

The NSW Stem Cell Network presents the

3rd Stem Cell Workshop

Tues 14th October, 2003 8:30 am to 12:30 pm Lecture Theatre & Functions Room Edmund Blacket Building Prince of Wales Hospital, Randwick

Welcome to the 3rd NSW Stem Cell Workshop!

The past few months have seen stem cell research continue to grow in various forms. This is cutting edge technology and advances are happening almost on a daily basis.

Research in NSW involving human embryos moved a step closer following our June Workshop with a historic conscience vote in the state's lower house of parliament. As I am sure you are aware, the Research *Involving Human Embryos (New South Wales) Act 2003* and the *Human Cloning and Other Prohibited Practices Act 2003* were passed by the NSW Parliament on 26 June 2003 and 1 July 2003 respectively. Both Acts commenced operation on 1 October 2003 forming a nationally consistent scheme to regulate research involving human embryos.

The NSW State Government continues to show their commitment to stem cell research and the NSW Stem Cell Network. We are grateful of the support shown by the Science and Medical Research Minister Frank Sartor, Cabinet Biounit and the NSW Premier Bob Carr who will open today's meeting.

The world's leading experts in stem cell research and regenerative medicine gathered this week to attend the First National Stem Cell Conference in Melbourne. The four day conference, "Stem Cells and Tissue Repair" has attracted twenty international speakers and was hosted by Australia's National Stem Cell Centre (NSCC). The NSW Stem Cell Network has coordinated today's satellite meeting to allow our local scientific community to benefit from the presence of two esteemed international speakers; Professor Ben Reubinoff from the Hadassah University Hospital in Jerusalem and Christine Mummery from the Utrecht University in The Netherlands. We will also cover exciting local scientific advancements with presentations from Rosanne Taylor from Sydney University, Lily Bai from the Diabetes Transplant Unit and Jason Kovacic from the Victor Chang Cardiac Research Institute.

The NSW Stem Cell Network continues to work in collaboration with national bodies including the NSCC and the National Health and Medical Research Council. They are represented here today by Alan Trounson and Graham Jenkin from the NSCC and Tony Rolfe who will update us on the process of making an application to the Stem Cell Licencing Committee of the NHMRC. Both organisations have seen recent changes and we welcome into their new positions, John (Jock) Findlay as chair of the NHMRC Licencing Committee and Hugh Niall as the NSCC chief executive officer.

Finally, thanks must be given to all our speakers, to the Prince of Wales Hospital for showing its support, to our sponsors for their generous contributions, Hayley Scott for assisting in organizing the Workshop and Euan Roberts for his initial input.

We hope that you find this Stem Cell Workshop a platform for generating new ideas and contacts and we will continue to keep in touch through the NSW Stem Cell Network.

Regards,

Prof. Bernie Tuch
Ms. Sarah Walke
NSW Stem Cell Network
www.diabetes.unsw.edu.au

The NSW Stem Cell Network is coordinated by Prof. Bernie Tuch and Dr. Daniella Goldberg.

8:30 am	Introduction by the NSW Premier, Bob Carr.				
THE	Session I LATEST RESEARCH.	Chaired by Prof. Bernie Tuch Diabetes Transplant Unit, POWH.			
8:40	Human embryonic stem cells for the treatment of neurological disorders. Ben Reubinoff, Hadassah University Hospital, Jerusalem.				
9:10	Endothelial progenitor cells for refractory ischaemic heart disease. Jason Kovacic, The Victor Chang Heart Institute.				
9:30	Prospects of repairing myelin with stem cells. Rosanne Taylor, Dept Veterinary Science, Sydney University.				
9:50	Converting embryonic stem cells into insulin-producing cells. Lily Bai, Diabetes Transplant Unit, Prince of Wales Hospital.				
10:10	Cardiomyocytes derived from human embryonic stem cells. Christine Mummery, University of Utrecht, Netherlands.				
10:40	MORNING TEA BREAK				
WHAT'S HA	Session II APPENING IN AUSTRALIA?	Chaired by Prof. David Martin The Victor Chang Cardiac Research Institute.			
11:10	A summary of the science presented at the First Stem Cell Conference. Prof. Alan Trounson, National Stem Cell Centre.				
11:30	The educational role of the National Stem Cell Centre. Graham Jenkin, National Stem Cell Centre.				
11:50	The Stem Cell Licensing Committee. Tony Rolfe, National Health and Medical Research Council.				
12:10	Intellectual Property and human embryonic stem cell lines. Tom Gumley, Freehills Carter Smith Beadle				
12:30	LUNCH SERVED				

Human Embryonic Stem Cells For The Treatment of Neurological Disorders

Hadassah's world renowned human embryonic stem cell research group led by Prof. Ben Reubinoff is focused on developing cell therapy cures for Parkinson's and other neuro-degenerative diseases.

