ASSCR
THE AUSTRALASIAN SOCIETY FOR STEM CELL RESEARCH

Volume 3 Issue 1

November 2010

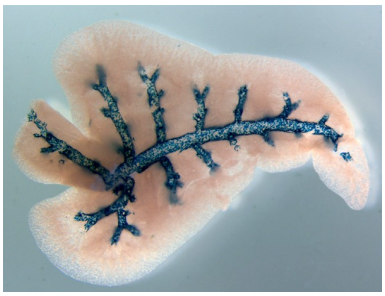
Professor Brigid Hogan to speak at AH&MRC

The ASSCR annual conference will this year be part of the Australian Health and Medical Research Congress being held in Melbourne from the 14th – 18th of November. This year we are delighted to have Professor Brigid Hogan, Chair of the Department of Cell Biology at Duke University, as the ASSCR invited plenary speaker.

Professor Brigid Hogan

Professor Hogan's research focuses on the basic mechanisms underlying organogenesis and tissue regeneration of the lung. She has used genetic lineage labeling techniques to identify a population of multipotent progenitor cells in the tips of the growing buds in the lung that give rise to all the specialized epithelial cell types of the adult lung. Professor Hogan has published seminal papers showing that epithelial basal cells in the mouse trachea and human airways behave as stem cells— by lineage tracing she has shown that these cells both self renew and give rise to secretory and ciliated cells, and have all the hallmarks of classical multipotent tissue stem cells. She has identified transcriptional profiles of these cell populations and characterised cell surface markers enabling her to define and purify human lung basal cells using FACS. She has also developed specialised culture conditions for these cells, providing an opportunity to assess the contribution of key genes to airway maintenance, remodelling and repair.

Professor Hogan has been chair of the Department of Cell Biology at Duke University Medical Center since the fall of 2002, and is the first woman to chair a basic science department at DUMC. She studied biochemistry at Cambridge University and did postdoctoral work at the Massachusetts Institute of Technology. Before moving to Vanderbilt University Medical Centre in Nashville in 1988, she was head of the Laboratory of Molecular Embryology at the National Institute for Medical Research in London. She came to Duke from Vanderbilt, where she was a Howard Hughes Medical Institute (HHMI) investigator and director of the stem cell and organogenesis program.



Section of lung from adult Scgb1a1-CreERx Rosa26lacZ mouse injected three times with Tmx to label mature and immature Clara cells in the airways (see Rawlins et al. 2009 Cell Stem Cell 4: 525-53.)

Professor Hogan's Talk is on Monday 15th November at 11.00am.

(Adapted from: dukemedicine.org, cellbio.duke.edu)

Inside this issue:

In Brief:

As always the Australasian Stem Cell Research Community is facing a number of challenges. Highlighted in this issue are imminent changes to the current legislation that governs our work. Megan Munsie and Justin St John look at the issues and legislation surrounding the use of iPS cells versus SCNT. They raise some key differences and pre-empt a possible movement against the use of SCNT. In our "in the news" section Garry Brook outlines the proposed changes to the Australian Therapeutic Goods Act and discusses what impact this might have on the translation of stem cell therapies, their advancement into the clinic and use in the broader community.

Finally, next week we have the 3rd annual ASSCR meeting being held at the 5th AHMRC in Melbourne. There is a very exciting program and I am sure all those attending will have a rewarding experience.

Louise Winteringham
Editor

Feature Article

Does SCNT still matter in an age of iPSC?

Megan Munsie[1] and Justin St John[2]
[1]Senior Manager – Research and Government, Australian Stem Cell Centre
[2]Professor and Director, Centre for Reproduction & Development, Monash Institute of Medical Research

During the review of the Commonwealth legislation in 2005, there was a sustained call from the Australian stem cell community to allow the creation of human embryos for embryonic stem cell research using the technique of somatic cell nuclear transfer (SCNT). At the time, this technique was seen by many scientists as the only means available to create stem cells with particular disease traits to enable disease modeling and advance drug development, as well as the potential to generate patient-matched stem cells for cellular therapies.

