BILL & MELINDA GATES foundation

Diversifying the Pipeline of Product Concepts for an HIV Vaccine

RFP Overview and Guidelines

The Collaboration for AIDS Vaccine Discovery

Table of Contents

I. INTRODUCTION

The need for a preventive HIV vaccine is greater today than ever before. HIV has infected more than 33 million people worldwide, with the majority of affected populations in developing countries, and an estimated 2.7 million people become newly infected with HIV every year. Life-saving antiretroviral therapy is now reaching millions, but for millions more who need therapy, the drugs are not yet available. For every 2 persons starting therapy, 5 become infected with HIV. A safe, effective, and affordable vaccine is needed to stem the tide of new infections, conserve valuable resources for prevention and treatment, and gain sustainable control over the pandemic.

The Bill & Melinda Gates Foundation has made major investments in the development of an HIV vaccine. The Collaboration for AIDS Vaccine Discovery (CAVD) initiative, launched by the foundation in 2006, established a new model of collaboration and cooperation in HIV vaccine research. By supporting several vaccine discovery consortia that are separately pursuing novel candidate vaccines but linked by a commitment to sharing of data and materials and supported by a common platform of centralized services, the CAVD enables the bold pursuit of novel vaccine concepts in a supportive and enabling environment. The focus of the CAVD has been on translational research, harnessing knowledge to develop new vaccine concepts and to advance the most promising of them to clinical trials.

The goal of this Request for Proposals (RFP) is to fortify our commitment to translational research, building on current successes while infusing even greater diversity into the pipeline of product concepts for HIV vaccines. In this second phase of the CAVD, we will measure success by how rapidly novel ideas and the latest scientific advances are captured as new product concepts, the efficiency with which a diverse portfolio of product concepts is explored, and the extent to which capacity to advance a range of products to clinical trials is ensured through the collective effort of major funders and implementers. While the foundation will continue to invest in innovative early discovery, support the development of advanced products, and invest in an enabling environment including centralized service facilities, this solicitation is focused solely on the diversification of the product concept pipeline, from product conceptualization to clinical trials at the stage of first-in-man.

2. BACKGROUND

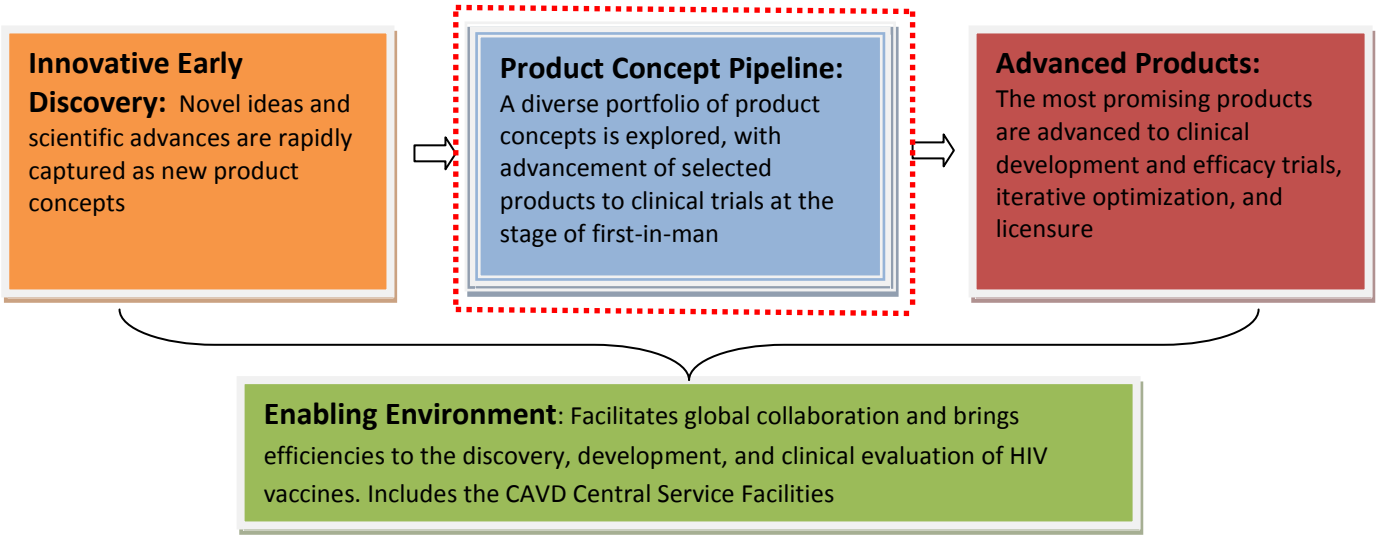
a. Bill & Melinda Gates Foundation's HIV Vaccine Strategy

