

Stem cell central

AS CONTROVERSY RAGES IN COUNTRIES SUCH AS AUSTRALIA AND THE US OVER THE USE OF EMBRYONIC STEM CELLS, SINGAPORE HAS EMERGED AS A HAVEN FOR BIOMEDICAL RESEARCH, WRITES DAVE HOSKIN.

Ironically, given its reputation for conservatism, Singapore has a history of being an early adopter of progressive medical techniques.

It was the veto heard round the world. Faced with the Stem Cell Research Enhancement Act, legislation that would have overturned America's restrictions on human embryonic stem cell research, George Bush, exercised in July the first veto of his presidency.

In August 2001, Bush had been the first president to allow federal funds to be used for such research, but with the caveat that scientists were restricted to stem cell lines already in existence. His decision did not affect private laboratories, but with the vast majority of the country's basic science research funded by the federal government, it still left US researchers at a disadvantage. There was wide public support for lifting these restrictions, and indeed the bill presented to Bush was the result of bipartisan co-operation in Congress.

But the legislation's advocates could not muster the two-thirds majority required to override Bush's veto, and while states such as California have attempted to fund their own research, California's proposed \$US3 billion (\$A4 billion) program is mired in legal battles.

Consequently, with the world's largest economic power unwilling to throw its full weight behind the field, places such as Singapore have emerged as a haven for biomedical research. Aware that key areas of its economy, such as low-cost manufacturing and electronics, were contracting, the Singapore Government launched a biomedical science initiative, the first step in establishing biotechnology as the city-state's economic "fourth pillar".

The timing of the initiative was well chosen, and local stem cell research,

already given a head start by the pioneering work of Professor Ariff Bongso, managed to catch the wave of progress.

Ironically, given its reputation for conservatism, Singapore has a history of being an early adopter of progressive medical techniques. Professor Bongso initially came to prominence serving as a fertility specialist for the team responsible for many of Asia's test tube baby breakthroughs. In vitro fertilisation was still a controversial treatment at the time, and other countries were slow to embrace it.

As a consequence, Singapore took the lead, and in 1987 Professor Bongso joined the staff of the National University Hospital to help establish a state-of-the-art IVF program.

It was during his work in IVF that he became fascinated by the potential of embryonic stem cells. In 1993, under strict guidelines imposed by the National University Hospital's ethics committee, he obtained spare embryos from the IVF program and began attempting to multiply stem cells without allowing them to differentiate.

His success was initially limited, and despite managing to isolate bona fide stem cells, they spontaneously differentiated into mature fibroblasts, cells found in connective tissue, after two generations. By keeping the stem cells dividing in a petri dish for any time at all though, he had achieved something that had never been done before.

Professor Bongso's fascination with embryonic stem cells was driven by the fact that they are pluripotent, i.e. capable of generating almost any cell type found in the adult body. In their early stages

these cells have no specialised function and, if cultured correctly, will produce billions of offspring.

The potential applications of the research were astounding. Professor Bongso hoped that his cultures could eventually create a gallery of cells for regenerative medicine and tissue replacement. Furthermore, observing stem cells promised to provide basic insight into disease processes, and this knowledge would hopefully one day translate into new drug therapies.

When he carried out his original research, he and his team were the only people in Singapore working on human embryonic stem cells. Today there are about 30 stem cell research groups in Singapore, a notable example being that of Professor Lee Eng Hin and Associate Professor James Goh and its focus on developing technologies in bone, cartilage and ligament regeneration.

In 2005 the team announced that it had successfully used mesenchymal stem cells derived from bone marrow to repair damaged cartilage in the knees of five people.

Another success story is that of ES Cell International, a company that recently moved from Melbourne to Singapore. Headed by Dr Alan Colman (one of the researchers involved in the cloning of Dolly the sheep), ES Cell International recently announced the production and banking of clinically compliant human embryonic stem cell lines, and is offering to sell them to researchers worldwide.

Singapore is not the only country to nurture stem cell research, but unlike other notable hubs such as Britain and



Professor John Rasko

biomedical giants such as Novartis, GlaxoSmithKline and Eli Lilly into the city-state. Companies such as these are housed in the massive BioPolis, a seven-building research centre.

Singapore has also aggressively recruited top scientists from overseas, investing heavily in their research as well as harnessing their expertise to train local scientists. The latter element of the initiative has progressed more slowly (and indeed Singapore's Agency for

Science Technology and Research pulled the plug on the local division of Johns Hopkins University, claiming it had failed to meet requirements in training students), but it is hoped that eventually Singapore's next generation of scientists will be able to take the reins.

The most compelling attraction for overseas researchers is the fact that Singapore's biotechnology industry is here to stay. The willingness to allow research to develop over longer periods than usual helps create an atmosphere of stability, and for scientists all too used to working in a controversial field, this is refreshing.

The Government has a strong commitment to research that translates

into benefits for patients, but as Professor Bongso puts it, "I think the approach is cautiously optimistic, evidence based, with no immediate hurry to run to the clinic."

