

Title of proposed program: Genetic Models of Complex Diseases

Submitting Source: Strategic Planning Meeting

What is the major obstacle/challenge/opportunity that the Common Fund should address? Developing preventative therapies aimed at reducing or delaying chronic diseases is an important priority for biomedical research. Traditional models of drug discovery have frequently failed, in particular as applied to the complex chronic diseases of the elderly (cancer, neurodegeneration, diabetes, cardiovascular disease, etc.). A better rate of success in translating studies from model organisms into clinical practice is badly needed. At the foundation of this issue is the importance of identifying suitable pre-clinical models of disease that can effectively model genetic complexity. Mice (predominantly C57BL/6 young male mice) have become central to biomedical research and often elaborate manipulations are used in order to approximate the human condition in this model. When used to test drug or treatment efficacy, these inbred murine strains often fall short. No species, much less a single inbred strain, should be expected to be “broadly applicable” to model all diseases, and nature offers a wide range of phenotypes of interest, which may be more comparable to what is observed in human diseases. Indeed, many models that better resemble human disease have been described but are not currently exploited to their maximal potential.

To maximize the use of animal models, genetic technologies for more species need to be developed, technologies for mice need to be enhanced to allow simultaneous mutation of multiple genes so that complex diseases are more effectively modeled, outbred strains need to be increasingly utilized, and zebrafish mutants should be more systematically phenotyped.

What would the goals of the program be? What initiatives might form the strategic plan for this topic? The overarching goal of the program would be to develop new animal models for the analysis of complex traits. The following activities could be covered by Common Fund within a five-year period:

- By convening a meeting of experts in major chronic diseases (CVD, cancer, inflammation, neurodegeneration) and evolutionary biologists / animal researchers, the program could stimulate fruitful discussion of those models that are most worthy of further development and of the opportunities for enhancing mutagenesis methods in mice.
- A series of FOAs could then foster the transfer of technologies needed to study causal relationships and to test candidate therapies in new models.
- Systematic phenotyping of zebrafish mutants could be undertaken.
- Technologies for the generation of multiple mutations in mice could be developed.
- In parallel, existing mouse models could be improved to better account for aging (where most chronic diseases develop), as well as genetic heterogeneity (as observed in human populations), by using newly developed tools such as the Collaborative Cross and the Diversity Outcross.
- A source or repository of such animals for easy use by the research community would need to be developed and maintained if outcomes so warranted. Support for these would be expected to emerge based on their research value and would transition beyond Common Fund support.

Why is a trans-NIH strategy needed to achieve these goals? Better translational models would benefit programs at several NIH ICs as well as trans-NIH endeavors. The program would leverage investments made in sequencing the genomes of a number of species and would provide a “proof of principle” with a clear deliverable at the end of the incubator period.

If a Common Fund program on this topic achieved its objectives, what would be the impact? Investment in this area will yield more relevant models in which to test pre-clinical hypotheses, improve the likelihood of success in translating from the bench to the clinic, and increase the translational success rate of a number of NIH programs. The potential impact will be to help increase the number of successful interventions available to provide relief for a variety of diseases and conditions and improve health in the U.S. and around the globe.