The overarching goal of the Edwin L. Steele Laboratories at the MGH Cancer Center in Boston is to improve the delivery and efficacy of anticancer therapies. Working on the hypothesis that the abnormal tumor microenvironment fuels tumor progression and treatment resistance, researchers have developed an array of novel imaging technologies and both animal and mathematical models to unravel the complex biology of tumors. For instance, intravital microscopy is a powerful imaging tool used to observe biological processes at high resolution in vivo. Optical frequency domain imaging (OFDI) is a novel form of intravital microscopy that overcomes the technical limitations of multiphoton microscopy to image and measure key features of the tumor microenvironment, including angiogenesis, lymphangiogenesis, and tissue viability. Another imaging technique, rotational side-view confocal endomicroscopy, has enabled the in vivo cellular imaging of events such as cell infiltration, vascular changes, and tumor progression in the mouse colon overall several months.

Using these tools, results show that the blood and lymphatic vasculature, fibroblasts, immune cells, and the extracellular matrix associated with tumors are abnormal. Moreover, these abnormalities create a hostile tumor microenvironment characterized by hypoxia, high fluid pressure, and high mechanical stress generated by tumor growth. Moreover, the combination of hypoxia, low pH, and pressure drive multiple downstream events leading to tumor invasion, metastasis, and resistance to multimodal therapy (Table 1).

In 2001, Dr. Jain had proposed that “reengineering” the tumor microenvironment by “normalizing” the blood vessels should alleviate hypoxia and improve the delivery and efficacy of anticancer treatment. Specifically, he and his collaborators showed that the judicious use of antiangiogenic agents, originally designed to starve tumors, transiently normalizes tumor vasculature, alleviates hypoxia, and increases the delivery of drugs and therapeutic immune cells. In animal models, antiangiogenic agents improve the outcome of radiation, chemotherapy, and immunotherapy. In the clinical setting, antiangiogenic therapy also appears to improve outcomes in a sub-set of patients undergoing treatment for glioblastoma (GBM). Cediranib is a small-molecule kinase inhibitor of vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3, as well as platelet derived growth factor receptor (PDGFR) and c-kit. In a phase Ib/II clinical trial, 46 patients with newly diagnosed GBM were treated with cediranib in combination with radiation and temozolomide. Advanced imaging showed a durable and consistent increase in microvessel tumor perfusion as early as day 1 of chemoradiation in 50% of GBM patients treated with cediranib, compared with only 7% of historic controls treated with chemoradiation alone. Moreover, GBM patients with improved microvessel tumor perfusion after cediranib had a significant increase in median overall survival (OS) of approximately 9 months (785 vs. 519 days; p=0.037) compared with those who demonstrated stable or decreased perfusion.

Additional studies have highlighted the importance of dose intensity of anti-VEGF therapy in patients undergoing standard therapy for GBM. In a retrospective analysis of patients with recurrent high-grade GBM, low-dose bevacizumab (<5 mg/kg/week) was associated with a significant improvement in progression-free survival (PFS; 12 vs. 2 months; p<0.0001) and OS (16 vs. 6 months; p=0.0002) compared with high-dose bevacizumab (5 mg/kg/week). Another retrospective analysis of patients with GBM who received bevacizumab following chemoradiation examined the impact of the administered dose, measured as bevacizumab administered dose-week (AUCBEV), on treatment outcomes. Patients treated below the
median AUCBEV (3.6 mg/wk/kg) had better outcomes than those treated above the median AUCBEV (p=0.003). Compared with patients treated at higher doses, the median OS for patients treated below the median AUCBEV was significantly better when bevacizumab was started 1 months after chemoradiation (45 vs. 68 weeks; p=0.012) or 3 months after chemoradiation (40 vs. 74 weeks; p=0.0085). These findings suggest that dosing bevacizumab at half the standard dose for progressive or recurrent GBM was at least equivalent to, or perhaps better than, standard bevacizumab dosing.7 Several studies are continuing to examine the optimal approach to anti-VEGF therapy in this patient population. The combination of plerixafor (AMD3100) and bevacizumab is currently under evaluation in a phase II trial of patients with recurrent high-grade GBM (NCT01339039).

Additional imaging studies demonstrated that the extracellular matrix compresses blood vessels and impedes drug delivery and efficacy in desmoplastic tumors. Widely prescribed angiotensin receptor blockers (ARBs) are capable of normalizing the extracellular matrix, opening compressed tumor vessels, and improving drug delivery and efficacy.8–11 This finding offers new hope for improving treatment of highly fibrotic tumors and has led to a phase II clinical trial at Massachusetts General Hospital of losartan and chemotherapy in patients with pancreatic ductal adenocarcinomas (NCT01821729).

### References


### Summary

Abnormal vessels and altered matrix create a hostile metabolic and mechanical tumor microenvironment characterized by hypoxia, low pH, and high interstitial fluid pressure. Together these abnormalities fuel tumor invasion, metastasis, immunosuppression, and induce treatment resistance. Vascular normalization is an emerging approach for improving clinical outcomes in response to a range of cancer therapies (e.g., chemotherapy, radiation therapy, immunotherapy). In particular, matrix normalization can improve perfusion in desmoplastic tumors and improve response to chemotherapy and immunotherapy. Normalization also appears to improve treatment outcomes associated with non-neoplastic diseases that affect 500 million individuals worldwide, including wet age-related macular degeneration (AMD), neurofibromatosis 2 (NF2), tuberculosis, and cirrhosis. Future directions include the role of tumor stroma reengineering to improve the treatment of brain metastases and pediatric brain tumors. Targeting the placental growth factor/neuropilin 1 (PIGF/Nrp1) pathway is a promising strategy to inhibit the growth and spread of pediatric medulloblastoma.13,14

### Financial Disclosures

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