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LETTERS

HIV-1 Diversity and Vaccine Development

The inexorable spread of the human immunodefiency virus (HIV) has prompted an urgent effort to develop an AIDS vaccine. The diversity of HIV in human populations poses an unprecedented challenge for the development of a highly effective vaccine. A recent meeting at the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases, National Institutes of Health, organized in collaboration with the World Health Organization and the Joint United Nations Programme on HIV/AIDS, focused on the genetic diversity of HIV and strategies to develop vaccine candidates. More than 95% of new HIV infections occur in developing countries, and effective vaccines would no doubt help to control the epidemic. A high level of diversity of HIV exists among different populations, and vaccine trials for the developing world will also need to address factors such as concurrent infectious diseases, access to health care, and the ability to deliver and test vaccines. The relevance of HIV genetic diversity to vaccine efficacy remains unknown.

The meeting led to consensus recommendations on how best to address this scientific issue in the context of current vaccine efforts. Parallel trials of vaccine candidates from different clades are needed to address their relevance to immune protection. Although clade B is the most frequent virus type in the Americas and in parts of Asia, clade C viral strains are most prevalent in southern Africa and Asia and represent the most abundant genetic subtype worldwide. In Africa, clades A, C, and D cause the vast majority of HIV-1 infections. Recent analyses of genetic relatedness indicate that the diversity within any one clade of HIV may be no greater than the diversity between clades (1, 2), although for specific gene products, such as Env, the intraclade diversity may be less than the variation between two clades. In addition, the degree of diversity varies according to viral gene product. Therefore, it is important when matching genetic sequences to consider the specific viral gene product used as an immunogen.

Although genetic diversity may affect immune responses to HIV-1, its significance for protective immunity is unknown. Significant cytolytic T lymphocyte cross-reactivity can be demonstrated between Gag proteins of clades B and C, but clade-specific epitopes are also evident. Similarly, antisera from one clade can neutralize another, and neutralization phenotype does not correlate with the clade of origin (3). Thus, the importance of matching clades in a vaccine candidate to the naturally occurring viruses in a geographic region has not been established. Although the genetic diversity among HIV-1 strains may be an obstacle to protective immunity, there is little scientific rationale for matching clades to the country from which they emanate. The consensus reached is that the testing of multivalent vaccines should proceed, but practical limitations dictate that vaccine candidates should be representative of clades, rather than country-specific. Extraordinary costs in dollars, man-hours, and time would result from the parallel testing of multiple parallel vaccine prototypes. At the same time, the importance of testing vaccines "relevant" to each country's HIV isolates is evident. Together, these

constraints dictate a finite representation of clades in a multivalent vaccine, and the group concluded that a combination clade vaccine--for example, including clades A, B, and C--would cover the majority of HIV-1 infections worldwide.

The efficacy of a multiple-clade versus single-clade HIV vaccine candidate remains an important, unanswered scientific question. The generation of such a multiclade candidate will be of international importance and should remain high on the scientific agenda. Unprecedented international agreement and interagency coordination will be required to advance such candidate into human testing and efficacy trials.

Gary Nabel,
Vaccine Research Center,
National Institutes of Health,
MSC-3005,
40 Convent Drive,
Bethesda, MD 20892,
USA.
E-mail: gnabel@mail.nih.gov

William Makgoba,
South Africa Medical Research Council,
Post Office Box 19070,
Tygerberg 7505,
South Africa.

Jose Esparza
World Health Organization-Joint United Nations Programme on HIV/AIDS,
1211 Geneva 27,
Switzerland.

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