Novel Small Molecule MYC inhibitors Suppress Mouse Prostate Cancer and Enhance Immunotherapy

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MYC (consisting of c-MYC, N-MYC and L-MYC) is an established oncoprotein that plays a pervasive role in the initiation, progression and recurrence of many cancers, including prostate cancer. MYC is particularly involved in many in late-stage, therapy-resistant cancers. While c-MYC has bene implicated in hormone sensitive and castration resistant prostate cancer, N-MYC plays a prominent role in neuroendocrine prostate cancer. An effective strategy to inhibit MYC is therefore likely to have a significant impact on this disease. Decades of mechanistic and in vivo mouse modeling studies support the potential of MYC as a target for cancer therapy. Furthermore, recent studies with an inducible dominant negative MYC inhibitor peptide indicate that a viable therapeutic window exists for MYC inhibition without any major deleterious effects on the animal. However, past efforts to develop specific small molecule inhibits of MYC have been hampered by a lack of potency, uncertain specificity and poor metabolic stability. To address this deficiency, we implemented an *in silico* screening strategy using a large library of 16 million compounds to identify a novel MYC inhibitor scaffold. Medicinal chemistry optimization led to the development of a series of small molecule inhibitors of MYC/MAX/DNA complex formation that are highly drug-like, possessing encouraging pharmacokinetic, toxicological and single agent anti-tumor activity profiles in preclinical models of prostate cancer and leukemia.

In tumor cells, our MYC inhibitors show evidence of target engagement by the cellular thermal shift assay (CETSA); decrease MYC/MAX complex formation; and inhibit MYC recruitment to chromatin by ChIP-Seq. Furthermore, the compounds lead to phosphorylation of MYC on threonine-58 (T58P) which promotes MYC degradation via the ubiquitin-proteasome pathway. Consequently, the MYC inhibitors reduced tumor cell proliferation and tumorigenicity in vitro and in vivo. The compounds also induced immunogenic cell death with release of HMGB1 and ATP and induction of cell surface calreticulin. Treatment of prostate cancer-bearing immunocompetent mice with the MYC inhibitors caused increased tumor infiltration by T cells, B cells and NK cells as well as induction of PD-L1 immune checkpoint protein expression on tumor cells. These observations provide a mechanistic rationale for combining MYC inhibition with anti-PD1/PD-L1 therapy. Indeed we observed synergy between MYC inhibitor and anti-PD1 antibody therapy in a trial in mice bearing MYC-driven prostate cancer allografts. In summary, our studies have identified a series of novel small molecule MYC inhibitors with in vivo efficacy for development as potential therapeutics in prostate and other cancers.

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