Title of proposed program: *Fibrotic Diseases: causes, consequences, prevention, and treatment*

What is the major obstacle/challenge/opportunity that the Common Fund should address?
The biology and pathophysiological progression of fibrotic diseases, which represent a major cause of morbidity and mortality worldwide, are poorly understood. Fibrotic disease can affect many organs, including liver, bone marrow, lung, kidney, GI tract, skin, eye, and endomyocardium, leading eventually to organ failure. Fibrosis of the liver represents a paradigm for this disease, as it may be reversible at early stages but become irreversible as it progresses to cirrhosis, resulting in liver cancer in addition to end stage disease. It has multiple potentially preventable etiologies; they include HBV and HCV infection, obesity, alcoholism, and aflatoxin among others; each presents opportunities for and serious barriers to primary and/or secondary prevention. For many other fibrotic diseases, the underlying etiologies are less clear, although many are associated with chronic production of proteolytic enzymes, fibrogenic cytokines, growth factors, and angiogenic factors, presumably secondary to triggering irritants (e.g., radiation, chronic infections, toxins). Others are congenital or associated with autoimmunity. For fibrosis of all types, the point of irreversibility and the molecular mechanisms by which it occurs are not well defined. Organ failure is the end-result of uncontrolled fibrosis.

Fibrotic diseases disproportionately affect minority populations and populations of developing countries around the world. For example, between 1990 and 2010 annual worldwide deaths from cirrhosis and liver cancer rose from 1.25 million to 1.75 million. In the US over the same period, deaths from these two causes increased from 44,000 to 69,000. Liver cancer is now the second most common cause of cancer deaths worldwide (~750,000 deaths per year, >90% mortality rate, >9% of all cancer deaths), while in the US there are ~20,000 deaths from this cancer, whose mortality rate is increasing faster than any other cancer. Worldwide, there are ~400 million HBV carriers, ~160 million HCV carriers. Worldwide incidence and prevalence rates of most fibrotic diseases are not known, since there are generally no reliable registries. However, the number affected by pulmonary fibrosis may be in the millions. Major obstacles, challenges, and opportunities lie in developing validated approaches to reduce the incidence and mortality attributable to the broad range of fibrotic diseases. A coordinated approach is necessary because, even though some aspects of etiology, pathogenesis, prevention, and management may be organ-specific, others will likely be common to the full spectrum of fibrotic diseases. Common and discordant findings among organs could provide insights into organ-specific versus shared pathways.

What would the goals of the program be?
The main goals would be to advance our understanding of the various etiologic risk factors that contribute to the pathogenesis of fibrosis and its downstream consequences; to improve primary and secondary prevention of these risk factors; and, to determine the degree to which successful secondary prevention can reduce the risk of fibrosis and its progression to irreversible states.

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

A major benefit of a Common Fund project on this topic would be to bring the research community together to approach this problem more cohesively and comprehensively. We envision a "hub and spoke" model in which the Common Fund "hub" would support cross-cutting projects and basic research, while ongoing and/or new projects from various IC's could still take organ-specific approaches. One possible "spoke" project could be to develop approaches that can identify more high-risk patients and implement successful interventions for primary and secondary prevention. For example, there is a need to identify and treat more patients who have prevalent HCV infection. Another "spoke" project could be to develop the biologic understanding of pathogenesis of idiopathic pulmonary fibrosis due to cellular derangements, and matrix component stiffness involved in initiation and persistence/resolution of fibrosis. On the other hand, a "hub" program could entail coordinated investigations into critical interactions among different cells, including epithelial-mesenchymal interactions to elucidate the mechanism of progression and could provide several intermediate targets amenable to intervention for the broad range of fibroses.

What initiatives might form the strategic plan for this topic?

1) Determining the degree to which interventions reverse prevalent risk factors for specific fibrotic diseases. 2) Improving understanding of the pathogenesis of fibrosis, including the search for determinants of progress common to multiple organ-specific fibrotic diseases. 3) Tissue engineering to develop artificial organs. For example, transplantation is a successful late intervention in the case of liver or heart failure; however, the number of available organs is much lower than the number of patients who could benefit from transplantation. In the case of many other fibrotic diseases, organ transplantation is not an option at all.

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

It could set the stage for increased understanding of the pathogenesis of fibrosis together with a reduction in incidence and mortality attributable to fibrosis and its downstream consequences in a variety of organ systems. Current focuses restricted to the role of inflammation in fibrotic disorders have been less than optimal, probably because multiple mechanisms are involved.