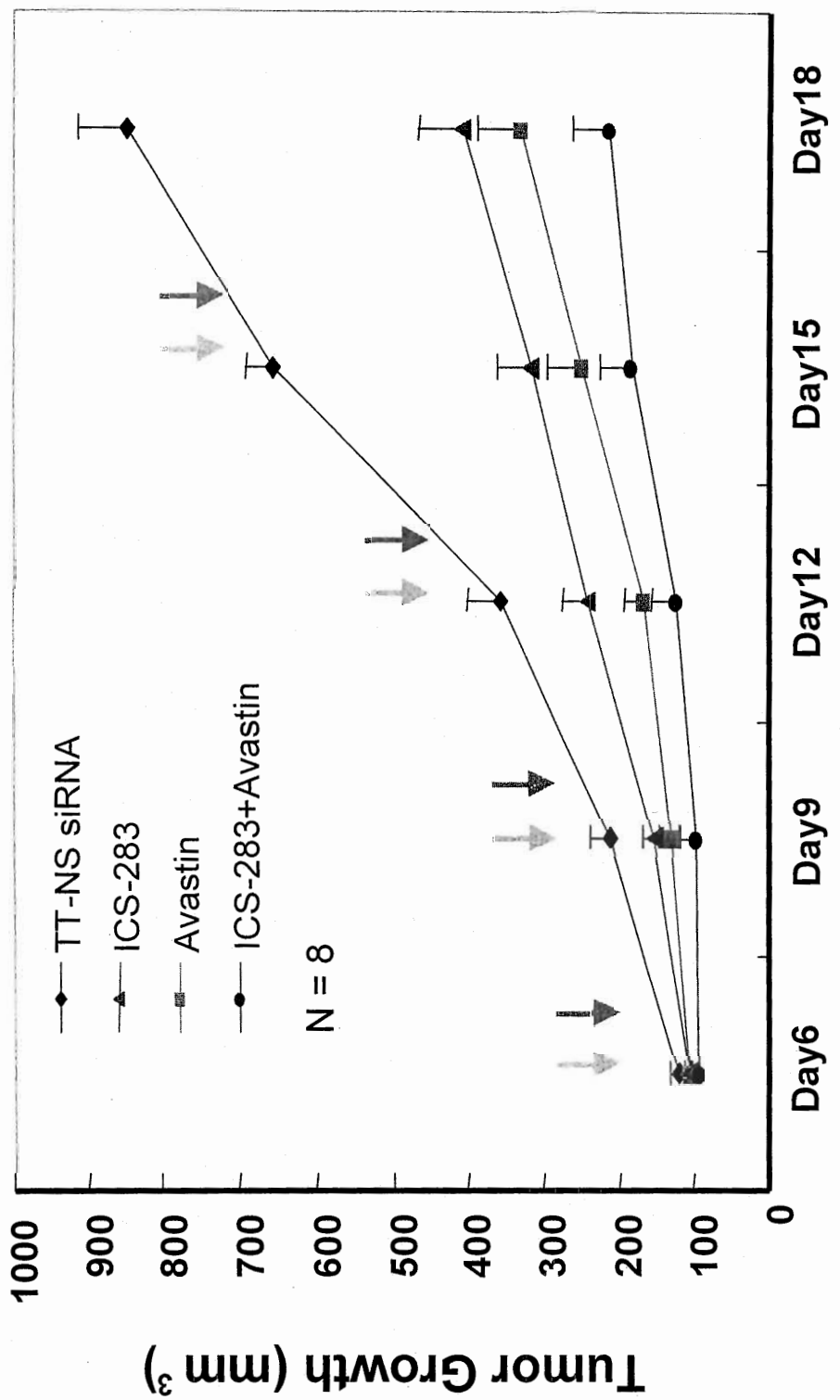


Figure 1. Stronger anti-tumor efficacy has been observed using a Combination cancer therapeutics with VEGFR2-siRNA inhibitor and Avastin (Bevacizumab) in the same treatment regimen, in a human colon Carcinoma (DLD-1) xenograft tumor model

