs received MUC 1 mRNA by electroporation, then administrated via intradermally. CTLs were cocultured with YPK 1 pancreatic cancer cell line expressing MUC 1 under the stimulation with IL 2, then administrated via intravenously.
Results
Male Female ratio was 1 to 1 (10 out of 10), Mean age was 60.6 y.o. (37 to 78), Mean times of administration of cells was 3.35 (1.5 to 27.9), Mean number of cells that were administrated was 46 million (DCs) and 1800 million (CTLs), Median observation period was 16.2 months (1.5 to 27.9). One year survival rate was 39 percent (median survival time, 6.9 months). When we focus on the patients with unresectable cancer, their one-year survival rate was 54 percent (median survival time, 18.4 months). In addition, patients received DCs of more than 10 million had 58 percent of one year survival rate, whereas no patient received less than 10 million DCs did survive in one year (median survival time, 5.8 months, p=0.048, Logrank). All of patients received the therapy as outpatients and showed no side effect.
Conclusion
First of all, this therapy is quit safe. Second, patients received DCs of more than 10 million had high one year survival rate suggesting high volume DCs in this combination therapy had high potential.

P18 Phase I/IIa Clinical Trials of Dendritic Cell-based Immunotherapy for Acute Myeloid Leukemia in Elderly Patients

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Immunotherapy has the potential capacity to improve the clinical outcome of elderly patients with acute myeloid leukemia (AML), the prognosis of whom remains dismal. We conducted two phase I/IIa clinical trials of dendritic cell (DC)-based immunotherapy for elderly patients with AML. In both trials, patients were first treated with chemotherapy to reduce the leukemia burden and restore normal hematopoiesis for DC vaccine production. To evaluate clinical efficacy, only patients with measurable leukemic cells were included in the study. Monocytes were enriched by elutriation from apheresis products, and cultured in the presence of granulocyte-macrophage colony-stimulating factor and interleukin-4 to generate immature DCs. In the first trial, autologous apoptotic leukemic cells were pulsed to DCs as antigens. One day before vaccination, injection sites were pretreated with OK-432, a preparation of killed Streptococcus pyogenes, to induce skin inflammation, which has been shown to facilitate DC migration to draining lymph nodes in a mouse model. In addition, the DCs were intradermally administered biweekly together with OK-432 to induce DC maturation *in vivo* for a total of five administrations. In the second trial, DCs were matured *in vitro* with tumor necrosis factor-alpha and prostaglandin E_2, and pulsed with the modified HLA-A*2402-restricted Wilms tumor 1 (WT1)$_{235\text{-}243}$ peptide (CYTWNQMNL) and zoledronate, which has been shown to enhance the expansion of peptide-specific T cells through the activation of gammadelta T cells in *in vitro* studies. The DCs were both intradermally and intravenously administered biweekly for a total of five administrations. Four and three patients were enrolled in the first and the second trials, respectively. In both trials, the treatments were feasible and well tolerated. Interferon-gamma enzyme-linked immunospot assay and HLA tetramer staining revealed inductions of anti-leukemic immunity in two of four and one of three patients in the first and second trial, respectively. The anti-leukemic immune responses were observed in bone marrow as well as in peripheral blood. In the first trial, one HLA-A*2402-positive patient showed the induction of $CD8^+$ T cell responses to WT1- and human telomerase reverse transcriptase (hTERT)-derived peptides, indicating cross-priming by DCs *in vivo*. In the second trial, although the vaccines appeared to induce fewer natural peptide-specific T cells than modified peptide-specific T cells, the former persisted longer than the latter after the completion of vaccination. In one patient in the first trial and one in the second trial, anti-leukemic immune responses were associated with transient reductions in leukemic cells. Moreover, the patients with anti-leukemic immune responses showed prolonged periods of disease stabilization compared with the ones without a response. These studies demonstrate the feasibility, safety and immunogenecity of DC-based immunotherapy for elderly patients with AML. Notably, in the first trial, *in vivo* cross-presentation of leukemia-associated antigens by DCs was demonstrated. The second trial suggests that a small fraction of T cells induced by modified WT1 peptide vaccination were cross-reactive to the natural epitope, and lived longer presumably by interacting with tumor cells presenting endogenous WT1 *in vivo*. These therapeutic approaches warrant further investigation.

