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Potent, Highly Specific TC-PTP Degrader for Treatment of Skin Cancer and Enhancement of CAR-T Therapy

A potent and highly selective small molecule degrader effectively arrests tumor growth by targeting and degrading the SHP2 protein, demonstrating nearly complete tumor regression in animal models.

Researchers at Purdue have designed a small molecule degrader, effective at low nanomolar concentrations, that stimulates a cell's protein degradation system to catalytically degrade T-cell protein tyrosine phosphatase (TC-PTP). Currently, clinical approaches to treat cancer through immunotherapy have failed to have consistent results in many patients, requiring further research for developing therapeutics. One approach that has garnered significant interest is to develop therapeutics that target specific protein tyrosine phosphatases (PTPs) while having high selectivity and bioavailability.

The researchers developed a small molecule degrader (dubbed TP1L) that is highly selective for TC-PTP, leaving all other relevant PTPs unaffected. This is evident by TP1L having a > 110-fold selectivity of TC-PTP over PTP1B (a very similar homolog to TC-PTP). By degrading TC-PTP through the ubiquitin proteasome pathway, TP1L allows cells to properly regulate IFN-gamma signaling, promoting anti-tumor activity. Additionally, it was found that by co-incubating 4M5.3 CAR-T cells and KB tumor cells with TP1L, the tumor-killing efficiency was increased through stimulation of CAR-T cells.

Technology Validation:

Degradation ability of TP1L evaluated by treating HEK293 cells with a range of concentrations of TP1L for 16 hours and measuring the levels of TC-PTP via Western blot, the DC50 (concentration needed to induce TC-PTP degradation by 50%) measured was 35.8 nM. The specificity of TP1L for TC-PTP was confirmed by treating HEK293 cells with 0.5 micrometer TP1L for 16 hours and measuring the levels of TC-PTP, PTP1B, SHP2, PTP-MEG2, PTEN, and 7 other proteins. Complete degradation of TC-PTP and zero degradation of the other proteins was observed. Increases in IFN-gamma signaling due to TP1L treatment observed by measuring the levels of phosphorylated JAK1,

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phosphorylated STAT1, and MHC-1 expression in HEK293 cells, while these levels were not changed by the TP1L treatment in TC-PTP knockout HEK293 cells. The CAR-T cell activation ability of TP1L was validated by measuring the CD69 and CD25 levels after co-culturing KB cells and CAR-T cells for 48 hours.

A 26% and 100% increase of CD25 and CD69 respectively, was observed after treatment with TP1L.

Advantages:

- Potent at degrading TC-PTP at low nanomolar concentrations

- Highly specific to TC-PTP, > 110-fold selectivity of TC-PTP over PTP1B

- Promotes IFN-gamma signaling, activating CAR-T cells and increasing tumor-killing efficiency

Applications:

- Cancer treatment

- CAR-T Therapy

- Further investigation of TC-PTP's role in human biology

Related Publication:

Discovery of a selective TC-PTP degrader for cancer immunotherapy

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Intellectual Property:

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