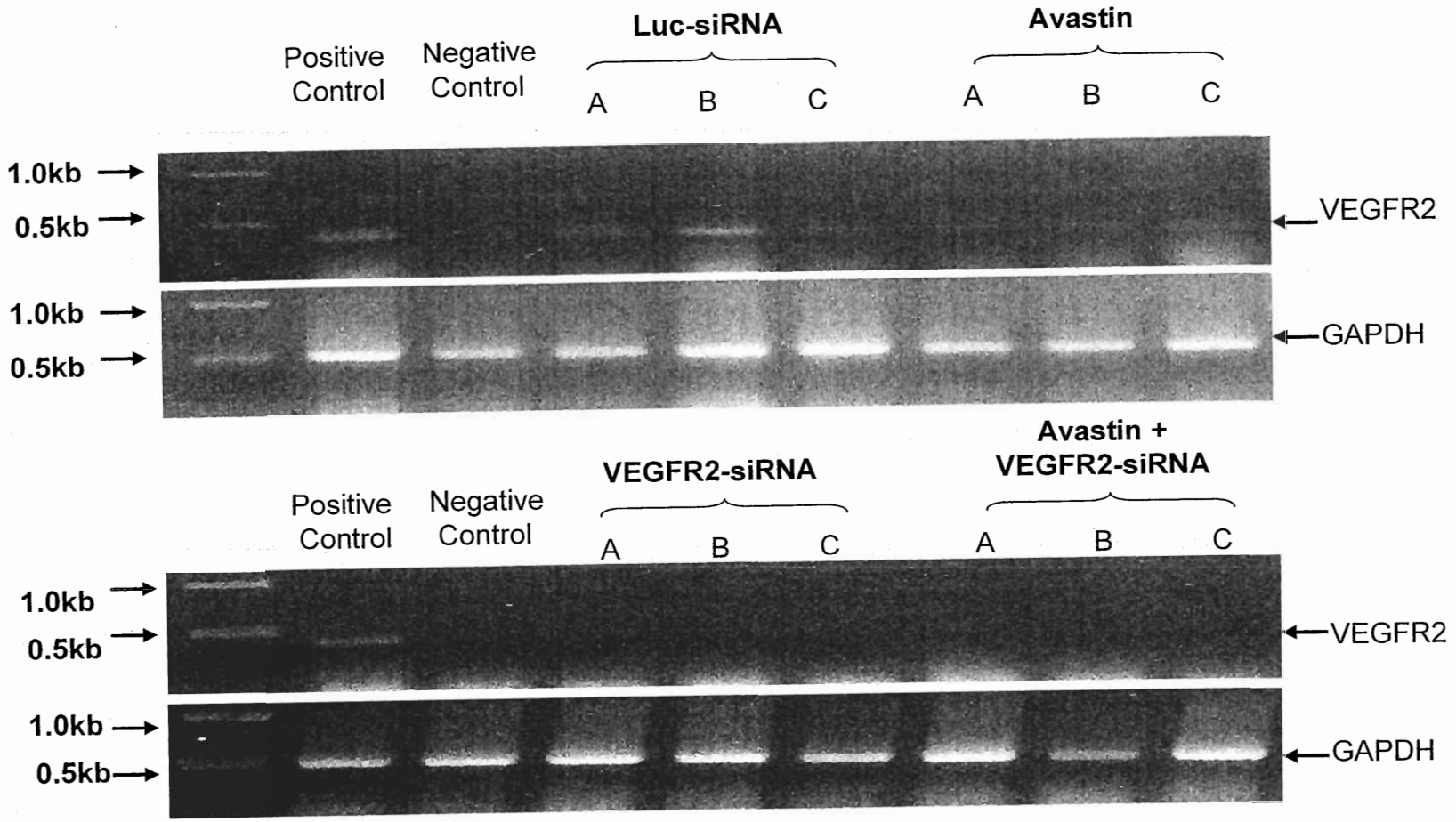


Figure 2. VEGFR2-siRNA nanoparticle targeting neovasculature through systemic delivery demonstrated potent efficacy in colon carcinoma xenograft mouse model (DLD-1 tumor) after four repeated administration every three days. RT-PCR results illustrate the knockdown of VEGFR2 gene expression at mRNA level

