Novel, Potent, and Selective Inhibitors of Hypoxia-Inducible Factor (HIF)-2α Reverse Pro-tumorigenic Transcriptional Programming in Cancer, Stromal, and Immune Cells


Abstract

Optimized Arcus inhibitors, such as Compound 3, potently bind to and selectively inhibit HIF-2α to derepress transcriptional and growth-promoting functions of tumor-initiating cells. While sparing CD8+ T cell functionality, Compound 3 efficiently inhibits angiogenesis in hypoxia-stimulated human tumor-derived HIF-2α-expressing colorectal (CRC) and pancreatic adenocarcinoma (PDAC) cell lines. Moreover, each cell type exhibited vastly different dependences upon HIF-2α induction of genes associated with metabolism, proliferation, and angiogenesis to reprogram the tumor microenvironment. A preclinical evaluation of Compound 3 is expected to enter clinical trials in 2021.

Overview

The solid tumor microenvironment (TME) can be hypoxic and cancer cells require adaptations of gene associated with metabolism, proliferation, and angiogenesis to circumvent these conditions. The master transcriptional regulator of hypoxia-induced genes is the Hypoxia-Inducible Factor (HIF). HIF consists of an oxygen-regulated α subunit and a constitutively expressed β subunit. Under normoxic conditions, the α subunit is targeted for degradation by the von Hippel-Lindau (VHL) tumor suppressor protein, whereas hypoxic conditions allow the α subunit to accumulate, undergo nuclear translocation, and dimerize with HIF-1β. HIF is essential for angiogenesis and cell proliferation under hypoxic conditions.

HIF-1 and HIF-2 are key proteins for angiogenesis and cell proliferation under hypoxic conditions. HIF-1α is stabilized and promotes the expression of proangiogenic genes. HIF-2α is activated in the tumor microenvironment and promotes the expression of proangiogenic genes. HIF-2α is activated in the tumor microenvironment and promotes the expression of proangiogenic genes. HIF-2α is activated in the tumor microenvironment and promotes the expression of proangiogenic genes. HIF-2α is activated in the tumor microenvironment and promotes the expression of proangiogenic genes. HIF-2α is activated in the tumor microenvironment and promotes the expression of proangiogenic genes. HIF-2α is activated in the tumor microenvironment and promotes the expression of proangiogenic genes. HIF-2α is activated in the tumor microenvironment and promotes the expression of proangiogenic genes. HIF-2α is activated in the tumor microenvironment and promotes the expression of proangiogenic genes. 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