Novel Tautomycetin Analogs Specifically Inhibit SHP-2, May Provide New Cancer Treatment

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The Wisconsin Alumni Research Foundation (WARF) is seeking commercial partners interested in developing novel tautomycetin analogs that inhibit SHP-2 and therefore may be useful in the treatment of several types of cancer and other disorders.

Overview

SHP-2 is an oncogene from the protein tyrosine phosphatase (PTP) superfamily. Mutations in SHP-2 can cause multiple forms of leukemia and solid tumors, as well as the autosomal dominant disorders Noonan syndrome and Leopard syndrome, making SHP-2 an attractive drug target. However, it has proven difficult to develop SHP-2 inhibitors with optimal potency and pharmacological properties.

Tautomycetin (TTN) may provide a promising lead for the development of new immunosuppressive and anti-tumor agents. TTN is a complex polyketide natural product produced by *Streptomyces griseochromogens*. It has been identified as a potent immunosuppressor of activated T cells in organ transplantation and also has been shown to inhibit growth of colorectal cancer cells.

The Invention

Researchers at UW–Madison and Indiana University have developed novel TTN analogs that inhibit SHP-2. These analogs can be used to treat diseases related to SHP-2, including Noonan syndrome, Leopard syndrome, leukemia and solid tumors.

The researchers showed that TTN and one of its engineered analogs, TTN D-1, specifically inhibit the activity of SHP-2. They also determined the X-ray crystal structure of SHP-2 with TTN D-1 bound to its active site. Together with the biochemical and cellular data, this structure supports the idea that SHP-2 is a cellular target for TTN and provides new insights for developing novel therapeutics that target SHP-2.

Applications

- Treating SHP-2-related cancers, including leukemia and solid tumors
- Treating Noonan syndrome
- Treating Leopard syndrome

Key Benefits

- TTN and TTN D-1 are the most potent and specific SHP-2 inhibitors currently known.
- Reduced SHP-2 activity by 80 to 90 percent at 10 μM concentration
- Highly specific for SHP-2, showing no significant inhibition of other PTP family members
- TTN is a natural product of microbial origin and can be produced by large-scale fermentation.
- Provides an inhibitor for a previously “undruggable” target

- May be administered in combination with other anticancer therapeutics or immunotherapeutic agents

Publications

- Liu S., Yu Z., Yu X., Huang S.X., Luo Y., Wu L., Shen W., Yang Z., Wang L., Gunawan A.M., Chan R.J., Shen B. and Zhang Z.Y. 2011. SHP2 is a Target of the Immunosuppressant Tautomycetin. Chem. Biol. 18, 101-110.

Tech Fields

- Therapeutics & Vaccines : Oncology

For current licensing status, please contact Rafael Diaz at rdiaz@warf.org or 608-960-9847