The number one global heath priority of the Bill & Melinda Gates Foundation is discovering and introducing vaccines for infectious diseases, including vaccines for HIV. The goal of the foundation's HIV vaccine strategy is to develop and ultimately deliver a preventive HIV vaccine that will significantly reduce HIV incidence, with acceptability and affordability in populations in developing countries most affected by HIV/AIDS. HIV vaccine investments will focus on three areas:

- Follow-on trials informed by the findings of the RV144 HIV vaccine trial in Thailand
- Discovering and developing promising vaccine candidates
- Encouraging greater collaboration and coordination among HIV vaccine scientists, funders, and advocates

To achieve these goals, the foundation will support four sub-initiatives:

- Priming the early concept pipeline with small investments in highly innovative high risk/high reward discovery projects
- Supporting a pipeline of novel product concepts that are outside of current paradigms and/or not sufficiently funded by others
- Efficiently advancing the most promising HIV vaccine candidates to human efficacy trials
- Continuing support for an enabling environment that facilitates global collaboration and brings efficiencies to the discovery, development and clinical evaluation of HIV vaccines. This sub-initiative includes the CAVD Central Service Facilities.



This RFP pertains to the product concept pipeline (the top middle box above).

b. The CAVD Framework

In 2006, the foundation launched a major initiative in HIV vaccines with the creation of the CAVD. The CAVD is an international network of scientists and experts dedicated to designing novel HIV vaccine candidates and advancing the most promising candidates to clinical trials. The CAVD operates on the principle that accelerating progress towards an HIV vaccine requires the creativity of individual investigators supported by a collaborative approach that emphasizes the sharing of scientific information and the standardization of laboratory techniques and data analysis. Within the framework of the CAVD, the foundation has funded 23 grants supporting more than 500 investigators across 100 institutions in 19 countries.

Since the inception of the CAVD, the benefits of the collaborative model have been definitively established, and several novel vaccine product concepts have been significantly advanced, some to the stage of early-phase human clinical trials. As a key partner and supporter of the Global HIV Vaccine Enterprise, the foundation has continued to shape its HIV vaccine investment to complement the work of other major funders, catalytically garner the support of others for new and novel vaccine product concepts, and continually evaluate the strengths and weaknesses of the CAVD and its enabling environment. As the foundation begins to fund additional projects within the

CAVD in 2011, the content and focus of the CAVD will evolve but the basic model will be retained and fortified.

c. Goal of this RFP

The goal of this RFP is to diversify the product concept pipeline, from product conceptualization to clinical trials at the stage of first-in-man. The focus of this solicitation is on HIV vaccine concepts that have the following characteristics:

- Novel
- Potential to become a product
- Insufficiently supported by other funders
- Require, or clearly benefit from, the CAVD collaborative model to advance to human clinical trials

The approaches under consideration for this call for applications include the following topic areas:

I. **HIV Vaccines for Containment at the Portal of Entry**
II. **Novel HIV Vaccines to Elicit Protective Antibodies**
III. **Replicating Viral Vectors for an HIV Vaccine**
IV. **Passive Immunization with Human Monoclonal Antibodies for HIV Prevention**

Additional detail for each topic area, including information of what will not be considered for funding, is listed under the individual topic headings below.

