Title of proposed program: Target Validation (G2P-P2G)

Submitting IC: NIH

What is the major obstacle/challenge/opportunity that the Common Fund should address? What would the goals of the program be? The genomics revolution has yet to transform therapeutics. Part of the reason for this translational gap is the high failure rate from discovering a genetic signal to identifying a target for a small molecule or biologic that can be developed into an effective therapeutic agent. In initial discussions from an NIH-Pharma meeting held in Nov 2011, two strategies were proposed. One, now known as "Genotype to Phenotype (G2P)," would combine available sequence data in large population samples and/or would sequence additional large population samples to identify rare signals, including loss of function variants, associated with disease phenotypes. Carriers of such variants would then be characterized in depth as to the phenotypic consequences of homozygous and heterozygous carrier states. A second approach, "Phenotype to Genotype (P2G)," would study the genomes of persons with informative phenotypes, such as healthy centenarians or non-demented *APOE**e4 carriers, to identify protective modifier variants that could serve as drug targets. Together, G2P and P2G approaches have been explored as a potential public-private partnership. The Common Fund could be the host of the NIH effort with a goal of creating a genomic resource with broad application for finding valid drug targets.

Why is a trans-NIH strategy needed to achieve these goals? What initiatives might form the strategic plan for this topic? Since this program will study genomic mechanisms operative in many different diseases relevant to many different ICs, as well as variant carriers potentially studied for one disease but found to have relevance to many others, a trans-NIH strategy is required for the program to meet its potential. The initiatives that would be needed for this strategic plan would include (a) combining existing sequencing data to identify carriers of genomic variants relevant to target validation; (b) identifying new, large population samples with characteristics relevant to target validation for large-scale sequencing; and (c) defining the genomic variants underlying unusual phenotypes relevant to target validation.

If a Common Fund program on this topic achieved its objectives, what would be the impact? This program would catalyze the rapid development of new therapeutics for diverse diseases by leveraging the power of genomics to find new targets. In addition, this program would stimulate fundamental biologic exploration around human proteins that are potentially "translatable."