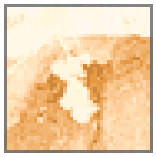
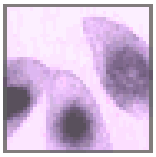
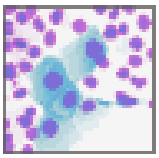
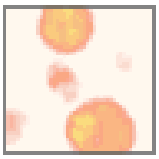
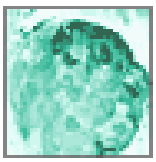
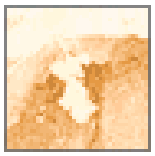
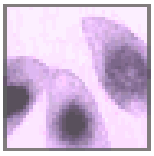
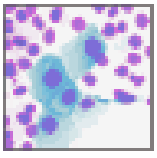
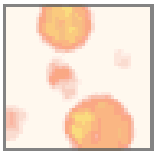
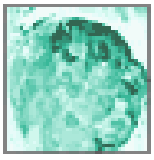











1st Annual Regenerative Medicine Symposium at Sydney University

Thursday 1st October, 2009
Kerry Packer Auditorium
Royal Prince Alfred Hospital

1st Annual Regenerative Medicine Symposium
at Sydney University

Program

10:00 – 10:30 - REGISTRATION -

Morning Session *Chaired by Prof Stephen Hunyor, Kolling Institute of Medical Research*

10:40 – 11:00 **Novel signalling mechanisms directing the differentiation of ES cells**
Dr Michael Morris, Embryonic Stem Cell Laboratory, Kolling Institute of Medical Research

11:00 – 11:20 **Regulation of Wnt ligands in stem cells and cardiogenesis**
Jason Seow, Cardiac Technology Centre, Kolling Institute of Medical Research

11:20 – 11:40 **Osteoblasts directly control lineage commitment of mesenchymal progenitor cells through Wnt signaling**
A/Prof Hong Zhou, Bone Research Program, ANZAC Research Institute, Concord Hospital

11:40 – 12:00 **Modulation of stress-induced tendon degeneration by mesenchymal stem cells**
Dr Margaret Smith, Raymond Purves Bone and Joint Research Laboratories, Kolling Institute

- LUNCH -

Afternoon Session *Chaired by Prof Tailoi Chan-Ling, Bosch Institute of Medical Research*

1:00 – 1:20 **Epidermal stem cells and skin regeneration**
Dr Zhe Li, Skin Laboratory, Concord Hospital

1:20 – 1:40 **The role of endothelial progenitor cells in new blood vessel formation**
Daniel Sieveking, Translational Research and Bioengineering Laboratory, Heart Research Institute

1:40 – 2:00 **Genetically defined patient-derived stem cells as a model of neurological disease**
A/Prof Carolyn Sue, Neurogenetics Group, Kolling Institute of Medical Research

2:00 – 2:20 **Bouncing stem cells into the clinic**
Prof John Rasko, Cell and Molecular Therapies, Royal Prince Alfred Hospital & Centenary Institute

2:20 – 2:30 **Brief summary of the 2009 Baltimore World Stem Cell Summit**
Prof Stephen Hunyor, Cardiac Technology Centre, Kolling Institute of Medical Research

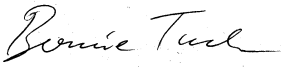
- AFTERNOON TEA -

INTRODUCTION

Welcome to the first annual Regenerative Medicine Symposium at Sydney University, an initiative designed to provide a yearly snapshot of stem cell research being undertaken at Sydney University and affiliated institutions. As the range of stem cell research continues to expand and new projects are instigated across all Sydney University affiliated institutions, the desire has grown for a forum that shines a light on their breath and illuminates connections.

The annual Regenerative Medicine Symposium aims to bring together researchers from the faculties of Medicine, Science, Engineering, Arts, and Law, who share an interest in stem cells. The idea is to create a new space for networking and information sharing, where laboratory leaders, senior and junior researchers share their visions, their insights and their advances. This year, scientists from a range of laboratories connected with Sydney University will update participants on the current state of their research. We are grateful for their participation and their enthusiasm for this exciting initiative.