P19 Basic Study on Peptide-pulsed Dendritic Cell-based Immunotherapy for Adult T-cell Leukemia

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Adult T cell leukemia (ATL) is an aggressive, poor prognostic CD4 T cell malignancy caused by human T-cell leukemia virus type 1 (HTLV-1). Cytotoxic T lymphocytes (CTLs), especially those for Tax, are considered to be essential to control the outgrowth of HTLV-1-infected cells as seen in many other viral infections. However, It has been reported that ATL patients are profoundly immunocompromised and some asymptomatic carriers also show a weak HTLV-1-specific CTL response, indicating that impairment of HTLV-1-specific CTL responses might be one of the risk factors for disease progression. Therefore, vaccines to restore optimal HTLV-1-specific CTL responses would be required to control the expansion of HTLV-1-infected or ATL cells and to prevent disease progression. For this purpose, dendritic cells (DCs) are the most attractive candidates since they are effective in stimulating antigen-specific naive and memory T cells. In a number of clinical studies, antigen-pulsed DC-based vaccines have been tested in multiple malignancies, such as melanoma and breast cancer, and have been found to induce tumor-specific T cell responses. In ATL, monocyte-derived dendritic cells (MDDCs) generated from patients with acute type of ATL have been reported to be less functional than those from healthy individuals, but the function of MDDCs from patients with chronic type of ATL (cATL) remains obscure. In this study, we examined whether MDDCs could be generated from cATL patients and evaluated their functions such as IL-12 production, antigen uptake, and antigen presentation. Moreover, we evaluated peptide-pulsed bone marrow-derived DC (BMDC) vaccine using HTLV-1-infected rat model that shows weak HTLV-1-specific T cell responses and elevated proviral load. Our results showed that it was possible to generate MDDCs from cATL patients and that these MDDCs expressed MHC-I, MHC-II, and co-stimulatory molecules (CD40, CD80, and CD86) and produced abundant amount of IL-12. Furthermore, immature MDDCs from cATL patients showed the ability to take up antigen and mature MDDCs were able to activate allogeneic CD4 T lymphocytes. In HTLV-1-infected rat model, CTL epitope peptide-pulsed BMDCs generated from BM cells of HTLV-1-infected rats could induce HTLV-1-specific CD8 T cells in HTLV-1-infected rats that showed impaired HTLV-1-specific T cell responses, suggesting peptide-pulsed DC vaccine for cATL patients may be a promising tool for restoration of HTLV-1-specific CTL responses and for reduction of HTLV-1-infected leukemic cells.

P20 Generation of Clinical Grade Dendritic Cells for Cancer Immunotherapy

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【Background and Purpose】Cancer immunotherapy trials using dendritic cells (DCs) have been carried out worldwide with limited efficacy. One of the major problems of these trials is the qualitative and quantitative differences in DC generated from each patient. DCs are commonly generated from peripheral blood monocytes isolated by a plastic dish-adherent method after luekapheresis. We examined several variables of this method to confirm whether we generated a reasonable amount and acceptable quality of DCs used for immunotherapy.

【Methods】33 cancer patients with various origins who were treated with DC vaccination were included in this study. Peripheral blood mononuclear cells (PBMCs) were collected by leukapheresis using Cobe Spectra apparatus and Ficoll-hypaque centrifugation. Monocytes were isolated by adhering them to a plastic dish and gentle washing technique. They were then cultured with GM-CSF and IL4 for 6 days. Non-adherent immature DCs were incubated with purified protein or tumor-cell lysate together with OK432 and PGE2 for one day for maturation. Mature DCs were harvested and the number of viable cells were counted. Phenotype of mature DC was analyzed by FACS.

【Results】Peripheral blood processed by a single leukapheresis was 5.0 l on average. The total number of PBMCs were 203.9±95.5x107. Total number of DC generated was 12.8±7.5x107 ,corresponding to 6.3% of initial number of PBMCs. The viability of DCs was 89.0±5.5%. The expression of surface marker was as follows: HLA-ABC 99.6%±0.92%, HLA-DR 89.4±12.1%, CD14 4.7±7.0%, CD11c 99.5±0.8%, CD83 68.9±23.0%, CD80 87.2±12.1%, CD86 92.1±19.0%, CD40 95.1±6.2%.

【Conclusions】These results demonstrated that mature DC sufficient for 1-2 courses of vaccination can be generated by this culture system. The viability and quality of DCs exceeded the quality level needed for clinical use.

P21 A Randomized Phase III Trial of NK Cell Therapy for Previously Untreated Diffuse Large B-cell Lymphoma Patients

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Backgrounds : Natural Killer(NK) cells influence innate and adaptive ummune system. Anti-cancer therapies using monoclonal antibodies(MoAb) rely on the antibody-dependent cellular cytotoxocity(ADCC) on NK cells since virtually all ADCC activity in peripheral blood mononuclear cells is mediated by NK cells. In many areas of the world, diffuse large B-Cell lymphoma(DLBCL) is the most common form of non-Hodgkin's lymphoma, accounting for 30-58% of NHL series. The anti-CD20, B-cell-specific MoAb, rituximab-containing chemotherapy(R-CHOP) has improved clinical outcome of DLBCL compared to CHOP. However, some patients with DLBCL progress through an aggressive course in spite of R-CHOP therapy. Under conditioning of high B-cell burden, exhaustion of the body's effector mechanisms, for example NK-cell-mediated killing, may lead to substantial decrease in the immunotherapeutic efficacy of rityximab.

