Faculties of Engineering & IT, Medicine,
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The University of Sydney

Sydney University Tissue Engineering Network

2nd Tissue Engineering Symposium

The University of Sydney
Darlington Centre

Thursday 13th November 2008

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CONTENTS

1. Foreword: Chancellor of the University of Sydney

Dear Colleagues

On behalf of the University of Sydney, it is my great pleasure to welcome you to the second Sydney University Tissue Engineering Network Symposium.

The challenge of this century for medicine and biomedical engineering will be the regeneration of diseased and damaged tissues and organs. Tissue engineering is the developing field of research which will enable this achievement. It focuses on the construction of biological substitute matrices containing viable and functioning cells for the restoration, maintenance or improvement of tissue function. This young field is attracting increasing numbers of investigators and growing support from granting agencies. This complex challenge requires the coordinated efforts of biologists, physicists, chemists, pharmacists, engineers, computer engineers, material scientists, surgeons and physicians. In response to a combination of these opportunities and increasing demand on campus, the Sydney University Tissue Engineering Network (SuTEN) was established in 2006.

The aim of this network is to allow scientists to expand their intellectual horizons and to build interdisciplinary partnerships. This symposium will gather scientists and students of tissue engineering, from the Faculties of Engineering, Medicine, Science, Pharmacy, Veterinary Science and Dentistry.

Distinguished national and international scientists will present updates and reviews on a range of scientific and clinical research into Tissue Engineering. Students and post-doctoral fellows will have the opportunity to highlight their discoveries and build collaborations that will enrich their research. We are grateful to the Faculties involved and the generous sponsors who have supported the meeting and made it possible. We hope that you will enjoy your scientific day at the University of Sydney.

The one day symposium is organised by the Biomaterials and Tissue Engineering Research Unit, Biomedical Engineering, School of Aerospace, Mechatronic, & Mechanical Engineering, Faculty of Engineering and Information Technologies.

We welcome you all and trust that you will enjoy a rewarding and stimulating program.

Her Excellency Professor Marie Bashir AC CVO

2. Program

8:00am		*Registration, Coffee, Tea and mini-muffins*
8:45		**Welcome and Opening Remarks** Her Excellency Professor Marie Bashir AC CVO, Chancellor Hala Zreiqat, Chair and Convenor – SuTEN
8:55	**SESSION 1:**	**Vascular Tissue Engineering** *Chair: Jennifer Gamble*
	Speaker 1.1	**Plenary – Vascularisation of Engineered Tissues** *Shulamit Levenberg*
9:30	Speaker 1.2	The genetic response of endothelial cells to matrix dimensionality *Jennifer Gamble*
9:45	Speaker 1.3	How do we realise the potential for lens epithelial cells to form functional lens-like structures? *John McAvoy*
10:00	Speaker 1.4	Increased angiogenesis in asthma: possible causes and consequences *Janet Burgess*
10:15am	**Morning tea and trade displays**	
10:40am	**SESSION 2:**	**Biomaterials modification for biological application** *Chair: Qing Li*
	Speaker 2.1	**Plenary - Functional Tissue Engineering: Combining Physics and Biology** *Hala Zreiqat*
11:15	Speaker 2.1	New surfaces for linker free covalent attachment of bioactive protein created using a plasma polymerization process with energetic ion bombardment *Marcela Bilek*
11:45am	**SESSION 3:**	New Investigator mini-posters competition finalists Short presentations
		Judges – Merlin Crossley, Judy Black, Greg Roger
12:45pm	**Lunch and Industry Session** Judging of the New Investigator short presentations, and mini-poster display	
1:45pm	**SESSION 4:**	**Cell-Cell Communication** *Chair: Gary Halliday*
		Plenary - Neural regulation of osteoblastic bone formation *Edith Gardiner*
2:20		Mechanisms underlying the beneficial effects of activated protein c in sepsis and wound healing *Chris Jackson*

2:35		The osteoblast, a key regulator of mesenchymal and haematopoietic cell lineage commitment and survival *Colin Dunstan*
2:50		Fibrocytes in burn wound healing: could regulation of these cells reduce scarring? *Andrew Holland*
3:05pm	**Afternoon tea and trade displays**	
3:35pm	**SESSION 5:**	**Musculoskeletal Tissue Engineering** *Chair: Chris Little*
		Plenary - Adult Stem Cells and Nanomatertials in Skeletal Tissue Engineering and Regeneration *Rocky Tuan*
4:15		Effective engraftment and enrichment of CD34+ve stem cells mouse skeletal muscles using chemotherapeutic drug selection: a paradigm for enhanced stem cell transplantation *Edna Hardeman*
4:30		Multifunctional materials for cartilage engineering *Lisa Capriotti*
4:45pm	**SESSION 6:**	**Discussion Panel - suggested topic: "Building a successful Tissue Engineering Network"**
		Chairs: *David Wiliams - Editor "Biomaterials", and David Sonnabend* ***Panel:*** *Bernie Tuch, Carol Armour, Tony Weiss*
5:30pm	**SESSION 7:**	**Prize Presentations, Closing Remarks, and Sponsor Booth Prizes** *Hala Zreiqat* Wine and nibbles