It is hoped that this symposium will stimulate discussion and open new possibilities for partnerships, which strengthen stem cell programs across the Sydney University research network. We trust that you will enjoy the program and be inspired by the combination of research strengths showcased.



Nola Camden
Manager

Dr Bernie Tuch
Director

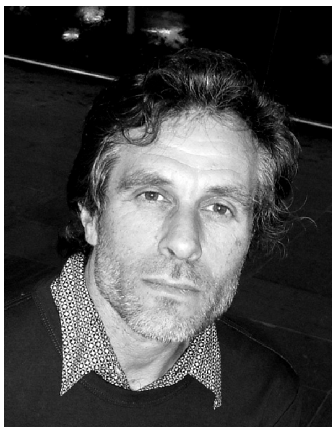
NSW Stem Cell Network

NOVEL SIGNALLING MECHANISMS DIRECTING THE DIFFERENTIATION OF ES CELLS

The phenotypic status of ES cells is controlled in part by cell signalling. An important extracellular protagonist in mouse ES cells is LIF (leukaemia inhibitory factor) which activates a number of signalling pathways, including STAT3, MEK/ERK and PI3K/Akt. These pathways, together with others, interact in complex and sometimes competing ways to generate the well-known phenotypic characteristics of mouse ES cells of self-renewal, high rates of proliferation, and pluripotence.

The addition of a second molecule, L-proline, to the extracellular environment stimulates the directed differentiation of ES cells. Inhibitor studies and kinome array analyses show that L-proline works by novel activation of a number of signalling pathways including some already stimulated by LIF. Stimulation of differentiation-mediated events by L-proline is very rare in eukaryotic systems and to our knowledge none occurs by the mechanisms we have uncovered.

Since ES cells act as a useful in vitro model of embryogenesis, we tested if L-proline and other amino acids could improve/stimulate development of mouse embryos in culture. We found that L-Pro and L-Gln appear to act in an autocrine-like manner to promote blastocyst formation and hatching. Potentially, they act via mechanisms already found for the directed differentiation of ES cells and might be used to improve the quality of IVF embryos.



Dr Michael Morris

Embryonic Stem Cell Laboratory, Kolling Institute of Medical Research, Royal North Shore Hospital

Michael Morris has undertaken commercially driven research for the Adelaide stem-cell company Bresagen and received funding from the Australian Stem Cell Centre for his research at the University of Adelaide. He returned to Sydney University in 2007 as Sesqui Senior Lecturer in embryonic stem cells at the Bosch Institute and Discipline of Physiology. His lab is located at the Sydney Centre for Developmental and Regenerative Medicine, Kolling Institute, Royal North Shore Hospital.

REGULATION OF WNT LIGANDS IN STEM CELLS AND CARDIOGENESIS

J. H.H. Seow, C. Jackson, S. Hunyor

Wingless (Wnt) is a family of secreted glycoproteins involved in the differentiation of embryonic and adult progenitor stem cells. Wnts possess a biphasic role during cellular development, and are able to promote or inhibit cardiogenesis. Recently resident-cardiac stem cells (CSCs), which could give rise to myocytes, smooth muscle, and endothelial cells, have been reported in the adult mammalian heart. However, the cellular mechanisms that elucidate cardiogenesis remain unclear.

5-Azacytidine (5-Aza), a chemical analogue of cytidine, has been extensively studied and was used to initiate stem cell cardiomyogenic differentiation, and cardiac homing in injured myocardium. Data from our laboratory have also showed that 5-Aza has the capability to differentiate sheep MSC to cardiac progenitor cell lineages. As Wnt signaling promotes cardiogenesis at various developmental stages, understanding the involvement of Wnts and 5-Aza to promote CSCs derivation of cardiac myocytes may provide insight into harness these CSCs for future cardiac reparative therapies.

