

## CpG methylation in the *TERT* promoter

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Epigenetic modifications in gene regulatory regions significantly contribute to the chromatin landscape that favors or disfavors transcriptional activation. One of the most abundant and least understood epigenetic modifications in eukaryotic DNA is methylation of cytosines at C-G dinucleotides (CpG). High levels of methylation in CpG rich gene promoters is typical of silenced genes; in contrast CpG methylation in gene bodies is canonically associated with expressed genes.

Telomerase reverse transcriptase (*TERT*) is an important oncogene on which 85-90% of all cancers rely for their indefinite replication. Methylation of the CpG island (cg11625005) in the proximal *TERT* promoter in cancer differs markedly from stem cells and differentiated cells. While normal cells exhibit little or no methylation at this locus, existing studies report that nearly all cancers exhibit significant levels of methylation at this CpG island. In contrast to expectations from other genes, numerous studies report that global demethylating agents such as azacytidine are detrimental to *TERT* mRNA expression in most cancers. We are working on understanding this confounding observation using a subset of cancer cells that express *TERT* monoallelically. In these cancers, in a single cell, one allele is active, while other *TERT* alleles are not expressed. Our data indicate that cancers with both active and silent alleles in the same cell display differential methylation patterns at cg11625005 on the different alleles. Targeted epigenome editing of these loci result in phenotypes that differ from previous reports that utilized global demethylating treatments. We conclude that the consequences of CpG methylation in the *TERT* promoter may be more complex than existing studies suggest.

### Biography:

Dr. Stern was awarded his Ph.D from the University of Sydney in Australia before commencing his postdoctoral training at the The University of Colorado in Boulder in the lab of Dr. Thomas Cech. Dr. Stern is focused on understanding the mechanisms that govern telomerase and telomere biology, in both normal and disease contexts, to identify therapeutic targets for the treatment of cancer, as well as other telomere-based diseases.