

A. Specific Aims

The goal of our research is to develop and validate imaging tools to speed drug development. New medicines have been crucial to the improvement of health over the past century and are viewed by the public as the payoff for biomedical research funding. However, the process of translating medicines from the laboratory to humans is not optimal: productivity has dropped in recent years, costs are increasing, and some worry that drug safety has occasionally been trumped by a focus on drug efficacy. Improvement of this process is sorely needed. We postulate that this process of translation can be improved by focusing on the critical period in the evaluation of a candidate medicine's safety and efficacy is when a drug is in early human testing. Specifically, available data suggest that far too many drugs succeed in animal models but fail in subsequent human testing. We hypothesize that by developing and incorporating medical imaging biomarkers—specifically advanced MRI, CT, and PET tools, and multimodal integration of these imaging approaches—drugs can be assessed much earlier using smaller patient populations, and key go/no-go decisions can therefore be made in a more efficient manner. We propose forming a partnership between imaging scientists, clinical researchers, government, and industry to test this hypothesis.

While human imaging is actually already in widespread informal use to estimate drug effect (for example, to estimate whether cancers are shrinking, or if joint erosion is slowed) the systematic application of imaging to drug development is just beginning, and, according to the US Food and Drug Administration (FDA) as well as others, is in need of further technical development. While the pharmaceutical industry out of self-interest funds some such development, the scope of their work is necessarily limited and typically not shared openly. Our partnership will focus on understanding the variance of imaging biomarkers that can add value to the development process in the near term (1) by studying diseases where imaging biomarkers already have substantial preliminary data suggesting a beneficial role in human drug testing in diseases affecting the brain, and (2) by focusing on pre-competitive technologies that do not favor any specific company or companies. The three specific therapeutic areas we will initially focus on are Alzheimer's disease, evaluation of anti-angiogenic drugs in brain cancer, and evaluation of treatment of acute ischemic stroke.

A major theme for our partnership is multimodal integration of information to overcome shortcomings in surrogate endpoints. This includes not only quantifying the benefit of differing imaging methods but also of integrating imaging with other types of genotypic and phenotypic information. We will also regularly assess the effectiveness of our approaches. Our partners include the imaging scientists and engineers at the A. A. Martinos Center for Biomedical Imaging (both Harvard and MIT faculty), clinicians at Massachusetts General Hospital, the resources of the MGH-HST Center for Biomarkers in Imaging including partnerships with the FDA and patient advocacy groups, manufacturers of imaging equipment, and drug developers (pharmaceutical companies). Our specific aims are:

Aim 1: Understand and reduce the variance in multicenter MRI hippocampal volume and cortical thickness assessments of Alzheimer's disease. We hypothesize that novel MRI data collection methods as well as novel advanced analysis can reduce variance; we will test this hypothesis on data collected locally and through the NIH- and industry-sponsored Alzheimer's Disease Neuroimaging Initiative.

Aim 2: Integrate anti-angiogenesis imaging tools to better evaluate efficacy and mechanisms of action of anti-angiogenic therapies for brain cancer. We hypothesize that more advanced physiologic MRI acquisition and analysis will reduce the variance of the typical methods of assessing angiogenesis in glial lesions.

Aim 3: Extend existing predictive models of tissue and clinical outcome in acute human ischemic stroke to incorporate new advances in analysis and multimodal data (other imaging data as well as molecular biomarkers including ApoE levels). We hypothesize that such methods can reduce the sample size needed to test novel therapies for ischemic stroke.

Aim 4: Develop multi-modal integration approaches for incorporating and assessing the added value of a variety of types of information: imaging (MRI, PET, CT, etc), phenotypic (e.g., clinical assessments), and genotypic. We hypothesize that this approach will not only reduce variance but also give us insight in to the sources of variance such as patient differences in responses to new medicines.

These efforts will be supported by two technology cores: an MRI technology core to capitalize on recent developments in high field and multi-channel systems (up to 96 separate RF channels), and a positron emission tomography (PET) core to facilitate quantification of glucose metabolism.

Overall, we believe that by getting earlier feedback on biomarkers of drug efficacy and safety, trials can be powered with fewer subjects and done in less time. Not only will this decrease costs, but it will expose fewer patients to ineffective drugs as well as decrease the time it takes for effective therapies to reach patients.