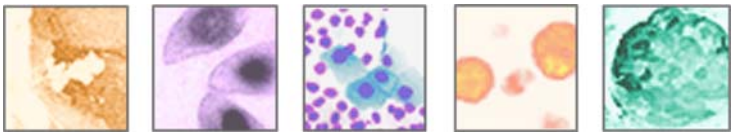
NSW Stem Cell Network

13th Stem Cell Workshop

Stem Cell Therapies to the Clinic

Friday 9th, April 2010
9:30am to 2:30pm
Darlington Centre
City Road, Camperdown
University of Sydney



Welcome to the 13th Stem Cell Workshop

Which prospective stem cell therapies are closest to the clinic and what still needs to be achieved before these therapies are generally available to the public?

Stem cells have been around for fifty years, with application to the clinic for a long time being restricted to haematological malignancies.

With the creation of the first human embryonic stem cell line in 1998 by James Thompson at the University of Wisconsin, a new revolution in medical research began. For the first time pluripotent, as compared to multipotent stem cells theoretically became available as a tool in regenerative medicine.

It usually takes fifteen or more years after a new discovery before its actual use becomes obvious. It is now twelve years since the stem cell revolution began and the application of these cells to the clinic has started.

This workshop covers the prospective applications of both the pluripotent stem cells and more novel applications of multipotent ones.

Enjoy this Workshop and we look forward to keeping in touch through the Network.

Kind regards,

Nola Camden ***Prof Bernie Tuch***
Manager ***Director***

NSW Stem Cell Network

WORKSHOP PROGRAM

9:00am	Registration opens / coffee
9:30	Opening address **Prof David Ma, Director of Haematology Research, St. Vincent's Hospital**
Session 1: Science advancing to the clinic Chair: Dr Meg Evans, CSIRO Molecular Health and Technologies, Biomaterials and Regenerative Medicine	
9:40	Turning liposuction leftovers into arthritis therapies **A/Prof Ben Herbert, Macquarie University and Regeneus**
10:00	Encapsulated human embryonic stem cells as a therapy For insulin-dependent diabetes **Dr Bernie Tuch, Australian Foundation for Diabetes Research**
10:20	Development, testing and validation of a microgel magnetic particulate probe for human stem cell imaging *in vivo* **Prof Ming Wang, Sydney Medical School, Sydney University, Westmead Hospital**
10:50	Production of placental mesenchymal stem cells for clinical trials **Dr Gary Brooke, Mater Medical Research Institute**
11:10	Clinical applications of allogeneic mesenchymal progenitors **Prof Silviu Itescu, Mesoblast Ltd.**
11:30	Curing partial blindness by coating contact lenses with stem cells **Dr Stephanie Watson, Prince of Wales Hospital**
12:00	Lunch / networking
Session 2: Regulating stem cell therapies Chair: Dr Olivia Harvey, School of History and Philosophy, The University of New South Wales	
1:00pm	Springing stem cells into the clinic **Prof John Rasko, Centenary Institute, Sydney University**
1:20	Translation and implementation **Dr Clive Morris, National Health and Medical Research Council**
1:40	Stem cells and intellectual property **Dr Daniel Shaft, Shelston IP**
2:00	The regulation of cell therapies **Dr Glenn Smith, Blood and Tissues Unit, Therapeutic Goods Administration**
2:40	Refreshments / networking

TURNING LIPOSUCTION LEFTOVERS INTO ARTHRITIS THERAPIES

Adipose tissue contains very large numbers of stem cells. Approximately 500 to 1000 fold more mesenchymal stem cells (MSCs) can be harvested from equivalent amounts of fat than bone marrow. Sufficiently large numbers of stem cells can be harvested from fat so that direct transplantation can occur without the need to amplify cell numbers by culture. This is a key point as it enables autologous same-day treatments. The procedure pioneered by Regeneus in Australia uses an enzyme preparation that breaks down the collagen connective tissue. The cells are then washed by centrifugation to remove the enzyme and the cells are injected into the patients' arthritic joints. The entire process takes less than 2 hours.