Assuming that proposals of sufficient merit are received, this solicitation is expected to fund grants in the range of approximately $0.5 to 3.0 million per year per grant over approximately three years. Subject to satisfactory attainment of the grant's negotiated milestones, an additional 2 to 3 years of funding may be possible for successful projects that are on a clear product development pathway. Grant awards against this solicitation will be made in 2011 and early 2012. Research under these or additional topic areas pertinent to the Product Concept Pipeline of the CAVD may also be solicited by mechanisms separate from this RFP.

3. TOPIC AREAS

I. HIV Vaccines for Containment at the Portal of Entry

Roadblock: Emerging science is painting a clear picture of the early events in HIV infection and the cascade of immune system damage that rapidly ensues. The "window of opportunity" for vaccine-mediated prevention of infection or early containment of HIV at the portal of entry may be more narrow than previously recognized. The majority of HIV transmission occurs across the genital or rectal mucosae, and novel vaccine concepts to block entry or eliminate HIV or HIV-infected cells, at the mucosae or before appreciable systemic spread has occurred, are urgently needed.

What We're Looking For: The goal of this topic is to identify, design and evaluate novel HIV vaccine product concepts targeted to the very earliest stages of HIV transmission at mucosal surfaces. The outcome of research under this topic area will be to define the requirements for, and to enable the clinical evaluation of, active immunization or other novel immune interventions for targeting and elimination of HIV or HIV-infected cells at the portal of entry.

Successful proposals will be focused on advancing a clear product concept and may include one or more of the following components, among others:

- Evaluation of the potential of antibodies in secretions to impede HIV transit through mucus and eliminate its infectivity, the nature and mode of action of these antibodies, and the development of vaccine concepts capable of eliciting such antibodies
- Studies of novel receptors and other virus/cell interactions required for transit of HIV across epithelial barriers, and development of vaccine concepts to elicit protective antibodies that block such receptors/interactions
- Exploration of the requirements of HIV interaction with specialized dendritic cells at mucosal surfaces, especially those that may facilitate transmission of virus to CD4 T cells *in situ* and the transit of virus through sub-mucosal tissues to target cell-rich areas, with a focus on vaccine concepts aimed at interrupting these interactions
- Technology-driven approaches for acceptable, efficient, and cost-effective collection of mucosal samples specifically required for the evaluation of vaccines targeted at the portals of entry for sexual transmission of HIV in humans and non-human primates
- Novel *in vitro* and *in vivo* systems for the evaluation of antibodies for HIV prevention at the portal of entry
- Development of product concepts for efficient and durable targeting and elimination of HIV-infected cells at the portal of entry
- Adaptation of non-human primate models of HIV/AIDS to permit efficient evaluation of strategies to block early events of HIV or SIV transmission, including vaccine combinations acting in the eclipse and early dissemination stages of infection, respectively
- Technical development of platforms for the sustained delivery of protective antibodies or other means of inhibiting HIV entry at anatomical sites where sexual transmission of HIV occurs, including but not limited to engineered commensal bacteria

For this initiative, we will not consider funding for:

- Basic research in mucosal immunology
- Studies aimed at the development of mucosal vaccines or adjuvants without a specific translational focus on products to contain HIV at the portals of entry for sexual transmission
- Basic research studies of HIV biology and immunology at mucosal surfaces without a clearly defined translational focus
- Products currently under clinical investigation.

II. Novel HIV Vaccines to Elicit Protective Antibodies

Roadblock: Elicitation of broad and potent neutralizing antibodies has been considered to be an important, if not an essential, component of a highly effective HIV vaccine, but effort to generate such antibodies by active vaccination has been largely unsuccessful. Emerging science has identified some of the roadblocks to the development of HIV-neutralizing antibodies, while other recent evidence suggests that non-neutralizing antibodies with different effector functions may also contribute to protection.

What We're Looking For: The goal of this topic is to identify and evaluate novel and innovative HIV vaccine product concepts for the elicitation of protective antibodies, including a broad range of antibody specificities and effector functions. Research under this topic area may include the development of new technologies insofar as they are clearly needed to efficiently develop and evaluate a specific product concept.

