NSW Stem Cell Network

9th Stem Cell Workshop

"Nuclear Reprogramming"

Tuesday 19, September 2006
12:30 pm to 5:30 pm
John M. Dwyer Lecture Theatre
Edmund Blacket Building
Prince of Wales Hospital
Randwick, NSW

Welcome to the 9th Stem Cell Workshop *supporting stem cell research and the emerging stem cell industry in Australia.*

The potential of adult and embryonic stem cells in science and medicine has become apparent in recent years. The prospect of deriving patient-specific and disease-specific embryonic stem cell lines to study disease cause, progression, diagnoses and treatment underscores the potential use of nuclear reprogramming in regenerative medicine.

Different reprogramming strategies have been used to induce the pluripotent embryonic state including somatic cell nuclear transfer commonly referred to as therapeutic cloning, cellular fusion, the use of cell extracts and culture-induced reprogramming.

Therapeutic cloning is currently banned in Australia, although legislation has now been tabled for review in Federal Parliament.

Come and find out how Australian scientists are researching alternative strategies in the first session.

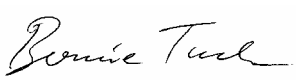
The second session promises to be lively with talks on the political and scientific debate surrounding the upcoming federal parliament decision on the future of therapeutic cloning in Australia. As well there will be a presentation on the recommendations of the Lockhart's Committee and findings from a recent Roy Morgan Poll on public perceptions of stem cells.

We would also like to thank our major sponsor Chemicon, and other sponsors Invitrogen, the Australian Stem Cell Centre, and Integrated Science for their commitment to supporting the NSW Stem Cell Network.

Thanks must also go to one of the leaders of our community, the Vice Chancellor of the University of New South Wales, Professor Fred Hilmer, AO, for agreeing to open the workshop.

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

Kind regards,



Sophie Diller ***Prof Bernie Tuch***
Manager ***Director***

NSW Stem Cell Network

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9th Stem Cell Workshop

Science and Politics of Nuclear Reprogramming

Presented by
NSW Stem Cell Network

12:30pm	Registration
1:00pm	Welcome **Professor Fred Hilmer AO, Vice Chancellor, University of NSW**
Session 1: NUCLEAR REPROGRAMMING TECHNOLOGIES Chair: Dr Kuldip Sidhu, Prince of Wales Hospital	
1:10pm	Lessons learned from different species about somatic cell nuclear transfer – would it be possible in humans? **Dr Teija Peura, Sydney IVF**
1:35pm	Autologous embryonic stem cells without SCNT; potential and hurdles **Dr Paul Verma, Monash Institute of Medical Research**
2:00pm	Disease-specific embryonic stem cells and inter-species nuclear transfer **Dr Tayfur Tecirlioglu, Monash University**
2:25pm	Afternoon Tea
Session 2: LEGISLATION, POLITICS AND PUBLIC PERCEPTIONS OF CLONING AND STEM CELL RESEARCH Chair: Professor Bernie Tuch, NSW Stem Cell Network	
3:00pm	Findings and Recommendations of the Lockhart Committee on cloning and stem cell research **Prof Loane Skene, University of Melbourne and Deputy Chair, Lockhart Committee**
3:25pm	Political debate in support of therapeutic cloning **Dr Mal Washer, Federal Member for Parliament**
3.50pm	Mad science or crazy politics **Dr Monique Baldwin, Research Scientist and Regulatory Affairs Associate**
4:15pm	Recent findings on public perception of stem cell research **Michele Levine, Chief Executive, Roy Morgan Research Pty**
4:40pm	Refreshments

LESSONS LEARNED FROM DIFFERENT SPECIES ABOUT SOMATIC CELL NUCLEAR TRANSFER –WILL IT BE POSSIBLE IN HUMANS?

The principle of cloning has a long history mainly in a horticultural context, as lovers of gardening will know, meaning duplication of a plant by taking a cutting and placing it in fertile soil or grafting it onto another plant.

The first report on successful Somatic Cell Nuclear Transfer (SCNT) leading to birth of Dolly the sheep shattered the firmly held paradigm about irreversibility of cellular differentiation and demonstrated cloning to be possibly also in the animal kingdom. Since then it has been shown that even the most terminally differentiated cell types can be reprogrammed to reverse back to a totipotent stage if provided with a suitable environment – equivalent of fertile soil. So far the only environment identified to induce comprehensive reprogramming is cytoplasm of an unfertilised oocyte.

