

## A 'systems approach' to vaccines

The stated goal is to develop an effective human immunodeficiency virus vaccine, yet the Gates initiative might revolutionize the entire vaccine field.

A much-needed global experiment is beginning that, if successful, could transform the process of vaccine design, development and delivery. On 19 July 2006, the Bill and Melinda Gates Foundation announced its funding of 16 grants, totaling some \$287 million over 5 years, focused on the single goal of developing an effective vaccine for human immunodeficiency virus (HIV). This vaccine initiative stems from the establishment of the Global HIV/AIDS Vaccine Enterprise, of which the Bill and Melinda Gates Foundation is a chief sponsor and serves as the coordinating secretariat. An unusual aspect of these grants is the requirement for networks of highly collaborative interactions. Unlike conventional vaccine development approaches, the HIV Vaccine Enterprise advocates the sharing of intellectual property, specimens and data among the international consortia, and the Gates Foundation stipulates this requirement for their grant awardees. In addition, a transparent evidence-based evaluation process is also mandated to identify the most promising avenues and to halt approaches that experimental data fail to support. These stipulations allow real-time course changes to the direction of research, should laboratory and/or clinical data provide evidence to do so. Not only will the new grants support basic science exploring how to elicit effective humoral and cell-mediated immunity to HIV, but also five grants focus on developing the infrastructure required to systematically evaluate the efficacy of vaccine candidates and to ensure that efficient vaccine production and delivery systems are in place through licensure to qualified national or regional facilities. In short, this discovery process spearheaded by the HIV Vaccine Enterprise represents a 'systems approach' to vaccine development.

In the more than two decades since HIV was identified as the etiological agent responsible for AIDS, the disease has spread around the globe affecting millions without regard to age, lifestyle or economic status (see Imami *et al.* in this issue of *Nature Immunology*). However, despite the expenditure of considerable effort, strong vaccine candidates are still lacking. HIV has shown itself to be a formidable foe, as noted by Gallo in a 2005 perspective (*Lancet* **366**, 1894–1898 (2005)), that draws on multiple evasion strategies to disarm or escape immune responses. Understanding how HIV is such a successful pathogen still constitutes an important research goal—one essential for successful vaccine discovery and development of other therapeutic interventions.

The HIV Vaccine Enterprise was first announced in 2003 after consultations with leading scientists and key health policy makers (*Science* **300**, 2036–2039 (2003)). The discussions identified various bottlenecks and hurdles (intellectual, scientific and infrastructural) that have precluded HIV vaccine discovery and/or development. A blueprint for the strategy adopted by the Global HIV/AIDS Vaccine Enterprise was outlined in early 2005 (*PLoS Medicine* **2**, e25 (2005)). What is unique about this endeavor is that sponsor funding is not limited to the BMGF; instead, other sponsors, such as the Wellcome Trust and various national or international

health organizations, including the US National Institute of Allergy and Infectious Diseases and the World Health Organization, participate in the HIV Vaccine Enterprise. However, the BMGF specifically states that funding awarded under its auspices should not duplicate efforts already funded by other sponsors. More unusually, lay people can also contribute to the effort coordinated by the HIV Vaccine Enterprise by donating spare computer processing time to Rosetta@home, which will harness this computing power to run massive parallel processing analyses of protein structural data and other analytical tasks. Thus, the project requires collaboration on the part of the sponsors in addition to collaboration among research consortia awarded funding.

Among the goals identified by the HIV Vaccine Enterprise is the establishment of central resource facilities that can test defined parameters using standardized assays with uniform reference samples, such that the efficacy of various vaccine candidates can be compared meaningfully. Likewise, training of both clinicians and laboratory technicians working in areas affected by AIDS or where clinical data will be collected is imperative to ensure that such data are sufficiently robust to undergo comparative analyses. Local infrastructure must be developed to have trained people recruit, test and monitor outcomes of research subjects when clinical trials are warranted. A common set of evaluation parameters will ensure that any differences noted among the various vaccination protocols can undergo statistical comparative analysis.

In the past, intellectual property rights have represented a nonscientific hurdle to vaccine and drug discovery. Accordingly, applicants for funding by the HIV Vaccine Enterprise must waive certain claims to potentially patentable material. Somewhat akin to open source computer code, participants are asked to share and/or improve on existing methodology to achieve the common goal of developing an effective vaccine that can be rapidly disseminated to the populations most vulnerable to infection.

Another consideration that has in the past plagued conventional vaccine or drug manufacturers is potential litigation arising from adverse effects due to vaccination or product testing. Reasonable protective mechanisms must be in place both to protect research subjects and to ensure that the vaccine development enterprise is not jeopardized. Whether a portion of the HIV Vaccine Enterprise funding will be dedicated to people harmed by adverse vaccine side effects remains to be clarified. Undoubtedly, negotiations with both national regulatory and legislative bodies will be required as the scientific discovery process identifies potential vaccine candidates or the means to elicit more effective immunization protocols.

An estimated 40 million people are now living with AIDS, and the disease shows no signs of abating. The social and economical costs to developing countries are devastating. It is imperative that an effective vaccine be developed to stem this relentless tide. Success, whether via the HIV Vaccine Enterprise or more conventional routes, cannot come soon enough. 