termis
Tissue Engineering International & Regenerative Medicine Society

*Inter*Link: Fall 2006 Volume I, Issue IV

In This Issue ...

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Letter from the Editor

Dear Colleagues and Friends,

I hope that you had a peaceful und relaxing holiday season and started the New Year with full vigor and energy.

As we all know, tissue engineering corresponds to the confluence of a multifaceted display of pre-existing disciplines from three quite different domains: namely clinical medicine, engineering, and science. The ultimate goal for tissue engineers should be to move their research into the clinical domain, and are best understood as specific examples of general problem-solving strategies employed by surgeons and physicians. For example, orthopedic surgeons have been investigating many different kinds of implants that may promote bone regeneration. From a clinical perspective, what matters is not so much as whether the active agent in a scaffold or matrix consists of stem cells, bone morphogenetic proteins, or gene therapy vectors, but whether it is therapeutically effective. Similarly, nephrologists may view the dialysis machine, as a tissue engineered "artificial kidney" or a functional, biocompatible micro renal support device created via nuclear transplantation as possibilities along a seamless spectrum of therapeutic options rather than in terms of the radically different underlying definitions or technologies they represent. Hence, I believe that the linkage of TE research with clinical medicine next to developmental biology should be our major focus in 21st century. It may take another generation or two before we derive with a large number of routine clinical applications of therapies based tissue engineering but we need to stay focused as the medical payoff for future generations that could eventually be spectacular.

The complexity of the science and the rapid proliferation of business, ethical and political issues pose a challenge for anyone wishing to stay well informed is challenging. Therefore, I would like to encourage you to participate in at least one meeting of our society per year. The organization of the Asian-Pacific, European and North American Chapter meetings for 2007 are proceeding nicely. We are expecting a large number of registrations from our society. I am glad that I can inform you that the programs for all three meetings are shaping up nicely.

Do not forget to visit our website regularly at www.termis.org for the latest news and developments. If you need additional information, do not hesitate to contact us. I hope to see and chat with you at one of the Chapter Meetings this year.

Yours sincerely,
Dietmar W. Hutmacher, PhD, MBA

NEWS FROM THE TERMIS-AP CHAPTER

Hai Bang Lee, PhD – Continental Chair

1. Taiwan

The Annual Symposium of Biomedical Engineering Society of 2006 will be held on Dec. 15- 16 at National Taiwan University, Taipei, Taiwan. The main themes are Biomaterials and Tissue engineering, Biomechanics and Medical image and devices. In addition, there is another symposium, 2006 International Symposium on Biomedical Engineering Taiwan (2006 ISOBME), held on Dec. 14- 16 at the same university. There will be about 300 ~ 400 local participants to attend both symposiums. Four keynote speakers are invited to give lectures in both symposiums. Among the keynote speakers, Dr. Terry Turney, the president of Asian Nano Forum, will give a lecture, "Evolved and Biomimetic Materials." Some of them give the topics. We wish both symposiums be successful. The detail programs of 2006 ISOBME can be accessed through the web site, http://www.tl.ntu.edu.tw/bmes/english/p-3.asp.

2. Malaysia

Two years after the birth of Tissue Engineering Society of Malaysia (TESMA), a bold step was finally taken to organize a TERM scientific meeting at a national level. Greatly encouraged by the support from our fellow TERMIS-AP counterparts from Singapore, Thailand, Japan and Korea, the meeting was aggressively promoted by our members from various institutions throughout the country. An unprecedented number of participants, 123 in total, attended the 2-day event. The meeting kicked off with high spirits as Professor Dr Eng Hin Lee, from National University of Singapore, presented an exciting plenary lecture entitled 'Cell-Based Therapy in Orthopaedic Surgery'. Among other distinguished speakers were Prof. Gilson Khang (Korea) and Prof. Anond Bunyaratvej (Thailand), both council members of TERMIS-AP and Prof. Hideaki Kagami (Japan).

Deeply inspired by the innovative 'Student-Mentor' session during the recent TERMIS World Congress in Pittsburg, the President of TESMA, Prof. Ruszymah Idrus proposed that a 'Student-Teacher Program' be incorporated in this meeting as part of the education outreach activities of TESMA. Drawing a total participation of 325 for the half day session, it provided varsity students an excellent opportunity to gain first hand knowledge from doctorate and PhD candidates who were actively pursuing research in the field of tissue engineering, covering projects involving cartilage, bone, skin and cornea regeneration.

Central to this meeting is the emphasis on the translation of research discoveries to clinical applications, in line with its theme 'Clinical Translations'. Thus, many speakers had shared their invaluable clinical trial experiences. Especially worth mentioning are the lectures by two entrepreneurs from the corporate end. Dr. Gary D Shipley from Cascade Biologics, drawing from his own experience in commercialization of animal product-free culture products, gave an honest and realistic approach to bringing research products into a new market. Dr. Aw Tar Choon from StemLife Sdn Bhd, gave a vivid perspective of the emerging applications of blood stem cells therapy rationalizing stem cell banking as a lucrative industry.

Finally, an intellectually rigorous panel discussion on issues pertaining to clinical translations of research products, such as, meeting the GMP facility requirements, marked a wonderful conclusion for the meeting.

By virtue of the small community, an intimate and collegial atmosphere could be felt throughout the meeting, and heightened during the social dinner. Nothing could be more satisfying than to see the close interaction and friendly exchanges among the attendees and the experts assembled.

A membership recruitment drive was strategically launched, in conjunction, with the meeting bringing the total number of TESMA members to 162. It is our hope that this success will be an impetus for TESMA to continue to forge ahead and serve this burgeoning community. Aimed at holding the event bi-annually, the 2nd NTERMS will tentatively be held in August 2008.

3. Japan

- 28th Annual Meeting of Japanese Society of Inflammation and Regeneration (JSIR) will be held on August 2~3, 2007 at Tokyo (Organizer: Hideyuki Okano).
-9th Annual Meeting of Japanese Society of Tissue Engineering (JSTE) was held in Koyto on Sept. 7~8. (Organizer: Prof Yasuiko Tabata)
- 5th Annual Meeting of Japan Society for Regenerative Medicine (JSRM) will be held on March 13~14, 2007 at Yokohama (Organizer: Toshihiro Akaike).
-10th Annual Meeting of Japan Society for Tissue Engineering (JSTE) will be held on November 8~9, 2007 at Tokyo (Organizer: Kazuo Tsubota).
-2007 TERMIS-AP Chapter Meeting will be held Dec 3~5 2007 at Tokyo. (Organizer: Teruo Okano and Tsuyoshi Takato)
- 1st Asian Biomaterials Congress (Integrated Congress of 6th Asian International Symposium on Biomaterials and 8th Asian Symposium on Biomedical Materials) will be held Dec 6~7 2007 at Epochal Tsukuba International Congress Center, Tsukuba, Japan. (Organizer: Profs Tetsuya Tateishi and Takashi Ushida)

4. Korea

- 2006 4th Seoul Stem Cell Symposium was held in Yonsei Millennium Hall, Seoul on Oct. 21 2006. Around 600 members were registered. (Organizer: Prof. Gilson Khang and Dong-Wook Kim)
- Korea/Germany Joint Symposium for Regenerative Medicine was held in COEX convention center on September 6, 2006 during the BIOKOREA2006 organized by Korean Ministry of Health and Welfare.
- 9th Annual Meeting of KTERMS will be held in Seoul National University on June 1, 2007. (Organizer: Prof. Chong Su Cho)
- Kick-off meeting for the Organizing Committee of 2009 2nd TERMIS World Congress was held on August 31, 2006 at the Jamsil Lotte Hotel. The Organizing Committee members in attendance were: Drs. Bob Nerem, Allan Russell, Hai Bang Lee, Kwang Won Kim, Jung Man Kim, Shin Yong Moon, Jeung Keuk Park, Dong-Wook Kim, Gilson Khang and Moon Suk Kim.

UPDATE from the TERMIS-EU Chapter

Ivan Martin, PhD – Continental Chair

TERMIS-EU AFTER THE MEETING IN ROTTERDAM

On October 8th to 11th, TERMIS-EU had its first official meeting in Rotterdam. The conference was attended by 437 people from a total of 34 countries, and was a success for both scientists and sponsors. Many thanks again to Gerjo van Osch and her bright team for an excellent organization!

In addition to the scientific program, the TERMIS-EU meeting included several activities organized by the highly active Student and Young Investigator Section (SYIS). These activities (e.g., student-meet-mentor, student social hour, poster tour, workshops) represent an important element that will be maintained and extended for the meetings to come.

During the General Assembly Meeting in Rotterdam, we have successfully completed the last legal actions to have TERMIS-EU as a Society registered in Germany and at the same time harmonized with the bylaws of the worldwide TERMIS. Special thanks go to Michael Sittinger and Ulrich Nöth for making this possible.

The TERMIS-EU Council has also formulated a first set of initiatives to support the organization, networking and integration of the tissue engineering community in Europe. For example, a searchable database is being set up within the TERMIS website, with keywords identifying the research background and interest of each member of TERMIS-EU. This tool is supposed to help the identification of partners for interdisciplinary projects, and could be used to set up new consortia in the context of EC-based funding (e.g., Framework Program VII). In addition, as a non-profit organization, TERMIS-EU is planning to apply for funding to the EC to be able to support selected student/young investigator members with dedicated fellowships and to organize summer (or winter) schools in the area of regenerative medicine.

The structure for the next TERMIS-EU meeting in London, September 4th to 7th, is currently being finalized by Robert Brown together with a highly prestigious international panel. I strongly encourage you to visit the website (http://www.termis.org/eu2007/) and get ready for abstract submissions.

Finally, I would like once again to consider that TERMIS-EU is a very young society, and much of the shape it will take and impact it will have critically depends on the contribution of its members. Thus, any feedback, suggestion or proposal you have will be most welcome.

All the best for an excellent start in 2007!
Ivan Martin
TERMIS-EU Chair

1st Summer School TERMIS-EU

The European Chapter of the Tissue Engineering and Regenerative Medicine International Society is happy to invite you to participate in the **1st Summer School TERMIS-EU**.

The 1st Summer School TERMIS-EU will focus on the ***Key Elements of Tissue Engineering*** and will be organized back to back with the InVENTS Marie Curie Series of Events - **3rd Marie Curie Cutting Edge Conference on *Biomineralisation of polymeric materials, bioactive biomaterials and biomimetic methodologies*** (http://www.inventscience.org).

It will take place in Funchal, Madeira (Portugal) from June 1 to 3, 2007 and chaired by Rui L. Reis (3B's Research Group, www.3bs.uminho.pt) with the support of the European Network of Excellence EXPERTISSUES (www.expertissues.org). Further information will soon be available online in the webpages of TERMIS, EXPERTISSUES and InVENTS.

Congratulations to Professor Raymund Horch on winning the Universität Erlangen-Nürnberg: Xue Hong und Hans Georg Geis Stiftungspreis: 100.000 Euros für Forschungenzum Aufbau von Gewebe aus der Retorte! For more information, visit http://www.uni-protokolle.de/nachrichten/id/129280/.

News from the TERMIS-NA Chapter

Anthony Atala, MD – Continental Chair

The year 2006 was one of significant accomplishment for TERMIS-NA. The year marked our first efforts as an organized group in North America bringing together the foresight to create a solid foundation from which to build our future. Not only is this accomplishment critical to present health and vigor of our Society, it also sets the stage for our organization to develop value added benefits for the membership and the tissue engineering and regenerative medicine industry worldwide.

