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Potent, Highly Selective SHP2 Degrader as Novel Anticancer Agent

A potent, selective Cdc14 phosphatase inhibitor is a novel therapeutic agent for broadly combating human and crop fungal infections as well as cancer.

Researchers at Purdue have developed a small molecule degrader, effective at low nanomolar concentrations, that can degrade Src homology region 2 - containing protein tyrosine phosphatase (SHP2). SHP2 is a protein tyrosine phosphatase (PTP) that is implicated in cancer cell proliferation and survival, making it a desirable target for designing anticancer drugs. While some small molecule degraders specific to SHP2 have been tested, currently, none have strong enough efficacies in vivo.

The researchers developed a small molecule inhibitor with an IC50 of 90 nM and tested to find the optimal linker to the E3 ligand. The degrader (dubbed P9) was found to degrade SHP2 at a dose and time dependent basis, with a DC50 of 35.2 Â± 1.5 nM, and highly specific targeting of SHP2 (no observed degradation of other PTP's and common cell proteins after incubation of 16 hours at 1 ÂµM in HEK293 cells). Finally, the anticancer ability of P9 was quantified by dosing a mouse xenograft model of KYSE-520 cells either 25 or 50 mg/kg of P9 daily. A decrease in tumor size and growth was observed with 25 mg/kg of P9 and a nearly complete tumor regression was observed for mice dosed with 50 mg/kg of P9, all with no change in weight or observed side effects.

Technology Validation:

Degradation ability of P9 measured in vitro against HEK293 cells by dosing cultures with increasing concentrations of P9 and measuring the levels of SHP2 via Western blot. Specificity of P9 to degrade SHP2 verified by incubating 1 ÂµM of P9 for 16 hours in HEK293 cells and observing the levels of SHP1, LYP, TC-PTP, PTP1B, PRL1, PRL2, AKT, ERK1/2, and Actin, after which, no degradation of other proteins was observed aside from SHP2. Anticancer ability of SHP2 degrader in vivo measured by injecting mice with KYSE-520 cancer cells on both of their flanks and measuring the tumor size with calipers according to the equation V = (W2 Ã— L)/2. At 200 mm3, daily

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injections of 0 (control), 25, or 50 mg/kg of P9 was conducted, with 50 mg/kg inducing nearly complete tumor regression and a decrease in SHP2 levels to 34 Â± 18 % compared to the control group.

Advantages:

- Potent, compound has DC50 of 35.2 Â± 1.5 nM

- Highly selective for SHP2 protein

- Effective at arresting tumor growth

Applications:

- Anticancer agent

- Biological investigation of SHP2 protein

Related Publication:

Discovery of a SHP2 Degrader with In Vivo Anti-Tumor Activity

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Intellectual Property:

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