Stem Cell Science On the Rise in China

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China's output in fundamental stem cell research has increased markedly in recent years. Vigorous public investment and infrastructure development have enabled major productivity gains, but challenges in regulation, governance, and the management of clinical expectations must be addressed to ensure scientific quality and sustainable growth.

China's scientific renaissance in recent years has been as dramatic as its economic rise, allowing the world's most populous country to also become one of the most prolific in terms of research output. Significant government investments in education, infrastructure, and funding—coupled with increasingly strong interactions between Chinese scientists both at home and overseas—have returned the nation to the front ranks of international scientific productivity. This is clearly the case in the field of stem cell research, which has been a focal point of the government's plan for developing the life sciences and biomedical sectors. In this Forum, we look at the public initiatives and research efforts that have led to China's emergence as a global stem cell power, examine present-day challenges and achievements, and look ahead to future directions.

The roots of stem cell research in China can be traced back nearly half a century to 1963, when embryologist Dizhou Tong generated the world's first cloned fish, an Asian carp, by somatic cell nuclear transfer (Tong et al., 1963). The following year, hematologist Dao-Pei Lu at Peking University People's Hospital performed China's first syngeneic bone marrow transplantation for the treatment of severe aplastic anemia (Lu, 1981). The work on mouse hematopoietic stem cell kinetics in the late 1970s led by Chu-tse Wu represented some of the earliest efforts in stem cell biology in China (Wu et al., 1985). These, together with many other achievements, stood for years as an early promise of things to come. Following 3 decades of economic restructuring and growth since the late 1970s, China is now increasingly able to address its national goals in higher education, research and development, and public health. As with many Asian countries looking to diversify their economies to embrace a more innovation-based approach, China has looked to stem cell research with great interest in recognition of its rapid pace of advances and tremendous clinical promise. The ensuing concentration of funding and facilities by national, provincial, and municipal governments—and the absence of public controversies that have hampered work in areas such as human embryonic stem cells (hESCs) in some countries in the West—has enabled China to build a stem cell research community nearly from the ground up in a single decade. Enormous strides have been made in the quantity and quality of China's research output in fundamental, translational, and clinical areas of the stem cell field, even as compared with the situation as recently as 5 years ago (Murray and Spar, 2006). While these efforts remain very much a work in progress, the rapid pace of development and increased research quality are promising signs of things to come.

Self-Renewal

In 1986, China launched a major applied research initiative known as the "863" plan, and a basic science research program under its later counterpart, the "973" plan, both administered by the Ministry of Science and Technology (MOST) (http://program.most.gov.cn/). In 2001, two independent stem cell 973 programs (led by Lingsong Li and Huizhen Sheng) were launched. Until recently, most stem cell basic research projects were funded under the Development and Reproduction Key Program, a derivative of the 973 plan. A number of subsequent funding initiatives intended to further promote stem cell research, applications, and public awareness have been established by MOST and other ministries and public agencies, as summarized in Table 1. Of these, the National Natural Science Foundation of China (NSFC) in particular has seen its budget increase by over 20% per annum since 1986; its 2011 budget stands at 12.4 billion RMB (~$1.95 billion), an increase of more than 50% from the previous year (of this amount, 226 million RMB [~$35.5 million] is allocated to stem cell research). In total, the national government's stem cell research funding commitment is estimated at more than 3 billion RMB (close to $500 million) over the next 5 years. This amount excludes local government funding, industry support, and other initiatives, such as the National New Drug Development Plan.

Clearly, stem cell research is enjoying significant investment by various funding agencies and sectors in China, but the country still needs to work out how to

Table 1. Stem Cell Research Funding Mechanisms in China

Agency	Program	Grant Size[a]	2011 Funding Level[b]
NSFC	general programs	92.3	1,405
	key program	452	224.4
	major program	3,000	6–9
	total stem cell funding	varies	223
MOST	863	1,000–5,000	–
	973	3,000–5,000	–
	stem cell program	4,600	40
	stem cell initiative for CAS	1,500	150
Other ministries, provinces, cities, major universities, industry	varies; mainly follow NSFC and/or MOST funding mechanisms	varies; usually smaller than similar NSFC programs, except for a few special initiatives	total annual funding estimated to exceed the NSFC total

[a] Unit = Thousands, US dollars.
[b] Unit = Millions, US dollars.

ensure that the funds are subject to transparent competition and effective use. While some laboratories may have received extraordinary funding for supplies and equipment, under the current policies most grants cannot be used for staff salaries, and principal investigators do not have the right to hire laboratory members at competitive compensation scales based on their actual funding levels, or to do so to reflect long-term goals. The lack of measures to link future funding allocations to objective indicators of scientific performance and impact is also problematic. Appropriate governance measures, such as ensuring that funding and hiring decisions are fair and transparent and providing mechanisms for monitoring research integrity and outcomes, will be crucial to the success of China's stem cell commitments.

