Mutations in the isocitrate dehydrogenase 1 (IDH1) and 2 (IDH2) genes are present in ~16% of acute myeloid leukemia, and cause a neomorphic enzyme activity that results in the production of 2-hydroxyglutarate (2HG). To investigate the intrinsic effect of 2HG on hematopoietic proliferation and differentiation, we transfected an erythroleukemia cell line (TF-1) with either IDH1 or IDH2 mutant alleles. These cells overexpress the mutant enzyme, have high levels of 2HG, and exhibit GM-CSF independent growth. Consistent with clinical observations, overexpression of the IDH mutant proteins led to hypermethylation of both histones and DNA. These results suggest that mutations in IDH1/2 could lead to epigenetic rewiring of cells that could facilitate the gain of function phenotype. To gain a broader understanding of the biological consequence of the IDH1/2 gain of function mutations we have generated small molecules that are capable of selectively inhibiting IDHm enzymes. We will discuss the studies we have conducted to elucidate the biological consequence of IDH mutations and describe the effect of pharmacological inhibition with a novel IDH mutant inhibitor.