

A. **Specific Aims**

The goal of our proposed research is to develop a new interdisciplinary science focused on the development of new therapies. Just as neuroscience and genomics have emerged as scientific disciplines greater than the sums of the pre-existing parts, we hypothesize that the many groups working on various aspects of drug (or device) development can beneficially come together to create a new and compelling discipline. This is already a very broad area of activity: billions of dollars per year and hundreds of thousands of people in the public and private sectors are focused discovering and/or developing new drugs or devices. Unfortunately, the current system is producing diminishing returns: the FDA approved only 21 new drugs in 2003, marking a steady decline from a peak of 53 in 1996. Furthermore, costs and complexity are skyrocketing, while effective therapies with no commercial potential are typically left undeveloped. Indeed, the NIH Roadmap calls for “re-engineering the clinical research enterprise” precisely to improve therapy development.

We believe a new, interdisciplinary scientific approach to therapy development is needed, and we propose that by focusing on two key themes we can advance this new interdisciplinary science. Our first theme is to increasingly make the human the experimental organism. Our second theme is to facilitate development of therapies that are commercially unattractive. Our underlying hypothesis is that these themes (1) are inter-related and (2) can both be addressed by the use of biomarkers. While biomarkers can be misleading if not used properly, over the past decade a growing body of science has begun to elucidate the failure modes of biomarkers and understand approaches to their validation and limitations. Our preliminary data suggest that biomarkers can serve as an informational link to bring scientists together, providing timely and insightful feedback and promoting an interdisciplinary approach.

We propose planning for three separate P50 centers: one centered on imaging biomarkers, one centered on molecular biomarkers (genetic, protein, and metabolic), and a third focused on the biostatistical tools and knowledge-bases for the integrative analysis approaches that will utilize biomarkers to speed drug and device development. Initial studies using imaging and molecular biomarkers in the drug development process suggest that not only can such biomarkers serve as a powerful mechanism to bring together disparate investigators, but they can also be quickly cost-efficient, thus encouraging early adoption. With these “core” centers in place, any of a variety of new therapies could then be developed in a more efficient process, and we propose as part of the planning process to study how drugs could actually be developed in an interdisciplinary way. Specifically, in this preliminary planning proposal our aims are:

Specific Aim 1: Develop an organizational and operational structure to appraise and engage participants in the therapy development arena, including those from academia, industry, and regulatory agencies, in order to develop approaches to test *Hypothesis 1*: Therapy development is a new interdisciplinary science. We aim to provide for a rich interplay between basic scientists and clinical investigators, portfolio managers and discovery teams, to translate information and tools across a broad scope of activity, and crucially, start to focus scientific questions across the entire process. However, to step from the broad range of activities to an interdisciplinary science, we will also undertake:

Specific Aim 2: Test the hypothesis that an interdisciplinary science of therapy development can be facilitated by providing a feedback loop of biomarker information between groups in two pilot examples:

Hypothesis 2.1: Using biomarkers to facilitate development of an ultra-low-cost effective treatment for acute human ischemic stroke will promote interdisciplinary teamwork. Our preliminary data suggest that imaging can be used successfully both to identify patients who might best be treated with hyperoxia and also monitor the effects of these treatments. Working through this pilot project will explore how interdisciplinary therapy development can be.

Hypothesis 2.2: Biomarkers provide a framework for selecting new ultra-low-cost effective treatments. Our planning teams will use the preliminary data on the variance of biomarkers (imaging and molecular) to select among potential low-cost treatments for a target illness such as glioblastoma or major depression. This selection process will also serve as a mechanism for monitoring signs of interdisciplinary activity.

Overall, we believe that the development of an interdisciplinary science of therapy development needs a common thread of information to bridge and tie these groups together, and this thread, we hypothesize, comes in the form of biomarkers. We further postulate that, of all the types of biomarkers that can be utilized, imaging biomarkers and molecular biomarkers are particularly compelling because of their non-invasive nature, their proximity to phenotypic expressions of diseases, and their richness of information by virtue of being able to provide insights at molecular, structural, as well as functional levels. We propose to focus these tools on the two themes of moving evaluation of therapies more quickly in to humans and finding ways to test drugs or devices that are not commercially viable in order to best bring scientists together to form a new interdisciplinary science.