Material and Methods: NKM (NK-cell mixture, NKBio, Sungnam, Korea) IND was approved by the Korean Food and Drug Administration for the treatment of lymphoma in 2007. Previously untreated patients with DLBCL, 20 to 70 years old were randomly assigned to receive either six cycles of R-CHOP every three weeks or six cycles of R-CHOP plus NKM given on day 16 of each cycle. They were stratified according to center and International Prognostic Index scores which are based on age, performance status, disease stage, LDH level, and extranodal involvement. The primary study end point was event-free survival (EFS).

Results: Among 276 patients of sample size, a total of 160 patients from 21 institutions were enrolled onto the study and treated; 78 were randomized to active group (R-CHOP plus NKM) and 82 to control group (R-CHOP). Patient characteristics were well balanced. There were no statistically significant differences between treatment groups at baseline. This study is ongoing.

Conclusions: We hypothesize that NK cell therapy as strategies augmenting the killing ability of NK cells can boost the immune system and enhance the effectiveness of rituximab-based therapies in DLBCL. We plan to evaluate 3-year EFS after the last patient will be enrolled onto the study. This is the first phase III trial utilizing NK-cell therapy for patient with DLBCL in Korea as well as in Asia.

Keywords: NK cell therapy, DLBCL, phase III trial, rituximab, ADCC

P22 Ex-vivo Expansion of Lymphocytes from Cord Blood Using Recombinant Human Fibronectin Fragment (CH-296; RETRONECTIN®)

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[Introduction] RetroNectin® (RN) is widely used in retroviral gene therapy to enhance gene transfer efficiency. Together with anti-CD3 antibody (OKT3), RN is known to enhance T-cell proliferation while conserving the naive phenotype. It has been demonstrated that in comparison to more differentiated phenotypes, naive T-cells are more active in mediating tumor regression. Thus, T-cells expanded with RN (RN-LAK cells) are expected to have greater potential to suppress tumor growth than T-cells expanded by conventional methods, which show differentiated phenotypes in vivo. Cord blood (CB) transplantation is a promising alternative when no human leukocyte antigen-matched donor is found, due to the rapid availability of the graft and its biological properties. However, immunologic features of CB hematopoietic stem cells and immune cells also result in significantly delayed engraftment, poorer immune reconstitution and increased risk of graft failure, which in turn increases the rate of infectious complications, recurrence and transplant-related mortality. Donor lymphocyte infusion (DLI) after hematopoietic stem cell transplantation has proven to be effective in treating residual or relapsed malignancy in some cases. Patients transplanted with unrelated CB lack this therapy option, and the low cell dose in the CB graft which rules out DLI preparation at the time of graft procurement. Ex-vivo expansion of T-cells from CB graft presents a way for overcoming the latter problem. In this study, we considered the potential of RN in ex-vivo expansion of CB mononuclear cells.

[Method] CB mononuclear cells were cultured in 6 well culture plates, coated with RN+OKT3 or OKT3 alone, for 4 days (day 0-4). At day 4, cells were transferred to T25 flasks, and cultured for another 10 days without RN nor OKT3. At day 14, cultured cells were counted and viability was calculated using Turk's stain solution and trypan blue stain solution. Flow cytometry was used to analyze cell surface markers of the cultured cells. We compared 9 media for proliferation efficiency in the number of cells.

[Results] From 9 media, we selected KBM550, which showed superior proliferation efficiency in the number of cells. 6.5×10^5 CB mononuclear cells could be expanded to approximately $5\text{-}27 \times 10^7$ RN-LAK cells. The number of expanded cells at day 14 was larger when compared to LAK cells expanded by a conventional method using anti-CD3 antibody alone.

[Discussion] We were able to sufficiently expand RN-LAK cells from cord blood. These cells may be useful in DLI or add-back therapy following cord blood transplantation. Further investigation is necessary to evaluate the potentials of these cells.

P23 The Study of Attitudes and Experiences toward Stem Cells among Researchers in Life Science.

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Purpose

This study examines the attitudes, experiences, current situations, and educational needs of researches in life science in order to develop an educational program for stem cell related research ethics.

Method

A total of 275 researchers in life science participated in this study. The instrument used was a self-reporting Likert-type questionnaire consisting of 38 assumptions related to stem cell ethics and stem cell related characteristics.