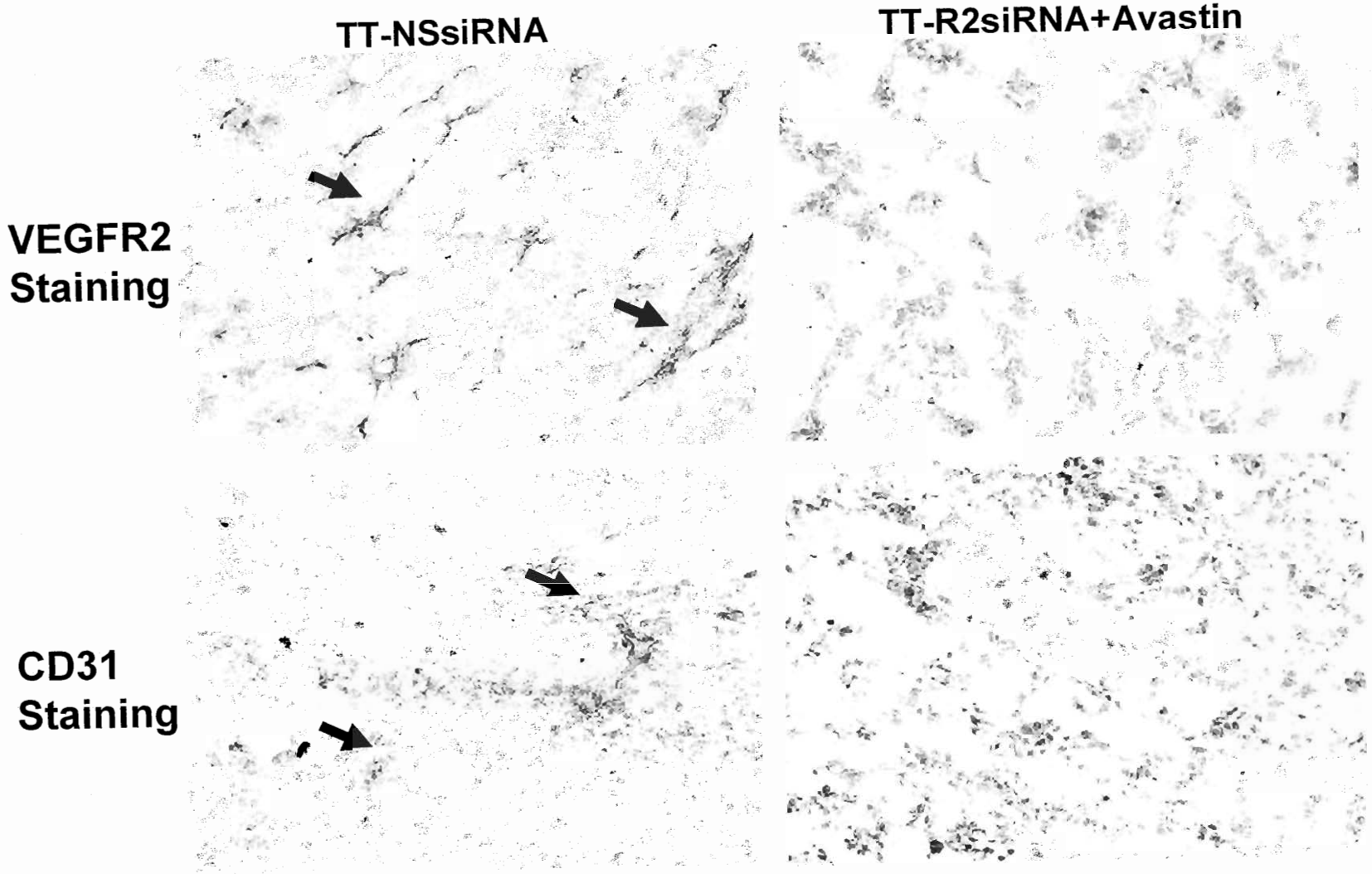


Figure 3. VEGFR2-siRNA nanoparticle targeting neovasculature through systemic delivery demonstrated potent efficacy in colon carcinoma xenograft mouse model (DLD-1 tumor) after four repeated administration every three days. Immunohistochemistry images show down regulation of VEGFR2 and CD 31 expression in the tumor tissue.

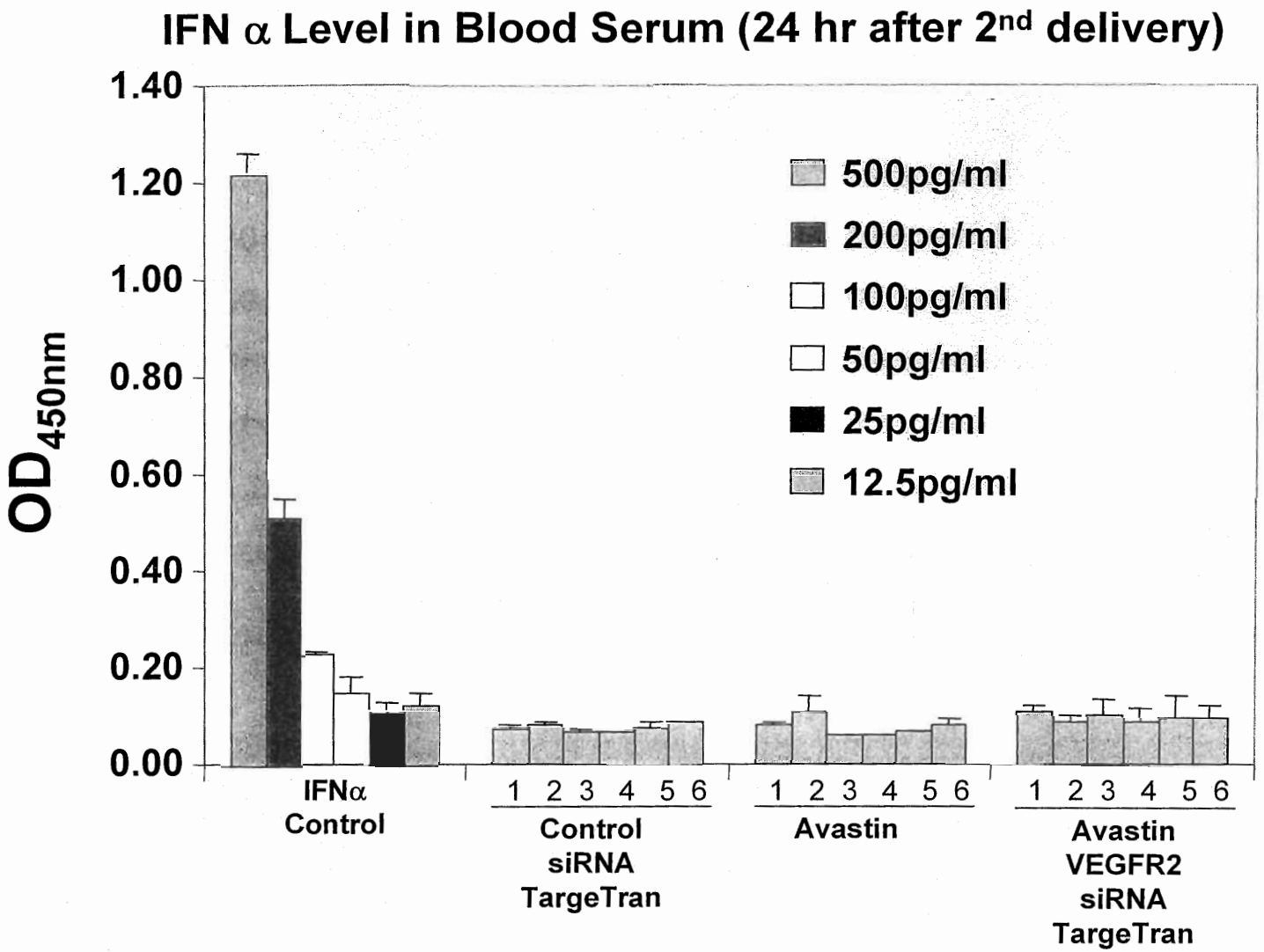


Figure 4. While VEGFR2-siRNA nanoparticle targeting neovasculature through systemic delivery demonstrated potent efficacy in colon carcinoma xenograft mouse model (DLD-1 tumor), no significant IFN-a induction observed in the mouse blood stream 24 hours after the 2nd delivery.

