



**Middle Atlantic Regional Center of Excellence
for Biodefense and Emerging Infectious
Diseases Research**
<http://marcebiodefense.org/>

Request For Proposals (RFP)

MARCE Solicitation for Research Projects to be Incorporated into the Overall Research Plan of the RCE Competitive Renewal

Posted:	February 5, 2008
Letter of Intent Deadline:	February 19, 2008 <i>(Tuesday by 11:59 PM EST)</i>
Application Receipt Deadlines:	March 9, 2008 - Electronic version (with or without full institutional signatures) <i>(Sunday by 11:59 PM EST)</i> March 24, 2008 - Original version with all necessary institutional signatures <i>(Monday by 5:00 PM EST)</i>
Approximate Award Date:	March 1, 2009

THE MIDDLE ATLANTIC REGIONAL CENTER OF EXCELLENCE (RCE) FOR BIODEFENSE AND EMERGING INFECTIOUS DISEASES RESEARCH (the MARCE)

The MARCE fosters research that contributes to the defense of the population of the United States of America against biological threats including the deliberate release of bioterror agents and the natural emergence or re-emergence of infectious diseases. As part of its formally defined mission, the MARCE also maintains interactions with public health authorities within the Middle Atlantic Region so that should the need arise, the consortium can mobilize its technical resources to assist the public health authorities in the face of a large or unusual outbreak of disease, presumed bioterror incident or other catastrophe. The MARCE is one of 10 RCEs, each located in a different region across the USA, as designated by NIH. The current MARCE consortium encompasses approximately 60 scientists from 17 research institutions who are engaged in a series of collaborative

research projects (almost all of which represent collaborations that extend across institutional boundaries). Dr. Myron M. Levine, M.D., D.T.P.H., the Grollman Distinguished Professor and Director of the Center for Vaccine Development of the University of Maryland School of Medicine, serves as the Principal Investigator and Director of the MARCE. Dr. Alison O'Brien, Ph.D., Chair of the Department of Microbiology of the Uniformed Services University of the Health Sciences, serves as Co-Principal Investigator.

At periodic intervals during the past four years, the MARCE has advertised research grant opportunities such as Developmental Grants (that encourage research on high risk, high yield hypotheses), Career Development Awards, New Opportunities Grants and solicitations for new Research Projects (similar to R01s). In the past, new research grant proposal submissions were reviewed by an independent Ad Hoc Review Committee composed of senior scientists who are not directly involved in MARCE research.

The current MARCE research program (MARCE-1) is entering its sixth year. Meanwhile, the National Institute of Allergy and Infectious Diseases (NIAID) is undertaking the competitive renewal for the RCEs with June 3, 2008 designated as the final date for submission of the renewal proposal. Accordingly, the MARCE's Management and Oversight Committee (MARCE-MOC), which is composed of leaders of MARCE's Research Programs and Cores and serves as the Steering Committee for the consortium, has crafted an overall Research Plan that includes six research sub-themes accompanied by six Research Programs which will form the backbone of the overall scientific program of the MARCE renewal (MARCE-2) application. It is anticipated that each MARCE-2 (P01-like) Research Program will be composed of 4-5 individual but inter-related (R01-like) Projects.

The purpose of this RFP is to solicit research proposals to be considered as R01-like projects for inclusion in one of five MARCE Research Programs that will be described in the MARCE Competitive Renewal Application. *(A separate supplemental RFP will be advertised at a later date to solicit projects for the sixth Research Program).*

Some Guidelines for Solicited MARCE Research Projects Gleaned from the RCE Competitive Renewal RFA and other NIH Publications

The RFA for the Competitive Renewal that has been issued by NIAID (<http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-08-002.html>) states that "the overall goal is to establish research and development activities to provide scientific information and translational research capacity that will facilitate the next generation of therapeutics, diagnostics and vaccines against the NIAID Category A-C Priority Pathogens (<http://www3.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/default.htm>) and emerging infectious diseases (EID) agents (<http://www3.niaid.nih.gov/research/topics/emerging/list.htm>)".