Result

In the attitude score toward stem cell research, average score of all subjects was 3.26. Items shown a positive response were *Informed consent*, *Moral superiority of adult stem cell research*, *Ethical control of science*, items shown a negative response were *Do not use the remaining fetal tissue*, *Replication of animal should be restrict*, *hESC research ought not to be allowed*, And, it was differ according to research field in *human cloning*, *informed consent* items.

And attitude score was differ according to age, gender, religion, necessity of stem cell ethics education, intention of ovum donation. Additionally, only 37.8 percent experienced stem cell ethics education, but most respondents agreed with need of education.

Conclusion

Finally, stem cell researchers should make an effort to identify ethical problem related to stem cell research in each specialization. Furthermore, there is an need to develop well-designed and integrating stem cell ethics education program for not only stem cell researchers but also life science and medical students.

P24 Two-component Messenger RNA-based Vaccines Generate a Strong Anti-tumor Effect in Combination with Radiation Therapy

Mariola Fotin-Mleczek[1)], Christina Lorenz[1)], Katharina M Duchardt[1)], Stephan Huber[2)], Karl-Josef Kallen[1)]

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Complexation of mRNA with the cationic protein protamine generates two-component tumor vaccines with two principle activities: antigen expression and concomitant immune activation.

Compared to their single components, two-component mRNA vaccines induce superior innate as well as balanced adaptive immune responses: these comprise humoral as well as T cell mediated immunity and include induction of memory T cells. Immunization of mice bearing ovalbumin (Ova) positive EG7 tumors with a two-component anti-Ova mRNA vaccine mediates a strong anti-tumor response also under therapeutic conditions. Anti-tumor efficacy diminishes though with the size of the established tumors.

To test whether a combination of our vaccine with radiotherapy could achieve a therapeutic effect against large, clinical size tumors, mice were inoculated with EG7 tumor cells and left untreated until the tumors reached a volume of around 200 to 250 mm^3. Mice were treated either with immunotherapy alone, radiation alone or combined radioimmunotherapy. Immunotherapy alone was only marginally effective against these large tumors, whereas radiation of the tumors induced transient growth stagnation for about 7 days. However, combined radioimmunotherapy dramatically improved anti-tumor efficacy. All mice thus treated showed pronounced tumor regression, causing complete and sustained eradication of the tumor in 3/7 mice. Median survival in the combination group was 45 days, compared to 9 days for untreated mice, 11 days for mice receiving immunotherapy and 17.5 days for mice in the radiation group.

These findings highlight that integration of immunotherapies with standard cancer therapies such as radiation creates highly synergistic anti-tumor effects, that may have the potential to enable long-term survival in cancer patients and ultimately to open a therapeutic avenue to cancer cure.

P25 The Anti-tumor Effect of Messenger RNA-based Vaccines is Mediated by Inducing Key Immune Response Pathways in the Tumor

Christina Lorenz, Mariola Fotin-Mleczek, Katharina M Duchardt, Karl-Josef Kallen

CureVac GmbH, Germany

Two-component tumor mRNA-based vaccines exhibit two principle activities: antigen expression and concomitant immune stimulation. Thus, innate as well as adaptive immune responses are induced. Intradermal vaccination of tumor-bearing mice with the two-component mRNA based vaccine mediates a strong anti-tumor response under therapeutic conditions.

Depletion experiments demonstrate that CD8 T cells mediate the anti-tumor effect, but also the necessity of CD4 T cell help. FACS analysis of tumor tissue revealed increased infiltration of activated CD8 T cells and their prolonged persistence at the tumor site in response to vaccination. Moreover, therapeutic vaccination inhibited a tumor-induced increase of myeloid derived suppressor cells (MDSCs) in the spleen and at the tumor site.

To further elucidate the the mechanism of our mRNA-based anti-cancer vaccine, tumor-bearing mice were vaccinated repeatedly and tumors removed at different time points. Microarray analysis of total mRNA extracted from removed tumors revealed clear differences between vaccinated and control mice. Already after two vaccinations, before the effect on tumor size became visible, a wide variety of immune response related genes was upregulated in vaccinated mice. A large proportion of these genes is associated with activation and cytotoxicity of NK and T cells, Th1 polarization or chemotaxis.

Our findings conclusively demonstrate the comprehensive nature of the immune response induced by our mRNA based vaccines and the variety of pathways involved in the anti-tumor effect. Better understanding of the mode of action allows further improvement of our vaccine approach and the selection of potential targets for combination therapies. Additionally, the approach opens new possibilities for targeted monitoring of induced immune responses.