Eventually every patient with Parkinson's disease reaches a stage where medications stop working and their life becomes pure misery. Anyone who knows such a patient is affected. A new source of hope for patients with Parkinson's and other neuro-degenerative diseases comes from the emerging field of cell therapy. In this new envisioned therapy, a neuro-surgeon will be able to order vials of neural cells and inject them into the damaged part of the brain, where they will grow and replace the functions lost by dead and dying brain cells.

The challenge for both neuroscientists and biotech industry is to produce neural cells that have the special properties required for regeneration of lost brain tissue and to produce them in quantities sufficient for therapeutic treatments. A particularly promising source of these cells is human embryonic stem cells that have been grown under conditions that guide them to develop into dopamine producing neurons.

Further Reading:

http://english.hadassah.org.il/departments/gen_ther/groups_esc.htm



Benjamin Reubinoff M.D., M.Sc.

Hadassah University Hospital

Ben was born in Jerusalem Israel, in 1959. He is married and father of two and heads the research group on human embryonic stem cells: A new avenue for treatment of human diseases at The Goldwyne Savad Institute of Gene Therapy, Hadassah University Hospital.

Education

- M.D. Hebrew University Hadassah Medical School, Jerusalem.
- M.Sc. in neurobiology, Hebrew University Hadassah Medical School.
- Residency in Obstetrics and Gynaecology, Hadassah University Hospital.
- Studies for a PhD degree at Monash University, Victoria, Australia

Research Interests

- Human embryonic stem cells growth and differentiation.
- The utilization of human embryonic stem cells for cell and gene therapy, gene discovery and for the study of early human development.
- Nuclear transfer and reprogramming.
- Genetic aspects of reproduction.

Clinical Interests

- Male and female infertility;
- In vitro fertilization (IVF) and other assisted reproductive technologies (ART) for the treatment of male and female infertility problems.
- Preimplantation genetic diagnosis (PGD) for the prevention of inherited diseases including sex-linked conditions.
- Reproductive endocrinology.

G-CSF Mobilised Autologous Endothelial Progenitor Cells For Refractory Ischaemic Heart Disease



Although The Victor Chang Cardiac Research Institute conducts research into all forms of heart disease, it has as a primary focus "the prevention, diagnosis and treatment of heart muscle diseases". Unique amongst the organs of the body and in contrast to other muscle tissues, the heart is fatigue resistant; it contracts approximately 70 times a minute, 100,000 times a day, two and a half billion times a lifetime. Although the first organ to begin functioning during embryonic life, heart muscle cells unfortunately are unable to divide after birth and thus, unable to repair injured heart tissue.

It is only recently with the development of powerful new research approaches involving molecular, cellular, developmental and structural biology that these illnesses can now begin to be addressed in a fundamental way.

The Victor Chang Institute is at the point of commencing an ambitious human clinical trial using embryonic stem cells. This presentation will touch on the current literature and present an overview of the trial design and execution of a clinical phase 1 human cardiac stem cell project titled "G-CSF mobilised autologous endothelial progenitor cells for refractory ischaemic heart disease". This trial will utilize both G-CSF and CD-133+ cells in an attempt to ameliorate chronic angina and myocardial dysfunction in a group of patients with ischaemic heart disease not amenable to any other form of revascularisation therapy.



Jason Kovacic B.Med.Sc., M.B, B.S PhD student, The Victor Chang Cardiac Research Institute

Jason gained his tertiary qualifications at the University of Melbourne. He is currently a PhD student with Bob Graham and Richard Harvey at The Victor Chang Cardiac Research Institute, as well as a Cardiology Fellow at St Vincent's Hospital. He has been a cardiology trainee at St Vincent's Hospital for three years. In 2003 Jason will complete his FRACP in Cardiology, whilst concurrently commencing a PhD in stem cell research at The Victor Chang Institute. The PhD will comprise a clinical component under the supervision of Bob Graham, which will be presented. There will also be a molecular/ laboratory component to the PhD, which Richard Harvey will supervise.

