

Molecular Imaging and Targeted Anti-Angiogenic Therapy in Cancer with $\alpha_v\beta_3$ -Targeted Nanoparticles

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INTRODUCTION: Anti-angiogenic therapies hold great promise as components of primary and adjunctive chemotherapeutic regimens for solid tumors. These agents promise to reduce the dosage and increase the effectiveness of current chemotherapeutic strategies by pruning the neovascular proliferation around tumors, which could provide higher local concentrations of drugs with better tumoral penetration. $\alpha_v\beta_3$ -Integrin targeted perfluorocarbon nanoparticles have been utilized for molecular imaging of angiogenesis in various tumor models and these technologies can be modified to deliver therapeutic drugs. Targeted nanoparticles can specifically deposit lipophilic agents into the cell membrane and elicit anti-angiogenic and anti-proliferative effects. This study presents preliminary results using targeted perfluorocarbon nanoparticles for targeted delivery of fumagillin (an anti-angiogenic drug) to nascent Vx2 tumors in rabbits with follow-on molecular imaging of therapeutic effect.

METHODS: New Zealand White rabbits were implanted with a 65 mm³ Vx2 carcinoma fragment in the popliteal fossa. Animals received $\alpha_v\beta_3$ -integrin targeted nanoparticles with (n=3) or without (n=3) 30 μ g/ml fumagillin (1 ml/kg; no gadolinium) on post-implantation days 6, 9 and 12. Sixteen days post-implantation, high-resolution, 3D, T1-weighted, fat suppressed gradient echo images of the leg (250 μ m by 250 μ m resolution, 500 μ m slices, TR/TE = 40/5.6 ms, 65° flip angle) were collected using a clinical 1.5 T scanner and a circular surface coil. Images were collected before and three hours post intravenous injection of $\alpha_v\beta_3$ -integrin-targeted paramagnetic nanoparticles (1 ml/kg; no fumagillin) to assess angiogenesis in the tumor. Enhancing MRI pixels were selected based on a threshold equal to three times the standard deviation of the tumor signal at baseline. Both the area of enhancement and the average signal increase were calculated. The tumor volume was calculated by summing the number of tumor pixels and multiplying by the voxel volume.

RESULTS: Sixteen days post-implantation, tumors treated serially with fumagillin nanoparticles were significantly smaller than control tumors (Figure 1, * p = 0.03). The overall extent (i.e., area) of MRI signal enhancement tended to be lower in fumagillin treated tumors compared to controls (Figure 2, # p = 0.19), suggesting that neovascular proliferation was markedly reduced but not eliminated. Fumagillin treated rabbits also tended to have lower MRI signal enhancement, but the difference did not reach significance given the small size of this pilot study.

CONCLUSION: The results of this pilot study suggest that integrin-targeted fumagillin nanoparticles may suppress angiogenesis and inhibit tumor development and/or accelerate cell-mediated rejection. If these trends continue with further replication, integrin-targeted fumagillin nanoparticles may prove useful in the treatment of early primary or metastatic tumors alone or in conjunction with adjuvant therapy. Moreover, these results further highlight the role of MRI for nanomedicine systems that combine the power of imaging with targeted therapy.

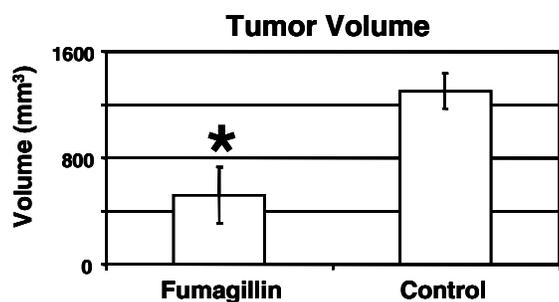


FIGURE 1: Treatment with $\alpha_v\beta_3$ -integrin targeted fumagillin nanoparticles reduced the tumor volume (* p = 0.03) compared to nanoparticles without drug, suggesting effective anti-angiogenic treatment.

Molecular Imaging of Tumor Angiogenesis

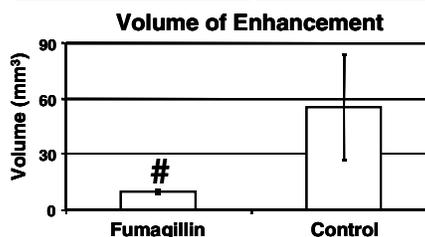
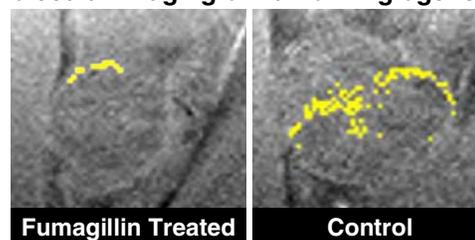


FIGURE 2: MRI molecular imaging of angiogenesis (TOP, yellow overlay) shows decreased angiogenesis in the tumor treated with targeted fumagillin nanoparticles compared to the untreated tumor. Targeted fumagillin treatment reduced the average extent of MRI signal enhancement by 82% (BOTTOM, # p = 0.19).