Title of proposed program: De-Orphanizing the Druggable Genome

Submitting Source: Strategic Planning Meetings

What is the major obstacle/challenge/opportunity that the Common Fund should address?

Over 90% of drugs target proteins in one of 4 protein classes: G-protein Coupled Receptors (GPCRs), Nuclear Hormone Receptors, Ion Channels, or Kinases. Although these proteins offer huge potential for new drugs, half of the human proteins in these groups are completely uncharacterized. They are therefore referred to as "Orphan" proteins. The challenge for a Common Fund protein would be to provide functional information about these proteins. This will lead to the identification of small molecules that target those proteins which have a role in disease-relevant processes.

What would the goals of the program be? What initiatives might form the strategic plan for this topic?

The overall goal of this program would be to provide functional information about Orphan GPCRs, Nuclear Hormone Receptors, Ion Channels, and Kinases. This program would take advantage of animal models and relevant human cell types through 4 initiatives: 1) Human Expression Atlas of Orphan Proteins – this would begin with RNA expression data for the Orphan genes but could be later verified with protein capture reagents. 2) Reagent libraries for functional analyses – siRNA libraries, morpholinos, or other types of validated reagents will be needed to provide functional information. In addition, this program would need to coordinate with two ongoing Common Fund programs. Mouse strains which have already been generated should receive top priority in the phenotyping phase of the KOMP project. The Protein Capture program should target these Orphan Proteins if feasibility is established in the current pilot phase of that program. 3) Database of Cellular Functions – Data from the Common Fund projects and from investigator-initiated awards that use Common Fund data and reagents should be gathered in a public database.

Why is a trans-NIH strategy needed to achieve these goals?

These Orphan Proteins will have wide ranging functions across many organ systems. A systematic approach is needed to enable the community to explore the function of these proteins.

If a Common Fund program on this topic achieved its objectives, what would be the impact?

This program will provide the foundation for drug discovery. New targets will be identified in many new tissues, and reagents to explore function will be provided. Functional analyses will be stimulated, and data from these studies will be publicly available for the community at large to use so that screens for compounds to interact with these proteins can be conducted.