Cell

Stem Cell Research in Singapore

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Singapore is investing heavily in stem cell research. This investment is part of an ambitious biomedical science initiative designed to enhance its thriving economy.

Science is a global enterprise. Nevertheless, postal codes tend to influence views about where it is possible to do good science. For example, following the announcement of the birth of Dolly the Sheep in Roslin, Scotland (Wilmut et al., 1997), many quipped "…but where is this place, Roslin?" In fact, Roslin was already notable for being a purported burial site of the Holy Grail (a fable embellished in the recent bestseller *The Da Vinci Code*). Singapore may lay no historical claim to the Grail but, not unlike Roslin, has emerged quite suddenly into the global biomedical science arena, jostling for attention in the face of considerable skepticism. But how can tiny Singapore hope to compete against larger nations with long-standing research programs? One strategy has been for Singapore to focus its efforts on select R&D targets, and one of these research areas is stem cells.

Singapore is a small densely populated city-state, situated one degree north of the Equator and dwarfed by its nearest neighbors, Malaysia and Indonesia. In land mass, it ranks 180th of 215 countries, but in terms of Purchasing Power Parity per capita, it was ranked 21st among 180 member countries by the International Monetary Fund in 2007. To date, Singapore's prosperity has been secured by astute financial management and investment in a strategically designed portfolio including chemicals, electronic manufacturing, port activities, and financial services. The 12-fold surge in per capita wealth between 1960 (Singapore won independence first from the UK and then from Malaysia in 1965) and 2000 (Hoon and Ho, 2006) signaled Singapore's movement from third world to first and was based primarily on manufacturing. But regional competition from cheaper labor locations has led Singapore to embrace knowledge-based industries, specifically the biomedical sciences, over the past 8 years. In 2000, the Singaporean Government set up the Agency for Science Technology and Research (A*STAR), and between 2001 and 2010, it will have invested more than US $4 billion in infrastructural and operational support for existing and new thematic research facilities and institutes in the biomedical sciences. A*STAR alone has established 14 new institutes with seven dedicated to the biomedical sciences (six of the seven are housed in the Biopolis complex, the brainchild of Sydney Brenner and Philip Yeo, which opened in 2003 and cost more than US $400 million). Stem cell research and regenerative medicine have a valued position in this sizable R&D initiative.

Why Stem Cell Research?

There is no doubt that the choice of stem cells as a key R&D area for Singapore was heavily influenced by the significant contributions of Ariff Bongso, a researcher in the Department of Obstetrics & Gynecology and Scientific Director of the In-Vitro Fertilization program at the National University Hospital of Singapore. It was Bongso's group that first derived human embryonic stem cells (hESCs) from 5-day-old human blastocysts (obtained with informed consent from local IVF programs; Bongso et al., 1994). His work paved the way for Jamie Thomson at the University of Wisconsin (Thomson et al., 1998) to produce long-lived hESC cultures by improving the disaggregation conditions and using permanent feeder cell layers. It was this ability to derive hESCs and to

Figure 1. Biomedical Research in Singapore
As part of the phase 2 expansion of the Biopolis biomedical sciences complex in Singapore, two new buildings opened on the Biopolis campus in October 2006. Neuros (left) and Immunos (right) currently host the A*STAR Institute of Medical Biology, which houses the Singapore Stem Cell Consortium, and the A*STAR Singapore Immunology Network. The buildings also provide space for start-up biomedical companies, and there are tentative plans to site a major neurobiology initiative here. Photo courtesy of Ascendas Pte Ltd.

maintain them in culture that triggered the tremendous excitement in stem cell research and its application to regenerative medicine in the late 1990s.

Following Bongso's discovery, Singapore established its first stem cell start-up company, ES Cell International Pte Ltd (ESI), in June 2000 (http://www.escellinternational.com). Singapore now has more than 40 research groups located at universities, hospitals, and research institutes that are pursuing various facets of stem cell research. Institute-based groups have access to core funding, whereas others can compete with the wider research community for government project and program grants. Since 2000, more than US $20 million has been granted for stem cell research in Singapore. More recently, scientists have been able to seek specific support from the A*STAR Singapore Stem Cell Consortium (SSCC; http://www.sscc.a-star.edu.sg). Housed in the new A*STAR Institute of Medical Biology—as part of phase 2 of the Biopolis expansion (Figure 1)—the SSCC will be administering ~US $75 million of government money for intramural and extramural stem cell research over 5 years. This compares favorably with the US $3 billion made available by Proposition 71 (in the form of repayable bonds) over a 10 year period for stem cell research in California.

Stem Cell Research and Economic Priorities

Ten of the world's leading pharma, biotech, and contract manufacturing companies have manufacturing facilities for pharmaceutical production in Singapore. In addition, Lonza, Genentech, and Novartis have set up commercial-scale biologics manufacturing facilities to produce protein therapeutics. Will stem cell research be able to bestow similar tangible benefits on the Singaporean economy?

A big goal is for Singapore to develop and manufacture cell-based therapies for treating a range of degenerative diseases including heart failure, eye disease, cartilage repair, and diabetes. In so doing, Singapore hopes to serve as a medical hub for foreign patients seeking stem cell-based treatments. This challenging objective will be facilitated by the new A*STAR Singapore Institute of Clinical Sciences (SICS) opened in 2007 and directed by Stanford cardiologist Judith Swain. SICS will be responsible for training clinician-scientists and will act as a critical bridge linking basic research undertaken by A*STAR research institutes and universities with clinical research programs in Singapore's hospitals and disease centers. Another bridge between academia and clinical medicine is provided by the Duke University-National University of Singapore Graduate Medical School campus established in 2005. Here, US faculty from Duke University in North Carolina train foreign and local medical graduates, as well as importing and implementing Duke's acclaimed expertise in translational medical research.

