Faculties of Engineering and IT, Science, and Veterinary Science

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Sydney University Tissue Engineering Network

3rd Tissue Engineering Symposium

The University of Sydney

Darlington Centre

Tuesday 9th November – Thursday 11th November 2010

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Tissue Engineering and Biomaterials Unit
Faculty of Engineering
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Professor Gordana Vunjak-Novakovic
Department of Biomedical Engineering
Columbia University
USA

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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 third Sydney University Tissue Engineering Network Symposium, whose inspirational and challenging theme is "Tissue Engineering and Regenerative Medicine: the next 20 years".

I would like to extend a most warm welcome to colleagues and friends who have joined us from the United States of America – from Columbia University, Harvard University, Massachusetts Institute of Technology, from the University of Pennsylvania, from Princeton University and from Yale University and Zimmer Orthopasedics. Despite the demands of this Symposium, I hope that there will also be time to enjoy something of the unique beauties of our hospitable city and beyond.

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 enhance opportunities for scientists to expand their intellectual horizons and to build interdisciplinary partnerships. This symposium will draw together scientists and students of tissue engineering from the Faculties of Engineering, Medicine, Science, Pharmacy, Veterinary Medicine 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 indeed grateful to the Faculties involved and the generous sponsors who have supported the meeting and made it possible. We hope that you will enjoy this significant scientific symposium at the University of Sydney which has been organised by the Tissue Engineering and Biomaterials Research Unit.

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

Her Excellency Professor Marie Bashir AC CVO
Chancellor
University of Sydney

Program

Day 1 - Tuesday 9th November 2010

8:00am		Registration and refreshments
8:40am		Arrival of Chancellor and Photo Shoot with Invited Speakers Her Excellency Professor Marie Bashir AC CVO, Chancellor
9:00am		**Welcome and Opening Remarks** Hala Zreiqat, Chair and Convenor - SuTEN
9:05am		Official Opening Her Excellency Professor Marie Bashir AC CVO, Chancellor
9:10am	**Session 1**	**Controlling Cell Differentiation and Tissue Morphogenesis** ***Chair:*** *Chris O'Neil, Sydney Centre for Developmental and Regenerative Medicine*
9:10am	Speaker 1.1	Myosin and Matrix in Cell Fate Decisions *Dennis E Discher, University of Pennsylvania, USA*
9:40am	Speaker 1.2	Microscale Engineered Tissue Morphogenesis *Celeste Nelson, Princeton University, USA*
10:10am	Speaker 1.3	Elasticity Preserves Primitive Murine and Human Haemopoietic Cells *John Rasko, Sydney Medical School, University of Sydney*
10:30am		**Morning Tea and Trade Displays**
11:00am	**Session 2**	**Transplant and Immune Biology** ***Chair:*** *Georges E.R. Grau, Discipline of Pathology, School of Medical Sciences*
11:00am	Speaker 2.1	The Effect of Three-Dimensional Matrix-Embedding of Endothelial Cells on The Humoral and Cellular Immune Response *Heiko Methe, MIT, USA*
11:30am	Speaker 2.2	The Translation of Dendritic Cell Biology into Diagnostics and Therapeutics *Derek Hart, University of Sydney*
12:00pm	Speaker 2.3	Alzheimer's Disease – Models and Treatment *Jürgen Götz, Alzheimer's and Parkinson's Disease Laboratory, BMRI, University of Sydney*
12:30pm		**Lunch and Industry Session**
1:45pm	**Session 3**	**Tissue Engineering** ***Chair:*** *Chris Little, Kolling Institute of Medical Research, University of Sydney*
1:45pm	Speaker 3.1	Engineering Human Tissues *Gordana Vunjak-Novakovic, Columbia University, USA*
2:15pm	Speaker 3.2	Skin Tissue Engineering for Burn Wound Treatment *Peter Maitz, Concord Hospital, University of Sydney*
2:45pm	**Session 4**	**Translation** ***Chair:*** *Jacqueline Center, Osteoporosis and Bone Biology, Garvan Institute, Sydney*
2:45pm	Speaker 4.1	Translation of Engineered Arteries *Laura Niklason, Yale University, USA*
3:15pm	Speaker 4.2	Translational Research in Orthopedics *Ross Garrett, Zimmer Orthobiologics, USA*

3:30pm	Speaker 4.3	Liver-Targeted Gene Therapy for Urea Cycle Defects: From Mouse to Man *Ian Alexander, Gene Therapy Research Unit, The Children's Hospital at Westmead and Children's Medical Research Institute*
3:45pm		**Afternoon Tea**
4:30pm	**Panel Discussion**	**A Road to Clinic** ***Moderator:*** *Gordana Vunjak-Novakovic* ***Panellists:*** *Ross Garrett, Levon Khachigian, Dennis E Discher, Colin Dunstan, Gordana Vunjak-Novakovic*
6:00pm		**Dinner for International Guests**

Day 2 - Wednesday 10th November 2010

8:55am		**Welcome and Introductions**
9:00am	**Session 5**	**Cell and Gene Therapy**
		Chair: *Dennis E Discher, University of Pennsylvania, USA*
9:00am	Speaker 5.1	Redefining Tissue Engineering at the Nanoscale *Rutledge Ellis-Behnke, Ophthalmology, Medical Faculty Mannheim, Heidelberg University*
9:20am	Speaker 5.2	Tissue-Regenerating, Vision-Restoring Corneal Epithelial Stem Cells *Nick Di Girolamo, School of Medical Sciences, University of NSW*
9:40am	Speaker 5.3	Translational Research – a Critical Path for Tissue Engineering, Cell and Gene Therapy *Stephen Hunyor, Cardiology, Kolling Institute of Medical Research, University of Sydney*
10:00am	Speaker 5.4	Discovering New Genes as Potential Therapeutic Targets for Neurodegenerative Disorders *Ian Blair, ANZAC Research Institute*
10:20am		**Morning Tea and Trade Displays**
11:00am	**Session 6**	**PhD and New Investigator Short Presentations**
		Chairs (& Prize Judges): *Laura Niklason, Celeste Nelson, Markus Siebel, Judy Black, Greg Roger*
12:15pm		**Lunch and Industry Session**
1:30pm	**Session 7**	**Tissue Engineering and Regenerative Medicine - The Next 20 Years**
		Chair: *Trevor Hambley, Faculty of Science, University of Sydney*
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1:45pm	Speaker 7.2	*Dennis E Discher, University of Pennsylvania, USA*
2:00pm	Speaker 7.3	*Gordana Vunjak-Novakovic, Columbia University, USA*
2:15pm	Speaker 7.4	*Dr Glenn Smith, TGA - Therapeutic Goods Administration*
2:30pm	Speaker 7.5	*Kerry Doyle, NSW Government*
2:45pm		**Prize Presentations, Closing Remarks and Sponsor Booth Prizes**
		Professor Archie Johnson, Dean of Engineering, University of Sydney
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Day 3 - Thursday 11th November 2010

9:30am		**Organovo Workshop in SIT Boardroom 124**
9:30am	Session 1	**NovoGen Bioprinting Demonstration, Q&A and 1:1 with customers**
11:00am	Session 2	**NovoGen Bioprinting Demonstration, Q&A and 1:1 with customers**

Session 1 – Controlling Cell Differentiation and Tissue Morphogenesis

1.1 Matrix and Myosin in Cell Fate Decisions

Professor Dennis E. Discher
[1]*Biophysical Engineering Lab, University of Pennsylvania, Philadelphia, USA*
**discher@seas.upenn.edu*

Dennis E. Discher is Professor at the University of Pennsylvania in the School of Engineering and Applied Science and in Graduate Groups in Cell & Molecular Biology and Physics. He received a Ph.D. from the University of California, Berkeley in 1993 for studies in cell and molecular biophysics, and was a US National Science Foundation International Fellow at the University of British Columbia until 1996. He has co-authored more than 150 publications with over 7000 citations that range in topic from matrix effects on stem cells and biochemical physics of protein folding to self-assembling polymers applied to disease, with papers appearing in *Cell, Science, Journal of Cell Biology, Nature Materials,* and *Nature Physics.* Honours and Service include a Presidential Early Career Award for Scientists and Engineers from the US- National Science Foundation, the Friedrich Wilhelm Bessel Award from the Humboldt Foundation of Germany, and membership on the editorial board for *Science.*

Abstract
Introduction: Adhesion of stem cells - like most tissue cells - is not just a membrane phenomenon. Most tissue cells need to adhere to a 'solid' for viability, and over the last decade it has become increasingly clear that the physical 'elasticity' of that solid is literally 'felt' by cells as they adhere. It should be appreciated, of course, that collagen and other matrix components are not only the most abundant proteins in animals but that their state of assembly and crosslinking differs between tissues in a surprisingly characteristic fashion.
Methods: Collagen is the most abundant protein in animals. Our standard in vitro systems are collagen-modeified hydrogels with elasticity characterized by AFM. Mouse models are used selectively.
Results & Conclusions: We have shown - and will add more data with comparison to clinically relevant soluble factors - that Mesenchymal Stem Cells (MSCs) specify lineage and commit to phenotypes with extreme sensitivity to the elasticity typical of tissues, at least with collagen-coated hydrogel matrices [Engler *Cell* 2006]. Great interest in heart repair with stem cells has prompted similar studies of embryo-derived cardiomyocytes [Engler *J Cell Sci* 2008], which also display a sensitivity to matrix elasticity in terms of beating and striation. And while Hematopoietic Stem Cells (HSCs) are generally not considered adherent, some processes such as cytokinesis and platelet formation are also regulated by myosin II's – a force generating motor protein that is common to all of these physical sensing pathways [Discher *Science* 2009]. We will describe the role of nonmuscle myosin II in megakaryocyte maturation of HSCs, in lineage specification of MSCs, in muscle striation, and – if time allows – even in immune recognition of stem cells [Tsai *J Cell Biol* 2008].
References: A. Engler, S. Sen, H.L. Sweeney, and D.E. Discher. Matrix elasticity directs stem cell lineage specification. ***Cell*** 126: 677-689 (2006); D.E. Discher, D.M. Mooney, P. Zandstra. Growth factors, matrices, and forces combine and control stem cells. ***Science*** 324: 1673-1677 (2009); A. Engler, C. Carag, C. Johnson, M. Raab, H-Y. Tang, D. Speicher, J. Sanger, J. Sanger, and D.E. Discher. Embryonic cardiomyocytes beat best on a matrix with heart-like elasticity: scar-like rigidity inhibits beating. ***Journal of Cell Science*** 121: 3794-3802 (2008); R. Tsai and D.E.

Discher. Inhibition of 'Self' Engulfment through deactivation of Myosin-II at the Phagocytic Synapse between Human Cells ***Journal of Cell Biology*** 180: 989-1003 (2008).

