NATIONAL CANCER INSTITUTE
Technology Transfer Center

Enhanced Cancer Chemotherapy Using the Bioactive Peptide Recifin And Its Analogues

Summary

Scientists at the National Cancer Institute (NCI) discovered that the cyclic peptide recifin inhibits the activity of tyrosyl-DNA phosphodiesterase 1 (TDP1), a molecular target for the sensitization of cancer cells to the topoisomerase 1 (TOP1) inhibitor camptothecin and its chemotherapeutic derivatives – such as topotecan and irinotecan. NCI seeks research co-development partners and/or licensees for the development of recifin and its analogues as new chemosensitizing agents in adjunct therapies to enhance the sensitivity of cancer cells to topotecan, irinotecan and related chemotherapeutic agents.

NIH Reference Number

E-202-2020

Product Type

- Therapeutics

Keywords

- Cancer, Chemotherapy, Chemosensitizing Agents, Cyclic Peptide, Recifin, Tyrosyl-DNA Phosphodiesterase 1 Inhibitors, TDP1, Topoisomerase 1 inhibitors, Topotecan, Irinotecan TOP1, O'Keefe

Collaboration Opportunity

This invention is available for licensing and co-development.

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Description of Technology

Topoisomerase enzymes play an important role in cancer progression by controlling changes in DNA structure through catalyzing the breaking and rejoining of the phosphodiester backbone of DNA strands during the normal cell cycle. Therefore, topoisomerases are important targets for cancer chemotherapy. Many topoisomerase 1 (TOP1) inhibitors such as camptothecin, rinotecan, and topotecan are widely used anti-cancer agents that work by stabilizing the TOP1-DNA cleavage complex. Stabilization

causes irreversible double-strand DNA breaks, eventually leading to the death of replicating cancer cells. Tyrosyl-DNA phosphodiesterase 1 (TDP1) is an enzyme that plays a role in allowing cells to escape from TOP1 inhibitor-induced cell death by catalyzing the clearance of TOP1-DNA complexes. This activity led researchers to consider TDP1 a molecular target for the sensitization of replicating cancer cells to camptothecin and related chemotherapeutic agents.

Scientists at the National Cancer Institute (NCI) discovered recifin, a unique cysteine-rich cyclic peptide that inhibits the human protein tyrosyl-DNA phosphodiesterase 1 (TDP1). The peptide was isolated from a natural source, the sponge Axinella sp. The three-dimensional structure of recifin was determined by NMR and found to represent a completely new structural class unlike previously published cyclic peptides. Recifin inhibits TDP1 via an allosteric mechanism of inhibition and is the first identified allosteric inhibitor of this protein. TDP1 is important for cancer chemotherapy because its inhibition can restore cancer-cell sensitivity to clinically-used topoisomerase inhibitors.

NCI seeks research co-development partners and/or licensees for the development of recifin and its analogues as new chemosensitizing agents in adjunct therapies with topotecan, irinotecan and related chemotherapeutic agents.

Potential Commercial Applications

- Treatment for various solid cancers previously chemoresistant to some degree – such as small cell lung and ovarian cancer
- Development of new chemosensitizing agents: inhibition of tyrosyl-DNA phosphodiesterase 1 (TDP1), an important DNA repair enzyme in humans and a promising inhibition target

Competitive Advantages

- Numerous commercialization and/or sub-licensing opportunities due to wide range of relevant cancers.
- First-in-class drug; Recifin is the first member of a new family of cyclic peptides that inhibits the enzyme tyrosyl-DNA phosphodiesterase 1 (TDP1)
- First-in-class with effective and safe chemosensitizer to TOP1 inhibitors
- Potential for improved clinical responses
- TDP1 inhibitors can sensitize cancer cells to chemotherapeutic agents – including topotecan and irinotecan
- Recifin is stable to protease digestion
- Scale-up manufacturing: recifin analogues could be created with simple, automated peptide synthesis
- Sensitizing cells to topoisomerase I (TOP1) inhibitors, including topotecan, irinotecan and related chemotherapeutic agents

Inventor(s)

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Development Stage

- Discovery (Lead Identification)

Publications

Bermingham A, et al. Identification of Natural Products That Inhibit the Catalytic Function of Human Tyrosyl-DNA Phosphodiesterase (TDP1) [PMID 28697309]

Patent Status

- **U.S. Provisional:** U.S. Provisional Patent Application Number 63/115418, Filed 18 Nov 2020

Therapeutic Area

- Cancer/Neoplasm

Updated

Tuesday, September 13, 2022