Title of proposed program: Uncovering Novel Drug Targets

Submitting Source: NIH

What is the major obstacle/challenge/opportunity that the Common Fund should address? What would the goals of the program be? The pharmaceutical sector's shift from phenotypic screening to target-based screening may be driving the more recent downward trend in the successful development of drugs with novel targets. Although optimizing a drug and avoiding toxic side-effects is much easier if the drug target is known, we simply don't know enough about the underlying biological mechanisms for most diseases to predict which molecules are likely to be the best drug targets.

One solution is to combine the strengths of phenotypic and target-based approaches: screen for compounds active in phenotypic screens, and then identify the molecular target of those compounds. The NIH-funded academic research community has a rich history of designing clever phenotypic assays, particularly in the context of basic research. With resources like the Roadmap Molecular Libraries centers, investigators are increasingly adapting these assays for chemical screening. The immediate goal of the proposed initiative is to enable researchers to take the next step, that is, to identify the precise targets of compounds that have emerged from phenotypic screens.

Why is a trans-NIH strategy needed to achieve these goals? What initiatives might form the strategic plan for this topic? Identifying drug targets can require specialized expertise and technology. Often the best strategies integrate multiple disciplines, including structural biology, chemical proteomics, and genomics (see http://www.nature.com/scibx/journal/v5/n15/full/scibx.2012.380.html for examples of how some groups are approaching target identification). By tackling this common challenge centrally, NIH can take advantage of economies of scale and attract the best minds and resources to offer solutions. The Common Fund could establish and fund target identification centers, where researchers could submit compounds that they have identified in phenotypic screens. The centers would design and implement multidisciplinary strategies to find the targets for those compounds, free-of-charge to the compound contributors. The NIH could bring together CROs that have proprietary target ID technologies (e.g., Cellzome, http://www.cellzome.com/technology.html) with academics who are pioneering new open-source approaches (e.g., Brian Shochiet at UCSF, who developed the computational Similarity Ensemble Approach, http://sea.bkslab.org/) to form the centers. Some pharma companies might be incentivized to make their own internal target identification services available to academic researchers through partnerships that would give the company a stake in the drug development opportunities that could result. The Common Fund could also support an initiative to encourage the development of new technologies to accelerate target identification.

If a Common Fund program on this topic achieved its objectives, what would be the impact?
If successful, this program could not only expand and accelerate the discovery of new drugs for diseases that currently lack effective treatments, but also catalyze a paradigm shift in the drug development process. Ideally, the NIH-supported discovery of novel drug targets would attract the interest of pharmaceutical companies for subsequent development and commercialization.