1.2 Microscale Engineered Tissue Morphogenesis

Dr Celeste Nelson
Assistant Professor of Chemical & Biological Engineering
Chemical & Biological Engineering and Molecular Biology, Princeton University
Princeton University
USA

Dr. Celeste Nelson did her PhD in Biomedical Engineering at the Johns Hopkins University School of Medicine, studying intercellular-mediated mechanotransduction. She joined the Chemical & Biological Engineering department at Princeton University in 2007 after completing postdoctoral research with Mina Bissell at Lawrence Berkeley National Laboratory, where she worked on mammary branching morphogenesis. Dr. Nelson's group is highly interdisciplinary and focuses on pattern formation during normal and abnormal development of the mammary gland and lung.

Abstract
The morphogenetic patterning that generates three-dimensional (3D) tissues requires dynamic concerted rearrangements of individual cells with respect to each other. We have developed lithography-based 3D culture models that recapitulate the architecture of epithelial ductal trees, enable micrometer-resolution control of tissue geometry and microenvironment, and provide quantitative 4D data in a physiologically relevant context. This approach has revealed that patterns within developing tissues can emerge from at least three orthogonal mechanisms: biochemical gradients, tissue mechanics, and differential cell motility. I will discuss how we combine engineered tissues and computational models to uncover and dissect the relative roles of each of these mechanisms.

1.3 Elasticity Preserves Primitive Murine and Human Haemopoietic Cells

Professor John Rasko
BSc (Med), MBBS (Hons), PhD, MAICD, FRCPA, FRACP
Royal Prince Alfred Hospital, Centenery Institute
University of Sydney
Australia

Professor Rasko is a Haematologist who directs Cell and Molecular Therapies at Royal Prince Alfred Hospital and heads the Gene and Stem Cell Therapy Program at the Centenary Institute, University of Sydney. His was the first formal appointment in clinical gene therapy in Australia. Professor Rasko is a past President of the Australasian Gene Therapy Society, Chairs the International Committee of the American Society of Gene and Cell Therapy and is Vice President of the International Society for Cellular Therapy. He is a member of the editorial boards of Pathology, Human Gene Therapy and The Journal of Gene Medicine. He serves on Hospital, philanthropic, state and national bodies including Chair of the Gene Technology Technical Advisory Committee of the federal Office of the Gene Technology Regulator. Professor Rasko has a productive track record in gene therapy, experimental haematology and cell biology. His research has been successful in uncovering new mechanisms of leukemia, understanding blood hormones and their mechanisms of action, and clinical trials of new biological therapies for cancer and bleeding disorders. He has authored approximately 100 publications including a book published by Cambridge University Press on the ethics of inheritable genetic

modification. In landmark papers in Nature Medicine in 2006 and 2007, with collaborators in the USA he reported the short-term clinical success and immunology of AAV-mediated liver-directed gene therapy for the treatment of haemophilia.

Abstract

John E.J. Rasko[1,2,7,8], Sarah Watson[1], Megan S. Lord[3], Steven S. Eamegdool[4], Daniel V. Bax[4], Lisa B. Nivison–Smith[4], Alexey Kondyurin[5], Liang Ma[6], Andres F. Oberhauser[6], Anthony S. Weiss4 and Jeff Holst[1,2].*

[1]Gene & Stem Cell Therapy Program, Centenary Institute, Camperdown, NSW 2050 Australia; [2]Sydney Medical School, University of Sydney, Australia; [3]Graduate School of Biomedical Engineering, The University of New South Wales, Sydney, Australia; [4]School of Molecular and Microbial Biosciences G08, University of Sydney, Australia; [5]School of Physics, University of Sydney, Australia; [6]Department of Neuroscience and Cell Biology, University of Texas Medical Branch, Galveston, Texas 77555, USA; and [7]Cell and Molecular Therapies, Sydney Cancer Centre, Royal Prince Alfred Hospital, Camperdown, Australia.

Surprisingly little is known regarding the effects of the physical microenvironmental niche on haemopoietic stem cells. We have explored the effects of matrix elasticity on stem cell properties using a unique synthetic substrate, tropoelastin, which we used to show that both murine and human primitive haemopoietic cells are more efficiently maintained on an elastically extensible substrate than controls including fibronectin and collagen, during *ex vivo* culture. These biological effects required substrate elasticity, as neither truncated nor crosslinked tropoelastin reproduced the phenomenon, and inhibition of mechanotransduction abrogated the effects. These experiments confirmed the necessity to maintain elastic extensibility rather than effects related to the integrin binding domain present in its carboxy–terminus. Atomic force measurements of truncations and crosslinked tropoelastin revealed a threshold level of extensional elasticity (~125 nm) that is required for increased maintenance of progenitors. These data strengthen the hypothesis that stem cells sense the elasticity of their microenvironment and differentiate appropriately as recently shown for mesenchymal stem cells (Engler *et. al.*, *Cell,* 2006, 126:4, 677-689). We suggest that the stem cell niche is a tensegrity structure that provides the appropriate extensional elasticity for maintenance of HSCs. A consequence of this idea is that alterations to niche elasticity in disease states may contribute to abnormal haemopoiesis. Further, elastic substrates such as tropoelastin may offer a new approach to biomaterial design to achieve optimal *ex vivo* culture conditions for primitive haemopoietic cells.

Session 2 – Transplant and Immune Biology

2.1 The Effect of Three-Dimensional Matrix-Embedding of Endothelial Cells on the Humoral and Cellular Immune Response

Associate Professor Heiko Methe
University Hospital Grosshadern
School of Medicine
Ludwig-Maximilians-University
Munich, Germany

Heiko Methe is currently an interventional cardiologist at the University Hospital Grosshadern and Associate Professor at the School of Medicine, Ludwig-Maximilians-University in Munich, Germany. In 1998 he obtained his medical degree at the Georg-August University Göttingen, Germany. After a post-doctoral research sabbatical at The Scripps Research Institute in LaJolla, California he spent 2.5 years at the Harvard-MIT Biomedical Engineering Center at the Massachusetts Institute of Technology, Cambridge, Massachusetts. His research focus is on the potential of endothelial tissue engineered constructs to influence vascular repair processes without endangering a host immune response. Heiko Methe currently is a research affiliate with the Biomedical Engineering Center. He is now involved in both clinical practice and laboratory research. Heiko Methe received the Daniel Steinberg New Investigator Award in Arteriosclerosis/Lipoproteins by the American Heart Association.

Abstract
The endothelium is a unique immunologic target. The first host-donor reaction in any cell, tissue or organ transplant occurs at the blood-tissue interface, the endothelium. When endothelial cells are themselves the primary component of the implant a second set of immunologic reactions arises. Injections of free endothelial cell implants elicit a profound major histocompatibility complex (MHC) II dominated immune response with significant sensitivity, cascade enhancement and immune memory. Endothelial cells embedded within three-dimensional matrices retain all the biosecretory capacity of quiescent endothelial cells. Perivascular implants of such cells are the most potent inhibitor of intimal hyperplasia and thrombosis following controlled vascular injury, but without any immune reactivity. Allo- and even xenogeneic endothelial cells evoke no significant humoral or cellular immune response in immunocompetent hosts when embedded within matrices. Moreover, endothelial implants are immunomodulatory, reducing the extent of the memory response to previous free cell implants. Attenuated immunogenicity results in muted activation of adaptive and innate immune cells. These findings point toward a pivotal role of matrix-cell-interconnectivity for the cellular immune phenotype and might therefore assist in the design of extracellular matrix components for successful tissue engineering.

2.2 The Translation of Dendritic Cell Biology into Diagnostics and Therapeutics

Derek Hart
ANZAC Research Institute, University of Sydney
Concord Hospital
Australia

Abstract

Derek NJ Hart[1,2], Georgina J Clark[1,2,3], Kenneth Bradstock[1,4]*

[1]*ANZAC Research Institute, University of Sydney, Concord Hospital, Sydney, New South Wales 2139, Australia;* [2]*CRC for Biomarker Translation, TransBio Limited, LaTrobe University, R&D Park, Burdoora, Victoria, 3083;* [3]*Mater Medical Research Institute, Aubigny Place, South Brisbane, Queensland, 4101, Australia;* [4]*Blood and Marrow Transplant Service, Westmead Hospital, Westmead, New South Wales, Australia.*

Dendritic cells (DC) represent unique populations of antigen presenting cells, which initiate and direct immune responses as well as reinforcing immunoregulatory mechanisms to maintain tolerance. The definition of DC in human blood, bone marrow, tonsil, lymph nodes, spleen and other tissues such as the skin, respiratory tract, heart, kidney, gut and liver has increased interest in how DC progenitors adapt to these unique locations and how they react to different signals to generate both innate and cognate immune responses, which maintain host homeostasis but may in certain circumstances contribute to pathogenic outcomes.

Previous observations defined several potential human blood DC populations, whilst more recent work has confirmed that the human CD141 DC population has unique characteristics, which distinguish it from the larger CD1c population (Jongbloed et al. J Exp Med 2010;207:1247). Ongoing proteomic analysis has identified unique cell surface markers associated with the CD1c DC subset and these will increase the pool of monoclonal antibodies (mAb) available to study the myeloid and plasmacytoid DC populations.

The CMRF-44 mAb detects the presence of activated DC and the presence of activated CD11c DC predicts for acute graft versus host disease (GVHD) after allogeneic bone marrow transplantation, raising the question as to whether these reflect systemic activation of blood DC or the migration of DC activated elsewhere. Recent data associating the expression of CCR5 on circulating CD11c DC with clinical AGVHD, supports the latter concept and is the subject of ongoing functional studies. In parallel with these diagnostic evaluations of DC surface markers, the prospect of clinical intervention with therapeutic anti CD83 mAb (Wilson et al. J Exp Med 2009;206:387) continues to progress with the recent production of a fully humanized mAb (Jones et al. J Immunol Methods 2010;354:85), that inhibits allogeneic responses *in vitro* and *in vivo*. The investigation of DC subpopulations in malignancies such as multiple myeloma and prostate cancer is yielding new information and strategies for using DC surface molecules to purify DC or target them in therapeutic vaccination strategies. Studies in inflammatory disease focusing initially on psoriasis have identified mechanisms, whereby defective plasmacytoid DC signalling may fail to generate appropriate Treg responses. These new insights into DC subpopulations and their cell surface molecules are now the subject of a wider translational DC Biology and Therapeutics Program that involves clinical colleagues in evaluating mAbs to DC surface molecules as potential diagnostic and therapeutic agents.

