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Stem Cell Research in Asia: A Critical View

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ABSTRACT
Stem cell research stands as a high-priority field in many countries across the Asia-Pacific region, and the past decade has seen remarkable investment into facilities and programs intended to increase competitiveness in the drive to find clinical applications. In the years roughly framed by Korean cloner Woo-Suk Hwang's meteoric ascent and fall, speculation was rampant that Asia was poised to overtake the West in this field of science. But that potential remains unfulfilled. In this article, I will look at some of the deficits in infrastructure and governance that underlie the East–West stem cell gap, and suggest a number of measures that might be taken to remedy them. J. Cell. Biochem. 107: 853–856, 2009.

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Shinya Yamanaka published his breakthrough report of reprogramming mouse fibroblast cells to pluripotency 5 years and a day after US President George W. Bush set strict limits on the use of federal funds for human embryonic stem cell research [Takahashi and Yamanaka, 2006]. That this watershed achievement of induced pluripotent stem (or iPS) cells came from a lab in Asia was somehow fitting, for the years following the establishment of the Bush administration's restrictive policy saw a great deal of attention paid to Asian countries that were seen as emerging powers in stem cell research. Commentators in both the scientific [Normile and Mann, 2005] and the mainstream [Einhorn et al., 2005] media speculated that, with scientists' hands tied in the US and other Western nations, such as Germany, labs in places like China and Singapore would steal a march in a field of potentially great medical and economic importance. The alarmism reached almost-fever pitch during the period between Woo-Suk Hwang's first report of a cloned human embryo in February 2004 [Hwang et al., 2004] and the subsequent revelations that his two most important results were marred by ethical breaches and fraud [Cyranoski, 2004b; Vogel, 2005, 2006]. The potent combination of strong government funding and public support, the absence of ethical barriers to research using early-stage human embryos, and the work ethic that had carried Asia to prominence in other areas such as engineering, nanotechnology, and photonics seemed to have propelled the region to the forefront of one of the hottest fields in the life sciences.

In 2009, however, the West, led by the United States, appears to have regained the momentum. Despite solid output from a handful of Asian labs, America alone has generated nearly double the number of stem cell papers published by Asian labs in the 2001 to 2009 period (Table I). The East–West divide widens even further if Europe is factored in (data not shown). Even in the field of induced pluripotency, Japan has failed to capitalize on its early lead; Yamanaka's publication of human iPS cells was followed in short order by similar reports from three American labs, and the first reports of patient-specific iPS cells and proof-of-concept experiments in cell therapy came from labs in the US.

It is to soon to tell whether Asia's significant investments into stem cell research will pay a future dividend, but results to date have failed to impress. Indeed, of the three countries (China, Korea, and Singapore) highlighted by a UK Department of Trade and Industry (now the Department for Business, Enterprise and Regulatory Reform) report as emerging giants, none is at present a major player in the stem cell arena. This despite significant national funding and infrastructure initiatives, and dedicated efforts to lure returnees and expatriate scientists to work in the field. Other Asian nations, such as India, Taiwan, and Thailand, which were ostensibly drawn in by the sense of opportunity and Asian empowerment following the hamstringing of federally funded hESC research in the US and Hwang's apparent successes have also remained only bit players. Within the region, only Japan and Australia (which is not in the strict sense in Asia) have made significant impacts.

In this article, I will review some of the reasons why Asian stem cell initiatives have failed to live up to their early promise (and hyperbole) so far, and propose changes to the research governance

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TABLE I. Stem Cell Publications by Country, 2001–2009

	Number of stem cell publications
Australia	663
China	946
India	157
Japan	2,852
Korea	703
Singapore	180
Taiwan	225
Thailand	31
England	1,863
Germany	2,594
Israel	408
Canada	996
USA	9,468

Figures are based on a search of the ISI Web of Knowledge reference database, using the following search parameters: TS = stem cell*, document type = research article, language = English and CU = country name. The search was performed on February 25, 2009.

in these countries that might remove some of the stumbling blocks that handicap scientists in this region.