The 2007 NIAID Strategic Plan for Biodefense Research (<http://www3.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/PDF/biosp2007.pdf>) describes an emphasis shift from the "one bug-one drug" approach towards a flexible broad-spectrum approach. Thus, special consideration will be given to projects whose

basic research or translational research is the development of products that are effective against a variety of pathogens and toxins.

Over-arching Research Theme for MARCE-2

The over-arching theme for the Research Programs that will be fostered under the MARCE renewal proposal is: **“Emerging pathogen-host interactions”**.

Sub-Themes and Their Associated Research Programs

MARCE will have six P01-like Research Programs, as listed below. You are being invited to submit a project grant proposal to be included in Research Programs I - V:

- ❑ Research Program I – Interaction of Emerging Viruses with Host Cell Pathways.
- ❑ Research Program II -- Emerging Virus Entry into Host Cells: Strategies for Inhibition.
- ❑ Research Program III – Bacteria and Protozoa that Invade via or Cause Disease of the Gastrointestinal Mucosa.
- ❑ Research Program IV -- Bacteria that Invade via or Cause Disease of the Respiratory Tract.
- ❑ Research Program V -- Interactions of Toxins and/or Adhesins from Emerging Bacterial Pathogens with Host Cells.
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- ❑ Research Program VI -- Diagnostics: Development, Support and Discovery.

(Please note that no project proposals that involve Diagnostics research will be accepted under this current RFP. However, in several weeks under a separate RFP the MARCE will solicit applications for Research Program VI -- Diagnostics: Development, Support and Discovery).

Your R01-like proposal for basic, translational, or clinical research must clearly state which P01-like Research Program you are applying under (I-V, above). Further information on each Program's specific goals can be found at the end of this RFP. Please contact the MARCE Research Coordinator, Jennifer Snyder, Ph.D. (jsnyder@medicine.umaryland.edu), for input regarding whether the concept you will be proposing fits within the scope of allowable activities.

Overall Points Encouraged:

- ❑ Collaborations with other investigators within and outside the MARCE Region.
- ❑ With regard to product development, projects are encouraged to address broad-spectrum activity, broad-spectrum technology, and broad-spectrum platforms.

NOT Allowed:

- ❑ According to the NIAID RFA, research on *Bacillus anthracis*, orthopox viruses, and influenza are well represented and not encouraged. Thus the MARCE will NOT accept any **new** proposals on these topics; however, **current** MARCE projects in these areas will be allowed to apply for renewal in one of the 5 Program areas listed above.
- ❑ Whereas small Phase 1 clinical trials are conceptually allowed according to the NIH RFA, Phase 2, 3, and 4 clinical trials will not be supported.
- ❑ Research related to diagnostics; this will be covered under a subsequent RFP.

Funding guidelines: Grants will be awarded in the amount of \$150,000 to \$175,000 (direct costs) per year for up to 5 years. In addition to direct cost, indirect costs will be funded at your anticipated institutional approved rate effective March 1, 2009. Please include direct and indirect costs in your budget.

Investigator requirements: Principle Investigators of applications in response to this RFA must be within the MARCE geographic region, which includes DE, D.C., MD, PA, VA and WV. Eligible organizations include for-profit organizations, non-profit organizations, public or private institutions, and other domestic institutions. Foreign institutions/organizations and PIs outside the MARCE region are not eligible to apply as the primary applicant, but may enter into collaborations with a primary applicant.

Applications must apply specifically for inclusion under one of the five above-mentioned Research Programs (I-V), and must include the following:

Letter of Intent:

A letter of intent is not mandatory and not binding, but it is strongly recommended. The information requested will allow the MARCE to estimate the potential review workload and plan the review accordingly.

- ❑ Title of proposed research
- ❑ Name, address, email, and telephone number of the Principal Investigator
- ❑ Names of any other significantly contributing authors
- ❑ Institution(s)
- ❑ Program number (I – V) to which you will be applying to
- ❑ If the title is not sufficiently descriptive, you may include 1-2 sentences about the proposed project that would be invaluable in organizing the review team

Full Research Proposal:

