PURDUE INNOVATES | Office of Technology Commercialization

Novel Anticancer Covalent Inhibitors of SHP2 Tyrosine Phosphatase Inspired from Natural Products

Natural-product inspired covalent inhibitors targeting SHP2 tyrosine phosphatase to provide high-potency cancer treatments with reduced dosages and fewer side effects.

Researchers at Purdue have developed a novel library of natural-product inspired covalent inhibitors of SHP2 tyrosine phosphatase. Misregulated SHP2 tyrosine phosphatase function is implicated in a variety of cancers, therefore, SHP2 is an emerging target for anti-cancer drug targets. Covalent inhibitors have high biochemical efficiency due to their ability to irreversibly bind to protein targets. This may allow for developing drugs and therapeutics with lower dosage and reduced side effects as compared to competitive inhibitor molecules, which reversibly bind to target proteins. However, current synthetic covalent inhibitor drug libraries lack structural diversity and are dominated by flat molecules, limiting their scope for targeting many desirable proteins.

Researchers at Purdue have designed covalent inhibitors of SHP2 tyrosine phosphatase based off natural products with many of these covalent inhibitors showing substantial inhibition. The researchers selected a family of natural products called ent-kaurene diterpenoids that have diverse structures and have a long history of research and medical applications in Eastern medicine. From this family, they identified and synthesized the bicyclo[3.2.1]octane ? -methylene ketone pharmacophore and attached to it a range of synthetic drug analogues. After testing the inhibitory activity of their natural-product inspired drug library with SHP2, they discovered a series of molecules that have from a 6 to 119-fold increase in inhibitory activity as compared to previously reported SHP2 covalent inhibitor phenyl vinyl sulfonate.

Technology Validation:

- Inhibitory activity of molecules tested in vitro by measuring the enzymatic cleavage of para-nitrophenyl phosphate with the SHP2 protein and selected

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Authors
Mingji Dai
Aaron Krabill
Weida Liang
Zhong-Yin Zhang

Further information
Joe Kasper
JRKasper@prf.org

Nathan Smith
nesmith@prf.org

View online

covalent inhibitor.

Advantages:

- Many compounds from series show significant inhibition as compared to previous literature.

- Distinct chemical structure from other covalent inhibitor molecules.

- Pharmacophore was found to be easy to prepare on a large scale from readily available starting materials.

Applications:

- Cancer treatment

- Medical diagnostics

TRL: 3

Intellectual Property:

Provisional-Gov. Funding, 2023-06-16, United States | PCT-Gov. Funding, 2024-06-03, WO | NATL-Patent, 2025-11-13, United States