

# Blood Vessel Blockade

*A VEGF-independent route to tumor angiogenesis suggests a new therapeutic strategy.*

Any student of military campaigns knows that cutting off supply routes can devastate an invading army. As cancers spread and grow, they spur angiogenesis, i.e., the development of new blood vessels, to supply their increasing numbers of cells. These new routes are also pathways to metastasis. Vascular endothelial growth factor (VEGF) is a key signaling molecule in angiogenesis and anti-VEGF therapies like Avastin (bevacizumab) have enjoyed significant therapeutic success, for example in certain lung and colon cancers.

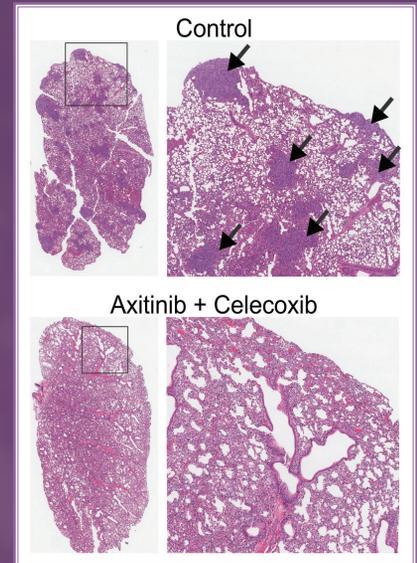
Unfortunately, in many cases, it is increasingly clear that VEGF blockade is not only insufficient to stop tumor growth, it may even promote the development of more aggressive tumors. Several other biological factors have been proposed as the source of this refractoriness, but none have been definitively established. In a recent *Science Translational Medicine* article, Brad St. Croix, Ph.D., Investigator in CCR's Mouse Cancer Genetics Program, and his colleagues identified prostaglandin E2 (PGE2) as a VEGF-independent promoter of angiogenesis in cancer, production of which may be blocked as a complementary therapeutic strategy.

St. Croix's laboratory has long been focused on identifying and blocking the factors that underlie tumor angiogenesis. In the course of their research, his team came across a human colon cancer cell

line, which formed tumors resistant to VEGF inhibitors when implanted into mice. Individual clonal populations from that cell line had variable success in establishing such xenograft tumors; and the researchers found that the highly tumorigenic clones were secreting a pro-angiogenic factor, which could be detected in the cell culture medium. So they took almost three gallons of this cellular broth and painstakingly separated out the active component, which turned out to be PGE2, a biological molecule with known angiogenic activity.

PGE2 is produced in cells through a series of biochemical reactions, one of which is controlled by the rate-limiting enzyme cyclooxygenase 2 (COX-2). COX-2 is known to be overexpressed in many tumors and the researchers were able to show that overexpression of COX-2 could convert the poorly tumorigenic clones into aggressively angiogenic cancers in xenograft models. They also showed that COX-2 inhibition could slow tumor growth and that this therapeutic effect was augmented by inhibition of VEGF. The cooperative actions of COX-2 and VEGF on angiogenesis and metastasis were confirmed in additional preclinical models of metastatic colon and breast cancer.

"Our hope is that cocktails of anti-angiogenic inhibitors will ultimately prove more effective than the current VEGF therapies," said



(Image: B. St. Croix, CCR)

Dual therapy with axitinib and celecoxib prevented the outgrowth of spontaneous breast cancer metastasis in the lung. Metastasis appeared as dense tumor cell clusters (arrows) in tissue sections.

St. Croix. "If our preclinical studies in mice translate into the clinical setting, then combining VEGF and COX-2 inhibitors could potentially prolong the survival of a subset of patients who have tumors with high levels of COX-2. However, not all tumors overexpress COX-2, so it will be important to screen patients to identify those that are most likely to benefit."

To learn more about Dr. St. Croix's research, please visit his CCR website at <https://ccr.cancer.gov/brad-st-croix>.