- ❑ Face page (Institutional signature is not required for the electronic submission)
- ❑ Abstract Page (Description, Performance Sites, Key Personnel, Other Significant Contributors, and Human Embryonic Stem Cells)
- ❑ Table of Contents
- ❑ Detailed Budget for Initial Period (modular budgets are not allowed)
- ❑ Budget for Entire Proposed Period of Support
- ❑ Budgets Pertaining to Consortium/Contractual Arrangements
- ❑ Biographical Sketches of Principal Investigator and all Key Personnel (Biosketches must be current)
- ❑ Resources and Environment
- ❑ Research Plan (**A maximum of 6 pages of text will be allowed for Sections A-D inclusive**)

Clearly state which of the five Research Programs you are specifically responding to at the beginning of Section A. Include a justification of the project in relation to the Program sub-theme. For applicants who are currently funded by MARCE-1, provide a list of publications that specifically cite MARCE support, as well as a brief description of other tangible accomplishments.

- A. Specific Aims
- B. Background and Significance
- C. Preliminary Studies/Progress Report
- D. Research Design and Methods
- E. Human Subjects Research

- F. Vertebrate Animals
- G. Select Agent Research
- H. Literature Cited
- I. Multiple PI Leadership Plan
- J. Consortium/Contractual Arrangements
- K. Resource Sharing
- L. Letters of Support (e.g. consultants)
- Checklist
- No Appendix materials will be allowed as part of the application.

Use PHS398 forms and follow the PHS398 instructions for formatting (<http://grants.nih.gov/grants/funding/phs398/phs398.html>).

Scientific Review Criteria:

In their deliberations, the Ad Hoc Review Committee reviewers will be asked to consider the following aspects of the application:

- 1) Significance (15 points)
- 2) Approach and scientific merit (35 points)
- 3) Innovation (15 points)
- 4) Investigator (15 points) (Note - For investigators who received funding during MARCE-1, their productivity based on that funding will be taken into consideration as part of the "Investigator" evaluation)
- 5) Environment (5 points)
- 6) Consistency with the MARCE research priorities and Program goals (10 points)
- 7) Description of how the research (either fundamental or translational) can lead to a product (i.e., a therapeutic, vaccine, or passive immunoprophylactic) (5 points)

Review and Approval:

- At least 3 (and up to 6) members of the Ad Hoc Review Committee will review each MARCE proposal. This external committee consists of senior investigators of national and international prominence who are not currently involved with the MARCE. To avoid further potential conflicts of interest, no reviewer will evaluate proposals from his/her home institution. In addition, the Ad Hoc Review Committee members will not be eligible to submit proposals for consideration under this Program so as to maintain the unbiased status of this Committee. The Committee will score on Criteria #1-7 as listed above.
- The MARCE-MOC will provide a second level of review intended to ensure that the top-scoring projects are clearly well aligned with the goals of the MARCE-2 overall Research Plan. This will be accomplished by the MOC assigning scores only on Criteria #6. The applicant's final score will be a 50-50 weighting of the Ad Hoc Committee's total score and the MARCE-MOC's score.
- The MARCE aims to select approximately 3 proposals submitted under this RFP for inclusion under each of the Research Programs.
- Selected projects will be submitted to the NIAID RCE Program Office as part of the MARCE Renewal. Final funding of projects must be approved by NIAID Program and Grants Management staff.

Submission of Application:

Letters of intent should be submitted electronically and emailed to rcegrants@medicine.umaryland.edu by 11:59 PM EST on Tuesday, February 19, 2008.

Completed applications are to be submitted electronically in a single word document and emailed to rcegrants@medicine.umaryland.edu by 11:59 PM EST on Sunday, March 9, 2008. The original application including the face page with PI and institutional signatures should be mailed to the MARCE Administrator at the address listed below, and must be received no later than 5:00 PM EST on March 24, 2008. If your proposal is selected for inclusion in the MARCE-2 research portfolio, you will be so advised circa April 15, 2008.

MARCE contact for information on scientific scope/research:

Jennifer A. Snyder, Ph.D.
MARCE Research Coordinator
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MARCE contact for information on budgets/forms:

Gloria Smedley, MBA
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Details on the 5 MARCE Research Programs:

Each P01-like Research Program will be headed by two Program leaders ("Shepherds"), who will work to facilitate collaborative research among the Program's investigators.

