Volume VII, Issue I
Winter '12

January—March 2012

InterLink

Linking the international community of TERMIS

Special points of interest:

- 2012 TERMIS World Congress—Early Registration Rate Available before May 30, 2012
- TERMIS-NA to TERMIS-AM
- Solicitation of Proposals to Host
  - 2014 AP Conference
  - 2014 AM Conference
  - 2015 World Congress (rotates to AM)
- TERMIS Thematic Group Updates

Inside this issue:

Letter from the Editor

Dear TERMIS Members,

Publishing is a daily business for us in the academic world and it has major implications on our careers, funding, job satisfaction etc. In the 21st century more and more journals come to the market and try to get an impact factor as soon as possible and then move up the ladder in the rankings; however the question is "does the science improve and progress or do we only add quantity and not quality to the system?". David Williams and I are planning a podium discussion on that topic with editors of leading journals in the biomaterials and tissue engineering field to be held at the upcoming TERMIS meeting in Vienna. Hence, I thought I would dedicate a few philosophical lines of to this topic.

Last month, I received the referee reports from one of the top journals in our field. The reports were quite opposite in nature; one said accepted without any changes and the other was rejected! I am sure you faced similar referee reports in the past and one might call them a deliberate paradox, or on a lighter note an oxymoron. In Zen Buddhism, a deliberate paradox is termed a"koan"; one of the best known being the sound of one hand clapping, which is used in mediation to impose reason to face up to the boundaries of the foreseeable, to trim down rational discourse to silence.

The analogy I like most to overcome my frustration receiving highly contradictory referee reports and replace it with a sense of humor is the one from my applied math colleague. We collaborate in the area of 3D cancer models and combine experimental and computational models and the nature of those manuscripts are often challenging, he called the other day a journal referee report of this kind "parallel collision". How funny, but somehow correct is that term! Since we learned at primary school, parallel lines are ones that do not intersect, or intersect only at infinity, which is for matter-of-fact never, and certainly beyond any dimension known or knowable to us. I hope I have stimulated your thoughts and wish you all the best of luck either way - in your next journal referee assignment or the receiving end of a referee report after submission of a manuscript!

I look forward seeing you at the podium discussion in Vienna!

Yours sincerely,

Professor Dietmar W. Hutmacher PhD (NUS), MBA (Henley)

