Title of proposed program: Technologies for Mitochondrial Biology (TMB): a trans-NIH effort to develop tools to study and manipulate mitochondria in vivo

Submitting IC: NIH

What is the major obstacle/challenge/opportunity that the Common Fund should address?
Mitochondrial activity affects many processes vital to cell physiology, including apoptosis, metabolism, response to starvation, and cell fate determination. While mitochondria have been studied for decades, they have been isolated and analyzed from cell types where they are abundant. It has become increasingly clear that mitochondria have cell-type specific proteomic components, have varying structures, and perform cell-type specific functions. Genetic heterogeneity of mitochondria is also difficult to analyze systematically. The heterogeneity of mitochondria in any given individual is likely to play an important role in tissue-specific phenotypes that are the hallmarks of mitochondrial disease. However, we have limited ability to explore the impact of mitochondrial heterogeneity in vivo or to manipulate the genetic content of mitochondria to test hypotheses related to heterogeneity. The major challenges are to develop technologies to analyze mitochondrial composition, structure, and function in diverse cell types in vivo and to manipulate the mitochondrial genome. A knowledge base of these mitochondrial attributes across tissues would be hypothesis-generating and transformative for the community.

What would the goals of the program be?
This program's goal would be to develop technologies to study the composition, function,and structure of mitochondria in humans, in vivo, in diverse tissues. Investigators funded through this initiative would be required to work together in a coordinated fashion to develop technologies and to use them to address mitochondrial composition, structure, and function. Tissue specific differences are expected, but overarching principles also need to be formulated. These studies will empower the mitochondrial community, which is already gathering composition data from some human cell types. Data coordination across the community would therefore also be a goal.

Why is a trans-NIH strategy needed to achieve these goals?
Mitochondrial activity affects many processes vital to cell physiology, including apoptosis, metabolism, response to starvation, and cell fate determination. New technologies are needed to enable investigators to study and manipulate the composition, function, and structure of mitochondria in humans, in vivo. Coordination in technology development and data gathering across tissues will be essential. The widespread funding of individual projects in mitochondrial biology from the ICs is indicative of the interest and understanding that mitochondrial function is critical for the mission of many ICs. However, a coordinated, trans-NIH approach to technology development and data repositing is unlikely to happen without dedicated funds from the Common Fund.

What initiatives might form the strategic plan for this topic?
This program would involve 3 initiatives: 1) Technologies to analyze mitochondrial composition, structure, and function in vivo in diverse cell types, 2) Technologies to manipulate the mitochondrial

genome, 3) Cell type-specific profiles of human mitochondrial composition and heterogeneity in tissues for which this type of analysis is currently intractable, and 4) a Community Coordinating Center, to serve as a community-wide reference for the many ongoing mitochondrial studies and to disseminate technologies and data gathered through the other 3 CF initiatives.

If a Common Fund program on this topic achieved its objectives, what would be the impact?
This program will enable the mitochondrial research community, as well as investigators who are increasingly interested in the role that mitochondria play in common diseases, to take entirely new approaches and will therefore lead to new paradigms for mitochondrial function. It will lead to a fundamental rethinking of the mechanistic basis of disease states and their manipulation through mitochondrial control.