Angiogenesis has become a major target in cancer therapy. However current therapeutic strategies have their limitations and pose several problems. In most tumors anti-angiogenesis treatment targeting the VEGF system is associated with chemotherapy and has only limited overall survival benefit. An important aspect of anti-angiogenesis therapy in cancer is possible resistance to anti-VEGF treatment. We have recently identified new genes up-regulated during avascular tumor growth on the chick-chorioallantoic membrane (CAM). Our results indicate that anti-angiogenesis in the experimental glioma model drives expression of critical genes which relate to disease aggressiveness in glioblastoma patients. There are mounting evidence that suggest that anti-VEGF may have deleterious effects on tumor cell invasion by selecting highly invasive tumor cells that escape angiogenesis-inhibition when VEGF is inhibited. There are different mechanisms of anti-VEGF-resistance that have been proposed including up-regulation of alternative pathways such as FGFs, selection of hypoxia-resistant cells and/or induction of genes triggering invasive programs. We have identified a molecular mechanism in tumor cells that allows the switch from an angiogenic to invasive program. Furthermore, we are focusing our research on alternative inhibitors that act, in part, independently of VEGF. These are endogenous molecules that play a role in the control of tumor growth and may constitute a starting point for further development.