2.3 Alzheimer's Disease – Models and Treatment

Professor Jürgen Götz
Alzheimer's and Parkinson's Disease Laboratory,
Brain and Mind Research Institute,
University of Sydney,
Australia

Professor Jürgen Götz is an internationally renowned expert in transgenic mouse models of Alzheimer's disease (AD). He generated the first tau transgenic mouse model with an early AD phenotype. Together with Dr. Hutton, he published the first mouse model with NFT formation (JBC 2001a). He provided long-sought evidence for the amyloid cascade hypothesis by combining a transgenic and a transplantation approach (Science 2001). This highly cited work was accompanied by an Editorial in the same issue of Science, and selected as 2001 Milestone Paper by the Alzheimer Research Forum (alzforum.org). Jürgen Götz further provided a role for FGF5 in the hair growth cycle, worked on prions, and showed that the catalytic subunit of PP2A is essential for development and that PP2A is a key enzyme in tau phosphorylation. He established the first in vitro model of Aß-induced tau filament formation (JBC 2003). Using transcriptomics and proteomics he provided evidence for mitochondrial dysfunction and a role for glyoxalase I in AD. He has been a continuous member of the GRP (Grant Review Panel) of the NHMRC since arriving in Australia in 2005, and a Chair in 2009. In 2005, Jürgen Götz received the BioFirst (NSW) award; and in 2009 he was awarded NSW Scientist of the Year (Category: Biomedical Sciences). Jürgen Götz continues to develop new transgenic animal models and to work on pathological functions of tau, with a focus on tau-targeted treatment approaches and on understanding how tau mediates Abeta toxicity. Another major interest is the commonality of type 2 diabetes and AD and what determines selective vulnerability in AD. In addition to primary neuronal cultures, C. elegans has been established as a model organism in the laboratory.

Abstract

J. Götz[1], *Lars Ittner*[1], *Christian Czech*[2], *Matthias Staufenbiel*[3], *Anne Eckert*[4]
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Introduction: Alzheimer's disease (AD) is an incurable disease with epidemic proportions. The AD brain is characterized by the deposition of amyloid-beta as plaques and of the protein tau as neurofibrillary tangles. My laboratory is interested in understanding how these proteins interact and how they cause toxicity.
Methods: Combinatorial transgenesis and functional genomics
Results/Discussion: We identified deregulated genes and proteins which we functionally validated. This identified mitochondrial dysfunction and an impaired unfolded protein response as pathomechanisms. We showed that while amyloid-beta augments a pre-existing tau pathology its toxicity depends on tau. We used this insight to develop a treatment with remarkable efficacy in AD mouse models. Furthermore, we developed a tau-based treatment in mice.
Conclusion: Our studies are an example of how animal studies contribute to a deeper understanding of pathomechanisms in disease and provide a basis for a therapy in humans.
References: Götz, J. et al. (2001) Formation of neurofibrillary tangles in P301L tau transgenic mice induced by Abeta42 fibrils, **Science 293**: 1491-1495; Götz J. & Ittner L.M. (2008) Animal models of Alzheimer's disease and frontotemporal dementia, Nature Rev Neurosci **9**: 532-544; Ittner L.M. et al. (2010) Dendritic Function of Tau Mediates Amyloid-beta Toxicity in Alzheimer's Disease Mouse Models, **Cell**, in press

Session 3 – Tissue Engineering

3.1 Engineering Human Tissues

Professor Gordana Vunjak-Novakovic
Department of Biomedical Engineering
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Gordana Vunjak-Novakovic is a Professor of Biomedical Engineering at Columbia University, where she directs the Laboratory for Stem Cells and Tissue Engineering (http://www.bme.columbia.edu/gvnweb), the Bioreactor Core of the NIH Tissue Engineering Resource Center, and the Stem Cell Imaging Core. Her lab is working on engineering of human tissues, for use in regenerative medicine and stem cell research. Gordana published 2 books, 45 book chapters, 210 peer-reviewed articles and 34 patents. She is a frequent advisor to governmental organizations on tissue engineering and regenerative medicine, and the chair of her NIH study section. In 2002, she was elected a Fellow of the American Institute for Medical and Biological Engineering. In 2007, she gave the Director' lecture at the NIH, as the first woman engineer to receive this distinction. In 2008, she was inducted into the Women in Technology International Hall of Fame "for developing biological substitutes to restore, maintain or improve tissue function". In 2009, she was elected to the New York Academy of Sciences. In 2010, she received the Clemson Award of the Biomaterials Society "for contributions to literature".

Abstract
The overall objective of tissue engineering is to fully restore the lost tissue function. Engineered tissues of sufficiently high fidelity can also provide physiologically relevant yet controllable models for fundamental research - for example, to study stem cells in a native-like three-dimensional context of development or disease. The utility of tissue engineering greatly depends on our ability to predictably direct the cells to express the right phenotype in the right place and at the right time. In general, the factors that regulate tissue development *in vivo* (molecular and physical) can be used to direct cell fate and tissue assembly *in vitro*.

The focus of our research is on engineering functional human tissues, by an integrated use of stem cells (the actual "tissue engineers"), biomaterial scaffolds (cell-instructive templates) and bioreactors (culture systems designed to regulate tissue development). This talk will discuss advanced technologies for regulation of stem cell fate and function, and their application to functional tissue engineering and study of development and disease, with focus on two distinctly different systems of great clinical importance: bone and heart. For both tissues, we describe tissue engineering *in vivo*, tissue repair *in vivo*, and the need for vascularization, in the context of graft survival and function.

3.2 Skin Tissue Engineering for Burn Wound Treatment

Professor Peter Maitz
Concord Hospital
University of Sydney
Australia

In 2008 a Chair of Burn Injury and Reconstructive Surgery has been created at the University of Sydney and Peter Maitz is the inaugural Professor. He is the Medical Director of the Burns Unit at Concord Hospital a teaching hospital of the University of Sydney since 2000. Prof. Maitz is a Plastic Surgeon trained at the University of Vienna/Austria and Harvard University Boston/USA and was awarded the Order of Australia in 2002 for his services to the Bali victims. Prof. Maitz designed and commissioned the Burns Unit at Concord Hospital, which offers state of the art equipment and techniques for the care of burned patients. His clinical work includes all areas of burn surgery with special interest in burn reconstruction especially in the head and neck area. In addition to his clinical work Prof. Maitz established the tissue culture laboratory at Concord Hospital, which supplies cultured skin substitutes to all patients in NSW and serves as a research basis. Main research areas include skin substitutes, cell technology and microsurgery. Prof. Maitz is the Chairman of the Education Committee of ANZBA and is heavily involved in teaching. The Emergency Management of Severe Burns course (EMSB) is now being administered under Prof Maitz's leadership in Australia, New Zealand, England, Holland, South Africa, Papua New Guinea, and Bangladesh. Prof. Maitz published extensively in peer reviewed journals and is member of numerous surgical societies worldwide.

Abstract

Peter Maitz[1], Zhe Li[1]*
[1]*Burns Unit, Concord Hospital, Concord NSW 2139*

Effective wound coverage and skin grafting in burns patients are critical for controlling infection, stopping body fluid loss and promoting wound healing. However, the dilemma in treating patients with extensive burn wounds is usually the lack of good donor sites for enough autologous skin grafts. Although allogeneic skin from cadaver donor or even xerogeneic grafts have been used in treating burns patients, their applications are only as an alternative for temporary wound coverage or wound bed preparation because of their immunological incompatibility. All these issues prompted the researches in order to find a better solution for burn wound treatment. Recent development in stem cells and tissue engineering technologies is changing the traditional strategies in treating severe burn wound. Cultured epidermal grafts and tissue-engineered skin equivalents are emerging as critical devices used for burn wound care. Under laboratory condition, autologous skin cells can be isolated from a small skin biopsy, expanded and grown into transplantable skin products using cellular and tissue engineering technology. It has been demonstrated great potential as an alternative for patients with limited donor site although improvement is still needed for better clinical outcome. The advantage of autologous cultured skin grafts in treating burns wound is obvious because of the tissue compatibility, small and easy-to-care donor site and biological safety. Progresses in the laboratory research and clinical application of cultured skin cells and engineered skin equivalents will be discussed.

Session 4 – Translation

4.1 Translation of Engineered Arteries

Professor Laura Niklason
Yale University
Departments of Anesthesia & Biomedical Engineering
**laura.niklason@yale.edu*
USA

Dr. Niklason is a Professor at Yale University in Biomedical Engineering and Anesthesia, and also serves as Vice-Chair for Anesthesia at Yale. She received her PhD in Biophysics from the University of Chicago in 1988, and her MD from the University of Michigan in 1991. She completed her residency training in anesthesia and intensive care unit medicine at the Massachusetts General Hospital in Boston, and completed post-doctoral scientific training at Massachusetts Institute of Technology. From there she went onto a faculty position at Duke University, where she remained from 1998-2005. During that time, Dr. Niklason founded a biotechnology company ("Humacyte, Inc."), which is working to bring engineered tissue replacements to patients. In 2006, Niklason moved to Yale University, where she continues to teach, maintain a vigorous scientific laboratory, and works to expand novel cellular therapies. During her scientific career, Dr. Niklason has become recognized as one of the world's leading experts in cellular therapies and regenerative medicine. (http://medicine.yale.edu/anesthesiology/research/translational.aspx) She has become a world-leader in the development of engineered blood vessels for implantation, and other cellular therapies. Dr. Niklason's research focuses primarily on regenerative strategies for cardiovascular tissues, and the impact of biomechanical and biochemical signals of tissue differentiation and development. Niklason speaks nationally and internationally on her research, and has received numerous national awards for scientific excellence, and was named one of only 19 "Innovators for the Next Century" by US News and World Report in 2001.

Abstract
Introduction: Vascular tissue engineering has progressed from initial proof-of-concept studies in the 1980's, though to implementation of completely autologous engineered arteries in patients. While substantial progress has been made in this field, there remain significant hurdles, with regard to high costs and long culture times for completely autologous engineered products.
Methods: We have evaluated the feasibility of producing engineered blood vessels that are made from allogeneic vascular smooth muscle cells. Such arteries are cultured in specialized, biomimetic bioreactors that provide pulsatile cues similar to the native cardiovascular system. Resultant engineered arteries are comprised of collagenous extracellular matrix and allogeneic smooth muscle. Careful decellularization of these constructs results in tissues that retain all of the important mechanical characteristics of the original tissues, but which lack immunogenic cellular components.
Results: Implantation of decellularized, tissue engineered arteries into several large animal models (pigs, dogs and non-human primates) will be presented. Results of multiple large animal studies show that these engineered arteries function well in the short- and long-term, and appear to be resistant to neointimal hyperplasia, which is one of the primary failure modes for synthetic grafts and vein grafts. Hence, decellularized engineered arteries may represent a platform for creating off-the-shelf and highly functional arterial grafts.
Discussion: Further work is needed to characterize the remodelling responses to these engineered vessels, both in large animal models and in human clinical trials.