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3. Abstracts: Session 1 Vascular Tissue Engineering

3.1 PLENARY - Vascularisation of engineered tissues

Dr Shulamit Levenberg
Senior Lecturer
Department of Biomedical Engineering
Technion
Haifa Israel 32000

Dr. Levenberg received her PhD in 1999 from the Weizmann Institute of Science, specializing in Molecular Cell Biology and Cell Adhesion. Upon completion of her postdoctoral training and research (1999-2004) at Prof. Langer's group at the department of Chemical Engineering at MIT, she received a faculty appointment in the Technion's department of Biomedical Engineering. At Technion she is conducting interdisciplinary research in the subjects of tissue engineering from human embryonic stem cells using biodegradable polymers.

Dr. Levenberg received the EMBO long term fellowship for her postdoctoral research, won the ASAIO William Kolff young investigator award and was appointed as a Landau Fellow in the "Leaders in Science and Technology" Technion program. Dr. Levenberg was awarded the 2006 Krill price of the Wolf foundation for excellence in scientific research. She was also nominated as a Research Leader in Tissue Engineering by the Scientific American Journal (the 2006 Scientific American 50 Award).

This recognition as a research leader was given to Dr. Levenberg for her breakthrough in vascularisation of engineered tissues, first published in Nature Biotechnology in 2005, demonstrating engineering skeletal muscle tissue constructs that contain endothelial blood vessels. Upon implantation, this vascularisation was shown to anastomose with the host vasculature and improve survival and perfusion of the engineered graft. This work was cited as a landmark paper in the field of Tissue engineering, showing the importance of co-cultures for engineering vascularised complex tissue structures. Dr. Levenberg's new research on vascularisation of cardiac tissue using human embryonic stem cells was recently published in Circulation Research journal (2007). Recently, Dr. Levenberg received The Henry Taub Prize for Academic Excellence and the France-Israel Foundation Prize for scientific excellence in stem cell research.

Abstract

Vascularisation of engineered tissue constructs, using endothelial cells or progenitors seeded on biodegradable polymer scaffolds, can provide new approach for inducing vessel network formation *in vitro* and *in vivo*.

To improve vascularisation of engineered muscle tissue we induced endothelial vessel networks in engineered skeletal muscle tissue constructs using a three-dimensional multi-culture system consisting of myoblasts, embryonic fibroblasts and endothelial cells, co seeded on highly porous, biodegradable polymer scaffolds. Analysis of the conditions for induction and stabilization of the vessels in vitro, showed that addition of embryonic fibroblasts promoted formation and stabilization of the endothelial vessels. In vivo results show that pre-vascularisation improves vascularisation, blood perfusion and survival of the muscle tissue construct after transplantation.

When human embryonic stem cell derived cardiomyocytes were co-seeded on three-dimensional scaffolds with hESC-derived endothelial cells and embryonic fibroblasts, vascularisation was promoted in the engineered cardiac tissue. The embryonic fibroblasts differentiated into mural cells and the later enhanced stabilisation, organisation, proliferation of the endothelial cells. Moreover, the presence of endothelial capillaries augmented cardiomyocyte proliferation. Biodegradable polymeric scaffolds have also been utilized to establish a three-dimensional co-culture system of endothelial cells and adult pancreatic islets. This model strives to mimic the natural anatomical context of pancreas vascularisation and analyze the effect of this vascular bed on the growth, survival, and function of the tissue and beta cells in particular. Our results revealed distinct differences in pancreatic islet survival dependent upon their co-culture with endothelial cells and embryonic fibroblasts.

Notes

3.2 The genetic response of endothelial cells to matrix dimensionality

Professor Jennifer Gamble
Centenary Institute of Cancer Medicine and Cell Biology
Locked Bag 6
Newtown 2042 NSW

Abstract

Jennifer R Gamble and Mathew A Vadas

The extracellular matrix (ECM) not only provides structural support but also delivers important signalling cues which can influence the phenotype of cells.

