“Genomic Damage by Activation Induced Deaminase"

Principal Investigator:

- Michel Nussenzweig, MD, PhD, The Rockefeller University

Co-Principal Investigator:

- David Root, PhD, The Broad Institute of MIT and Harvard

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Abstract: Chromosome translocations involving antigen receptor genes and oncogenes are a frequent cause of lymphoid malignancy. These events require formation of paired double strand DNA breaks in the two target chromosomes. In mature lymphoid cells, the DNA breaks in antigen receptor genes are formed by activation induced cytidine deaminase (AID). This enzyme converts cytidine to uracyl in single stranded DNA thereby creating U:G mismatches that are recognized and processed by mismatch repair enzymes or uracyl DNA glycosylase (UNG) to produce point mutations or DNA breaks. Although AID prefers antigen receptor genes, Dalla Favera and other investigators have shown that this enzyme can also produce mutations in cancer associated genes such as Bcl6. We have recently discovered that AID is also responsible for producing the double strand breaks that lead to lymphoma associated c-myc/IgH translocations. How AID targets antibody genes or oncogenes is not known and neither is the extent of damage AID produces in other locations in the genome. To explore this issue we have developed mouse models in which AID expression leads to extensive genomic damage in primary B cells and to cancer producing translocations. The object of the proposed research is to use newly available sequencing technology to determine the sites in the genome that are targeted by AID in primary B cells and B cell tumors. The long-term goal of the proposal is to understand how abnormalities in the molecular regulation of antigen receptor diversification lead to genomic instability and to cancer causing chromosome translocations.