

TARGETING VEGF: FROM BENCH TO BEDSIDE

Napoleone Ferrara

Department of Molecular Oncology
Genentech, Inc, South San Francisco, CA, 94080, USA.
ferrara.napoleone@gene.com

Vascular endothelial growth factor (VEGF) is an endothelial cell-specific mitogen *in vitro* and an angiogenic inducer in a variety of *in vivo* models (1). The tyrosine kinases Flt-1 (VEGFR-1) and Flk-1/KDR (VEGFR-2) are known to be high affinity VEGF receptors (1). The pivotal role of VEGF in developmental angiogenesis is emphasized by the finding that loss of a single VEGF allele results in defective vascularization and early embryonic lethality (2). Substantial experimental evidence also implicates VEGF as a mediator of pathological angiogenesis. *In situ* hybridization studies demonstrate intense expression of VEGF mRNA in the majority of human tumors so far examined. Anti-VEGF monoclonal antibodies have the ability to block the growth and neovascularization of a broad variety of human tumor cell lines in nude mice (3). A humanized variant of an anti-VEGF monoclonal antibody (Bevacizumab, Avastin) is presently undergoing clinical trials in multiple types of cancer patients. Recent studies have shown that Avastin results in a significant increase in time to progression in patients with renal cell carcinoma. A pivotal phase III study in patients with previously untreated metastatic colorectal cancer (MCR) has shown that addition of Avastin to IFL regimen (irinotecan, 5-fluorouracil, leucovorin) results in a significant increase in progression-free survival and survival compared to IFL alone (4). These findings represent the first clinical validation in a large phase III study of the hypothesis that blocking angiogenesis may be an effective cancer treatment and led to the FDA approval of Avastin as a first-line treatment for MCR. Very recent data indicate that the addition of Avastin to the FOLFOX4 regimen (5-fluorouracil, leucovorin, oxaliplatin) results in increased survival even in second-line MCR patients. Several trials are currently ongoing to determine whether the benefit of anti-VEGF therapy may extend to other malignancies. Furthermore, VEGF is implicated in intraocular neovascularization associated with active proliferative retinopathies and age-related macular degeneration (AMD). A humanized anti-VEGF Fab (ranibizuman, Lucentis) is presently in phase III for the treatment of the wet form of AMD and preliminary results indicate that the treatment maintains or even improves vision.

References

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