A number of achievements helped define our first year of service. During the past year the Board of Directors has successfully formed two working committees; the finance committee and the membership committee. In addition our members have been elected to significant positions on the TERMIS Global Board and are serving in various committee capacities representing our interests on an International level. We have also successfully negotiated a partnership with PTEI for the Regenerate Conference. This conference will serve as the membership's annual meeting in 2007 and we are currently working with PTEI to establish a long-term relationship so that this meeting will continue to represent the member's and the community's best interests long into the future. In addition to Regenerate, the Council is forging new relationships for educational and membership outreach with the Society for Biomaterials (SFB), the AABB (the Association for Advancing Transfusion and Cellular Therapies Worldwide), Biomedical Engineering Society (BMES) and others. And finally, the Council is developing programs and activities to launch in 2007 that will establish its educational portfolio as well as begin to provide opportunities for the membership to come together outside the annual meeting. These new alliances and activities offer considerable benefits to our members. TERMIS-NA will gain an expanded presence, strengthened relationship between core and peripheral technology groups and bring value-added services to the membership.

Building a strong organization takes the efforts of many people and I'm grateful to all of you who have step up to play an active role with the Council as well as to all of our members who have endured the many changes and continue to support the organization.

As TERMIS-NA continues to expand and fine-tune its national and international presence, we proudly recall our efforts over the past several years of advancing regenerative medicine therapies worldwide and we look forward to experiencing all of the scientific and engineering innovations, solutions and breakthroughs that will help define our future.

Regards,
Anthony Atala, MD
TERMIS-NA Chair

REGISTRATION Now OPEN!
Abstract deadline extended to February 2!

Join us in Toronto, Ontario for
TERMIS - North America
2007 Conference and Exposition
June 13-16, 2007, Westin Harbour Castle, Toronto, Canada

New Insights. New Technologies. New Opportunities.

Registration is now open for the **TERMIS NA 2007 Conference and Exposition** (formerly REGENERATE 2007.) The conference will feature an outstanding scientific and business program plus an industry-focused trade show. This conference brings together an international community of scientists, clinicians, students, business leaders, entrepreneurs, and representatives of government funding agencies engaged or interested in the fields cellular therapies, medical devices and artificial organs, biomaterials, bioengineering and clinical translation. This year in particular will have a special focus on **stem cells**, **imaging,** and **transplantation**, as reflected in plenary speakers in each of these areas followed by additional sessions. Moreover, this year will include a star-studded plenary panel of **industry leaders in regenerative medicine**.

Be a Part of this Significant Event!
Now more than ever, technological advances and new discoveries are changing the paradigm of the global tissue engineering and regenerative medicine industry. No other conference so completely focuses on the advancements that drive these changes. **Share in this Vision!** Abstracts are invited for consideration for the TERMIS NA 2007conference, June 13 - 16, 2007 at the Westin Harbour Castle Hotel, Toronto, Canada. Visit http://www.regenerate-online.com/presentations_call.php for more information about our Call for Presentations.

Experts from academia and commerce are invited to present timely information from current research to successful implementation of new technologies in all areas of tissue engineering/regenerative medicine including specific sessions on these topics:

- 3D Patterned Scaffolds
- Addressing Immune System Response
- Adult Stem Cells
- Biomechanical Training of Tissue Constructs
- Bioreactors and Microvascularization
- Cancer & Regenerative Medicine
- Cardiac
- Cell Integration into Natural & Synthetic Matrices
- Cell Sourcing
- Cell Tracking and Imaging
- Controlling the Cellular Microenvironment
- Embryonic Stem Cells
- Funding Tissue Engineering and Regenerative Medicine Research
- Gene Therapy in Tissue Engineering
- Metabolic Tissue Engineering
- Methodologies of Clinical Trials
- Nano-biotechnology
- Neural
- Oral/Dental/Craniofacial
- Orthopedic
- Skin/Wound Healing
- Smart Biomaterials
- Soft Tissue Repair
- Structural and Biomechanical Characterization: Synthetic Scaffolds
- Structural and Biomechanical Characterization: Biological Scaffolds
- Scaffolds and Cells for Musculoskeletal Regeneration
- Tissue Engineering & Regenerative Medicine in the Clinic
- A Transplantation Perspective on Regenerative Medicine
- Vascular

Details about the format and procedure for submitting abstracts for the **TERMIS NA 2007 Conference and Exposition are available at www.regenerate-online.com. Abstract submission deadline is February 2, 2007.**

For more information about abstract content, format and submission procedure, contact Andrea Lubienski, Forecast Technology Group, Inc., alubienski@conferencestrategists.com

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For more information about the **TERMIS NA 2007 Conference and Exposition** visit http://www.regenerate-online.com/.

TERMIS-NA Participates in Submitting Ideas on the Roadmap Trans-NIH Strategic Initiatives

In November 2006, the TERMIS-NA Continental Council, chaired by Dr. Anthony Atala from the Wake Forest Institute of Regenerative Medicine, came together to provide their feedback on a white paper published by the NIBIB that discussed strategic initiatives to enhance the NIBIB Tissue Engineering Program. The white paper was developed through discussions held in June 2005 in Atlanta, Georgia, that brought together key researchers and members of the NIBIB staff. Their main focus was to discuss key issues that will enhance research opportunities within the tissue engineering and regenerative medicine research fields.

The feedback from the TERMIS-NA Council was collected by Jeremy Mao, from Columbia University and Sarah Wilburn, the TERMIS Administrator. The comments were then submitted to the NIH online submission process and will collectively be used to identify new ideas for the Roadmap Trans-NIH Strategic Initiatives for FY2008.

For more information on the Roadmap for the Trans-NIH Strategic Initiative, please visit http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-011.html.

Feature on Tissue Engineering Laboratory
Asia-Pacific

Field of Tissue Engineering at the Institute for Frontier Medical Sciences, Kyoto University

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Biomaterials Department belongs to the Institute for Frontier Medical Sciences, Kyoto University which is composed of 4 fields (16 departments) and 2 centers (stem cells and nanobiotechnology). Our Institute is quite unique in terms of the Institute organization to promote and realize the interdisplinary research field between the Engineering and the clinical / basic medicine. It is recognized that involvement, merging, and integration of various research fields, such as biological science, medicine, and engineering, is a key to succeed in achieving our goals. To achieve this, our Institute has established an open environment where researchers from different backgrounds can work together and promote the exchange of ideas and expertise. The main role as an institution is to seek and engage in the development of basic science in regenerative medicine and its application for clinical uses. In order to realize the mission to work in both the basic science and its application in regenerative medicine, Every research group is encouraged to find its specific aim and role at the Institute within four main research categories; basic biomedical research for regenerative medicine, stem cell research, tissue engineering, biomedical engineering. Biomaterials play an important and pivotal role in all the research and development (R&D) for the four research categories.

The main objective of Biomaterials Department is to investigate and develop materials, technologies, and methodologies which are applicable to basic and clinical medicines as well as basic biology on the basis of material sciences. The materials to use in the body and to contact biological substances, like proteins and cells, are defined as biomaterials. In the Biomaterials Department, various types of biodegradable and non-biodegradable biomaterials of polymers metals, ceramics, and their composites, are designed and created aiming at their clinical applications as well as the development of experimental tools necessary for basic researches of medicine and biology which scientifically support clinical medicine. We are investigating biomaterials to assist reconstructive surgery and to apply to drug delivery systems (DDS) for the biomaterials-based improvement of therapeutic efficacy. However, it is often difficult for patients to improve their Quality of Life (QOL) only by the therapeutic procedure of reconstructive surgery because the biomaterials applied are of poor biocompatibility and functional substitution. For organ transplantation, there are several problems to be resolved, such as the lack of donor tissue and organ or the reverse effects of immunosuppressive agents. The two present advanced medicines are clinically limited in terms of the therapeutic procedure and potential. In these circumstances, a new therapeutic trial, in which disease healing can be achieved based on the natural healing potential of patients themselves, has been explored. This is termed the therapy of regenerative medicine, where the regeneration of tissues and organs is naturally induced to therapeutically treat diseases by artificially promoting the proliferation and differentiation of cells. The objective of regenerative therapy is to treat diseases by regenerating injured or lost tissues and substituting organ functions by making use of cells. The regenerative medical therapy is quite different from the reconstructive surgery and organ transplantation from the viewpoint of no use of biomaterials and medical devices and no need of immunosuppressive agents, respectively. The basic idea of regenerative therapy is to give cells an environment site suitable to promote their proliferation and differentiation, resulting in the cell-based induction of tissue and organ regeneration. It is tissue engineering that is a biomedical technology or methodology to create this environment of regeneration induction. Generally, there are three factors necessary to induce tissue regeneration, such as cells, the scaffold for cell proliferation and differentiation, and biological signal molecules of growth factors and genes, which are fundamentally 3 components constituting the body tissue. For successful regenerative therapy of tissue and organ, it is indispensable to efficiently take advantage of various biomaterials and the related technologies recombining with all the body components. Among biomaterials, biodegradable biomaterials play an important role in these medical applications. Since there are few metals and ceramics with biodegradable nature, polymer materials of biodegradability have been mainly used for this purpose. If a biomaterial is degraded to disappear in the body, it is not always necessary to retrieve the material from the body after the function expected is accomplished. In addition, the material should be degraded at the right time profile not to allow to physically impairing the physical process of natural tissue regeneration by the material remaining. Thus, biodegradable biomaterials are indispensable for the research and development (R&D) of regenerative medical therapy, DDS or basic biology and medicine.

Our research goal is to design and create biomaterials mainly from polymers which are practically applicable for regenerative medical therapy, stem cell technology, DDS, and medical therapy of reconstructive surgery and internal medicine. More detailed explanation about every project is described.

1) Biomaterials for the Therapy of Regenerative Medicine

It is well recognized that cells are present in the living tissue interacting with the extracellular matrix (ECM) of natural scaffold for the proliferation and differentiation of cells or their morphogenesis. When the body tissue is largely lost, the ECM itself also disappears. In such a case, only by supplying cells to

the defect, we cannot always expect the tissue regeneration at the large defect. One of the possible ways to achieve successful tissue regeneration is to provide a temporary scaffold for the proliferation and differentiation of cells to the defect. We are designing and creating 3-dimensional and porous constructs of biodegradability as this temporary cell scaffold which is an artificial ECM.

This scaffold approach with collagen sponges and the tube of poly(glycolic acid) and gelatin has been clinically applied to demonstrate successful regeneration of skin dermis, esophagus, trachea, peripheral nerve, and dura matter (**Figure 1**).