P26 In Vivo Delivery of Interferon Gene Enhances Antitumor Immunity after Autologous Hematopoietic Stem Cell Transplantation

Kenta Narumi, Kazunori Aoki

Section for Studies on Host-Immunre response, National Cancer Center Research Institute, Japan

Purpose: In an autologous hematopoietic stem cell transplantation (HSCT), the transfused T cells recognize low-affinity self antigens including tumor-associated antigens under the condition of lymphopenia-induced homeostatic proliferation (HP) and lead to a break in tolerance against tumors. HP-driven antitumor responses, however, decay gradually since they are vulnerable to a development of tolerance. Type I interferon (IFN) has important roles in regulating the innate and adaptive immune system. In this study, we examined whether HP-induced antitumor activity can be enhanced by IFN-alpha gene transfer during a physiologic immune reconstitution and investigated mechanisms of the enhancement of antitumor immunity. **Methods**: BALB/c mice received a lethal (9 Gy) irradiation, and were injected intravenously with bone marrow cells and splenic T cells from donor BALB/c mice. Then, murine colon cancer cells (CT26) were injected subcutaneously into both legs of transplanted BALB/c mice. When the subcutaneous tumor was established, it was injected with IFN-alpha-expressing plasmid (pIFN-alpha) complexed with cationic liposome (DMRIE-DOPE). **Results and discussion**: An intratumoral IFN-alpha gene transfer resulted in synergistic tumor suppression, and the antitumor effect was evident even in distant subcutaneous tumors that were not transduced with the IFN-alpha vector. As another model of distant metastasis, luciferase gene-expressing CT26 cells (CT26-Luc) were injected beneath the splenic capsule to generate liver metastasis, and CT26 cells were inoculated into the right leg. Intratumoral IFN-alpha gene transfer into subcutaneous tumors on the legs suppressed the growth of abdominal tumors and liver metastases, which were evaluated by photon-counts on the IVIS imaging system. There was no significant toxicity in the treated animals. Regarding the timing of intratumoral IFN-alpha gene transfer, the injection of pIFN-alpha at 8 weeks after transplantation did not enhance the antitumor immunity, whereas a substantial antitumor effect was observed by IFN-alpha gene transfer in the earlier period (2-6 weeks) after the transplantation, suggesting that intratumoral IFN-alpha gene transfer during immune reconstitution can induce a synergistic antitumor effect. To analyze antitumor immune mechanisms of the combination therapy, we isolated $CD11c^+$ cells from the IFN plasmid-injected tumors in syngeneic HSCT mice. The intratumoral delivery of the IFN-alpha gene promoted the maturation of $CD11c^+$ cells in the regional lymph nodes and effectively augmented the antigen-presentation capacity of the cells. An analysis of the cytokine profile showed that the $CD11c^+$ cells in the treated tumors secreted a large amount of immune-stimulatory cytokines including IL-6. The $CD11c^+$ cells rescued effector T-cell proliferation from regulatory T cell-mediated suppression, and IL-6 may play a major role in this phenomenon. A combination of the intratumoral IFN gene transfer with autologous HSCT is a promising immunotherapy for solid cancers, enabling a unique synergism between the activation of tumor-specific immunity and suppression of immunotolerant environment.

P27 The Next Generation TCR Gene Therapy Using siTCR Vector and RetroNectin Expansion Method

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Adoptive T cell therapy with gene-modified lymphocytes to express tumor antigen specific T-cell receptor (TCR) has been shown as an attractive strategy to treat patients with malignancy. However, the limited efficacy of TCR gene therapy has been reported to be associated with inefficient surface expression of transduced TCRs. The introduced TCR alpha and beta chains have been reported to mispair with endogenous TCR alpha and beta chains, resulting in insufficient formation of heterodimers of therapeutic TCR. Moreover, a serious safety concern on the generation of T cells with unexpected specificities, including self-reactive T cells caused by TCR mispairing has been postulated. In addition, endogenous TCR competes with introduced TCR for CD3 molecules, resulting in inefficient cell surface expression of the therapeutic TCR heterodimers, because the stable cell surface expression of TCRs requires TCR assembly with CD3 molecules. The expression level of the transgene can be enhanced by increasing the vector copy number in the transduced cells, however, the risk of infusing cells with aberrant vector insertion site that could promote proto-oncogenic activation, tumor suppressor gene inactivation, or chromosomal instability has been suggested to be decreased by restricting vector copy number of transduced cells. Therefore, a strategy for achieving high expression of the transduced TCRs with low copy numbers is required for clinical application. Also, in TCR gene therapy, it has been still problematic to set up a large number of cells because apheresis gives patients a big burden, so development of efficient T cell expansion method from small amount of blood is desired.