Angiogenesis is the process of new blood vessels from pre-existing vessels and is essential during embryogenesis and the female reproductive cycle and is a hallmark of diseases such as solid tumour growth, diabetic retinopathy and rheumatoid arthritis. Angiogenesis is stimulated by growth factors such as vascular endothelial cell growth factor but is also influenced by the ECM where fibrin and collagen type1 deposition provide a pro-angiogenic milieu for endothelial cells.

The reprogramming of endothelial cells to permit and promote angiogenesis, and also to inhibit and resolve the angiogenic response is complex. We will present data showing that endothelial cells can sense the dimensionality of their ECM and under an angiogenic permissive milieu, specific genes, miRNAs and signalling pathways are regulated which culminate in the angiogenic response.

Notes

3.3 How do we realise the potential for lens epithelial cells to form functional lens-like structures?

Professor John McAvoy
Clinical Ophthalmology and Eye Health
University of Sydney
Save Sight Institute
Sydney Eye Hospital
Macquarie Street
Sydney NSW

Abstract

J.W. McAvoy[1], M.D. O'Connor[1], Y. Chen[1], and F.J. Lovicu[2].
Save Sight Institute[1], Bosch Institute[2], University of Sydney, NSW, Australia.

Posterior capsule opacification (PCO) is a common complication of cataract surgery that is caused by aberrant growth and differentiation of residual lens epithelial cells. Given increases in the incidence of cataract surgery and the growing magnitude of the problem, we aim to devise strategies to promote lens epithelial cells to regenerate structures with normal functional properties and in so doing circumvent aberrant cell behaviour. Lenses from postnatal rats were used to prepare epithelial explants. These were arranged in pairs with the apical surfaces of epithelial cells juxtaposed. Explant-pairs were cultured for up to 43 days in medium containing 50% vitreous humor. Lens-like structures were routinely generated in culture. They were comprised of ordered epithelial and fiber cells that were transparent and because of their curvature had some focusing and magnifying ability. Other studies with transgenic mice indicate that the organization of the lens fiber cell cytoskeleton plays a key role in determining lens curvature. Understanding the molecular basis of these processes is fundamental to devising strategies for promoting lens reconstruction after cataract surgery.

Notes

3.4 Increased angiogenesis in asthma: an opportunity for tissue modulation?

Dr Janette K. Burgess
CRC for Asthma and Airways
Discipline of Pharmacology
The University of Sydney
Woolcock Institute of Medical Research Sydney NSW

Abstract

There are a number of prominent structural changes in the airways of asthmatics. Referred to as airway remodelling, these changes include increased extracellular matrix (ECM) deposition, increased airway smooth muscle (ASM) mass and an increase in the number of blood vessels (angiogenesis). Angiogenesis is regulated by a balance between endogenous pro and anti-angiogenic factors. Many pro-angiogenic factors are up-regulated in asthma, whereas, collagen IV is decreased. Collagen IV has six α chains, each consisting of a 7S domain at the amino terminus, a central collagenous domain and a non-collagenous domain-1 (NC1) which can have anti-angiogenic properties. Tumstatin, an endogenous angiogenic inhibitor, is the NC1 of the α3 chain of collagen IV. We have recently demonstrated that tumstatin is absent in the airways of asthmatic individuals.

Understanding the role of pro and anti-angiogenic factors in the regulation of angiogenesis in disease may lead to the development of novel therapies. Modulation of the levels of endogenous anti-angiogenic factors (eg tumstatin), where these factors are missing or expressed at low levels, may have implications for the management of asthma.

The proangiogenic factors, connective tissue growth factor (CTGF) and vascular endothelial growth factor (VEGF) may play a role in the ECM remodelling. ASM cells release VEGF and CTGF. CTGF binds VEGF thereby inhibiting the angiogenic activity of VEGF. Little is known about the role of the interaction of CTGF and VEGF in asthma.

Whilst tumstatin is absent from asthmatic airways all six collagen IV α chain NCI domains are detected in nonasthmatic airways. In a murine model of allergic airway disease mice chronically exposed to ovalbumin develop angiogenesis and airway hyperresponsiveness, both of which are inhibited by tumstatin.

The increase in pro-angiogenic factors and the absence of an endogenous anti-angiogenic factor in asthmatic airways may indicate potential for therapeutic intervention for regulating angiogenesis in airway remodelling.

Notes

4. Abstracts: Session 2
Biomaterials for Biological Application

4.1 PLENARY - Functional tissue engineering: combining physics and biology

Dr Hala Zreiqat
Head - Tissue Engineering & Biomaterials Research Unit
Biomedical Engineering, School of AMME J07 and Bosch Institute
University of Sydney, NSW 2006
AUSTRALIA

Dr. Zreiqat is a National Health and Medical Research (NH&MRC) Council Fellow and Head of the Tissue Engineering and Biomaterials Research Unit in the Faculty of Engineering, University of Sydney. She specialises in engineered biomaterials for skeletal tissue applications. Dr. Zreiqat was recruited by Sydney University in January 2006 to establish the new Tissue Engineering and Biomaterials research Unit, bringing medical research and engineering together.

