Amendment #1

to RFP-NIH-NIAID-DMID-04-21

"TB Vaccine Testing and Research Materials"

Amendment to Solicitation No.:	NIH-NIAID-DMID-04-21
Amendment No.:	1
Amendment Date:	November 17, 2003
RFP Issue Date:	October 8, 2003
Issued By:	Jacqueline Holden Senior Contracting Officer NIH/NIAID Contract Management Branch 6700-B Rockledge Drive Room 2230, MSC 7612 Bethesda, Maryland 20892-7612
Point of Contact:	Hank Durand, Contract Specialist
Name and Address of Offeror:	To All Offerors

The above numbered solicitation is hereby amended to **replace** the Statement of Work and Notes to Offerors as follows:

For Information Purposes: Paragraphs A.3, A.5., A.6., B.1., C.2., and Note 5 are modified.

- Except as provided herein, all terms and conditions of the RFP document NIH-NIAID-DMID 04-21remains unchanged and in full force and effect.
- The hour and date specified for receipt of offers REMAINS: **February 06, 2004, 4:00PM, EST.**
- Offerors must acknowledge receipt of this Amendment #1, on each copy of the proposal submitted.

Failure to receive your acknowledgement of this amendment may result in the rejection of your offer.

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Statement of Work
TB Vaccine Testing and Research Materials
RFP DMID-04-21

Statement of Work

Independently and not as an agent of the Government, the Contractor shall furnish all necessary services, qualified professional and technical personnel, materials, equipment, and facilities, not otherwise provided by the Government under the terms of this contract as needed to perform the work set forth below.

[GENERAL NOTE TO OFFEROR]

A. Development, Production and Characterization of Research Reagents and Mycobacterial Strains:

As directed by the Project Officer, the contractor shall:

A1.Systematically characterize virulent clinical strains/isolates and commonly used virulent reference strains of Mtb as well as of *M. bovis* BCG with regard to:

a. Their protein expression profile and antigen composition when grown under a series of identical laboratory conditions.

b. Their virulence in animal models of infection and disease by assessing parameters such as, but not limited to, growth kinetics, organ burden and other relevant measures.

c. Their suitability as challenge strains when used with standardized vaccine constructs under identical test conditions.

d. Any potential difference among strains when used as challenge material in standardized vaccine testing models with reference vaccines.

[NOTE 1 TO OFFEROR]

A2. Develop methods and protocols for the preparation, scale up, purification, characterization and quality control of recombinant and native mycobacterial antigens, proteins, lipids and lipoglycans,

monoclonal and polyclonal antibodies, as well as mycobacterial cellular fractions.

a. Using selected and well characterized reference strains of Mtb, develop or utilize optimized techniques and methods for the preparation of non-recombinant mycobacterial antigens, proteins, lipids and lipoglycans, and of cellular fractions and make these methods available to the research community (as publications or upon request).

b. Develop methods to produce recombinant mycobacterial proteins in appropriate hosts. For this, develop or implement molecular techniques to clone and express selected recombinant antigens/proteins. Furthermore, evaluate appropriate bacterial species for their suitability to express active and/or immunogenic mycobacterial proteins, and for their suitability to facilitate large scale production and purification of recombinant mycobacterial proteins.

c. Develop suitable assays to characterize and validated the biological activity of native and recombinant antigens and proteins and lipids from large-scale preparations as well as from selected small scale preparations, where appropriate.

d. Prepare short protocols for protein expression, quality control and suggested purification to be distributed with recombinant clones and plasmids carrying recombinant mycobacterial proteins. This is to facilitate production of these proteins by outside investigators.

e. Develop and validate methods for inactivation of virulent mycobacterial cells harvests that are intended for distribution to outside investigators or that will be used for the preparation of research reagents. Cell inactivation shall be done using methods that will not interfere with the intended use of the preparations. These methods may include, but are not limited to gamma irradiation, heat or chemical inactivation. Quality control procedures for verification of cell death shall also be developed.

