



Request For Proposals (RFP)

Project Title: In Silico Modeling of Biomarkers of Atherosclerosis: Estimating Risk Reduction and Residual Risk From Statin Therapy

RFP Objective: Solicit applications from organizations with experience in developing in silico models from public and patient level data

Issued by: The Biomarkers Consortium of the Foundation for the National Institutes of Health (FNIH) on May 18, 2011

Responses: due on July 20, 2011

Eligibility: Any organization from the private and public sector is eligible to apply as long as it can meet the requirements below. It is acceptable for more than one organization to collaborate and submit a joint response.

Selection Date: September 12, 2011

Responsible Persons: David Fryburg, M.D., ROI BioPharma Consulting (dfryburg@roibiopharma.com), Maria Vassileva, Ph.D., Foundation for the NIH Biomarkers Consortium (vassilevam@mail.nih.gov)

Atherosclerosis *In Silico* Modeling RFP

The Atherosclerosis Modeling Project Overview: This project is overseen by the Foundation for the NIH Biomarkers Consortium (FNIH BC), a public-private partnership of government, academia, non-profit, and industry. A fundamental principle of the consortium is to collaborate across stakeholder sector on biomarker issues and to make public the results of these collaborations. The general goals of the FNIH BC include:

1. Facilitate the development and qualification of biomarkers using new and existing technologies
2. Help qualify biomarkers for specific applications in diagnosing disease, predicting therapeutic response, or improving clinical practice
3. Generate useful information to inform regulatory decision-making
4. Make consortium project results broadly available to the entire scientific community

More information on the consortium can be found at <http://www.biomarkersconsortium.org/>.

The Atherosclerosis Modeling Project Team is one of several teams developing or managing these cross-sector, collaborative projects. The team is composed of experts from NIH, FDA, academia, and the pharmaceutical industry. Please refer to a recent publication that describes the rationale of the project and operational structure in greater detail (Fryburg and Vassileva: Atherosclerosis Drug Development In Jeopardy: Need for Predictive Markers of Response. Science Trans Med 3:16-19, 2011).

Project Objectives: The overarching objective is to establish a model incorporating relevant physiological and pathophysiological processes to predict cardiovascular outcomes from short-term change in a panel of biomarkers. “Biomarkers” includes many different types beyond the more apparent lipid levels and CRP, such as burden of disease markers like imaging or pulse wave velocity, or brain natriuretic peptide and neopterin.

The specific objectives of the RFP for this pilot project include:

1. Identify a panel of biomarkers that predicts outcomes in statin-treated patients with established atherosclerotic cardiovascular disease
2. Determine markers of residual risk of atherosclerotic cardiovascular disease in statin-treated subjects
3. Determine if these biomarkers are as predictive in diabetic patients with atherosclerotic cardiovascular disease as in non-diabetic patients with atherosclerotic cardiovascular disease
4. Create the operational structure to facilitate data-sharing and common use, exploitation, and expansion of the model.

Rationale: A major obstacle in the development of new, non-LDL based therapies for atherosclerosis is the lack of early clinical biomarkers that can predict cardiovascular outcomes (e.g., MI) in Phase III clinical trials. That is, despite the plethora of available biomarkers, there is no consensus biomarker or panel of biomarkers that predicts long-term clinical cardiovascular outcomes from shorter-term biomarker changes. This conundrum must be resolved to increase the probability of success for efficacy programs in atherosclerosis. If such a biomarker panel could be identified, it is possible that it could also be used to identify adverse changes in cardiovascular risk – e.g., as a side effect of a new diabetes drug.