4.2 Translational Research in Orthopedics

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Dr. Garrett was born and raised in Sydney, Australia but moved to Adelaide, Australia in 1969 and attended the University of Adelaide there. He obtained a degree in Biochemistry and Organic Chemistry from the University of Adelaide and a Graduate Diploma in Medical Technology from the South Australian Institute of Technology. In 1979 he was employed by the Institute of Medical and Veterinary Science in the Tissue Pathology Department studying the host response to prosthetic wear debris. He then earned his Ph.D. from the University of Adelaide studying metal containing anti-inflammatory drugs. In 1985 he moved to San Antonio to the University of Texas Science Center at San Antonio to do a Ph.D. fellowship with Dr. Gregory Mundy in bone and cartilage metabolism and then in 1988 joined OsteoSA at its inception. At OsteoSA he was responsible for the identification of bone growth peptides, which would stimulate bone formation. In 1982 he joined OsteoScreen and in 2001 was made Scientific Director responsible for developing novel assays and approaches for determining the effects of drugs on bone formation. In 2007 he joined Zimmer as Director of Bone and Drug Device at Zimmer Orthobiologics in Austin Texas. In 2010 he was promoted to Senior Director at Zimmer Orthobiologics. Dr. Garrett has over 22 years of experience in the area of cell biology and animal models of disease particularly in the field of bone and cartilage research and is adept at identifying novel drugs that work with disease states involving these tissues.

Abstract
Translational research has tremendous potential as a tool to reduce health disparities in the world. It is often associated with the idea of ''bench to bedside,'' but the expedited movement of biomedical advances from the laboratory to clinical trials is only the first phase of the translational process. The second phase of translation, wherein innovations are moved from the bedside to real-world practice, is equally important, but it receives far less attention and is the mainly the province of industry. Advances in orthopedics are somewhat unique where clinical data, translated as clinical unmet needs, traditionally drives the newer innovations into real-world practice. Although numerous orthopedic unmet needs exist, three examples indicate various stages of translational research. Firstly, newer fixation technologies, currently available on a host of orthopedic implants, were implemented as a consequence of the clinical need for faster and longer term bone integration. Secondly the suitable treatment for bone deficit conditions and spine fusion is a major unmet need. Through directed and extensive translational research involving bench testing, pre-clinical evaluation and finally clinical trials, BMP2 was successfully moved into real world practice as an active biological agent for this. Finally, orthopedic implant related infections present a real clinical problem and although the incidence rate is low, the end result is devastating and life threatening. Laboratory research implicates these implants as primary causative events in the progression of these infections. Although a considerable amount of studies are underway this research has not yet translated to an effective "real-world" therapeutic.

4.3 Liver-Targeted Gene Therapy for Urea Cycle Defects: From Mouse to Man

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Professor Alexander is head of the Gene Therapy Research Unit, a joint initiative of The Children's Hospital at Westmead and Children's Medical Research Institute in Sydney. Within the hospital he also holds appointments as a senior staff specialist and Director of laboratory research. His training and day-to-day activities in both clinical medicine and laboratory research reflect his interest in translating research progress into improved health outcomes for children. After completing specialty training in paediatrics at Prince of Wales Children's Hospital he obtained a PhD in Molecular Biology from the Garvan Institute in Sydney before completing clinical genetics training at the Murdoch Institute in Melbourne. He then undertook postdoctoral studies at the Fred Hutchinson Cancer Research Institute in Seattle before returning to Australia to take up his current position. He has since established a translational research program and developed the specialised infrastructure and skill sets required to take promising novel therapies through to clinical application. His specific expertise and interests include virus-mediated gene transfer with a focus on organs including the liver and bone marrow, both of which have immense promise as targets for the treatment genetic disease in children. His team became the first in Australia to treat a genetic disease (SCID-X1) by gene therapy and are recognised leaders in the establishment of this exciting field in Australia. This is evidenced by his election as the inaugural president of the Australasian Gene Therapy Society in 2001, his recent award of Life membership of the Society and his appointment in 2007 as Chair of the NHMRC Cellular Therapies Advisory Committee. He was also recently appointed to the position of Professor in Paediatrics and Molecular Medicine at the University of Sydney. International recognition includes membership of the gene therapy sub-committee of the International Society for Cellular Therapy, Associate Editorship on the Journal of Gene Medicine and membership of the editorial board of Human Gene Therapy.

Abstract

Introduction: Recent advances in the development of vectors from adeno-associated virus (AAV) have delivered *in vivo* gene transfer efficiencies in liver and skeletal muscle of mice approaching 100%. The liver is an especially exciting target given the number of genetic-metabolic disease phenotypes potentially amenable to liver-targeted gene therapy (1). To this end we have been exploring AAV-mediated correction of ornithine transcarbamylase (OTC) deficiency (a urea cycle defect). **Methods:** AAV2 vector genomes were engineered using standard molecular techniques and pseudoserotyped with the AAV8 capsid using a three plasmid transfection system in 293 cells. Titres were assigned by qPCR of vector genomes. Phenotype correction in *spf^{ash}* mice was followed by analysis of urinary orotic acid levels and liver OTC enzymatic activity. **Results:** We have exhaustively characterised the transduction performance of rAAV2/8 vectors encoding eGFP in the murine liver, including the effects of administration route, liver growth and gender (2,3). Guided by the data obtained we next undertook phenotype correction studies in OTC-deficient *spf^{ash}* mice using a vector encoding the mouse OTC cDNA, and found that a single intra-peritoneal injection of 5×10^{10} vg/mouse conferred robust life-long phenotype correction (4). With a view to human clinical translation, we are currently optimising vector configuration and delivery to primary human hepatocytes *in vivo* using chimeric mouse-human livers established in FRG mice. **Conclusions:** AAV shows exceptional gene transfer efficiency in the mouse liver, but is not predictive of performance in humans. Data obtained from studies of gene transfer to chimeric mouse-human livers may help address this challenge.

References: (1) Alexander I.E., Cunningham S.C., Logan G.L. and Christodoulou J. (2008) Potential of AAV Vectors in the Treatment of Metabolic Disease. Invited Review. *Gene Therapy* 15(11):831-839**; (**2) Cunningham S.C., Dane A.P., Spinoulas A., Logan G.J. and Alexander I.E. (2008) Gene delivery to the juvenile mouse liver using AAV2/8 vectors. *Molecular Therapy* 16(6):1081-1088**; (**3) Dane A.P., Cunningham S.C., Graf N.S. and Alexander I.E. (2009) Sexually Dimorphic Patterns of Episomal rAAV Genome Persistence in the Adult Mouse Liver and Correlation with Hepatocellular Proliferation. *Molecular Therapy,* 17(9):1548-1554**; (**4) Cunningham S.C., Spinoulas A., Carpenter K., Wilcken B., Kuchel P. and Alexander I.E. (2009) AAV2/8-mediated correction of OTC deficiency is robust in adult but not neonatal *spf*^{ash} mice. *Molecular Therapy,* 17(8):1340-1346

Panel Discussion – A Road to Clinic

Panellists

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Zimmer Orthobiologics
USA

Professor Levon Kachigian
University of New South Wales
Australia

Professor Dennis E. Discher
University of Pennsylvania
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Associate Professor Colin Dunstan
Biomedical Engineering
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Professor Gordana Vunjak-Novakovic
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Session 5 – Cell and Gene Therapy

5.1 Redefining Tissue Engineering at the Nanoscale

Professor Rutledge Ellis-Behnke
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Research Affiliate, MIT

Rutledge Ellis-Behnke is a Professor at Heidelberg University Mannheim Faculty of Medicine where he is the Director of the Nanomedicine Translational Think Tank. In addition, he is a Research Affiliate in the Brain and Cognitive Sciences department at the Massachusetts Institute of Technology. Previously he was Associate Director of the Technology Transfer Office and Associate Professor in the Faculty of Medicine at the University of Hong Kong. His primary research interest is using nanotechnology to reconnect the disconnected parts of the brain in order to restore function. Ellis-Behnke received his PhD from MIT in Neuroscience, BSci from Rutgers University and graduated from Harvard Business School's International Senior Manager's Program (AMP/ISMP). Prior to returning to school to pursue his PhD, Ellis-Behnke held various management positions including Senior Vice President of Huntingdon, a public company for testing and consulting services and Co-founder/CEO in 1995 of one of the first internet companies to do online commerce. Ellis-Behnke is Associate Editor/Neurology for the journal Nanomedicine: Nanotechnology, Biology and Medicine; member of both the Executive and Scientific Advisory Boards for the Glaucoma Foundation; member of the Executive Board of the Asia Foundation for Cancer Research; member of the China Spinal Cord Clinical Trial Network, Society for Neuroscience, American Chemical Society, Association for Research in Vision and Ophthalmology and Sigma Xi, the scientific research society. Technology Review named his "Nanohealing" discoveries one of the "Top 10 Emerging Technologies of 2007." His "Nano Neuro Knitting" and "Immediate Hemostasis" technologies have each been licensed for translation to humans. In addition to his work in neuroscience and nanomedicine Ellis-Behnke introduced the TabletPC to MIT and the University of Hong Kong as part of the migration to the paperless classroom to deliver all course material and texts to the students digitally.

Abstract
Working at the nanoscale means to completely rethink how to approach engineering in the body. In nanomedicine, tissue engineering is the ability to influence an environment either by adding, subtracting or manipulating that environment to allow it to be more conducive for its purpose. The goal is to function at the optimum state, or to return to that optimum state. Additive tissue engineering replaces cells or tissue, or tries to get something to grow that is no longer there. Arrestive tissue engineering tries to stop aberrant growth which, if left uncontrolled, would result in a decrease in function. Nano delivery of therapeutics can perform both additive and arrestive functions influencing the environment either way, depending on the targeting. By manipulating the environment at the nanoscale, the rate and distribution of healing can be controlled. Looking towards the future, focus is on how nanoscale tissue engineering can be and is being used to influence that local environment.

5.2 Tissue-Regenerating, Vision-Restoring Corneal Epithelial Stem Cells

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Associate Professor Nick Di Girolamo is the Director of the Ocular Diseases Research Unit at the University of New South Wales, Australia. He is a Science graduate from the University of Sydney with over 20-years experience in ocular disease that completed his PhD on the "Mechanisms of Tissue Destruction in Inflammatory Eye Disease" in 1998. His research interests include anterior segment disorders including, uveitis, pterygia, ocular surface neoplasia, and limbal stem cell deficiency (LSCD). He has published over 60 articles in peer reviewed medical journals and has attracted over $3M in funds to support his research program. He is on the editorial board of the Journal of Biomedicine and Biotechnology, a panel member that reviews grants for the National Health & Medical Research Council of Australia and reviewer of manuscripts for over 30 medical journals. He has a national and international reputation for his knowledge and expertise in matrix metalloproteinase and stem cell biology and was recently awarded 'Inventor of the Year' in 2009 by the ABCs New Inventors for developing a novel technique to treat partially blind patients with insufficient corneal stem cells.