Upcoming TERMIS Conferences

2012 TERMIS World Congress

September 5-8, 2012

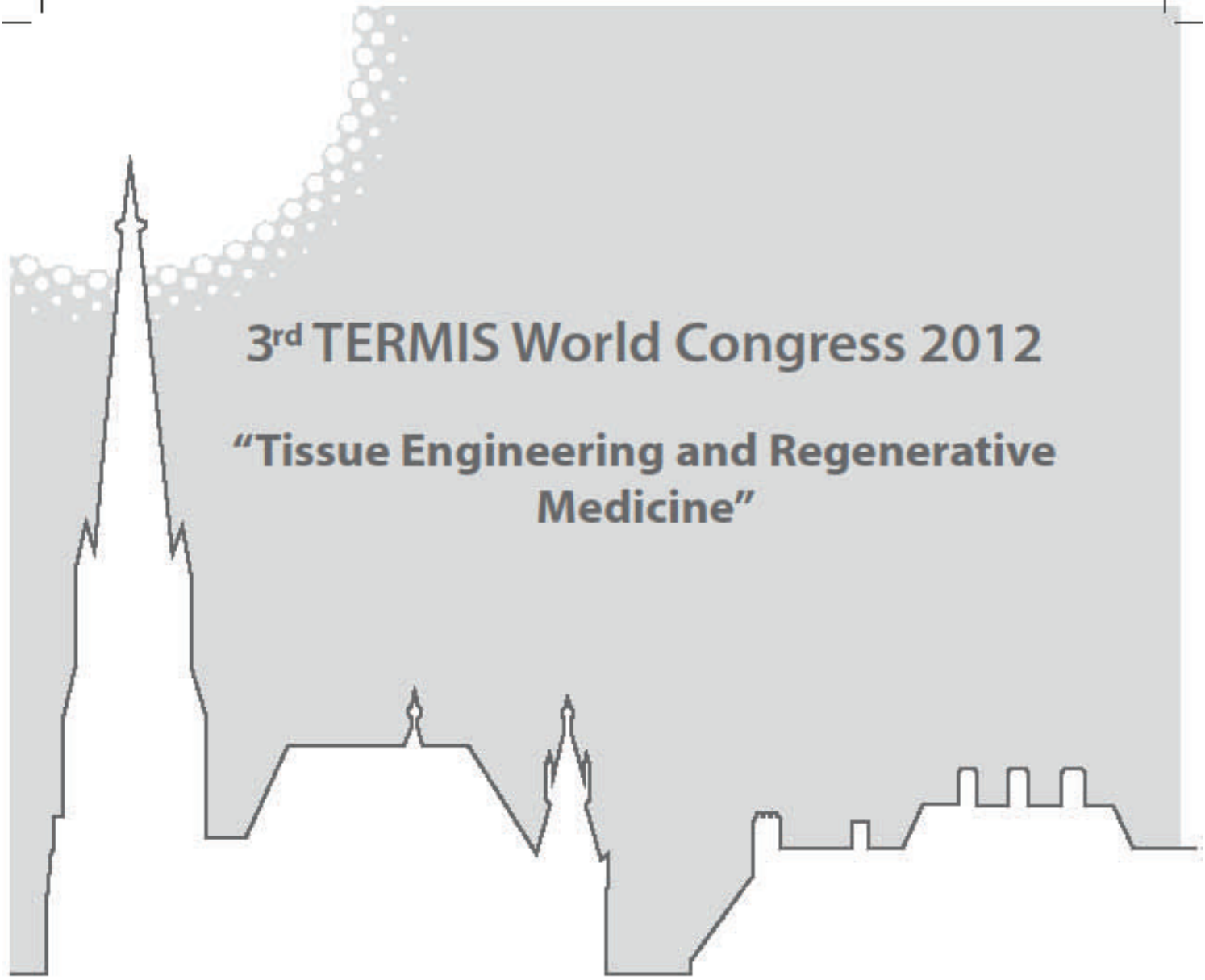
Vienna, Austria

www.termis.org/wc2012

2013 TERMIS-EU: Istanbul, Turkey
Conference Dates: June 12-15, 2013
Conference Chair: Erhan Pişkin, PhD

2013 TERMIS-AP: P. R. China
Conference Dates: October 2013
Conference Chair: Yilin Cao, MD, PhD

2013 TERMIS-AM: Atlanta, GA
Conference Date: December 2013
Conference Chair: Robert E. Guldberg, PhD



3rd TERMIS World Congress 2012

"Tissue Engineering and Regenerative Medicine"

September 5 - 8, 2012 Vienna, Austria

www.termis.org/wc2012

LBI Trauma

termis.

Society of the Advancement of Research in Shock and Tissue Engineering

EXPERTISSUES

ADVA

2012 TERMIS World Congress—Vienna, Austria

The abstract submission is now closed!

The 2012 World Congress organizers have received approximately 2,000 abstracts. The scientific program committee is now reviewing all of the abstracts. Notifications will be sent in April 2012.

Thank you to everyone who submitted an abstract. The organizers will be in contact with you in April 2012.

Early registration will be open in April. The early registration will be available until May 30, 2012.

Registration includes admission to the congress sessions, the exhibit area, coffee breaks, conference bags, work lunches, and the social events on Thursday and Friday.

Hofburg Congress Centre

www.termis.org/wc2012

Pre-Meetings & TERMIS Evening Event

"Stem Cell Update Salzburg" Symposium Tour

September 3rd-5th, 2012

Price: €750 per person—Includes symposium, coffee break, all meals for 3 days, hotels, coach bus, guide and entrance fee)

A minimum of 35 participants is required (100 maximum)

Registration is separate.

International Society for Cellular Therapy (ISCT) pre conference meeting will be held on Wednesday, September 5th, 2012.

2nd International Meeting of the International Placenta Stem Cell Society (IPLASS) will be held on Wednesday, September 5th, 2012.

A special event is planned for Sunday, September 9th, 2012 at Haydn Mass at Pfarre St. Josef ob der Laimbrube at 9:30.

"Early registration OPENS in April 2012!"

Why Become an Exhibitor or Sponsor of the 2012 TERMIS World Congress?

- Exposure to local, national and international audience of decision makers and influential people involved with TE/RM.
- Opportunities to raise your company's profile amaongst a valuable target audience before, during and after this event
- Recognition including acknowledgement and clear demonstration of your organization's involvement, commitment and support with this market.
- Valuable insights, information and exposure to the latest developments in this field.
- Feel free to attend the scientific sessions.
- Multidisciplinary audience: clinicians, specialized scientists, engineers and researchers in top academic institutions and companies.
- There are **NO OTHER TERMIS meetings in 2012**

To received more information on exhibiting or sponsoring the 2012 World Congress, contact:

Mr. Klaus Ehrenmüller
Med.ex medical exhibition company
klause@medex.co.at

TERMIS-North America to TERMIS-Americas

A Message from the TERMIS President—Stephen Badylak

I congratulate the leadership of the North American chapter for their willingness to embrace this forward thinking strategy in renaming of the "North American chapter". TERMIS recognizes the continuously expanding geographic interest and activity in tissue engineering / regenerative medicine. Our goal is to provide an inclusive structure from an organizational perspective, and it is clear that the new name (TERMIS-AM) reflects the contributions of individuals from the furthest reaches of Canada to the southern tip of South America. We initiated these discussions almost 2 years ago and I want to thank the former North American chair – Tony Mikos – and the present Americas chair – Bob Guldberg – for their efforts in making this change a reality.

Sincerely,

Stephen F. Badylak, DVM, PhD, MD

President of TERMIS

TERMIS-NA Name Change to TERMIS-AM

Dear TERMIS Members,

Over the last 18 months, with encouragement by the TERMIS Board, the TERMIS-NA Council and the TERMIS-NA Membership Committee has been discussing the possibility of changing the name of TERMIS-NA to TERMIS-Americas. The rationale for this was to provide our Latin American members a home under TERMIS-Americas. TERMIS-NA did not want to rush into this decision without receiving feedback from the Latin American community. A survey was conducted and distributed to the members within Latin America. Throughout the process, it was very important for the committee to have input from the Latin American community and to keep the lines of communication open. From the responses, it was unanimous that incorporating the Latin American community into the North American Chapter would benefit all parties.

In December 2011, the TERMIS-NA Council unanimously approved the change of the TERMIS-North America to TERMIS-Americas. We are happy to announce that as of last week the name of the Tissue Engineering and Regenerative Medicine International Society of North America (TERMIS-NA) has been officially changed to the Tissue Engineering and Regenerative Medicine International Society – Americas (TERMIS-AM).

The members within Latin America are considered members of TERMIS-AM, but would not be subjected to paying membership dues. The members within Latin America are still considered part of the emerging countries, but have a home in the TERMIS-AM.