Mesenchymal cells have well documented anti-inflammatory effects and promote wound healing and regeneration. The Regeneus process produces a fresh cell population with high viability and functionality as measured by the levels of important secreted proteins. Since 2008 over 250 dogs have been treated with this procedure. It has proven safety and has been efficacious in reducing pain in over 80% of the canines treated. In April 2009 a preclinical study on seven humans began. The assessment of the human patients includes molecular pro and anti- inflammatory inflammation marker analysis and the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) standardised assessment. In association with Professors Philip Sambrook and Lyn March we are in the final stages of planning a double blind clinical trial at Royal North Shore Hospital in Sydney.

A/Prof Ben Herbert

Vice Chancellor's Innovation Fellow at Macquarie University

Ben Herbert was one of the founding scientists at the Australian Proteome Analysis Facility (APAF) at Macquarie University. His core expertise is in proteomics and protein chemistry, with particular expertise in sample preparation, fractionation and separation of complex mixtures; establishment and management of core facilities providing cutting edge technologies and large-project support for proteomics and systems biology. He is also a co-founder of Proteome Systems Ltd and Regeneus Pty Ltd and a non-executive director of Regeneus. Ben Herbert has developed and commercialised technology with Bio-Rad, Sigma-Aldrich, Proteome Systems and Regeneus.

ENCAPSULATED HUMAN EMBRYONIC STEM CELLS AS A THERAPY FOR INSULIN-DEPENDENT DIABETES

It has been 12 years since the first human embryonic stem cell (hESC) line was derived from a spare fertilized egg. Much progress has been made since then, and we now know how to differentiate these pluripotent stem cells into pancreatic progenitors (PP). This is a 12 day procedure requiring several changes of culture medium and growth factors, before PDX-1 +ve PP are derived. To differentiate PP into glucose-responsive insulin-secreting cells can be achieved by transplanting the PP, and waiting many weeks for the maturing process to occur. The nature of this process is still somewhat of a mystery, and cannot as yet be achieved in vitro.

Placing cells inside microcapsules made of alginate prior to transplanting them is a way of preventing the immune cells of the recipients attacking the graft. The capsules have pores with a cut-off size of 150kDa. This is too small to allow entry of immune cells and IgM, but large enough for passage of nutrients and insulin. Encapsulated insulin-producing cells do survive and function when transplanted. These encapsulated cells will normalize blood glucose levels when allografted into diabetic mice. As few as 750 encapsulated human islets are sufficient to normalize blood glucose levels of diabetic immunodeficient recipient mice. The safety of transplanting encapsulated human islets was recently shown in a phase 1/2a first-in-human clinical trial. Finally, fetal islet-like cell clusters (ICC), which are akin to PP derived from ESC, mature and normalize blood glucose levels of diabetic recipient mice in the same amount of time as that required for non-encapsulated ICC to achieve this outcome.

These background data have led to the push for translating encapsulated PP into the clinic. There are several steps required to achieve this goal:

1. Show proof-of-principle that encapsulated PP produce mature β cells when transplanted into rodents, and that teratomas do not form.
2. Scale up the production of PP, with up to 350 million required per person.
3. Obtain approval from the HREC and TGA, the key issue being safety.
4. Commence phase1/2a clinical trials.

It is anticipated that over the next 5 years these challenges will be met, to allow hESC to be trialed as a therapy in Australia.

Dr Bernie Tuch

Director, Australian Foundation for Diabetes Research

Dr Bernie Tuch is a practicing endocrinologist who has been carrying out cutting-edge research with stem cells for the past decade. This complements his earlier experience with human fetal pancreatic tissue, which he transplanted into diabetic humans in the late 1980's. His knowledge of the immature β cells is well recognized internationally, and he has written 10 book chapters and several dozen manuscripts on the properties of these cells. He has recently published the results of the first use of alginate microcapsules in diabetic Australians, and is promoting its use in other areas of medicine, including chronic liver disease. He is the Director of the NSW Stem Cell Network, and recently left his position as Professor of Medicine at the University of New South Wales to devote more time to his research interests.