Prospects of Repairing Myelin with Stem Cells

Stem cells from a range of sources have potential for treating myelin disorders in the brain. Recent studies demonstrate the capability of neural stem cells in mediating myelin repair in mouse models of dysmyelination and immune mediated damage. While neural stem cells are the natural choice for implantation in the brain, due to their capacity for migration, differentiation and appropriate function, other stem cell sources are emerging with potential.

Our studies centre on stem cell transplantation combined with gene transfer for cell marking and modulation of the local conditions in the brain to promote repair. Using a severe, progressive model of demyelination we have demonstrated extensive engraftment, migration, differentiation and function of neural stem cells. We are also investigating other stem cell sources; marrow derived and treated embryonic stem cells in this model.



Rosanne Taylor Senior Lecturer, Dept Veterinary Science, Sydney University

Rosanne Taylor is a Veterinary Science graduate of the University of Sydney (1982) who worked in large animal veterinary practice (awarded a DVCS) before completing a PhD on treatment of a lysosomal storage disease by bone marrow transplantation. She was a Veterinary Officer and Branch Manager of NSW Animal Welfare Branch (NSW Government), implementing animal research legislation, before a postdoctoral fellowship in gene therapy at the University of Pennsylvania. Her work provided early evidence of the value of stem cell and gene therapy for treating severe brain disease (published in Nature, Nature Medicine).

Rosanne returned to Sydney University in 1994 and is now an associate professor, teaching in neuroscience, physiology, animal biotechnology and animal science. She is active in researching and improving University teaching, completing a Graduate Certificate in Higher Education. She received the Pfizer Teaching Award and Grace Mary Mitchell Award in 2001, the Vice Chancellors Award for Outstanding Teaching in 2002 and was a national finalist in biological sciences category for the Australian University Teaching Awards in 2002. Rosanne is Chair of the Faculty Teaching and Learning Committee and leads an education innovations project in the Faculty to develop activities that support learning through inquiry in veterinary and animal science. Rosanne is researching treatment of demyelinating disease with a variety of stem cell and gene therapy approaches and investigating enzyme replacement therapy for lysosomal disease. Her research achievements were recognised by the Australian College of Veterinary Sciences Ian Clunies Ross Award in 1999.

Converting Embryonic Stem Cells into Insulin-Producing Cells



Lijun BAI, Graham MEREDITH, Pauline KHOURY& Bernard E TUCH Diabetes Transplant Unit, Prince of Wales Hospital, Sydney, Australia

Embryonic stem (ES) cells have the ability to proliferate while remaining in an undifferentiated state, thus providing a potentially unlimited source of cells for medical/scientific purposes. ES cells are pluripotent, having the capacity to develop all cell lineages, ecto-, meso- and endoderm. Endodermal cells represent a source of pancreatic stem cells that can develop into insulin-producing cells.

This project aims to convert mouse ES cells into insulin-producing cells by varying culture conditions using a modification of a 5-stage method previously described (Science 2001; 292: 1389-94). The novel strategy of this approach is the addition of a gut hormone, glucagon-like peptide-1 (GLP-1) at stage 5 to enhance differentiation. We have demonstrated that GLP-1 promotes the differentiation of □ cells from fetal pancreatic precursor cells (Endocrinology 2002; 143: 3505-14).

Cell development was characterized at each stage of culture by gene expression, using markers specific for pancreatic development. mRNA for pancreatic transcription factors PDX-1 and NeuroD was detected from stage 1, HNF3 and insulin 2 from stage 2, GLUT2 from stage 3 and other cell markers at stages 4-5. Addition of GLP-1 (100nM) in addition to nicotinamide (10 mM) at stage 5 resulted in a 50% increase in insulin content compared with nicotinamide alone. Insulin secretion, following addition of both growth factors, was enhanced 4-fold when exposed to 20 mM glucose. However, when stage 5 cells, treated with both growth factors, were transplanted under the renal capsule of NOD-SCID mice, all mice developed teratomas. Teratomas display features of tissues arising from 3 germ layers.

We conclude that it is possible to convert mouse ES cells into glucoseresponsive insulin producing cells by varying the culture conditions, and addition of GLP-1 enhances this conversion. The culture conditions need to be optimized to enhance efficiency of this conversion



Dr. Lily Bai
Diabetes Transplant Unit,
Prince of Wales Hospital

Lily is a clinician who trained and worked in Beijing China before migrating to Australia in 1996 to do a PhD looking at the effect of human cytokines on fetal pig pancreatic beta cells. As a post-doctorate at the DTU, Lily is now involved in cutting edge embryonic stem cell research as well as continuing to do research following on from her PhD project.