In SCNT the nuclear material of the donor cell is transferred into recipient oocyte to replace the oocyte's own nuclear material; the "grafted" oocyte is activated to initiate subsequent cellular development. The critical events of de-programming and reprogramming of donor nuclei entail extensive modifications of introduced DNA, including exchanges and modifications of DNA associated proteins similar to the way sperm DNA is modified after fertilisation. Cell cycle compatibility between the recipient cytoplasm and donor nucleus plays a crucial role in controlling DNA replication in a timely manner. Other critical events involve re-activation of the donor genome and the kinetics of chromosome segregation and the first mitotic division. The latter can be influenced by the method of enucleation, as removal of oocyte nuclear material usually also leads to the removal of important chromosome associated factors needed in later development.

Although it is not the aim in human stem cell research, in animal experiments success in SCNT is defined as the production of viable offspring. After successful SCNT in sheep and cattle it took a few years to achieve success in mice and even longer with species such as the pig, rat, rabbit, cat, horse and dog. In most cases the underlying physiological events of the nuclear transfer itself were not inherently different or difficult, but the main problems lay in adapting the used methods to suit the normal reproductive physiology and development of the species in question. The first success in non-human primates was achieved in 1997 with embryonic blastomeres as nuclear donors; however, no offspring has been obtained so far with somatic cells.

Why, however, would we want to do this in humans? The answer is that we don't. We recognize the extreme hazards of such "reproductive cloning", and for this reason SCNT in humans is aimed only at producing early cloned cells and cell lines, genetically identical to the person providing the donor cell. This "therapeutic cloning" is needed for basic research into specific diseases by employing the unique characteristics of disease-specific embryonic stem cells, and in the future, for person-specific therapies.

The enthusiasm that followed the announced success in human SCNT and embryonic stem cell derivation in Korea in 2004 and 2005 soon transformed into disenchantment as the work was proven fraudulent. Less sensational but very solid science has been done both before and after

the Korean events, mainly in the USA and UK. At least two organisations have proclaimed development of human SCNT reconstructed oocytes to the stages where ESC derivation is possible. Likewise, development to similar stages has recently also been achieved with SCNT in rhesus monkeys, making the goal of obtaining SCNT-derived ESC lines in primates even closer to reality. Studies with human and non-human primates have detected few specific differences in the physiological peculiarities in these species, and since their identification it is only a matter of time and more studies to find ways around them – just like with any other species. However, research attempts are hampered by the lack of material and ethical sensitivities, both in primate and human area.

Dr Teija Peura

Senior Research Scientist, Sydney IVF

Dr. Teija Peura has been involved in several aspects of animal and human embryology since starting her research career at the University of Kuopio in her native country Finland. Her work on cattle transgenesis by pronuclear DNA-microinjection culminated in the first reported birth of transgenic dairy cattle from transgene-analysed and sexed embryos produced in vitro. This work, aimed at therapeutical protein production in the milk of transgenic cattle, eventually led to the biotech company established by the university team being acquired by a Dutch biotechnology company Gene-Pharming.

At about this time in 1994 she migrated to Australia to work with Prof. Alan Trounson at the Monash University in Melbourne on cattle embryonic cloning – these were times before Dolly the sheep and pre-implantation stage embryos were still generally used as nuclear donors. After five years and several cloned calves later she made the move to somatic cell nuclear transfer in sheep, at the South Australian Research and Development Institute (SARDI). After several years and SCNT lambs later in 2003 she moved to Sydney to join the expanding research department at Sydney IVF to establish human embryonic stem cell laboratory.

In Sydney she was in charge of derivation of Australia's first human embryonic stem cell lines, obtained within two months from receiving the first NHMRC embryo research licences under the *Research Involving Human Embryos Act 2002*. Most recently Sydney IVF scientists have moved stem cell activities closer to the clinical applications by deriving hESC lines under cGMP conditions with a Singapore based stem cell company. She has also been involved with collaborators in Europe in China in the area of human somatic cell nuclear transfer for stem cell derivation purposes.

AUTOLOGOUS EMBRYONIC STEM CELLS WITH OUT SCNT; POTENTIAL AND HURDLES

My talk will outline the concepts of cell therapy and highlight the anticipated issues of immuno-rejection of transplanted cells. In vitro approaches to produce patient specific cells by reprogramming of somatic cells without the use of SCNT will be discussed. In addition, I will present some of the work conducted in my lab on mouse models aimed at reprogramming somatic cells by fusion with ES cells.

