TARGETING HYPOXIA INDUCIBLE FACTOR 1 (HIF-1) FOR CANCER THERAPY

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HIF-1α is an attractive target for development of novel cancer therapeutics, in particular for its involvement in angiogenesis, tumor metabolism and metastasis. HIF-1 is not only expressed in cancer cells but also in stromal infiltrating cells and endothelial cells, thus representing a common molecular determinant of the tumor microenvironment. HIF-1 expression in macrophages regulates genes, including the inducible nitric oxide synthase gene, which may promote tumor growth. HIF-1 alpha expression in endothelial cells is essential for angiogenesis and response to growth factors. Therefore, strategies to target the expression and function of HIF-1 may represent a novel approach to concurrently inhibit multiple cellular components of the tumor microenvironment.
Despite the increasing number of HIF-1 inhibitors described in the literature it is unclear which is the most effective way to inhibit HIF-1 and how these agents should be developed. Over the last few years the Developmental Therapeutics Program of the National Cancer Institute has identified several novel HIF-1α inhibitors, including topotecan, a topoisomerase I poison that inhibit HIF-1α expression by a DNA-damage independent mechanism and echinomycin, a bis-intercalator that blocks HIF-1 DNA binding activity. In an effort to validate HIF-1 inhibition in the clinic, we are conducting a clinical trial of oral topotecan on a 2-week schedule in patients whose cancers over-express HIF-1α, as assessed by IHC. Since inhibition of HIF-1α alone may be insufficient to generate meaningful therapeutic responses we have also initiated combination studies with antiangiogenic agents. Results of the combination of topotecan with Avastin®, an anti-VEGF antibody, in xenograft models will be discussed.
In conclusion, efforts should be aimed at validating the activity of HIF-1 inhibitors in relevant animal models and in early clinical studies. Combination of HIF-1 inhibitors with novel molecular targeted agents should be explored to maximize the potential therapeutic effects of HIF-1 inhibition.