DEVELOPMENT, TESTING AND VALIDATION OF A MICROGEL MAGNETIC PARTICULATE PROBE FOR HUMAN STEM CELL IMAGING IN VIVO

MR imaging of iron-oxide labeled cells allows serial tracking of transplanted stem cells *in vivo*. Current technologies utilising clinical iron oxide (FeO) particles <150 nm (e.g., Ferucarbotran) are hampered by the large number of cells required for visualization because of limited uptake by non-phagocytotic cells. Human fetal mesenchymal stem cells (hfMSC) are multipotential cell types which have been shown to home into areas of tissue injury. We describe the synthesis, magnetic characterisation and cellular uptake of novel biocompatible microgel-encapsulated iron oxide particles (MGIO), and MRI tracking of MGIO-labelled hfMSC in a rat stroke model.

We have demonstrated that novel MGIO particles are taken up by hfMSCs efficiently without affecting stem cell properties, and that MGIO labeling of hfMSCs allows visualisation of small groups of cells after cellular migration to a stroke site *in vivo* with a standard 1.5T system. However despite immunosuppression these labeled cells were no longer present by 10 days after injection, and the iron label had been engulfed by host macrophages. Visualisation of the iron label is insufficient evidence for the presence of the labeled stem cells in such xenograft models.

Prof Shih-chang (Ming) Wang

Parker Hughes Chair of Diagnostic Radiology
Imaging, Western Clinical School

Dr. Wang graduated from Sydney University and trained in Radiology at the Royal North Shore Hospital, where he was staff specialist from 1989 to 1997. He worked at the National University of Singapore from 1998 to 2008 as Associate Professor and then Head of Diagnostic Radiology, and returned to take up the Parker-Hughes Chair of Diagnostic Radiology at the University of Sydney in mid-2008. He is very active in clinical radiology teaching internationally, and has wide research interests in clinical and preclinical imaging, especially breast imaging, interventional oncology, novel MR contrast agents and computerised analysis of medical images. He is the Chief Censor of the RANZCR, Head of the Discipline of Medical Imaging for the Sydney Medical School, and is actively involved in the planning of new research imaging facilities for the University. He has delivered over 140 lectures and training workshops internationally, organised several scientific meetings, and is an author of more than 80 scientific presentations, 65 scientific journal articles, 55 book chapters, and one book.

PRODUCTION OF PLACENTAL MESENCHYMAL STEM/STROMAL CELLS FOR CLINICAL TRIALS

Mesenchymal stem cells (MSC) are now often and perhaps more appropriately termed mesenchymal multipotent progenitor cells (MSC). MSC are being suggested as a potential cellular therapy for a broad range of conditions. This not only includes regenerative therapies, but also treatment of drug retractile graft-versus-host-disease. The rationale behind the latter is due to their potent immune-inhibitory properties. This property also leads to a possible further advantage – that of transplantation into an unrelated individual without the need for immunosuppression. Currently MSC are usually generated from bone marrow or fat aspirates. However, we have been investigating an alternative and more readily available source, namely the placenta. With over 3000 births at the Mater Mothers hospital alone, this tissue could potentially be an important source of MSC for clinical trials. I will discuss the use of this novel tissue as a source for MSC in clinical trials.

Dr Garry Brooke

Adult Stem Cell Team, Mater Medical Research Institute, Brisbane

Gary Brooke is currently the senior research scientist in the Adult Stem Cell Team under the leadership of Professor Atkinson at the Mater Medical Research Institute. Gary originally obtained his PhD at the University of London, UK and worked in Oxford University in the immunology field for several years. Since coming to Australia, Gary has been focussing his efforts on researching the regenerative abilities of adult stem cells. Gary is aiming to transfer stem cell technologies to the clinic and has played an integral role as scientific project manager in the optimisation of mesenchymal stem/stromal cell growth under cGMP conditions. This has led to the initiation of two clinical trials in collaboration with the Westmead Hospital (Sydney) and the Prince Charles Hospital (Brisbane).

CLINICAL APPLICATIONS OF ALLOGENEIC MESENCHYMAL PROGENITORS

Prof Silviu Itescu

Executive Director, Mesoblast Ltd.