Successful proposals will be focused on advancing a clear product concept and may include one or more of the following components, among others:

- New approaches to overcome limitations on the generation of broadly active HIV-neutralizing antibodies, including but not limited to those imposed by the germline antibody repertoire, immune tolerance mechanisms, or requirements for exceptionally high levels of somatic hypermutation/affinity maturation
- Development of novel product concepts based on natural or artificial HIV envelope immunogens, provided they are based on a clearly articulated principle or mode of action within the range of potentially protective neutralizing or non-neutralizing antibody functions
- Technical development of high throughput, low cost assays for isolation of human monoclonal antibodies that mediate non-neutralizing HIV-inhibitory activities, including ADCC, ADCVI, and others
- Optimization of non-human primate models of mucosally-acquired HIV/AIDS for the evaluation of product concepts designed for the elicitation of non-neutralizing, protective antibodies
- Research on receptor-mediated antibody effector functions that may contribute to protection from HIV infection, with a clearly defined translational focus and linked to the development of novel product concepts to elicit such protective antibodies.

For this initiative, we will not consider funding for:

- Approaches that include *in vitro* or *in vivo* genetic manipulations of human cells
- Strategies that contemplate non-specific immune activation or suppression, or abrogation of central tolerance mechanisms
- Basic research on HIV-neutralizing antibodies or the ontogeny of B-cell lineages from which they are derived
- Approaches based solely on traditional "reverse engineering" or "rational immunogen design" without a clear pathway to evaluation of a product concept in man
- Studies based solely on the development of novel adjuvants
- Products currently under clinical investigation.

III. Replicating Viral Vectors for an HIV Vaccine

Roadblock: Vaccines elicit memory T-cells that require time to respond to infection and to fully manifest their protective effect. Soon after infection, HIV mediates extensive damage to the immune system and sets up an unfavorable environment for the coordination of a memory T-cell response. Shortening the lag period between HIV infection and a secondary immune response in vaccinated individuals could preserve vaccine-elicited immunity, with the potential to prevent infection or to control HIV replication to an extent that significantly slows disease progression and/or prevents secondary transmission.

What We're Looking For: The goal of this topic is to identify and evaluate novel HIV vaccine product concepts for more persistently stimulated or more rapidly recalled memory responses upon HIV infection. The focus will be to develop HIV vaccines using replicating vectors based on other viruses, selected for lack of pathogenicity in man and including, but not limited to, those capable of persistent replication.

Successful proposals will be focused on advancing a clear product concept and may include one or more of the following components, among others:

- Development of novel and safe live replicating viral vectors to express HIV antigens while maintaining replication capacity in humans.
- Studies with replicating vectors to delineate the relationships between target cells and organs, levels of vector replication and expression of HIV transgenes, and the maintenance of immune memory capable of rapid response to and elimination of HIV infection
- Utilization of non-human primate models of mucosally-acquired HIV/AIDS to evaluate the localization, homing properties and timing of memory responses to infection and the levels of protection or viral control attained with replicating vectors
- Genetic engineering of viral vectors with the goal of systematically improving or modulating one or more of the following: replication, persistence, safety in man, with specific focus on translational research on HIV vaccines for the developing world
- Surveillance in populations at high risk for HIV infection for the frequency and levels of pre-existing immunity to candidate replicating vectors

For this initiative, we will not consider funding for:

- Vaccines based on live attenuated or whole inactivated HIV
- Vectors capable of integration into human chromosomes
- Serotypes/genotypes of vectors with significant seroprevalence in populations at risk for HIV infection in the developing world when there is clear potential or precedent for prior immunity to decrease immunogenicity or to decrease the safety of the vector in these populations
- Products currently under clinical investigation

IV. Passive Immunization with Human Monoclonal Antibodies for HIV Prevention

Roadblock: The elicitation of broad and potent HIV-neutralizing antibodies by active immunization has been a major challenge in HIV vaccine development. While HIV-neutralizing human monoclonal antibodies of considerable potency and breadth have been identified recently, it is not known whether passive delivery of these or similar antibodies, or of antibody combinations, can offer significant protection from HIV infection, and in what epidemiologic settings passive immunization could play a significant role in HIV prevention.

