Principal Investigator:
- Jessica Tyler, PhD - Weill Cornell Medicine

Co-Principal Investigators:
- Scott Keeney, PhD - Memorial Sloan Kettering Cancer Center
- Jayanta Chaudhuri, PhD - Memorial Sloan Kettering Cancer Center
- Barry Sleckman, MD, PhD - Weill Cornell Medicine
- Marcin Imielinski, MD, PhD - Weill Cornell Medicine

Abstract: Genomic instability is a hallmark of all cancers. DNA double-strand breaks (DSBs) are a particularly dangerous type of DNA lesion that, if repaired aberrantly, can lead to gross chromosomal rearrangements (translocations, deletions and inversions) that can alter the expression of neighboring genes. These chromosomal lesions can cause transformation of normal cells and improve the fitness of cells that have already been transformed, forming tumors. Despite intensive study, the factors that determine where DSBs occur in the genome and which DSBs are at risk for being resolved aberrantly remains poorly understood. We propose to remedy this knowledge gap in the context of developing and mature lymphocytes where programmed DSB formation and repair occur as part of a physiologic process and where errors in DSB repair are a direct cause of many lymphoid cancers. DSBs are generated throughout the genome by topoisomerase II during DNA transactions such as transcription and replication. It is our hypothesis that these DSBs are major participants in the formation of genome rearrangements and that differences in the chromatin landscape dictate both the DSB frequency and the frequency of aberrant DSB repair. Although we will focus on genomic rearrangements in lymphocytes, our findings will be broadly applicable to the mechanisms of genome instability in all tumors. As such, our findings will reveal targets that can be therapeutically manipulated to ameliorate the risk of genomic rearrangements that are drivers of genome evolution of therapy resistance in cancer cells.