Many biomarkers have been described to characterize the multi-faceted pathophysiologic components of atherosclerosis, including lipid metabolism, inflammation, vascular dysfunction, anatomic changes, and rheological alterations, among others. Much of the existing atherosclerosis biomarker literature is devoted to characterizing single biomarkers in at-risk individuals or in patients with established atherosclerotic cardiovascular disease. In some studies, the incremental predictive value of these biomarkers to risk engines such as Framingham is assessed. That is, does the measurement of CRP, for example, add to the predictive value of a model like Framingham in aiding a physician to counsel a patient regarding risk as well as to adjust the level of aggressiveness in treating that patient? The current literature shows that, in general, the addition of individual biomarkers yields relatively little improvement to the predictive power of engines like Framingham, as measured by the AUC of a ROC curve or reclassification indices. There are relatively few studies, however, that combine multiple markers in their analysis. Risk models like Framingham, however, are not applicable to experimental drug trials. In the experimental setting, we are trying to assess a change in risk (= efficacy) from the baseline state through biomarker use. Most of the variables in the Framingham model are either immutable or simple binary (yes/no) elements that would likely not be sensitive to intervention in a drug trial.

Thus, the goal of this project is not to improve upon Framingham; it is to develop a panel of markers and predictive models that are fit-for-use in a clinical experiment. The specific context of use for the model is to determine the utility of these biomarkers or biomarker panels in predicting Phase III outcomes based on data available in Phase II clinical studies. To achieve this goal, the model must have variables that are dynamic and responsive to change within a relatively short period of time (up to one year). Given that many markers co-represent a cluster or grouping of markers (e.g., CRP, IL-6, TNF, and neopterin for inflammation), it is anticipated that representation of inflammation in the model would likely not include several markers from the same cluster (although the model could include more than one marker from the same cluster or pathway if justified). Given the differential contributions of pathophysiologic elements across a population of patients, markers representing these facets are important to consider in development of a model. Finally, the model should include other

types of biomarkers, especially those that reflect the burden of disease or the activity of the atherosclerotic process (e.g., imaging and/or functional parameters).

The key questions of this RFP: The statin class of drugs has been extensively studied and shown to be exceptionally effective in treating atherosclerotic cardiovascular disease. As most contemporary trials in atherosclerosis will likely be conducted on a background of statin treatment, a key focus of this project is to understand residual risk in those subjects who have received statins. Understanding residual risk in statin recipients, however, requires comprehension of the biomarkers that are changing due to statins (or building biomarker models to describe the effects of statins) as well as those that are not. There are several questions that should be addressed in a step-wise fashion:

1. What are the biomarkers that change in the short-term due to statins?
2. How do these biomarker responses predict change in clinical outcome due to statins?
3. Taking into consideration the factors listed below, what combination(s) of biomarkers would constitute a promising panel for the prediction of changes in long-term CV risk?
 - a. Magnitude and time course of biomarker changes upon treatment with statins
 - b. Plausible mechanistic link to CV risk
 - c. Comprehensive coverage of the pathophysiologies believed to contribute to CV risk (e.g., lipids, inflammation, endothelial function, coagulation)
 - d. Availability of robust and reliable assays
4. Identification of markers of residual risk of disease: Although statins favorably alter multiple markers of atherosclerotic cardiovascular disease, they may not restore these markers to a “normal” range. And while statins are effective at reducing events and mortality from atherosclerotic cardiovascular disease, they do not eliminate all risk. Are there biomarkers that reflect this residual risk of disease? Are there known markers of disease that do not change in response to statins? Do these need to be represented in the model?
5. Does the analysis of individual-subject data from statin clinical trials support the proposed biomarker panel(s)?
6. Can a quantitative relationship between short-term biomarker changes and cardiovascular outcomes be established from individual-subject data from statin clinical trials?
7. Does the pattern of these markers differ in diabetic v. non-diabetic subjects?

As described above, the central question of this effort is to focus on the changes in a panel of biomarkers that predict the change in outcomes. Thus, the principal question to address relates to change in risk as predicted by a change in the marker panel. However, it is also of interest as to what the prediction of baseline risk. That is, does the biomarker-based panel also predict baseline risk comparably to a clinical risk engine such as Framingham?

Future work with this model will need to examine the effects of other interventions. For example, how does the biomarker panel that predicts outcome with statins compare to that of fibrates, niacin, and PPARs? Can the panel be generalized to extend to these and other therapeutic modalities?