What We're Looking For: The goal of this topic is to advance selected human monoclonal antibodies with demonstrated potency and breadth of HIV neutralization to human clinical trials at the stage of first-in-man. The outcome of research in this topic area will be to enable passive protection studies in selected populations at high risk for infection, to determine the requirements for protection, and to elucidate the potential contribution of passive immunization for temporary protection from HIV infection in defined and appropriate settings.

Successful proposals will be focused on advancing a clear product concept and may include one or more of the following components, among others:

- Technology-driven, *highly cost effective* approaches for the isolation of natural human monoclonal antibodies with broad and potent HIV-neutralizing activity, including the corresponding antibody genes.
- Strategies for efficient genetic engineering of human monoclonal antibodies for improved HIV-neutralization, modulation of effector functions, or improved pharmacokinetics *in vivo*
- Development and optimization of *more efficient* production technologies for research and clinical grade HIV-neutralizing monoclonal antibodies, with the ultimate goal of minimizing cost-of-goods for application of passive immunization for HIV prevention in the developing world
- Approaches to selectively combine human HIV-neutralizing antibodies to significantly improve potency and/or breadth, with the goal of complete coverage of HIV strains in the pandemic
- Utilization of non-human primate models of mucosally-acquired HIV/AIDS for efficient evaluation of the requirements, and of the levels and modes of protection, afforded by natural or engineered HIV-neutralizing monoclonal antibodies
- Novel technologies to improve the deliverability and durability of protection afforded by passively administered HIV-neutralizing monoclonal antibodies in developing world applications
- Technology-driven approaches for minimizing the potential for immunogenicity of HIV-neutralizing human monoclonal antibodies when passively delivered in humans of diverse genetic backgrounds
- Evaluation and optimization of HIV-neutralizing antibody safety and pharmacokinetics in Phase I clinical trials
- Studies of passively delivered HIV-neutralizing antibodies in HIV-positive individuals provided that they are on a clear path to the development of these antibodies for prevention

For this initiative, we will not consider funding for:

- Studies aimed at the elicitation of HIV-neutralizing antibodies by active vaccination, including immunogen design
- Basic research studies of HIV-neutralizing antibodies or antibody genes without a clearly defined

translational focus
- Development or optimization of vectors for gene transfer of antibody genes
- Development of new *in vitro* systems or animal models to study parameters of HIV neutralization

4. APPLICATION SUBMISSION PROCESS

a. Application Submission Process Overview

This RFP will make use of a mandatory two-step application process:

Step 1: Submission of a Letter of Inquiry (LOI) to the Bill & Melinda Gates Foundation. There is a five page limit on the LOI. Applicant organizations submitting an LOI MUST fully meet the eligibility criteria listed on page 12. Foundation staff will evaluate the LOIs. Applicants should generally receive a decision regarding whether or not the applicant will be invited to submit a full proposal within 60 business days of the November 1, 2010 or April 1, 2011 LOI Review Dates. Those applicants who are eligible and have projects of further interest will be invited to submit a full proposal.

- Letters of Inquiry must be submitted electronically, using the forms and process described at the following address: http://www.cavd.org/Pages/RFPOverview.aspx
- Each LOI must indicate which topic area (I-IV, page 5) is being addressed
- Applicants addressing more than one topic area must submit a separate LOI for each topic area. More than one LOI from the same organization is permitted.
- At the LOI step, it is important to read carefully the full guidelines for applicants given below to make certain that the applicant organization is fully capable of complying with all the requirements and terms of an award.

Step 2: If the LOI is successful, the applicant will be invited to submit a full proposal. Instructions on the preparation of full proposals will be provided at that time to the selected applicants.

b. Application Schedule

Timeline for Submissions, Review, and Awards

1. **August 2010:** RFP Launched
2. **September 1, 2010 through March 31, 2011:** LOI Submission Period
3. **November 1, 2010:** First Review Date for LOIs
4. **April 1, 2011:** Second Review Date for LOIs
5. **December 2010 through June 2011:** Invitations to Submit Full Proposals Sent
6. **Proposal deadlines:** Within 90 business days after receipt of invitation to submit full proposal
7. **June 2011 through June 2012:** Grants Awarded

c. Application Instructions

Please limit the response to 5 pages using 10-point font and 1-inch margins. Page size must be set to U.S. letter standard 8.5 x 11.0 inches. The filename of the completed LOI document should include the Principle Investigator's last name, institution, and shortened name for project (example: PI Name_Institution X_LOI Application.doc). Specific application instructions may be found in the *Letter of Inquiry instructions*.

