Telomere Crisis and Chromosome Shattering in Cancer

Principal Investigator:

- Titia de Lange, PhD – The Rockefeller University

Co-Principal Investigators:

- Levi Garraway, MD, PhD – The Broad Institute of MIT & Harvard
- Achim Jungbluth, MD – Memorial Sloan Kettering Cancer Center

Abstract: Although cancer development involves gradual step-wise mutational alterations, recent work has pointed to an additional contribution of episodic massive chromosome shattering phenomena, including chromoplexy and chromothripsis. How chromoplexy and chromothripsis are initiated is unknown. We hypothesize that chromosome shattering originates from end-to-end fused dicentric chromosomes, which occur when severe telomere erosion leads to telomere crisis. We propose that such dicentrics become fragmented and that subsequent mis-repair causes chromothripsis. Our preliminary data have provided strong evidence for this model. Chromoplexy could arise when multiple dicentrics are broken and are subsequently repaired incorrectly. To test our hypothesis, we will use live-cell imaging to monitor the behavior of experimentally-induced end-to-end fused dicentric chromosomes (Aim 1). Our preliminary data indicate that dicentrics develop into chromatin bridges that are shattered by the cytoplasmic nuclease TREX1, which gains access to the chromatin upon nuclear envelope rupture. We will expand our characterization of how dicentrics are fragmented and determine whether the preliminary data are generally applicable to cells in telomere crisis. In Aim 2, expanding on our preliminary finding of chromothripsis, we will further define the genomic rearrangements resulting from experimentally-induced telomere crisis. Finally, we will examine tumors with chromothripsis or chromoplexy for the specific genomic and cell biological indicators of (past) telomere crisis (Aim 3). This project aims to define the role of telomere crisis in chromosome shattering and other cancer-relevant genome rearrangements.