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An open letter to the FDA and other regulatory agencies: Preclinical drug development must consider the impact on metastasis

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Recently, two landmark papers on antiangiogenic therapy were published: Paez-Ribes et al., Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. *Cancer Cell* 15: 220-231, 2009; Ebos et al., Accelerated metastasis after short-term treatment with a potent inhibitor of tumor angiogenesis. *Cancer Cell* 15:232-239, 2009. The Board of the Metastasis Research Society (MRS) congratulates the authors (1) (2) for their informative articles that help to explain the puzzle of why antiangiogenic agents have had a relatively minor or no significant impact on patient survival. Using four model systems and several different strategies, these researchers showed that inhibition of angiogenesis reduced primary tumor growth and microvessel density in keeping with many earlier reports, but strikingly, accelerated invasion and metastasis.

It is well known that the majority of cancer patients who succumb to their disease do so following development of incurable metastatic disease. However, the emphasis on preclinical testing of new compounds still rests on the responses of subcutaneous or orthotopic primary tumors from various mouse models over a relatively short timeframe. The papers of Ebos et al (2009) and Paez-Ribes et al (2009) elegantly reveal the limitations of this approach, at least with regard to targeting of angiogenesis.

It is important to reflect on the fact that other drugs and preclinical compounds, when tested for both primary tumor size and metastasis, have exhibited discordant results. For example, cyclophosphamide inhibited primary lung adenocarcinoma but promoted metastasis to the lung and liver (3), and the Hsp90 inhibitor 17-AAG inhibited primary breast cancer but promoted metastasis to the bone (4) Vandetanib, a VEGF-C inhibitor, reduced the growth of primary fibrosarcomas, but had no effect on their metastasis (5). Interestingly, a number of agents have been shown to exert no significant effects on primary tumor size, but still had the capacity to inhibit metastasis (6-13). Given the fact that primary tumors can often be controlled using conventional therapies, could agents that act specifically on the process of metastasis be more likely to increase long term patient survival?

Based on these new reports and earlier data, we propose that preclinical drug development in general -- and not only for antiangiogenic compounds-- be required to show efficacy in at least one metastasis model, preferably incorporating metastasis from an orthotopic site. Robust models are available with relevant histology (i.e., similar to human) and imaging for quantification. The FDA, other regulatory agencies and their clients, patients considering entrance into a clinical trial, currently have access to detailed information such as weight loss in mice exposed to a compound. In our opinion, it is just as important to reveal information on the capacity of a new compound to accelerate or inhibit tumor metastasis.

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