Dr Paul J. Verma

Senior Scientist, Centre for Reproduction & Development, Monash Institute of Medical Research

Dr Paul Verma has worked on biotechnology in a number of species including mammals and fish. He obtained his PhD at Adelaide University and subsequently joined BresaGen Ltd, Adelaide in 1995, working on transgenesis and nuclear transfer aimed at developing pigs with organs suitable for xenotransplantation. He later joined the Luminis-BresaGen Cell Therapy Program, where he established a research program on cell reprogramming aimed at providing alternates to therapeutic cloning.

Dr Verma moved to Melbourne in 2001 and is continuing his research into reprogramming somatic cells, isolation and characterization of embryonic and adult stem cells in mouse, cow and human as a Senior Research Fellow at MIMR. He has published scientific papers and edited a book on transgenesis, cloning and stem cells, and is principal inventor on eight granted and provisional patents in the field of cell reprogramming and stem cells.

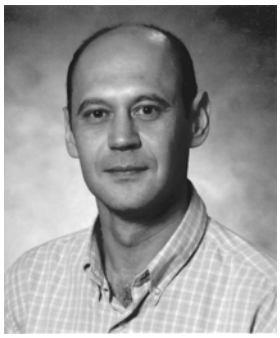
Recent peer review responsibilities include grant reviews for National Health & Medical Research Council of Australia, serving on the editorial board of Animal Reproduction Science and manuscript referee for several international journals. Dr Verma is Group Leader of a laboratory consisting of a dynamic team of 4 postdoctoral fellows, 6 research assistants and 6 postgraduate students.

DISEASE-SPECIFIC PLURIPOTENTIAL STEM CELLS (DS-ESC) AND INTER-SPECIES SOMATIC CELL NUCLEAR TRANSFER (ISCNT),

R. Tayfur Tecirlioglu and Alan O. Trounson

Disease specific pluripotential stem cells (DS-ESC) can be defined as stem cell lines that are derived from patients that have serious, complex disease (eg.cancers or neurodegenerative disease where the cause is unknown). Somatic Cell Nuclear Transfer (SCNT) is a technique whereby an egg is enucleated and a somatic cell nucleus from a patient is inserted into the egg to create a reconstituted SCNT embryo-like entity that is capable of generating DS-ESC. These reconstituted pluripotential stem cell lines can be used to interrogate the nature and cause of the disease (genetic, epigenetic or environmental cue) to develop a better understanding of the disease state and to develop new strategies to retard, block or reverse the expression of the disease. Many human diseases, such a Duchenne, muscular dystrophy, cystic fibrosis, and Huntington's Disease arise from a single gene defects. Millions of Australians are carrying a defective gene for these and other diseases and are at risk for passing it on to their children. These pluripotential DS-ESC can be derived from discarded embryos of patients undergoing preimplantation genetic diagnosis in IVF clinics. DS-ESC research can also provide an opportunity to study the expression of these diseases and how we may interfere with phenotype and severity of the disease state. Pharmaceutical and biotechnology companies now view these disease specific stem cell lines as an important resource to test the efficacy and safety of new candidate drugs.

Patient specific pluripotential stem cells may be tailored *ad personam* would constitute an extremely valuable histocompatible resource for therapeutic purposes. However, this could be demanding on resources and the need for large numbers of human oocytes. Utilization of eggs from other species which are accessible and abundant, such as the cow and rabbit, could resolve some of the efficiency issues relating to human SCNT to derive DS-ESC lines for *in vitro* drug discovery and disease prevention studies. The potential of inter-species SCNT (ISCNT) to generate DS-ESC lines may enable scientists to determine the nature of the egg cytoplasmic factors needed for reprogramming pluripotentiality of somatic cells, enable the determination the exact cause of complex diseases, develop new drugs and to generate new therapeutic approaches for containment of these diseases.



Dr Tayfur Tecirlioglu

Research Fellow, Monash Immunology and Stem Cell Laboratories (MISCL), Monash University, Melbourne, Australia

Dr. Tayfur Tecirlioglu completed his Doctor of Veterinary Medicine (University of Ankara, Ankara, Turkey), Master of Veterinary Science (Royal Veterinary College, London, UK), Master of Clinical Embryology (Monash University, Melbourne, Australia) and PhD (University of Queensland, Brisbane, Australia) in reproduction and embryology. He is co-inventor of patented "hand made cloning" method and obtained the World's first offspring derived from this method. His current research interests are: the derivation of both human and horse embryonic stem cells, and inter-species nuclear transfer in horses. He is currently a Research Fellow at Monash Immunology and Stem Cell Laboratories, Monash University in Melbourne.