We welcome the Latin American community as members within the TERMIS-AM. This is a very exciting time and we look forward to working closely together in future endeavors. If you have additional feedback on initiatives to encourage collaboration, please do not hesitate to contact us.

Sincerely,

Robert Guldberg
TERMIS-AM Chair

And

John Fisher
On behalf of the TERMIS-AM Membership Committee

And

Stephen Badylak
TERMIS President

TERMIS Chapter Updates

Asian-Pacific Chapter

Solicitation of Proposals for the 2014 TERMIS-AP Chapter Meeting

The TERMIS-AP Chapter Council would like to announce the solicitation of proposals for hosting the 2014 TERMIS-AP Chapter meeting. If you are interested in hosting the 2014 TERMIS-AP Chapter meeting, please submit your request to Sarah Wilburn at swilburn@termis.org. You will be provided with a meeting host form that asks detailed questions about the meeting organizers, location/venue, program, and meeting financials. When proposals are submitted, they are reviewed by the respective chapter council and an official vote is conducted. Click here to view details about hosting a TERMIS meeting.

The deadline for submitting proposals for the 2014 TERMIS-AP Chapter Meeting is Monday, April 30, 2012.

Americas Chapter

2012 TERMIS-AM Awards Program

The TERMIS-Americas Awards Program will be accepting nominations for the various TERMIS-Americas awards this year. **The deadline to submit nomination packages for the 2012 TERMIS-AM Awards Program is Friday, May 25, 2012.**

The complete list of awards is available for viewing online. The criteria for submitting a nomination must be followed in order for the nomination to be accepted.

The awardees will be presented with their award at the 2012 TERMIS World Congress in Vienna in September.

Americas Chapter

The TERMIS-Americas Council and TERMIS-Americas Meetings Committee would like to announce the solicitation of proposals to host the 2014 TEMRIS-Americas Chapter Conference.

If you are interested in hosting the 2014 TERMIS-Americas conference, please submit your request to Sarah Wilburn at swilburn@termis.org. You will be provided with a meeting host form that asks detailed questions about the meeting organizers, location/venue, program, and meeting financials. When proposals are submitted, they are reviewed and selected by the TERMIS-Americas Meetings Committee and approved by the TERMIS-Americas Council.

The deadline for submitting proposals for the 2014 TERMIS-Americas conference is Wednesday, May 30, 2012.

Solicitation of Proposals for the 2015 TERMIS World Congress

The TERMIS-Americas Chapter Council would like to announce the solicitation of proposals for hosting the 2015 TERMIS World Congress that rotates to North America. If you are interested in hosting the 2015 TERMIS World Congress, please submit your request to the administrator, Sarah Wilburn at swilburn@termis.org. You will be provided with a meeting host form that asks detailed questions about the meeting organizers, location/venue, program, and meeting financials. When proposals are submitted, they will be reviewed by the TERMIS-Americas Meetings Committee & TERMIS-Americas Council and an official vote is conducted.

The deadline to submit proposals is Friday, June 29, 2012.

For more information on the solicitation of proposals for any chapter meetings ,

please contact Sarah Wilburn.

Overview of the 2011 TERMIS-NA Houston Conference

Approximately 800 people attended the TERMIS-North America 2011 annual conference in December in Houston. The annual meeting is the premier networking and educational event for the regenerative medicine and tissue engineering industry.

This year's meeting was hosted by Rice University, with **Dr. Antonios Mikos, Director, Center for Excellence in Tissue Engineering and the J.W. Cox Laboratory for Biomedical Engineering, and Dr. Jennifer West,** Chair of the Department of Bioengineering, as the General Co-Chairs. Dr. West, along with **Dr. K. Jane Grande-Allen**, Associate Professor, Department of Bioengineering, served as the Scientific Co-Chairs. The main theme of this year's conference was "Scaffolds in Tissue Engineering: Bridging Matrix Biology and Biomaterials Science". The event focused on the latest tissue engineering/regenerative medicine approaches to restoring the function of damaged and diseased tissues and organs. Presentations focused on the platform/enabling technologies and many of the broader cross-cutting challenges facing an international community of scientists, clinicians, students, business leaders, entrepreneurs, and representatives of government funding agencies.

Keynote lecturers included: **Kristi S. Anseth, Ph.D.,** University of Colorado; **Christopher S. Chen, M.D., Ph.D.,** University of Pennsylvania; and **Molly S. Shoichet, Ph.D.,** University of Toronto.

Altogether, the conference had over 180 oral presentations, over 300 poster presentations, and 40 sponsors and exhibitors. The meeting drew attendees from almost every state, and received registrations from international participants from over 30 countries. The audience included a mix of academicians, corporate professionals, and government representatives, with CEOs, principal investigators, post-doctoral fellows, pre–doctoral students, and other researchers.

The conference provided an ideal setting for academic networking, encouraging the formation of new exchanges and collaborations. Research presentations have continued to increase in this young field, and the meeting was full of poster and platform presentations, deliberately positioned within the exhibit areas for increased exposure and community interaction.

TERMIS-NA has established several award mechanisms to recognize outstanding scientists in the field, including the **Lifetime Achievement Award,** awarded to **Dr. Robert S. Langer;** the **Senior Scientist Award,** presented to **Dr. David J. Mooney;** the Mary Ann Liebert, Inc. Outstanding Student Award, awarded to Dr. Jessica A. DeQuach; and the Young Investigator Award which was given to Dr. F. Kurtis Kasper. In addition, **Brian O. Diekman and Melissa Krebs, Ph.D.** were presented with the **4th annual Wake Forest Institute for Regenerative Medicine Young Investigator** Awards to recognize outstanding achievements.