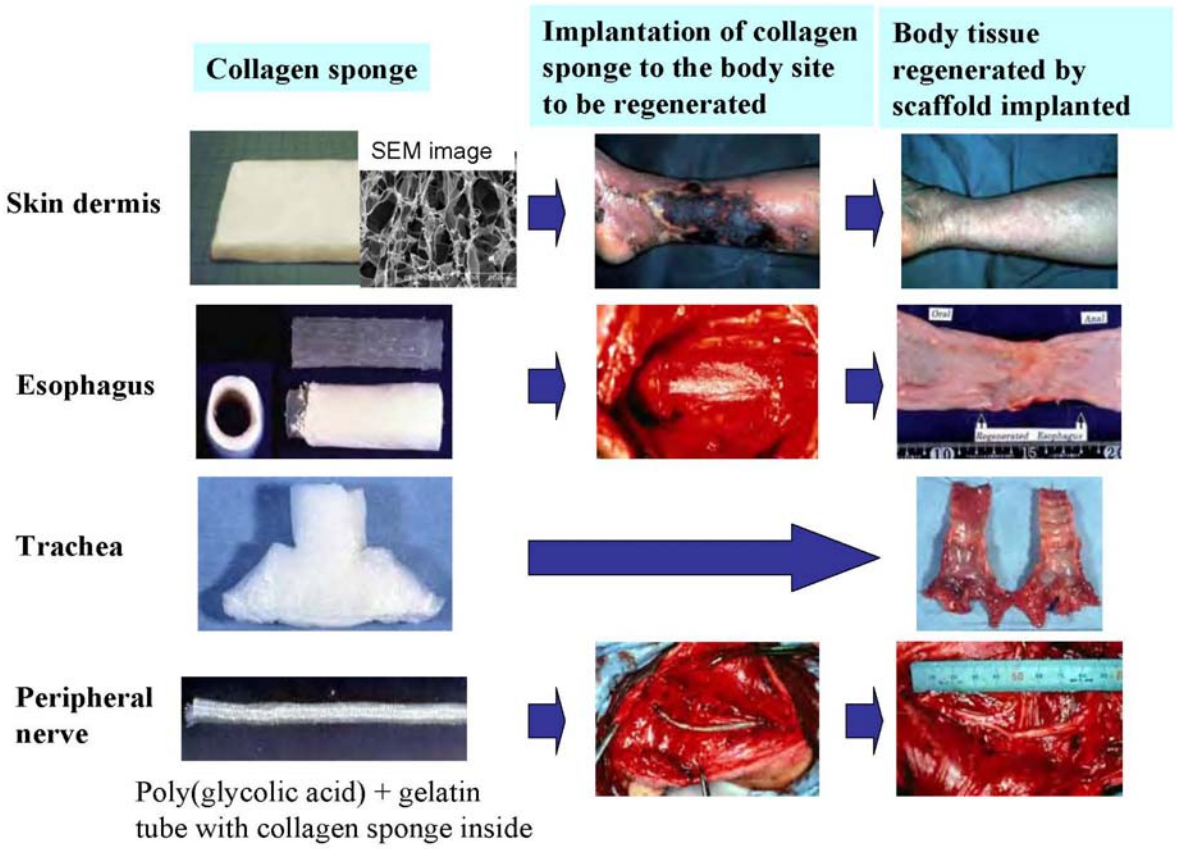

Figure 1.

However, even if a superior scaffold is supplied to the tissue defect, the tissue regeneration will not be achieved without sufficient number of cells and the amount of cell proliferation cue signals. It is one of the practically possible ways to use growth factors for promoted proliferation and differentiation of cells. It is, however, necessary for in vivo use of growth factors to contrive their administration form because of the in vivo short half-life and instability. One possible way to break through the problem is to use the controlled release of growth factor or the related gene at the tissue site to be regenerated over an extended time period by incorporating the factor or gene into an appropriate carrier. This release technology enables the growth factor to efficiently exert the biological activity, resulting in promoted tissue regeneration. We are designing and preparing the biodegradable carrier of growth factors and genes from gelatin and its derivatives.

The induction of tissue and organ regeneration by the controlled release of various biologically active growth factors has been achieved. Among them, human experiments of angiogenic and bone regeneration therapies have been started by the controlled release technology of basic fibroblast growth factor(bFGF) and the good therapeutic efficacy is clinically demonstrated (**Figure 2**).

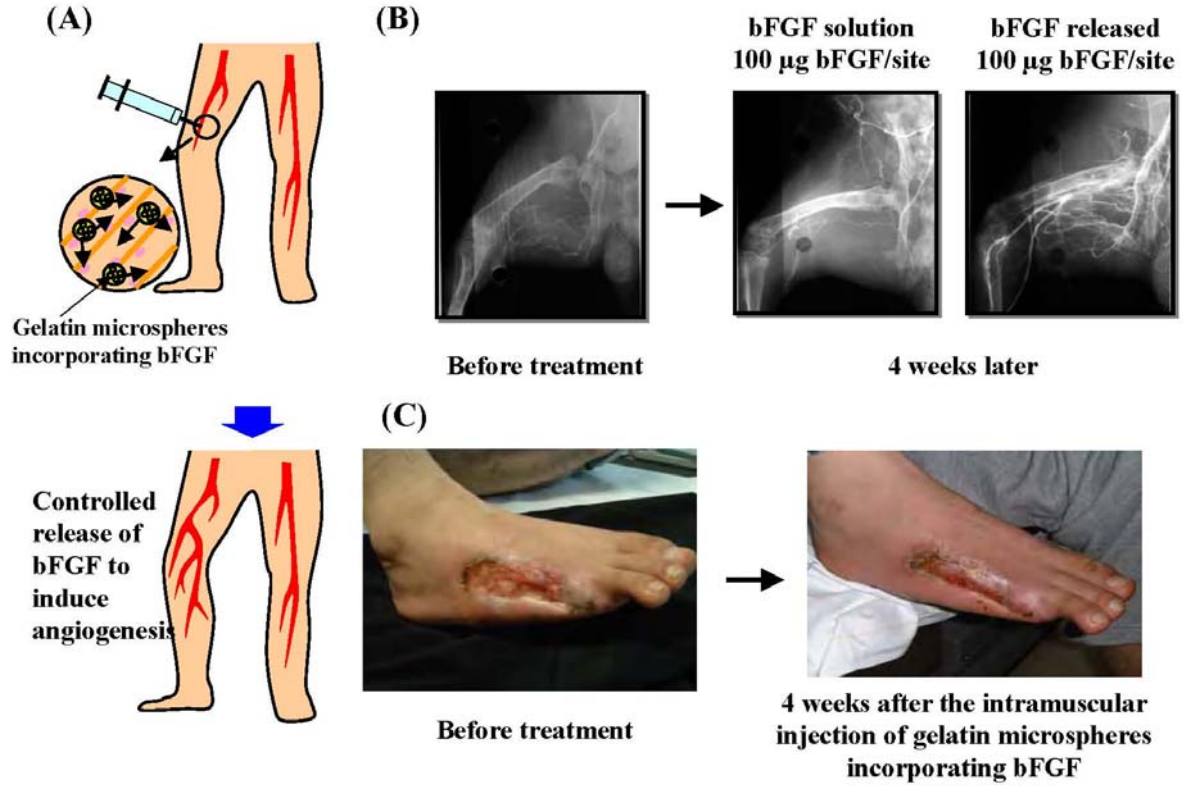

Figure 2.

Generally, in the chronic fibrotic disease, such as diluted cardiomyopathy, liver cirrhosis, lung fibrosis, and chronic nephritis, the damaged portion of organ is often occupied with the fibrous tissue, which causes organ dysfunction. It is highly possible that if the fibrosis is enzymatically loosen or digested by a proper way, the fibrotic site is naturally regenerated and repaired on the basis of the inherent regenerative potential of the surrounding normal tissue and consequently the organ function is regeneration recovered. We are designing and preparing a system of drug targeting and the local release with polymers of an organ affinity to achieve the regeneration-induced therapy for chronic disease based on the natural regeneration potential of patients. Based on the drug administration therapy, which has been clinically used in internal medicine, this is called as physical regenerative therapy of internal medicine (**Figure 3**).

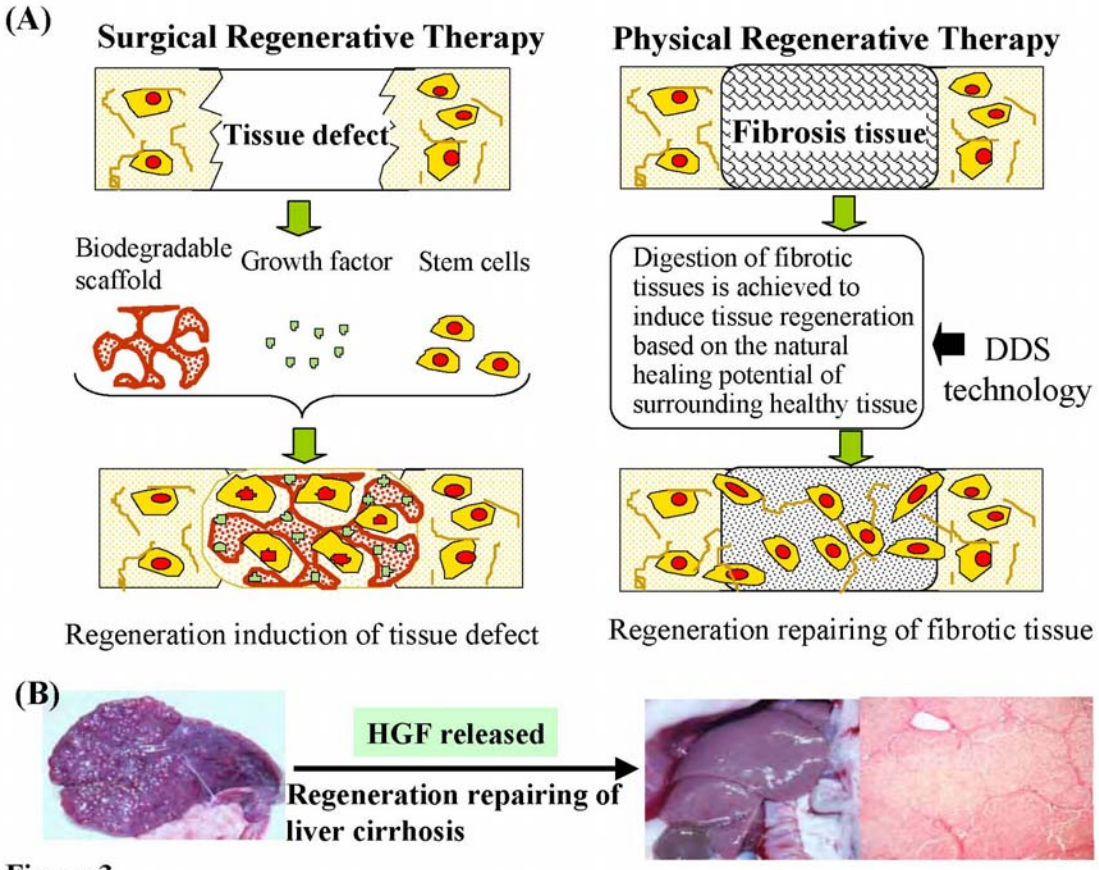

Figure 3.

This is a therapeutic approach different from the conventional regenerative therapy of surgery where cells, the scaffold, and signal molecules or the combinations are surgically applied to a tissue defect for regeneration induction thereat. The two surgical and physical regenerative therapies are conceptually identical from the viewpoint of the positive use of natural healing potential. In addition, the basic idea of regenerative therapy will be combined with internal medical therapy to open a new therapeutic field in the future. For example, the combination with aneurysm catheter therapy has been tried, and consequently the aneurysm occlusion by the regenerated tissue-based organization has been succeeded by the bFGF release system. On the other hard, new non-viral gene carriers and cell culture technologies are being developed to enhance the expression level of nucleic acid compounds, such as decoy DNA and small interfering RNA (siRNA), aiming at the genetic manipulation of cells for their biological functions and differentiation fate.