While the provision to allow SCNT technology was seen to be objectionable by some members of the Australian scientific community and a minority of the general public because of its reliance on human eggs and the creation of an embryo specifically for research purposes, the Legislative Review Committee recommended that the existing legislation should be amended to allow SCNT under strict regulation. After extensive parliamentary debate, and a rare conscience vote, legislation adopting this recommendation was passed in December 2006. To date three licenses have been granted in Australia by the NHMRC for projects using SCNT technology. However, no embryonic stem cell lines have been created in Australia, or indeed overseas, using this approach, despite significant endeavors. In addition, the public image of such research has been tarnished by the wrong-doings of Woo-Suk Hwang.

Around the same time that this significant change occurred in the Australian regulatory environment, Japanese scientists announced that they could create pluripotent stem cells in mice from adult somatic cells without the use of eggs or embryos, referred to as induced pluripotent stem cells (iPSC). In a relatively short period, scientists around the globe have extended this discovery to make human iPSC, refine the technology, create disease-specific stem cell lines, and develop platforms for drug screening and development.

Given the relative ease and accessibility of this technology, calls have been made to abandon SCNT research, and even the future derivation of human embryonic stem cells (hESC), in favour of iPSC. As we approach the fourth anniversary of the introduction of the amending legislation to allow SCNT in Australia, and the stipulated deadline for another independent review of the operations of the Acts, it is likely that such calls will intensify. However such a step should be viewed with caution. Comparative models allow us to determine the specific patterns and mechanisms associated with the normal default approach. For example, SCNT has aided understanding of epigenetic regulation of gene expression and transmission of mitochondrial DNA, and its segregation and replication during early differentiation and development. Reprogramming of somatic cells through SCNT opened the door to iPSC. Thus, it does not pay to be exclusive but recognise inclusivity drives scientific research and allows hypotheses to be tested in multiple experimental systems. Indeed recent studies indicate that nuclear transfer derived ES cells are more similar to "classical" embryonic stem cells than iPSC.

Rather than abandon SCNT, Australian scientists need to retain the possibility of pursuing this avenue of investigation as required. We only need to look at the recent developments associated with iPSC, unexpected by many, to see that we cannot always predict where the next line of enquiry will take us. Removing or altering the provision to conduct SCNT research in Australia would be a retrograde action which we consider ill advised.

When thinking about the forthcoming review there is another matter worth considering. Should Australian scientists be able to use animal eggs in human SCNT research? This was originally recommended by the Legislation Review Committee in 2005 but did not make it into the amended legislation because of concerns raised regarding the reliance on animal eggs and potential exploitation of animals. While the use of animal eggs offers the potential to generate human embryonic stem cells, there are concerns about mixing human and animal DNA as a small amount of animal mitochondrial DNA would remain in the cytoplasm of the egg

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after its chromosomes had been removed. However, the scientific community possesses sufficient knowledge to resolve such an issue, whereby any resultant embryonic stem cells would consist of human only DNA. The ability to utilise such approaches would bring Australian legislation into alignment with UK legislation and enable us to identify the all-important factors necessary to improve the process of generating stem cells in a non-egg environment.

Over the next six months, it is likely that you are going to be asked what you think about the current legislation governing the use of human embryos in research. We believe the current legislation provides appropriate safeguards for the Australian community yet allows researchers to pursue legitimate lines of enquiry, except for derivation of animal/human SCNT. What do you think?