Research Program I – Interaction of Emerging Viruses with Host Cell Pathways. Program Shepherds: Robert Doms (University of Pennsylvania) and Judith M. White (University of Virginia)

The central theme of the Emerging Virus-Host Cell Interaction Research Program will be the in-depth analysis of virus-host cell interactions, the identification of therapeutic targets, and the development and application of high-throughput assays to identify antiviral agents. New high-throughput, live-cell screening technologies make it possible to study virus-host interactions in new ways, and to identify novel antiviral agents. Gene silencing technologies have matured to the point where whole-genome siRNA screens may be performed. The emphasis of this research program will be on how under-studied, emerging viruses interact with host cells, with the goal being to

identify cellular proteins and host cell pathways that may be targeted for high throughput assay development. Projects directed towards vaccine development will not be considered.

Category A viruses, as well as diseases caused by important emerging viruses, will be emphasized, with preference given to viruses that are significantly under-represented in the NIAID research portfolio. Examples of under-studied Category A and Emerging viruses include specific bunyaviruses (such as hantaviruses and Rift Valley Fever virus), New World arenaviruses (such as Junin and Machupo), and Hendra virus. Research projects directed towards studying better-funded Category A viruses, such as filoviruses and poxviruses (the later must be a continuation of MARCE I projects), need to be highly innovative and focused on the development of antiviral agents.

Research projects will be united by the utilization of innovative, high throughput technologies to identify host pathways with which viral pathogens interact and to identify and characterize potential antiviral agents. Research will emphasize the translation of basic research to product development, with an emphasis shift from the 'one bug-one drug' approach towards a more flexible, broad-spectrum approach. Thus, research projects should either target several related viruses, or interact with other research projects in a manner that addresses this central theme. We anticipate that most projects will focus on viruses about which relatively little is known. As a result, in most cases basic studies using innovative approaches will be needed to identify host cell factors that are needed for virus replication, or that suppress virus replication (such as innate immune factors). However, the long-term goal of these projects must be the identification of therapeutic targets, and ultimately the design of high throughput assays designed to identify new classes of antiviral agents for these under-studied human pathogens. It is possible that some projects may be proposed in which targets have been identified and screening attempts are now called for. Such advanced projects could involve better-studied viruses such as filoviruses and poxviruses, and could strengthen the overall Program by enabling it to encompass projects, at its inception, that span from basic target identification studies to high-throughput screens to identify antiviral agents.

**Research Program II -- Emerging Virus Entry into Host Cells: Strategies for Inhibition.
Program Shepherds: Christopher Broder (Uniformed Services University of the Health
Sciences) and Stuart Isaacs (University of Pennsylvania)**

The central theme of the Entry and Inhibition of Emerging Viruses Program will be the identification of viral receptors and other host proteins involved in the entry process, viral proteins involved in the entry pathway, and the development of assays that will employ high throughput technologies to identify virus entry inhibitors. The recent licensure of two HIV entry inhibitors provides proof of principle for this approach towards therapeutic development. Category A viruses will be emphasized, as well as important emerging viral diseases, with preference given to viruses that are significantly under-represented in the NIAID research portfolio. We anticipate that for some viruses sufficient knowledge will be available to immediately design and utilize assays to identify entry inhibitors, while for certain other viral agents more basic research will be needed to identify host and viral proteins involved in the entry process. In this case, the long-term goals will be to develop inhibitors of virus infection, and progress towards this goal will be an important component in how projects will be assessed in the post-award period. Emphasis will be on Category A viruses as well as emerging viral pathogens. Collaborations within the MARCE as well as with scientists within federal agencies, foreign institutions, and with other RCE investigators are encouraged.

Research Program III -- Bacteria and Protozoa that Invade via or Cause Disease of the Gastrointestinal Mucosa.