2) Biomaterials for Stem Cells Technology and Basic Researches of Medicine and Biology

There are two approaches to practically realize regeneration medical therapy. One is the tissue engineering-based approach of tissue regeneration described above. The other is cell transplantation therapy to induce tissue regeneration. For the latter approach, it is of prime importance to efficiently obtain and prepare cells with a high potential of proliferation and differentiation, such as stem cells, precursors, blastic cells, and matured cells. In the Biomaterials Department, the technology and methodology of cell culture with various biomaterials and bioreactors have been explored to efficiently isolate, proliferate, and

differentiate into stem cells, precursors, and blastic cells. A series of this study not only aims at the preparation of cells suitable for the therapy of regenerative medicine, but also the R&D of materials, technologies, and methodologies for basic medicine and biology. In addition, non-viral for vectors for plasmid DNA and siRNA have been investigated to design the DDS system for in vitro and in vivo gene transfection which can biologically analyze the functions of stem cells and genetically engineer cells to activate the biological functions for cell transplantation therapy. For example, we have developed a new system for the controlled release of plasmid DNA inside cells and succeeded in enhancing the level of gene transfection and the consequent gene expression as high as or higher than that of viral vector system. In addition, a new technology of cell culturing on plasmid DNA-coated substrates with or without the combination of bioreactor systems has been developed and enhanced the level of gene expression as well as prolonged the expressed period. This reverse transfection system is effective in the gene transfection for stem and matured cells which have not been readily transfected by the conventional method while it can be applied for cell internalization of low-molecular weight compounds, peptides, proteins, and nucleic acids (siRNA and decoy DNA).

3) Biomaterials for DDS

Generally there are few drugs which have a specific selectivity for the site of action. Therefore, the high-dose administration of drugs is necessary to achieve their in vivo therapeutic efficacy, while this often causes the adverse effects of drugs. DDS is an engineering trial which allows a drug to act at the right time the right site of action at the necessary concentration. The objective of DDS includes the controlled release of drug, the prolongation of drug life-time, the acceleration of drug absorption, and the drug targeting. Various biomaterials are inevitably required to achieve every DDS objective. In the Biomaterials Department, various research projects of DDS for drug and gene therapies are carried out from the viewpoint of polymer material sciences. Our definition of "drug" is not limited to therapeutic substances, but it means every substance with a certain biological activity and function. The DDS technology and methodology are also being developed for prophylactic and diagnostic substances to enhance the in vivo efficacy of vaccination and diagnosis, such as magnetic resonance imaging (MRI), ultrasound diagnosis or molecular imaging. We are also developing DDS technology and methodology which are applicable to the research and development of cosmetics and health care sciences.

4) Biomaterials for Surgical and Physical Therapies

The Biomaterials Department is partly originated from the division of Molecular Design and Biomaterials of the former Research Center for Biomedical Engineering where the medical applications of polymer materials have been investigated extensively. Among the research activities, we continue to molecularly design and create biomaterials and medical devices indispensable for surgical and physical therapies mainly from biodegradable polymers.

From the viewpoint of biomaterial sciences, we are pursuing comprehensive biological and medical researches on the scaffold for the cell proliferation and differentiation, the DDS of growth factors and the related genes, and the material-based technology or methodology to use stem, precursor, and blast cells and in addition, their medical applications. Through several R&D collaborations with medical, dental, and veterinary schools as well as private companies, we are planning to apply our basic research results to realize the regeneration induction therapy of various tissues and organs, such as the skin, fat, bone, cartilage, nerve, hair, blood vessels, periodontium, myocardium, and kidney as well as the DDS technologies

for therapeutic, prophylactic, and diagnostic medicines, while some biomaterials are applicable for basic of medicine and biology as the research tools.

The research projects have been actively performed with about 360 collaborators with different scientific and technology backgrounds and students and colleagues (**Figure 4)**

Figure 4.

Please visit our website at http://www.frontier.kyoto-u.ac.jp/te02/index-j.php3 for detailed information.

Dr. Yasuhiko Tabata is the Professor and Chairman of the Department of Biomaterials at the Institute for Frontier Medical Sciences, Kyoto University, Japan and a Professor of the Course of Advanced Medicine, the Graduate School of Medicine, Osaka University, Japan. He also lectures at 12 universities (medical /dental/engineering/pharmaceutical school). Dr. Tabata received my BD in Polymer Chemistry (1981), PhD (1988) in Technology, D.Med.Sc.(2002), and D.Pharm.(2003) all at Kyoto University. He was a Visiting Scientist at the Massachusetts Institute of Technology (Professor Robert Langer) and Harvard University Medical School (1991-92). He received the Young Investigator Award (1990) and the Scientific Award from the Japanese Society for Biomaterials (2002). He has published 620 scientific papers and book chapters, including 70 review articles, and has 120 patents. He is a governing broad member of the Japanese Society of Biomaterials, the Japanese Tissue Engineering Society, and Tissue

Engineering and Regenerative Medicine Society International, and a council of the Japan Society of Drug Delivery System, the Japanese Society of Inflammation and Regeneration, and the Japanese Society for Wound Healing, while he is an associate member of Science council of Japan. He serves on the Executive Editor of Tissue Engineering, the Editorial Board of Journal Biomaterial Science, Polymer Edition, Journal of Controlled Release, and J. Biomedical Nanotechnology.

Figure Legends

Figure 1. Several clinical applications of sponge and tube scaffolds to the regeneration of skin dermis, esophagus, trachea, and peripheral nerve.
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Figure 2. Angiogenic therapy of ischemic diseases by the controlled release of basic fibroblast growth factor (bFGF). (A) Conceptual scheme of bFGF-induced angiogenic therapy for ischemic leg diseases. (B) The controlled relase of bFGF induced angiogenesis at the ischemic leg of diabetic rats, in marked contrast to bFGF solution. (C) The controlled release of bFGF effectively healed the foot ulcer of a human patient with Buerger disease.

Figure 3. (A) Conceptual illustrations of the conventional surgical regenerative therapy and physical regenerative therapy of internal medicine. (B) A representative example of physical regenerative therapy. Controlled release of hepatocyte growth factor (HGF) with an anti-fibrotic property successfully induced physical regeneration of liver tissue.

Figure 4. Dr. Tabata with his students, colleagues, and collaborators in the Biomaterials Department.

Feature on Tissue Engineering Laboratory
Europe

Tissue Engineering and Regenerative Medicine (TERM) at Imperial College London

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The first part this article outlines the current areas of active TERM related research at Imperial College London (UK) in the framework of the Imperial Regenerative Medicine Consortium (www.imperial.ac.uk/medicine/about/institutes/tissue/). In the second part of the article research being carried out in the Department of Materials, Imperial College London, under supervision of the author is summarised. In future issues of TERMIS Newsletter we hope to report in more detail on the breadth of research activities carried out by other laboratories based at Imperial College London in the general areas of tissue engineering and regenerative medicine.

I. Overview of Imperial College London TERM research activities

Regenerative Medicine, Tissue Engineering and associated disciplines at Imperial College span many Departments in the Faculties of Medicine, Natural Science and Engineering. The Tissue Engineering and

Regenerative Medicine Centre (TERM Centre) based at Chelsea and Westminster Hospital was Imperial's first example of a collaborative enterprise between Translational Biological Research and Materials Science to stimulate new paradigms in tissue engineering. This was the pioneering enterprise of Dame Julia Polak (Medicine) in collaboration with Professor Larry L. Hench (Materials). Professor Julia Polak, although officially retired, is still active as an Emeritus Professor and has recently been elected to the Steering Committee of the UK Stem Cell Collaboration. The legacy of TERM continues in the Regenerative Medicine Consortium, operating through Interfaculty study groups based around specific tissues (e.g. heart, endoderm, bone) and technologies (bioprocessing, imaging, biomaterials) as well as many collaborative links between the key centres in Imperial College such as the Institute for Reproductive and Developmental Biology, the Institute of Biomedical Engineering (www.imperial.ac.uk/biomedeng) and the National Heart and Lung Institute (www.imperial.ac.uk/medicine/about/divisions/nhli/). Much of the activity falls within the Imperial College Stem Cell Research Theme (www.imperial.ac.uk/medicine/about/institutes/irdb/).

Part of TERM Centre's research now continues in the Stem Cell and Regenerative Medicine Group based at the Hammersmith Hospital Campus in the Section on Experimental Medicine & Toxicology (www.imperial.ac.uk/medicine/about/divisions/medicine/exp_med_toxicology/) under the directorship of Professor Martin Wilkins.

Bone tissue engineering research activities are based in the South Kensington campus of Imperial College in the Department of Materials and the Institute of Biomedical Engineering. Four academics in the Department of Materials (www.imperial.ac.uk/materials) carry out research in the area of bone tissue engineering: Dr Molly Stevens, Dr Julian Jones, Prof. Robert Hill and Dr. Aldo R. Boccaccini. Other active researchers are: Dr. Nick Evans, Dr. Eileen Gentleman, Dr. Qizhi Chen and Dr. Oana Bretcanu. Further research in the field of bone engineering is being carried out in the Department of Chemical Engineering led by Dr. Sakis Mantalaris. Some areas of current active research with emphasis on in-vitro and in-vivo investigations are briefly described below.

Stem Cell Bioprocessing

Stem cell bioprocessing is a collaboration between Professor Dame Julia Polak and Dr A. Mantalaris, a system engineering, expert on bioreactors and cell encapsulation technologies. The overall aim of this project, which is based in the Department of Chemical Engineering (www.imperial.ac.uk/bsel), is the development of bioprocess technology for the successful transfer of laboratory-based practice of stem cells and tissue culture to the clinic as therapeutics, through the application of engineering principles and practices. It aims to have products which are cost effective, rapid in outcome, robust, reliable and reproducible.

Cardiac Regenerative Medicine

Cardiac regenerative medicine is mainly located at the National Heart and Lung Institute at the Harefield (Heart Science Centre) and Brompton Hospital Campuses. It encompasses work with bone marrow, skeletal myoblast and embryonic stem cells (human and mouse), using cell co-culture and whole models. Tissue engineering to create valve implants, and to combine embryonic stem cells with novel biomaterials for grafting and heart patches development is being done in collaboration with the research group of Dr Aldo R. Boccaccini in the Department of Materials, as described further below. In separate research, a clinical trial to track bone marrow cell implantation is in progress under the direction of Prof Eric Alton.

Regenerative Strategies for Liver

Advances in stem cell biology and the discovery of pluripotent stem cells have made the prospect of cell therapy and tissue regeneration a possible clinical reality. At Hammersmith Hospital, a morphologically and phenotypically homogeneous population of CD34+ cells that exhibits the necessary properties has been isolated from mobilised and leukapheresed blood. It has been demonstrated that these cells (Omnicytes) express genes corresponding to stem cells, haemopoietic, hepatic, cardiac and neuronal cell differentiation. This growing body of research has been a joint project led by Professor Nagy Habib (Department of Surgery) and Professor Myrtle Gordon (Department of Haematology). Work performed on-site as well as at collaborating institutes has shown homing and engraftment to tissue injury along with functional improvement. Furthermore, a phase I safety, toxicity and feasibility clinical study in patients with hepatic insufficiency has been carried out at Hammersmith Hospital. The treatment proved to be safe and no obvious toxicity was observed. This study documented the existence of stem cells that can be directly and reproducibly isolated from an accessible in-vivo source and have considerable promise for clinical application. The spectrum of clinical interest both at the basic/in-vivo level as well as the clinical trial level is bein expanded.