1. Legislation Review Committee Reports, December 2005 http://www.nhmrc.gov.au/_files_nhmrc/file/research/embryos/review/legislation_review_reports_full_doc_19dec05.pdf
2. In a poll conducted by Research Australia in 2006, 18% of Australians oppose the use of SCNT for health and medical research with 58% supportive and remainder neutral or non-committed. http://researchaustralia.org/content/documents/e_OpinionPoll2006.pdf
3. *Research Involving Human Embryos Act 2002* and the *Prohibition of Human Cloning Act 2002*.
4. The *Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Act 2006* (formerly known as the Patterson Bill) amended the 2002 Acts.
5. http://www.nhmrc.gov.au/research/embryos/monitor/database/index.htm
6. Holden (2005) *Science* 310:1402-1403.
7. Takahashi *et al* (2006) *Cell* 126: 663–76.
8. Yu *et al* (2007) *Science* 318:1917-20 and Takahashi *et al* (2007) *Cell* 131:861-72.
9. Yusa *et al* (2009) *Nat Methods* 6:363-9.
10. Park et al (2008) *Cell* 134:877-86.
11. Ebert and Svendsen (2010) *Nat Rev Drug Discov* 9:367-72.
12. http://www.telegraph.co.uk/science/science-news/3314696/Dolly-creator-Prof-Ian-Wilmut-shuns-cloning.html
13. Kim *et al* (2010) *Nature* 467:285-290.

ASSCR at Australian Health and Medical Research Congress 2010

The ASSCR 3rd Annual Meeting will be held as a part of the 5th Australian Health & Medical Research Congress 2010. This allows us to co-organise a number of sessions with other societies participating in the Congress and will provide members with greater opportunities to discuss progress in stem cell research as well as to network. Session themes include: Repairing Heart, Lung Regeneration & Stem Cells, Cellular Origin of Gastrointestinal Cancers, Stem Cells and their Environment. One session will be dedicated to speakers invited from submitted abstracts. There will also be a Poster Session.

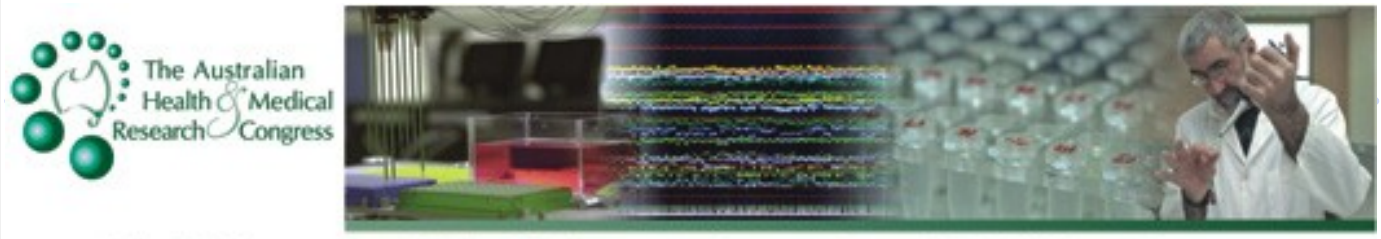
Our Plenary Speaker this year is Professor Brigid Hogan, Duke University, USA. Professor Hogan studies lung development during embryogenesis and a role the stem cells play in adult lung repair.

We are also very pleased to have the following international session speakers presenting this year: Kenneth Chien (Harvard University, US) - Cardiac Stem Cells; David Tosh (University of Bath, UK) - Transdifferentiation; Phillip Crosier (University of Auckland, NZ) - Hematopoietic Stem Cells in Zebrafish; Vivek Mittal (Cornell University, US) - Tumor Growth and Metastasis.

For a full list of speakers please visit the ASSCR website http://www.asscr.org

In addition to the symposia, the ASSCR will host a panel discussion – *Is Regenerative Medicine Lost in Translation?* Stem cell researchers, biotech professionals and clinicians will discuss what areas of regenerative medicine are close to clinical or pharmaceutical outcomes. How feasible will this be in Australia and New Zealand? Is this research ready for translation?

This is shaping to be another exiting and stimulating meeting, make sure you mark 14 – 16 November in you diary and we look forward to seeing you in Melbourne.



