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Combination Therapy Obliterates New Vessel Growth in Tumors and Retinopathy

By Eric Sauter

Using a new and dramatically effective treatment approach, scientists at The Scripps Research Institute have for the first time achieved complete inhibition of new blood vessel growth in animal models of a highly vascular brain tumor and of neovascular eye diseases with little or no effect on normal tissue vasculature.

The paper was published online on January 8, 2007 in *The Proceedings of the National Academy of Sciences*.

"While a number of new drugs that inhibit new blood vessel growth are now available the clinics, no one so far has been cured with available anti-angiogenic agents," said Martin Friedlander, a professor at Scripps Research and retina specialist at Scripps Clinic who led the study. "Our study shows that combining anti-angiogenic agents that target multiple angiogenic pathways can significantly increase the effectiveness of such a therapeutic approach. Such combination angiostatic therapy provides a whole new range of treatment options for patients with neovascular diseases, where complete inhibition of new blood vessel growth is the desired result."

While new blood vessel growth from preexisting capillaries ("angiogenesis") is fundamental to survival, the abnormal formation of new blood vessels ("neovascularization") contributes to the pathogenesis of tumor growth and metastasis as well as the vast majority of diseases that lead to catastrophic loss of vision. A number of angiostatic molecules have been used to impair blood vessel formation as clinical adjuncts to conventional radio- and chemotherapy. Others have proven to be modestly effective in treating neovascular eye diseases.

The new study combined the actions of three classes of angiostatic compounds, each targeting different angiogenic pathways, and showed striking results in the treatment of an animal model of glioblastoma, a highly malignant brain cancer, and ischemic retinopathy, excessive blood vessel growth in the eye that is a major cause of blindness worldwide.

"Our combination therapy reduced tumor mass and increased survival in the glioblastoma model," Friedlander said. "In models of neovascular eye diseases, the therapy resulted in complete inhibition of pathological neovascularization in more than 60 percent of the eyes; over 90 percent had greater than 75 percent inhibition of new vessel growth with no adverse affects on normal tissue vasculature. In contrast, individual therapies with comparable doses of individual drugs were minimally effective, if at all."

Importantly, Friedlander notes that the use of single therapies can result in the activation of alternative compensatory pro-angiogenic pathways designed to stimulate new vessel growth, while the combination approach significantly reduced such compensatory upregulation.

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Professor Martin Friedlander's new study provides a proof-of-concept that combination anti-angiogenic therapy can be more effective than single agents.

New Vessel Growth

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"The fact that multiple angiogenic pathways are activated in response to single therapies, but not to combination treatment, supports the hypothesis that compensatory mechanisms might prevent single angiostatics from inhibiting neovascularization," he said. "These results suggest that combination therapy prevents this natural compensation, enhancing the overall anti-angiogenesis effect."

In combination, the angiostatic therapies were effective at much lower concentrations than when used as individual monotherapies. Even when diluted up to 100-fold, the triple combination inhibited angiogenesis at levels comparable to optimal doses of any single therapy. A ten-fold dilution of the triple combination demonstrated extensive neovascular inhibition with complete inhibition observed in 44 percent of the treated retinas. At these same concentrations, the angiostatic activity of each monotherapy was negligible, indicating that combining multiple angiostatic drugs was synergistic rather than additive.

The effectiveness of combination therapies at relatively low doses may be a distinct advantage in therapy, the study noted. In the elderly or diabetic patients, high levels of circulating angiostatics could precipitate stroke or heart attack due to the fact that such patients make collateral blood vessels in hearts and brains that are starved for oxygen from vascular diseases such as arteriosclerosis, hypertension, and diabetes. For these and other patients, the use of lower doses of angiostatic therapies could minimize potential adverse side effects.

"The point of the study was to show proof-of-concept that targeting multiple angiogenic pathways will be more effective than inhibiting single ones due to potential compensatory upregulation," Friedlander said. "As more and more anti-angiogenic agents reach the market, there will be even more combinations to choose from. In our laboratory, we're now looking at new combinations of approved angiostatic drugs to see if we can achieve similar promising results that can have immediate translation into the clinic."

Other authors of the study, *Combination Angiostatic Therapy Completely Inhibits Ocular and Tumor Angiogenesis*, were Michael I. Dorrell, Edith Aguilar, Lea Scheppke, and Faith H. Barnett of The Scripps Research Institute. See *Proceedings of the National Academy of Sciences of the United States of America* at: http://www.pnas.org/cgi/content/abstract/0607542104v1

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