Patrick Spicer, a graduate student from Rice University, chaired the committee involved in developing programming for the Student and Young Investigator Section of North America (SYIS-NA.) The role of SYIS is to assist and encourage young researchers to network and interact with experts in the field and to foster personal professional development. A few of the onsite activities available to student attendees included a Career Panel discussion, the Student-Meet-Mentor lunch where students have the opportunity to meet one-on-one with mentors in their particular fields of interest, and a student reception that included tours of the Rice University Lab.

A few new one-day specialty workshops were introduced to the conference this year, including **Advances in Tissue Engineering for Pediatric Applications**, organized by Drs. Jane Grande-Allen and Jeffrey Jacot of Rice University, and sponsored by Texas Children's Hospital. This forum featured presentations from various experts describing research investigations on pediatric tissue engineering applications, including but not limited to: **cardiovascular, orthopedic, maxillofacial, gastrointestinal, and urological** discoveries. Another half-day event, entitled **Cells, gels and alginate - An Alginate Technology Tutorial,** was organized and sponsored by NovaMatrix. The intent of this hands-on tutorial was to give participants a working knowledge of this biopolymer and to have experienced some of the alginate-based technologies relevant to tissue engineering and regenerative medicine. The last day of the conference featured "**Regenerative Medicine's Challenge to Cure",** organized by Mark E. K. Wong, DDS, Chairman and Program Director, Department of Oral and Maxillofacial Surgery, The University of Texas School of Dentistry at Houston. By presenting the clinical pathways and challenges for some of the most disabling and debilitating diseases and injuries, researchers offered in-depth discussions on the latest therapies available for several of the world's most problematic diseases and injuries. Presenters described the challenges they have faced in discovering cures or treatments.

Tissue engineering and regenerative medicine have become critical scientific disciplines. The TERMIS-AM meeting continues to grow and mature every year, and it has now become the major venue for the presentation of basic research, and its clinical application. For over 10 years, this meeting continues to foster interactions among basic scientists engaged in discovery and development, translational researchers who bring scientific discoveries to the clinical forefront, clinicians, and those engaged with funding, regulatory and commercial endeavors.

Note: The next TERMIS-Americas Conference will be held in 2013 in Atlanta, Georgia, and will be hosted by Georgia Tech.

The 2012 TERMIS World Congress, held every three years at a venue where all TERMIS chapters meet as a whole, will be held September 5-8 in Vienna, Austria. Visit the TERMIS main website for more details, www.termis.org.

For more information, contact Anita Caufield, Executive Producer, for TERMIS-Americas.

The name of the TERMIS-NA officially changed to TERMIS-AM in March 2012.

TERMIS Thematic Groups Updates

Biofabrication Thematic Group

Chair:

Prof. Dr. Wei Sun

Vice Chair:

Dr. Lorenzo Moroni

Secretary:

Dr. Tim Woodfield

The aim of the Biofabrication thematic group is to stimulate discussion and collaborations around fundamental and applied research activities focused on 3D cell model and functional tissue regeneration. The proposed thematic group will focus on the development of using novel physical, chemical, biological, and/or engineering process for: 1) 3D tissue scaffolds and tissue constructs; 2) computer-aided biofabrication and tissue engineering; 3) cell/tissue printing, patterning and organ printing; 4) construction of cell assemblies as tissues for regenerative medicine, disease models and drug models; 5) integrated bio-nano fabrication and bio-micro fabrication; 6) cell-integrated biological systems, microfluidic devices, biosensors, and biochips; and 7) protein/biomolecule printing and patterning.

The Biofabrication thematic group was founded in November 2011 by founding members coming from the three continental chapters of TERMIS and of the International Society of Biofabrication. The group is chaired by Prof. Wei Sun and Dr. Lorenzo Moroni (secretary: Dr. Tim Woodfield) and will meet for the first time in June 2012 in occasion of the World Biomaterials Conference in China where the founding members will discuss its implementation.

A symposium on Biofabrication will be also organized at the 2012 TERMIS World Congress in Vienna this year, which will be followed by the International conference on Biofabrication in Manchester at the end of October. We warmly invite all TERMIS members and conference participants to join us in the symposium and participate to the Biofabrication conference in Manchester for a "taste" of the scientific topics treated within the biofabrication thematic group.

Musculoskeletal Thematic Group

The main objective of our group is to facilitate swifter clinical application of new technologies. This has been and will further on be achieved by establishing a network consisting of clinicians, scientists, researchers and engineers. The respective network ensures a fast and efficient communication between its members and guarantees that new research results reach clinicians and surgeons as well as university students in a short time.

To obtain the best results, it is paramount for all stake-holders to collaborate more closely. This especially applies to the interaction between clinicians, scientists and engineers.

In addition to establishing an efficient network of experts, the focus of research has to be extended. So far, research has predominantly concentrated on scaffolds, stem cells and signaling molecules. Thus more research on biomechanical stimulation and angiogenesis for remodeling of musculoskeletal tissue for long term efficacy and prevention of resorption is urgently required.

Our priority is to promote more research in vascularisation and in understanding the regulation of cytokines during the growth of different types of new tissue. The discontinuous release of cytokines seems to play an important role and has previously been ignored in many publications.

Finally, the time-frame of releasing new research findings has to be condensed. Manuscripts concerning new research results have to be published faster.

In conclusion, to successfully address complex tissue engineering issues and to achieve the regeneration of complete organic systems requires efficient and encompassing interdisciplinary cooperation and collaboration involving all stakeholders.