Stem Cell Imaging

Stem cell research is undergoing a critical transition from being a discipline of the basic sciences to being recognized as a potential component of medical practice. Cell transplants to replace cells lost due to injury or degenerative diseases, for which there are currently no cures, are being pursued in a wide range of experimental models under leadership of Dr. K. Bhakoo (Biological Imaging Centre, Faculty of Medicine). The monitoring of cellular grafts, non-invasively, is an important aspect of the ongoing efficiency and safety assessment of cell-based therapies. Magnetic resonance imaging methods are potentially well suited for such an application as they produce non-invasive "images" of opaque tissues. For transplanted stem cells to be visualised and tracked by MRI, they need to be tagged so that they are 'MR visible'. Imperial College reearchers are developing and implementing a programme of molecular imaging in pre-clinical models that is directed towards improving understanding of stem cell migration in the context of the whole organism. In order to achieve these goals novel MRI contrast agents are being engineered developing specific tagging molecules to deliver efficient amounts of contrast agents into stem cells. The intracellular contrast agents are based on either paramagnetic nanoparticles, such as dextran-coated iron oxide, or other MR contrast agents. Methods for monitoring implanted stem cells non-invasively in vivo will greatly facilitate the clinical realisation and optimisation of the opportunities of stem cell based therapies.

II. Dr. Boccaccini's research group, Department of Materials, Imperial College London

Aldo R. Boccaccini is one of four academics in the Department of Materials, Imperial College London, leading a large research programme in the area of biomaterials for tissue engineering and regenerative medicine. The research group includes 4 post-doctoral researchers, six PhD students, and several MSc, undergraduate

and visiting students. Most of the projects are supported by European Community grants or from national governmental contracts. The research is carried out in collaboration with an extensive network of national and international universities or research centres. The group hosts more than 10 academic visitors each year and a number of visiting students mainly from continental Europe carry out each year their final project or

thesis in the group. In the last 5 years, several biomaterial processing technologies to produce bioactive scaffolds for tissue engineering have been developed. The main research areas are described in the following paragraphs.

Bioactive scaffolds for bone tissue engineering

One of the main research areas in Dr. Boccaccini's laboratory is the development of three-dimensional (3D), highly porous foam-like composite scaffolds based on biopolymers and bioactive glass (e.g. 45S5 Bioglass®) for bone tissue engineering. Bioglass® is a well known bioactive material, developed for the first time in the early 70s by Prof. Larry Hench with whom Dr. Boccaccini worked until Prof. Hench's retirement in 2005. Bioactive glasses, which constitute one of the major material systems used in bone engineering, meet three basic criteria for ideal scaffolds: excellent osteoconductivity and bioactivity, ability to deliver cells, and controllable biodegradability. It has been also reported that the dissolution products of 45S5 Bioglass® cause rapid expression of genes that regulate osteogenesis and the production of growth factors. These advantages make bioactive glasses not only successful filling materials for bone repair but also promising scaffold materials for tissue engineering. The most popular bioactive glass composition, 45S5 Bioglass®, which contains 45% SiO_2, 24.5% Na_2O, 24.4% CaO and 6% P_2O_5 by weight percent, has been approved by the US Food and the Drug Administration and has been applied clinically as a filling material for bone repair and dental implants during the last 20 years.

The first group of materials investigated for bone tissue engineering are Poly(D,L-lactic acid) (PDLLA) foams incorporating Bioglass® particles either as filler or coating, which are fabricated by thermal induced phase separation technique. The materials, produced for the first time in 2002 [1] have been optimised in terms of microstructure, mechanical properties, degradation behaviour, bioactivity, e.g. formation of hydroxyapatite layer on the composite surfaces upon immersion in simulated body fluid (SBF), as well as in-vitro and in-vivo performance [2,3]. The microstructure of an optimised PDLLA/Bioglass® (5wt%) composite foam scaffold is shown in Figure 1. The effect of Bioglass® on angiogenesis has been also investigated. Results have shown that dissolution products of Bioglass® in an in-vivo situation can stimulate the growth of blood vessels and angiogenesis in the new tissue [4]. As an alternative to established biopolymers such as PDLLA or PLGA, our group is investigating polyhydroxyalkanoate (PHA) biosynthesis from structurally unrelated carbon sources by a newly characterised *Bacillus spp.*, using novel biotechnology approaches in collaboration with the research team led by Dr Ipsita Roy at the University of Westminster, London, UK [5]

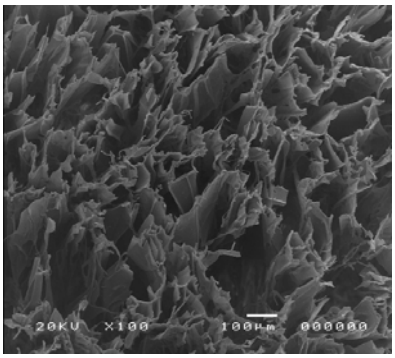
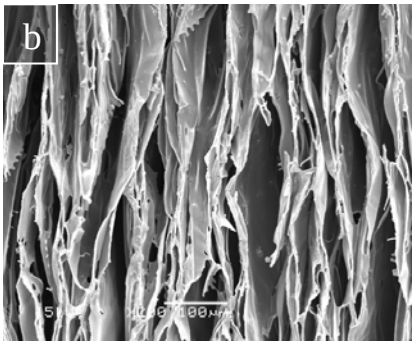
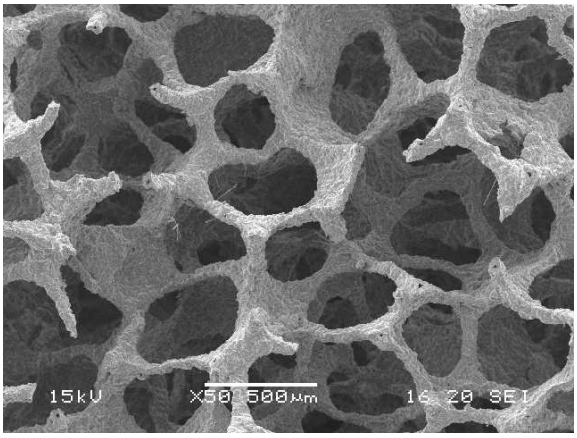


Fig 1. SEM micrographs showing the microstructure of PDLLA/Bioglass®-filled composite foams (5 wt% Bioglass®): (a) orthogonal to the pore direction and (b) parallel to the pore direction.



A second group of scaffolds designed for bone tissue engineering are those based on a patented technology to develop 3D Bioglass® based glass-ceramic foams by the replica technique [6]. This method involves preparation of green bodies by coating a polyurethane (PU) foam with a glass slurry. The glass used is a melt-derived 45S5 Bioglass® powder (particle size < 5 μm). Different types of fully reticulated polyester-based polyurethane foams can be used as sacrificial templates. After impregnation of the polymer foam with the glass slurry, the green body is sintered at high temperatures, up to 1100°C. The partially crystallised scaffolds degrade to a calcium phosphate layer upon immersion in SBF and hydroxyapatite forms on the scaffold surface after 1 week in SBF. The glass-ceramic scaffolds have a highly porous structure (around 80-85 % porosity) with highly interconnected pores (see Figure 2). Cell support function as well as cell proliferation on highly porous Bioglass®-derived glass-ceramic scaffolds have been confirmed in vitro using osteoblast-like cells (MG 63) cultured for up to 6 days, in collaboration with Dr. V. Salih (University College London, UK) (Figure 3). The mechanical properties of the scaffolds are improved by coating the struts with biodegradable polymers such as polylactic acid (PDLLA) or poly hydroxybutyrate (PHB). The polymer coating does not affect the interconnectivity of the pore structure but the presence of the thin polymer layer induces a major improvement of the work of fracture [7]. Further collaborations, particularly on the development of biocomposite scaffolds based on biodegradable polymers and bioactive glasses has been established with Prof. F. Torres (Catholic University of Peru) [8].

Fig 2. Microstructure of a Bioglass®-based glass-ceramic scaffold obtained by the foam replica technique after sintering at 1100°C



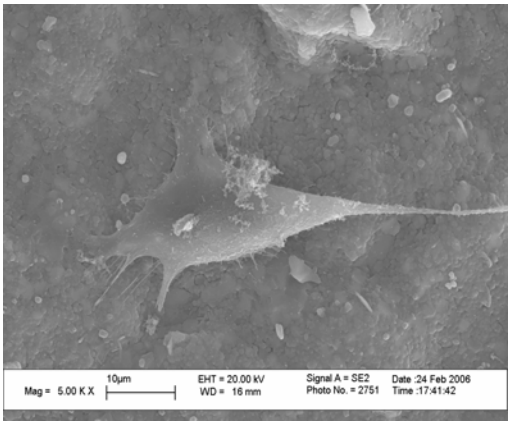


Fig 3. SEM micrograph of cultured MG 63 osteoblast-like cells on 45S5 Bioglass®-derived glass-ceramic after 1 day, showing cell attachment

Engineered heart patches using embryonic stem cells and biopolymers

Heart attack is the single most common cause of death in developed countries. Cardiac tissue engineering and regeneration has been attempted using cells to repair a broken heart. At present, the preferred method of introduction of these cells is by injection either into the myocardium directly, or into the coronary vessels with the hope that they will spontaneously cross the numerous barriers and implant in the desired area of the heart. In this project, which is collaborative investigation between Imperial College London (UK) and Szczecin University of Technology (Poland), the alternative of developing preformed patches of myocardial cells attached to a biodegradable engineered

support is explored. In vitro and in vivo research based on embryonic stem cells is being carried out under direction of Prof. S. Harding and Dr. N. Ali at NHLI (www.imperial.ac.uk/medicine/about/divisions/nhli/). The heart patch will be sutured to the heart, with the aim that the support substrate degrades as the myocytes integrate into the surrounding myocardium, as well as overcoming the problems of cell injection. Multiblock poly(aliphatic/aromatic-ester)s containing phthalic acid sequences (as in poly(ethylene terephthalate)(PET) and a dimmer fatty acid (DFA) are being designed and applied for the fabrication of the patches. An initial assessment has shown that this material can deliver healthy and functional cardiomyocytes, which are derived from embryonic stem cells.

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Feature on Tissue Engineering Laboratory
North America

Cartilage by Nature and by Design: Cartilage Tissue Engineering Laboratory at University of California, San Diego

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The Cartilage Tissue Engineering (CTE) laboratory was formed at University of California, San Diego in July, 1992. Principal Investigators of the lab are the director, Prof. Robert Sah, MD, ScD (Bioengineering), Prof. William Bugbee, MD (Orthopaedic Surgery), and Prof. Deborah Watson, MD (Facial Plastic and Reconstructive Surgery). The research missions of the CTE lab are to use bioengineering and translational approaches in order to (1) better understand the processes of cartilage development & growth, aging, degeneration, repair, regeneration, and replacement, and (2) improve the clinical treatment, diagnosis, prevention of cartilage injury and disease. To address these missions, the CTE lab takes the approaches of (1) elucidating the relationships between cartilage biomechanics, metabolism, composition, and structure, integrated within the host environment, and (2) developing and using translational model systems.