[NOTE 2 TO OFFEROR]

A3. Using methods validated in Statement of Work A2, identify and prepare relevant antigens, proteins, lipids, lipoglycans and cellular fractions, as well as monoclonal and polyclonal antibodies potentially useful for, but not limited to, a) the development of diagnostic tools, b) the identification of surrogate markers of disease progression, and correlates of protective immunity; c) the detection of host immune response to infection; and d) immunological assays to support research in TB:

a. Produce large scale batches of wet cell paste for distribution to outside investigators and for use under Statement of Work A3b. For virulent mycobacterial strains, cell pastes are to be inactivated as listed under Statement of Work A2e before making them available to outside investigators. It is anticipated that approximately 25 liters batches of culture may be grown per week and that approximately 2.5 kg of wet call past may be produced per year.

b. Prepare native mycobacterial antigens, proteins, lipids and lipoglycans using well characterized mycobacterial laboratory or clinical strains. It is anticipated that approximately 10 individual native mycobacterial proteins, and approximately 100 mg of lipids/lipoglycans

will be produced per year.

c. Prepare mycobacterial cell fractions including, but not limited to culture filtrates, cell wall and surface fractions, membrane proteins, soluble and cytoplasmic fractions. It is anticipated that approximately 5 g of cellular fractions will be produced per year.

d. Prepare sufficient stock cultures of recombinant bacterial clones, expression hosts or sufficient quantities of plasmids carrying recombinant genes for mycobacterial antigens, developed under Statement of Work A2b., for distribution to outside investigators; It is expected that per year approximately 10 new bacterial expression constructs will be developed and that approximately 10 ug of plasmid DNA will be provided to outside investigators.

e. Prepare sufficient quantities of recombinant proteins, developed under Statement of Work A2b. for distribution to outside investigators; It is expected that approximately 10 mycobacterial proteins will be routinely produced in recombinant bacterial hosts and that approximately 500 mg of recombinant protein may be produced per year.

f. Produce polyclonal sera and, where relevant, also purified monoclonal antibodies and culture supernatants to selected antigens. It is anticipated that monoclonal antibodies for approximately 10 antigens may be produced per year and that quantities of approximately 20 mg per purified antibody or 200ml of culture supernatant will be produced.

g. Provide customized large scale preparations of selected reagents to outside investigators where justified. Justification for the need of large scale preparations shall be solicited from requesting investigator and shall be discussed with the Project Officer.

[NOTE 3 TO OFFEROR]

A4. Provide and distribute well-characterized strains/isolates of Mtb and *M. bovis* BCG, as evaluated under statement of Work A1 to qualified researchers. It is expected that approximately 50 stock vials of each strain will be maintained.

A5. Produce purified genomic DNA from selected mycobacterial species, including virulent clinical strains/isolates . It is anticipated that genomic DNA will be prepared from up to 5 strains/isolates and approximately 1.5 mg of genomic DNA will be produced per strain/isolate.

A6. Provide and distribute to qualified investigators purified high molecular weight DNA preparations, produced under Statement of Work A5..

A7.Develop customized postgenomic resources for distribution to the qualified researchers and for use under the contract.

a. Produce customized microarray slides for selected mycobacterial species, including multi-species arrays. It is anticipated that approximately 200 array slides may be produced per year.

b. Develop molecular techniques that will facilitate the execution of relevant sections of the statement of work of this contract, such as the characterization of mycobacterial strains as listed in Statement of Work A1. The development of these techniques is not to exceed 5% of total contract activities.

A8. Initiate research collaborations to facilitate custom support through the contract. As part of research collaborations, the contractor shall:

a. Perform custom culture of selected mutant mycobacterial species or reference strains under conditions developed after consultation with outside investigators.

b. Produce reagents from mycobacterial strains submitted by outside investigators.

c. Utilize specialized methods or approaches for custom preparation of mycobacterial reagents.

d. Produce specialized custom genomic and post-genomic reagents as designed after consultation with outside investigators.

e. Conduct custom studies to characterize selected mycobacterial strains and constructs.

[NOTE 4 TO OFFEROR]

B. Organization, Maintenance and Distribution of Research Reagents:

As directed by the Project Officer, the contractor shall:

B1. Organize well characterized research reagents, produced as described in Statement of Work A., in a research reagent bank.

a. Maintain frozen stocks of characterized mycobacterial strains under controlled laboratory conditions.

b. Develop a computerized database to track and control the inventory of these reagents, document requests and shipment, and maintain electronic records of quality control performance.

c. Develop a contract web page summarizing all reagents, services and collaborations available through the contract, listing contact personnel and offering printable forms and instructions for reagent ordering; This web page is expected to be operational no later than 6 month after contract award and is expected to be updated when new reagents become available.

d. Develop quality control procedures and protocols for the characterization of each batch of antigen, protein, lipid and lipoglycans, cell fraction and genetic and genomic material.

e. Establish quality control procedures and protocols for the maintenance of bacterial stocks, seed stock and culture preparations.

f. Establish quality control data sheets for all reagents produced under this contract. These data sheets are intended to disclose the level of purity and the extent of characterization performed for each reagent.

g. Verify the biological activity in relevant assays for large scale preparation of native or recombinant protein, where possible. Biological activity of small scale preparations shall only be performed where relevant.

h. As part of the validation of alternative expression systems for recombinant proteins, where possible, evaluate the biological activity of recombinant proteins in appropriate biological assays.

i. Provide data sheets and culture instructions for each characterized mycobacterial strain as part of the reagent shipment.

j. Within 3 months of contract award, develop material transfer agreements to cover distribution of all research reagents listed above.

k. Within 3 month of contract award, establish criteria by which to determine qualifications that have to be met by outside investigators to receive research reagents, including post-genomic reagents, through the contract.

l. Package and ship, according to local and federal regulations covering the shipment of potentially infectious and/or hazardous material, requested research reagents to investigators worldwide. It is expected that shipping costs will be paid by the requestor.