CALL FOR EXPERTS IN THE SPECIFIC AREAS OF STEM CELL RESEARCH

While general media queries about ASSCR, stem cells and ethics etc can be addressed by the members of the following committee, if you would like to engage with media on your specific field of stem cells, please provide your name, area of expertise and contact details (please indicate your contact details that should appear on the ASSCR web site) to the undersigned ASAP:

Thanks for your cooperation

Kuldip Sidhu
(Communications Officer Australia)
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Media Liaison, Public Education/ Communication Committee

In the news:

Changes to the Australian Therapeutic Goods Act Legislature; Impact on Stem Cell Therapies

A/Prof Gary Brooke

Mater Medical Research Institute, Mater Hospital, South Brisbane, Queensland

There has been some debate recently about proposed new changes in the Australian legislation for therapeutic goods. These proposed changes will have effects on the way biologicals and in particular stem cells are prepared that are destined to be therapeutic goods. In Australia, control of therapeutic goods is currently overseen by the Therapeutic Goods Administration (TGA). The main role of the TGA is to ensure that therapeutic goods are safe, of an acceptable standard and have efficacy. At the same time, this is balanced with the aim of ensuring that Australians have access to therapeutic advances. To achieve this, the TGA also allows clinical trials of novel therapies to test their safety and effectiveness.

The current Therapeutic Goods Act was passed in 1989 and requires that any therapeutic good was listed in the Australian Register of Therapeutic Goods (ARTG). There were some exceptions and exclusions to this e.g. whole organ transplants, but most medicines and medical devices were included.

In Australia, few cell therapies (let alone stem cell therapies) are currently recognised as "approved" therapeutic goods and therefore registered on ARTG. Perhaps the best example of a stem cell in use is the haematopoietic stem/progenitor cells that are used for bone marrow and blood reconstitution following chemotherapy. However, haematopoietic stem cells can be prepared from mobilised blood, bone marrow or from cord blood with fairly minimal manipulation. Experimental therapies including stem cell therapies are currently classed as "unapproved" therapeutic goods and are exempt from ARTG registration. However, for registration with ARTG, problems start arising when more extensive manipulation of cells is required prior to their use as therapeutics.

Advances in technology and scientific knowledge in many areas of biology have increased the prospects of success for these types of therapies in the clinic, but there is also an increased risk associated with the complexities of their production and usage. As such, a revised biological framework was thought to be needed in Australia. In particular, the safety implications meant that tighter regulation of therapies registered on the ARTG was thought to be required. The legislation for this is currently passing through parliament and is expected to be implemented in the near future (2010/11). Therefore, the effects of these changes in legislation on the use of cellular therapies are imminent.

As part of the framework, biological goods (including stem cells) will be divided into four main classes based on risk factor, where risk factor is generally determined by either the extent of manipulation required, or whether the product is to be used in a manner other than its original biological function. These classes will determine the level of control that is required for registration with the ARTG. The classes are divided as such:

There has been some confusion amongst scien-

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Class	Level of Manipulation	Level of compliance
Class 1	Minimal manipulation of the biological; e.g. not banked or processed	Compliance with standards is declared.
Class 2	Minimal processing of the biological; e.g. it is banked/stored, but not otherwise processed	Compliance with standards should be demonstrated and GMP conformance is required for their manufacture.
Class 3	Manipulation of the biological is sufficient to alter the structure or properties of the cells/ tissue. However, the cells/tissue will still be used for original biological function.	Safety, quality and efficacy has been demonstrated and GMP conformance is required for manufacture
Class 4	Tissue is processed in a manner that deliberately manipulates its biological properties, or the intended use is not its original biological function.	Demonstration of safety, quality and efficacy, including clinical data and analysis, GMP conformance is required for manufacture

