Why not wild-type IDH1? Finding novel chemical matter for the forgotten isotype

Clarissa G. Jakob

AbbVie, Dept. R467, Bldg. AP10-LL, 1 North Waukegan Rd. North Chicago, IL 60065-6098, Clarissa.jakob@abbvie.com

Isocitrate dehydrogenase 1(IDH1) is a cytosolic enzyme which converts isocitrate to α-ketogluterate with the concomitant conversion of NADP+ to NADPH. Since IDH1 is a known oncogene, recent drug discovery efforts have been focused on identifying inhibitors for mutants identified in various cancer cell types including secondary glioblastomas and AML.[1-6] These efforts have yielded selective compounds that target the mutant forms of IDH1, and several are now being evaluated in the clinical setting.[7-11] More recently, our scientists hypothesized that inhibition of wild-type IDH1 might provide some advantage for treating clear cell renal carcinoma (ccRCC). In the absence of the tumor suppressor VHL, cells preferentially use reductive glutaminolysis for lipid synthesis (i.e. reverse reaction) converting glutamine to citrate with the conversion of NADPH to NADP+. As such VHL mutant cells may demonstrate an increased dependence on IDH1 for survival. Nearly 70% of kidney cancer diagnoses (>63K in US annually) will be VHL-null mutant ccRCC. In order to test this hypothesis, a potent, selective wild-type IDH1 tool compound was needed. Additionally, because of the lack of suitable pharmacological tools, the effects of inhibiting wt-IDH1 had not been thoroughly interrogated even though it plays a key role in multiple metabolic pathways and is a major source of cytosolic NADPH. It is interesting to note that wt-IDH1 is a highly reversible enzyme which can dramatically up-regulate flux through IDH1-dependant reductive glutaminolysis in response to various types of cellular stress. This presentation will cover the rationale for targeting wt-IDH1, screening strategy, and chemistry follow-up with a major focus on the detailed structural evaluation of compounds which inhibit the protein by three different mechanisms.

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