NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
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Cellular, Organs and Systems Pathobiology Branch

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Concept Clearance

Transgenerational Inheritance in Mammals after Exposure (TIME Consortium) – A DERT-NTP Collaborative Research Program

Introduction

The goal of this proposal is to establish a consortium of researchers performing comprehensive analyses of Transgenerational Inheritance in Mammals after Exposure (TIME). The TIME consortium, a collaborative effort between DERT and the NTP, will be composed of three sub-initiatives: a centralized mouse core (housed at the NTP), 6-8 phenotyping centers, and an epigenetics/bioinformatics core. Together, the TIME consortium will investigate one of the most critical questions facing the environmental health sciences: Are the effects of exposure transmitted to subsequent generations?

Phenotypic traits are generally inherited via a genetic mechanism, where changes in the DNA sequence are transmitted to future generations through meiosis. However, numerous examples have been identified that do not follow this simple mode of inheritance, and point to the existence of alternative mechanisms. In many cases, such traits are induced by exposure to chemicals or other environmental stressors. Often, these induced traits can be transmitted through multiple generations, even in the absence of a change in the DNA sequence or the continued presence of the inducing factor. This phenomenon is known as transgenerational inheritance. A gestational exposure to an F0 dam directly exposes both the developing F1 fetus and the primordial germ cells that will result in the F2 animal. Thus, it is important to consider that true transgenerational inheritance must occur through at least the F3 generation following gestational exposures.

Although examples of transgenerational inheritance have been observed in a wide range of organisms in response to a variety of stimuli, few examples have been well-documented in mammals. The available data suggests that, at least in mammals, 1) transgenerational inheritance occurs primarily through the male germline, 2) the window of exposure is critical, 3) that genetic factors may influence the likelihood of transgenerational effects, and 4) that this phenomenon may have an epigenetic basis. Still, the idea that transgenerational inheritance occurs in mammals remains quite controversial. Although new examples have continued to arise, the majority of data supporting this hypothesis surrounds a single environmental chemical (vinclozolin), was generated by one group of investigators, and focuses on a limited number of phenotypic

endpoints. Furthermore, several groups have reported difficulty in replicating these studies.

If exposures in one generation can truly impact health outcomes for generations to come, this would have an enormous impact on public health and policy. We feel it is crucially important to move this emerging field forward. In order to achieve this, we have developed a comprehensive, multi-component collaborative research program aimed at investigating the phenomenon of transgenerational inheritance in mammals.

Research Goals and Scope

The overarching goal of this proposal is the formation of a collaborative extramural/NTP consortium to investigate Transgenerational Inheritance in Mammals after Exposure (TIME). The TIME consortium will investigate whether prenatal exposure (in the F0 generation) can cause phenotypes that are inherited through at least the F3 generation, and attempt to determine the mechanism by which this occurs. The consortium will be structured as follows:

1. DERT will fund 6-8 Transgenerational Phenotyping Centers (TPC). This FOA will solicit applications from investigators with expertise in specific organ systems or phenotypes (such as obesity, immune, cardiovascular, neurological, etc.). Each phenotyping center will have a specific organ/disease focus and perform a battery of phenotyping assays in F1 and F3 mice, to identify phenotypes that are inherited by the F3.
2. The NTP will house the Transgenerational Mouse Core (TMC). All exposures and mouse breeding will be conducted by the mouse core. The mouse core will distribute mice or tissues as required for phenotyping by the phenotyping centers. If necessary, a TPC may make arrangements to perform phenotyping assays on site at the NTP.
3. Starting in the second year of the program, DERT will fund an Epigenetics/Bioinformatics Core Center (EBCC). The EBCC will receive tissues and germ cells from F1 and F3 mice and perform a range of epigenetic analyses (including DNA methylation, histone modification, ncRNA assays) in an effort to identify changes that may contribute to transgenerational inheritance.

The charge of the TIME consortium will be:

- Investigate a variety of environmental toxicants to determine if they are capable of inducing transgenerationally inherited phenotypes
- Test different exposure paramaters (such as timing of exposure, dose) to determine the key variables
- Identify the range of resulting phenotypes and organ systems affected
- Investigate sex differences in transgenerational inheritance
- Analyze DNA methylation, histone modification, and other epigenetic features to determine the mechanism by which transgenerational inheritance occurs

As soon as the phenotyping centers are awarded, the TPC PIs and NTP scientists will come together with NIEHS program scientists to finalize breeding/dosing paradigms and select and prioritize toxicants to be examined.

Mechanism and Justification

This initiative will use the U01 mechanism to develop a consortium of externally-funded researchers to collaborate with NTP scientists. Utilizing the U mechanism will allow NIEHS staff to have input on the toxicants and dosages selected.