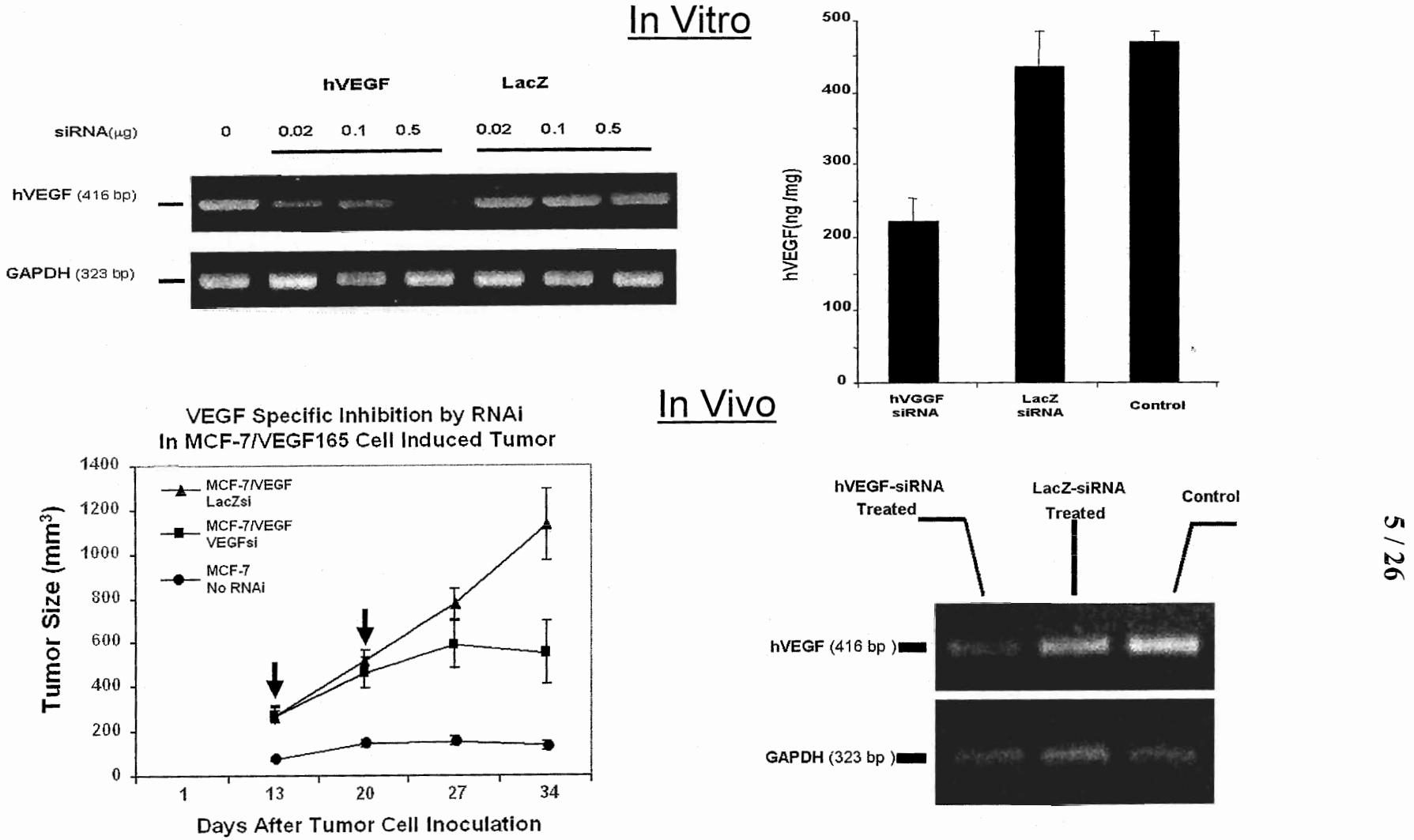


Figure 5. Human VEGF-siRNA (19 base pair with 3' end overhangs) is effective for silencing hVEGF expression in vitro and in vivo, at both mRNA level and protein level, evaluated by RT-PCR and ELISA. Two upper figures demonstrated significant hVEGF knockdown at both mRNA and protein levels. The lower panel shows the anti-tumor activity of siRNA-mediated hVEGF Knockdown in a MCF-7/VEGF-165 cell induced xenograft model, where the hVEGF expression Was significantly down regulated in the tumor tissue

