

Therapeutic Targeting of *IDH1* and *IDH2* Mutations in Acute Myeloid Leukemia (AML) and Chondrosarcoma

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Abstract: Recurrent somatic mutations in the isocitrate dehydrogenase I (*IDH1* and *IDH2*) genes have been identified in gliomas, acute myeloid leukemias (AML), cholangiocarcinoma and most recently in cartilaginous neoplasms. The IDH family of enzymes catalyzes the oxidative decarboxylation of isocitrate to produce CO₂ and alpha ketoglutarate. Mutations in these genes lead to impaired ability of IDH1 and IDH2 to catalyze the conversion of isocitrate to alpha ketoglutarate, and to gain of a neomorphic enzymatic activity which results in conversion of alpha ketoglutarate to the oncometabolite 2-hydroxyglutarate (2-HG). The overarching hypotheses of this research are: 1, acquisition of *IDH1* and *IDH2* mutations confer a gain-of-function phenotype to produce 2-HG in chondrosarcoma as well as in AML; 2, these mutations result in epigenetic changes that critically impact cell growth and differentiation; 3, the net effect of these epigenetic changes is to alter differentiation, proliferation and self-renewal pathways that are operant within the tumor cell; 4, the role of additional disease alleles in *IDH1* and *IDH2*-mutant tumors needs to be established; and 5, systematic knowledge of the mechanisms of transformation by IDH mutations will facilitate the development of new targeted drugs against *IDH1* and *IDH2* mutant cancers including chondrosarcoma and AML. By combining our collective expertise in two different diseases which are characterized by IDH mutations, one hematopoietic and the other solid tumor, we can elucidate both cell-type specific epigenetic signatures, and more importantly, reveal deeper insights into the epigenetic, reversible mechanisms underlying disease initiation and progression in *IDH* mutant malignancies.