



## **Reservoirs of Antibiotic Resistance (ROAR) 2005 Request for Proposals December 1, 2005**

### **APUA and the ROAR PROJECT**

The Alliance for the Prudent Use of Antibiotics (APUA) is an independent non-profit organization dedicated to curbing antibiotic resistance through education and research activities (see [APUA.org](http://APUA.org)). APUA coordinates the Reservoirs<sup>1</sup> of Antibiotic Resistance (ROAR) Project.

The central hypothesis of the ROAR Project is that resistance genes are flowing from commensals to pathogens; and that characterizing and tracking resistance genes in commensal bacteria could help to predict the emergence of new forms of resistance genes in pathogenic bacteria. Under the leadership of APUA President Dr. Stuart Levy and Dr. Abigail Salyers of the University of Illinois, the first phase of the ROAR Project was initiated in 1997 to encourage global research and assemble information on the genotypes and phenotypes of commensal bacteria that serve as reservoirs of antibiotic resistance determinants. In 2002 APUA launched the ROAR II project, a five-year Cooperative Agreement with the National Institute of Allergy and Infectious Diseases (NIAID). ROAR II represents an unprecedented systematic effort to improve scientific understanding of the role of commensal bacteria in the spread of antimicrobial resistance. This is approached by 1) encouraging, funding, and directing research efforts to evaluate antibiotic resistance in commensals; 2) compiling existing commensal isolate data and literature into a Web-based bioinformatics tool (see <http://db.roarproject.org/ROAR/account/databases.htm>) and 3) using statistical, risk analysis, and mathematical modeling techniques to analyze the data in order to determine if the frequency of antibiotic resistance genes in commensals can predict the subsequent emergence of antibiotic resistance in pathogenic bacterial populations. Now in its fourth year, the ROAR II Project has awarded six research sub-grants addressing crucial aspects of the flow of resistance genes from commensal to disease-associated bacteria.

### **RFP OBJECTIVES**

Though commensal bacteria have long been suspected reservoirs of antibiotic resistance genes, little is known about the abundance, diversity, and distribution of resistance genes within commensal species. The transfer of such genes from commensal to pathogenic bacteria is equally poorly understood. ROAR is requesting proposals for projects that address the association of antibiotic resistance genes among commensal bacteria and disease-associated bacterial populations. Funded studies will address the concept that commensal bacteria serve as reservoirs for the emergence and continued proliferation of antibiotic resistance genes in disease-associated bacteria. Funded studies should aim to provide data appropriate to populate the ROAR Isolate Database, the cornerstone of ROAR's online interactive bioinformatics resource for the scientific community. The ROAR Isolate Database is a password-protected, searchable repository of raw isolate-by-isolate commensal phenotypic, genetic, geographic, temporal, and source data. Preference will be given to those studies which produce a volume of data sufficient to facilitate risk

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<sup>1</sup> The ROAR Project defines an antibiotic resistance reservoir as a population of bacteria that have acquired resistance genes that have the capability of being transferred to other bacteria, especially human pathogens.

analysis and mathematical modeling, providing a basis for ROAR’s quantitative assessment of the relationship between resistance in commensals and resistance in pathogens.

Preference will be given to proposed projects that address one or more of the following areas:

1) *Modeling of antibiotic resistance.* Projects can address both the ecology and the evolution of resistance. Projects that use novel DNA sequence-based approaches to understand the spread of antibiotic resistance or that address the evolution of antibiotic resistance in specific lineages will be given extra consideration.

2) *Characterization of antibiotic resistance in commensals.* Strong projects will characterize epidemiologically and ecologically relevant bacterial strain collections in order to establish a population genetic and phylogenetic framework for antibiotic resistance. Strain collections can include pathogens, but should focus on commensals. Characterization methods should include multi-locus sequence typing, standard antibiotic susceptibility testing, antibiotic resistance genotyping, virulence factor typing, and plasmid incompatibility typing. The use of strain collections that have already been characterized by one or more of these methods is preferred. Use of strain collections where the data can be used to generate or answer additional hypotheses regarding the ecology and evolution of antibiotic resistance is also preferable. While characterization of gram-positive bacteria, particularly *Enterococcus*, is of strong interest, other species will be considered if there is sufficient clinical or theoretical merit.

3) *Development of phylogenetically informative genome-based typing schemes.* The ability to rapidly type strains is an important tool in understanding the spread and transfer of antibiotic resistance. Ideally, one objective of any rapid typing scheme would be to acquire phylogenetically relevant information that will aid in the reconstruction of antibiotic resistance gene transfer. Projects will use available genomic data in *E. coli* and *Shigella* to identify SNPs and/or a gene presence/absence system that yield phylogenetic information.

**CRITERIA FOR RESEARCH PROJECT SELECTION**

Under the direction of APUA’s Research Director, proposals will be evaluated by a Peer Review Committee comprised of members of the ROAR II Steering Committee and APUA’s Scientific Advisory Board. Proposals will be judged according to the criteria below. Proposal funding priority will be based on the score given using the 100-point scale described.