Execution of this pilot project: This project will be executed in two stages. The first stage would include questions 1-4 and also begin to address question 7. It is anticipated that during this stage the respondent would utilize publicly available data to build the initial model(s) that address the Atherosclerosis In Silico Modeling Project Team's questions. These first efforts in Stage 1 will be the basis towards building a refined model using subject-level data.

It is also anticipated by the Project Team that subject-level data could be very important to addressing these questions, especially questions 5-6 (as well as augmenting the model(s) relevant to questions 1-4 & 7). It is critical, however, to discern which subject-level data are needed, i.e., identify the trials, variables, and time points. Based on the models produced and the markers that are initially identified in Stage 1, requests for subject-level data from specific pharmaceutical and research organizations for Stage 2 will be considered. However, requests for limited subject-level data from specific pharmaceutical and government research organizations will be considered during Stage 1 of the project, but justification for the accelerated request beyond publicly available data will have to be provided. Included in this request will be specification of exactly what data are required and how the data will be used.

Please note that the Atherosclerosis In Silico Modeling Project Team is not specifying in advance the biomarkers to include in the model. Rather, the respondents should propose what they believe is most important to include. It is also important to note that more than one model may be appropriate to address these questions.

A proposed biomarker panel from Stage 1 could then be evaluated against individual-subject data on biomarker changes and cardiovascular outcomes from statin clinical-trial data provided by pharmaceutical or governmental sponsors in Stage 2. Although the focus of the model(s) and its context of use is the prediction of human response in the clinical trial setting, the Project Team recognizes that, in some cases where human data are limited, the model may incorporate information extrapolated from animal studies. However, the inclusion of non-clinical data would have to be documented and justified, and the assumptions clearly stated in how the nonclinical data were applied.

Expectations: The response to this RFP should include the following:

1. Prior history re: creation of models as described in this RFP
2. Your organization's approach to addressing the needs of the RFP—what components would you include and how?
3. What would you need to be successful in completing stages 1 & 2?

4. Describe verification and validation of the model(s)
5. Define success—what criteria will you use to support a position that the model has been successfully developed?
6. Ability to examine modeling methods: please describe how the details regarding modeling methodology will be available for review. A critical component of this project is to be able to share methods and results in the public domain. The degree of willingness to share methodology should be described. Subject-level data will not be placed in the public domain unless agreed to by the owner of the data and the project team.
7. Data storage and protection: what capabilities does your organization have to store and protect confidential data?
8. Please include a list of which datasets are needed to include in the model
9. Please include a list of milestones to judge progress against
10. Please note that the FNIH Biomarkers consortium reserves the right to suspend or terminate funding depending on demonstrable progression of the effort.

Application Process: Organizations that submit high-caliber, focused, and detailed responses to this RFP will be invited to meet in-person with the Atherosclerosis *In Silico* Modeling Project Team. The purpose of the meeting is to allow for appropriate discussion of possible next steps as well as provide the opportunity for the respondent to ask questions of the multi-stakeholder Project Team. After the presentations and discussions, one organization will be selected to work on the model and an award will be made by the Foundation for the NIH in conjunction with the Atherosclerosis *In Silico* Modeling Project.

Moving from Stage 1 to Stage 2: Pending successful completion of Stage 1, the respondent organization would continue on to Stage 2. At that time, plans for Stage 2 would be reviewed and approved by the Atherosclerosis *In Silico* Modeling Project Team. These plans would include the identification of subject-level data required for completion of the project.

Budget: For the first two stages of this pilot initiative, the anticipated budget for this project is capped at \$400,000 per year (1.2M total for the three years of the project). As the FNIH Biomarkers Consortium is a collaborative effort to which organizations voluntarily contribute, there is no guarantee that an award will be made to one of the teams submitting an application in response to this RFP.

For More Information: Please contact Dr. Maria Vassileva (vassilevam@mail.nih.gov) or Dr. David Fryburg (dfryburg@roibiopharma.com) for more information. Feel free to ask questions to enable preparation of your responses.