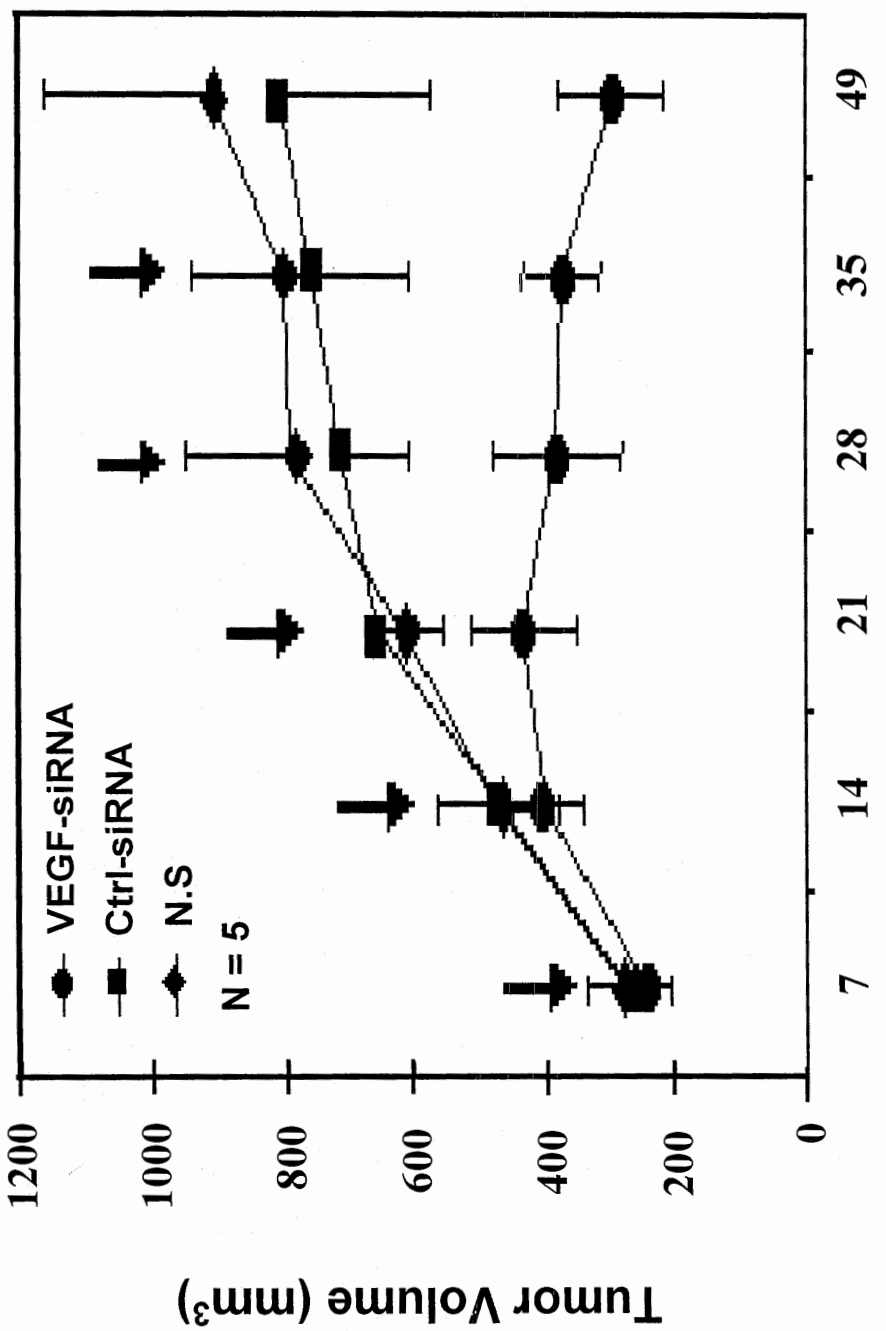


Figure 6. Human VEGF-siRNA (19 base pair with 3' end overhangs) is effective for silencing hVEGF expression in vivo resulting in tumor growth inhibition (HNSCC 1483 Cell). Five times repeated intratumoral delivery with electroporation enhancement with 7 days interval.