Rapid Proliferation

A look at international publication trends shows how the country's investments are already beginning to pay a dividend in scientific productivity. From 2006 to 2010, China's stem cell research output jumped from 176 articles to 677, a 285% increase (see Table 2). This represents an increase from less than 3% of the world total of stem cell research publications to more than 7%. While this represents only about one-fifth of the US total (US stem cell publications comprise 38% of the world total), China's prolific output has neared that of Japan, and stands to outpace it in 2011 if current trends continue.

Some of China's stem cell work has already gained international recognition. Following the first report of induced pluripotent stem cells (iPSCs), Chinese scientists were quick to adopt the technology and soon made contributions to this rapidly developing field, such as identification of p53 as a major barrier for iPSC generation (Zhao et al., 2008), some of the first evidence for the pluripotency of mouse iPSCs (Kang et al., 2009; Zhao et al., 2009), and the importance of mesenchymal-epithelial transition (MET) to iPSC induction (Li et al., 2010). A number of iPSC lines have also been derived from novel species, such as rat, pig, and rhesus monkey (Wu et al., 2009). In addition, studies on intestinal stem cells (Lin et al., 2008), direct conversion of fibroblasts into hepatocytes (Huang et al., 2011), and demonstration of Tet3 in germ cell reprogramming (He et al., 2011) have also received considerable attention in the field.

The country's translational research efforts meanwhile have focused on stem cell banking, large animal models, biomarkers, bioengineering, small molecules, and clinical transplantation, leading to the filing of numerous patent applications, many of which have been granted. In one example of its facility-building efforts, China boasts the world's largest cord blood stem cell bank, based in Tianjin and co-owned by the country's largest hematology institute and hospital within the Chinese Academy of Medical Sciences (Peking Medical Union College) system. Many of these accomplishments have been made through international collaborations, in which China-born, Western-trained stem cell scientists have played instrumental roles.

China has also actively participated in global stem cell research efforts, such as the International Stem Cell Forum, and organized or co-organized a number of high-profile international conferences on stem cell research (http://www.selectbiosciences.com/conferences/IFSC2010/). National and local stem cell research organizations have also been active, with at least three independent national stem cell societies and two major stem cell industrialization alliances in existence at present, although the scope of each varies considerably. A more consolidated, better-coordinated approach would doubtless further enhance the country's productivity and opportunities for exchange, and highlight the best of China's stem cell science to the world. The recently established National Oversight and Coordination Committee on Stem Cell Research, chaired by the Minister of Science and Technology of China (Gang Wan), will likely boost collaborative efforts between stem cell researchers in China. Further participation by China's researchers, especially those of the younger generation, in international meetings will also be critical to achieving these goals.

While trends of stem cell research are promising, concerns have also been raised about the scientific quality of some publications; while recent years have seen indications of more innovative contributions, too much of China's output remains derivative or incremental. It will be critical for China to redouble its efforts to instill in all of its students and research scientists a sense of the primary importance of maintaining the highest

Table 2. Stem Cell Research Publications, 2006–2010

	2006	2007	2008	2009	2010
China	176	277	409	526	677
Japan	519	615	682	672	741
USA	2,422	2,829	3,155	3,482	3,643
World total	6,310	7,537	8,411	9,067	9,608
China (%)	2.79	3.68	4.86	5.80	7.05

Note: All publication counts were obtained from an ISI Thomson Web of Science search on 06/30/2011. Search terms used therein: CU, country name; TS, stem cell.

standards of rigor and creativity. In addition to a basic knowledge of biology and laboratory techniques, students must uniformly be taught the critical thinking and standards of research conduct they will need to make lasting contributions to the field.

Population Effects

Even granting such concerns, one evident factor in China's stem cell research success is the increasingly high quality of its research scientists and the facilities that accommodate them. Thanks to recent efforts by national and local governments, universities, and various ministries and agencies in providing financial and research incentives, there has been a surge of well-trained talent returning from abroad, particularly in the stem cell field. The Ministry of Personnel has stated that engaging ''internationally renowned'' returnees in the science sector is of primary importance during its 11th Five Year Plan for 2006–2010, and MOST also states its aim to ''set a stage for the outstanding overseas Chinese people to return home to serve the country'' directly in the 973 program. Heavy investments into infrastructure have raised many facilities to world-class levels, and support for education continues to skyrocket. Funding for research institutions such as the Chinese Academy of Science (CAS), the Chinese Academy of Medical Sciences (CAMS), and the National Institute of Biological Sciences (NIBS) has also increased dramatically, through mechanisms such as the State Key Laboratories initiative.