Her team includes multidisciplinary scientists, biomedical engineers and histologists with the aim of developing novel prosthetic devices and scaffolds for skeletal tissue regeneration; and gaining a greater understanding of the biology of bone/cartilage and endothelial cells when in contact with engineered biomaterials

Abstract

There is increasing demand for synthetic materials that can regenerate lost or diseased bone and cartilage. Clinically available modalities for treating large bone defects, are limited in their success. Significant challenges remain in the regeneration of these biomechanically functional tissues. Implanted materials are known to affect cellular physiology and function. Using the basis of "functional tissue engineering" we have developed novel 3D scaffolds with clinically relevant attributes for skeletal tissue and vascular ingrowth. These scaffolds exhibited mechanical properties that are superior to the clinically available ones, as measured by compressive strength. Such highly porous, interconnected and mechanically strong scaffolds are suitable for treating large bone defects in load-bearing applications.

Scaffolds and biomaterials used for skeletal tissue regeneration need to be biocompatible, osteo-inductive, osteoconductive and mechanically compatible with bone/cartilage to meet the requirements for skeletal tissue engineering. The current generation of synthetic scaffolds does not combine the required porosity, mechanical properties and bioactivity.

This presentation will highlight some of our newly developed novel highly porous and mechanically strong scaffolds that promote the migration, proliferation and differentiation of bone and endothelial cells for effective skeletal tissue integration and vascularisation. Innovative biodegradable and bioactive biomaterials for bone/cartilage augmentation will permit greater control over the location and quality of bone regeneration, allowing faster healing.

Notes

4.2 New surfaces for linker free covalent attachment of bioactive protein created using a plasma polymerization process with energetic ion bombardment

Professor Marcela Bilek
Professor of Applied Physics
School of Physics
The University of Sydney
NSW 2006 Australia

Abstract

M. Bilek, A. Kondyurin, Y. Yin, N. Nosworthy, D. Bax, C. MacDonald, D.R. McKenzie

We have developed a new organic surface capable of covalently attaching bioactive protein without relying on chemical linkers. In this paper we present a plasma polymerization process, which utilizes energetic ions to integrate a plasma polymer surface into a range of underlying substrates and to tune the surface properties. The process is compatible with CMOS manufacturing and thus suitable for the preparation of on chip bio-devices. The new surface which combines a highly reactive uppermost layer with a cross-linked polymeric subsurface, is shown to provide a platform for the covalent attachment of proteins whilst preserving their bioactivity. As such it may also be suitable for robustly attaching a biointerface of selected key proteins to initiate desirable cellular responses at surfaces for applications in prosthetics and tissue engineering. The key parameters of the plasma polymerization process and their influence on the effectiveness of the surfaces are discussed.

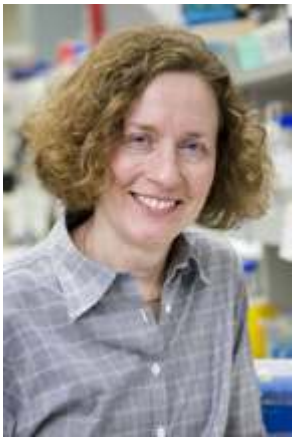
Performance of the new surfaces for immobilization of enzymes, is investigated using FTIR spectroscopy, AFM, surface plasmon resonance (SPR), spectroscopic ellipsometry and colorimetric activity assays. Our results show that the enzymes are covalently bound to the surfaces after a simple incubation in enzyme containing buffer solution. Their bioactivity is retained over many days while exposed to repeated washing in fresh buffer. The immobilization process does not involve the use of linker molecules or associated wet chemistry and the surfaces outperform commonly used commercially available protein binding surfaces both in terms of the density and life time of the active attached protein. We conclude our report with a discussion of proposed mechanisms for this new form of covalent protein attachment.

Notes

5. Abstracts: Session 4
Cell-Cell Communication

5.1 PLENARY - Neural regulation of osteoblastic bone formation

Associate Professor Edith Gardiner
Research Leader, Bone Biology Group
Diamantina Institute for Cancer, Immunology and Metabolic Medicine
The University of Queensland
QLD 4102 Australia



Edith Gardiner is a bone cell biologist with a focus on the neural control of bone formation. She earned a PhD in Human Genetics at Medical School of Yale University prior to postdoctoral studies in the Biology Department at Yale and subsequently at the Garvan Institute of Medical Research in Sydney. She joined the University of Queensland faculty in 2004 where she now directs a bone biology research group at the UQ Diamantina Institute. She is presently on sabbatical leave undertaking collaborative research in the Department of Orthopaedics at the University of Washington Medical School in Seattle, USA.