Cardiomyocytes Derived From Human Embryonic Stem Cells

Christine Mummery studied Physics at the University Of Nottingham, UK followed by a PhD in Biophysics at Guy's Hospital Medical School, London. She moved to the Hubrecht Laboratory in the Netherlands as a postdoc to study the differentiation of neuroblastoma cells and regulation of the cell cycle. In 1981 she introduced mouse embryonal carcinoma cells into the laboratory and 3 years later human embryonal carcinoma cells. This was largely in collaboration with Drs C. Graham, J. Heath and M. Pera in Oxford. In 1985 derived mES cell lines with Dr C. Stewart, then at the EMBL in Heidelberg, and introduced that technology to the Hubrecht Laboratory. These cells were used for the studying control of growth and differentiation in early development.

In November 2000, collaboration with Dr M. Pera and A.Trounson in Melbourne was re-initiated to study human embryonic stem cells, which they had as second in the world derived successfully. Their hES cell lines were introduced into the Netherlands at the end of that year to study mesoderm differentiation. First results on cardiomycoyte differentiation of hES cells were published recently (Mummery et al, 2003).



Christine Mummery
University of Utrecht
The Netherlands

Christine Mummery obtained a PhD in Biophysics at the University of London in 1978. She then worked as a post-doc at the Hubrecht Laboratory, the Netherlands Institute for Developmental Biology (http://www.niob.knaw.nl/) where she became interested in mechanisms of differentiation in early embryonic development. In 1993 Christine Mummery became group leader in the Hubrecht Laboratory she has recently been appointed as Professor of Cardiovascular Development at the Faculty of Medicine, University of Utrecht.

Her current research focuses on the functional analysis of TGFB signalling in early differentiation in mammalian development using transgenic and knock out mouse embryos, and cultures of human and mouse embryonic stem cells and embryonal carcinoma cells as model systems. More recently, her research has also addressed the possible use of human stem cells as a source of cardiomyocytes for transplantation to infarcted or ischemic hearts. More information about these research interests including a selection of papers is the of available on web site the Hubrecht Laboratory (http://www.niob.knaw.nl/researchpages/mummery/mummery1.htm).

In addition, Christine Mummery also functions as spokesperson for the Netherlands Institute of Developmental Biology on human embryonic stem cell technology (see a recent interview in NRC Handelblad: http://www.nrc.nl/nieuws/binnenland/1007015542165.html).

The Science Presented at the First Stem Cell Conference. (Melbourne, 9 – 12 October, 2003)



The National Stem Cell Centre (NSCC) is a major Australian collaborative initiative uniting many of the country's leading academic researchers with the biotechnology industry to develop innovative therapeutic products to treat a range of serious injuries and debilitating diseases.

The Centre continues to build on Australia's existing expertise in stem cell and related platform technologies to lay the foundations for delivering stem cell therapies. The NSCC also runs a variety of conference and symposia for scientists and health professionals, as well as public lectures.

The First National Stem Cell Centre Scientific Conference titled "Stem Cells and Tissue Repair" was held in Melbourne on Oct 9-12. A major international event in the field of Stem Cell Research, the conference has attracted many highly respected scientists and is potentially a very important discussion for the field. As a satellite event, the 3rd Stem Cell Workshop is thrilled to present two international speakers from the conference, Christine Mummery and Ben Reubinoff.

Professor Alan Trounson will present a summary of the science presented at the conference. **Major themes covered included**;

Human embryonic stem cells ¥ Adult stem cells: biology and application ¥ Stem cell signalling pathways ¥ Laboratory techniques for isolation and propagation of human embryonic stem cells ¥ Use of markers for characterisation of stem cell populations ¥ Transplantation tolerance ¥ Use of stem cells for treatment of diabetes and of neural disorders ¥ Commercialisation of stem cell science ¥ Differentiation of embryonic and adult stem cells ¥ Guidelines for human embryonic stem cell research ¥ Tissue engineering and clinical applications ¥ Community perspectives and scientific education



Prof. Alan Trounson

Founder and Executive Vice Chairman Global Science Strategic Advisor National Stem Cell Centre

Alan Trounson, Ph.D., is Professor of Stem Cell Sciences and Director of the Centre for Stem Cells, Immunology and Tissue Repair at Monash University. He is the Founder and Executive Vice Chairman of the National Biotechnology Centre of Excellence – 'National Stem Cell Centre', as well as Global Scientific Strategy Advisor.