David Seow

Cardiac Technology Centre, Kolling Institute of Medical Research, Royal North Shore Hospital

David Seow graduated from the University of Queensland with a Bachelor of Science in Biomedical science, with honours in Developmental Cell Biology. He worked in Singapore from 2005 to 2007 in the Molecular and Cell Biology Institute and the Genomic Institute of Singapore. David has done extensive work on mouse embryo manipulation, transgenic mice, and methylation, specifically concerning the ribosomal genes in cancer formation.

OSTEOBLASTS DIRECTLY CONTROL LINEAGE COMMITMENT OF MESENCHYMAL PROGENITOR CELLS THROUGH WNT SIGNALLING

Hong Zhou, Wendy Mak, Yu Zheng, Colin R Dunstan, Markus J Seibel

Lineage commitment of mesenchymal progenitor cells is still poorly understood. Using a transgenic mouse model in which transgenic (tg) expression of 11beta-hydroxysteroid dehydrogenase type 2 (HSD2), a glucocorticoid (GC) inactivating enzyme, under the control of a 2.3Kb collagen type I promoter (Col2.3-HSD2) abrogates intracellular GC signalling in mature osteoblasts, we demonstrate that Wnt signalling by osteoblasts is essential for mesenchymal progenitor cells to differentiate away from a default adipogenic into an osteoblastic lineage.

Dominant adipogenesis and reduced osteoblasto¬genesis were observed in calvarial cell cultures from transgenic mice characterized by osteo¬blast-targeted disruption of glucocorticoid signa¬ling. This phenotypic shift in mesenchymal progenitor cell commitment was associated with reciprocal regulation of early adipogenic and osteoblasto¬genic transcription factors, and with a reduction in Wnt7b and Wnt10b mRNA and catenin protein levels in transgenic vs. non-transgenic cultures. Transwell co-culture of transgenic mesenchymal progenitor cells with wild type osteoblasts restored commitment to the osteoblast lineage. This effect was blocked by adding sFRP1, a Wnt inhibitor, to the co-culture. Treatment of transgenic cultures with Wnt3a resulted in stimulation of osteoblastogenesis and suppression of adipogenesis.

Our findings suggest a novel cellular mechanism in bone cell biology, in which osteoblasts exert direct control over the lineage commitment of their mesenchymal progenitor through Wnt signaling. This glucocorticoid-dependent forward control function indicates a central role for osteoblasts in the regulation of early osteo-blastogenesis.

A/Prof Hong Zhou

Bone Research Program, ANZAC Research Institute, Concord Hospital

A/Prof Hong Zhou is an associated professor in Bone Research Program, ANZAC Research Institute, The University of Sydney. A/Prof Zhou has a long-standing track record in basic research into bone biology. She has extensive experience in bone cell and molecular biology and in the use and analysis of animal models of bone disease, fracture healing, cancer and arthritis, including genetically modified animals models.

In recent years, Hong Zhou has made significant discoveries investigating the role of endogenous glucocorticoids in bone. She was the first to describe how glucocorticoids control mature osteoblasts to direct mesenchymal progenitor lineage commitment through Wnt signalling

(Zhou et al. JBC 2008; Kalak et al., Bone 2009). She further found that glucocorticoid signalling in osteoblasts is essential for normal bone development (Zhou et al., Development 2009) and modulate K/BxN serum-induced arthritis in vivo (Arthritis and Rheumatism, 2009). Her research has found international recognition in the bone field, receiving several awards (e.g. Outstanding Paper Award, 2nd Intl. Conference on Osteoporosis and Bone Research, Cheng-Du, China, 2005; Best Basic Abstract Award, ANZBMS, Queenstown, NZ, 2007) and has been presented in oral and plenary poster form at numerous national and international meetings. In addition, A/Prof Zhou is active in researching the biology of breast and prostate cancer bone metastases, the results of which have recently been published in 'Bone' (2007) and 'Cancer Research'(2007).