Abstract

Skeletal homeostasis is maintained by continuous bone remodeling, an energy-requiring process in which osteoblastic bone formation and osteoclastic bone resorption are tightly coupled. There is accumulating evidence that bone homeostasis is linked to energy metabolism through mechanisms involving peripheral hormones and hypothalamic circuits. Leptin, a hormone produced by adipose tissue, crosses the hypothalamic blood brain barrier where it can regulate energy homeostasis and limit bone formation[1]. The evidence indicates that this skeletal regulation occurs through the sympathetic nervous system via activation of the osteoblastic beta 2-adrenergic receptor and subsequent alteration of peripheral clock gene expression in the bone forming cell[1]. Intact neuropeptide Y receptor genes in the hypothalamus and peripheral tissue are also required for the normal hypothalamic regulation of skeletal biology and energy metabolism[2]. The evidence further indicates that disruption of the hypothalamic NPY regulatory circuit increases a prospectively sorted population of multipotential progenitor cells in bone tissue that is capable of differentiation along both bone forming and adipocytic cell lineages[3]. Further investigations are necessary to elucidate how the hypothalamic NPY bone control circuit interacts with other endocrine and paracrine regulators of bone biology.

[1]Ducy et al. Cell 100: 197 (2000); Takeda et al. Cell 111: 305 (2002); Fu et al. Cell 122: 308 (2005)

[2]Baldock et al. J Clin Invest 14: 1908 (2002); Baldock et al. J Biol Chem 282: 19092 (2007)

[3]Lundberg et al. J Biol Chem 282: 19082 (2007)

Notes

5.2 Mechanisms underlying the beneficial effects of activated protein C in sepsis and wound healing

Associate Professor Chris Jackson
Sutton Arthritis Research Laboratory
Institute for Bone and Joint Research
Kolling Institute of Medical Research
University of Sydney at Royal North Shore Hospital

Abstract

Nikita Minhas, Meilang Xue, and Chris Jackson

Activated protein C (APC) is a physiological anticoagulant which acts by degrading two essential factors in the coagulation cascade. APC also exerts cytoprotective effects which are reflected in its efficacy as a treatment for sepsis. A recent human pilot study has confirmed results from in vitro and rodent experiments showing that APC promotes cutaneous wound healing and is likely to be of therapeutic value in patients with chronic wounds. APC can rapidly, directly and specifically activate matrix metalloproteinase-2, an enzyme that plays an important role in cellular invasive processes that occur during angiogenesis and re-epithelialisation. APC dose-dependently upregulates gene and protein expression of the angiogenic factors, interleukin(IL)-6, IL-8 and vascular endothelial growth factor and promotes angiogenesis in the chick embryo chorio-allantoic membrane (CAM) and rabbit corneal models. Unlike other angiogenic factors, APC stimulates new blood vessels whilst potently inhibiting inflammation. Recent in vitro and preclinical data have revealed that APC exerts its protective effects via an intriguing mechanism requiring endothelial protein C receptor and protease activated receptor-1. Here, we show that APC utilises a similar pathway to control the angiopoietin (Ang)/Tie2 axis and endothelial barrier integrity. APC dose-dependently (0.01-10 μg/ml) upregulates expression of Tie2 and its agonist, Ang1, whereas it markedly inhibits expression of the Tie2 antagonist, Ang2. Endothelial permeability, measured using Evans blue dye transfer, is reduced in the presence of APC and, in concordance, the tight junction associated protein, ZO-1, is upregulated and localized peripherally around cells. APC also acts on smooth muscle cells to enhance Ang1 production in a dose-dependent manner and stimulate their migration towards endothelium. Thus, APC exerts novel effects on the Ang/Tie2 axis which would enhance vascular barrier integrity and are likely to contribute to its therapeutic effect in sepsis and wound healing.

Notes

5.3 The osteoblast, a key regulator of mesenchymal and haematopoietic cell lineage commitment and survival

Associate Professor Colin Dunstan
Biomedical Engineering
School of Aerospace, Mechanical and Mechatronic Engineering
Faculty of Engineering & IT
The University of Sydney

Abstract

Osteoblasts have an essential role in bone formation as the cells that secrete collagen type 1 and other bone matrix components and orchestrate bone mineralisation. However, osteoblasts are now becoming understood as cells with a number of key regulatory functions. Osteblasts regulate bone remodelling by controlling the differentiation and activity of osteoclasts (bone resorbing cells of the monocyte/macrophage lineage). Occasional osteoblasts become encapsulated as osteocytes in bone where they communicate with neighbours via a dense network of canaliculae and signal to the bone surface information regarding levels of bone strain and fatigue damage. At the local tissue level, osteoblasts influence the lineage commitment of mesenchymal stem cells to the adipocyte, chondrocyte and osteoblast lineages.