To ensure a top-level and up-to-date state of research, our group organized symposia at various TERMIS meetings:

During the EU 2011 Annual Meeting in Granada in June 2011, Prof. Dr. Martijn van Griensven, Prof. Dr. Peter ten Dijke and Dr. Karl-Heinz Schuckert held a symposium titled "Translational Bone Engineering".

Prof. Dr. Swee-Hin Teoh and Prof. Dr. Hae-Ryong Song organized a symposium during the Asia Pacific Meeting in August 2011; and during the North American Meeting in Houston in December 2011 our group was represented by Dr. Karl-Heinz Schuckert, Prof. Dr. Martijn van Griensven, and Prof. Hae-Ryong Song in a symposium called "Musculoskeletal Tissue Engineering from Research via Translation to Clinical Application".

The upcoming TERMIS World Congress in Vienna in September 2012 offers us a platform to hold a symposium titled "Tissue Engineering from Lab via Translation to Clinical Application" only with keynote presentations of our group members: Prof. Dr. Molly Stevens and Prof. Dr. Swee-Hin Teoh will present their latest research results; Prof. Dr. James Kirkpatrick and Prof. Dr. John A. Jansen will give a talk in the subject area "translation", and Prof. Dr. Martijn van Griensven and Dr. Karl-Heinz Schuckert will present tissue engineering in clinical application.

TERMIS Thematic Groups Updates

Musculoskeletal Thematic Group

In addition to these symposia a special meeting of all attendant group members was held during the International Bone-Tissue-Engineering Congress, bone-tec 2011, in October 2011 and will again be held during the TERMIS World Congress in Vienna in September 2012. A special item of discussion during the bone-tec group meeting was a talk held by Shannon Layland, IT-specialist, presenting IT-tools and processes to enhance peer review of scientific manuscripts.

These internal meetings offer us the possibility to advance our main objectives and to discuss new challenges in Tissue Engineering.

Karl-Heinz Schuckert, MD, DDS, PhD
Head of INDENTE
Institute of Innovative Oral Surgery and Medicine
Centre for Tissue Engineering
TERMIS Group Musculoskeletal Tissue Engineering

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Chair:
Dr. Karl-Heinz Schuckert, Institute Indente

Vice-chair:
Prof. Dr. Swee-Hin Teoh, National University of Singapore

Secretary:
Tanja Helberg, Institute Indente

Laboratory Feature

Laboratory of BioProcess Systems Engineering—Osaka University of Japan

Laboratory of BioProcess Systems Engineering, Department of Biotechnology, Graduate School of Engineering, Osaka University, Japan

Dr. Masahiro Kino-oka
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Department of Biotechnology,
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2-1 Yamadaoka, Suita, Osaka 5650871, Japan
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Laboratory of BioProcess Systems Engineering (BPSE) has been organized by Prof. Kino-oka since April 2009. The laboratory mission is to bring a good fortune in human life through the elucidation and utilization of "bio-potential" by understanding sequential biological events (BioProcess) in the reaction field (Systems). The main stream in BPSE, as shown in Fig.1, is the bioprocess designs in stem cell and tissue engineering. The research interests, which are targeted for the biological elements governing the reactions (*ie.* cellular differentiation, undifferentiation, de-undifferentiation, maturation, tissue self-assembling, functionalization etc.) as well as the regions providing the reaction field (*ie.* 2-D colonies and 3-D spherical and sheet aggregates), are to establish methodologies for process and quality controls in bio-production including the analysis, simulation, forecasting, making great contribution to the stem cell industry (*ie.* the outputs for manufacturing transplants through design of process and quality controls, for drug screening systems through development of bio-mimic structure, and for mass productions of human biologics through design of scale-up). The outcome includes the establishment of manufacturing process & quality controls (*ie*. culture design, bioreactor development, monitoring, process automation, etc.), the development of human resources as biochemical engineers, and establishment of standardizations and guidelines for stem cell industrialization.

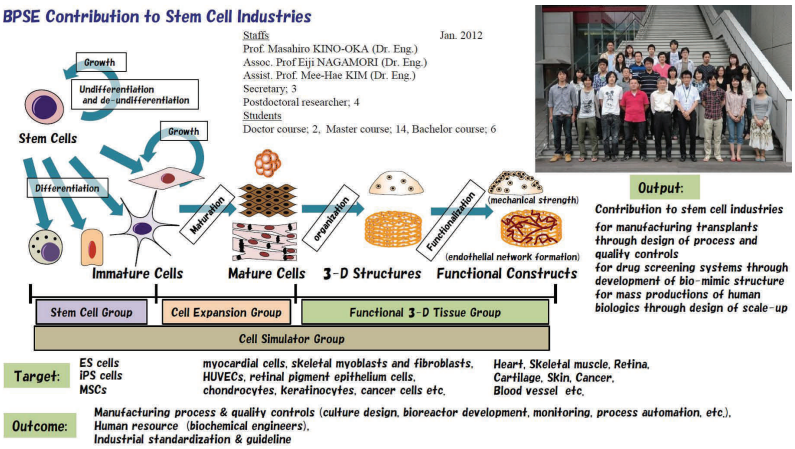

Fig. 1 Mission BPSE

BPSE were organized with four groups, (A) stem cell group for the maintenance of undifferentiation to prevent de-undifferentiation and for the directional regulation of differentiation, (B) cell expansion group for designs of culture process and intelligent automation system, (C) functional 3-D tissue group for vascular network formation a Local habitat distribution in multilayered cell sheet and mechanical strength in cultured tissue, and (D) culture simulation group for process and quality controls as an interdisciplinary technology supported by the above academic fields.

