agree with Hedge et al.1 that one of the most important questions is whether sufficient quantities of Δ12-PGJ3 are formed in vivo to exert any biologic activity. Here, we comment on this eminently crucial issue from pharmacologic and nutrition perspectives.

PGJ1 and PGJ2 are the dehydrated products of PGD1 and PGD2 formed in vivo from eicosapentaenoic acid (EPA) and arachidonic acid (ARA), respectively, by the catalytic action of cyclooxygenase (COX). PGJ1 and PGJ2 are further dehydrated and isomerized to produce Δ12-PGJ1 and 15d-PGJ1 and 5d-PGJ2, respectively. Common feature of Δ12-PGJ1 and 15d-PGJ1 is the highly reactive cyclopentenone ring, which is readily attacked by low- and high-molecular-mass thiol s to form theoethers (Figure 1). Thiolation of Δ12-PGJ1 and 15d-PGJ1 is likely to reduce both availability and bioactivity of Δ12-PGJ1 and 15d-PGJ2. So far, there are no data about excretion of Δ12-PGJ1 and 15d-PGJ1. We (Figure 1) and others1 found only pM-concentrations of 15d-PGJ2 in human urine, while PGJ1 metabolites including 15d-PGJ1 were below the detection limit of our method (30 pM) in urine. This may suggest that basal PGJ1 biosynthesis from EPA is several fold lower than PGJ2 from ARA. Dietary EPA has been shown to increase formation of prostaglandin I2 (PGI2) and thromboxane A2 (TXA2), but EPA, even at very high doses, did not increase PGJ1 and TXA2 synthesis to a degree comparable with that of PGJ2 and TXA2 from ARA.4

Δ12-PGJ1 and 15d-PGJ1 are considered potentially useful therapeutic agents for the treatment of cancer.1,2 Dietary EPA supplementation is unlikely to produce nM-concentrations of Δ12-PGJ1 required for antileukemic activity, but topical administration of considerable amounts of synthetic Δ12-PGJ3 would be required.

Response:
Endogenous levels of D12-PGJ3 derived from eicosapentaenoic acid

In response to the comment by Tsikas and Stichtenoth,1 we would like to provide clarification for their views and address the questions. First, while it is correct that the reactivity of the 2 electrophilic centers could make these classes of compounds less bioavailable, our data clearly demonstrate that intraperitoneal administration of D12-PGJ3 completely eradicates leukemia stem cells in the bone marrow and spleen. This suggests that the formation of Michael adducts does not affect their antileukemic activity nor systemic bioavailability. Second, it is not surprising to find that the pM concentrations of 2- and 3-series CyPGs (of the J class) in the urine. Our studies show (see Figure 1 in Hegde et al.5 that macrophages cultured with 50μM EPA for a week, produce D12-PGJ3 in the cell culture media in quantities (nM) sufficient to target leukemia stem cells. The authors show very low levels (pM) of these metabolites in urine. However they did not measure levels in the serum and it would be difficult to infer serum concentrations from these measurements. Moreover, it is not surprising that given the low rate of conversion, the level of D12-PGJ3 from ARA-derived EPA is likely to be in the pM range as described. In the future, quantitation of these metabolites in the serum will be necessary to provide a true measure of their concentration, particularly in EPA-supplemented individuals. Unpublished studies from our laboratory confirm the metabolism of dietary EPA generates D12-PGJ3 at concentrations in the serum high enough to induce apoptosis in leukemia stem cells in vitro. A manuscript with these results is being currently prepared for submission.

K. Sandeep Prabhu
Center for Molecular Immunology and Infectious Disease and Center for Molecular Toxicology and Carcinogenesis, Department of Veterinary and Biomedical Sciences, The Pennsylvania State University; University Park, PA

Robert F. Paulson
Center for Molecular Immunology and Infectious Disease, Department of Veterinary and Biomedical Sciences, The Pennsylvania State University; University Park, PA

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Correspondence: K. Sandeep Prabhu or Robert F. Paulson, Department of Veterinary and Biomedical Sciences, The Pennsylvania State University, 115 Henning Bld, Shortridge Rd, University Park, PA 16802; e-mail: ksprabhu@psu.edu or rfp5@psu.edu.

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K. Sandeep Prabhu and Robert F. Paulson