Instructions for the preparation of full proposals will be provided to those invited to submit a full proposal. Invited full proposals must define a novel product concept for an HIV vaccine or vaccine-related approach and propose clear project goals. The applicant must clearly state the interim objectives to be achieved during the project, identify impediments or critical decision points that could require a revision in the work plan or milestones, and provide a detailed schedule or time line for the attainment of each milestone and/or goal.

d. Frequently Asked Questions

Answers to frequently asked questions about the RFP may be found in the document *Diversifying the Pipeline of Product Concepts for an HIV Vaccine: Frequently Asked Questions*.

5. APPLICATION REVIEW PROCESS

a. Application Review Process Overview

Foundation staff will review all completed Letters of Intent (LOI) received by the specified review dates and will select from among them projects for which the foundation would like to receive a full proposal. Due to expected high volumes, individual critiques or feedback as to why LOIs were not selected will not be provided.

The foundation will use internal and external reviewers to advise on the merit of full proposals but final selection decisions will be made by foundation staff.

b. Evaluation Criteria

- Novel: Is the proposal likely to result in, or significantly advance, a novel product concept for an HIV vaccine?
- Potential Product: Does the potential for a defined product result from the proposed research, and what is the putative mechanism by which it would protect from HIV infection in humans?
- Collaboration: Can it be demonstrated that the research requires, or clearly benefits from, participation in the CAVD collaborative model?
- Other Support: Would the Bill & Melinda Gates Foundation's support, wholly or in part, of this research advance a product concept in a way that could not readily be achieved

through other funding mechanisms? Would funding from the foundation leverage additional funding from other sources?

- Significance: If successful, would the project make a major contribution to the development of an HIV vaccine?
- Topic Responsiveness: Does the application appropriately respond to one of the RFP topic areas?
- Proposal quality: Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the proposal? Does the proposal acknowledge potential problem areas and consider alternative tactics? Are the proposed time line and interim milestones appropriate, feasible and technically sound?
- Organizational and Investigator Capability: Is the research and development team appropriately trained, experienced and well suited to carry out this work? Is there strong evidence of substantive organizational capability and commitment? Does the environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environments including partnerships with industry or employ useful collaborative arrangements? Is there adequate evidence of institutional support?

6. RULES AND GUIDELINES

a. Eligibility Criteria

Applicant organizations must be individual non-profit organizations, for-profit companies or other recognized institutions that can successfully execute the activities in their respective technical area. Applicants awarded projects will be expected to actively collaborate within the CAVD and sign the CAVD Data & Materials Sharing Agreement (described in Section 6.f).

b. Allowable Costs

Grant funds may be used for the following costs: personnel, necessary travel, supplies, contracted services, sub-grants, and consultants. Partial or full support for equipment may be requested subject to the circumstances described below. Please provide budget estimates according to these categories.

- Project Manager: For larger consortia, assume that you will need to budget at least half time of a Project Manager to participate in the CAVD.
- Equipment: Use of any equipment purchased with grant funds is limited by law to charitable purposes for the depreciable life of the equipment. Please note that for many non- U.S. entities, U.S. tax law considerations may affect whether the Bill & Melinda Gates Foundation will permit purchase of equipment with a depreciable life

that is greater than the grant period being requested. In such cases, leasing would be preferable.