A number of metropolitan areas, such as Beijing, Tianjin, Shanghai, Guangzhou, Hangzhou, Wuhan, and Chengdu, have attracted the lion's share of stem cell research funding, infrastructure, and talent, and research synergies can be clearly seen in these cities. This has allowed the establishment of a number of centers for stem cell research in major institutions, such as the CAS and CAMS systems, Peking University, Tsinghua University, Shanghai Jiao Tong University, Tongji University, Sun Yat-Sen University, and Zhejiang University, which have become national powerhouses in the field. Researchers from smaller cities or less visible institutes continue to have less favorable chances at receiving adequate funding, but this too is changing as the top universities and institutions slow recruitment and greater numbers of highly qualified researchers are recruited to other top universities in China, such as the so-called ''985'' and ''211'' universities (which can access special funds from the Chinese national and local governments).

China is also churning out myriad talented graduates who have received excellent undergraduate education and high-caliber graduate training, more of whom are realizing that a stint overseas is no longer their sole option for top-quality training. Indeed, some are being trained in the laboratories of returnee scientists. Many of these young researchers will doubtless continue their work at academic and industry workplaces, thus further adding to the productivity of China's basic and applied research. Furthermore, the likelihood of returning to China for those who choose to get further training abroad (Ph.D. or postdoctoral) continues to increase. However, unlike many other developed countries, China currently does not have a sizable workforce of postdoctoral trainees. This situation may evolve as the stature of stem cell research rises and the infrastructure continues to improve.

Transformation in Culture

China's policymakers must next formulate workable strategies for developing its burgeoning stem cell enterprise, as has been achieved in many other areas over the past 30 years, specifically with an eye to coordinating the many diverse initiatives to prevent redundancy and promote cooperation. While publications are important for the country to demonstrate its ability to keep pace with the cutting edge of the field, they are not the ultimate goal of its investments. China's research force and funding scale are both only a fraction of that of the United States or many countries in Europe, and incremental new findings in basic research will not win China a leading position in this arena. What China can offer uniquely are some of the largest resources for medical research and innovation in the world. Confronted with the healthcare needs of a rapidly aging population of nearly 1.4 billion, the impetus behind much stem cell research to date has understandably been clinical translation and development. The vast size of its demographic, however, also represents a remarkable opportunity for physician-scientists to work with large, treatment-naive patient populations in medical conditions that may be underrepresented in clinical research in other countries. With economic modernization, cancer and heart disease have rapidly become leading causes of death, and diabetes, obesity, and metabolic syndrome are all on the rise. Traffic and workplace accidents have left China with more spinal cord injury patients than any country in the world, and endemic hepatitis B virus affects more than 100 million patients across the country. Thalassemias are common in southern China, while Keshan disease, a congestive cardiomyopathy caused by selenium deficiency, is prevalent in the northeast. For this reason, stem cell research in China should further emphasize its translational potential to better meet the needs of patients suffering a broad spectrum of diseases. In basic research as well, more emphasis should be given to the roles and impact of stem cells in disease, a critical prerequisite yet underinvestigated area in stem cell medicine.

Before China can capitalize on its growing investments and tremendous medical opportunities, it will need to further strengthen its regulatory pathways to the clinic. China's regulation of fundamental stem cell research provides an excellent precedent, as it was one of the first countries in the world to adopt specific guidelines governing the production and research use of hESCs, with joint regulations issued by MOST and the Ministry of Health (MOH) in 2001, and to ban reproductive cloning in the following year. This permissive approach was a boon for Chinese scientists seeking to enter hESC research, as it provided a clear set of ethical guidelines for the work in stem cell laboratories.

The regulatory picture for clinical application of stem cells, however, remained muddled for many years, allowing some hospitals and private clinics to market various implausible "stem cell" remedies with little oversight or scientific evidence. In 2007, MOH published its guidelines, "Biomedical research ethics review regulations relating to research on human subjects (clinical trials)" in an effort to standardize government monitoring of research using human subjects, including that involving stem cells. And in 2009, the Ministry promulgated a new law on advanced medical technologies, requiring those engaged in highly experimental or ethically charged medical practices (such as many stem cell treatments) to obtain prior MOH approval or face legal consequences. These measures appear to have been only partially effective to date because enforcement is the duty of regional administrations, and certain special economic zones and military and armed police force hospitals operate with apparent impunity. More effective policies and uniform enforcement by a national regulatory agency will be a key prerequisite for China's successful development of translational stem cell medicine.

China has made an impressive start in its drive to build a truly world-class stem cell research enterprise. Now it will need to exercise sure judgment in sustaining those efforts that have borne fruit, and taking a fresh look at those that have not. All indicators suggest that the country is on the fast track to reestablishing itself as one of the world's foremost producers of scientific and technological innovation. This can only be a good thing for the future of stem cell research and the remarkable promise it holds.

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