However it is now coming apparent that osteoblasts regulate processes beyond those directly associated with the skeleton. Osteoblasts establish the niche in bone essential for haematopoietic stem cell survival. There is now also evidence that osteoblasts secrete factors that contribute to the regulation of energy metabolism at the systemic level. This presentation will review our growing understanding of the mature osteoblast as a regulatory cell secreting cytokines and growth factors to orchestrate bone remodelling, cartilage degradation, mesenchymal stem cell differentiation and energy metabolism.

Notes

5.4 Fibrocytes in burn wound healing: could regulation of these cells reduce scarring?

Associate Professor Andrew J A Holland
Director, The Children's Hospital at Westmead Burns Research Institute
The University of Sydney

Abstract

Fibrocytes are a subpopulation of leucocytes with a distinctive set of haemopoietic and stromal cell surface markers expressed at certain time points in the cells development. Fibrocytes appear attracted to sites of tissue injury, where they produce collagen, α smooth muscle actin (αSMA) and other extracellular matrix components. Fibrocytes have been reported in hypertrophic postburn scar tissue in which both their number and differentiation along a fibroblast type phenotype appears positively correlated with the concentration of the regulatory cytokine Transforming Growth Factor β1. The levels of TGF-β1 have been shown to be elevated in burn patients, with maximal levels typically achieved at between 15 and 21 days postburn. Our centre has been investigating the possible role of these cells in paediatric burn patients. This presentation will discuss the identification of fibrocytes in acute paediatric burn wounds; the correlation of their presence with the subsequent development of hypertrophic scarring and the link between the presence of fibrocytes and inflammatory cytokines. This work paves the way for the development of agents to modify fibrocyte activation and expression, potentially reducing the development of hypertrophic scarring following burn injury.

Notes

6. Abstracts: Session 5
Musculoskeletal Tissue Engineering

6.1 PLENARY - Adult stem cells and nanomaterials in skeletal tissue engineering and regeneration

Dr Rocky S. Tuan
Chief, Cartilage Biology and Orthopaedics Branch
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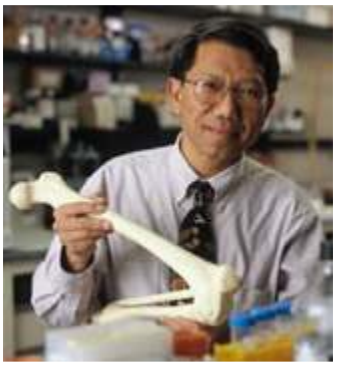
(Email: tuanr@mail.nih.gov)



Rocky S. Tuan, PhD received his bachelor's degree in Chemistry in 1972. He received his PhD in 1977 from the Rockefeller University in New York, under the mentorship of the late Zanvil A. Cohn, MD. His postdoctoral research fellowship was at Harvard Medical School in Boston, first with Melvin J. Glimcher, MD in the Department of Orthopaedic Surgery at the Children's Hospital, and then from 1978 to 1980 with Jerome Gross, MD, in the Developmental Biology Laboratory at the Massachusetts General Hospital.

In 1980, Dr. Tuan was appointed as Assistant Professor in the Department of Biology, University of Pennsylvania in Philadelphia, and was promoted to Associate Professor in 1986. In 1988, Dr. Tuan joined Thomas Jefferson University, Philadelphia, to be the Director of Orthopaedic Research and Professor and later Vice Chairman in the Department of Orthopaedic Surgery with a joint appointment in the Department of Biochemistry and Molecular Biology. From 1992-1995, Dr. Tuan was the Academic Director of the MD/PhD program at Jefferson, and in 1997, he established the nation's first Cell and Tissue Engineering PhD program at Jefferson, with the mission of training the next generation of "cross-cultural" biomedical scientists committed to regenerative medicine and the development of functional tissue substitutes. In the fall of 2001, Dr. Tuan joined the Intramural Research Program of the National Institute of Arthritis, and Musculoskeletal and Skin Diseases (NIAMS), National Institutes of Health (NIH), as Chief of the newly created Cartilage Biology and Orthopaedics Branch. In 2004, Dr. Tuan received the Marshal Urist Award of the Orthopaedic Research Society.

