

PARP Inhibitors for Chemoprevention—Reply

Ciric To, Michael B. Sporn, and Karen T. Liby

We thank Brody and colleagues (1) for their thoughtful letter that raised three major issues about PARP inhibitors for chemoprevention: (i) long-term toxicity, (ii) secondary tumors, and (iii) drug resistance. We appreciate their desire to open a dialogue, as we agree that these important challenges must be addressed.

Whether low doses of platinum-based compounds are effective in our animal model will be tested. If low doses of cytotoxic drugs delay tumor development, these drugs could be considered for chemoprevention. However, because chemotherapy drugs can harm healthy cells, the idea of using them in patients without symptomatic cancer is likely to generate significant resistance from the FDA and many clinicians. Although PARP inhibitors also cause side effects, they are generally less severe, and intermittent or combination therapies might alleviate this toxicity. Even though PARP inhibitors were well tolerated in our model, toxicity could develop over time so the effects of PARP inhibitors in normal tissues will require careful monitoring in the clinic.

The possibility that PARP inhibitors could be protumorigenic when given to homologous recombination (HR)-heterozygous genetic carriers is also a serious concern. Testing PARP inhibitors in a model with heterozygous BRCA1 mutations would be ideal, but these mice do

not develop tumors. The incidence of mammary tumors in mice with heterozygous BRCA1 and p53 mutations occurs at such a low frequency that it is not feasible to use these models for drug testing. Even in mice with BRCA1 deficiency and p53 heterozygosity, tumors do not develop for 6 to 9 months. Additional studies testing the effects of PARP inhibitors on chromosomal instability and homologous recombination in normal cells and in cells with HR-heterozygosity should be done, using relevant drug concentrations. As clinical testing of PARP inhibitors proceeds, more information on PARP inhibitors and secondary tumors will become available.

Finally, the development of drug resistance is a problem with many drugs. Because of their limitations, no animal model fully replicates a human disease. Even the best drugs will only delay the development of tumors in models with genetic abnormalities found in every mammary epithelial cell. However, additional studies will test whether tumors that develop following intermittent olaparib treatment are still sensitive to the combination of a PARP inhibitor and cisplatin.

Our article demonstrated the chemopreventive effects of PARP inhibitors in BRCA1-deficient mice. Although valid concerns have been raised about the potential clinical translation of these studies, we hope that this work and future studies will contribute to the development of effective approaches for preventing and treating cancer in patients with BRCA1 mutations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received August 19, 2014; accepted August 27, 2014; published online November 3, 2014.

Department of Pharmacology, Dartmouth Medical School, Hanover, New Hampshire.

Corresponding Author: Karen T. Liby, Geisel School of Medicine at Dartmouth, Remsen 524, HB7650, Hanover, NH 03755. Phone: 603-650-1682; Fax: 603-650-1129; E-mail: Karen.T.Liby@dartmouth.edu

doi: 10.1158/1940-6207.CAPR-14-0264

©2014 American Association for Cancer Research.

Reference

1. Chand SN, Blanco FF, Jimbo M, Tsangaris TN, Cristofanilli M, Yeo CJ, et al. PARP inhibitors for chemoprevention. *Cancer Prev Res* 2014;7:1170–71.

Cancer Prevention Research

PARP Inhibitors for Chemoprevention—Reply

Ciric To, Michael B. Sporn and Karen T. Liby

Cancer Prev Res 2014;7:1172.

Updated version Access the most recent version of this article at:
<http://cancerpreventionresearch.aacrjournals.org/content/7/11/1172>

Cited articles This article cites 1 articles, 1 of which you can access for free at:
<http://cancerpreventionresearch.aacrjournals.org/content/7/11/1172.full#ref-list-1>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link <http://cancerpreventionresearch.aacrjournals.org/content/7/11/1172>. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.