Induction of cancer cell death by selective DNA misincorporation

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Telomeres cap and protect the ends of all human chromosomes. In healthy adult tissue, telomeres shorten with each round of cell division as part of the natural aging process. By limiting human cells to a finite number of divisions before induction of programmed cell death, telomere erosion functions as a tumor suppressor. Conversely, in cancer cells, an enzyme called telomerase is upregulated to synthesize telomere DNA and, thus, nullify the limited number of cell divisions. The upregulation of telomerase in ~90% of metastatic tumors is a primary contributor to the cancer cell's unlimited proliferative properties. Due to this unique and critical role in cancer biology, telomerase provides a novel target for innovative therapeutics. As such, direct telomerase inhibitors are currently being developed, with several compounds showing promise in treating a wide range of human cancers. However, the primary shortcoming with this methodology is that even after telomerase inhibition, the cancer cells must go through multiple rounds of division before telomere attrition results in replicative senescence. This delay allows cancer cells to develop other mechanisms of survival, such as alternative lengthening of telomere mechanisms, to overcome the effects of telomere shortening caused by telomerase inhibition.

This project is designed to explore a novel mechanism to use telomerase to deliver small molecule drugs to cancer cells specifically. Telomere DNA is bound and protected by specialized proteins including telomere repeat binding factors 1 and 2 (TRF1 and TRF2) and protection of telomeres 1 (POT1) proteins. TRF1/2 and POT1 bind telomere DNA with high specificity, such that a single change in telomere DNA sequence drastically reduces the binding efficiency. Abrogation of POT1 or TRF1/2 binding to telomeres induces an immediate DNA damage response. We are investigating whether the misincorporation of non-native nucleotide analogs by telomerase into telomeric DNA will abrogate POT1/TRF1/TRF2 binding. The inability of telomere proteins to bind and protect the telomeres should elicit an immediate DNA damage response and initiate cell death specifically within cancer cells. Measuring potency and selectivity against telomerase-positive and telomerase-negative cancer cells is used to validate the cell-killing potential, and molecular mechanism, of these non-native nucleotide compounds.