Abstract

Introduction: The cornea provides us with exquisite vision but unlike other vital tissues, it is poorly protected from the environment and thus relies on a self-renewal program to preserve its integrity. This function is reserved for corneal epithelial stem cells (SCs) located in the basal layer of the limbus, a narrow transition zone that segregates cornea from conjunctiva. Under physiological conditions, these cells replenish the corneal epithelium when mature or traumatized cells are lost. However, when the limbus is extensively damaged, SC activity is compromised, resulting in a condition known as limbal stem cell deficiency (LSCD). This disease is characterized by corneal neovascularisation and persistent epithelial defects, both of which impair vision.

Methods: Over the past 20 years a myriad of treatment options have been developed for LSCD, most incorporate SC transplantation. Due to the disadvantages associated with the use of allogeneic and xenogeneic material, researchers are currently focusing on refining techniques involving autologous limbal tissue transplantation and are delving into the possibility that SCs found in other organs can provide an alternative source of corneal epithelium.

Results: Our recently described technique which utilizes small explants of autologous ocular surface epithelium grown on therapeutic contact lenses appears to overcome many of the disadvantages associated with previously published methods and was able to rehabilitate the cornea to a healthy state and restore vision in patients with LSCD[1].

Conclusion: Understanding how this innovative cell therapy works may provide novel insights into the mechanism of corneal wound healing and may further be refined to treat more common corneal disorders.

Reference: Di Girolamo N, Bosch M, Zamora K, Coroneo MT, Wakefield D, Watson S. (2009) A contact lens-based technique for expansion and transplantation of autologous epithelial progenitors for ocular surface reconstruction. Transplantation. **87**: 1571-1578.

5.3 Translational Research – a Critical Path for Tissue Engineering, Cell and Gene Therapy

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Stephen Hunyor is a Cardiologist, Professor of Medicine and Director of the Cardiac Technology Centre in the Kolling Institute, University of Sydney at Royal North Shore Hospital. His principal interest has been in translational research, studying heart damage and repair with a focus on heart failure and its treatment with devices and more recently cellular therapy. His group specialises in "whole heart" response in terms of hemodynamics and cardiac mechanics and energetics. He was Director of the Cooperative Research Centre (CRC) for Cardiac Technology (1992-99) which had a major program in Polymer research and which involved highly effective collaboration between hospitals, Universities, CSIRO and industry. Professor Hunyor was co-Founder of the North Shore Heart Research Foundation, and a Member of Scientific/Research Advisory Committees to that Foundation and to the Heart Research Institute - Sydney (2007-), NHMRC Project Grants Review Panel Member (2006-) and Founder and former Chairman (2005-2007) Heart Assist Technologies Pty Ltd – a "start-up" company to develop a unique implantable heart assist device. He advised government on R&D policy; was Chair of Australia's 1st "Commercializing Health Innovations Forum" (CHIF '97), and established the Intellectual Property Unit within the NSW State Health Department. He has published > 180 papers, edited 4 books, and is co-inventor of 4 Patents (USA, China, Australia, Hungary, Canada).

Abstract
The market in Tissue Engineering, Cell and Gene products has been "hyped" over the past decade. The promise of "Tissue engineered products in USA" (*Medtech Insight*): 2003 (projected $125bill in 2013), and 2010 (CV only >$22.8bill by 2019) is hard to assess. Nonetheless creative and technological progress has been phenomenal. This presentation is focussed on developments in the field of cardiovascular therapies that illustrate accelerating sophistication.
The multidisciplinary approach covering bio/materials science, nanotechnology, tissue engineering, molecular biology, genetics and cell biology is the profound strength of this field, but also demands end-user involvement at an early stage. Success of the complex path for effective delivery of health benefits is ultimately dependent on the outcomes of translational research.
Progress in the areas of vascular stents, heart valves, pacemakers and defibrillators, mechanical heart assist devices and Total Artificial Hearts, scaffolds for various applications, stem cell and gene therapies, and drug delivery vehicles will be analysed.
The potential for adverse responses to implanted "foreign bodies" is high when there is fragile electrical stability in a damaged heart, when vascular endothelium is damaged with alteration of the clotting profile, or when any object is introduced into the central circulation.
"Tissue Engineering" has entered the public domain and is the subject of common interest. However, the way it has been used, or abused in some circumstances, has led to scepticism and confusion. Managing expectations in the community is a high priority.

5.4 Discovering New Genes as Potential Therapeutic Targets for Neurodegenerative Disorders

Dr Ian Blair
Senior Scientist, ANZAC Research Institute
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Australia

Dr Blair is a senior scientist at the ANZAC Research Institute and clinical senior lecturer, University of Sydney. Dr Blair's research career has focused on determining the molecular basis of neurological disorders including amyotrophic lateral sclerosis (ALS, also called motor neuron disease, MND), hereditary sensory neuropathy (HSN), Charcot Marie Tooth disorder (CMT), the spinal cerebellar ataxias (SCA), Joubert syndrome, and bipolar disorder. His scientific achievements include the recent identification of ALS/MND mutations in the genes encoding TDP-43 (published in Science 2008) and FUS (Science 2009). Mutations in TDP-43 provided the first compelling evidence that this protein, which is abnormal in almost all ALS/MND cases, plays a crucial role in the disease. These recent discoveries have opened new chapters in ALS/MND research worldwide. In 2004, he played a key role in determining the genetic basis of ALS type 4 as well as mapping another novel MND gene in 2007. Dr Blair was also lead scientist in the identification of a susceptibility gene for bipolar disorder in 2006. This was another major breakthrough that was widely reported in scientific and public media. He previously played a key role in mapping the gene for HSN type 1 (leading to identification of the responsible gene), and establishing insights into the molecular basis of CMT1A, SCA, and Joubert syndrome. His work on ALS/MND, CMT and HSN1 has led to the development of effective diagnostic tests that have been implemented in hospital diagnostic settings.

Abstract

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Neurodegenerative diseases, including Alzheimer's disease, frontotemporal lobar degeneration (FTLD), Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS), are adult/late-onset disorders that affect specific nerve populations. While the affected nerve populations differ between these diseases, there are overlaps at the molecular level. Many of these diseases include familial and sporadic forms. The familial forms offer a unique opportunity to identify molecular defects that are relevant to both familial and sporadic disease. These molecules and pathways are potential diagnostic, prognostic and therapeutic targets. However, mutations are often identified in apparently unrelated genes, including genes not formerly considered to play a role in the disease. Studies that seek to identify disease genes and therapeutic targets based solely upon predicted function often fail. Next-generation sequencing technologies combined with traditional genetic approaches are leading to gene discoveries that are opening new chapters in neurodegenerative disease research. This is well illustrated by the recent identification of related pathogenic molecules, TDP-43 and FUS, in ALS and FTLD. These have now been more widely implicated in other neurodegenerative diseases. There is a pressing need to develop more effective diagnostic tools and treatments for these disorders. For example, the insights gained from previously known ALS genes have been insufficient to develop effective treatments in humans, despite the promise shown in mouse models. Novel animal models based upon newly identified genes are currently being developed. These may be the most relevant models to-date for investigating disease biology and testing the efficacy of candidate therapies.

Session 6 – PhD and New Investigator Short Presentations

6.1 PhD Students – Abstracts

6.1.1 Tropoelastin Promotes Spreading and Proliferation of Primary Human Dermal Fibroblasts and is Associated with Altered ECM-Related Gene Expression

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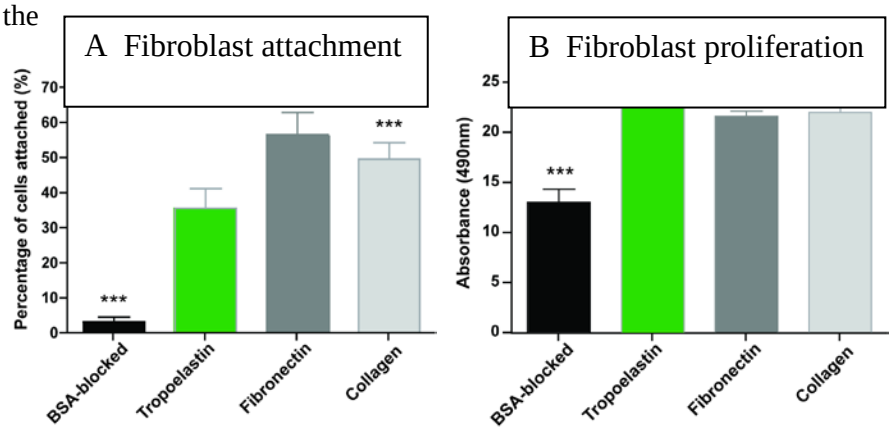
Introduction: The presence of essential extracellular matrix (ECM) proteins and integral cell types, notably dermal fibroblasts and epidermal keratinocytes, is critical to skin regeneration. Elastin is an essential ECM protein providing elasticity and cell signalling properties to tissue. We grew primary human dermal fibroblasts obtained from burns patients on surfaces coated with recombinant human tropoelastin and studied the growth and gene expression of the cells.

Methods and results: Cell attachment and proliferation of primary human dermal fibroblasts were quantified on tropoelastin-coated surfaces by crystal violet staining and a MTS assay. At 60 minutes post-seeding (Fig A), 35.3±5.5% of cells seeded were attached to tropoelastin compared to 63.1±11.1% on fibronectin ($p<0.001$) and 49.3±4.6% on type I collagen ($p<0.001$). Despite the delay in cell attachment, cell proliferation on tropoelastin (0.96 ±0.08) was comparable to fibronectin (0.93 ±0.01) and type I collagen (0.96 ±0.02). Dermal fibroblasts spread and proliferated on tropoelastin, which is beneficial to the wound healing process.



Relative gene expression was measured using Affymetrix HuGene 1.0 ST v1 microarray chips. Microarray analysis identified a subset of genes that are up-regulated in cells on tropoelastin-coated relative to control surfaces. These include MMP-12 (9.0 fold increase), PAI-2 (7.5 fold increase) and TFPI2 (3.0 fold increase), which are involved in modulating the extracellular matrix and a cluster of cytokines, IL-8 (5.0 fold increase), ENA-78 (4.5 fold increase) and MGSA (3.4 fold increase). Microarray analysis was confirmed by real-time PCR.

Conclusion: Tropoelastin has important mechanical and cell signalling properties. These data support favourable fibroblast interactions with tropoelastin with implications for its use in skin repair.