Program Shepherds: Richard L. Guerrant (University of Virginia) and James B. Kaper (University of Maryland)

Enteric pathogens display an array of virulence features and interact with the host gastrointestinal mucosa in a variety of ways. Some pathogens, through the effect of enterotoxins, cause prominent clinical illness without discernible pathology of the mucosa; other pathogens result in a variety of pathological changes; yet other pathogens that invade via the gastrointestinal mucosa progress to systemic blood stream and distant organ invasion. A feature common to all enteropathogen/host interactions is that host immune defenses of different types can disarm these pathogens at various levels and steps in their pathogenesis. Immune defenses at the mucosal surface constitute a common early barrier for all the afore-mentioned pathogens, including the highly invasive bacteria that cause enteric fever. The operative immune mechanisms that protect the gut include non-specific innate defenses in non-immune hosts and various effector arms of the adaptive immune system such as mucosal SIgA, serum antibodies (including transuded IgG that may function at the mucosal surface), and an array of cell-mediated immune mechanisms. Recent research has begun to hone in on the complexities of immunity to bacterial enteropathogens in animal models and humans, including the interaction between the innate immune system and specific adaptive immune responses, the molecular and physiologic basis for the homing phenomenon of B and T cells to the gut mucosa and ways to measure B and T memory cells. Intensive further research in this area can result in a new generation of vaccines and therapeutics with broad-spectrum activity against emerging bacterial enteric pathogens.

This Program will encourage the submission of Project proposals to study: 1) gut pathogen/host interactions that involve more detailed understanding of the innate immune mechanisms operative along the gut mucosa that influence the adaptive immune response to certain NIAID Category A-C emerging enteric pathogens; 2) broadly active mucosal adjuvants that can markedly enhance the immune responses to a variety of enteric vaccines administered via the mucosal surface; 3) animal models that can elucidate the relative importance of specific host factors to explain the enhanced virulence of certain pathogens (e.g., non-typhoidal *Salmonella*) in recognized high risk hosts (e.g., young infants, persons with hemoglobinopathies, etc.); 4) broad-spectrum vaccines that prevent disease caused by the most common emerging pathogens associated with a clinical syndrome (e.g., an enteric fever vaccine; a broad spectrum traveler's diarrhea vaccine; a vaccine that broadly protects against the most common non-typhoidal *Salmonella* associated with gastroenteritis and bacteremia); 5) broad spectrum therapeutics that diminish the clinical severity of diarrheal illness caused by an array of gastrointestinal pathogens through the effect of the drugs on common pathways. The ultimate goal for most of the projects will be the discovery and development of broad-spectrum enteric vaccines or therapeutic agents or the elucidation of ways to markedly enhance the effectiveness and spectrum of existing products.

The emerging bacterial enteropathogens of highest interest will include *Shigella*, enteric fever *Salmonella* (Typhi, Paratyphi A & B), non-typhoidal *Salmonella*, enteroaggregative *E. coli*, enterotoxigenic *E. coli* (ETEC), enterohemorrhagic *E. coli* and Shiga toxin-producing *E. coli* (EHEC & STEC) and *Clostridium difficile*. Among protozoa, the emerging pathogen of highest interest will be *Cryptosporidium*. (For reasons of focus, we are limiting the scope of this Program to bacteria and protozoa).

Research Program IV -- Bacteria that Invade via or Cause Disease of the Respiratory Tract.

Program Shepherds: Alan Cross (University of Maryland School of Medicine) and Joanna Goldberg (University of Virginia School of Medicine)

By dint of its contact with the environment through the physiological act of respiration, multiple sites along the respiratory tract may be exposed to airborne bacterial and viral pathogens. Among the points through which pathogens can invade are M-like cells overlying nasal associated lymphoid tissue, upper respiratory epithelial cells, pharyngeal and tonsillar lymphoid tissue, bronchial and bronchiolar mucosal cells and alveoli. Particle size as well as characteristics of the pathogen and the host determine the site of entry. Large droplets (i.e., ~ 50 – 100 micra) remain in the upper respiratory tract. In contrast, minute droplet nuclei of < 3 micra can reach the alveoli. For certain agents, such as *Francisella tularensis* and *Bacillus anthracis* spores, their delivery as small particle aerosols can increase the virulence of these potentially fearsome bioterror pathogens.