1. Multi-Scale Biomechanics of Cartilage in Health and Disease

The biomechanical properties of cartilage are examined in order to delineate how cartilage structures deform under applied loads over a variety of length and time scales. During normal activities (e.g., walking), joint loading and articulation impose axial and transverse loads, respectively, on the articular cartilage lining of joints (**Fig. 1A**). The application of video microscopy to biomechanical testing of cartilage was developed in the CTE lab in 1993, and has been used to characterize the micro-scale deformation of cartilage. In configurations resembling the apposed cartilage surfaces in the joint (**Fig. 1B**), axial loading was found to cause cartilage compression in a depth-dependent manner, with the superficial region being relatively soft and compressed significantly more than deeper regions (**Fig. 1C**). Superimposed transverse loading induced shear strains that also were higher near the articular surface (**Fig. 1D**). The understanding of cartilage biomechanics at the micro-scale helps to elucidate the basis for the spatial and temporal behavior of cartilage under applied load as well as mechanobiological regulatory mechanisms in cartilage health and disease.

2. Pathogenesis of Biomechanical Deterioration of Articular Cartilage in Osteoarthritis

The mechanisms for the biomechanical deterioration of human articular cartilage in aging and osteoarthritis are also studied. The temporal and spatial sequence of change in selected properties of human articular cartilage has been elucidated for samples isolated from knee joint specimens (**Fig. 2**). These studies have been made possible through collaborations and core resources of a Program Project Grant, *Studies of Joint Aging and Osteoarthritis*, sponsored by the National Institutes of Health – National Institutes of Aging (Program Principal Investigator, Martin Lotz, MD, The Scripps Research Institute). Aging-related weakening of articular cartilage tensile properties appears to coincide with subtle roughening at the articular surface, consistent with a wear-related process. Subsequently, cell density of the superficial zone diminishes, and then cells undergo clone formation, matrix proteoglycan and collagen are degraded, and cartilage

biomechanical properties deteriorate further. Using cartilage explants, the degradation of collagen, but not proteoglycan, was associated with tensile weakening, typical of that observed in the progression of cartilage damage to the stage of joint osteoarthritis. These studies have highlighted surface wear and weakening as early events in age-associated cartilage deterioration and supported a revived interest in cartilage lubrication. Enhancement of cartilage lubrication has emerged as a biomechanical target for therapeutic intervention.

3. Bioengineering the Growth of Cartilage

With focal cartilage defects and osteoarthritic erosion, there is a need to bioengineer cartilaginous tissue for therapeutic purposes. Such tissue engineering, whether *in vivo* or *in vitro*, would benefit from a better understanding of articular cartilage growth and tools to manipulate such growth. Using a bovine

model, articular cartilage tissue from different stages of growth (late fetus, calf, and adult) has been characterized to gage variations in biomechanical function, composition, and structure. The structural analysis includes the identification of individual chondrocytes within large volumes of cartilage, using the method of digital volumetric imaging (Microscience Group) and image processing (**Fig. 3**). To examine cartilage dynamics, cartilage growth *in vitro* has been studied under defined chemical and mechanical environments. In particular, studies have examined the role in cartilage growth for the balance between the swelling effect of the glycosaminoglycan fixed charge and the restraining effect of the collagen network; collaborations with Prof. Stephen Klisch (California State University—San Luis Obispo) and Profs. Koichi Masuda and Eugene Thonar (Rush Medical College) have facilitated *in silico* growth mixture models and *in vitro* cartilage growth experiments (**Fig. 4**). Interpretation of experimental data within the theoretical framework has helped to infer the role for matrix remodeling. For fetal (A) and calf (B) cartilage explants, incubation *in vitro* under anabolic conditions led to growth, not to the adult-like state (i.e., to C), but rather to a more immature (fetal-like) state (D). Blocking collagen crosslink formation led to an exaggeration of expansive growth and tensile weakening (E). Removal of glycosaminoglycan from calf (B) cartilage tissue by several treatment methods caused a functional stiffening (F), analogous to that which occurs during normal maturation. When such explants were subsequently incubated under anabolic conditions, matrix glycosaminoglyan was restored, the enhanced tensile properties were maintained, and the resultant tissue features were characteristic of the mature adult state (G). *In vitro* mechanical stimuli such as compression, shear, and bending have also been found to markedly modulate metrics of tissue growth and shape. Particular chemical and mechanical stimuli are thus becoming part of the tissue engineer's toolbox for directing cartilage growth.

4. Tissue Engineering of Articular Cartilage

Other studies have the goal of using cells for *in vitro* fabrication of cartilaginous tissue that will effectively restore normally functional articular cartilage. In collaboration with Profs. Masuda and Thonar, the alginate-recovered chondrocyte (ARC) method was modified to form stratified tissue. The ARC method facilitates cartilage formation directly from chondrocytes. Chondrocytes are first incubated in alginate to allow formation of a pericellular matrix. Then, the ARC cells with their newly formed matrix are released from the alginate, seeded at high density, and allowed to coalesce into cartilaginous tissue. ARC tissue constructs exhibit phenotypic characteristics typical of native articular cartilage, including abundant aggrecan and type II collagen, and little type I collagen. This two-step strategy was modified to create stratified constructs that recapitulate the zonal architecture of native cartilage, using sequential seeding of chondrocyte subpopulations isolated from the superficial and deeper zones. These stratified constructs have exhibited depth-varying properties similar to those seen in native cartilage, including PRG4 lubricant secretion localized to the surface, an increase in matrix accumulation deeper within the construct, and a depth-varying compressive modulus. A tissue-engineered cartilaginous implant with depth-dependent mechanical and biochemical properties may be capable of performing the zone-specific functions typical of native articular cartilage. Continuum models of tissue-engineered construct formation, including the synthesis, binding, transport, and degradation of important matrix molecules, have also been used to elucidate how culture conditions and metabolic regulation may be useful in modulating construct properties.

5. Tissue Engineering of Human Septal Cartilage

Under the direction of Prof. Watson, the CTE lab seeks to develop a scientific and practical basis for fabricating human cartilaginous tissue for use in surgery to repair cartilaginous defects of the head and neck, particularly the nasal septum. Such defects are created by trauma, surgical resection (e.g., of tumors), or congenital deformities. For repair of these defects, a source of graft tissue is limiting, and harvest of graft

tissue from distant sites is associated with morbidity. Nasal septal cartilage, itself, is limited by the relatively small amount available and, sometimes, by prior trauma to the nasal septum. Prof. Watson's group has developed methods to use a small biopsy of human septal cartilage for isolation and expansion of chondrocytes to clinically useful cell numbers for tissue engineering. They have identified culture conditions, such as medium composition, growth factor additives, cell seeding density, scaffold properties, and physical stimuli that can stimulate the ability of expanded cells to produce cartilaginous matrix and form cartilaginous tissue using the ARC method. Considering safety and practical issues, autologous human serum was investigated as a growth supplement and found to markedly enhance the formation of cartilaginous tissue. These studies have advanced human septal cartilage tissue engineering closer to the clinic.

6. Enhancing the Application and Efficacy of Osteochondral Allografts

Under the direction of Prof. Bugbee, the CTE lab investigates osteochondral allografting. Osteochondral allografts are used effectively in surgical treatment of large chondral defects in the knee (**Fig. 5**). A primary limitation of the allograft procedure is the lack of donor tissue; this is due, in part, to the relatively short storage time after retrieval that is deemed acceptable. Through collaborative efforts with Prof. David Amiel (UCSD Orthopaedics), conditions have been developed to prolong the storage duration for maintaining chondrocyte viability within allograft tissue. Chondrocyte survival has also been found to be affected by the technique of insertion used during surgical grafting. Such translational research on storage and grafting techniques has directly influenced clinical practice for cartilage repair and replacement with osteochondral allografts.

7. Bioengineering Synovial Joints: Lubrication MechanoBiology

Synovial joints are composed of interacting tissues, including articular cartilage, synovium, and synovial fluid. The cartilage bears load and slides with low-friction and low-wear properties due to the lubricant behavior of synovial fluid. Synovial fluid constituents are retained within the synovial joint cavity by the semi-permeable nature of the synovium tissue lining (**Fig. 6**). Lubricating molecules in synovial fluid are secreted by the chondrocytes in the superficial zone of cartilage and by the synoviocytes in the synovium, and these molecules include proteoglycan 4 (PRG4), hyaluronan (HA), and, possibly, surface-active phospholipids. Using a novel cartilage-on-cartilage friction test system, the dose-dependent boundary lubrication function of synovial fluid has recently been quantified, and the important roles of PRG4 and HA have been identified. Other studies by the CTE labs, and other labs, have shown that cellular secretion of these lubricants is markedly regulated by environmental factors, notably chemical and mechanical stimuli. The cytokines TGF-β1 and IL-1α, as well as mechanical compression and shear, regulate secretion of PRG4 by chondrocytes in cartilage explants. The finding that shear markedly upregulates PRG4 secretion by cartilage suggests that the synovial joint performs as a bioactive feedback-regulated lubrication system. At the whole joint scale, through collaboration with engineers at Breg, Inc., a continuous passive motion rehabilitation device was adapted to create a dynamic motion bioreactor. Like the shearing of cartilage explants, rehabilitative motion of knee joints stimulated PRG4 secretion. To better understand lubricant dynamics, the synovial joint has been modeled as a system of communicating compartments. The analysis of lubrication at the joint scale may enhance current and future therapies, ranging from arthroplasty to injection of cells and lubricants, transplantation of tissues, and bioengineering whole biological joints.

Summary

The CTE lab welcomes inquiries, particularly from fellow cartilageholics. Please visit us at our URL, http://cte.ucsd.edu.

Acknowledgments

Figures and text were provided by Megan Blewis and Greg Williams, as well as Dr. Anya Asanbaeva, Dr. Won Bae, Dr. Albert Chen, Kenneth Gratz, Jennifer Hwang, Dr. Kyle Jadin, Dr. Gayle Nugent, Benjamin Wong, Dr. Michele Temple. Research support has been from National Institutes of Health, a Professor's Award to UCSD from the Howard Hughes Medical Institute, National Science Foundation, Veterans Administration Medical Center, National Aeronautics and Space Administration, Arthritis Foundation, UCSD Powell Foundation, Whitaker Foundation, Articular Engineering, Advanced Tissue Sciences, Seikagaku Corporation, AlloSource, Musculoskeletal Transplant Foundation, National Football League Charities, UCSD von Liebig Center for Entrepreneurship, Synthasome, Baxter, BREG, Arthrex, Regen Biologics, Genzyme Biosurgery, and Wyeth.

