Report 61: Basic Research on Mutagenic Mechanisms Using Model Systems

Convener: Phil Hanawalt

Brief History: Fundamental study of the mechanisms of genomic maintenance has been a subject of world-class research across NIH, but especially through the NIEHS intramural and extramural programs. Discoveries using model systems have led to, for example, the role of mismatch repair in colon cancer, the mechanism of triplet repeat expansions in neurological disease, and in general, the development of screening tools and test systems for identifying genotoxicants. Molecular structures are being determined for relevant enzymes to reveal mechanisms and to yield crucial information for intervention (e.g., through small molecule inhibitors). Model systems promote understanding of the factors involved in response to damaging agents and may help to simplify the assessment of environmental risks to humans. New sequencing technologies can now be applied to single cells and simple organisms used as models for repair. Mechanistic research facilitates the understanding and interpretation of sequence changes and "mutational fingerprints" of environmental exposures.

Discussion Highlights:

- Our current understanding of how cells respond to environmental genotoxicants (for example, development of the Ames test) are only possible because of fundamental research in DNA repair.
- There are still great untapped opportunities for understanding the function of genes in model organisms that respond to DNA damage. For example, in *E. coli*, the recN gene is the most highly upregulated gene in response to damage. Yet, the function of this gene is not currently known.
- Research on effects, for example, of unusual secondary or alternative structures (non-B DNA) point to increased susceptibility to damage from toxicants as well as reduced repair in these sequences. Although some effects are likely subtle, all contribute to overall disease risk.
- Model systems permit the application of single and multiple gene knockdowns to dissect the genetic contributions to damage response and to understand basic mechanisms.
- Fundamental research in DNA damage/repair related to environmental exposures supports studies of cancer etiology, neurological disease and aging.
- Basic research should encompass studies at multiple layers of complexity, from studies with naked DNA through chromatin organization in higher organisms.

Recommendations:

- NIEHS should continue to promote cutting-edge, mechanistic research that maintains the Institute as a world leader in understanding environmental genetic toxicology and disease.
- We should take advantage of new sequencing technologies and other novel tools for single cell genomic sequencing to obtain mutational fingerprints from environmental exposures and to

understand repair mechanisms that are operative. Information from these efforts will be crucial for advances in intervention and prevention.

- Among systems for mechanistic studies, we should not overlook the importance of bacteria, yeast, and other model systems. Basic research gives us insights into the limitations of various test systems (including rodent models) as surrogates for humans. Comparative analysis of different systems is therefore critical.
- We should continue to explore potential translation of fundamental discoveries to environmental health issues.

Discussion Participants: Hanawalt, Worth, Adelman, Williams, Shaughnessy, Tyson, Mural