- Indirect costs: The Bill & Melinda Gates Foundation provides a limited amount of indirect costs, if any, based on the nature of the applicant organization.
- Travel funds to participate in meetings twice a year for key members of the team.

c. Privacy Notice

To help foundation staff in their evaluation and analysis of projects, all proposals, documents, communications, and associated materials submitted to the Bill & Melinda Gates Foundation (collectively, "Submission Materials") will become the property of the Bill & Melinda Gates Foundation and may be subject to confidential external review by independent subject matter experts and potential co-funders in addition to analysis by the Bill & Melinda Gates Foundation staff. Please carefully consider the information included in the Submission Materials. If you have any doubts about the wisdom of disclosure of confidential or proprietary information, the Bill & Melinda Gates Foundation recommends you consult with your legal counsel and take any steps you deem necessary to protect your intellectual property. You may wish to consider whether such information is critical for evaluating the submission, and whether more general, non-confidential information may be adequate as an alternative for these purposes.

We respect confidential information we receive. Nonetheless, notwithstanding your characterization of any information as being confidential, the Bill & Melinda Gates Foundation may publicly disclose all information contained in Submission Materials to the extent as may be required by law and as is necessary for potential co-funders and external reviewers, such as government entities, to evaluate them and the manner and scope of potential funding consistent with appropriate regulations and their internal guidelines and policies.

d. Warranty

By providing any Submission Materials, the sender warrants the Bill & Melinda Gates Foundation that they have the right to provide the information submitted.

Applicants with questions concerning the contents of their Submission Materials may contact the Bill & Melinda Gates Foundation at: cavdinfo@gatesfoundation.org

e. Global Access

Grant recipients will be required to use good faith efforts to conduct and manage the research, technologies, data and innovations involved in funded projects in a manner that enables (a) the knowledge gained during the project to be promptly and broadly disseminated, and (b) the intended product(s) to be made available and accessible at reasonable cost to the developing countries of the world. The Foundation refers to this as "Global Access."

As part of the foundation's review and evaluation of each full proposal, due diligence will be conducted with respect to each applicant's ability and commitment to manage technologies, data, and materials in a manner consistent with the Global Access objectives. Due diligence activities may include inquiry into an applicant's:

1) Freedom to operate (FTO) and ability to freely use and acquire needed background technology;
2) Commitment to share data and materials generated through the project with other CAVD members as well as the broader scientific community; and
3) Commitment to promote the utilization, commercialization and availability of technologies (including a final vaccine) invented or further developed for public benefit in developing countries.

In order to facilitate this due diligence process applicants are encouraged to provide information with respect to items 1-3 above in their submission materials.

f. Data & Materials Sharing

The primary goals of the CAVD are to (i) accelerate the development of an HIV vaccine through the development and use of innovative technologies and consistent laboratory practices and (ii) conduct activities within the CAVD Projects in a manner that is consistent with and in furtherance of the Global Access objectives. Consistent with these goals, grant recipients will be expected to communicate and collaborate on a periodic basis with other CAVD grantees pursuing similar overarching goals, as well as with other partners of the Global HIV Vaccine Enterprise. Specifically, a primary focus of the CAVD has been the creation and implementation of a set of principles and guidelines to facilitate the rapid and widespread sharing of data and other vaccine-related scientific information within the CAVD network and to the broader scientific community. These principles, described within the CAVD Data & Materials Sharing Agreement (DMSA), have been formally agreed to by all members of the CAVD network.

Recipients of grant funds under this RFA will be expected to sign up to the DMSA principles, and, in particular, will be expected to use best efforts to work in a collaborative fashion with collaborators, partners, sponsors and other CAVD grantees to achieve an exchange of information to the greatest extent possible and to make available to qualified researchers any new technologies, materials, modified organisms, non-human specimens, and other novel creations discovered or produced with grant funds.

7. RESEARCH ASSURANCES

While not necessary for the LOI, as applicable to the individual project, the Bill & Melinda Gates Foundation will require that for each venue in which any part of the project is conducted (either by your organization or a subgrantee or subcontractor) all legal and regulatory approvals for the

activities being conducted will be obtained in advance of commencing the regulated activity. The foundation will further require you to agree that no funds will be expended to enroll human subjects until the necessary regulatory and ethical bodies' approvals are obtained.

a. Research Involving Human Subjects

You agree that no funds will be expended to enroll human subjects in any research project subject to Institution Review Board (IRB) or independent ethics committee (IEC) approval until such approval has been obtained for each site.