In this study, we developed novel "siTCR" retroviral vectors encoding both siRNA constructs that specifically knockdown endogenous TCRs and codon-optimized, siRNA-resistant TCR alpha/beta chains specific for human tumor antigens. Human lymphocytes transduced with these vectors exhibited high expression of the introduced tumor-specific TCR on the cell surface accompanied with reduced endogenous TCR at low proviral copy numbers, resulting in enhanced cytotoxic activity against antigen-expressing tumor cells. Because the target of this novel strategy is endogenous TCR, siTCR vectors may work as a powerful tool for any TCR gene therapy without dependency of TCR variation.

We have also developed an efficient expansion method to generate large numbers (over 10^9 cells) of genetically modified T cells from small amount of whole blood (50-100 ml) without apheresis. "RetroNectin" a recombinant human fibronectin fragment, is well known as a strong enhancer of gene transfer in retroviral transduction, and is also a powerful tool for a large scale T cells preparation because its co-stimulation with anti-CD3 mAb enhanced cell proliferation while conserving the CCR7+CD45RA+ naive phenotype of T cells.

We are in process to start clinical trials using siTCR vectors expressing HLA-A*2402 restricted MAGE-A4 or WT1 specific TCRs, combined with RetroNectin expansion method.

<Late Break Abstract>

P28 Suicide Gene Modified T Lymphocyte Infusion Therapy Against Relapsed Leukemia After Allogeneic Stem Cell Transplantation

Shin Kaneko[1),2)], Yasushi Okoshi[2)], Noriko Nemoto[3)], Yuichi Hasegawa[2)], Kazumi Susukawa[2)], Takashi Fukushima[4)], Makoto Otsu[1)], Ryo Sumazaki[4)], Chiara Bonini[5)], Craudio Bordignon[5)], Yoshio Harada[4)], Hiromitsu Nakauchi[1)], Shigeru Chiba[2)]

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Peripheral T lymphocytes exert their proliferative potential and effector functions by recognizing antigens on tumor cells and play a central role in tumor immunity, and therefore, a substantial number of clinical protocols have been proposed using manipulated and ex vivo expanded T lymphocytes (June CH,J Clin Invest, 2007). To date, however, such highly expanded T lymphocytes have not been proven fully effective in treating diseases, because, at least in part, those cells are usually differentiated terminally and lose potentials of long-term survival, proliferation, and effector functions (Krevanoff CA, Immunol. Rev., 2006).

To avoid such inefficiency caused by an ordinary ex vivo expansion protocol with OKT-3 (anti-CD3 antibody) stimulation alone, we have established a new ex vivo T lymphocyte manipulation protocol with anti-CD3/anti-CD28 antibody-conjugated magnetic beads and common gamma chain cytokines. This method allows us to preserve genetically modified, alloreactive, and self-renewing central memory T lymphocytes (Kaneko S, Blood, 2009). According to favorable results obtained from a set of humanized animal experiments, a cell processing protocol of TK-DLI gene therapy, which is conducted as a clinical trial against relapsed leukemia in Tsukuba University Hospital, has been changed to the new one. By the end of 2009, the internal review board and the Ministry of Health, Labour, and Welfare approved the amended TK-DLI clinical protocol for other 5 relapsed leukemia patients. The protocol is now open for the registration.

We expect a better clinical outcome with the new protocol than the former one (1 complete remission in 5 relapsed leukemia patients). At the meeting, we will discuss details of the amended protocol and progression of the clinical trial.

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* The end declaration went out on August 27th, 2010.