6.1.2 The Adhesion of Human Embryonic Stem Cells on 3D Poly Lactic co Glycolic Acid Scaffolds and Their Differentiation Towards Definitive Endoderm

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The generation of insulin producing cells from human embryonic stem cells (hESCs) has shown great promise as a cellular replacement therapy for the treatment of type I diabetes. Mature functional ß-cell surrogates however, have yet to be successfully generated *in vivo*. One approach to potentially improve current differentiation protocols is the use of 3 dimensional (3D) scaffolds. The present study aimed to explore the feasibility of using single hESCs seeded on laminin or Matrigel coated 3D poly(lactic-*co*-glycolic) acid (PLGA) scaffolds to derive definitive endoderm, the first vital stage of endoderm tissue differentiation. Our results demonstrated that hESCs cultured on laminin or Matrigel coated 3D scaffolds can be successfully coaxed to differentiate into definitive endoderm. The cells generated on 3D PLGA scaffolds were at least comparable to those generated on conventional 2D monolayer cultures in terms of gene and protein expression. However, differences in gene expression profile of the endoderm genes *SOX17, FOXA2, CER* and *CXCR4* were observed between the cells cultured in a 2D or 3D environment which underlined an impact of 3D culturing on hESC differentiation.

6.1.3 Characterization of P-gp Expression and Transport vs. Time and Passage in the Calu-3 Air-Interface Model for Drug Delivery to the Lung

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Introduction: Calu-3, as a sub-bronchial epithelial cell line, has been shown to be a reliable model for the *in vitro* investigation of inhalation drug delivery (1). The Calu-3 air-interface (AIC) model has not been fully investigated for P-glycoprotein (P-gp) expression; a protein actively involved in 'pushing' a wide range of drugs out of cells. Another factor that may affect drug transport is the presence of mucous. The aim of this investigation was to characterize the Calu-3 AIC model for mucous secretion and cell surface P-gp expression and function.
Methods: Calu-3 cells were grown and seeded onto Transwell inserts. Cell surface P-gp was determined by labelling the cells with surface antibodies. The cells were then analysed by flow cytometer. The permeability of rhodamine 123 across cell monolayers was measured, using excitation and emission wavelengths of 500 and 540 nm to determine the functionality of the P-gp. Mucus secretion was measured using alcian blue staining. Images were analysed using Image J. The ratio of blue was then calculated for each image.
Results: Following immuno-labelling, a time dependant cell surface P-gp expression for Calu-3 cell line was determined. Mean fluorescence intensity values reached a plateau at day 11. Rh123

directional flux was observed with a significant 2.4 fold greater permeability in the basal to apical direction. Alcian blue staining of Calu-3 monolayer allowed for detection of the acidic mucosubstance on the apical surface. Mucus secretion increased with respect to culture time. However, a confluent mucus coat was not observed until day 11.
Discussion: The effect of time in culture significantly impacts on the extent of P-gp involvement and mucus secretion in the Calu-3 model. For the first time, under standardized conditions, we show time dependence of these parameters and provide initial guidelines for the optimization of this model.
Conclusion: These findings could have an important impact when Calu-3 *in vitro* cell model are used for assessing drug delivery to the lung *in vivo*.
References:
Grainger, C. I., Greenwell, L. L., Lockely, D. J., Martin, G. P. and Forbes, B. (2006), "Culture of Calu-3 cells at the air interface provides a representative model of the airway epithelial barrier," *Pharm. Res.*, 23**:** 1482-90.

6.1.4 BMP-13 Expression and Its Capacity to Upregulate Chondrogenic Gene Expression in Bone Marrow Mesenchymal Stromal Cells

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Introduction: Study responses of bone marrow mesenchymal stromal cells (BM MSCs) to bone morphogenetic protein 13 (BMP-13) stimulation and potency of BMP-13 in the development of chondrogenic phenotype.
Methods: BM MSCs isolated from surgically discarded tissues were cultured in basic growth medium and stimulated with 0 ng/ml, 100 ng/ml and 500 ng/ml of BMP-13 respectively for 2 weeks. For each BMP-13 treated group, samples from triplicate cultures were collected for gene and protein expression analysis by real-time PCR, histological and immunohistochemical assays. The endogenous BMP-13 expression was detected using monoclonal anti-human BMP-13 antibody derived from our laboratory.
Results: Upregulation of chondrocytic gene expression of BM MSCs under BMP-13 stimulation were observed in a dose dependent manner. Expression of aggrecan (*ACAN*), cartilage oligomeric matrix protein (*COMP*) and transcription factor *Sox9* were increased by 2.9-, 3.4- and 1.9-fold respectively under 500 ng/ml of BMP-13 stimulation. BMP-13 at 500 ng/ml increased both type X and type XI collagen (*COL10A1, COL11A1*) expression by 3.8- and 2.0-fold at the early time during chondrogenic differentiation of BM MSCs, indicating the role of *COL10A1* as early marker of chondrogenesis. BMP-13 stimulation slightly decreased the expression of osteogenic marker, type I collagen (*COL1A1*). Particularly, BMP-13 downregulated asporin (*ASPN*) expression by 1.4-fold, suggesting the role of BMP-13 in promoting chondrogenic differentiation. Immunohistochemical analysis of BMP-13 stimulated BM MSCs showed enhanced protein expression of BMP receptor I-B.
Conclusion: Our preliminary results demonstrated a chondrogenic response of BM MSCs to BMP-13 stimulation, providing evidence of BMP-13's therapeutic potential for IVD regeneration.

6.1.5 Silk-Modified Strontium-Hardystonite Scaffolds for Bone Tissue Engineering

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Introduction: We recently developed bioactive Strontium-Hardystonite ($Sr\text{-}Ca_2ZnSi_2O_7$, Sr-HT) scaffolds [1] which have superb properties for bone tissue engineering applications, but a limiting factor is the inherent brittleness of ceramics. This study explores the modification of Sr-HT scaffolds with a natural biopolymer, silkworm silk fibroin, in order to produce composite scaffolds with improved properties for bone regeneration in load-bearing defects.
Methods: Sr-HT ceramic powder was synthesised via the sol-gel method, from which Sr-HT scaffolds (cubic, $5mm^3$) were prepared and sintered at 1250°C for 2 hours. Composite scaffolds were prepared by coating Sr-HT scaffolds with a 3wt% silk fibroin aqueous solution. Morphological, material and biological properties of the composite and control Sr-HT scaffolds were evaluated and compared.
Results & Discussion: μCT imaging and scanning electron microscopy showed that the silk-modified composite scaffolds had cancellous bone-like architecture similar to control Sr-HT scaffolds, with 95% porosity and pore size of 400-500μm. Mechanical testing demonstrated a more than 2-fold increase in compressive strength and Young's modulus of the composite scaffolds, likely due to reduced scaffold brittleness as the uniform silk coating filled micro-cracks in the Sr-HT scaffold. The composite scaffolds exhibited much slower degradation than controls, which may be beneficial for new bone ingrowth. *In vitro* studies demonstrated better cellular response on the composite scaffolds, with favourable human osteoblast-like cell attachment and consistent cell proliferation over 7 days of culture.
Conclusion: The silk-modified Sr-HT composite scaffolds fabricated in this study exhibit improved properties which underline their potential use as bone graft substitutes in the reconstruction of load-bearing bone defects.
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6.1.6 Plasma Immersion Ion Implantation Treatment of Poly-Ether Ether Ketone for the Immobilization of Biomolecules on Surfaces

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Introduction: Poly-ether ether ketone (PEEK) has emerged as a leading biomaterial for replacing metal implant components due to its outstanding physical properties. Interest has been focused on improving the bioactivity of PEEK by developing the polymer with bioactive materials such as hydroxyapatite, either as a composite filler, or as a surface coating. Recently, a research group led by Marcela Bilek and David McKenzie from the Applied Plasma Physics department of the University of Sydney showed largely improved biological responses after using Plasma Immersion Ion Implantation (PIII) to treat a range of polymeric biomaterials. They demonstrated that the convenient PIII treatment not only improves the bioactivity and blood compatibility of the surfaces, but also provides a one-step method to covalently immobilize biomolecules such as proteins onto the treated surfaces.

Methods: The goal of this project is to improve bone cell responses to PEEK by immobilizing bone matrix proteins onto PEEK surfaces by means of the PIII treatment procedure in order to mimic the bone microenvironment. The performance of the materials created will be evaluated by means of cell attachment assays, SDS washing assays for protein attachment, MTT assays to assess effects on proliferation, and alkaline phospatase assays and RT-PCR to assess bone cell differentiation.
Results: Preliminary results have confirmed that the PIII treatment of PEEK surfaces alone increases the bone cell attachment rate by approximately 80~90% compared to unmodified PEEK materials.
Conclusion: The project is still in its early stages but this technology will be potentially useful in creating biological surfaces for use in sensors and orthopaedic implants.
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6.1.7 The Effect of Surface Topography on Protein Adsorption and Platelet Responses Using Model Diamond Like Carbon and Titania Surfaces

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Introduction: The host-biomaterial response is a dynamic and complex process that is still poorly understood and is of utmost importance for advances in the development of haemocompatible materials. This project aims to understand the effect of surface topography on the adsorption of plasma proteins, albumin and fibrinogen, including their conformation, through analysis of the adsorbed protein layer and subsequent platelet interaction events using model metallic and diamond like carbon (DLC) surfaces with defined roughnesses.
Methods: Surfaces were characterised by atomic force microscopy (AFM) and scanning electron microscopy (SEM) and found to have roughnesses in the 0.1, and 1 nm range. Protein adsorption onto these surfaces was analysed by ELISA and quartz crystal microbalance with dissipation (QCM-D). Albumin and fibrinogen were each found to form monolayers on the surfaces while when exposed in combination, while fibrinogen preferentially absorbed onto both, titania and DLC surfaces. More than 80% of the adsorbed mass attached within the first few minutes, after which the rate of adsorption saturated.
Results: Platelet attachment varied between protein coated surfaces. Titanium and DLC surfaces pre-coated with serum or fibrinogen supported platelet attachment, while surfaces pre-coated with albumin did not. Platelets attached on fibrinogen pre-coated surfaces showed rounded morphology and expressed the GP IIb/IIIa. This indicates that platelets can exist in their activated state without spreading.
Conclusion: Future experiments will focus on the conformation of absorbed fibrinogen on these surfaces and correlate the results with platelet responses.

