IMS-P5 NAMPT Is the Cellular Target of STF-31-Like Small-Molecule Probes

◯Daisuke ITO[1,5], Drew J. ADAMS[2], Matthew G. REES[2], Brinton SEASHORE-LUDLOW[2], Xiaoling PUYANG[1], Alex H. RAMOS[1], Jaime H. CHEAH[2], Paul A. CLEMONS[2], Markus WARMUTH[1], Ping ZHU[1], Alykhan F. SHAMJI[2], Stuart L. SCHREIBER[2,3,4]

[1]H3 Biomedicine, Inc., [2]Center for the Science of Therapeutics, [3]Howard Hughes Medical Institute, Broad Institute, [4]Department of Chemistry and Chemical Biology, Harvard University, [5]Eisai Co., Ltd.

The small-molecule probes STF-31 and its analogue compound 146 were discovered as a direct inhibitor of the glucose transporter GLUT1. We profiled the sensitivity of 679 cancer cell lines to STF-31 and found that the pattern of response is tightly correlated with sensitivity to three different inhibitors of nicotinamide phosphoribosyltransferase (NAMPT). We also performed whole-exome next-generation sequencing of compound 146-resistant HCT116 clones and identified a recurrent NAMPT-H191R mutation. Ectopic expression of NAMPT-H191R conferred resistance to both STF-31 and compound 146 in cell lines. Together, our cancer-cell profiling and genomic approaches identify NAMPT inhibition as a critical mechanism by which STF-31-like compounds inhibit cancer cells.