Perhaps the most pressing problem confronting Asian stem cell researchers is confusion at the governmental level as to whether funding commitments are made primarily as support for basic research with no immediate prospects for application or economic benefit, or whether they are made with clear economic goals. Lip service is certainly paid to the importance of fundamental science, but in many countries employment and market size milestones have featured prominently in stem cell funding initiatives. Korea's Bio-Vision 2016, which included 430 billion won (approximately $454 million US at the exchange rate in 2006; roughly $277 million as of March 2009) in funding from four ministries over 10 years for stem cell research had the stated goals of building a $6.5 billion US market for biotechnology [Yuan, 2009] and driving Korean stem cell research to among the top three nations in the world [Normile, 2006]. Singapore [Cyranoski, 2005] and India [Jayaraman, 2005] drafted similarly ambitious roadmaps, with stem cell research forming a significant component of their ambitions to benefit from the speculative future profitability of the biotechnology sector. (Ironically, recent analyses have shown that, in its first 30 years, the biotechnology industry has proven to be a remarkably powerful engine of wealth destruction [Pisano, 2006; WSJ, 2007].)

Given the framing of stem cell research in many Asian nations as an exercise geared toward stimulating economic growth rather than one of simply expanding the frontiers of human knowledge, it is perhaps unsurprising that significant amounts of funding are granted by ministries and agencies with an industrial or economic remit. Singapore's A*STAR, which is the chief funding agency for the majority of the country's stem cell labs and the headquarters of the Singapore Stem cell Consortium, sits squarely beneath the Economic Development Board on government organizational charts. In other countries as well, the impetus behind the funding of stem cell research (and biotechnology in general) has been provided by the urgent sense of need to make the transition from manufacturing to knowledge or innovation-based economies [Sipp, 2007]. The priority placed on the presumed economic value of stem cell research has translated into governance structures and practices that can be heavy-handed, intrusive and wonkish [Holden and Demeritt, 2008], making them to some extent incompatible with the mindset cultivated in academe.

Problems of governance and intellectual infrastructure lie at the heart of many of the difficulties that confront stem cell scientists in Asian countries. The lack of robust support systems for life sciences research at the national level is perhaps unsurprising, given the relatively shallow history of modern biological research in Asia outside of Japan. This is not to say that individual laboratories have not made contributions, only that Asian countries have historically tended to focus their energies on immediate problems of public health and welfare, social stability, and economic growth rather than the relative luxury item of basic research. But the lack of experience in shepherding basic biological research programs at a national scale has resulted in suboptimal conditions for the conduct of science.

China in particular appears to be struggling. Despite a heavy investment into reproductive and developmental biology (which includes stem cell research) as part of its 15-year Science and Technology Plan, ambitious research cluster developments in Beijing and Shanghai, and a slew of programs designed to lure top scientists back to the country, Chinese stem cell research has been mired in controversy and weak performance. Funding programs place excessive emphasis on "big" projects, while shortchanging smaller labs, students and postdocs. Bonuses are handed out on the basis of publications in high impact journals, creating perverse incentives for scientists to pursue easy themes and low-hanging fruit [Hao, 2008], or (even worse) to tweak their results. Poor communications between individual labs and the country's multiple funding agencies, coupled with the lack of a stem cell research society have further resulted in redundancies and needless competition. In the heyday of the excitement over human embryonic stem cells, for example, Chinese labs may have generated in excess of 100 new lines, but the lack of English language publications and the failure of the labs to register their lines on international databases has made this impossible to confirm, and the lines have made no international impact. (And no less than four domestic stem cell banks have been set up independently to store and distribute them.) Funding decisions in general take place in a black box that opens the process up to accusations of cronyism and bias [Cyranoski, 2004a]. Returnee scientists face challenges in reintegrating into the entrenched ranks of academia, while at the same time shouldering significant burdens in simultaneously running well-funded research programs, training students and postdocs, serving on committees and government advisory boards, and exploring potential industry collaborations [Sipp, 2007]. Scientists even cite difficulties obtaining equipment and reagents in a timely fashion [Cyranoski, 2008].

Similar problems, on a smaller scale, have hampered stem cell initiatives in Taiwan and Korea. These are compounded by the difficulty in recruiting non-native scientists to any of these countries, due to the significant disparities in salary and infrastructure, as well as intangibles such as linguistic and sociocultural differences and the sense of geographical isolation from tradition research hubs. Even the comparatively wealthy Japan has had little success in attracting foreign scientific talent, a situation made all the more difficult in a highly competitive field such as stem cell research. Australia, too, has experienced a brain drain of some of its top stem cell biologists, including Martin Pera, Paul Simmons, and Alan Trounson, in the past 5 years, all of whom left for positions in the United States. Only Singapore has had success in luring world-class researchers to work at domestic institutes, primarily in the A*STAR-funded Biopolis complex. But many of the high-profile recruits have been late-career scientists, often in advisory or purely ceremonial roles, and few have sunk permanent roots there. It remains to be seen whether the country's two-stage strategy, in which the preponderance of scientists in the first phase come from overseas gradually to be replaced in the second by newly minted Singaporean researchers returning from study and work abroad, will bear fruit.

