

Targeting Telomeres for Cancer Therapy

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An almost universal hallmark of all cancer types is telomerase activation [1, 2]. Telomerase is a ribonucleoprotein holoenzyme complex responsible for elongating telomeres that protects the integrity of chromosome ends. While absent in most normal adult human cells, telomerase is active in cancer cells, allowing continuous cell divisions and immortality [1]. How telomerase is activated as part of aging and cancer remains a central question but some new insights are emerging [3]. We determined that the nucleoside analogue 6-thio-dG (6-thio-2'-deoxyguanosine) is preferentially recognized by the telomerase holoenzyme (activated in ~90% of all advanced malignancies) and is incorporated into *de novo* synthesized telomeres. This results in structurally and functionally modified telomeres leading to uncapped dysfunctional telomeres and rapid cell death, but only in cells expressing telomerase [4].

Current treatments for most advanced cancers are targeted therapies such as BRAF inhibitors in melanoma and EGFR inhibitors for lung cancer. In addition, immune checkpoint inhibitors are rapidly becoming front line therapy for cancer, but only a small subset of patients respond to such therapies and those that do respond are often limited by acquired therapy resistance [5,6]. We exploited telomerase dependency in most advanced cancers as a strategy to target different forms of therapy resistant tumors with 6-thio-dG [5,6]. Using a large panel of human cancer cell lines and patient derived xenografts with acquired resistance to targeted therapies we have demonstrated a general sensitivity of these cells to 6-thio-dG both *in vitro* and *in vivo* [4-7]. These results indicate that 6-thio-dG may provide a new telomere-addressed telomerase-dependent anti-cancer approach that may prolong control of therapy-resistant tumors.

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