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Editorial

# IDH1 Mutations in Glioma: Considerations for Radiotracer Development

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## Editorial

Isocitrate dehydrogenases IDH1 and IDH2 are closely-related metabolic enzymes which catalyze the conversion of isocitrate to α-ketoglutarate (α-KG) by oxidative decarboxylation and simultaneously generate NADPH in cells. IDH1 and IDH2 are frequently mutated in WHO grade II and grade III gliomas and in secondary glioblastoma. In gliomas, IDH mutations are highly specific for the amino acid arginine in IDH1 enzyme's substrate binding site, resulting in substitution of the arginine at 132 with histidine (R132H) in >80% of all IDH mutations [1]. IDH mutations result in production and accumulation of the metabolite D-2-hydroxyglutarate (D-2-HG) in IDH1 mutated cells, which greatly impacts the cellular metabolism and also contributes to tumor pathogenesis [2,3].

Several aspects of IDH mutations make them highly significant molecular markers for imaging and therapeutic targeting in IDH-mutated gliomas as well as other cancers that carry these mutations. IDH mutations are generally associated with longer survival in gliomas, and were confirmed as independent predictors of favorable outcome in multivariate analyses [1]. As a genetic mutation occurring at the tumor precursor cell stage, IDH1 mutation or mutant IDH1 expression is expected to be stable and homogenous among all tumor cells within an IDH1-mutated glioma. Hence, the ability to noninvasively image mutant IDH1 expression in gliomas can serve as a valuable tool in the clinical setting to diagnose mutant IDH1 tumors, predict prognosis and to evaluate treatment response based on IDH1 mutation status.

Positron Emission Tomography (PET) is a translational molecular imaging technique which uses specific probes that are labeled with positron-emitting radioisotopes for quantitative measurement of biological processes *in vivo* with high sensitivity (typically in picomoles with regard to probe detection in the target tissue). Development of radiotracers for mutant IDH1 as a novel imaging target is scientifically challenging and requires that various aspects of the mutant IDH1 are taken into account for the design and development of radiotracers. As an enzyme, mutant IDH1 is an intracellular target which excludes the possibility of developing imaging probes based on macromolecules as they cannot freely cross the cell membrane (e.g. monoclonal antibodies H09 or IMab-1 that recognize IDH1-R132H). For radiotracers based on small molecules, the compound should have sufficient lipophilicity, ideally a log *P* of >0.8, for efficient penetration through the cell membrane and to be able to reach the target in sufficient concentration. For imaging mutant IDH1 expression in brain tumors, the blood-brain barrier (BBB) may play a significant role in the uptake and clearance of the labeled compounds in the tumor tissue. However, preclinical studies suggest that an IDH1-R132H mutation in the CNS may cause disruption of the BBB by D-2-HG-mediated impairment of basement membranes surrounding the endothelial cells [4].

In view of its gain-of-function and the putative role of D-2-HG as an oncometabolite, inhibition of mutant IDH enzyme with small molecule inhibitors has been proposed as a therapeutic strategy for direct targeting of IDH mutations in cancers. To this end, several classes of mutant IDH1 inhibitors have been developed by high-throughput screening by pharmaceutical companies, and have shown high inhibitory potency and excellent selectivity for the mutant IDH1 vs. the WT-IDH1 (e.g. AGI-5198; $IC_{50}$: 70 nM) [5]. Mechanism-of-inhibition and crystallography studies have revealed different modes of binding and/or mutant IDH1 inhibition by these inhibitors depending on the chemical scaffold, and includes competitive binding with respect to α-KG, a mixed mode of competitive/non-competitive binding, as well as binding to an allosteric binding site on the mutant IDH1 [5,6]. This available medicinal chemistry information on the mutant IDH1 inhibitors can help in designing and guiding the development of radiotracers for the mutant IDH1. In IDH1-mutated gliomas, the levels of α-KG, which is used as a substrate by the mutant IDH1 enzyme, are much lower compared to that for D-2-HG (< 0.1 μmol/g vs. 5-35 μmol/g tumor for D-2-HG) or some of

the other TCA cycle intermediates [2]. However, since the mass of the injected probe for PET imaging studies is usually in nmoles, ideally, the candidate radiotracers should not have to compete with α-KG for binding to the mutant IDH1. Some of the reported inhibitors such as AGI-5198 also contain fluorine in their chemical structure which can be substituted with the PET radioisotope $^{18}F$ ($t_{1/2}$: 109.8 min) in a manner that can fully preserve the inhibitory potency of the compound [5]. In general, the selection of radioisotope for labeling can be guided by the binding affinity of the non-radioactive analog for the mutant IDH1, amenability of the compound for labeling with a particular PET radioisotope (e.g. $^{11}C$, $^{18}F$ and $^{124}I$), and the anticipated pharmacokinetics of the compound *in vivo*. The goal would be to achieve high tumor uptake and high tumor-to-background ratios for the labeled compounds in mutant-IDH1 tumors *in vivo* within 2-3 half-lives of the selected radioisotope. *In vitro* and *in vivo* evaluation of candidate radiotracers should include tumor cell lines that closely represent IDH1-mutated gliomas in patients, as well as appropriate control systems (e.g. isogenic WT-IDH1 cell lines) to identify promising lead compounds for clinical evaluation.

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