For four decades, our research has focused on one challenge: improving the delivery and efficacy of anti-cancer therapies. Working on the hypothesis that the abnormal tumor microenvironment fuels tumor progression and treatment resistance, we developed an array of novel imaging technologies and animal models as well as mathematical models to unravel the complex biology of tumors. Using these tools, we demonstrated that the blood and lymphatic vasculature, fibroblasts, immune cells and the extracellular matrix associated with tumors are abnormal, which together create a hostile biochemical and physical tumor microenvironment (e.g., hypoxia, high interstitial fluid pressure, high solid stress). Our work also revealed how these abnormalities fuel tumor progression and metastasis, while preventing treatments from reaching and attacking tumor cells.

We next hypothesized that if we could reengineer the tumor microenvironment, we should be able to improve the treatment outcome. Indeed, we demonstrated that judicious use of antiangiogenic agents—originally designed to starve tumors—could transiently “normalize” the tumor vasculature, alleviate hypoxia, increase delivery of drugs and anti-tumor immune cells, and improve the outcome of radiation, chemotherapy and immunotherapy in a number of animal models. Moreover, our trials of antiangiogenics in newly diagnosed and recurrent brain tumor (glioblastoma) patients supported this concept. They revealed that the patients whose tumor blood perfusion/oxygenation increased in response to cediranib – a pan-VEGFR TKI – survived 6-9 months longer than those whose blood perfusion/oxygenation did not increase. The normalization hypothesis also explained how anti-VEGF agents could improve vision in patients with wet age-related macular degeneration, and opened doors to treating other non-malignant diseases harboring abnormal vasculature that afflict more than 500 million people worldwide [e.g., neurofibromatosis-2 (NF2), which can lead to deafness; tuberculosis; plaque rupture]. Our clinical finding led to the approval of bevacizumab for NF2 patients in UK in 2014.

In parallel, by imaging collagen and measuring diffusion and perfusion in tumors in vivo, we discovered that the host cells and the extracellular matrix compress blood vessels and impede drug delivery in desmoplastic tumors (e.g., pancreatic cancer, triple negative breast cancers). We subsequently discovered that angiotensin blockers – widely prescribed to control hypertension – are capable of “normalizing” the extracellular matrix, opening compressed tumor vessels, and improving the delivery and efficacy of molecular and nano-therapeutics. This finding offers new hope for improving treatment of highly fibrotic tumors and led to a phase II clinical trial at MGH on losartan and chemo-radiation therapy in pancreatic ductal adenocarcinomas (PDAC) (NCT01821729). Interim analysis of the clinical data demonstrates that the addition of losartan to the standard of care doubled the resection rate of locally advanced PDAC and dramatically improved survival of these PDAC patients. In my presentation I’ll also discuss how these two broad strategies – “vascular normalization” and “matrix normalization” – can also improve efficacy of immunotherapies.
REFERENCES