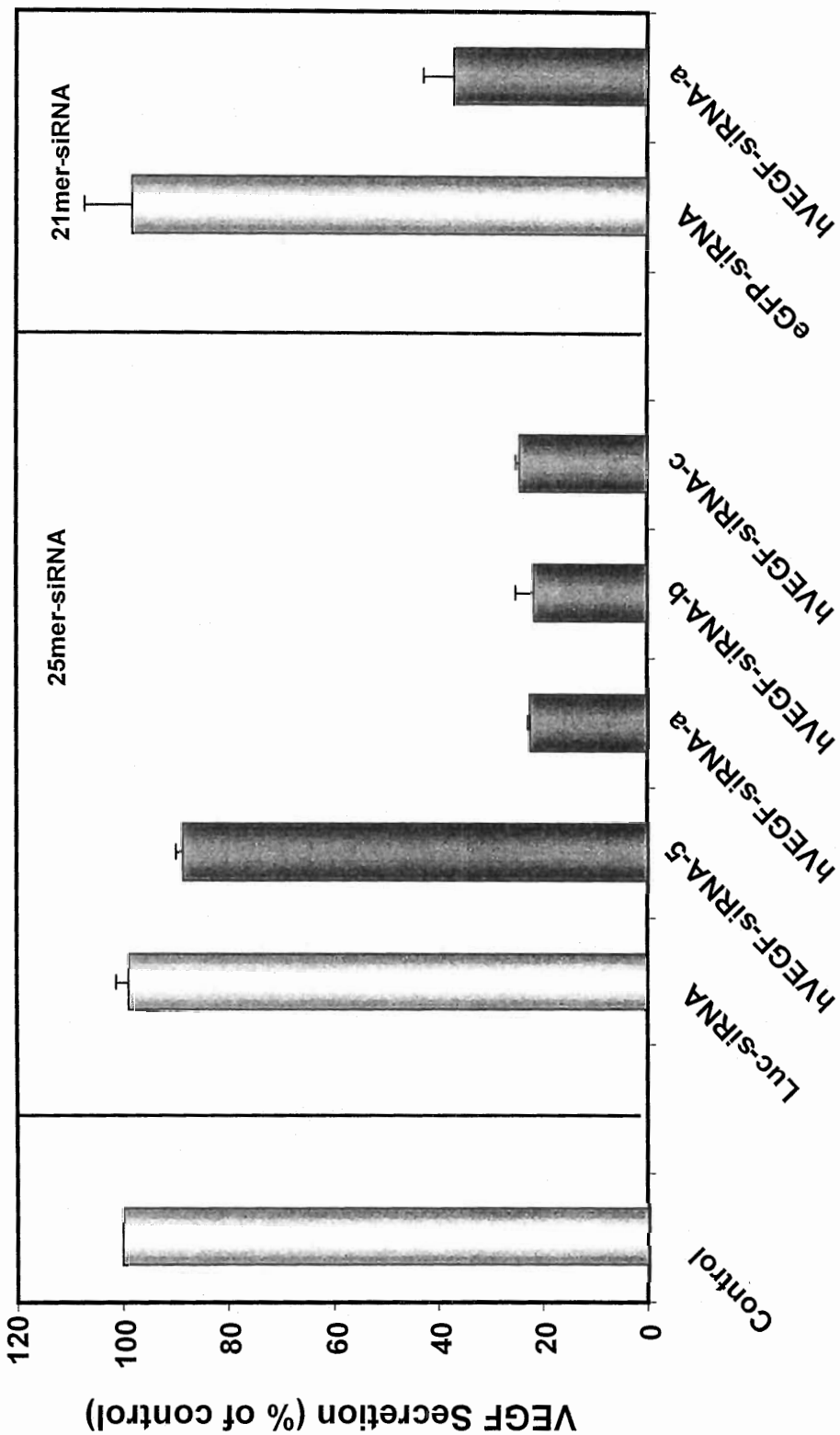


Figure 7. Human VEGF-siRNA (25 basepair blunt end) is more effective For silencing hVEGF expression in vitro and stronger than the 19 base pair siRNA.

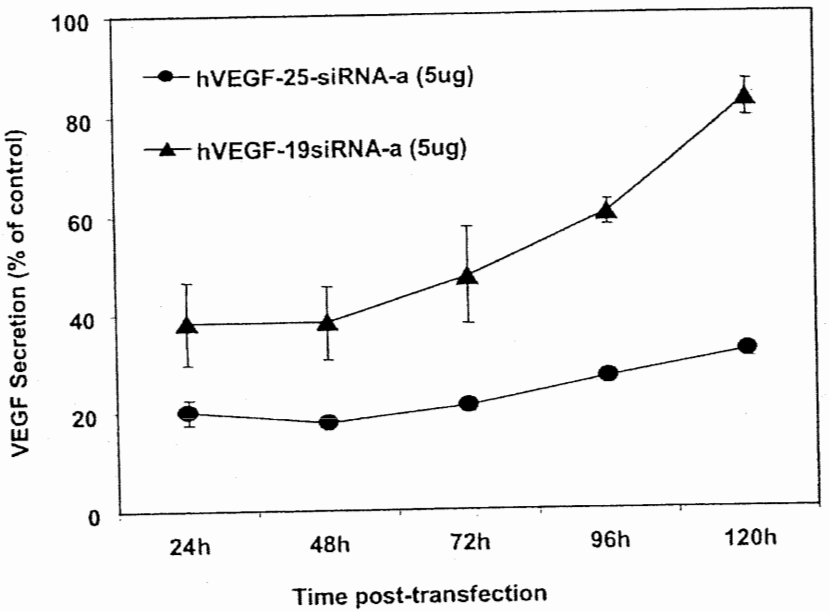


Figure 8. Human VEGF-siRNA (25 basepair blunt end) is effective for silencing hVEGF expression in vitro and has longer duration than that of the 19 basepair siRNAs.