[NOTE 5 TO OFFEROR]

C. Vaccine Testing and Optimization of Animal Models:

As directed by the Project Officer, the contractor shall:

C1. Validate and/or optimize existing small animal models of Mtb infection and TB disease for the purpose of estimating the efficacy of experimental agents. For the purpose of this solicitation, experimental agents shall be vaccines, adjuvants and immunomodulatory agents, and may include novel reagents suitable to produce immune protection against Mtb infection or TB disease or enhance the activity of other vaccines and or adjuvants.

a. Establish suitable testing models in mice, guinea pigs or rabbits, utilizing appropriate methods of infection and challenge to result in reproducible endpoints to estimate immune protection of experimental agents.

b. Evaluate the suitability of using multiple parallel or sequential animal models to obtain maximum information about particular experimental agents.

c. Develop standardized protocols and define performance expectations for each model that shall include quality control agents and data on acceptable experimental variability.

d. Establish baseline data for each model with a series of standard reference vaccines, vaccine/adjuvant combinations and/or immunomodulatory agents which will serve as controls for testing of novel candidate agents.

e. Establish activity ranges by which to demonstrate significant differences between reference agents and experimental agents to estimate efficacy.

f. Establish a series of animal models to be used for the evaluation of experimental agents at advanced stages of development for which more detailed assessment of activity is warranted. These models may include endpoints other than bacterial organ burden and may include or histological and immunological readouts.

g. Periodically develop, with input from the Program Officer and the expert panel of advisors, a limited set of scientific questions that need to be addressed to continuously improve the animal models and make them consistent with current scientific advances and findings.

[NOTE 6 TO OFFEROR]

C2. Implement standardized animal models validated under Statement of Work C1 at the relevant contract site(s) to test experimental agents as a service to the research community. Candidates for testing shall be reviewed together with the Project Officer and after consultation with an expert panel of advisors and shall be approved by the Project Officer.

a. Evaluate approved experimental agents in appropriate standardized animal models to estimate immunoprotective efficacy against challenge with virulent Mtb. While procedures shall be standardized, experimental protocols may be modified to obtain relevant information and maximal information about an experimental agent ant to determine its utility for advanced development and testing. It is estimated that approximately 10 novel experimental agents will be tested in approximately 10-20 experiments per year and that approximately 5 advanced candidates will be evaluated.

b. Evaluate preliminary safety and suitability of live, attenuated vaccine candidates, where appropriate, in animal models prior to initiating challenge studies.

c. Conduct preliminary evaluations, where appropriate, to determine optimal protocols and combinations of experimental agents prior to initiating challenge experiments**.**

d. Utilize standardized infection methods for each model and provide methods but may be

modified for each test agent.

[NOTE 7 TO OFFEROR]

C3. Within 6 months of contract award, establish standard operating procedures for receipt, review and acceptance of experimental agents for testing. These shall include:

a. Standardized testing request forms, available through the contract web site to specify a set of minimum information that must be submitted as part of each request for testing.

b. Minimum quality control data/information for each experimental agent that must be provided by each investigator submitting an approved experimental agent for testing. This may include, but is not limited to, purity data for proteins and nucleic acids, restriction maps for nucleic acids, and growth characteristics and safety of attenuated live vaccines in animal models. This process is to assure that only high quality, characterized agents will be submitted for testing and that reproducible data will be obtained. The responsibility for producing these data lies with the submitting investigator. The contractor may wish to verify the identity of an experimental agent using these data as a guide.

c. Development of procedures for interaction with outside investigators to assure confidentiality for data obtained through evaluation of experimental agents in animal models.

[NOTE 8 TO OFFEROR]

D. Contract Administration and Performance:

D1. Establish a coordinated plan for the integration of contract services and scientific studies. Scientific studies are to be designed so that contract activities can be improved on a continuous basis and that relevant findings from the research community can be translated to benefit contract activities. This plan is also to include coordination between all activities of the contract that require testing in animals. Close integration of all aspects of the contract is highly desirable will be an expectation for contract performance.