1. Significance: Goal and rationale of the project; topic significance; local and regional priority; potential clinical impact, fit with ROAR’s previous granted studies	20
2. Approach: Study design, including methods, projected results, potential problems, prospective approach, innovation	30
3. Investigator: Personnel qualifications and organizational capacity, including partnerships	20
4. Environment: Generality of findings to other biological systems	10
5. Management plan, including timetable and plans for monitoring and evaluation	10
6. Budget rationale	10
<b>Total</b>	<b>100</b>

Reviewers will provide a written evaluation of the proposal and a numerical score. Rigorously designed projects will be given funding priority. Identification of the specific populations and variables under study will be required, as well as specific definitions of the outcomes. In order to facilitate the development of such proposals, APUA staff will be made available for consultation during all stages of the proposal development.

## **AWARDS**

- Awards for proposals are **up to \$60,000** for a **maximum of one year** with anticipated project start date of **June 1, 2006**. Provision is not offered for funding of indirect costs.
- Funds may only be used for the salary and fringe benefits of faculty or study personnel and for research-related tests and supplies. No funds may be expended for equipment or travel.
- Awards will be made once per year and will be limited to one year's duration. Awards may be renewed for a second year only under special circumstances and with approval by APUA.
- Release of funds is contingent on final approval of selected projects by the NIH.

## **PROPOSAL GUIDELINES**

Research proposals should carefully define the bacterial populations being sampled, with respect to the genes, resistance and environment(s) in which they are isolated. Proposals should provide a rationale for studying specific bacterial collections. Proposals should carefully define the isolation environment, the genes or resistances studied, and the clinical relevance of the study. Submitted proposals should contain the following information, preferably using NIH PHS398 form pages (<http://grants1.nih.gov/grants/funding/phs398/phs398.html>):

1. A face page with proposal title, applicant contact information, and funds requested: <http://grants.nih.gov/grants/funding/phs398/fp1.doc>.
2. A four to five-page project description that includes specific aims, background and significance, preliminary studies, and research design and methods (additional pages may be used for figures and literature cited). Specific aims should include bacterial populations of interest and associated human health implications. The project description should include specific description of the methodology used for data collection, detailed data management and analysis plan, and a management plan for monitoring and evaluating the project, including a timetable for achievement of results for each step. Use NIH continuation pages: <http://grants.nih.gov/grants/funding/phs398/continuation.doc>.
3. A biographical sketch of the Principal Investigator, and any supported personnel (i.e., students or post-docs): <http://grants.nih.gov/grants/funding/phs398/biosketchsample.doc>.
4. A description of available resources: <http://grants.nih.gov/grants/funding/phs398/resources.doc>. Please note additional resources such as collaborative efforts that will enhance the proposed project's effectiveness or impact.
5. A detailed, itemized budget: <http://grants.nih.gov/grants/funding/phs398/fp4.doc>.
6. A description of any animal or human research that is necessary to complete the project (refer to NIH PHS398 instructions for human and animal research guidelines). Indicate whether human/animal research protocols have been approved by a PHS-approved IRB/IACUC.

Human and animal research protocols must be approved by the applicant institution's Institutional Review Board (IRB) or Institutional Animal Care and Use Committee (IACUC), respectively, before funding may be released. Proposals selected for funding will be fully transferred to NIH format by the applicant with ROAR staff assistance. Please consult ROAR staff for questions regarding proposal format. Font type is to be no less than 10 points, with 1-inch page margins.

## **PROGRESS REPORTING**

- Investigators are asked to notify the ROAR Principal Investigator in writing of significant changes in the focus of the research or allocation of funds during the project.
- APUA requires that funded investigators provide a progress report 6 months into project implementation.

- Within 60 days of project completion, the investigator must submit a final progress report stating scientific findings, publications resulting from the research, and an accounting of unexpended funds.
- Final progress reports will also be used to evaluate extension of funding into a second year if requested by the investigator. Recipients will also be asked to report applications or publications that result from this project on an annual basis for two years after the completion of the project.
- ROAR funding must be acknowledged in publications and presentations resulting from the project. Raw commensal data generated by the project must be provided to the ROAR principal investigator for inclusion in the ROAR isolate database.

### **APPLICATION PROCEDURE**

Questions regarding this RFP should be directed to Dr. Michael Feldgarden ([Michael.feldgarden@tufts.edu](mailto:Michael.feldgarden@tufts.edu), 617-636-3576) or Amelie Peryea ([amelie.peryea@tufts.edu](mailto:amelie.peryea@tufts.edu), 617-636-0427). Completed proposals should be sent electronically to the following address and are due no later than **February 1, 2006**:

Katherine Corso, ROAR Project Assistant

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Projects will be selected in early March for funding beginning June 1, 2006.