At the NIAMS, Dr. Tuan directs a multidisciplinary research program, which focus on orthopaedic research as a study of the biological activities that are important for the development, growth, function, and health of skeletal tissues, and the utilization of this

knowledge to develop technologies that will regenerate and/or restore function to diseased and damaged skeletal tissues. Ongoing research projects focus on multiple aspects of skeletal and related biology, including skeletal development, growth factor biology, bone-biomaterial interaction, cell-matrix interaction and signaling, biomaterials, stem cells, and musculoskeletal tissue engineering, utilizing an integrated experimental approach combining contemporary technologies of biochemistry, cell and molecular biology, embryology and development, cellular imaging, and engineering.

Abstract

Nanoscale materials are the fundamental building blocks and functional subunits of cells, including subcellular organelles and extracellular matrix components. Currently, there is growing recognition of the importance of understanding and incorporating nanobiology into biomedical applications. This issue is of particular importance in the emerging field of regenerative medicine, the goal of which is to develop methods to repair, replace, and regenerate diseased, injured, or non-functional tissues. Towards this goal, stem or progenitor cells have been considered a highly desirable candidate cell type, because of their expandability and potential to be induced toward specific cell differentiation lineages. A key requirement in tissue engineering and regenerative medicine is that ultimately the "regenerate tissue" needs to be a three-dimensional structure. In weight-bearing musculoskeletal tissues, this requirement is particularly critical. Musculoskeletal disorders affect one out of seven Americans. This severe disease burden underscores the need to develop novel and effective treatment protocols.

This lecture will present the promises as well as the challenges in the field of skeletal tissue engineering and regeneration, specifically the application of adult stem cells and nanomaterial scaffolds. The biology of human adult mesenchymal stem cells, particularly the mechanisms regulating their proliferation *versus* differentiation into specific lineages, is intricately regulated by cell-cell interactions, signaling by extracellular bioactive factors, and transcriptional and epigenetic activities. More importantly, the extracellular matrix milieu provides critical cues, both architectural and structure-dependent, to guide cell-based tissue morphogenesis. We have developed biomimetic and biodegradable nanofibrous biomaterials to serve as scaffolds for cell-based tissue engineering. Information on the fabrication and biological basis of the scale-dependent bioactivities of the nanofibrous scaffold will be presented. Cell-nanofibrous constructs are currently being developed for the engineering of cartilaginous tissues, including articular cartilage and intervertebral disc. In conclusion, tissue engineering represents a unique, emerging inter-disciplinary research field that is a natural platform for life scientists, engineers, and clinicians working together to advance regenerative medicine.

Notes

Notes

6.2 *Effective engraftment and enrichment of CD34^{+ve} stem cells mouse skeletal muscles using chemotherapeutic drug selection: a paradigm for enhanced stem cell transplantation*

Professor Edna Hardeman
Department of Anatomy
School of Medical Sciences
The University of New South Wales

Abstract

EC Hardeman[1], ASJ Lee[2], P Kahatapitiya[2], B Kramer[2], JE Joya[3], R Liu[3], G McCowage[4], I Alexander[5], D Montarras[6], PW Gunning[2,7]

[1]Department of Anatomy, School of Medical Sciences, University of New South Wales; [2]Oncology Research Unit, The Children's Hospital at Westmead; [3]Muscle Development Unit, Children's Medical Research Institute, Westmead; [4]Department of Oncology, [5]Gene Therapy Research Unit, The Children's Hospital at Westmead; [6]CNRS URA 2578, Department of Developmental Biology, Pasteur Institute, Paris, France; [7]Department of Pharmacology, School of Medical Sciences, University of New South Wales

We describe a novel application of a selective cell enrichment strategy, initially established for hematopoietic cells, in a skeletal muscle system with a view to enhancing muscle-derived stem cell transplantation. Cells expressing a mutant form of the drug resistance gene methylguanine methyltransferase (MGMT-P140K) are resistant to the cytotoxic effects of carmustine (BCNU) plus O^6benzylguanine (O^6BG) treatment; whereas, wild-type cells exhibit cytotoxicity. *In vitro* studies using the C2C12 muscle cell line and human myoblasts showed selective enrichment of the MGMT-P140K^{+ve} cells in response to the drugs. A transgenic mouse over-expressing MGMT-P140K in muscles was used to determine whether MGMT-P140K^{+ve} satellite cells, when stimulated to proliferate *in situ*, are resistant to BCNU plus O^6BG. Drug treatment of a regenerating muscle bed resulted in successful regeneration, while the wild-type control had a suppressed regenerative response. These data indicate that MGMT-P140K expression in satellite cells results in selective cell survival in response to BCNU plus O^6BG treatment.