6.1.8 Tissue Engineering an Arterial Wall Model

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Introduction: Large arteries are complex, multilayered structures consisting of an intraluminal layer of endothelial cells followed by layers of smooth muscle cells interspersed between thin lamellae of elastin[1]. Current tissue engineered arteries rarely incorporate elastin into the supportive scaffold. Recombinant human tropoelastin can be cross-linked into 3D synthetic elastin arrays[2]. We explored its potential as a biological scaffold for tissue engineered arteries as it more closely mimics the native structure.
Methods: Biological scaffolds were formed by electrospinning and cross-linking tropoelastin fibres to form thin insoluble scaffolds. Vascular cells were then seeded onto these scaffolds and cellular interactions investigated using scanning electron microscopy, histology and immunohistochemistry.
Results & Discussion: Endothelial and smooth muscle cells proliferated to form monolayers on scaffolds after 7 days in culture[3]. Spreading of smooth muscle cells could be directed by aligning electrospun fibres. Immunohistochemistry confirmed that both cell types retained expression of marker proteins. Cells were successfully co-cultured on opposite sides of a single scaffold, mimicking the native structure of the arterial wall.
Conclusion: Electrospun synthetic elastin scaffolds could support two vascular cells types and retain their phenotypic characteristics. Control of cell growth and orientation on these scaffolds point to the value of this system as an *in vitro* model for the vascular vessel wall.
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6.1.9 Dermal Repair: Electrospun Elastin-Based Dermal Substitutes for the Treatment of Severe Burns

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Introduction: Severe burn injuries cause excessive scarring and skin contractures. Scar tissue lacks elasticity, flexibility and strength of the normal skin and consequently limits movement, causes pain and is cosmetically undesirable. Elastin is a major structural and functional component of the skin dermis where it conveys elasticity and resilience and signals a range of essential cellular processes. It does not adequately regenerate following burn injury and its distribution is disrupted in scars. Tissue elasticity is increasingly recognised as a modulator of cell physiology and has the potential to limit skin contraction and scar formation. Our aim is to develop an advanced, elastic dermal substitute that will reduce skin contraction and scarring following burn injury.
Methods and Results: We have electrospun recombinant human tropoelastin (rhTE), a soluble precursor of elastin, into highly porous, open-weave scaffolds consisting of thin, ribbon-like fibres

(Figure 1A) [1-2]. These scaffolds have been comprehensively assessed *in vitro* and are currently undergoing *in vivo* testing. rhTE is chemically cross-linked to form synthetic human elastin (SHE). SHE scaffolds displayed elasticity close to that of natural elastin. Fibroblasts attached (Figure 1B), spread and proliferated on SHE fibres and infiltrated into open-weave SHE scaffolds [2]. The cells persisted on SHE scaffolds for at least 35 days post-seeding and expressed ECM proteins fibronectin and type I collagen. Preliminary *in vivo* studies in rat full thickness wounds demonstrated the safety and biocompatibility of these scaffolds.

Conclusion: Electrospun SHE scaffolds are novel, highly elastic, fibrous scaffolds that promote interactions with dermal fibroblasts and as such show great promise as dermal substitute scaffolds.

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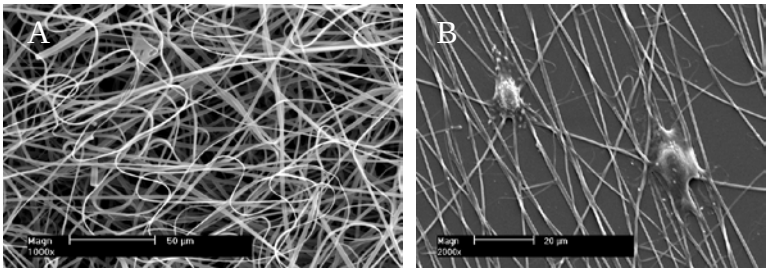

Figure 1. (A) Electrospun tropoelastin fibres (B) Dermal fibroblast interactions with SHE fibres at 30 min post-seeding.

6.1.10 Stimulation of MMPs and Cartilage Degradation by S100A8 and S100A9

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Introduction: S100A8 and S100A9 are expressed in cartilage and are up-regulated in chronic and acute inflammatory arthritis; however their role in osteoarthritis is unclear. In experimental osteoarthritis in mice, *S100a8* and *S100a9* were increased at early time-points. S100A8 and S100A9 also induce catabolic gene expression in isolated chondrocytes. This study aimed to determine if these proteins induced a similar response in cartilage explants.

Methods: Ovine articular cartilage explants were cultured for 4 days in serum-free media ± 10^{-7}M human S100A8, S100A9 or S100A8/S100A9 (n=3/treatment). Gene expression of *S100a8*, *S100a9*, cartilage proteins, metalloproteinases and their inhibitors was measured using real time RT-PCR.

Results: *Adamts-1*, *Adamts-5*, *Mmp-1*, and *Mmp-3* mRNA levels were up-regulated by S100A8 and S100A9 ($p<0.05$), no change was seen in *Mmp-2*, *Mmp-9*, *Mmp-14*, *Timp-1*, *Timp-2* or *Timp-3*. *Mmp-13* was increased by S100A8 (≈100 fold; $p<0.05$) and S100A9 (≈20 fold), but down -regulated by S100A8/S100A9 (≈25 fold; $p<0.05$). *S100a9* expression was up-regulated by S100A8 and S100A9 ($p<0.04$). *S100a8* expression was low but increased in response to S100A8. Only in response to

S100A8 we observed: increased GAG release; activation of pro-MMP-2; secretion of pro-MMP-9 and pro-MMP-13.
Discussion: These results largely match those of isolated articular chondrocytes. During the time-course of this experiment, S100A8 was more pro-catabolic than S100A9, and S100A8/S100A9 did not induce any significant responses, except for *Mmp-13* down-regulation. Chondrocyte *S100a9* and *S100a8* expression has been previously shown to be increased by IL-1, and this data also suggests some degree of auto-regulation.
Conclusion: These results confirm that S100A8 and S100A9 are involved in chondrocyte-mediated cartilage degradation.

6.1.11 Development of a Bioengineered Stent with Enhanced Biocompatibility

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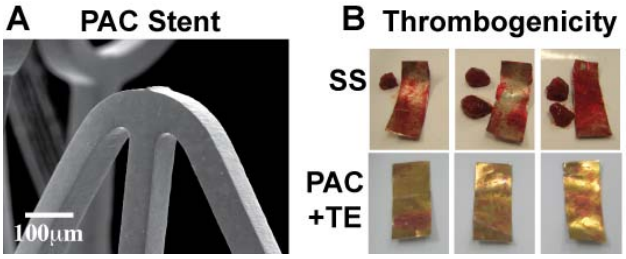
Introduction: Current metallic endovascular stents used to treat coronary artery disease have suboptimal biocompatibility reducing their clinical efficacy. Our multidisciplinary team has produced a robust, biocompatible plasma-activated coating (PAC) by plasma deposition on 316L stainless steel (SS). This covalently binds proteins in their bioactive state to metallic surfaces, to achieve biointegration. We bound recombinant human tropoelastin (TE), a major regulator of vascular cells *in vivo*, to enhance biocompatibility.
Methods and results: PAC was generated by pulsed plasma deposition of acetylene with nitrogen and argon on stainless steel. PAC has a hydrophilic contact angle of 63±1°, is extremely smooth (1-2nm rms roughness) and resists delamination after stent expansion (Fig A). Horseradish peroxidase activity (a probe for retention of protein conformation) remained higher after 10 days when bound to PAC *vs* SS. TE remained attached to PAC despite SDS washing, and incubation with supraphysiological serum enzymes, indicating covalent binding. The PAC+TE coating dramatically enhanced endothelial cell attachment and proliferation by 86.3±10.5% ($p<0.01$) & 76.9±6.4% ($p<0.001$ vs Control) respectively. Moreover, thrombus weight was reduced on the PAC & PAC+TE by 94.0±0.9% and 93±1.2% respectively ($p<0.001$ *vs* Control; Fig.B) in a modified Chandler loop and time to thrombus formation was reduced 3-fold. Serum soluble P-selectin was reduced by 25.3±8.7% and 24.5±8.7% on PAC and PAC+TE respectively, $p<0.05$ representing a decrease in platelet activation.



Conclusion: The PAC is durable, non-thrombogenic and enables covalent binding of bioactive proteins to stents. PAC+TE enhanced endothelialisation and remained non-thrombogenic. This has profound potential to improve stent efficacy.
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6.2 New Investigators – Abstracts

6.2.1 Human Fetal Brain Derived Neurosphere Monolayers Express Functional Purinergic Receptors Coupled to Intracellular Calcium Signalling

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Introduction: Little is known about the signalling mechanisms utilised during human neural stem cell development. Recent findings in mouse neural stem cell cultures showed adenosine triphosphate (ATP) and signalling via purinergic (P2X/P2Y) receptors is critically involved in self-renewal, and that ATP release and purinergic receptor expression are down-regulated in differentiation and development. Hence purinergic signalling may have multiple significant roles in human neurodevelopment that are unexplored.
Methods: Calcium imaging of second-trimester human fetal brain-derived neurosphere monolayers used confocal and widefield calcium imaging. Quinacrine staining of ATP-containing vesicles used confocal and TIRF microscopy.
Results: Human neuron and astrocyte precursor cells (hNPCs) respond to ATP and related agonists by a rise in intracellular calcium, predominantly from thapsigargin-sensitive stores. ATP, ADP, UTP and UDP evoked rapid calcium transients, suggesting the involvement of different P2Y receptor subtypes, whilst P2X receptor agonists gave a minimal to moderate response which was correlated to lineage via post-calcium imaging immunostaining. Propagation of calcium fluxes between adjacent cells with ATP showed three distinct responses, correlated to single, double and multiple increases of calcium. We also demonstrated the existence of quinacrine-stained vesicles in hNPCs, known previously to contain ATP and other neurotransmitters for exocytotic release.
Discussion: Collectively, this the first report of purinergic signalling in hNPCs, demonstrating the mechanisms of calcium responses, involvement of specific receptor subtypes and existence of ATP-containing vesicles.
Conclusion: This study demonstrates that hNPCs are fully functional and mimic the mature neuronal/astrocytic interactions in the CNS, suggesting their likely integration in transplant models for cell therapy.

6.2.2 Rod Shaped Hydroxyapatite Nanoparticles Provide an Optimal Osteogenic Niche for Stem Cell Differentiation by Interacting with Osteoblasts

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Introduction: Following the clinical insertion of a bone biomaterial, osetoblasts migrate and attach to the implant surface fostering a microenvironment which largely determines the differentiation fate of the co-migrated mesenchymal stem cells (MSCs) from the surroundings. This process might be crucial for the subsequent successful osseointegration.
Materials and Methods: In this study we incorporated hydroxyapatite nanoparticles (nHA) of different shapes into a Poly(ε-caprolactone) (PCL) films to fabricate PCL-spherical nHA and PCL-

rod nHA films respectively. We investigated 1) how different shapes of nHA, when interact with human osteoblasts (HOBs), affect their differentiation; 2) how the microenvironment rendered by their interaction affects osteogenic differentiation of adipose tissue-derived mesenchymal stem cells (ASCs); and the underlying mechanism(s) contributing to this interaction. HOBs were seeded on PCL, PCL-spherical nHA and PCL-rod nHA films, respectively.
Results: When cultured alone, HOBs on PCL-rod nHA films showed most efficient osteoblastic differentiation compared with those on PCL or PCL-spherical nHA films. When co-cultured with ASCs in an indirect co-culture system, only the HOBs interacting with PCL rod nHA up-regulated the gene expression levels for Runx2, bone sialoprotein, and osteocalcin in ASCs. HOB interacting with PCL-rod nHA showed significant up-regulation of BMP2 gene expression and induced the most significant phosphorylated Smad1/5 protein expression levels in ASCs. In addition, the treatment of the co-culture medium with BMP2 inhibitor (Noggin) largely abolished the osteoinduction of ASCs when co-cultured with HOBs on PCL-rod nHA film.
Conclusion: In conclusion, the incorporation of rod-like nHA into PCL films provides an excellent tool for fabricating the biomaterials for bone tissue engineering by not only preserving the phenotype of osteoblasts but also to render an optimal osteogenic niche for the differentiation of stem cells.

