

Inhibitors of DNA topoisomerase and its repair enzymes in cancer treatment

By Deepa Singh

Fellows of Laboratory of Molecular Genetics (LMG) welcomed pharmacologist Yves Pommier, M.D., Ph.D., for a talk on cancer therapeutic research Aug. 12 at NIEHS. The event was hosted by Jordan St. Charles, Ph.D., a postdoctoral fellow in the DNA Replication Fidelity Group, headed by Thomas Kunkel, Ph.D.

Pommier

(<http://www3.cancer.gov/intra/LMP/YPBIO.HTM>)

described his work with DNA topoisomerases, a target of several anticancer drugs routinely used today. Most of the topoisomerase inhibitors approved by the U.S. Food and Drug Administration are utilized to treat colon, lung, and ovarian cancer, as well as pediatric tumors. These inhibitors target DNA or its activities, such as replication, recombination, and repair, to impede malignant cell proliferation.

Pommier is chief of the Laboratory of Molecular Pharmacology at the National Cancer Institute. In an effort to discover novel topoisomerase inhibitors and optimize their use in combination with other anticancer agents, Pommier's lab has been working with [Mark Cushman, Ph.D.](http://www.mcmp.purdue.edu/faculty/?uid=cushman), of Purdue University, to develop a new family of topoisomerase inhibitors now in phase I clinical trials at NIH.

DNA topoisomerase - a popular target for anticancer drugs

DNA topoisomerases, also known as the vertebrate DNA untwisting enzymes, are found in a variety of organisms and act to regulate DNA supercoiling. DNA topoisomerase 1 (Top1), which belongs to type IB and was the focus of Pommier's talk, is found in the nuclear genome and is not transported into the mitochondria, at least in mammals. However, research in Pommier's lab led to the discovery of a topoisomerase gene that is specific for mitochondrial DNA (Top1mt). As Pommier explained, "There is a division of labor in the vertebrate cell for the two genomes, nuclear and mitochondrial, each of them having its own Top1."

This enzyme cleaves the DNA by covalently attaching its tyrosine residue to the 3'-end of the DNA. This Top1 cleavage complex (Top1cc) can be trapped by ubiquitous DNA alterations. Pommier's group has demonstrated, using many different substrates, that Top1 can be trapped on DNA sites containing lesions, such as single mismatch, as well as an abasic site or an oxidized base present on the DNA.

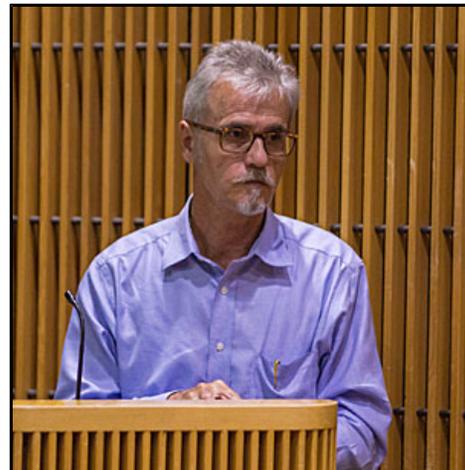
Developing the next generation of cancer therapies

Anticancer drugs, such as camptothecin (CPT) and several of its derivatives, also efficiently trap Top1, using a similar mechanism as seen for the DNA lesions. Using X-ray crystallography, Pommier's group has shown that, while interacting with Top1, CPT stacks itself between the DNA bases, thereby preventing the DNA re-ligation. Thus the trapped Top1cc generates cytotoxicity and anticancer activity.

This mechanism, known as interfacial inhibition, is unique and is different from the classical catalytic inhibition. Because CPT is chemically unstable, Pommier's lab has synthesized new compounds that are not activated chemically and can trap Top1 at different genomic sites.

Pommier's group is continuing efforts to characterize human cancer cell lines, to determine the factors and genes that govern drug susceptibility. Ongoing research is looking at novel ways to capitalize on the synergistic potential of multiple agents and design selectively targeted cancer treatments that also reduce the harmful side effects of currently used therapies (see [text box](#)).

(Deepa Singh, Ph.D., is a visiting fellow in the NIEHS Mechanisms of Mutation Group.)



Pommier received an NIH merit award for his contribution in elucidating the function of DNA topoisomerases as targets for anticancer drugs, as well as a Federal Technology Transfer Award for studies on DNA topoisomerase inhibitors. (Photo courtesy of Michael Garske)



NIEHS DNA Repair and Nucleic Acid Enzymology Group head Samuel Wilson, M.D., center, was one of several LMG and Laboratory of Structural Biology lead researchers on hand for Pommier's talk. (Photo courtesy of Michael Garske)



NIEHS Chromosome Stability Group cancer researchers, from left, staff scientist Daniel Menendez, Ph.D., postdoctoral fellow Steven Roberts, Ph.D., and senior associate scientist Dmitry Gordenin, Ph.D., also attended the talk. (Photo courtesy of Michael Garske)



As host, St. Charles, center, moderated the questions that followed Pommier's talk. (Photo courtesy of Michael Garske)

Targeting Top1 repair enzymes

In his search for better inhibitors, or the best combination of different inhibitors, Pommier focused on enzymatic pathways that closely work with Top1. These are the repair pathways that clean up the Top1-DNA adduct, before the DNA is religated. One such enzyme is tyrosyl-DNA phosphodiesterase (TDP1), which hydrolyses the bond between Top1 and DNA. Pommier's team and other groups have demonstrated that TDP1-deficient human cells are hypersensitive to CPT. In his recent work, Pommier has shown that TDP1 can also remove chain-terminating nucleoside analogs (CTNAs) that are widely used as antiviral and anticancer drugs. These CTNAs block the 3'-end of a single-strand DNA, forming a DNA lesion. "This work carries important implications in anticancer therapy, as it lets us understand how cells repair the DNA damage induced by CTNAs," he said of the findings.

Similarly, another enzyme, poly (ADP-ribose) polymerase (PARP) 1, binds and reseals the single-strand breaks (SSBs) in the DNA during the repair of Top1cc. Thus, PARP1 and TDP1 have epistatic roles in the repair of Top1cc. It is also known that inhibitors of PARP have an antitumor effect, as they block the repair of SSBs. Pommier's lab has shown that these inhibitors act like a poison and trap PARP at damaged DNA, similar to CPT. This finding suggests that PARP inhibitors could also be used effectively in the treatment of cancer.

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