An array of non-specific defense mechanisms (e.g., nasal conchae, mucus, ciliated bronchial epithelium and cough) constitute formidable barriers. The innate immune system provides additional non-specific defenses. However, in the respiratory tract the innate immune system responses must be tightly controlled lest over zealous responses lead to physiological derangement. Lastly, various specific immune responses contribute to protection, including local mucosal SIgA antibodies, serum antibodies and cell-mediated immune responses. Studies of virulence factors of bacterial respiratory pathogens, host defenses and the interplay between the two will be the focus of this Research Program. Specifically, proposals characterizing common themes among mechanisms of bacterial respiratory pathogenesis as well as in the host responses to these pathogens (both innate and adaptive responses) are encouraged. For proposals that explore therapeutic interventions, strategies that enhance basic mechanisms of respiratory host defenses (e.g. respiratory mucosal adjuvants) and/or target a broad spectrum of respiratory pathogens will be particularly welcome.

In order to focus, the MARCE-2 Research Plan puts an emphasis on seeking proposals that involve *Francisella tularensis*, *Burkholderia pseudomallei*, *Burkholderia mallei*, *Coxiella burnetti* and *Bacillus anthracis* as model pathogens, although other Category A-C bacterial agents will be considered (albeit with less enthusiasm). Note - anthrax projects will be limited to proposals representing extensions of MARCE-1 projects.

Research Program V -- Interactions of Toxins and/or Adhesins from Emerging Bacterial Pathogens with Host Cells.

Program Shepherds: Alison O'Brien (USUHS) and Erik Hewlett (University of Virginia School of Medicine)

Subject Areas: The Toxins and/or Adhesins from Emerging Bacterial Pathogens Research Program of the MARCE will focus on bacterial toxins and adhesins from NIAID Category A-C pathogens and emerging agents, how they interact with host cells, the consequences of those interactions and how they can be prevented. Among the group of toxins, particular emphasis will be placed on those that play a major role in damage to the host during infection or that act alone to cause harm. In the area of adhesins, the target will be known adhesins, defined as fimbriae or outer membrane proteins, from bacteria that are under study in the MARCE program and are hypothesized to be or known to be involved in affecting cellular functions and/or critical for bacterial colonization of the host. Examples of relevant toxins include all those on the CDC Select Agent list that fall under category A or B (ricin, Shiga toxin, botulinum toxins, *Staphylococcus aureus* enterotoxins,

Clostridium perfringens epsilon toxin as well as toxins such as anthrax lethal toxin and *Clostridium difficile* toxins. Examples of bacterial adhesins, which can serve as adhesins and/or modulate the functions of host cells, include those found on *E. coli*, *Burkholderia* and other less well-studied agents. The scope of projects in this program is anticipated to encompass basic investigation of the interface of toxins and/or adhesins with the host cell membrane and pathways usurped/modulated by these molecules to harm the host. The ultimate purpose for most of the projects should be the discovery and development of broad-spectrum therapeutic agents or vaccines.

The objective of the toxin projects will be the analysis of toxin-host interactions to include identification of toxin receptors and pathways of cellular intoxication as a means of defining targets for intervention. The use of physiologically relevant cells types for these studies is highly encouraged. One area of particular interest will be the delineation of intervention strategies aimed at already intoxicated cells with the idea that such therapeutics could ultimately be used to treat individuals exposed to or already ill from a potent, potentially lethal bacterial toxin. Wherever possible, such anti- toxin approaches, which may require high throughput assays to define potential therapeutics, should be broad and encompass more than one mechanistically related toxin (botulinum toxin family, or *Staphylococcus aureus* enterotoxins, or ricin and Shiga toxin, for example). Multivalent toxoid approaches, particularly if combined with a novel platform or one already in use in the MARCE will also be considered. The aim of work on adhesins will be to identify and characterize these bacterially expressed ligands for surface receptors on host cells (particularly from less well studied pathogens), and to evaluate how they bind to and affect physiologically relevant cells. The long-range goal will be to devise a means of blocking the attachment of the adhesin to cells so as to interfere with the resultant signaling, as well as the capacity of the organism to colonize the host. Creative therapeutic approaches as well as vaccine strategies are welcome.

Research Program VI – Diagnostics: Development, Support and Discovery
Program Shepherds: Richard Rothman (Johns Hopkins University School of Medicine)
and Chris Geddes (University of Maryland Biotechnology Institute)

Note -- The current RFP is not soliciting projects for the Diagnostics Research Program. Rather, in several weeks MARCE will distribute a separate RFP that will be specifically aimed at soliciting proposals for Diagnostics research.