His scientific accomplishments include; the pioneering of human in vitro fertilisation (IVF) and associated reproductive technologies; the diagnosis of inherited genetic disease in preimplantation embryos; the discovery and production of human embryonic stem cells and their ability to be directed into neurones, prostate tissue and respiratory tissue. His present research interests are focused on human embryonic stem cells and their suitability for transplantation for the treatment of inflammatory lung disease and cystic fibrosis.

The Educational Role of the National Stem Cell Centre

The NSCC's education program provides academic educational services and promotes public understanding of research in stem cells and tissue repair. It is committed to providing the wider community with information on related legal, social and ethical issues.

Education is a crucial aspect for the NSCC's reputation and that of the associated members. The training of outstanding scientists, business people and information managers is essential in developing valuable intellectual capital and supporting growth of the biotechnology industry in Australia. The CEdO, Dr Graham Jenkin, will implement the education program, the components of which will be developed by an Education Committee.

The Centre will attract the very best students from Australia, as well as from other countries, to pursue training in stem cell and related biotechnologies in the nodes within the Centre. This will be facilitated by the provision of postgraduate scholarships and postdoctoral fellowships to outstanding applicants.

The NSCC also runs a variety of conference and symposia for scientists and health professionals, as well as public lectures, particularly those which foster the ethics debate.



Graham Jenkin
Chief Education Officer, National Stem Cell Centre.

Professor Graham Jenkin has worked for many years in both a research and teaching capacity in the Department of Physiology at Monash University. A respected reproductive biologist and Fellow of the Institute of Biology, Professor Jenkin's studies have led to important observations on the development and control of ovarian function, the restoration of fertility in women and endangered native species and the maintenance of fetal well being.

The Stem Cell Licensing Committee

Mr Rolfe will give brief outline on the role and functions of the newly established National Health and Medical Research Council Licensing Committee, and its consideration of applications for licences to use excess IVF embryos. This will include a description of relevant legislation, the expertise of the committee, procedural matters, and advice from the committee to applicants.

Tony Rolfe

National Health and Medical Research Council

Currently the Director of the Licensing & Evaluation Section within the NHMRC Centre for Compliance and Evaluation and in that position is also the Executive Secretary of the Embryo Research Licensing Committee of the NHMRC. Tony leads the secretariat group within NHMRC supporting the Licensing Committee and is directly involved in both the development and implementation of policies and procedures as well as the assessment and consideration of applications for licences to use excess ART embryos.

Tony has been with the NHMRC since early 1998 and, prior to taking up his current role late in 2002, he had been leading the team managing NHMRC Project Grants.

A long career with the Commonwealth has seen Tony working with the Department of Community Services and its amalgamation with the Department of Health. Prior to NHMRC, Tony spent five years managing the community education programs within the government's National AIDS Strategy focussing on Indigenous health issues and treatment and prevention research in HIV/AIDS, hepatitis and other communicable diseases

Intellectual Property and Human Embryonic Stem Cell Lines

As a consequence of the nature of stem cells and methodologies employed for studying these, stem cell researchers must give due consideration to patent infringement issues before embarking on a line of research activity. This presentation will cover the patent infringement issues that are particularly relevant to the stem cell sciences.



Tom Gumley
Senior Associate
Freehills Carter Smith Beadle

Tom is a Registered Patent Attorney in the biotechnology practice of Freehills Carter Smith Beadle, Sydney.

Tom's expertise is in patent protection of biotechnology intellectual property. He has particular experience in preparation, filing and prosecution of Australian and foreign patent applications, in critical review of patent specifications and in patent portfolio management including audit and review of intellectual property.

He provides patent attorney services to local start –up companies, universities and research institutes.

Tom was awarded a Bachelor of Science Honours degree in 1990 from the University of Melbourne. He was awarded a PhD from the Faculty of Medicine, University of Melbourne in 1993.

He is a registered patent and trade marks attorney and a Fellow of the Institute Of Patent And Trade Marks Attorneys Of Australia.

Thankyou to all those who attended today's workshop.

I welcome all feedback, comments and enquiries.

Sarah Walke
Events Manager, 3rd Stem Cell Workshop
NSW Stem Cell Network
swalke@bigpond.net.au
Mob. 0402 091 017
Ph. 02 9382 4840
www.diabetes.unsw.edu.au

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