MODULATION OF STRESS-INDUCED TENDON DEGENERATION BY MESENCHYMAL STEM CELLS

Degeneration and tearing of rotator cuff tendon causes significant morbidity in our ageing population. While conservative treatment is favoured, there are no drug therapies to specifically treat cuff or other tendon injuries. Surgical repairs are common (over 14,000 annually in Australia); unfortunately half of these repairs fail within 12 months. An animal model of shoulder tendon injury induced by partial infraspinatus tendon transection, has been established in our laboratories. The pathology progresses with time and we have defined the temporal molecular mechanisms that underlie the regional tendon degeneration. We have now shown in pilot studies, acute modulation of overload-induced molecular change in tendon by local heterologous MSC injection. We are now extending these exciting preliminary findings by determining the long-term utility and underlying mechanism of MSCs in both abrogating the development of tendon degeneration after injury and in treating established tendinopathy. We hope to define the therapeutic dose, temporal efficacy and mechanistic pathway of a novel, clinically applicable therapy to treat this debilitating musculoskeletal disorder.

Dr Margaret Smith

Raymond Purves Bone and Joint Research Laboratories, Kolling Institute of Medical Research, Royal North Shore Hospital

Margaret graduated from University of NSW with a PhD in biochemistry in 1984. Her thesis described the isolation and characterisation of the polyol pathway in human brain, important in diabetic complications. She then joined the Raymond Purves Labs, where, over the past 25 years, she has worked on many projects, particularly in developing animal models to test treatment modalities for osteoarthritis, rheumatoid arthritis, spinal disorders and traumatic joint injuries.

Margaret is currently Chairman of the Scientific Staff Council at RNSH, an editorial board member for the American Journal of Sports Medicine and a non-executive board member of Sylvan Scientific (Australia) Ltd. She is an ex-President of the Matrix Biology Society of Australia and New Zealand and has recently been nominated as an Australian Ambassador for the Bone and Joint Decade (a WHO initiative).

EPIDERMAL STEM CELLS AND SKIN REGENERATION

Lack of skin donor sites remains the most challenging issue in treating severe burn injuries. Cultured autologous keratinocytes derived from the epidermis have been used for many years to produce grafts that regenerate an epidermis over a full-thickness burn wound. But there are still many issues associated with the cultured skin graft. Skin tissue engineering, a technology of bio-scaffold guided skin regeneration under in vitro conditions produces a better version of living skin substitute for grafting full-thickness skin wounds. It has become clear that the essential feature of the graft is the presence of an adequate number of epidermal stem cells. Advances in epidermal stem cell technology and skin regeneration have been made in recent years. Better understanding of epidermal stem cells and other cells involved in skin regeneration will facilitate the engineering of better skin, with structures comparable to normal human skin. Dr Zhe Li will give an overview the current developments in epidermal stem cell research and engineered skin tissue regeneration.

Dr Zhe Li

Skin Laboratory, Concord Hospital

Dr Zhe Li is chief scientist at the Skin Laboratory at Concord Hospital. He obtained his medical degrees in China and then a PhD degree from the University of Sydney. He runs the Skin Laboratory to provide cultured skin autografts to severe burns patients in all burns units under NSW state-wide burn injury services.

Before joining the Skin Laboratory in 2002, he held senior research positions in a number of hospitals and universities in Sydney. He has had extensive research training and experience in medical microbiology, embryology, cell biology and molecular biology, in addition to his medical background. He has played key roles in the research program of the Skin Laboratory and Burns Unit at Concord Hospital. He is also associated with the newly-formed Burns and Reconstructive Surgery research program at ANZAC Research Institute, Concord Hospital. His current interests and expertise cover a number of fields including skin biology, skin regeneration, cultured living skin substitute and wound healing. Dr Zhe Li was awarded the prestigious Winston Churchill Fellowship of Australia in 2008 for his work in cultured skin and burn wound healing.