Singapore plans to become a provider of new human embryonic and adult stem cell lines and of reagents for drug discovery and drug testing, an objective facilitated by the new A*STAR Experimental Therapeutics Centre also opened last year and led by British cancer researcher David Lane. In this center, cutting-edge scientific drug discovery teams will cohabit with business development operations.

The wide variety of new research initiatives create much-needed additional PhD and postdoctoral opportunities for Singaporeans. Training of the next several generations of home-grown scientists is central to the Government's vision of economic development and will involve public sector research facilities as well as privately funded research endeavors like the Temasek Life Sciences Institute. By 2015, A*STAR alone aims to produce a further 1000 PhD level Singaporean scientists trained both locally and in selected institutions abroad. In addition, Singapore has proved remarkably adept at attracting top scientists from around the world—the latest recruit is embryologist Davor Solter, previously Director of the Max Planck Institute of Immunobiology in Freiburg, Germany, who joined the Institute of Medical Biology last month as a principal investigator. Currently, there are over 5000 PhDs working in R&D in Singapore, over half of whom hold foreign citizenship.

Stem Cells: From Bench to Bedside

Given the history, it is not surprising that there is a focus in Singapore on basic hESC research recently exemplified by work on pluripotency genes and the hESC epigenetic landscape (Zhang et al., 2006; Zhao et al., 2007). In addition, ESI has generated six new hESC lines (grown on human feeder layers) to Good Manufacturing Practice (GMP) standards (Crook et al., 2007), furthering Singapore's goal of being an important provider of hESC lines. (ESI already provides 6 of the 21 NIH-registered hESC lines that became eligible for US federal research funding by presidential decree on August 9, 2001.) The new hESC lines hopefully will simplify the entry of hESC-derived cell products to the clinic. Most hESC lines are derived using mouse cell feeder layers, which is problematic for clinical application because exposure of hESCs to live animal cells greatly complicates the design and operation of any clinical trial.

In contrast to, for example, the United States and Germany, Singapore does not have unduly onerous political or legislative restrictions on hESC research and has not enacted any specific legislation on the generation and use of hESCs. Instead, researchers in Singapore adhere strictly to guidelines drafted in 2002 by the Bioethics Advisory Committee (and subsequently endorsed by the Government), which were modeled on existing UK legislation. Singapore does regulate by law the activities of all fertility centers in Singapore, which could provide human eggs or embryos for research. Although the upcoming US presidential election may result in lifting of the ban on federal support for hESC research in the United States, other impediments to such research remain. For example, the 1996 Dickey-Wicker Amendment forbids U.S. federal support of research involving the creation or destruction of human eggs and embryos.

In a recent remarkable development, Japanese researcher Shinya Yamanaka and his colleagues (Takahashi et al., 2007) succeeded in converting adult human somatic cells into induced pluripotent stem (iPS) cells with very similar properties to hESCs (see Review by R. Jaenisch and R. Young in this issue of *Cell*). This demonstration may remove the stigma attached to working with hESCs in some countries, but the challenge of correctly directing the differentiation of any stem cell, whether an hESC or an iPS cell, is still a daunting one. Although purity, scale up, and efficacy present significant hurdles to the clinical development of all stem cell products, use of hESCs poses particular safety risks including the formation of teratomas. This and the need to avoid immunogenicity issues by using autologous sources of starting material make it more likely that adult stem cell-derived products will be the first to achieve marketing approval.

There has been progress in Singapore in moving adult human stem cells from the bench into the clinic. For example, preclinical work with rabbits and pigs has led to early clinical trials in which patients receive autologous mesenchymal stem cell transplants to effect cartilage repair (Lee et al., 2007). Meanwhile, at the Singapore Eye Research Institute, investigators have performed surgery on 48 patients with a variety of ocular surface injuries using autologous transplants of cultivated human conjuctival stem cell explants and limbal stem cell explants (Tan et al., 2004).

Yet despite the investment in stem cell research in Singapore and the strong pharma presence, many financial challenges remain before stem cells can be translated into viable clinical products. For example, the investment by large pharmaceutical/biotech companies into in-house or externally sponsored cell therapy has been noticeably lacking in Singapore as it has been elsewhere (with the exception of Genzyme-sponsored autologous myoblast transplantation clinical trials in Europe). Although many of these companies regard stem cell research as extremely important for drug discovery and screening (see Essay by L. Rubin in this issue), they are concerned about the timelines of getting robust cell-based products to the market and remain unconvinced by the business case for cell therapy. This same reticence to invest is shared by many venture capitalists making it very difficult for private cell therapy companies to survive (see Analysis by A. Parson in this issue).

Future Prospects

With its generous funding and an ultramodern centralized and integrated scientific and clinical infrastructure, Singapore is well placed to tackle the big technical challenges of bringing stem cells from the laboratory into the clinic. Singapore is also well positioned to address the regulatory (safety, efficacy) and commercial (affordable products) challenges that stem cells, in particular hESCs, pose for translational medicine. The drive to attract foreign talent and to nurture home-grown talent continues and will not abate for the foreseeable future. Indeed, the Singaporean Government views its investment in biomedical R&D as at least a 20 year project. The bottom line is that Singapore's continued survival as a rich nation depends on each pillar of its economy thriving optimally. Few motivations for success in research can be quite as strong as this.

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