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tists and clinicians involved in clinical trials about how this legislation will affect them. Biologicals undergoing clinical trials are currently, and will continue to be, exempt from ARTG registration, but will still be required to be registered with the TGA. Two types of exemption exist; the clinical trial notification scheme (CTN) and the clinical trial exemption scheme (CTX). The TGA states that; "*application under the Clinical Trial Exemption (CTX) scheme (or notification under the CTN scheme) is required for clinical investigational use of: any medicine or device not entered in the ARTG, including any new formulation of an existing product or any new route of administration; or a marketed medicine or device beyond the conditions of its marketing approval, including new indications extending the use of the product to a new patient group and the extension of doses or duration of treatments outside the approved range. A sponsor cannot commence a CTX trial until: written approval has been received from the TGA regarding the application; and approval for the conduct of the trial has been obtained from an ethics committee and the institution at which the trial will be conducted.*"

Stem cell therapies generally require considerable manipulation prior to their use and are often used for purposes other than their original biological function (e.g. the use of mesenchymal stem cells to treat graft-versus-host-disease). As such, these will be considered class 4 biologicals and will require CTX notification from the TGA for clinical trials. It is my understanding that an incremental approach will be implemented by the TGA for control of therapies in CTX trials that gradually brings them in line with standards required for registration on the ARTG as a class 4 biological. As stated above, CTX trials will always require written approval from the TGA and will require approval from a human research ethics committee. Initial testing (e.g. phase I safety trials), in general will not require any further standards other than good laboratory practise (GLP). However, later trials (some phase II and possibly all large scale phase III/IV efficacy trials) will require manufacturing conditions to conform to good manufacturing practise (GMP) standards. Conforming to the GMP standards means that a "Quality System" is in place, whose role is to ensure safety and accountability at every stage of manufacture. This is a very robust and rigorous system that requires purpose built facilities and highly qualified staff, and as such, it is also an order of magnitude more complex and expensive and not lightly undertaken. However, I suspect that the exact nature of the levels of control required will most likely have to be dealt with on an individual basis with the TGA.

To assist with the increased costs associated with these later phase clinical trials, and to assist in the short-fall of facilities that meet the rigorous standards required, the Australian Federal Government has provided $7.6m in funding over four years for a non-profit company called Research Infrastructure Support Services (RISS). The aim of RISS is to promote investment in infrastructure for manufacture of human cell and cellular based products for therapeutic use. Research centres are already benefiting from this small, but welcome investment in the future of cellular therapies in Australia. However, with the rapidly increasing numbers of translational research centres being built in Australia, it remains to be seen what type of funding model will emerge that will ensure that these facilities are used to their maximum potential. Clearly, the overstretched NHMRC will not suffice in support of translational research. Do we rely on investment from the private sector? My feeling is that this will not happen without a big boost from venture capital and large pharmaceuticals who have a relatively small presence in Australia. These companies in turn will not invest in Australia unless they feel that there is a solid base of research expertise, facilities and most importantly, novel stem cell therapies. Hopefully supporters of translational medicine in Australia such as the Australasian Society for Stem Cell Research and the Australian Society for Medical Research can assist the government in deciding how best to encourage investment to develop our future potential in this exciting area.

Further information can be found at these web sites;

1. Therapeutics Good Administration (TGA) http://www.tga.gov.au
2. Implementation of the Biologicals framework http://www.tga.gov.au/bt/hct.htm
3. Regulation of blood and tissues http://www.tga.gov.au/bt/index.htm
4. Clinical trials in Australia http://www.tga.gov.au/ct/index.htm
5. Australian New Zealand Clinical Trials Registry http://www.anzctr.org.au
6. Research Infrastructure Support Services (RISS) http://www.rissltd.com

