

China and HIV Vaccine Research: An Old Country with a New Commitment

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In 2010, China invested approximately US \$18.3 million in HIV vaccine research and development, becoming the third largest HIV vaccine funder globally, behind the United States' investment of \$859 million and the European Commission's investment of US\$18.5 billion [1,2]. Recently, the Chinese government has also pledged to further boost funding for HIV vaccine development by at least 20 percent in 2011-2015 in its twelfth five-year plan [3]. Despite other countries' decreasing funding, such as the US with the largest decline of US \$ 17 million from 2009 to 2010, China has been going against the trend by investing significantly more money in HIV vaccine research. Why is China doing this? What is the outlook of China's role in the global search of an effective vaccine against HIV? Let's look at the HIV/AIDS epidemic and HIV vaccine research in China to try to answer these questions.

HIV/AIDS in China

Since its first AIDS case was identified in 1985, China's HIV/AIDS epidemic has expanded in size and spread in regions throughout the country. By 2002, HIV-positive people were present in all Chinese mainland provinces, municipalities, and autonomous regions [4]. In 2008, AIDS became China's number one killer infectious disease [5]. Joint research by the Health Ministry of China and WHO estimated total HIV infection cases of 0.74 million, with more than 0.13 million AIDS cases in China in 2010 [6]. In 2011, more than 48,000 new HIV infections were reported, and mortality from AIDS was almost 30,000 [7].

Although China's HIV epidemic remains at low prevalence overall (0.1% among adults) given its large population size, considerable concerns have been raised to the public and government officials regarding pockets of high infection rates among several sub-populations including Former Plasma Donors (FPD), Injecting Drug Users (IDU), Men who have Sex with Men (MSM), and most recently discordant heterosexual couples (DHC). HIV transmission in FPDs was greatly reduced after the banning of unregulated commercial blood collection in 1996 [8,9]. However, in IDU populations, HIV prevalence of more than 20% was reported in cities along or close to the drug trafficking road in the Province of Yunnan, Xinjiang, Sichuan, Guizhou, Hunan and Guangxi in 2004 [7]. A cohort study conducted between 2002-2005 reported an HIV incidence rate of 2.3 per 100 person-years in a drug trafficking city in southwest China [10]. In MSM populations, HIV transmission through homosexual sex accounts for 42% of new infections in 2009 [11] with an alarmingly high incidence rate of 5-8 per 100 person-years in some regions of China such as Shenyang [12] and Beijing [13]. The epidemic continues to spread further into the general population mostly through heterosexual transmission. In 2009 around 42 percent of people newly infected with HIV became infected through heterosexual sex [11]. A meta-analysis of heterosexual transmission among HIV discordant couples in China estimated an HIV sero-conversion rate of 1.2 (95% CI: 0.9- 1.7) per 100 person-year with an overall prevalence estimate of 11.5% (95% CI: 8.2% - 15.2%) for HIV prevalence through heterosexual transmission in discordant couples [14].

These statistics have resulted in enormous pressure on the Chinese

government to carry out effective prevention and imperative control of the HIV/AIDS epidemic in China. In the 1950's, the newly established People's Republic also faced serious public health challenges when 10% of national minorities, 5% of Chinese city dwellers and 2-3% of Chinese rural residents had syphilis, and the majority of sex workers living in urban areas had one or more Sexually Transmitted Diseases (STDs) [15,16]. The Chinese government was able to achieve virtual eradication of sexually transmitted diseases by massive health campaigns that were mostly portrayed as patriotic [17]. However, today the value of freedom, personal wealth and happiness, as influenced by western culture since China reopened its doors to the west in the 1980's, often dominates the public's patriotic emotions towards government's campaigns. The government also realized that propaganda of drastic measures that worked before is no longer as effective to solve public health problems in China [18,19]. As a result, more science-based strategies have been implemented in China. For example, reduction of HIV transmission has been observed among the IDU populations due to the government's few strategies including the implementation of needle exchange programs since 1999 [20,21] and Methadone maintenance treatment program since 2004 [22,23]. However, effective interventions among other high risk groups have been difficult to reach high coverage primarily due to their massiveness and underground nature. Discordant heterosexual couples are partially hidden and hard to reach because they are mainly comprised of migrant workers, their families, under-ground sex workers and their clients, and, covert gay men and their wives. Although homosexuality is becoming more tolerated in the cities, MSMs are often in a heterosexual marriage to conceal their true sexual orientation due to high levels of stigma toward homosexual sex in the Asian culture.

HIV Vaccine Research in China

More recently, the Chinese government realized the development of a safe and effective HIV vaccine could provide the best hope to control the HIV/AIDS epidemic, particularly among those hard-to-reach risk groups and in resource-constrained regions. Such a commitment was highlighted during a visit to China CDC by Chinese Premier Wen Jiabao on the World AIDS Day in 2011, when he stressed on the importance of HIV vaccine research [24]. Such a strong political commitment in China often translates into important financial support.