A. Stem Cell group

The main topics in this group are the methodological development for regulation of cytoskeletal signaling (Rho GTPase family of Rac1, cdc42, RhoA) by changing the cellular morphology with dynamic behaviors on the glucose-displaying dendrimer surface as shown in Fig.2.

BPSE proposed a possible mechanism underlying the cell anchoring and morphological changes in cultures of human epithelial cells on D-glucose-displaying surfaces (1-8). The variation in the ratio of D-glucose displayed caused cellular morphological changes that depended on the presence or absence of insulin. In addition, fluorescence microscopy of F-actin, vinculin, and GLUTs clarified the localization of integrin-mediated as well as GLUT-mediated anchoring, leading to the consideration that the morphological changes of cells are responsible for the variation in the balance between the quantities of D-glucose on the culture surface and GLUTs on the cytoplasmic membrane, which is associated with the promotion of focal contact formation mediated by GLUTs. The review article (6) mentioned that the designs using the surfaces are based on the novel cell binding mechanism in which GLUTs are key elements responsible for regulating cell attachment and morphologies as well as development of the cellular phenotypes.

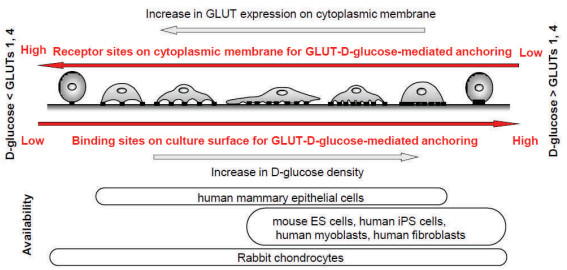

Fig. 2 Availability of D-glucose displaying dendrimer surfaces

Laboratory Feature Continued...

BPSE proposed the idea for cytodifferentiation of stem cells accompanied by the regulation of cytoskeletal formation through cell morphological variation as well as the intracellular signal transduction through cell aggregate formation. BPSE recently reported that the alterations in Rho family GTPase activities derived from cytoskeletal formation can lead to guidance of cardiomyogenic differentiation of human mesenchymal stem cells (hMSCs) during *in vitro* culture without any supplement of differentiation factors (8). To regulate the cytoskeletal formation of hMSCs, a dendrimer-immobilized substrate that displayed D-glucose was employed (Fig.3). With an increase in the dendrimer generation number (G1, G3, G5), the cells exhibited active migration, accompanied by cell morphological changes of stretching and contracting without any modification of culture media. On the 5th-generation dendrimer surface (G5), in particular, the cells exhibited RhoA down-regulation and Rac1 up-regulation during the culture, associated with alterations in the cellular morphology and migratory behaviors. It was also found that cell aggregate formation was promoted on this surface, supporting the notion that an increase in N-cadherin-mediated cell-cell contacts and Wnt pathway signaling regulate hMSC differentiation into cardiomyocyte-like cells. This suggests that the changes in the cytoskeletal organization have a direct impact on the cardiomyogenic differentiation of hMSCs in relation to Rho family GTPase-dependent signaling pathways. Thus, the transporter-mediating anchoring (D-glucose displaying on the surface) is one of the powerful techniques to realize the regulation of the cellular morphology accompanied by the cytoskeletal variation, leading to commitment of stem cells to different lineages. This technique currently applied to the maintenance culture of human iPS cells and can make the directional control to stay undifferentiated state of iPS cells without any derivation to de-undifferentiated state.

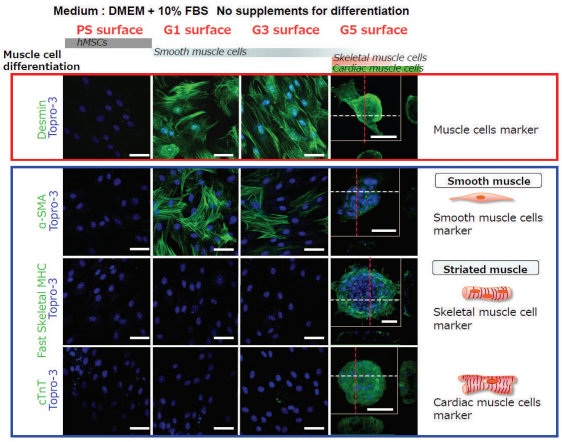

Fig. 3 Cardiomyogenic differentiation capacities of hMSCs (7 days)

2. Cell Expansion group

Bioreactors are a core element to produce high-value materials in biological processes using animal cells. In the cultures of animal cells, the major features are the mechanical fragility and low growth rate of these cells, which leads to the strategy of high cell density culture by maintaining the cells within bioreactors with an external medium flow. In recent decades, technologies for cell and tissue therapies have emerged in the field of regenerative medicine.

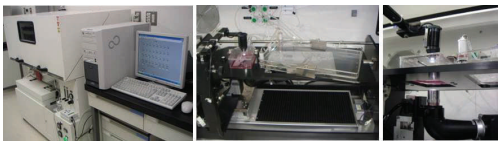

Fig. 4 Intelligent bioreactor system for passage automation

BPSE has developed the automation for expansion process including the operations of seeding, medium change, passage as well as observation (9,10), and proposed the intelligent culture system accompanied by automated operations (liquid transfer and cell passage) to perform serial cultures of human skeletal muscle myoblasts, as shown in Fig.4 (11). An automated culture system that could manage two serial cultures by monitoring the confluence degree was constructed. The automated operation with the intelligent determination of the time for passage was successfully performed without serious loss of growth activity, compared with manual operation using conventional flasks. This intelligent culture system can be applied to cultures of other adherent cells and will lead to the qualitative stability of products in the practical manufacturing of cells available for transplantation. In other words, the culture system will contribute to the process control as well as the quality control.