Professor Silviu Itescu is the Executive Director and Founder of Mesoblast Limited and its United States-based associate company, Angioblast Systems Inc. The Companies' adult stem cell technology platform is based on novel technology using mesenchymal precursor cells developed by world-leading Australian scientists at South Australia's Hanson institute over more than 10 years.

Mesoblast and Angioblast are conducting Phase 2 trials in the United States and Australia using allogeneic, or 'off the shelf', adult stem cell products for indications including spinal fusion, congestive heart failure, heart attack, osteoarthritis and regeneration of bone marrow.

Professor Itescu has advised both the United States President's Council on Bioethics and the United States Food and Drug Administration's Biological Response Modifiers Advisory Committee on cell therapy. He is a member of numerous national and international scientific bodies and professional societies and has consulted widely for international pharmaceutical companies. Professor Itescu's research interests extend from basic to clinical, across the fields of stem cell biology, autoimmune diseases, organ transplantation and heart failure.

CURING PARTIAL BLINDNESS BY COATING CONTACT LENSES WITH STEM CELLS

Limbal stem cells are responsible for an intact corneal surface. In limbal stem cell failure, opacity of the cornea (the eye's window) leads to loss of vision and discomfort. Current techniques for treating limbal stem cell failure are limited as they use foreign or non-FDA approved materials. We have developed an autologous technique for transferring stem cells to the cornea using a contact lens. Treated patients have regained vision and improved their ocular comfort. The results of laboratory studies of the cell-laden contact lens will be presented as they support the clinical findings.

Dr Stephanie Watson

Prince of Wales Hospital, Sydney Children's Hospital and Sydney Eye Hospital

Dr Watson is a specialist in cornea at the Prince of Wales, Sydney Children's and Sydney Eye Hospitals. She completed sub-speciality training at Moorfields Eye Hospital, London and was awarded a PhD for the development of a new dry eye therapy. She is a conjoint senior lecturer at the University of New South Wales, a Director of the Ophthalmic Research Institute of Australia and Editor for the Cochrane Eyes and Vision Group. She has been supported by an NHMRC Fellowship, Fight for Sight Bursary, Moorfields Eye Hospital Special Trustees, Eye Bank Association of America, Alcon-RANZCO Scholarship, RANZCO-John Parr Scholarship, and the Tear Film and Ocular Surface Society Young Investigator award. Her stem cell research has been featured in the international, national and local news. She was invited to appear on the 'New Inventors' programme on the ABC and was the episode and people's choice award winner.

SPRINGING STEM CELLS INTO THE CLINIC

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. We have shown that culturing primitive murine and human cord blood haemopoietic cells on tropoelastin in vitro led to increases in cell number, clonogenicity, proliferation and engraftment following transplantation. Atomic force measurements of truncations and crosslinked tropoelastin strengthen the hypothesis that stem cells sense the elasticity of their microenvironment. 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 aimed to achieve optimal ex vivo culture conditions for primitive haemopoietic cells. In order to take advantage of this type of observation arising from the basic research laboratory (and many other opportunities in cellular therapies), a basic introduction in the principles and regulatory aspects of good manufacturing practice of cellular therapeutics will be provided.

Prof John Rasko

Cell and Molecular Therapies, Royal Prince Alfred Hospital and 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.

TRANSLATION AND IMPLEMENTATION

This presentation will discuss how NHMRC supports the development of Australia's capacity in stem cell translation and how this relates to health and medical research.

Dr Clive Morris

National Health and Medical Research Council (NHMRC)

Dr Clive Morris is NHMRC's Deputy Head and General Manager. Dr Morris has been part of NHMRC's senior management team since mid-2000, and during that time has held a number of senior roles. His previous Commonwealth appointments include heading the Molecular Biology Section at the Therapeutic Goods Administration, overseeing the assessment of new biological medicines and tests for safety and quality, and as a senior toxicologist with Food Standards Australia and New Zealand (FSANZ). Prior to joining the Commonwealth Public Service he was an active researcher in cell biology.

STEM CELLS AND INTELLECTUAL PROPERTY

The Australian Patent Office has considered the patentability of stem cell-related inventions in two pivotal cases. The dividing lines between patentable and non-patentable inventions provided by the Patent Office draw interesting distinctions between various aspects of stem cell research. Daniel Schaft has extensive research experience in the use of stem cell technology and will illustrate some of the difficulties in assessing whether an invention relating to stem cells can be considered patentable under Australian law.