In transplantation trials, CD34^{+ve} donor cells isolated from skeletal muscles of male MGMT-P140K expressing transgenics were co-injected with a myotoxin, notexin, intramuscularly and BCNU intravenously into syngeneic wild-type female hosts. O^6BG was injected IP. Muscles injected with MGMT-P140K^{+ve} donor cells showed more extensive regeneration, a significantly higher ($p<0.001$) male DNA content as determined by quantitative RT-PCR, and a significantly greater number of male donor nuclei in regenerated fibers as determined by fluorescent *in situ* hybridisation (FISH) in comparison with muscles injected with wild-type donor cells. Preliminary results from allogeneic transplantations of CD34^{+ve} cells isolated from muscles of MGMT-P140K transgenics into muscles of *dystrophin*-null *mdx* mice (model for human Duchenne Muscular Dystrophy) with the drug treatment showed donor-derived dystrophin^{+ve} fibres within the dystrophin-deficient *mdx* muscle.

We conclude that it is possible to apply this selection strategy to enhance the efficacy of muscle-derived stem cell therapy.

Notes

6.3 Multifunctional materials for cartilage engineering

Dr Lisa Capriotti
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Johns Hopkins University
3400 N. Charles St
Clark Hall 102
Baltimore, MD 21218
USA

Abstract

One of the challenges facing the field of tissue engineering and regenerative medicine is the design of biomaterial scaffolds which not only support cell viability, but also maintain cell phenotype. To this end the rational design of materials integrating a synthetic scaffold with native tissue matrix elements can significantly improve the quality of the regenerated tissue. This is particularly important in cartilage engineering. Efforts to reverse the effects of trauma and degenerative disease on cartilaginous joint tissues by autologous cell transplantion and microfracture have been productive; however, the return of normal cartilage function is often slow or marked by fibrocartilage formation. The complex hierarchy of joint cartilage helps to explain why this tissue is so difficult to reconstruct. By incorporating elements from natural biological matrices of the joint space with existing polymeric frameworks, it is possible to recapitulate the complex signaling essential for the maintenance and regeneration of healthy joint tissue. A number of extracellular matrix (ECM) components are essential in healthy cartilage including Type II collagen and glucosaminoglycans like hyaluronic acid and chondroitin sulfate. This talk will discuss the design of biomaterials which incorporate elements of native cartilage tissue and materials designed to specifically interact with collagen and glucosaminoglycans. These interactions promote chondrogenic differentiation marked by the production of new Type II collagen and GAG's and may ultimately enhance the regeneration of normal cartilage.

Notes

7. Discussion Panel: Building a Successful Tissue Engineering Network

Chairs

David Williams

Professor Williams is the Editor-in-Chief of *Biomaterials*. He has had 40 years experience in the biomaterials, medical device and tissue engineering fields. During his research career he has published over 30 books and around 400 papers, and has received the major awards from the US, European and Indian societies of biomaterials. He has been a scientific adviser to the European Commission and written many Opinions on which European laws in health technology and nanotechnology are based. In 1999 he was elected as a Fellow of the Royal Academy of Engineering in recognition of his contributions to engineering in medicine.

Professor Williams left the University of Liverpool, UK, in 2007, where he has been Head of Clinical Engineering and Director, UK Centre for Tissue Engineering. While retaining the title of Emeritus Professor at Liverpool, he is currently Professor and Director of International Affairs, Wake Forest Institute of Regenerative Medicine, North Carolina, USA, a Visiting Professor in the Christiaan Barnard Department of Cardiothoracic Surgery, Cape Town, South Africa, a Visiting Professorial Fellow at the Graduate School of Biomedical Engineering, University of New South Wales, Australia, and a Guest Professor, Tsinghua University, Beijing, China.

David Sonnabend
Professor of Orthopaedic Surgery
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Panelists

Carol Armour
Pro-Vice-Chancellor (Research)
Professor of Pharmacy
The University of Sydney

Bernie Tuch
Director of the Diabetes Transplant Unit, Prince of Wales Hospital
Professor of Medicine, University of New South Wales
Executive Committee, NSW Stem Cell Network

Tony Weiss
Professor
Molecular and Microbial Biosciences
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Notes

8. List of Participants

(*In alphabetical order)*

Name			Research Group/Company
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Prof	Marcela	Bilek	School of Physics, Faculty of Science
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Dr	Margaret	Evans	Biomaterials Group - CSIRO
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Prof	Greg	Hancock	Faculty of Engineering and IT
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Dr	Natalie	James	Cochlear
Dr	Katie	Jones	Biomedical Engineering, School of AMME

Name			Research Group/Company
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