D2. Investigator Training and interaction with the research community to enhance contract activities.

a. Key personnel involved in the design and production of research reagents shall attend at least one scientific meeting or training course over the course of the period of the contract on requirements and quality control procedures for the production of biological materials.

b. Key personnel involved in the evaluation of vaccines, adjuvants and immunomodulatory agents are to attend at least one meeting or training course over the course of the period of the contract, on regulatory requirement for vaccines to be considered for clinical trials and/or the use of animal models in product development.

c. Key personnel is to attend periodic scientific meetings to communicate contract activities, solicit input and present scientific findings derived from contract activities to the community.

d. Conduct work in accordance with the CDC and NIH Guidelines for Biosafety in Microbiological and Biomedical Laboratories, and NIH guidelines for animal care and use. A copy of the applicable Biosafety guidelines can be obtained at: http://www.cdc.gov/od/ohs/biosfty/bmbl4/bmbl4toc.htm . These guidelines will also apply to all animal models that may be used as part of this contract.

e. Together with the Project Officer, establish an expert panel of advisors no later than 3 month after the contract award. This panel is to participate in the review of requests for testing of experimental agents in animal models, is to participate in annual contract meetings and provide advice to the contractor and the Project Officer on selected topics.

f. Schedule yearly meetings with the Project officer and the expert panel of advisors to discuss contract progress, pending issues and suggestions for improvement.

[NOTE 9 TO OFFEROR]

NOTES TO OFFEROR

[GENERAL NOTE TO OFFEROR] As part of the Technical Proposal, the offeror is expected to list examples for all approaches, techniques, protocols, models and procedures listed under the Statement of Work, as well as a solid rationale for their selection. Furthermore, the offeror is to demonstrate knowledge in the field of mycobacteriology and relevant animal models by discussing approaches to meet the work outlined in this solicitation. This information shall be in sufficient detail so that the quality of the Technical Proposal can be evaluated. The offeror should also list any shortfalls and alternative approaches that may need to be developed to meet the performance expectations set forth under the Statement of Work. It will be especially critical to address quality control procedures and minimum quality criteria that will be applied to reagents produced under the contract. The offeror is to list these criteria for sample reagents. The procedures and reagents proposed by the offeror may not be the final products produced under this contract. The offeror is to demonstrate expertise in all evaluations that are proposed and shall propose sub-contractors where appropriate. For the development of the Business Proposal, the offeror is to consider quantities and performance expectations listed in the Statement of Work and shall consider flexible production and testing schedules.

[NOTE 1 TO OFFEROR] As part of the Technical Proposal, the offeror shall propose reference strains, provide sample protocols for culture and evaluation of protein profiles of mycobacterial strains and shall provide a justification for their selection. The offeror shall also provide examples of studies to assess virulence and pathogenicity of mycobacterial strains. These evaluations should address whether differences in protein expression exist among reference strains maintained by different laboratories and under different growth conditions and whether these differences may affect results obtained with standardized vaccine candidates in challenge experiments. Clinical strains collected as part of the contract may be drug sensitive or drug resistant. As part of the Business Proposal, assume that a maximum of 10 strains will be characterized each year. These activities are to involve no more than 10% of the overall contract activities.

[NOTE 2 TO OFFEROR] As part of the Technical Proposal, the offeror shall propose a list of research reagents, and a rationale for their selection, that may be produced as part of this contract. The offeror shall furthermore list draft methods and protocols for preparation of selected reagents that may be applicable for work under the contract. This is to include examples for antigens, proteins, lipids and lipoglycans, as well as cell fractions The offeror shall also describe methods and bacterial hosts that may be useful for the production of active and antigenic recombinant proteins from mycobacterial species. The offeror shall furthermore demonstrate that facilities for irradiation of mycobacterial cell cultures, as well as facilities for the large scale production of mycobacterial cultures are available. Reagents provided by the current contract (see *http://www.cvmbs.colostate.edu/microbiology/tb/top.htm*) may be used as a guide for selection of materials proposed for production. Furthermore, the offeror shall outline quality control procedures that will be implemented for characterization of large scale and small scale protein batches and associated assays for characterization of biological activity, where appropriate, and shall propose methods and quality control procedures for suitable inactivation of virulent Mtb cell harvests.

[NOTE 3 TO OFFEROR] As part of the Technical and Business proposal, the offeror shall outline resources and techniques that may be required to produce research reagents as described in this section of the Statement of Work. The offeror shall also describe what infrastructure and facilities are available to produce these reagents at the extent requested. Statement of Work A3, d lists that approximately 10 ug of plasmid will be provided to outside investigators. Assume that this is an estimate of the total amount of plasmid DNA to be distributed by the contract per year and does not constitute estimates of amounts of

plasmid DNA distributed to individual investigators

[NOTE 4 TO OFFEROR] As part of the Business Proposal, assume that 2-3 active collaborations may be ongoing per year and that these activities will not exceed 5% of contract activities.

