Novel Strategies for the Reversal of Cancer Cell Immortality

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Glioblastoma (GBM) is the most common malignant adult brain tumor. With minimal clinical innovation, the prognosis for GBM patients remains grim. However, there is a commonality between 83% of GBMs: Telomerase Reverse Transcriptase promoter (TERTp) mutations. TERT, the catalytic component of telomerase, is responsible for telomere elongation and maintenance. The TERTp mutation creates a de novo ETS motif, allowing the GA-binding protein (GABP) transcription factor complex to specifically bind and reactivate the mutant allele. While direct targeting of telomerase has proven broadly toxic, targeting GABP to silence expression from the mutant TERTp is a potential alternative. However, direct small-molecule inhibition of transcription factors like GABP is challenging. To overcome this therapeutic barrier, I designed, engineered, and evaluated a GABPB1L transactivation-domain-null dominant-negative (B1-DN) transgene. I hypothesize that the B1-DN will sterically displace wildtype GABPB1L from the mutant TERTp, resulting in loss of TERT expression. Indeed, the B1-DN reduced TERT expression by up to 75% in TERTp mutant GBM, melanoma, and bladder cancer cell lines, but not in TERTp wildtype cells. This inhibitory effect was sustained throughout a 60-day time course, shortening telomeres throughout. Furthermore, since I have determined that GABP is a regulator of the mutant TERTp across 16 distinct cancer types, this B1-DN could eventually be valuable to the treatment of more than a million patients diagnosed with TERTp mutant tumors per year. Studies investigating the use of replicating retroviral vectors as a clinically relevant means to deliver the B1-DN are ongoing. In summary, this transgene may be able to reverse tumor cell immortality across all TERTp mutant cancers.

Awards Won:
Second Award of $2,000