Title of proposed program: PK-profiling for Personalized Medicine

Submitting Source: NIH

What is the major obstacle/challenge/opportunity that the Common Fund should address? What would the goals of the program be?

A non-trivial number of drug compounds are likely to fail the stringent FDA process because of toxicity issues. Even when a compound succeeds to market, the next challenge is predicting the effectiveness of the medication. Collecting information on pharmacokinetic (PK) gene variant profiling may be a relatively efficient and cost-effective approach to maximize efficacy by reducing drug toxicities, reducing debilitating side-effects, and increasing dose accuracy. The goal of this CF proposal is to address how PK genetic variations may be incorporated into personalized approaches by using genetic screening early in the drug development process to identify areas of possible risk due to drug metabolism issues, and to leverage PK variants for informing dose. To this end, PK-profiles will be screened and evaluated for their usefulness in optimizing efficacy and aiding clinical decisions for using specified pharmacotherapies for specified diseases.

Why is a trans-NIH strategy needed to achieve these goals? What initiatives might form the strategic plan for this topic?

Trans-NIH groups are needed to: 1) identify all phase II and phase III clinical trials for testing of new compounds (e.g. through CTSAs) to evaluate usefulness of PK-profiling for predicting risk for overt toxicities and other side-effects; and 2) identify and prioritize medications that are used for treatment but have a high rate of ineffectiveness due to unwarranted side effects (e.g. through PGRN). A second need is to establish (or identify and procure) an "out of the box" platform(s), such as the DMET Affy Chip or similar array, for which to screen relevant phase I and phase II metabolizing genetic variants, ideally these variants should screened in CLIA-certified labs and be aligned with variants already on FDA-approved devices. The third is to develop initiatives for identifying and obtaining clinical trial and/or clinic-based samples for screening the PK-profiles, and possibly other known biomarkers for the given therapeutic. The fourth is a centralized initiative(s) to establish analytics and data warehousing for the PK-profiles that can be easily accessed by qualified investigators. Finally, IC-specific funds can then support projects that will leverage the information obtained to develop personalized approaches for guiding clinical decision making.

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

PK profiles will provide a fourfold benefit to the clinical and scientific community: i) It will enable researchers to more accurately and reproducibly compare genetic variant data and potentially other biomarkers across studies; ii) it will provide a standardized platform enriched with SNPs from phase I and II metabolizing enzymes and receptors; iii) it will provide a standardized platform for evaluating the application of PK profiles on toxicity, side-effects, and posology, and iv) it will provide a resource for enhancing personalized approaches to pharmacotherapies.

The PK-profiling is intended to provide clinician scientists with more information about the prospects of optimizing efficacy of medications and provide support for treatment decisions as more data is collected to analyze gene (and/or biomarker) x treatment predictions. By the end of the program, PK-profiles should be in a position to be evaluated for: 1) their ability to be easily and cost-effectively used in clinical trials and/or clinics, and 2) if and how they can reliably inform clinical decision making.