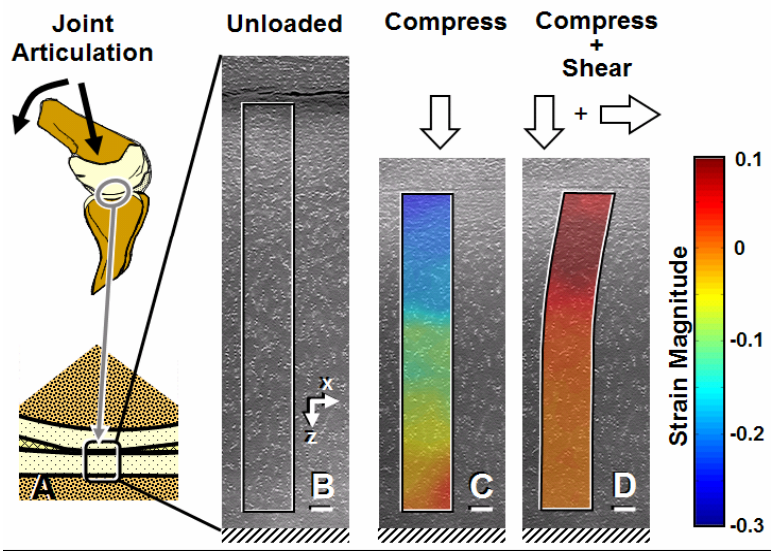

Figure 1. Joint loading and articulation (**A**) impose axial and transverse loads on the cartilage lining the joint, and can be studied using fluorescent cell labels and microscopy (**B**) to reveal compressive (**C**) and shear (**D**) strain.

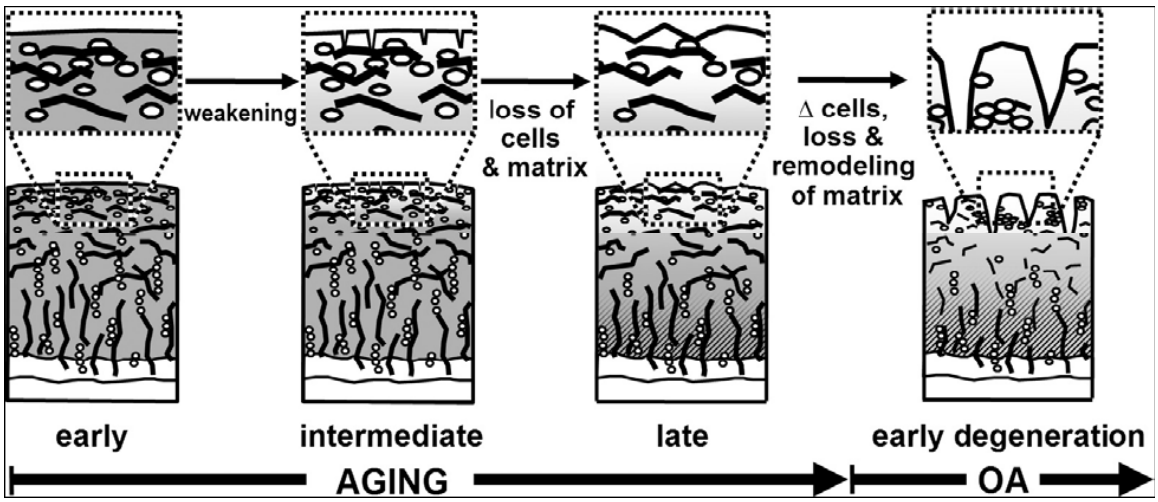

Figure 2. Sequence of age-associated degenerative changes in articular cartilage: roughening and weakening of the articular surface; loss of cells and matrix; degradation of proteoglycans and collagen network along with cellular proliferation and activation.

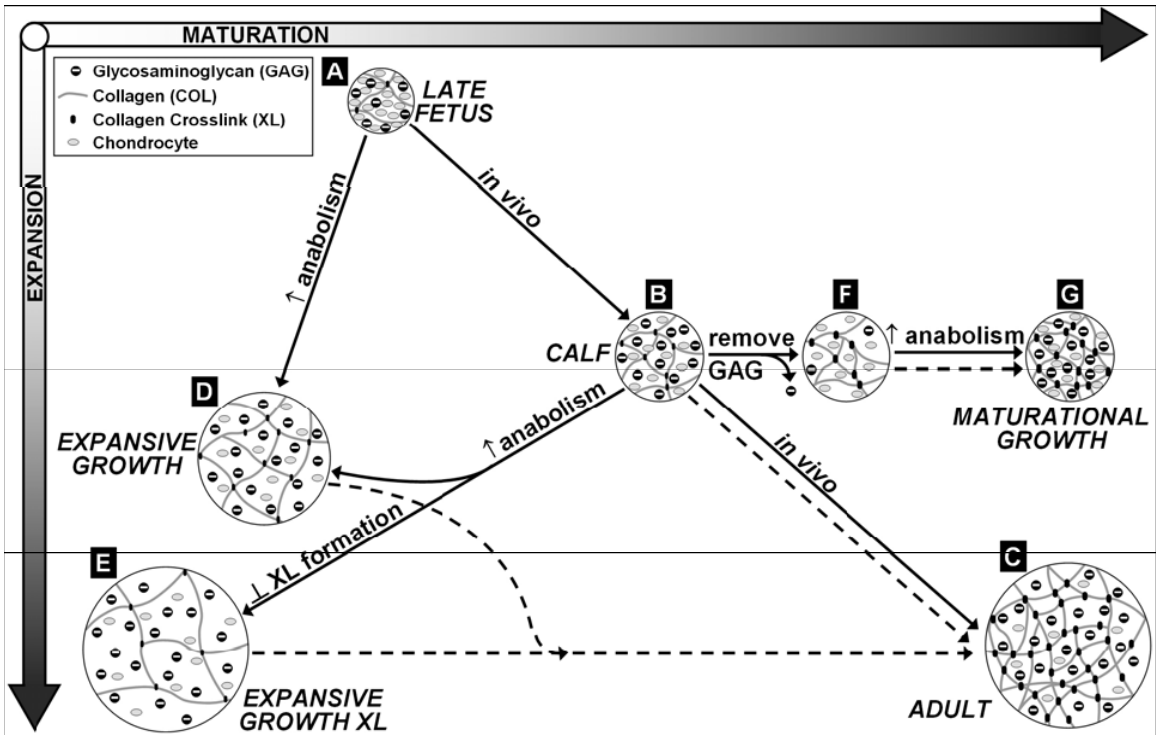

Figure 3. Stress balance hypothesis whereby cartilage expansion (growth) and maturation (strengthening) are associated with a change in the stress balance between proteoglycan swelling and collagen network restraint. The resultant growth is depicted as native (**A** **B** **C**) or altered by specific manipulations (**D**, **E**, **F**, **G**).

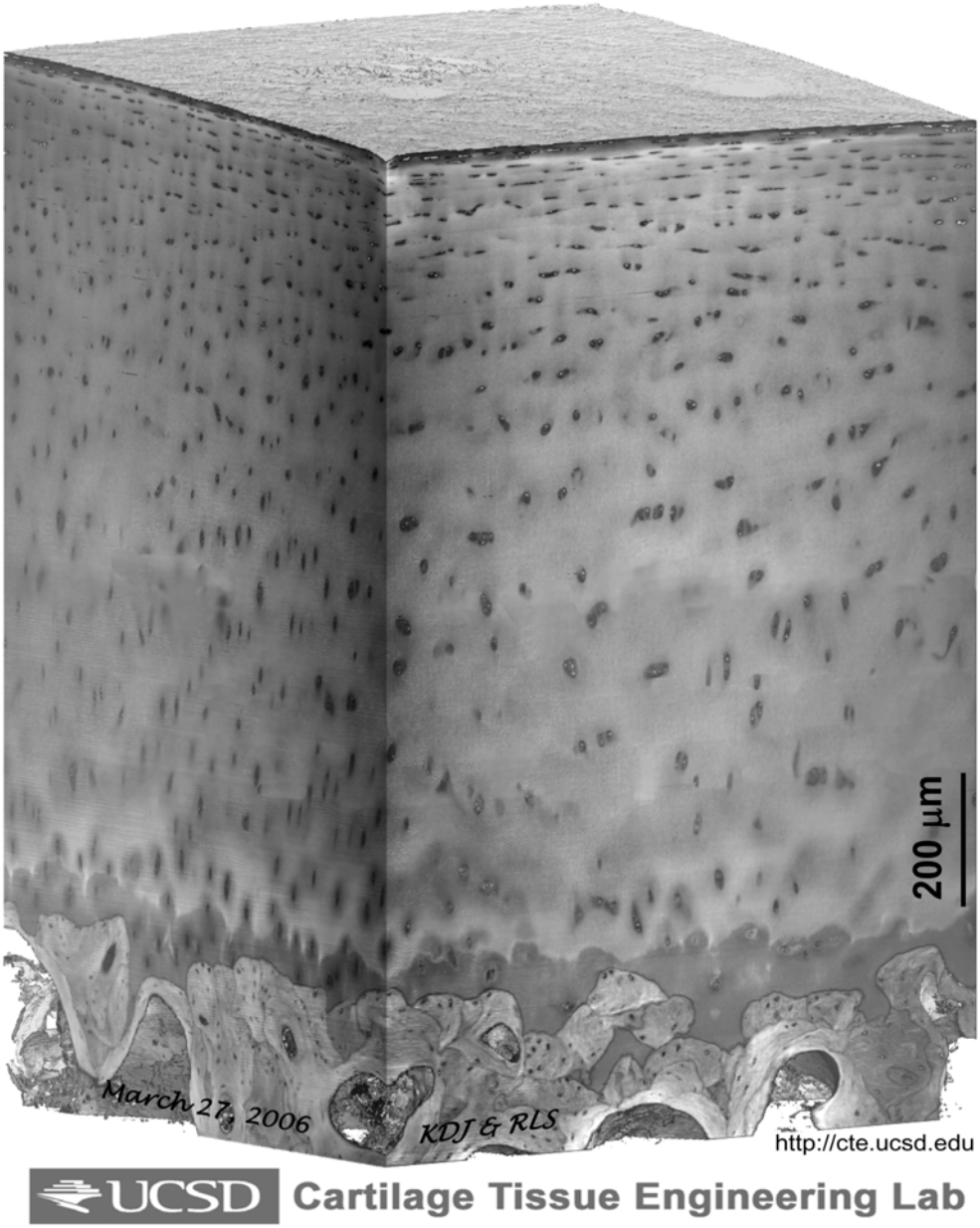

Figure 4. Three-dimensional image of a block of adult human articular cartilage.

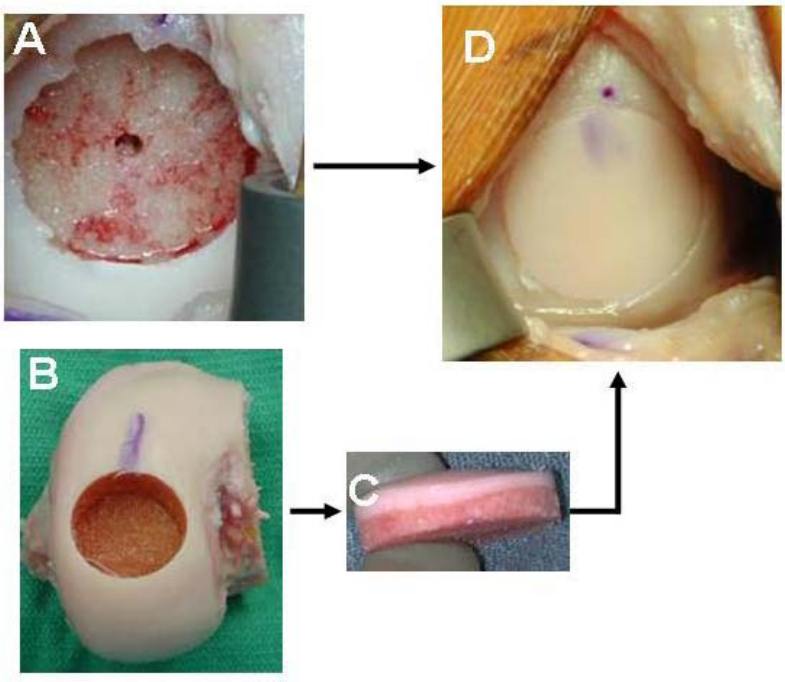

Figure 5. Osteochondral allografting procedure. (**A**) Defect site is prepared to appropriate size to accommodate implant. (**B**) Donor allograft tissue from which osteochondral allograft (**C**) is prepared and inserted into recipient socket, resulting in (**D**) repaired defect. Line and dot on surface of articular cartilage provide orientation.

