Therapies targeting vascular endothelial growth factor and its receptors have become part of standard tumor therapy for most forms of cancer within the last 7 years. However, it is increasingly recognized that the efficacy of such therapies is limited and transient. In fact, the limited clinical efficacy of established antiangiogenic tumor therapies has raised the concern that the moderate gain in cancer patient care may not justify the significant societal investment in such therapies. In turn, it needs to be considered that the first generation of approved antivascular endothelial growth factor/vascular endothelial growth factor receptor drugs mark only the beginning of a new era of antitumor therapy that goes beyond classical direct tumor cell targeting strategies to attack the nonneoplastically transformed tumor-associated stroma.

Clearly, the development of antistroma therapies is only at its beginning, and the hunt for additional targets to interfere with tumor progression concentrates particularly on molecules that may affect both the tumor cell compartment and tumor-associated stromal cell mechanisms.

Several families of neuronal guidance molecules have been identified in recent years to exert guidance and assembly functions in the vascular system. These include semaphorins, ephrins, netrins, and slit molecules and their corresponding neuropilin/plexin, Eph, Unc, and Robo receptors, respectively.3,4 In the present issue of *Arteriosclerosis, Thrombosis and Vascular Biology*, Casazza et al5 present a very systematic analysis of the role of semaphorin3A (SEMA3A) in tumor angiogenesis and progression. By exploiting multiple experimental tumor models, the authors show that systemic as well as targeted delivery of SEMA3A inhibits primary tumor growth by disrupting angiogenesis and preventing metastatic dissemination and colonization by restricting tumor cell motility (Figure). By overexpressing SEMA3A in 3 different tumor cell lines, the authors show that SEMA3A inhibits tumor cell motility and metastatic colonization by interacting with its obligate receptor neuropilin-1. Conversely, tumor cell–secreted SEMA3A inhibits angiogenesis by negatively acting on tumor-associated endothelial cells and by impeding pericyte recruitment. As a second experimental approach, the authors show that systemic delivery of SEMA3A has similar effects. Third, the authors engineered Tie2-positive monocytes to overexpress SEMA3A and took advantage of the fact that Tie2-positive monocytes preferentially home to tumor-associated blood vessels. Thereby, it was possible to selectively deliver SEMA3A through an elegant tumor targeting strategy to circumvent eventual side effects of systemic SEMA3A delivery.

Contrary to what was previously reported,6 SEMA3A is dispensable for embryonic vascular development.7 However, several studies have established that SEMA3A acts as a negative regulator of pathological angiogenesis by inhibiting endothelial cell migration and inducing endothelial cell apoptosis.8,9 SEMA3A has been suggested to act as an endogenous inhibitor of tumor angiogenesis in the transgenic RipTag tumor model. Consequently, forced reexpression of SEMA3A in tumor-bearing RipTag2 mice inhibited angiogenesis and tumor growth.10 The work of Casazza et al5 goes beyond these previous studies by systematically using different tumor models and exploiting different SEMA3A delivery strategies (autocrine, systemic, paracrine cell–delivered). Most notably, the authors convincingly demonstrate the dual targeting modality of SEMA3A by inhibiting angiogenesis and tumor cell motility. Such a combination of vascular and tumor cell targeting may be particularly attractive. Effective antiangiogenic monotherapy leads to a buildup of hypoxia in the tumor microenvironment, eventually driving tumor cells into apoptosis or necrosis. In turn, it is now well established that such prohypoxic therapy may promote tumor cell invasion and metastasis.11,12 As such, negatively acting guidance molecules interfering with endothelial cell, pericyte, and tumor cell motility may enable a particularly attractive double targeting attack on tumors.

The solid demonstration of potent dual antivascular and antitumor effects of SEMA3A supports the concept that vascular and tumor cell invasion controlling guidance mole-
cules may be exploited as druggable targets, particularly when delivered by specific tumor targeting mechanisms. Clearly, the pleiotropic nature of guidance molecules strongly argues for tumor-specific targeting to avoid the risk of unwanted side effects of such therapy. This may also be important in light of the contextual nature of class 3 semaphorin function, which results in inhibiting as well as activating effects, eg, as highlighted by the observation that inhibitors of SEMA3A are in development to enhance regenerative responses following spinal cord injury.13

References
Double Attack on Tumors by Targeting With Guidance Molecules
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Arterioscler Thromb Vasc Biol. 2011;31:721-722
doi: 10.1161/ATVBAHA.110.222240
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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