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Novel small molecules for chemotherapy sensitization

Novel phenoxyphenyldeazaflavin compounds that sensitize cancer cells to widely used topoisomerase 2 poisons.

Technology No. 20180203

IP Status: Issued US Patent; **Application #:** 16/267,274

Applications

- Combination chemotherapy: coadministration with widely-used Top2 poisons (e.g. etoposide, teniposide, doxorubicin or daunorubicin) to sensitize cancer cells.
- Basic cancer research

Key Benefits & Differentiators

- **Orange Book extension:** Phenoxyphenyldeazaflavin compounds in combination with existing Top2 poisons could extend drug exclusivity.
- **Accesses cells while minimizing toxicity:** In cell assays illustrate favorable cytotoxicity and cell permeability profiles.
- **Applicable to many cancers:** Works with Top2 poisons that are currently used to treat a wide variety of solid tumors and hematologic malignancies.

TDP2 inhibition sensitizes cancer cells toward anticancer therapies

Topoisomerase II (topo II or Top2) poisons, are a major class of drugs widely used to treat cancers including testicular cancer, lung cancer, lymphoma, leukemia, neuroblastoma and ovarian cancer. These drugs work by generating DNA damage. However, drug resistance can limit the efficacy of treatment. Human tyrosyl-DNA phosphodiesterase II (TDP2) counteracts the effect of Top2 poisons thus repairing the damaged DNA and leading to chemotherapeutic resistance. To mitigate this form of cancer drug-resistance, Dr .Zhengqiang Wang (University of Minnesota) and Dr. Yves Pommier (National Cancer Institute) developed novel phenoxyphenyldeazaflavin compounds that effectively inhibit TDP2 in cancer cell lines. Through the inhibition of DNA damage repair machinery, these compounds functionally

sensitize cancer cells toward widely-used anticancer Top2 poisons.

Demonstrated efficacy in cancer cell lines

While previous deazaflavin compounds inhibit TDP2 in biochemical assays, they have not shown strong efficacy in cancer cells. This new technology, which modifies the critical structure of the deazaflavin core, generates the first-ever compounds that demonstrate strong efficacy in cancer cell lines. Using these new compounds in conjunction with Top2 poisons cancer therapies inhibits TDP2, keeping Top2 poisons effective and preventing resistance.

Secondary mode of action for cancer therapeutic sensitization

At concentrations as low as 3 nM, one of the deazaflavin analogs substantially increased the intracellular concentration of Top2 poisons, likely by inhibiting transporter-mediated efflux. This modality will allow the technology to be used much more broadly in combination with cancer drugs which suffer from poor efficacy due to efflux.

Phase of Development

- In Vitro Assessment: Compounds' anticancer activity demonstrated in biochemical and cell models. Assays carried out show favorable cell permeability and cytotoxicity.

Researchers

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Professor, Center for Drug Design (CDD)
External Link (drugdesign.umn.edu)
Yves Pommier
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Publications

Deazaflavin Inhibitors of Tyrosyl-DNA Phosphodiesterase 2 (TDP2) Specific for the Human Enzyme and Active against Cellular TDP2
ACS Chem. Biol. , 2016, 11 (7), pp 1925–1933
Novel Deazaflavin Analogues Potently Inhibited Tyrosyl DNA Phosphodiesterase 2 (TDP2) and Strongly Sensitized Cancer Cells toward Treatment with Topoisomerase II (TOP2) Poison Etoposide"
J. Med. Chem., 2019, 62, 9, 4669–4682

Desired Partnerships

This technology is now available for:

- License
- Sponsored research
- Co-development

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