Role of manganese superoxide dismutase in cancer

To the editor:

I read with great interest the report by Samlowski *et al.* entitled, "A nonpeptidyl mimic of superoxide dismutase, M40403, inhibits dose-limiting hypotension associated with interleukin-2 and increases its antitumor effects."[1] These findings are potentially important in reducing the capillary leakage associated with interleukin-2 therapy, and other disorders of capillary leakage including acute respiratory distress syndrome. However, the antitumor effect of M40403 *in vivo* may be due in part to inhibition of reactive oxygen in tumor cells themselves. We have previously shown that genes that generate reactive oxygen can cause transformation associated with increased angiogenesis, and that reduction of reactive oxygen in these transformed tumor cells leads to decreased angiogenesis[2]. Certain tumors, namely those associated with high levels of mitogen-associated protein kinase activation and loss of the tumor-suppressor gene *CDKN2A*, are also associated with high levels of reactive oxygen[3–5]. Melanoma is one such tumor, and introduction of manganese superoxide dismutase (MnSOD) into melanoma cells reduces tumorigenicity *in vivo*[6].

Samlowski *et al.* show that at a single-dose level, M40403 has no effect on tumor growth *in vivo* (see figure on p. 753 of the June issue). Two possibilities come to mind to explain why introduction of MnSOD into melanoma cells has a direct antitumor effect[6], whereas M40403 did not at the particular dose examined in this study. First, there is the matter of dosage. Higher doses of M40403 may have direct antitumor activity *in vivo*. Second, high levels of reactive oxygen are associated with resistance to interferon-α- and interferon-β-mediated cell killing[7], and perhaps to interleukin-12-mediated cell death. The reduction of reactive oxygen in the tumor cells themselves with M40403 may sensitize the cells to immune-mediated destruction. The use of systemic MnSOD mimics without systemic toxicity is encouraging; these agents may act through several mechanisms, including reducing vascular leakage, inhibiting the production of angiogenic factors and stimulating apoptosis through inhibition of reactive oxygen and NF-κB signaling.

COMPETING INTERESTS STATEMENT
The authors declare that they have no competing financial interests

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Salvemini et al. reply

We would like to thank Dr. Arbiser for his pertinent comments on our manuscript. The rationale that reactive oxygen species are involved in cancer has been appreciated for quite some time in a number of areas. For example, Larry Oberley's pioneering work over the last twenty years or so has clearly shown that overexpression of MnSOD inhibits *in vitro* and *in vivo* growth of various tumor cells. In addition, and as correctly pointed out by Arbiser, reactive oxygen species can trigger the activation of certain transcription factors (such as NF-κB), which in turn induce genes that can cause transformation and increased angiogenesis. Reduction of reactive oxygen in these tumor cells leads to decreased angiogenesis. Therefore, removal of superoxide by a superoxide dismutase mimetic such as M40403 should, in theory, have antitumor effects. Our experiments show that when used at a single low dose, M40403 has no effect on tumor growth *in vivo*. As Arbiser correctly notes, increasing the doses of M40403 or manipulating the dosing regimen might have allowed M40403 to exert an antitumor effect. However, our experiments were not aimed at addressing whether M40403 has direct antitumor effects. Rather, we wanted to determine whether a low dose of M40403 would enhance the antitumor action of IL-2, which it did. In response to Arbiser's comment regarding direct antitumor potential of SOD mimetics, our hypothesis, which is currently being evaluated, is that SOD mimetics will attenuate tumor cell growth *in vivo* when the doses are increased and when the appropriate dosing regimens are identified. This hypothesis is based on the proliferative literature that points to superoxide as an important mediator of cancer, and on our own preliminary data indicating that M40403 (and other SOD mimetics) has direct antitumor effects *in vitro*. We also have data showing that M40403 inhibits epithelial growth factor–induced tumor cell proliferation through inhibition of NF-κB activation. In general, multiple pathways are used by superoxide to modulate oncogenesis. Removal of reactive oxygen species with a SOD mimetic is a viable therapeutic opportunity in cancer.

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