FINDINGS AND RECOMMENDATIONS OF THE LOCKHART COMMITTEE ON CLONING AND STEM CELL RESEARCH

Professor Skene will discuss the recent report of the Lockhart Committee on Human Cloning and Embryo Research. She will explain the Committee's principal recommendations and the reasons for them. She will also respond to a number of frequently asked questions.

Prof Loane Skene,

Professor of Law University of Melbourne

Loane Skene came to the University of Melbourne in 1992 after working as a solicitor in Melbourne and England; and a policy adviser in Canada and Melbourne (10 years with the Victorian Law Reform Commission). She specialises in Health and Medical Law and is a Professor of Law in the Faculty of Law and an Adjunct Professor of Law in the Faculty of Medicine, Dentistry and Health Sciences. She is the author of two books: *Law and Medical Practice: Rights, Duties, Claims and Defences*, (1st ed, Butterworths, 1998; 2nd ed, Lexis-Nexis, 2004); and *You, Your Doctor and the Law* (OUP, 1990). She has also published numerous chapters in book and articles in Australian and overseas legal, medical and scientific journals.

Loane has served on many federal and state policy committees, especially in relation to the legal regulation of genetic testing. Her research interests also include the legal regulation of genetic testing, assisted reproductive technology and euthanasia. She is Deputy Director of the Centre for Law and Genetics at the University of Tasmania and the University of Melbourne; Program Director, Medical Ethics, Centre for Applied Philosophy and Public Ethics (CAPPE), Charles Sturt University and The University of Melbourne, and Board member, Australian and New Zealand Institute of Health, Law and Ethics (ANZIHLE), formerly the Australian Institute of Health, Law and Ethics (AIHLE).

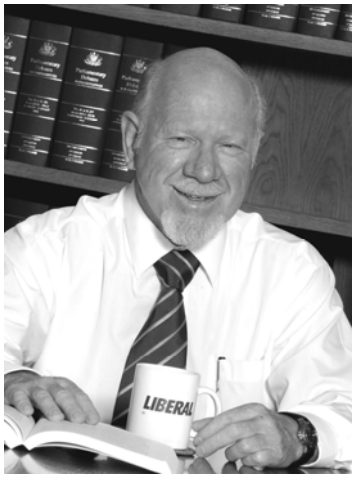
Her other University and Faculty responsibilities include President of the Academic Board of the University; and member of the Council of the University of Melbourne and Pro Vice-Chancellor of that University.

POLITICAL DEBATE IN SUPPORT OF THERAPEUTIC CLONING

Member for Parliament and liberal backbencher Dr Mal Washer has been at the centre of the political debate on the future of stem cell research and cloning in Australia and is one of government's strongest advocate of stem cell research. Since the Lockhart Review committee's findings were publicly released in February 2006, Dr Washer has actively lobbied for the report's recommendations to be fully implemented into national legislation. In particular he has relentlessly argued for therapeutic cloning also known as SCNT, to be legalised in Australia. Dr Washer firmly believes that Australian scientists should be allowed to use this technology to develop patient specific and disease specific stem cell lines.

Dr Washer's campaign became more determined after Prime Minister John Howard reportedly told Coalition MP on June 21 that cabinet had resolved to reject the recommendations of the Lockhart inquiry into stem cell laws and retain the status quo. Dr Washer led the backbencher descent in party room discussions during August parliamentary sittings that resulted in the Prime Minister retracting his earlier decision and announce on August 16 that therapeutic cloning recommendations would be decided on by conscience vote in Parliament before the end of the year.

The issue has divided coalition MPs and both camps have listened to experts briefings in efforts to sway their vote. With the release last week of a private member bill by Liberal backbencher Senator Kay Patterson and a second foreshadowed bill from Democrat Senator Natasha Stott Despoja, a senate committee has been set up to examine the bills. Federal Parliament could yet pass the bill allowing therapeutic cloning. As the situation changes daily, Dr Washer is well positioned to present at today's workshop the latest in developments from Canberra.