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Researcher /Developer	Vaccine candidate	Development stage
Jilin University	DNA/MVA	Phase II
National Center for AIDS/STD Control and Prevention, China CDC	DNA/TiantanVaccinia	Phase II
Institute of Virology, China CDC	DNA/MVA (therapeutic)	Phase I
Tsinghua University, Hongkong University, Chinese Academy of Science	Modified TiantanVaccinia/ Ad5	Pre-clinical
Nanjing Medical University	DNA + gp120	Pre-clinical
Shanghai Pasteur Institute, Chinese Academy of Science	DNA /VLP	Pre-clinical

Table 1: Ongoing Pre-clinical and Clinical Trials of HIV/AIDS Vaccine in China.

Specifically, China has targeted AIDS vaccine research in its National Key Science and Technology projects to encourage Chinese scientists and institutions to participate in international collaboration. In the newly released Eleventh Five-Year plan (2011-2015), AIDS vaccine research was again set as an important special-funded area in the infectious diseases prevention and control mega science and technology projects. Such a position in the country's strategic planning suggests China's capability and willingness to shoulder more responsibility in HIV vaccine research especially after it overtook Japan to become the world's second-largest investor in R&D after the United States in 2009 [25]. In the same year, six Chinese AIDS vaccine research teams from 28 institutes established the China AIDS Vaccine Initiative (CAVI) to work together on AIDS vaccine research and collaborate with international partners [26-28]. Meanwhile, the Chinese government has also planned to sponsor China's first large scale HIV vaccine trial to evaluate the efficacy of the vaccine candidate in high risk population in 2014-2015, adding to the short list of five HIV vaccine efficacy trials that have been conducted so far in the past 30 years [29-33]. Recently, China's Natural Science Foundation has provided joint funding with the US National Institute of Health (NIH) to support an international collaboration between Chinese and US researchers on the design and planning of this trial [34].

Although a short list, HIV vaccine candidates in the pipeline for evaluation in China (Table 1) expands the diversity of vaccine products in the global HIV vaccine research community. Particularly, scientists at China CDC are currently evaluating the safety and immunogenicity of recombinant DNA boosted by replicating Tiantan Vaccinia virus vector (rTV) with HIV gene inserts from HIV-1 CN54(B'/C) in a Phase IIa clinical trial among high risk MSMs [35]. China's self-developed HIV vaccine candidate, DNA + rTV, has been proven to be safe and immunogenic in Phase Ia and Ib clinical trials [36,37]. Given that the vast majority of HIV vaccine resources are currently devoted to development and testing of non-replicating vector vaccines [38], findings from such a trial is expected to be of high interest to the HIV vaccine research community worldwide.

In addition, with dominant HIV circulating strains of CRF01_AE, CRF07_B'C, and subtype B [39], China is in a unique bridging position to translate findings in China to other regions of the world that share common HIV subtypes in the circulating strains, including Latin America, North America, the Caribbean and Western Europe. Given its massive population and often centralized and well-equipped clinical sites and laboratory facilities, China is also in a unique position to speed up the evaluation of HIV vaccine candidates with strong commitment from its government.

The outlook of HIV vaccine research in China does not only have its rosy side; there are certainly challenges in effectively engaging China

within the global HIV vaccine research realm. The Chinese government calls for more international collaborations in HIV vaccine research and has taken it seriously. For example, every other year China has held a high level international AIDS meeting and conducted national HIV/AIDS estimates and program evaluations with the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) since 2005. Large national HIV vaccine programs, such as the *Comprehensive International Program for Research on AIDS (CIPRA)* and CAVI, invited prominent foreign scientist as chairs and members on their Scientific Advisory Board, with active engagement from major international agencies and organizations including UNAIDS, WHO, US National Institute of Health, Bill and Melinda Gates Foundation, HIV Vaccine Trials Network and the International AIDS Vaccine Initiative. However, China still often receives criticism for being guarded in information sharing with international collaborators. While there may be a greater need of transparency and openness from the Chinese government and scientists to collaborate with international stakeholders, there is also a need for foreign governments and organizations to better understand the cultural and societal background in China's research community. For example, historically dominated by a largely shame-based Confucian culture in which "... men hesitated to speak, for if their conduct fall short of what is said, it would be shameful." (*Analects of Confucius 4: 22*), China is still "culturally-inclined" to cautiously share "uncertain" information with outsiders. This caution, however, should not be confused with an unwillingness to collaborate. Investment in a collaborative relationship of mutual trust and understanding with clear and common research goals can result in an openness of information sharing sufficient to support the collaboration. Another challenge is that China, being more frequently in the spotlight for economic growth and human rights, has a strong desire to make impact on its own effort. Although not unique to China, this certainly requires nuance and sensitivity in handling international collaboration with China. Last but not least, relatively tight regulatory requirements on early phase human clinical trials may also place constraints on the development of a successful HIV vaccine in China.

Nevertheless, China is a large and open country that possesses sufficient social and political motivations, as well as financial resources and scientific capability to play an important and unique role in the global search for an effective vaccine against HIV. Although the discovery of a successful HIV vaccine may seem elusive after three decades of concerted effort, the HIV vaccine field must not despair especially given the development of a successful vaccine had typically required decades to accomplish. China is now poised to fully engage its considerable resources in this effort and take its place among the global leaders in the search for a safe and effective HIV vaccine. This could not come at a better time.

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