Endocrine Society comments in response to NOT-RM-23-013, "Request for Information: NIH Common Fund is Soliciting Ideas for NIH-wide Challenges and Opportunities"

This response was developed by the Research Affairs Core Committee of the Endocrine Society

Comments submitted electronically via online submission form on August 11, 2023.

Suggested title to describe your idea

Sex differences research to inform medicine

A critical challenge or exciting emerging opportunity in biomedical/behavioral research

Significant sex biases exist in the development and presentation of diseases such as obesity, autism spectrum disorders, and many types of cancers. Despite sex being a significant factor in predictors of health or the risk of an individual in the development of many diseases, it is unclear to what extent these differences are due to intrinsic factors, such as the impact of sex chromosomes on gene regulation, or extrinsic factors, like sex hormones or the environment.

Until the implementation of the NIH's "Sex as a Biological Variable" (SABV) policy, basic and clinical research was skewed toward the study of male animals and cells. This created and perpetuated an inequity in health care knowledge, and ultimately the quality of available treatments, depending on the sex of the patient. It has now been 7 years since the implementation of the SABV policy, and studies are showing that sex impacts processes well beyond reproduction, from cellular physiology to brain organization. However, there is still a lack of a fundamental, systematic data catalog of sex differences across healthy tissues and disease states.

The aim of this common fund proposal is to understand the fundamental biological differences between sexes. Data generated from these studies will be a critical step towards making improved precision medicine.

Resources, tools, or knowledge that are needed to address the important challenge or opportunity (500 wds max)

There are many resources and tools that could be utilized to address this proposal through the genetic, hormonal, and environmental lens. For example, work recently published by David Page has demonstrated that some gene expression changes in response to different numbers of X chromosomes. This provides justification to examine how sex chromosome dosing may be impacting different cell types, either by assessing differential gene expression or protein composition by tissue in XX vs. XY cells at different ages. To broaden the scope, different methods could be interchanged: instead of measuring gene expression, for example, one could

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measure hormones, epigenetic differences, burden of exogenous chemicals, etc. These would help identify the fundamental differences underlying sex biology and by also examining tissues in diseases with a sex-bias, understand the drivers or protectors from disease. Including the study of intersex cells, those receiving hormone therapy, individuals who have been exposed to high levels of endocrine disrupting compounds from their environment, and other variables will be particularly insightful in determining causal relationships.

Scientific advancements or other factors that make addressing the important challenge or opportunity particularly timely

The ambitious All of Us biobank provides specimens and participant provided information to investigate sex differences in diverse datasets. The development of this resource provides the opportunity to perform the research proposed by this common fund idea at reduced costs. These investigations also extend existing HuBMAP and SenNet resources and data by utilizing the experimental pipelines and protocols that interrogate cellular neighborhood communication and utilize large -omics datasets on human specimens.

Other comments or input you wish to provide
N/A

Suggested title to describe your idea

The Mitochondrial Dysfunction Hub & The Mitochondrial Transplantation Regenerative Initiative

A critical challenge or exciting emerging opportunity in biomedical/behavioral research

Emerging data show mitochondrial dysfunction in a variety of pathogentic states, such as cardiovascular disease, exposure to endocrine disrupting chemicals, and cancer. Recent scientific advancements have revealed a promising strategy known as mitochondrial transplantation, which involves transferring healthy mitochondria into cells with dysfunctional ones, for potential therapeutic effects. This common fund idea aims to characterize mitochondria in disease states and explore the potential for therapeutic intervention via mitochondrial transplantation.

Resources, tools, or knowledge that are needed to address the important challenge or opportunity

Mapping the extent of Mitochondrial Dysfunction across different biological systems: We need to understand what level of mitochondrial dysfunction is currently described in the literature, across all organs/systems and their pathophysiological associations. Similar to NIH's Cellular Senescence Network, which characterizes differences in senescent cells, this common fund program would create a mitochondrial database across tissues and ages.

Broad Applications: Systematic research is necessary to identify the full spectrum of conditions that could benefit from mitochondrial transplantation. This involves expanding preclinical studies to various disease models.

Improved Delivery Methods: We need to develop more efficient, targeted methods for mitochondrial delivery to specific tissues and cells. This requires advancements in bioengineering and nanotechnology to allow for precise targeting and delivery.

Long-term Effects: Longitudinal studies are needed to understand the long-term effects and potential risks of mitochondrial transplantation. This includes understanding how introduced mitochondria interact with host cells over time.

Safety Protocols: Rigorous safety protocols need to be developed. This includes comprehensive *in vitro* and *in vivo* testing to evaluate potential off-target effects and immune responses to transplanted mitochondria.

Scientific advancements or other factors that make addressing the important challenge or opportunity particularly timely

Recent advancements in our understanding of mitochondrial biology, the development of techniques for isolating and characterizing mitochondria, and promising preliminary findings from experimental studies of mitochondrial transplantation make this an opportune moment for concentrated research efforts in this area. Additionally, ongoing developments in nanotechnology and bioengineering provide novel avenues for improving mitochondrial delivery methods.

Other comments or input you wish to provide

Given the central role of mitochondria in cellular function and health, the impact of successfully developing mitochondrial transplantation therapies could be transformative. These therapies could address a broad range of conditions that are currently difficult to treat effectively, providing new hope for patients and healthcare providers. Therefore, it is crucial that we invest in this area of research, fostering collaboration across disciplines, to fully realize the potential of mitochondrial transplantation in the treatment of human disease.