Meeting report

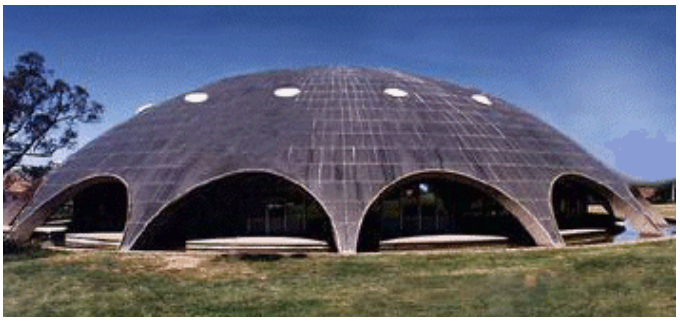
The 2nd Annual Meeting of the Australasian Society for Stem Cell Research November 2009

The 2nd Annual Meeting of the Australasian Society for Stem Cell Research (ASSCR) was held at the Shine Dome in Canberra, the headquarters of the Australian Academy of Science, on 22nd- 24th November 2009.

The resounding success of our first 'stand alone' meeting was evidenced by the large number of participants. The meeting attracted 188 delegates from Australia, New Zealand and Singapore, including 44 students; to assist young researchers to participate in the meeting, the Society funded ten conference travel awards. Such a large audience was a clear indication that more and more researchers in our region are becoming involved in cutting-edge stem cell science. It was great to see so many people, many of them students and early career researchers, come to this meeting to celebrate their passion for stem cell research.

The meeting was officially opened by Professor Warwick Anderson, the Chief Executive Officer of the National Health and Medical Research Council of Australia. Over the two days there were 26 oral and 74 poster presentations covering diverse areas such as regeneration, embryonic, adult and cancer stem cells, new technologies as well as ethical issues surrounding stem cell research and use. Two plenary talks were given by prominent speakers: Professor George Yeoh from the University of Western Australia, and Professor Huck Hui Ng, from the National University of Singapore. As part of the meeting, the ASSCR and the Australian Science Communicators hosted a public event in the Canberra Labor Club: "Stem Cells in the News – is it all Hype?"

The conference dinner was held at the Boathouse by the Lake and we were honored to have Professor Alan Trounson, President of the California Institute for Regenerative Medicine, as a guest speaker. Alan was given a challenging task to share his thoughts on progress and funding of Australian stem cell science in a current financial climate.



The Shine Dome, Canberra

The meeting achieved a significant trade and industry support with 24 trade representatives attending and demonstrating a wide range of tools for stem cell research.

The ASSCR awarded one prize for the best oral presentation by a student and two prizes for best poster presentation by an early career researcher and a student. Each prize consisted of $300 cheque, a free registration for the 2010 ASSCR meeting and a diploma. Congratulations to the 2009 ASSCR prize winners Rebecca, Katarina and Sebastian for their excellent presentations (see below)!

Overall this was an exiting and enjoyable meeting that provided ample opportunities for both formal and informal discussions, exchanging ideas and forging collaborations, as well as renewing old and making new friends. On behalf of the Organising Committee I would like to thank all those who attended and presented their work at this meeting.

I would like to acknowledge a generous sponsorship of the following companies: Applied Biosystems, Invitrogen, Millipore, Australian Stem Cell Centre, Lonza, Miltenyi Biotec and Cancer Council Western Australia.

I would also like to take this opportunity to acknowledge and thank the members of the Meeting Organising Committee and the meeting's secretariat, the ASN Events, for their endless energy and commitment during organization and running of the 2nd Annual Meeting of the ASSCR.

Anna Michalska
Chair, ASSCR Meeting Organising Committee

2009 ASSCR prize recipients

The best oral presentation:

Rebecca Neaves, a PhD student from Australian Stem Cell Centre and Monash University for her talk: "Murine hematopoietic stem cells and mature megakaryocytes in the endosteal stem cell niche".

The best poster presentation:

Sebastian Carotta, an early career researcher from Walter and Elisa Hall Institute for Medical Research for his poster: "Coordinating the intrinsic and extrinsic arms of hematopoietic lineage commitment".

Katarina Kollar, a PhD student from Mater Medical Research Institute for her poster: "Mesenchymal stromal cell migration towards CXCL12 and CCL7 can be enhanced in vitro".