Dr Mal Washer

Federal Liberal Member for Parliament

Mal Washer completed his Bachelor of Medicine at the University of Western Australia and started practising medicine in the northern suburbs of Perth in 1972. He went on to establish several successful medical centres, including Seacrest Medical Centre, which is now one of the major single private primary care medical facilities in Australia. Mal's caring and dedicated manner resulted in him becoming one of the most sought after doctors in Perth. Mal's interest in horticulture saw the establishment of Avowest, one of the largest avocado farms in W.A which operates from the family property at Carabooda.

Mal has been a member of the Liberal Party since 1987. In October 1998, he was elected to the Federal seat of Moore, and was re-elected in 2001 and again in 2004. In November 2004 he was appointed Chair of the joint Parliamentary Standing Committee on Environment and Heritage. Mal is also a member of several other parliamentary committees, including the House of Representatives Standing Committee on Science and Innovation; Industry and Resources; Legal and Constitutional Affairs; and the Government Back Bench Policy Committee on Health and Ageing. He is also a member of Chinese Parliamentary Friendship Group.

Mal is passionate about science and innovation and the roles they play in keeping Australia competitive and at the forefront of research and development.

MAD SCIENCE OR CRAZY POLITICS

The average person is baffled by the stem cell debate. Blastocysts, mitochondria, cytoplasm, somatic cell nuclear transfer and dozens of other words are terms most people never even learned in high school science. But you don't need to be a research scientist to understand the importance of the ethical controversy which has put stem cells on the front pages of newspapers around the world.

Stem cell research is an exciting field with enormous potential for repairing damaged organs and body parts with human stem cells. A lot of progress has been made using adult stem cells. However, most media attention is on embryonic stem cells and the urgent pressure to use them in treatments and perhaps cure chronic diseases that are currently untreatable.

Under existing Australian legislation experimentation is allowed on human embryos in excess from IVF programs. However, preparation of the human embryo for research remains a significant ethical obstacle for a substantial portion of the community. Since the licensing system was introduced in 2002 there have been no discoveries through this work to support arguments of an urgent need for somatic cell nuclear transfer, often called "therapeutic cloning".

In addition, cloning needs human eggs and extracting eggs from women involves an operation with its own risks.

There are no specific, credible reasons why Australia needs to approve therapeutic cloning. Last month in "Cell" it was reported that it is possible to "reprogram" an adult cell by providing it with a set of specific genes - 4 in number - and finish with cells that can behave virtually as ES cells in the tests that were applied. In a Commentary on the paper in the same issue of Cell by independent scientists from the Harvard Stem Cell group, a number of points of detail were raised, but they conclude that this work *"represents a significant step toward a rational approach for generating patient-specific ES cell lines that could be used either as a source of autologous tissue for transplantation or for modelling different diseases. This method is encumbered by neither the logistical constraints nor the societal concerns presented by somatic cell nuclear transfer"*.

Science and ethics have unfairly been portrayed in this debate as being opposed to one another. But good science is ethical science. This recent publication illustrates how rapidly good science is progressing within the legislative boundaries already existing in Australia.

Dr Monique Baldwin

Research Scientist and drug regulatory affairs associate

Monique Baldwin has a PhD in neuroscience and works as a drug regulatory affairs associate for a pharmaceutical company, facilitating approval for patients to access new therapies in Australia.

RECENT FINDINGS ON PUBLIC PERCEPTIONS OF STEM CELL RESEARCH

Roy Morgan Research has been conducting surveys on public perception of IVF technology since 1981 and stem cells since 2001. These long running data set provides useful insights into changing perceptions of Australians. The latest survey released on June 21 this year provides public perception data on the use of excess embryos, adult and embryonic stem cell research.

MICHELE LEVINE

Chief Executive Officer, Roy Morgan Research

With over 20 years of experience in the field of research, Michele Levine has designed and implemented hundreds of surveys and research programs. For the last 12 years as CEO of Roy Morgan Research, Michele has directed and been responsible for the quality of the research conducted at Roy Morgan Research.

Michele Levine refocused and re-engineered Roy Morgan Research to achieve 100% growth in 4 years, ISO 9001 accreditation, and to prepare the company for international commercialisation of its core product, a single-source database research tool that tracks the media and product/service consumption habits and opinions in Australia (a database of about 55,000 respondents annually), in New Zealand , USA, UK and Indonesia.

NSW Stem Cell Network

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