Fig. 6 Automation system of sheet assembly based on the fMP

In manufacturing, strict management against contamination and human error is compelled due to direct use of un-sterilable products and the laboriousness of culture operations, respectively. Therefore, the development of processing systems for cell and tissue cultures is one of the critical issues for ensuring a stable process and quality of therapeutic products. However, the siting criterion of culture systems to date has not been made clear. BPSE review article classifies some of the known processing systems into ‘sealed-chamber’ and ‘sealed-vessel’ culture systems based on the difference in their aseptic spaces, and describes the potential advantages of these systems and current states of culture systems (12).

The comparison of management between cell processing facility (CPF) and cell aseptic processing system (CAPS) based on the isolator system revealed that CAPS leads to reductions of the running cost as well as operational laboriousness in the small production. Recently, BPSE, as shown in Fig.5, proposed a novel design of manufacturing facility based on a flexible Modular Platform (fMP) which will reach the compactness of aseptic processing area and quick change-over for multi-purposes and patients, leading to cost-saving with safety and security .

As shown in Fig.6, BPSE collaborates with Profs. Okano and Shimizu in Tokyo Women’s Medical University and several companies to develop the isolator system for the sheet assembly based on the fMP, which will make automated formation of multilayered sheets and their incubation. The machinery operations were successfully performed. And this system can realize some procedures by having flexible connections with various modules required for the culture operations under sterile conditions, suggesting the broad versatility for the production in other types of multilayered sheets.

Laboratory Feature Continued...

3. Functional 3-D tissue group

The spatial growth in a scaffold leads to distribution in cell density owing to limitation of nutrient supply, causing the variation in quality of cultured tissues (spatial heterogeneity). Therefore, it is necessary to evaluate the population heterogeneity as an indicator for state of differentiation during the subcultures, and to estimate spatial distribution of cell aggregate in cultured tissues. These techniques will be contributable to QC especially for efficacy of cultured tissues (13). Many techniques for the QC were developed mainly for safety of cultured tissues.

The strategic construction to estimate the QC for efficacy is inevitable. BPSE, as shown in Fig.7, has focused on the tool development for spatial estimation of cells in cultured tissues (14-16). The stereoscopic image analysis of fluorescence-labeled chondrocyte cells for cytoplasm and nucleus was performed for the quantitative determination of spatial cell distribution as well as cell aggregate size in the collagen-embedded culture. The three-dimensional histomorphometric data indicated that the cells in the gels formed aggregates by cell division, and the size of aggregates increased with elapsed culture time, revealing the mechanism of the spatial heterogeneity in cell distribution. This imaging technique was applied to estimate the densities of total and proliferative cells by staining of whole nuclei and proliferative nuclei, respectively in 3-D epithelial sheets (17).

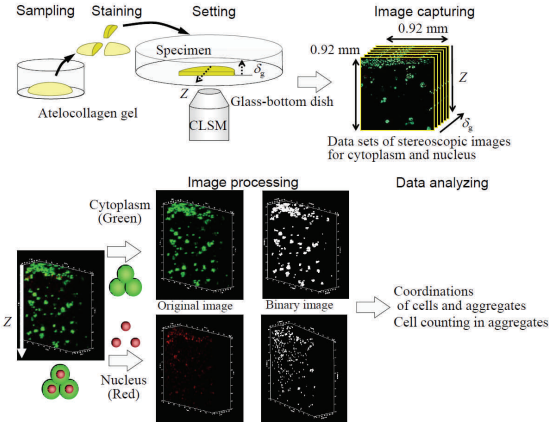

Fig. 7 Experimental procedures with spatial cell distribution analyzer consisting of image capturing and its processing

The cell sheet engineering is emerging as an advanced technique with preparation of scaffold-free three-dimensional (3-D) tissue, not only for transplantations, but also for *in vitro* researches. Recently autologous transplantation of multilayered myoblast sheet has been attracting attention as a new technique for curing myocardial infarction, which is associated with the dysfunction of cardiomyocytes and irreversible cell loss. This method can overcome the disadvantages such as less take ratio of transplanted cells through the direct injection of myoblast suspension. Skeletal myoblasts, which are easy to be harvested from patients, have ability to become active, self-renew and differentiate, permitting muscle regeneration upon muscle injury. As shown in Fig.8, the sheet of myoblasts also has ability to source the cytokines which improve heart function due to paracrine system including the facilitation of angiogenesis and the attraction of progenitors on affected part. From manufacturing point of view, the system development for process and quality controls is important to be concerned, leading to the active commercialization using the cell sheets. Many researches have been tackled concerning cell source exploring, cell culture, sheet assembling, and *in vivo* animal tests. However, the method for quality control of myoblast sheet, especially for transplant efficacy, has not been systematized. The image analysis technique described above was applied to the culture system that uses multilayered sheet containing stained target cells in the basal layer and confocal laser scanning microscopy, and realizes clear observation of target cell behaviors in the vertical direction, enabling mono-dimensional analysis of vertical cell distribution inside the sheet (18). The reduced spatial dimension makes easy to analyze cell migration, compared to the full 3-D analysis required of spherically shaped aggregates. Thus, the system developed in the present study can be a powerful tool for elucidating dynamic phenomena in 3-D constructs.