6.2.3 Nanostructured Glass-Ceramic Coatings for Orthopaedic Applications

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Introduction: To overcome drawbacks of Ti-6Al-4V implants, various surface coatings have been used to endow them with good bone-fixation ability. The efficacy of the coating is strongly dependant on its chemical and surface topographical (at both micron- and nano-levels) characteristics.
Methods: Atmospheric plasma spray technique was used to deposit hardystonite (HT) and sphene (SP) coatings on Ti-6Al-4V alloys. Their potential uses as implant coatings were investigated.
Results: Both types of coatings were composed of glass-ceramic and exhibited a micron-sized topography superimposed by nanostructures (less than 50nm). Their bonding strength and nano-hardness were higher than the reported values of clinical-used hydroxyapatite (HAp) coatings. Mushroom-like Ca & P compounds were formed on HT coatings after 5 h incubation in cell-free culture medium, indicating its good acellular mineralization ability. HOBs attached, spread, proliferated and differentiated well on both types of coatings indicating their good biocompatibility.
Discussion: Ca and Si ions released from the coatings are important for both acellular mineralization ability and cell behaviours of HT and SP coatings. Nanostructured surfaces of both HT and SP coatings are also thought to be responsible for the good interaction between coatings and HOBs.
Conclusion: Results point to the potential uses of HT and SP coatings for orthopaedic applications.

6.2.4 Synthetic Recombinant Human Elastin-Based Vascular Grafts with Biological and Mechanical Properties Matching the Human Vasculature

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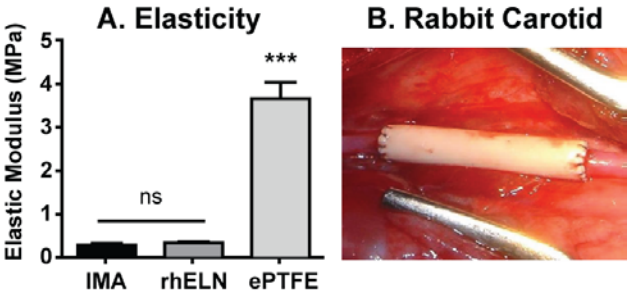
Introduction: Clinically effective small diameter synthetic vascular grafts are lacking. Conventional graft polymers such as ePTFE are non-compliant and lack biocompatibility. Elastin, a major component of arteries, provides compliance and favourable biological properties[1]. We report the development and evaluation of a novel tissue-engineered vascular conduit, comprising recombinant human elastin (rhELN) with biological and mechanical properties matching the internal mammary artery (IMA).

Methods & Results: Vascular biological properties of rhELN were assessed by standard in vitro assays. Compared to BSA-coated plastic, rhELN enhanced endothelial cell (EC) attachment by 3-fold ($p<0.001$) & proliferation by 54.7±1.1% ($p<0.001$). rhELN exhibited low thrombogenicity characterised by: 1) plasma recalcification showing reduced contact activation by 60.4±8.2% ($p<0.001$); 2) reduced In^{111}-labelled platelet attachment (53.4±6.5%;$p<0.01$) and; 3) whole-blood clotting times not different to saline control by APTT assay. Similarly, rhELN-coated ePTFE also exhibited superior EC attachment, proliferation and platelet binding compared to ePTFE ($p<0.01$). Multilayered synthetic conduits were produced by electrospinning. The outer layers comprised hybrids of rhELN and polycaprolactone (compliance), while the inner layer was 100% rhELN (biocompatibility). Our rhELN conduit exhibited biomechanical properties superior to ePTFE and identical to IMA (Fig.A; elastic modulus 320±24kPa; burst pressure 1922±197mmHg). rhELN conduits implanted in a rabbit carotid interposition model sutured well, did not leak and were well tolerated up to 30d (Fig.B).



Conclusion: Recombinant elastin can be bioengineered as a synthetic vascular conduit with biomechanical and biological properties markedly superior to existing synthetic conduits and identical to those of a human IMA[2], with strong implications for coronary artery bypass grafting.

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6.2.5 Adhesion of Chemically Deposited Hydroxyapatite Coating to Pre-Treated Ti Substrates

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Introduction: Hydroxyapatite (HA) coating on titanium (Ti) implant can be used as a drug delivery device. A controlled release of bone forming drug (e.g., bone morphogenetic proteins) around the implant requires the incorporation of drug into the coating material during the coating process.
Objectives: Prepare strongly adherent HA coating on pre-treated Ti implant surface in conditions that allow the incorporation of bone forming drug into the coating materials.
Methods: Ti substrates were prepared by grinding, grit-blasting, oxidation, acidic and alkali treatments. Monetite coatings were deposited onto the pre-treated Ti substrates using chemical deposition, followed by hydrothermal conversion of monetite into HA at 75°C in alkali solution.
Results: EDS confirmed calcium phosphate nature of the coatings. XRD analysis confirmed the formation of monetite phase, which was transformed into HA phase by hydrothermal conversion. SEM revealed that HA crystals were about 100 nm in length. The highest adhesion strength of the HA coating was measured by a scratch tester on a grit-blasted Ti surface 86.8 ± 1.3 MPa.
Conclusion: HA coatings, which chemically and morphologically resemble the human bone at nano-scale, were successfully prepared on pre-treated Ti substrates using chemical deposition method, which allows the incorporation of the protein-based drugs during the formation of the HA coating. The adhesion strength of the HA coating prepared on a grit-blasted Ti substrate is comparable to that of the conventional plasma spraying method, which is between 30 to 100 MPa.

6.2.6 Improved Cell Response to Polymers by the Incorporation of Ti-Doped Phosphate Glass

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Introduction: It is hypothesised that with using glass as a component (filler) of polymer based medical devices it is possible to improve cells activity and trigger osteoblastic differentiation ensuring low inflammatory reaction for bone tissue regeneration devices. This improvement is a result of specific, tuneable chemistry and degradation of the filler.
Methods: In the study PLDL (Purac) was used. Titanium doped phosphate glass powder with concentration 10, 20 and 40 vol.%, and β-tricalcium phosphate (TCP) 10 vol.% as a control filler were used. Advancing contact angle, ζ-potentials, mechanical (DMA) and thermal (DSC) properties, and human osteoblast cells responses (spreading, immunostaining – cytoskeleton, differentiation – osteocalcin, osteopontin) to the materials were evaluated.
Results & discussion: ζ-potentials drop, and wettability and stiffness improvement were observed with increasing glass filler loading. Cell cytoskeletons were very well developed on the samples with

glass content up to 20 vol.%, and response was more favourable then observed for TCP filled samples (fig.1). Expression of osteocalcin and ostopontin was positive for all the samples including pure PLDL.

Conclusion: Improved wetting behaviour, lower ζ-potentials, and specific chemistry of the glass filled polymer enabled the modulation of cell response, and bioactivity improvement in comparison with β-TCP filler. Changes to the mechanical properties of the materials filled with the glass were less pronounced than for β-TCP filled materials. It was concluded that biochemical cues related to the glass filler composition were critical to improve cell response.

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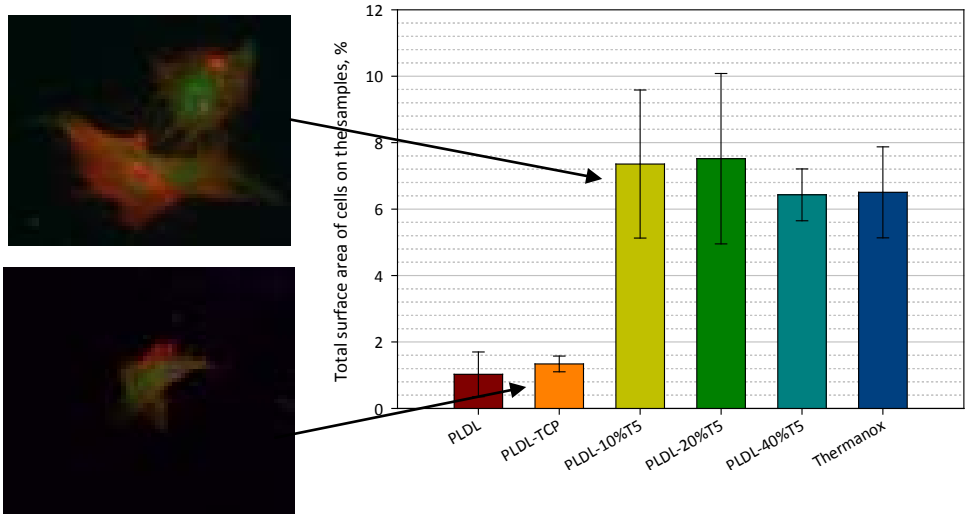

Fig. 1 Total surface area (%) of Human primary osteoblasts growing on the surface of test samples after 3 days in culture. Cytoskeletons (average cell) of the cells grown on PLDL-TCP and PLDL-20vol%T5.

Session 7 – Tissue Engineering and Regenerative Medicine: The Next 20 Years – Challenges and Opportunities

Speaker 1

Professor Laura Niklasen
Yale University
USA

Speaker 2

Professor Dennis E. Discher
University of Pennsylvania
USA

Speaker 3

Professor Gordana Vunjak-Novakovic
Columbia University
USA

Speaker 4

Dr Glenn Smith
Therapeutic Goods Administration
Australia

Speaker 5

Kerry Doyle
Executive Director of Innovation, Science and Industry Analysis, NSW Government
Australia

Organovo Workshop

Thursday 11th November, 9:30am – 12:30pm

SIT Board room 124 Building J12

Session 1:

9:30 - 10:30: NovoGen Bioprinting Presentation

10:30 - 11:00: Q/A and 1:1 with customers

Session 2:

11:00 - 12:00: NovoGen Bioprinting Presentation

12:00 - 12:30: Q/A and 1:1 with customers

Organovo is a regenerative medicine company focused on delivering breakthrough three dimensional biology capabilities to create tissue on demand for research and surgical applications. The NovoGen MMX Bioprinter is at the forefront of sculpting three dimensional and functional tissue consisting of multiple cell types and biomaterials for research and therapeutic development.

Please come visit us at the SuTEN workshops to explore how the NovoGen bioprinting process can add value to your current research programs. For more information, please visit us at **www.organovo.com**.

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Notes

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