TLR effects on T helper or other cells, ERD did not occur.

In summary, FI-RSV failed to protect primarily as a result of poor avidity, as germline antibodies continued to recognize protective epitopes. Moreover, specifically maturing FI-RSV–specific antibody would not have solved the problem. Last, no nonreplicating vaccine against RSV will be safe for infants if it fails to elicit affinity maturation.

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Will integrin inhibitors have proangiogenic effects in the clinic?

To the Editor:

In a comprehensive analysis, Reynolds *et al.*[1] recently reported that RGD-mimetic agents such as cilengitide may, under certain experimental conditions, promote rather than inhibit angiogenesis. They accordingly express their reservations regarding the clinical exploration of such agents in human patients with cancer.

On the basis of promising phase 2 data[2,3], cilengitide in combination with temozolomide-based radiochemotherapy is currently being explored in a phase 3 registration trial for newly diagnosed glioblastoma with O^6-methylguanine methyltransferase (*MGMT*) promoter methylation (CENTRIC trial, European Organisation for Research and Treatment of Cancer 26071–22072). This new paradigm of seeking approval for a first-in-class agent in a molecularly defined subpopulation of individuals with glioblastoma was based on the observation that the apparent clinical benefit derived from cilengitide in the phase 2 trial was prominent only in this patient population[3]. Do the proangiogenic preclinical data of Reynolds *et al.*[1] raise serious concerns regarding the potential for paradoxical effects of cilengitide in individuals with glioma *in vivo*? We believe that this may not be the case.

First, the clinical importance of the tumor models used by Reynolds *et al.*[1] may be questioned. Although the major target disease of the current clinical development of cilengitide is glioblastoma, no glioma model was studied.

Second, *in vitro* analyses suggest that there are multiple actions of cilengitide that mediate a clinical benefit in glioblastoma, including direct cytolytic effects on tumor cells, cytolytic effects on endothelial cells and inhibition of cell adhesion, migration and invasion[4]. Although the functional consequences of the interactions of cilengitide with its target integrins are probably complex in the context of glioma biology, the overall net effect in the clinic seems to be growth inhibitory rather than growth promoting[2].

Third, in the current clinical setting, cilengitide is used in combination with chemotherapy and radiotherapy, again on the basis of preclinical data showing strong sensitization to radiotherapy in rodent glioma models[5].

Fourth, pulse treatment as used in the clinical trials did not result in adverse effects in any of the models studied by Reynolds *et al.*[1]. In fact, the scheduling claimed to be tumor growth–promoting in their study[1] is not used in humans.

Fifth, cilengitide used at flat doses of 2,000 mg twice weekly results in peak plasma cilengitide concentrations of >200 μM, which, by orders of magnitude, exceed the concentrations shown by Reynolds *et al.*[1] to promote angiogenesis. In fact, simulations based on population pharmacokinetic models show that concentrations in the angiogenesis-promoting range (0.2–20 nM)[1] are not reached in 75% of patients treated with biweekly intravenous infusions of 2,000 mg cilengitide (J. Grevel (Merck Serono), personal communication). Micromolar concentrations of cilengitide have also been measured in the tumor tissue of patients with glioma exposed to the drug before surgery for recurrent disease[6]. Admittedly, the extent of blood-brain and blood-tumor barrier penetration of cilengitide in humans with glioma remains uncertain, and it remains uncertain whether potentially proangiogenic concentrations of cilengitide may be operational at least transiently in the tumor tissue.

Finally, although Reynolds *et al.*[1] suggest that cilengitide mediates angiogenesis by enhancing the effect of vascular endothelial-derived growth factor (VEGF), the striking neuroradiological responses to cilengitide seen in some individuals with glioblastoma[7,8] morphologically closely resemble the effects of VEGF-antagonizing agents such as bevacizumab[9]. On the basis of these considerations, we acknowledge that Reynolds *et al.*[1] have assembled an interesting and unexpected set of data in preclinical models. In fact, a paradoxical proangiogenic effect of cilengitide may be operative in certain settings and contribute to an antitumor effect of cilengitide in combination with radiotherapy or chemotherapy. This consideration relates to the vascular normalization effect of antiangiogenic agents, which we have proposed to underlie the preferential clinical benefit apparently seen in glioblastoma patients with *MGMT* promoter methylation[2]. The clinical importance, however, of the complex effects of cilengitide reported by Reynolds *et al.*[1] as well as by Alghisi *et al.*[10] can be assessed only in appropriately designed clinical trials.

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COMPETING INTERESTS STATEMENT
The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturemedicine/.

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