Public support for science and the lack of debate over "embryonic rights" were among the factors mentioned both by commentators on the promise of Asian research and scientists who relocated to Singapore in the immediate aftermath of the Bush policy on human ES research [Du, 2004; Einhorn et al., 2005]. Certainly, differences in the rules governing research using human embryos and the legality of procedures such as somatic cell nuclear transfer using human cells or genetic material represented an early advantage for many Asian countries. But the lack of sufficient regulations in other areas, particularly the clinical translation of stem cells, has harmed the region's scientific reputation. Clinics offering unproven treatments using putative stem cells of various types operate with impunity in China, Thailand, India, Korea and even Japan. In a number of countries, there has even been overt government support for these businesses [Kiatpongsan and Sipp, 2009], as well as for businesses based on the storage of cord blood in private banks for (highly speculative) future clinical use.

The lack of communication and coordination seen within individual nations is even more severe at the regional level, again giving rise to redundancies and missed opportunities for collaboration. The difficulties in building scientific networks in the Asia-Pacific are not peculiar to stem cells. A meeting convened in Tokyo in 2007 highlighted some of the historical, structural, and perceptual issues that drive Asian scientists to collaborate more extensively with their Western colleagues more than they do with each other [NPG, 2007]. It was as a result of that meeting, however, that leading scientists from Australia, China, India, Japan, Korea, Singapore, Taiwan, and Thailand agreed to form a stem cell network within the region "to promote a broad set of initiatives, including eliminating redundancies in regional stem cell meetings, providing local opportunities for students and young scientists, and developing infrastructure and programs to support intraregional collaboration and exchange of information" [SNAP, 2009]. The absence of region-wide funding schemes, however, has prevented the network from developing more substantive activities to foster such collaboration and exchange, and the lower visibility of both institutional and individual research programs has made it difficult even to identify areas of common ground.

In order for Asian stem cell research to live up to its great promise, reforms are needed in the way that science is funded and overseen in each country. Basic researchers should be free to look where nature and curiosity leads without expectations to contribute to the bottom line and, for those whose work shows commercial promise, opt-in systems should be put in place to enable business development by entrepreneurial scientists. The distinction between fundamental and applied and clinical science needs to be drawn with a brighter line. Funding decisions should be made more transparently by unbiased scientific bodies (including referees from other countries) to ensure fair competition, and a portion of every stem cell initiative should be earmarked for blue-sky projects. Employment practices and pay scales need also to be reformed in order to stem the loss of young talent to other countries and to attract more experienced scientists home.

Clear guidelines and, where necessary, laws should be established, promulgated and enforced to prevent profit-chasing by mavericks who exploit patients with unfounded promises of stem cell cures, and to allow well-intentioned translational researchers to know how to proceed responsibly. The majority of Asian countries adopted sensible regulations covering human ES cell research, reproductive cloning and somatic cell nuclear transfer relatively quickly, often with explicit reference to rules that had already been established in other countries (such as those set forth by the Human Fertilisation and Embryology Authority in the UK). Both the US Food and Drug Administration and the European Medicines Agency have developed clear frameworks for the introduction of cell-based interventions into the clinical market; countries that lack their own regulations might do well by adapting these existing rule sets to fit their local circumstances.

The sharing of information at the national, regional, and global level needs to be encouraged by institutions and carried out by the scientists themselves. English-language websites are a reasonably simple means of opening a window into the activities being undertaken by each nation and the themes of interest in individual labs, and would go a long way to fostering better communications, avoiding duplication of effort, and cultivating new collaborations. The Singapore Stem Cell Consortium, the Taiwanese Society for Stem Cell Research and the Stem Cell Research Forum of India offer good preliminary examples of how a national stem cell community might self-organize and provide a first point of contact for others to learn more about activities in those countries. Japan, Korea, and China would do well to emulate their effort. Much more needs to be done to integrate research programs in Asia into the international community and to ensure that achievements by Asian labs do not go unrecognized. Participation in worldwide programs such as the stem cell characterization and banking initiatives coordinated by the International Stem Cell Forum and the submission of information in open registries of cell lines, such as the International Stem Cell Registry maintained by the University of Massachusetts, provide straightforward opportunities for Asia to join the rest of the world in driving the field forward.

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