LETTER

Reply to Ciccolini et al.: Using mathematical modeling to predict response to antiangiogenic therapy in cancer patients

We thank Ciccolini et al. (1) for their interest in our report (2) on a clinical study, published recently in PNAS. In that paper, we report that improved tumor vascular function after anti-VEGF therapy with carboplatin and nab-paclitaxel associates with survival in non-small cell lung cancer (NSCLC) patients. We also suggest that imaging and circulating markers of vascular normalization could be useful biomarkers of response to bevacizumab-based therapies in NSCLC patients.

Although generally in agreement with the results of our study, the letter by Ciccolini et al. suggests another strategy for optimizing the efficacy of antiangiogenic treatment when combined with chemotherapy (1). Ciccolini et al.'s strategy would be based on the predictions of a pharmacokinetic/pharmacodynamic mathematical model, which could predict the effect of antiangiogenic treatment on "vasculature quality and resulting tumor blood flow" (1). However, the published model referenced by the authors consists of a simplified set of ordinary differential equations, which are based on phenomenological and not physiological parameters of tumor pathophysiology. Specifically, the model does not take into consideration parameters such as the hyper-permeability and tortuosity of the tumor vessels, the structure of the vascular network, the remodeling of the network in response to the antiangiogenic treatment, as well as actual calculations of tumor blood flow. These are important parameters of structural and functional vascular normalization after antiangiogenic treatment. In addition, tumor blood flow can be calculated only by solving the equations of fluid flow within the vascular network. Of note, various groups, including ours, have previously developed mathematical models that account for these parameters and would be useful in developing a predictive model Ciccolini et al. (1) propose to develop (3–6). Finally, a refined pharmacokinetic/pharmacodynamic model would require rigorous validation using experimental data before it could be used as a guide for treatment planning. The letter by Ciccolini et al. (1) provides a starting point for the potential utility of this strategy to predict response to antiangiogenic therapy in patients.

Dan G. Duda[a], Rebecca S. Heist[b], Dushyant V. Sahani[c], Triantafyllos Stylianopoulos[a], Jeffrey A. Engelman[b], and Rakesh K. Jain[a,1]

[a]Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114; [b]Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114; and [c]Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114

1 Ciccolini J, Benzekry S, Lacarelle B, Barbolosi D, Barlési F (2015) Improving efficacy of the combination between antiangiogenic and chemotherapy: Time for mathematical modeling support. *Proc Natl Acad Sci USA* 112:E3453.

2 Heist RS, et al. (2015) Improved tumor vascularization after anti-VEGF therapy with carboplatin and nab-paclitaxel associates with survival in lung cancer. *Proc Natl Acad Sci USA* 112(5): 1547–1552.

3 Macklin P, et al. (2009) Multiscale modelling and nonlinear simulation of vascular tumour growth. *J Math Biol* 58(4-5): 765–798.

4 Cai Y, Xu S, Wu J, Long Q (2011) Coupled modelling of tumour angiogenesis, tumour growth and blood perfusion. *J Theor Biol* 279(1):90–101.

5 Pries AR, et al. (2009) Structural adaptation and heterogeneity of normal and tumor microvascular networks. *PLOS Comput Biol* 5(5): e1000394.

6 Stylianopoulos T, Jain RK (2013) Combining two strategies to improve perfusion and drug delivery in solid tumors. *Proc Natl Acad Sci USA* 110(46):18632–18637.

Author contributions: D.G.D., R.S.H., D.V.S., T.S., J.A.E., and R.K.J. wrote the paper.

The authors declare no conflict of interest.

[1]To whom correspondence should be addressed. Email: jain@steele.mgh.harvard.edu.

www.pnas.org/cgi/doi/10.1073/pnas.1507225112