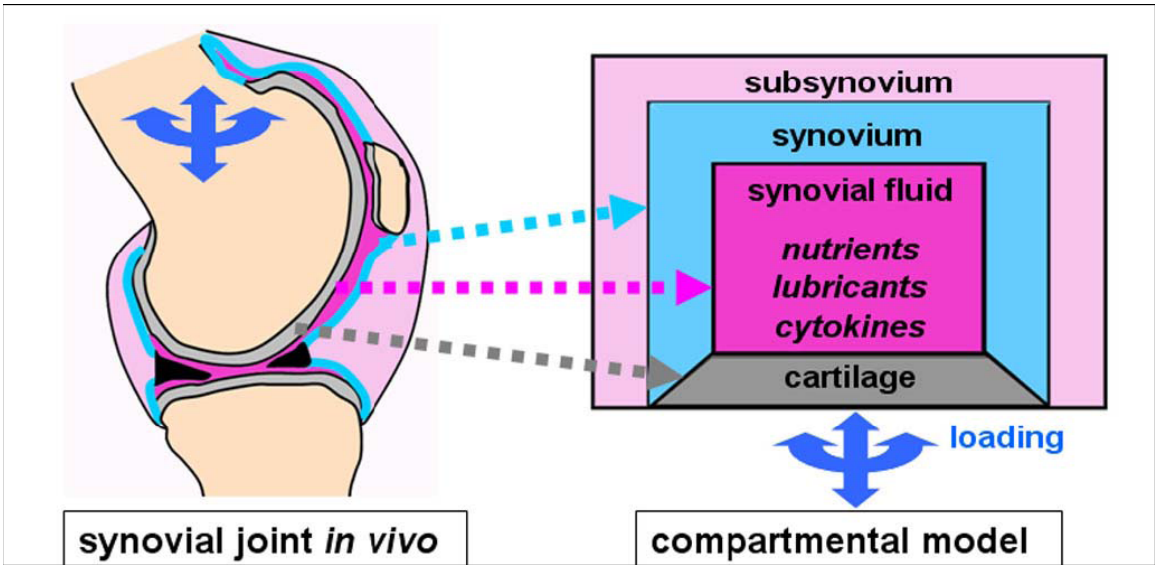

Figure 6. Consideration of synovial joint as interacting compartments, comprising a mechanically active and responsive system for synovial joint lubrication.

TERMIS-SYIS: Student and Young Investigator Section

The SYIS members have elected their new Council Members. Congratulations to all the newly elected SYIS Council Members! The winners of the elections are as follows:

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Vice-Chair: Henry Ko
Secretary: Soon Hee Kim
Treasurer: Zheng Ye

Europe
Chair: Catarina Alves
Vice-Chair: Eric Farell
Secretary: Yvonne Jenniskens
Treasurer: Joaqim Miguel Antunes de Oliveria

North America
Chair: Tiffany Sellaro
Vice-Chair: Dawn Delo
Secretary: Jolene Valentin
Treasurer: Alison McGuigan

Emerging Countries
Chair: Rania El-Backly

To learn more about SYIS, please visit http://www.termis.org/students.php.

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TERMIS Chapter and World Congress Meetings

Mark Your Calendars!

Updates on the meeting will be provided on the TERMIS website, www.termis.org.

June 2007
TERMIS-North America: Toronto, Ontario
Westin Harbour Castle
Meeting Chair: Molly Shoichet
June 13-17, 2007
www.regenerate-online.com

September 2007
TERMIS-Europe: London, England
Regent's College Conference Centre
Meeting Chair: Robert Brown
4-7 September 2007
www.termis.org/eu2007

November 2007
TERMIS-Asia-Pacific: Tokyo, Japan
Sankei Plaza
Meeting Chair: Prof. Kazuo Tsubota
November 8-9, 2007

June 2008
TERMIS-Europe: Porto, Portugal
Porto Congress Center – Alfândega
Meeting Chair: Rui Reis
23-27 June 2008
www.termis.org/eu2008

November 2008
TERMIS-Asia-Pacific: Chinese, Taipei
Taipei International Convention Center
Meeting Chair: Prof. Ging-Ho Hsiue
November 7-8, 2008

December 2008
TERMIS-North America: San Diego, California
Hyatt Regency La Jolla
Meeting Chairs:
Bill Tawil, Bob Sah and Anthony Ratcliffe
December 6-10, 2008

August 2009
2nd World Congress: Seoul, Korea
Hotel Lotte World, Jamsil
Meeting Chair: Shin-Yong Moon
August 31 – September 3, 2009

August 2010
TERMIS-Europe: Galway, Ireland
Galway Radisson SAS Hotel
Meeting Chair: Dr. Abhay Pandit
29 August to 2 September 2010

Asia-Pacific 2010
Sydney Australia
Meeting Chair: A/Prof. Geoffrey McKellar
More details coming soon!

TERMIS Membership

How to Become a Member of TERMIS:

Membership to TERMIS is open to individuals who are interested in the field of tissue engineering and regenerative medicine and support the mission of the Society.

There are two (2) ways to become a TERMIS Member:

1. **Attend a TERMIS World Congress or a Chapter Meeting.**

By attending a TERMIS meeting, you automatically become a member or renew your membership until the end of the following year.

Example: You attend either the World Congress in Pittsburgh or the TERMIS-EU Chapter meeting in Rotterdam in 2006. You are automatically a member of the Society until December 31, 2007. If you then attend any of the Chapter meetings in 2007, you automatically remain a member until December 31, 2008, and so on.

2. **Pay the Annual Dues.**

Dues have been structured to encourage participation by students, in particular, as follows:

a. Regular Membership (annual dues: $100.00) – Any individual who does not qualify as a Student Member.

b. Student Membership (annual dues: $25.00) – Any individual, who is engaged as a full-time graduate or undergraduate, in a university or college program and is actively involved in research in the field of tissue engineering and regenerative medicine. A copy of your student ID needs to be presented at the time of joining the Society.

The individuals residing within the countries that have been identified as Emerging Countries within the Continental Chapters are exempt from paying membership dues. Even though dues will not be collected, you must complete the online membership form.

Membership Benefits

How TERMIS Membership Benefits You:

1. Free online access to the Society's official journal, Tissue Engineering, and reduced subscription rates for the print edition;
2. Opportunity for TERMIS members to purchase a Regenerative Medicine Online Package that includes online access to: Tissue Engineering, Rejuvenation Research, Stem Cells and Development and Cloning and Stem Cells for $295.00;
3. One year complimentary subscription to Genetic Engineering News. Visit the TERMIS website for further details;
4. The Society's quarterly newsletter, interlink;
5. Reduced registration fees to the meetings sponsored or endorsed by the Society;
6. Posting career opportunities on the TERMIS website free for one month.

Your participation in TERMIS as a member helps the Society become a leading international voice in addressing key issues affecting research and clinical developments in the field of tissue engineering and regenerative medicine.

If you have any questions about the membership benefits offered to TERMIS members, please contact Sarah Wilburn at swilburn@termis.org.

Tissue Engineering Journal
Subscription Information

Free Online Access to *Tissue Engineering*

The online version of the journal, *Tissue Engineering*, the official journal of TERMIS, is now available for free to members only. The online journal can be accessed 24 hours a day, 7 days a week by logging on to the online journal website, http://www.termis.org/journal.php.

All members of TERMIS have been issued a username and password to access the online version of the journal. If you are experiencing problems logging on to view the online journal or have any questions, please contact Sarah Wilburn either by email at swilburn@termis.org or by phone at +1 (410) 931-7838.

Regenerative Medicine Online Journal Package

Mary Ann Liebert Publishers, Inc. is providing TERMIS members with the opportunity to purchase a Regenerative Medicine Online Journal Package that includes the following journals:

Tissue Engineering
Rejuvenation Research
Stem Cells and Development
Cloning and Stem Cells

The Online Journal Package can be purchased for $295.00. If you are interested in ordering the journal package, please check the corresponding box that is included within the TERMIS online membership form.

Encourage Your Institution to Subscribe to the journal, *Tissue Engineering*

If your institution does not currently subscribe to the journal, *Tissue Engineering*, we ask that you please complete the library recommendation form and fax to your institution's librarian encouraging them to subscribe to the journal today. (A copy of the librarian recommendation form can be found at http://www.termis.org/docs/libraryRecommendForm.doc) Your institution's library can benefit in subscribing to *Tissue Engineering* by providing a publications outlet for yourself and other colleagues within the field of tissue engineering keeping you up-to-date with the latest papers and research. The journal now offers an online version, which offers convenience and ease of accessibility.

Please take a moment to complete the form and fax to your librarian today!

Genetic Engineering News (GEN)

In view of your membership with TERMIS a one year complimentary subscription to Genetic Engineering News (GEN) has been reserved for you. Act now to receive 21 free issues of GEN for 2006.

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Post Your Job Openings

Members of TERMIS have the opportunity to post job openings on the TERMIS website for one month FREE. If you are interested in posting a job opening, please send the job description to Sarah Wilburn at swilburn@termis.org. The TERMIS-SYIS will also post the job openings on the SYIS forum.

Upcoming Meetings Endorsed by TERMIS

April 2007

- PharmaMedDevice 2007

April 24-26, 2007 at the Jacob K. Javits Convention Center, New York, NY

- MTEC 2007

April 20-21, 2007 in Ann Arbor, Michigan.
Submission of abstracts deadline: February 5, 2007

May 2007

- Stem Cell & Tissue Engineering in Plastic, Reconstructive and Aesthetic Surgery

The Symposium will be held from May 10-12, 2007 in Samsun, Turkey.
Submission of abstracts deadline: March 3, 2007.

October 2007

- 3rd World Congress on Regenerative Medicine

Conference Dates: October 17-19, 2007
Location: Leipzig, Germany
Themes: Translation of Regenerative Technologies and Personalized Regenerative Medicine

December 2007

- 2nd International Conference on Mechanics of Biomaterials & Tissues

Conference Dates: December 8013, 2007
Location: Lihue - Kau'i, Hawaii
Organizers: Elsevier in association with Engineering Fracture Mechanics and International Journal of Fatigue
Call for Papers Abstract Deadline: April 27, 2007

May 2008

- 8th World Biomaterials Congress

May 28 through June 1 in Amsterdam, The Netherlands. Please contact info.wbc2008@ics-online.nl for further details.

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