Pathologists in Australia note that one of the most fundamental differences between Down Under and Singapore is the latter's liberal attitude towards stem cell research, in particular the practice of therapeutic cloning.

Therapeutic cloning is defined as the application of cloning technology to produce tissue for therapeutic purposes, without the creation of a complete animal or human being. For instance, in the case of a researcher attempting to develop a therapy for diabetes, a doctor would take a sample of skin cells from the patient and isolate their DNA. Next, a donor egg cell would be hollowed of its own genetic contents and injected with the patient's DNA.

The resultant embryo would be nurtured to grow and divide into a blastocyst. Some blastocyst cells are harvested and then coaxed with growth factors to mature into insulin producing cells. Finally, millions of these insulin-producing cells would be injected back into the patient. In an ideal world, the patient's diabetes could then be

South Korea, Singapore's Government displays an unabashed enthusiasm for the field. Where other countries speak of governmental funding in terms of tens of millions, Singapore speaks in billions. In 2005 it committed \$S12 billion (\$A10 billion) over the next five years to further strengthen research and development, more than doubling the commitment made in the previous five-year period.

Unsurprisingly therefore, Singapore's biomedical industry has rapidly expanded in the past six years, with the Government going out of its way to attract research. There is a strong emphasis on the protection of intellectual property rights, and tax incentives have already enticed



Professor Ariff Bongso

temporarily “reversed” with no side effects such as tissue rejection.

Like Australia, many countries have banned this practice as part of a general moratorium on human cloning, but there is a compelling case for therapeutic cloning to be allowed under strict ethical and legal guidelines. Certainly the ethical framework developed by Singapore was not arrived at lightly, and it is interesting to contrast its review of the subject with that of Australia's.

Formed in December 2000, Singapore's Bioethics Advisory Committee sought guidance on human stem cell research and cloning both internationally and locally. In November 2001, a consultation paper containing interim recommendations was released to 39 of Singapore's professional groups (such as teachers, lawyers and engineers), as well as its numerous religious groups.

Opinions were canvassed regarding the use of stem cells in medicine, and whether IVF embryos were an appropriate source for material. Once the dialogue was concluded, a strong, transparent framework was established, with the use of embryos from IVF and therapeutic cloning being allowed under Singaporean law.

"The framework has very fair checks and balances," says Professor Bongso.

Opinions were canvassed regarding the use of stem cells in medicine, and whether IVF embryos were an appropriate source for material. Once the dialogue was concluded, a strong, transparent framework was established, with the use of embryos from IVF and therapeutic cloning being allowed under Singaporean law.

"Stem cell scientists know what they can do and what they cannot do. We know where our boundaries are."

Despite reaching similar conclusions, the review commissioned by the Australian Government has not been so readily accepted. The Lockhart review comprised a six-member committee tasked with examining the Prohibition of Human Cloning Act 2002 and the Research Involving Human Embryos Act 2002. In passing this legislation, the Australian Government had agreed to fund stem cell research, but it banned human cloning.

However, after a six-month review of the legislation, one of the many recommendations of the Lockhart committee was that the ban on therapeutic cloning be lifted. The fact that the review has received little enthusiasm from the Government concerns Australian researchers, and they feel that a cogent, thoughtful report is being needlessly ignored.

"There has not been a great deal of leadership in terms of deciding what the path should be for the country," says Professor John Rasko, a haematologist involved in research on adult stem cells at Royal Prince Alfred Hospital and the Centenary Institute.

"In Singapore there really does seem to be an immediate familiarity among senior politicians about the issues. Whereas to hear someone like (Australian Treasurer Peter Costello) recently say (nine months after the report was delivered) that he wanted to learn what the issues were, and was going to read the Lockhart review, was a bit disappointing."

It is clear that local researchers admire the work being done in Singapore, but they also warn that failing to learn by their example could leave us in a similar situation to the Americans. Associate

Professor Chris O'Neill, a researcher studying the genetic predisposition of embryos that form stem cell lines, is careful to point out that the current discussion about therapeutic cloning does not detract from the real contributions the Australian Government has made to stem cell research.

But he also feels that the situation is not ideal. "I think that when you look at the amount of money that is going into stem cell research around the world and the amount that's going in here in Australia, there's a very obvious discrepancy, such that there is a bit of a brain drain," he says.

"As soon as you have to do things offshore then you lose a certain amount of the intellectual capital associated with that. I think we are losing intellectual capital as well as intellectuals."

At the time of writing, there did appear to be some movement on the issue, with Prime Minister John Howard agreeing to allow a conscience vote on any Lockhart-style legislation introduced to Parliament.

The ensuing debate would doubtless be highly politicised, but as Singapore has managed to demonstrate, ethics and economic benefits need not be mutually exclusive. It is the balance that is important, and for Ariff Bongso it is his Government's careful attempts to find that balance that he identifies as the bottom line.

"(We have) good infrastructure, discipline, a good and transparent regulatory framework, ample funding, encouragement and support from the higher echelons of Government," he says. "What more can one ask?" 📌

GPs NOTE: This article is available for patients at <http://pathway.rcpa.edu.au>