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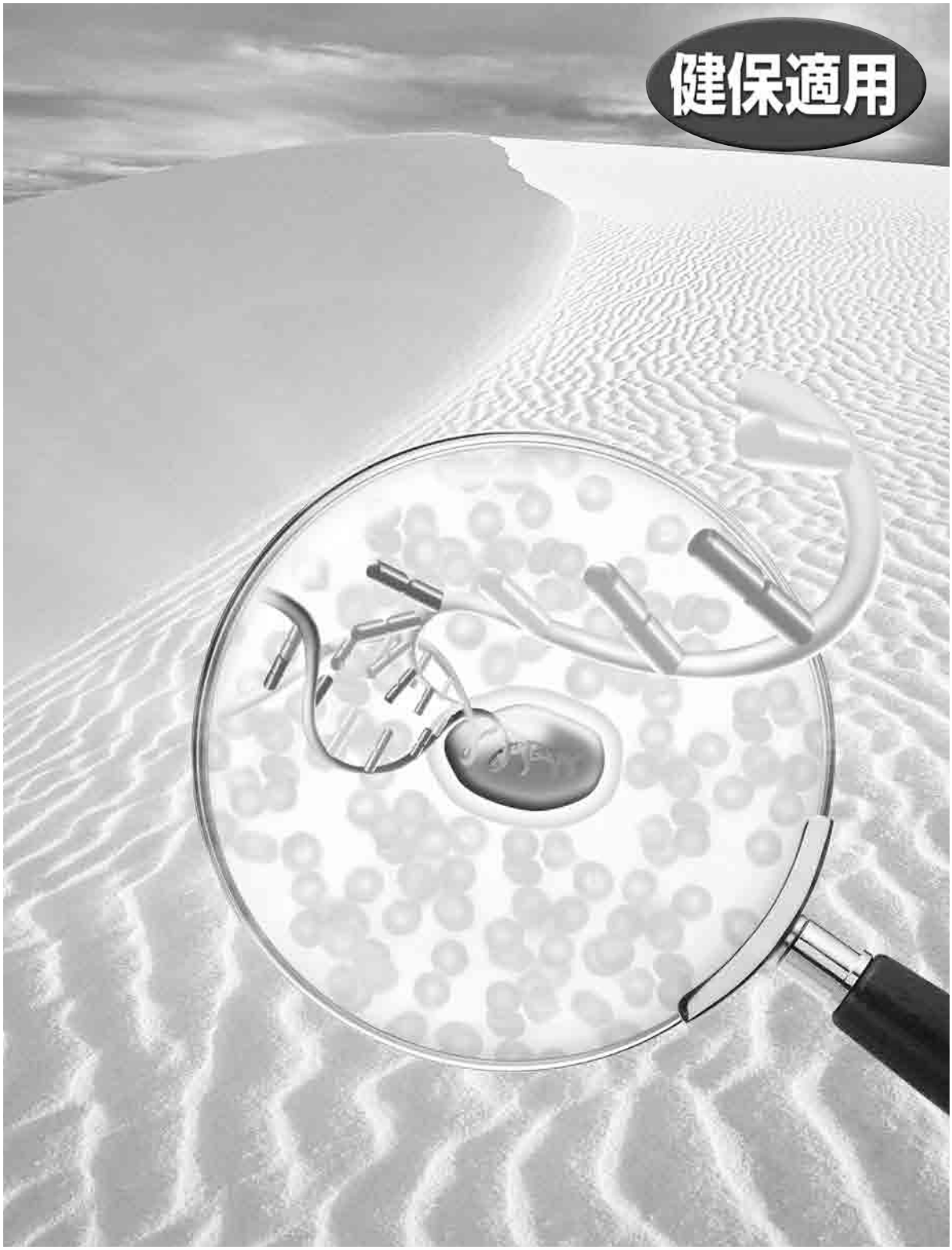

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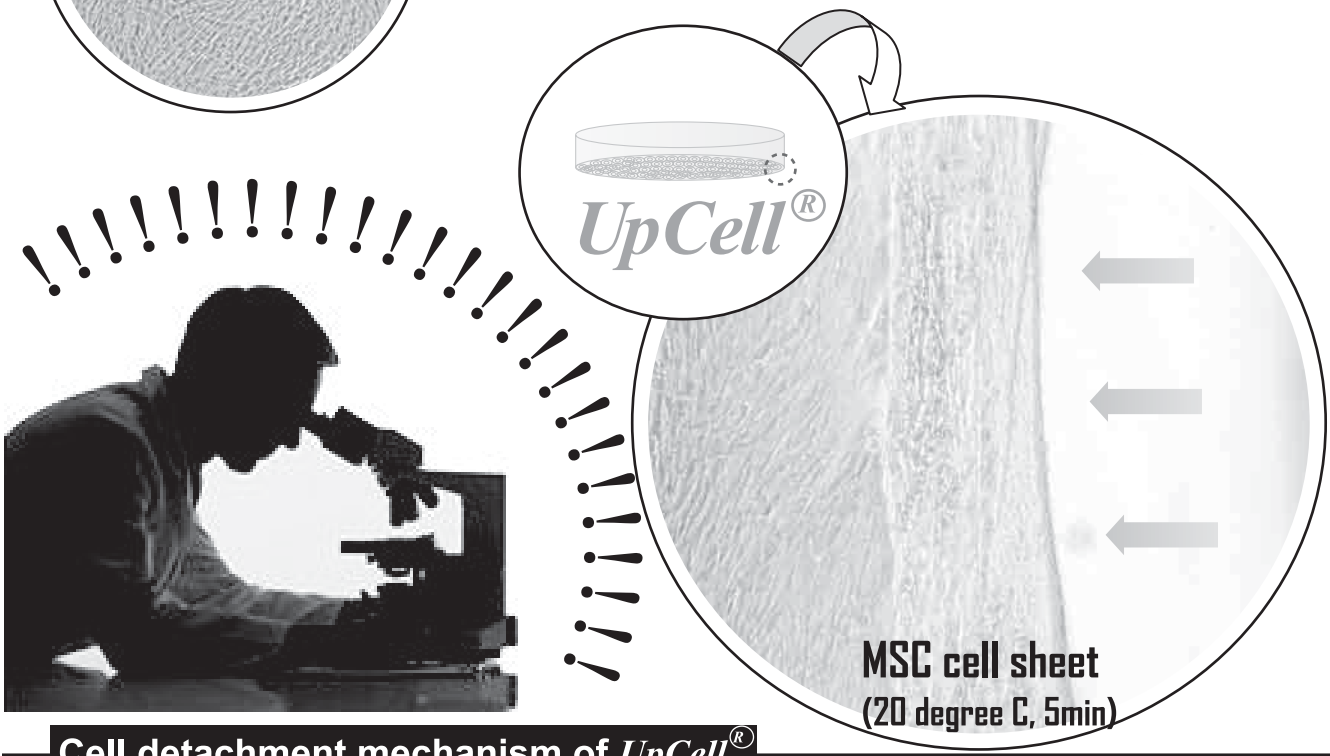