Dr Daniel Schaft

Shelston IP

Daniel holds a doctorate degree (Dr. rer. nat.) from the University of Giessen, Germany, a PhD from the European Molecular Biology Laboratory (EMBL) Heidelberg, Germany and a Master of Industrial Property (MIP) from the University of Technology Sydney. He works in the specialist intellectual property firm Shelston IP and practises in the fields of biotechnology, stem cell biology, pharmaceuticals, molecular and developmental biology.

During his PhD Daniel developed biochemical and proteomic techniques to characterize chromatin modifying protein complexes. Upon completion of his PhD, he worked as a Postdoctoral fellow at the University of Technical Sciences in Dresden, Germany and, in Australia as a Fellow of the Human Frontiers Science Program at the Victor Chang Cardiac Research Institute in Sydney. His research has focused on mechanisms of chromatin regulation and transcriptional control underlying the development of congenital heart disease.

Daniel is a member of the NSW Stem Cell Network, the Australia and New Zealand Society for Cell and Developmental Biology (ANZSCDB), the Intellectual Property Society of Australia and New Zealand (IPSANZ) and the Institute of Patent and Trade Mark Attorneys of Australia (IPTA).

THE REGULATION OF CELL THERAPIES

This presentation will discuss the role of the Therapeutic Goods Administration (TGA), how clinical trials are currently administrated by the TGA and the proposed implementation of a new regulatory framework for human cell and tissue therapies/biologicals.

The TGA is responsible for ensuring the quality, safety and efficiency of therapeutic goods supplied in Australia. This is achieved via a number of mechanisms including pre and post market evaluation and review and ensuring products supplied in Australia conform to applicable standards.

Clinical trials conducted using 'unapproved therapeutic goods' in Australia, that is goods which have not been evaluated by the TGA for quality, safety and efficacy and entered into the Australian Register of Therapeutic Goods (ARTG) for general marketing, are required to make use of the Clinical Trial Notification (CTN) or Clinical Trial Exemption (CTX) schemes. All clinical trails in Australia require review and approval of trial proposals by an ethics committee. In the case of the CTN and CTX schemes, such a committee must have notified its existence to the Australian Health Ethics Committee(AHEC) of the National Health and Medical Research Council (NHMRC) and provide assurances that it is operating within its guidelines.

The existing therapeutic goods regulatory frameworks are not well adapted for human cell and tissue therapies (HCT). In response to this in 2006 the Australian Health Ministers Conference agreed to the TGA implementing a National HCT regulatory framework. Solid organs and hematopoietic progenitor cells where not included pending further consultation. Assisted reproductive tissues are excluded.

The TGA is currently in the process of developing legislation, standards and guidelines for the new HCT framework, now known as the Biological Framework. It is anticipated that the framework will be implemented in 2010 with a transition period for biological products to move into the new scheme.

Dr Glenn Smith

Blood and Tissue Unit of the Therapeutic Goods Administration

Dr Glenn Smith is the Director of the Blood and Tissue Unit of the Therapeutic Goods Administration (TGA) in Canberra. The Unit contributes to the evaluation of a number of therapeutic areas including labile blood components, cellular therapies, prescription medicines, devices, as well as providing service evaluations across the TGA for viral and prion safety. The unit is also currently implementing a new regulatory framework for human cell and tissue therapies/biologicals. Glenn represents the TGA in a number of international forums, including the World Health Organisation (WHO) and the European Directorate for the Quality of Medicines (EDQM). Prior to joining the TGA, Glenn worked in medical and translational research, including leading a project that resulted in the successful completion of a phase1/2 clinical trial (involving over 20 patients), of a recombinant monocolonal antibody for the treatment of colorectal cancer.

Contact: Nola Camden
Tel: 02 9382 4856
Fax: 02 9382 4826
Email: stemcellinfo@stemcellnetwork.org.au
URL: www.stemcellnetwork.org.au

Thanks to our sponsors