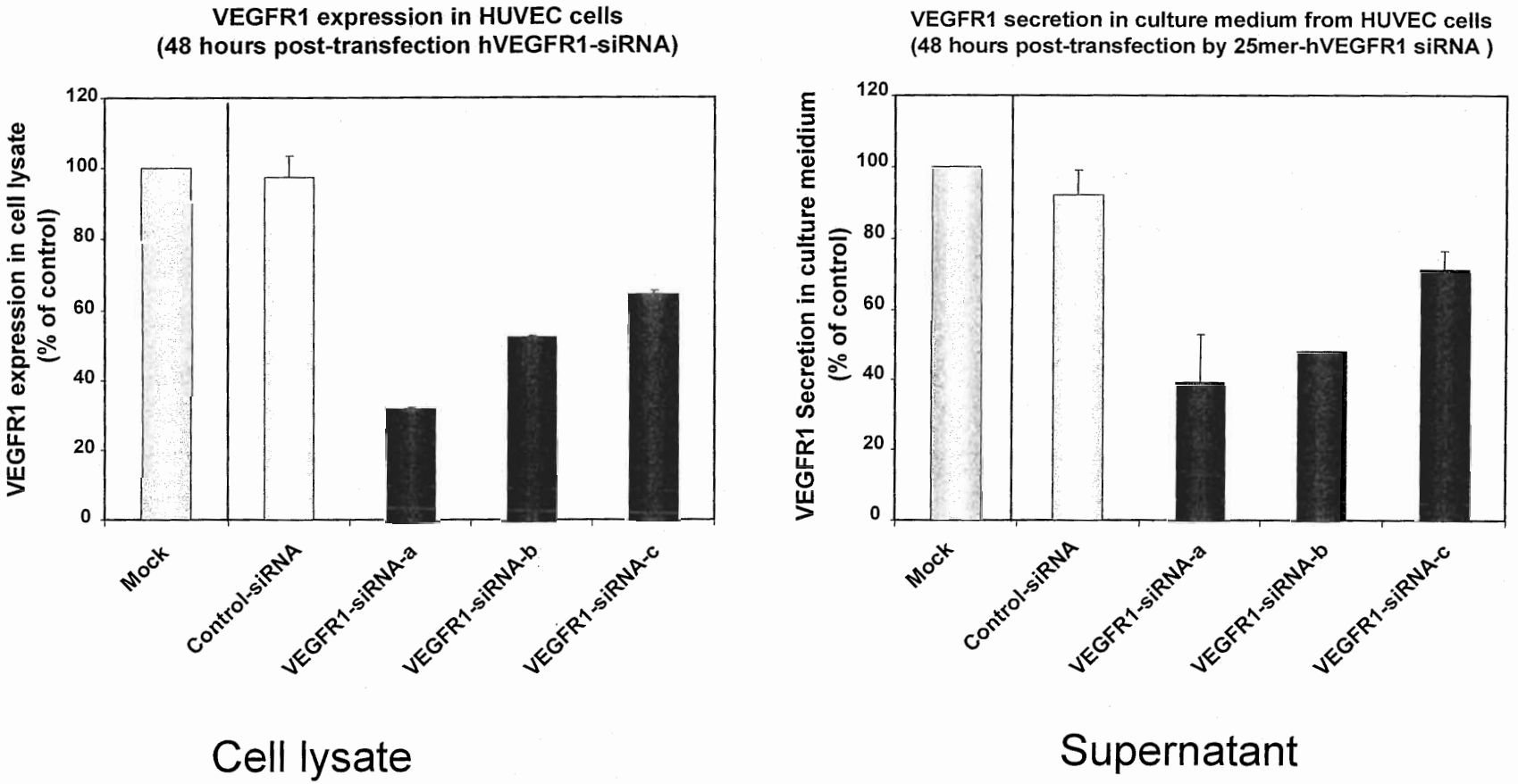
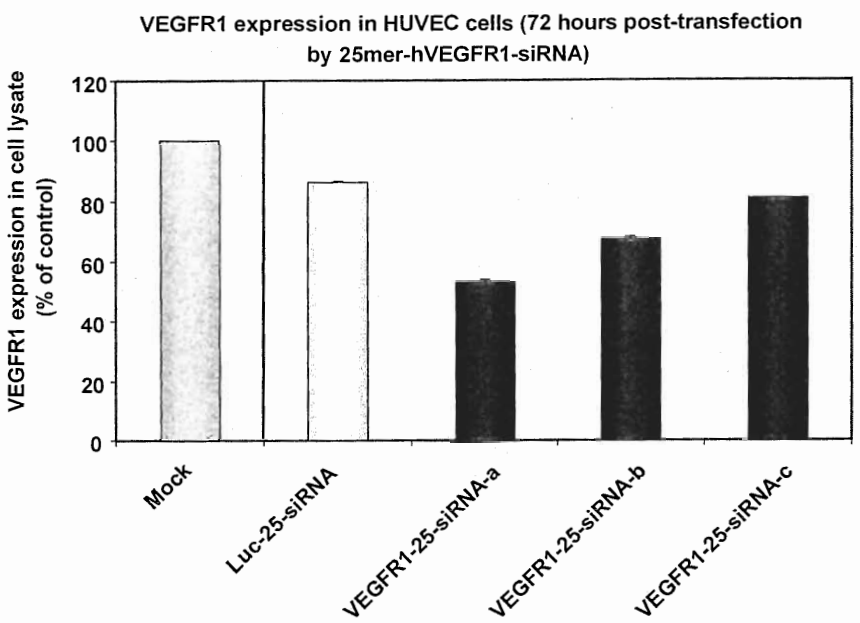
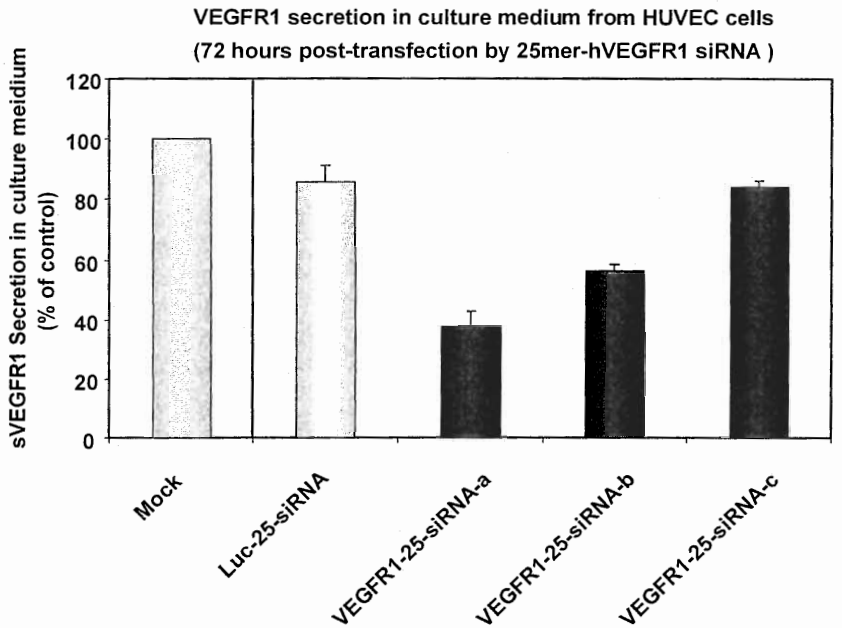


