Gut feeling about Camptosar

By Lauren Martz, Staff Writer

Pfizer Inc.'s Camptosar irinotecan is a part of standard therapy for colorectal cancer, but many patients are forced to discontinue treatment because of severe GI toxicity. Now, a group at **The University of North Carolina at Chapel Hill** has found that inhibiting a bacterial enzyme in the gut called β -glucuronidase could solve the GI problems, thus allowing more patients to receive Camptosar for longer periods of time.¹

Camptosar (CPT-11) is a camptothecin derivative that inhibits topoisomerase I (TOP1). Up to 40% of patients cannot tolerate an effective dose of the drug because of severe diarrhea.²

The drug's GI toxicity results from a complex cascade of activation and metabolism. Camptosar's active metabolite, SN38, is filtered by the liver and inactivated before excretion to the GI tract. However, β -glucuronidase (GUSB) enzymes produced by commensal bacteria in the GI tract can reactivate SN38, thus causing toxic levels of the drug to accumulate in the intestine.³

According to Andrea Stringer, a research scientist in the Mucositis Research Group at **The University of Adelaide**, one strategy to decrease Camptosar-associated GI toxicities is antidiarrheal drugs, which have only a limited effect.

The other strategy, said Stringer, is antibiotic treatment, which also doesn't significantly reduce diarrhea and can disrupt the gut microbiome. Intestinal bacteria are necessary for normal digestion and metabolism, and removing the commensal bacteria in healthy individuals can allow pathogenic bacteria to colonize the GI tract. The risk is even higher for cancer patients with immune systems damaged by chemotherapeutics.⁴

Now, in a paper published in *Science*, Matthew Redinbo and colleagues have proposed a more targeted approach to decreasing toxicity: inhibiting just the bacterial enzymes rather than the entire organism.

Redinbo is professor and chair of the Department of Chemistry and professor in both the Department of Biochemistry and Biophysics and the Department of Microbiology and Immunology at UNC Chapel Hill.

The paper also included researchers from the **Albert Einstein College of Medicine of Yeshiva University** and **North Carolina Central University**.

First, the researchers solved the crystal structure of *Escherichia coli* GUSB alone and in combination with a low-affinity inhibitor of the

enzyme. The crystal structure showed a 17-residue loop in the active site of the bacterial enzyme that was absent in the human ortholog.

Only some commensal bacteria produce GUSBs. Of the GI commensal bacteria that produce GUSB, 98% of these bacterial enzymes contain at least part of the 17-residue loop, according to the Human Microbiome Project. Those results hint that inhibitors can be developed that are selective for the bacterial GUSBs.

Indeed, the Redinbo-led team ran a high throughput screen of 10,240 compounds and identified 4 that were potent *E. coli* GUSB inhibitors. The compounds did not have any effect on a mammalian GUSB, and the molecules did not show efficacy in *E. coli* GUSB lacking the active site bacterial loop.

The research team next tested if the inhibitors would be effective against a range of bacterial enzymes. In cultures of *E. coli* or two other GUSB-producing bacteria known to inhabit the GI tract, the compounds inhibited GUSB activity compared with no treatment.

In mice, an oral GUSB inhibitor plus intraperitoneal irinotecan significantly decreased both diarrhea and bloody diarrhea compared with irinotecan alone. The inhibitor also protected against irinotecan-induced intestinal epithelial lining damage. Mice receiving either the GUSB inhibitor alone or vehicle alone did not have GI side effects.

"At least 30% of CPT-11 patients experience intense toxicity, and as far as I am aware, there are no effective strategies for toxicity reduction other than dose limitation. Our approach, if suc-

cessful, could provide a new tool to improve the tolerance of a widely used antineoplastic drug," Redinbo told *SciBX*.

"If the team can prove safety, there wouldn't be any reason not to always include this inhibitor" in combination with Camptosar, said Kevin Sill, CSO of **Intezyne Technologies Inc.** "What they need to do next is to prove the safety profile of the combination of compounds for use in humans."

Intezyne plans to file an IND for its IT141 to treat metastatic colorectal cancer during 1Q11. IT141 is a formulation of SN38 encapsulated by a polymeric nanoparticle using the company's IVECT platform technology. The goal is to minimize SN38 exposure in healthy tissues.

Habib Skaff, CEO of Intezyne, told *SciBX* that " β -glucuronidase inhibitors could be complementary to our approach" because regardless of the level of tumor-specific delivery achieved, there will likely always be some level of drug exposure outside of the tumors. "It would be nice to have a complementary measure like this to further neutralize the effect of the drug in the gastrointestinal tract."

Ruling out side effects

Redinbo told *SciBX* his team's next steps are "preclinical pharmacokinetic and toxicity studies and dosing and efficacy trials in a model system. After that comes microdosing in humans."

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—Joanne Bowen,
The University of Adelaide

Joanne Bowen, research fellow and associate lecturer of medicine at The University of Adelaide, said the team's next step should be to look at the GUSB inhibitors in animal models of cancer.

"With any agent aimed at preventing normal tissue toxicity, it is vital to know that the agent does not also protect the cancer or increase tumor growth. This work should be repeated in a tumor-bearing animal model to ensure safety," she said.

To further show that the UNC team's GUSB inhibitors do not have off-target effects, Michael Teifel, senior director and head of preclinical development at **Aeterna Zentaris Inc.**, suggested developing a strategy for localized delivery to the gut.

Aeterna Zentaris and partner **Keryx Biopharmaceuticals Inc.** are developing perifosine, an orally available inhibitor of phosphoinositide 3-kinase (PI3K) and protein kinase B (PKB; Akt) that is in Phase III development to treat colorectal cancer in combination with **Roche's** Xeloda capecitabine. Xeloda is approved to treat breast, colorectal and gastric cancer.

Redinbo's team hasn't yet examined localized delivery but thinks that it might not be necessary because efficacy in the initial oral dosing trials suggests that the inhibitors are reaching the GI tract. "The fact that the first dose we tried was successful via oral administration in these animals is very promising," he said.

Although the combination of Camptosar and a GUSB inhibitor could decrease the chemotherapeutic's major dose-limiting toxicity and open the door to higher doses, the Aeterna Zentaris researchers question whether higher doses would be beneficial.

"The efficacy of irinotecan has been evaluated for the doses currently applied in the clinic. With the lack of clinical data, it cannot be predicted whether higher doses applicable with a new regimen would translate to higher efficacy," said Joachim Fensterle, director of business development and vaccine development at Aeterna Zentaris.

Cytotoxic substances can lead to a variety of side effects, Teifel also

noted, and eliminating one dose-limiting toxicity might not help if another toxicity occurs at only slightly higher doses.

"Still, significantly higher concentrations of a cytotoxic drug have the chance to result in better efficacy," continued Fensterle. Even if higher doses and greater efficacy are not achievable, he added, a combined treatment could be advantageous because patients could experience fewer GI side effects from the treatment if dosing remains unchanged. It may allow patients to be treated with the current dose who otherwise would not be able to tolerate it or benefit from it.

Redinbo told *SciBX* that UNC has filed a provisional patent application covering GUSB inhibitors to decrease toxicity of irinotecan as well as related compounds. The IP is unlicensed.

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