b. Clinical Trials

Should you be funded to conduct clinical trials on human subjects, a condition of the grant is your agreement that the appropriate Institutional Review Boards ("IRBs") and ethical committees will review and approve the clinical protocols prior to trial initiation. You further agree to conduct clinical trials associated with the project under the generally accepted principles of "Good Clinical Practices" as defined by the International Conference on Harmonization (ICH) E-6 Standard, the United States Food and Drug Administration (FDA) or the European Agency for the Evaluation of Medicinal Products (EMEA), as applicable. You acknowledge and agree that, as between you and the Foundation, you take and will have full responsibility for all compliance, data safety, monitoring, and audit requirements of the relevant regulatory agencies, both for yourself and all other sites included in the project, including those activities conducted through subgrants, subcontracts or other collaborative efforts. You acknowledge and agree that any activities by the Foundation as the grantor funding the Project, including its review of the Proposal or suggested modifications to the Project, does not modify the provisions of this paragraph or constitute the basis for any claim by you against the Foundation

c. Coverage for Research Sites

You agree that for each venue in which any part of the Project is conducted (either by your organization or a subgrantee or subcontractor) all legal and regulatory approvals for the activities being conducted will be obtained in advance of commencing the regulated activity. You further specifically agree that no funds will be expended to enroll human subjects until the necessary regulatory and ethical bodies' approvals are obtained.

d. Regulated Activities

The coverage requirements set forth in the preceding paragraph include but are not limited to regulations relating to: research involving human subjects; clinical trials, including management of data confidentiality; research involving animals; research using substances or organisms classified as Select Agents by the U.S. Government; use or release of genetically modified organisms; research use of recombinant DNA; and/or use of any

organism, substance or material considered to be a biohazard, including adherence to all applicable standards for transport of specimens, both locally and internationally, as appropriate. As applicable, regulated activities and their documentation are to be conducted under the applicable international, national, and local standards. Documentation of research results should be consistent with regulations and the need to establish corroborated dates of invention and reduction to practice with respect to inventions where this is relevant.

e. Institutional Review Board Approval

You agree to obtain the review and approval of all final protocols by the appropriate Institutional Review Boards (IRB) and ethical committees prior to enrollment of the first human subject and when using human material. A similar provision applies to Institutional Animal Care and Use Committee approval of studies involving animals, and Institutional Biosafety Committee for biohazards and recombinant DNA. You agree to provide prompt notice to the Foundation if the facts and circumstances change regarding the approval status of the IRBs or ethical committees for any final protocol(s).

f. Provision of Care for Human Subjects Research

In keeping with "Good Clinical Practice" standards, you will disclose to subjects and the IRBs what care and/or referrals will be available through participation in the study. Institutional policies regarding what care will be provided to personnel who are injured as a result of their work on the Project should be similarly be developed, approved and implemented with notice to the employees.

g. Use of Animals in Research

You agree to be responsible for the humane care and treatment of animals in projects supported in part or whole by Foundation funds; and to adhere to the official guidelines for animal research applicable in the country and locality where the trial is being conducted. No grant funds may be expended on studies involving animals until all requisite approvals are in place, and notification to that effect has been provided to the Foundation. For purposes of this provision, an "animal" is defined as any live, vertebrate animal used or intended for use in research, research training, experimentation, biological testing or for related purposes. In the case of multi-national collaborations, the standards of each country may be followed, as long as (i) differences do not interfere with the design and analysis of the Project, and (ii) regulations in your institution and host country do not conflict with the management of the Project.

You agree to take responsibility for compliance of all subgrantees or subcontractors (if any) with the appropriate animal welfare laws, rules and regulations. You must report annually

as a part of your progress report that the activities are being conducted in accordance with applicable laws in each respective venue (e.g., U.S. grantees must use the U.S. Public Health Service standards. Non-U.S. grantees may cite national laws or the CIOMS International Guiding Principles for Biomedical Research Involving Animals (see http://www.CIOMS.ch/frame_1985_texts_of_guidelines.htm) if there is not relevant national standard.