

PHOSPHODIESTERASE AS A TARGET FOR CANCER THERAPEUTICS

SUMMARY

Investigators at the National Cancer Institute have discovered fluoroquinolone derivatives as specific Tdp1 inhibitors that could potentiate the pharmacological action of Top1 inhibitors currently used in cancer treatment.

REFERENCE NUMBER

E-199-2010

PRODUCT TYPE

- Therapeutics

KEYWORDS

- phosphodiesterase
- Tdp1 inhibitors
- fluoroquinolone

COLLABORATION OPPORTUNITY

This invention is available for licensing and co-development.

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DESCRIPTION OF TECHNOLOGY

Tyrosyl-DNA phosphodiesterase 1 (Tdp1) is a recently discovered enzyme that catalyzes the hydrolysis of 3'-phosphotyrosyl bonds. Such linkages form in vivo following the DNA processing activity of topoisomerase I (Top1). For this reason, Tdp1 has been implicated in the repair of irreversible Top1-DNA covalent complexes, which can be generated by either exogenous or endogenous factors. Tdp1 has been regarded as a potential therapeutic co-target of Top1 in that it seemingly counteracts the effects of Top1 inhibitors, such as camptothecin and its derivatives used clinically. Thus, by reducing the repair of Top1-DNA lesions, Tdp1 inhibitors have the potential to augment the anticancer activity of Top1 inhibitors provided there is a presence of genetic abnormalities related to DNA checkpoint and repair pathways.

Tyrosyl-DNA phosphodiesterase 1 (Tdp1) is a DNA repair enzyme involved in the repair of DNA lesions created when the activity of the Topoisomerase 1 (Top1) is inhibited. Tdp1 has been regarded as a potential therapeutic co-target of Top1 in that it seemingly counteracts the effects of Top1 inhibitors,

such as camptothecin. By reducing the repair of Top1-DNA lesions, Tdp1 inhibitors have the potential to augment the anticancer activity of Top1 inhibitors.

POTENTIAL COMMERCIAL APPLICATIONS

Tdp1 has been regarded as a potential therapeutic co-target of Top1 in that it seemingly counteracts the effects of Top1 inhibitors, such as camptothecin and its derivatives used clinically.

COMPETITIVE ADVANTAGES

Tdp1 inhibitors have the potential to augment the anticancer activity of Top1 inhibitors provided there is a presence of genetic abnormalities related to DNA checkpoint and repair pathways.

INVENTOR(S)

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DEVELOPMENT STAGE

- Discovery (Lead Identification)

PUBLICATIONS

- Dexheimer TS, et al. 4-Pregnen-21-ol-3,20-dione-21-(4-bromobenzenesulfonate) and related novel steroid derivatives as tyrosyl-DNA phosphodiesterase (Tdp1) inhibitors. *J Med Chem.* 2009 Nov 26;52(22):7122-7131. [PubMed: 19883083]
- Marchand C, et al. Identification of phosphotyrosine mimetic inhibitors of human tyrosyl-DNA phosphodiesterase I by a novel AlphaScreen high-throughput assay. *Mol Cancer Ther.* 2009 Jan;8(1):240-248. [PubMed: 19139134]

PATENT STATUS

- **U.S. Issued:** US Patent 8,716,295

THERAPEUTIC AREA

- Cancer/Neoplasm