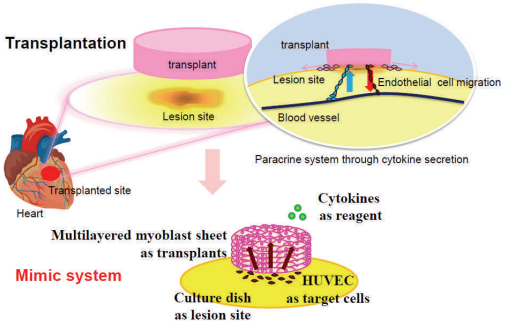

Fig. 8 Conceptual drawing of new approach for quality evaluations of multiplayer sheet through angiogenesis and network formation of HUVE C in multilayered sheet

Five-layered myoblast sheet was fabricated as a 3-D model to evaluate vertical cell migration by confocal laser scanning microscopy with image processing. And BPSE establishes the mimic system of transplantation which consists of endothelial cells (HUVECs) on culture dish as target cells on lesion site and five-layered myoblast sheet as transplants, and focus on understanding angiogenesis procedure as post transplantation.

4. Culture Simulation group

In manufacturing, the “raw materials” of cells isolated from patients (or donors) are of heterogeneity in cell states, and the “products” of cultured tissues have variation in the required volume for individual cultured tissues (products). During the three-dimensional culture, the spatial distribution and aggregation of target cells in the cultured constructs is considered to occur owing to the limitation of oxygen and protein supplies. The reliable and robust process is required for manufacturing the products with high quality while considering the instability and fluctuation in conditions of the raw materials.

The spatial distribution of target cells in the construct is very important information for evaluation of cultured tissues and it is desired to estimate the potentials of population doublings in the 3-D cultures. In particular, a feasible method to evaluate culture states is needed to support the operators who have to judge the cessation of 3-D cultures with useful information. To analyze the growth manner, a kinetic model is a promising tool for the prediction of spatial heterogeneity which affects the quality of cultured tissues (19).

Laboratory Feature Continued...

BPSE proposed the stochastic modeling based on cellular automaton which can be introduced to express the complex dynamics of cell proliferation in the construct (19-20). As shown in Fig.9, this model revealed that the special distribution of cell aggregates depends on the culture time and cell seeding density. The profiles of cell number and aggregate distribution are attributed to the limitation of oxygen supply as well as spatial contact inhibition due to the loss of space capable for cell division, similarly to those derived from the observation data, being a useful tool to estimate the overall cell propagation and spatial cell distribution in the collagen-gel embedded culture of chondrocytes.

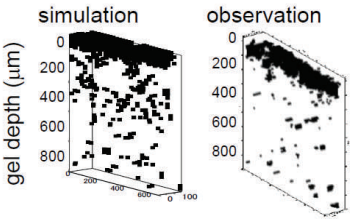

Fig. 9 Spatial cell distribution in cultured cartilage at 21 days

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-End

All conferences listed have been reviewed and approved for endorsement by the TERMIS Endorsement Committee.

Upcoming Conferences

April 2012

7th Symposium on Biologic Scaffolds for Regenerative Medicine
Symposium Dates: April 26-28, 2012
Symposium Location: The Silverado Resort, Napa Valley, CA
Symposium Organizer: Stephen F. Badylak, DVM, PhD, MD
Keynote Speaker: Mina J. Bissell

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May 2012

Griboi 2012 - The 22nd Interdisciplinary Research Conference on Injectable Biomaterials
Conference Theme: Minimal invasive therapies using injectable materials
Conference Location: Uppsala, Sweden
Conference Dates: May 10-12, 2012
Conference Chairs: Hakan Engqvist and Jons Hilborn

ICRS 2012 - 10th World Congress of the International Cartilage Repair Society
World Congress Dates: May 12-15, 2012
World Congress Location: Montreal, Quebec, Canada

Cell-Based Therapies & Tissue Engineering (CTTE 2012)
Course Dates: May 21-23, 2012
Course Location: Cleveland, OH

June 2012

2012 Stem Cells & Bioprocessing
Conference Dates: 27-28 June 2012
Conference Location: London, England
TERMIS members will receive a 15% discount off the price of registration if you register by 17th May 2012.

August 2012

Rice University's Advances in Tissue Engineering Short Course
Short Course Dates: August 8-11, 2012
Short Course Location: Rice University BioScience Research Collaborative
Short Course Director: Dr. Antonios G. Mikos

2012 ISOMRM
2nd International Symposium of Materials on Regenerative Medicine
Symposium Dates: August 29-31, 2012
Taipei, Taiwan, ROC
10% registration discount will be available for TERMIS members

September 2012

2012 3rd TERMIS World Congress: Vienna, Austria
Conference Dates: September 5-8, 2012
Conference Location: Hofburg Congress Center in Vienna, Austria
Conference Chair: Heinz Redl, PhD

To request further information, please contact:

Dr. Heinz Redl

November 2012

2012 ASMB Meeting
Meeting Dates: November 11-14, 2012
The 2012 meeting will be held jointly with the Society for Glycobiology.

June 2013

2013 TERMIS-EU: Istanbul, Turkey
Conference Dates: June 12-15, 2013
Conference Location: Istanbul, Turkey
Conference Chair: Erhan Pişkin, PhD

October 2013

2013 TERMIS-AP: P. R. China
Conference Dates: October 2013
Conference Chair: Yilin Cao, MD, PhD

December 2013

2013 TERMIS-Americas: Atlanta, GA
Conference Location: Atlanta, Georgia
Conference Chair: Robert E. Guldberg, PhD
Conference Program Chair: Todd C. McDevitt, PhD
More details to follow.

June 2014

2014 TERMIS-EU: Genoa, Italy
Conference Dates: 10-13 June 2014
Conference Co-Chairs: Ranieri Cancedda and Claudio Migliaresi
More details to follow.

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