[NOTE 5 TO OFFEROR] As part of the Technical Proposal, the offeror shall list examples of web-pages and databases that may be used to meet this section of the Statement of Work and how these electronic tools will be utilized to optimize performance under this contract. The offeror shall furthermore provide examples of data, quality control protocols, quality data sheets and biological assays that may will be provided with individual batches of antigens/protein, as well as provide examples of biological assays that may be useful for the characterization of key or large scale antigens/proteins. The offeror is to provide documentation that space and equipment that will be needed to establish and maintain a reagent bank, and that includes adequate back-up systems, are available. The offeror shall provide examples of Material Transfer Agreements (MTA) as part of the proposal. These MTA shall address confidentiality and shall cover appropriate use of all research materials that may become available through the contract. This is to include prohibited use of research materials for use in humans as part of clinical trials but allow use of research reagents as part of clinical studies when used in laboratory assays with human derived materials. The offeror is to provide examples of criteria that will have to be met by outside investigators to receive reagents through the contract. The offeror is to address specifically using appropriate examples, how post-genomic reagents will be distributed and what qualifications are expected of outside researchers to receive these reagents through he contract. As part of the Business Proposal, assume that on-line ordering and maintenance of an interactive web-infrastructure may be part of this contract if it cost/benefit can be demonstrated and that any proposed infrastructure should be limited in scope and complexity. Also assume that up to 10 shipments will be made each week.

[NOTE 6 TO OFFEROR] As part of the Technical Proposal, the offeror shall provide protocols describing suitable challenge models in relevant small animal models and shall describe how experimental agents may be characterized in these models. The offeror should propose specific scientific questions that will be addressed and that are geared towards developing a better understanding of the respective animal models and their utility for vaccine testing. This is NOT to include basic research on animal models of infection and disease, but rather how best to design and employ challenge models to estimate vaccine efficacy and potentially, safety.

[NOTE 7 TO OFFEROR] As part of the Technical Proposal, the offeror shall provide examples of how testing of novel experimental, and also more advanced candidates will be conducted as part of the contract. This is to include hypothetical experimental agents and shall address how decisions will be made to move a candidate to different models and/or what performance would be expected from an active agent.

[NOTE 8 TO OFFEROR] As part of the Technical Proposal, the offeror shall provide examples of standard requirements for submitted reagents and a rationale for their selection. The offeror is to propose evaluation criteria for the acceptance of experimental agents and is to proposed decision points to move agents to more advance models.

[NOTE 9 TO OFFEROR] As part of the Technical Proposal, the offeror is to propose plans on how to integrate contract services and contract related research. The Technical Proposal is to include a detailed description of the expertise of the principal investigator and other key personnel or collaborators in working with all aspects of mycobacterial species, particularly virulent Mtb. under BSL-3 conditions, including experience in the design and execution of animal models of Mtb infection and TB disease, and the evaluation of vaccine candidates and related agents in challenge models of tuberculosis, molecular manipulation of mycobacteria, and expression and proteomic technologies and how these individuals will interact to bring their combined expertise to bear on the performance of this contract. The offeror shall also describe expertise utilizing biohazardous and potentially toxic materials, as well as radioisotopes, if the use of the latter is included in the proposal. In addition, procedures for the care of experimental animals shall be discussed. The offeror is to refrain from listing names of past collaborators that may have been involved in contract related activities. The offeror shall propose one overall Principal Investigator for the contract but may propose co-Principal investigators for any of the sub-components of the Statement of Work. The Business Proposal shall include funds for 1-2 key personnel involved in the production of research reagents and 1-2 key personnel involved in vaccine testing to attend the requested courses once during this contract period. The Business Proposal furthermore is to include funds to provide travel costs and per diem (estimates are to be based on government per diem rates) for the expert panel of advisors to attend one contract meeting per year in Bethesda, MD to meet with the Project Officer. Assume that the expert panel will consist of 3-4 scientists, of whom one individual may be from an institution outside the US. It is expected that the PI and Co-PIs will attend this meeting together with 2-3 additional support personnel. The business proposal is also to include funds for one scientific meeting per year for up to 2 key personnel (2 scientific meetings in total per year). One of these meetings may be an international meeting. These meetings are to provide the contractor the opportunity to interact with the research community and provide public updates on contract activities and to communicate important findings.