Identifying therapeutically targetable vulnerabilities induced by *(R)*-2HG in *IDH2-mutant* AML

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Abstract**:** All cancer-associated *Isocitrate Dehydrogenase* mutants (*mIDH1/2*) produce the oncometabolite *(R)*-2-hydroxyglutarate (*(R)*-2HG). Although this implies that the consequences of *mIDH1* and *mIDH2* should be identical, the frequencies of *IDH* mutations vary dramatically across tumor types. In AML, *mIDH1* and *mIDH*2 occur at similar frequencies, but in glioma, the *mIDH1:mIDH2* ratio is ~20:1. We posit that this skewing is related to IDH1 being cytosolic and IDH2 being mitochondrial. Our hypothesis is that, in mIDH2-transformed cells, compensatory mechanisms mitigate the toxic effects of high levels of mitochondrial *(R)*-2HG to permit transformation; mechanisms that are less operative in tumors such as glioma that rarely harbor *mIDH2*. Targeting such compensatory mechanisms has the potential to have therapeutic efficacy in *mIDH2* tumors. Our primary objective is to identify novel approaches to treat *mIDH2* cancers. In Aim 1, we will perform genome-wideCRISPR-Cas9 screens in isogenic AML cells transformed by mIDH1 or mIDH2 to identify mIDH2-specificdependencies. In Aim 2, we will perform genome-wide CRISPRCas9 screens in mIDH2-transformed cells treated with a small molecule that enhances mIDH2 activity and specifically suppresses the proliferation of mIDH2 AML cells with the goal of identifying genes that modulate the cytotoxicity induced by excessive *(R)*-2HG. Our expectation is that we will identify *mIDH2*-specific dependencies that can be targeted therapeutically, either alone or in combination with mIDH2 hyperactivators. This work will not only advance the development of novel treatments for patients with *mIDH2* tumors but will also advance our long-term objective of understanding how dysregulated metabolism can be exploited to treat cancer.