

## **The role of telomerase in healing broken chromosomes in cancer**

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**Abstract:** In this project, we will test our hypothesis that telomerase-mediated healing of broken chromosomes allows cancer cells to tolerate genome instability. Activation of telomerase is generally thought to be required to replenish the telomere reserve, thereby counteracting telomere attrition with cell divisions. We hypothesize that telomerase has a second (previously unrecognized) role in tumor development involving generation of new telomeres rather than extending existing telomeres. Our preliminary data suggests that human telomerase, like telomerases in unicellular organisms, can add new telomeres (neotelomeres) to double-strand breaks (DSBs). We speculate that addition of neotelomeres to broken chromosomes can be adaptive in cancer cells, especially in cells with dicentric chromosomes that instigate ongoing Breakage-Fusion-Bridge (BFB) cycles. In cancer, dicentric chromosomes originate from a variety of intrinsic sources of DNA damage, including defective regulation of DNA replication, mutations in DNA repair genes (e.g. BRCA1 and BRCA2), and loss of telomere function due to telomere attrition. In each setting, DSB repair pathways acting on broken chromosomes can form unstable dicentric chromosomes that give rise to additional broken ends upon cell division. Such self-perpetuating BFB cycles are likely to have a considerable fitness cost. We speculate that neotelomere formation by telomerase terminates BFB cycles, thereby improving the fitness of cancer cells bearing dicentric chromosomes. Our collaboration will combine our expertise in telomere biology, chromosome instability, and cancer genomics to test this hypothesis and explore the relevance of telomerase-mediated neotelomere formation to cancer development. This project could redefine the role of telomerase in cancer.