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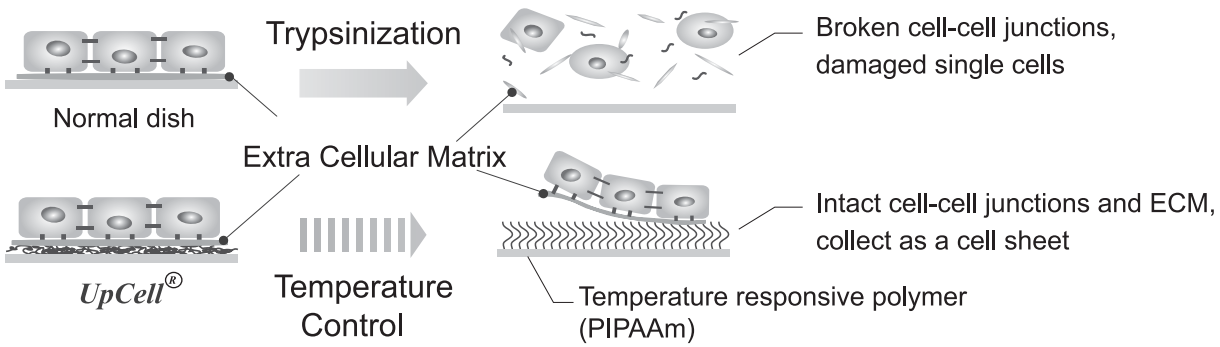

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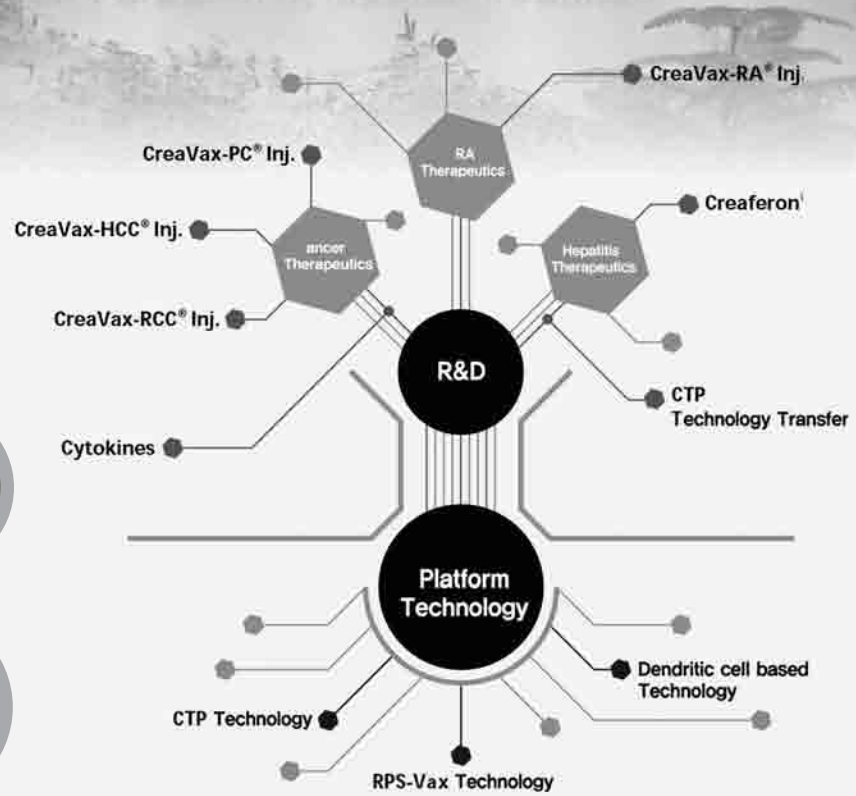

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