THE ROLE OF ENDOTHELIAL PROGENITOR CELLS IN NEW BLOOD VESSEL FORMATION

Angiogenesis, the growth of new blood vessels, is essential for organ development and is critical to cardiovascular repair/regeneration. It is a highly coordinated process involving branching or elongation of existent vessels by the migration and proliferation of endothelial cells. Indeed, the endothelium plays a critical role in cardiovascular homeostasis, however mature endothelial cells (ECs) have limited regenerative capacity. The description just over a decade ago, of putative endothelial progenitor cells (EPCs) that could mobilise from bone marrow to participate in neovascularisation at sites of ischaemia was enthusiastically greeted for the potential they hold for cardiovascular repair/regeneration. However, confusion regarding the precise identity and role these cells play has hampered the translation of therapies involving these cells. We have recently revealed that two putative EPC populations have strikingly different angiogenic properties with implications for the optimisation of cell therapies. This talk will discuss the impact of different disease states on the number and function of these cells as well as other cellular and molecular approaches to therapeutic angiogenesis.

Daniel Sieveking

Translational Research and Bioengineering Laboratory, Heart Research Institute

Daniel completed a BSc (Hons) in 2001 at the University of New South Wales majoring in medical microbiology and Immunology. He joined the Heart Research Institute in 2003 as a research assistant, and began a PhD in 2006. His research relates to the processes of cardiovascular repair and regeneration with a focus on angiogenesis. He has just completed his PhD which investigated sex-dependent differences in cardiovascular disease, focussing on the role of male sex hormones in angiogenesis.

GENETICALLY DEFINED PATIENT-DERIVED STEM CELLS AS A MODEL OF NEUROLOGIAL DISEASE

We have developed a new approach to investigate what happens to neurons in neurological disorders such as Parkinson's disease. We have successfully grown olfactory neurospheres (that contain olfactory stem cells) from nasal mucosal biopsies taken from patients with genetically defined Parkinson's disease. Different types of neurons can be differentiated from the olfactory stem cells (neurospheres) and can then be used in our experiments to investigate the pathogenic mechanisms that contribute to cellular degeneration in Parkinson's disease. Parkinson's disease is a neurodegenerative disorder that predominantly affects the dopaminergic neurones in the substantia nigra. The reason why these cells are particularly vulnerable is unclear. By using these cells we are able to investigate the neurologic effects that underlie Parkinson's disease and they may serve as a model to investigate the cellular vulnerability characteristic of this disorder. Results of our stem cell research will be discussed in this presentation.

A/Prof Carolyn Sue

Neurogenetics Group, Kolling Institute of Medical Research, Royal North Shore Hospital

Dr Carolyn Sue is a neurologist, currently appointed as Associate Professor at the University of Sydney, the Director of Neurogenetics at the Kolling Institute, Director of the National Centre for Adult Stem Cell Research (Sydney node) and Senior Staff Specialist in the Department of Neurology at Royal North Shore Hospital. She completed her post-doctoral studies at Columbia University, New York, USA. She has dual research interests, mirroring her clinical interests in the diagnosis and management of mitochondrial disease and movement disorders (mainly Parkinson's disease). At present her research involves the use of adult stem cell models to investigate the pathophysiology underlying neurological disorders such as mitochondrial and Parkinson's disease.

Dr Sue founded the Neurogenetics clinic and familial Parkinson's Disease research clinic at Royal North Shore Hospital, and has coordinated National collaborative genetic studies in Parkinson's disease. She was instrumental in the set up of the Australian Mitochondrial Disease Foundation (AMDF). She is regularly invited to speak at national and international meetings and currently serves on the Board of the AMDF and the Scientific Advisory Board for the NSW Parkinson's disease Association.

BOUNCING STEM CELLS INTO THE CLINIC

Professor John Rasko will discuss initiatives in New South Wales towards good manufacturing practice of cellular therapeutics. He will also outline research into the haemopoietic stem cell micro-environment being undertaken by his Gene and Stem Cell Therapy Group at the Centenary Institute of Cancer Medicine and Cell Biology

Prof John Rasko

Cell and Molecular Therapies, Royal Prince Alfred Hospital & Centenary Institute

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.

NSW Stem Cell Network

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