

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES  
Division of Extramural Research and Training  
Susceptibility and Population Health Branch

**NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL**  
February 16 - 17, 2011

Concept Clearance

Environmental Influences on Stem Cells in Development, Health, and Disease

**Introduction**

Environmental health studies are lacking on stem cells, the fundamental source from which all tissues ultimately derive. Exposures that alter stem cells but allow them to survive may alter their fate and the cellular composition of the resulting tissues. While most organs are formed in the womb, many continue to develop after birth.

Reproductive tissues, for example, begin a lengthy maturation process that begins with puberty. Mammary glands notably do not completely mature until pregnancy and the glands degenerate somewhat after lactation ceases, but the tissues continue to include stem and self-renewing cells. The final devolution of the mammary gland does not take place until menopause at about age fifty. As a result, such cells and tissues are in proliferative stages for many decades and may be particularly vulnerable to insults and toxicants, that may accumulate over time.

Little is known of the affect of long-term, physiologically relevant environmental exposures on essential cell processes in stem cells that could progress to a pathogenic state. Alteration to the stem cell populations and their progeny likely sets the stage for tissues that become either resistant or pre-disposed to disease. There is an overriding need to resolve the role of either embryonic or adult stem cells in the genesis of tumors or pre-cursors of degenerative diseases. One important question is whether adult stem or progenitor cells behave more like somatic cells or embryonic stem cells with respect, for example, to cell cycle regulatory mechanisms and suppression of mutations. Defining mechanisms of action of exposures on stem cells is key to these issues and, perhaps, to individual and population susceptibility, especially at specific developmental stages. Thus, insight is needed into the effects of chemical exposures that can potentially alter stem cell capacity to differentiate, function properly, and maintain genetic integrity.

**Research Goals and Scope**

Based on the compelling needs indicated above, NIEHS convened a Workshop on Exploring Environmental Effects on Stem Cells (June 3 - 4, 2010). The workshop included experts in environmental health, as well pioneers in stem cell research (roster attached) and this program concept is based on their recommendations.

One direction that was highly prioritized by the Workshop is investigation on stem cells that elucidate the limits of the Windows of Susceptibility (WOS), the concept that individuals are more at risk to develop disease from exposure at certain points in the developmental timeline. There is compelling evidence for WOS, for example, from studies of female survivors of the Hiroshima atom bomb who were much more likely to develop breast cancer as adults if they were in pre-pubertal or pubertal periods at the time of the explosion. WOS include, but are not necessarily limited to in utero, puberty, pregnancy, and menopause, periods in which stem cells could play a role as targets for hormonal imbalance and hormone-mimicking substances. Studies of stem cells would be expected to lead to improved definition, understanding, and mechanisms of WOS. However, investigations have rarely explored the response to exposure of stem cell populations with regard to fate and lineage, population composition, epigenetics, or DNA repair. These parameters need to be illuminated in order to produce a comprehensive model of WOS that will translate into improved understanding of disease risk over the lifespan of an individual.

The proposed program will support novel research directions leading to understanding of the role of exposures of common environmental chemicals - at human physiologic concentrations - in function, proliferation, survival, fate, and differentiation of stem cells. Supported studies are expected to approach the nature and susceptibility to exposure and the micro-environment of critical stem cells and cell sub-populations and the mechanisms and limitations of windows of susceptibility. The results of these investigations likely lead to new insights into the mechanisms by which progenitor cells are or could become vulnerable to disease or even to become the source of pathogenesis. In order to have greater impact with the limited funds available, the program will be limited to environmental health research on stem cells in the endocrine, reproductive, immune / hematopoietic, and central nervous systems.

Potential topics for applications include, but are not limited, to the following illustrations:

- Characterize the roles of stromal cells in the timing and mechanisms of Windows of Susceptibility in, for example, mammary gland. Exploring the mechanisms of common environmental exposures such as endocrine disruptors in affecting the parameters of the “window?”
- Investigate modification by exposure of the characteristics of neurons or glial cell precursors that could explain different sensitivity of children and adults to pesticides such as Chlorpyrifos. Determine specific cell receptors and pathways mediate the critical changes.
- Examine how cellular regulatory pathways (e.g. gene expression, epigenetic or proteomic phenotype) that determine lineage and eventual fate are altered by specific environmental influences and the pathways that might lead to disease initiation, onset, or progression.

- Investigate genotoxic or non-genotoxic environmental agents that alter stem cell differentiation and lineage, proliferation, and composition of cell populations.
- Determine the DNA repair capacity of specific stem cells / populations and the efficiency of repair following chemical or dietary exposure as contrasted to differentiated cells.
- Explore the mechanisms by which common chemical exposures, such as pesticides, phthalates, or arsenic, alter the composition of cells among hematopoietic stem cells or progenitor populations that might contribute to chemical sensitivity or pre-dispose to disease.

### **Mechanism and Budget**

The program is estimated at \$2.5M annually to support 6 – 8 R01 projects.

This proposal is a cross-divisional NIEHS effort and includes the comments of members of the Division of Extramural Research and Training and the Division of Intramural Research.

**Workshop on Exploring Environmental Effects on Stem Cells**  
National Academy of Sciences – Keck Building  
June 3 – 4, 2010

Roster

Ricardo Dolmetsch	Department of Neurobiology, Stanford University
Susan Fisher	Professor of Obstetrics, Gynecology, Reproductive Sciences & Pediatrics, UCSF
Tom Gasiewicz	Professor, Chair, Dept of Environmental Medicine, University of Rochester
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Jose Russo	Director, Breast Cancer Research Laboratory, Fox Chase Cancer Center Philadelphia
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