Figure 9. Human VEGFR1-siRNA (25 base pair blunt end) is effective for silencing hVEGFR1 expression in vitro after 48 hr.

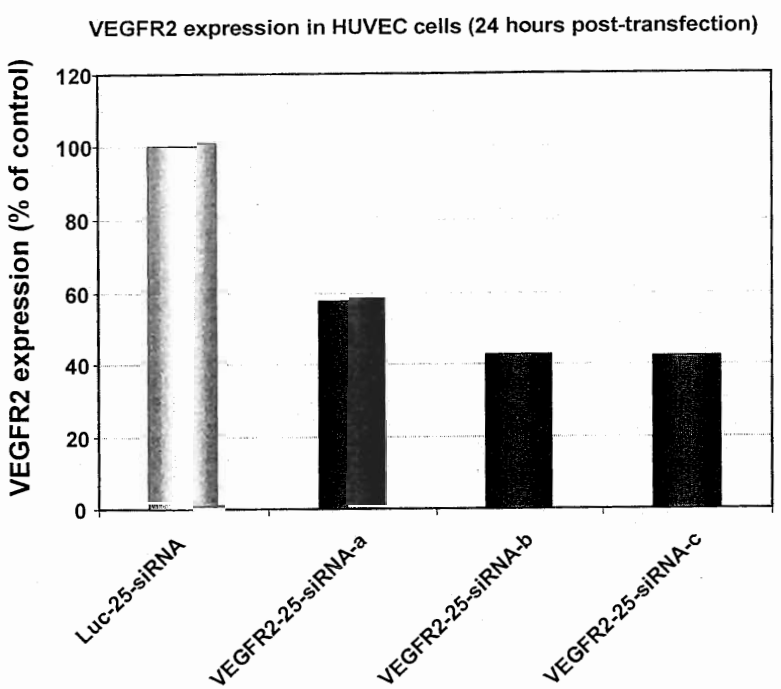


Cell lysate



Supernatant

Figure 10. Human VEGFR1-siRNA (25 base pair blunt end) is effective for silencing hVEGFR1 expression in vitro after 72 hr.



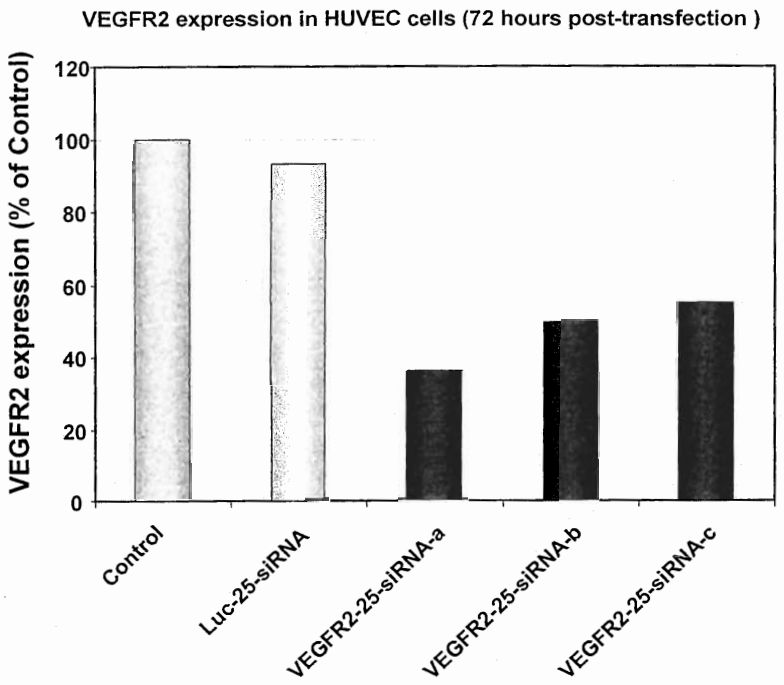


Figure 11. Human VEGFR2-siRNA (25 base pair blunt end) is effective For silencing hVEGFR2 expression in vitro at two different time points.

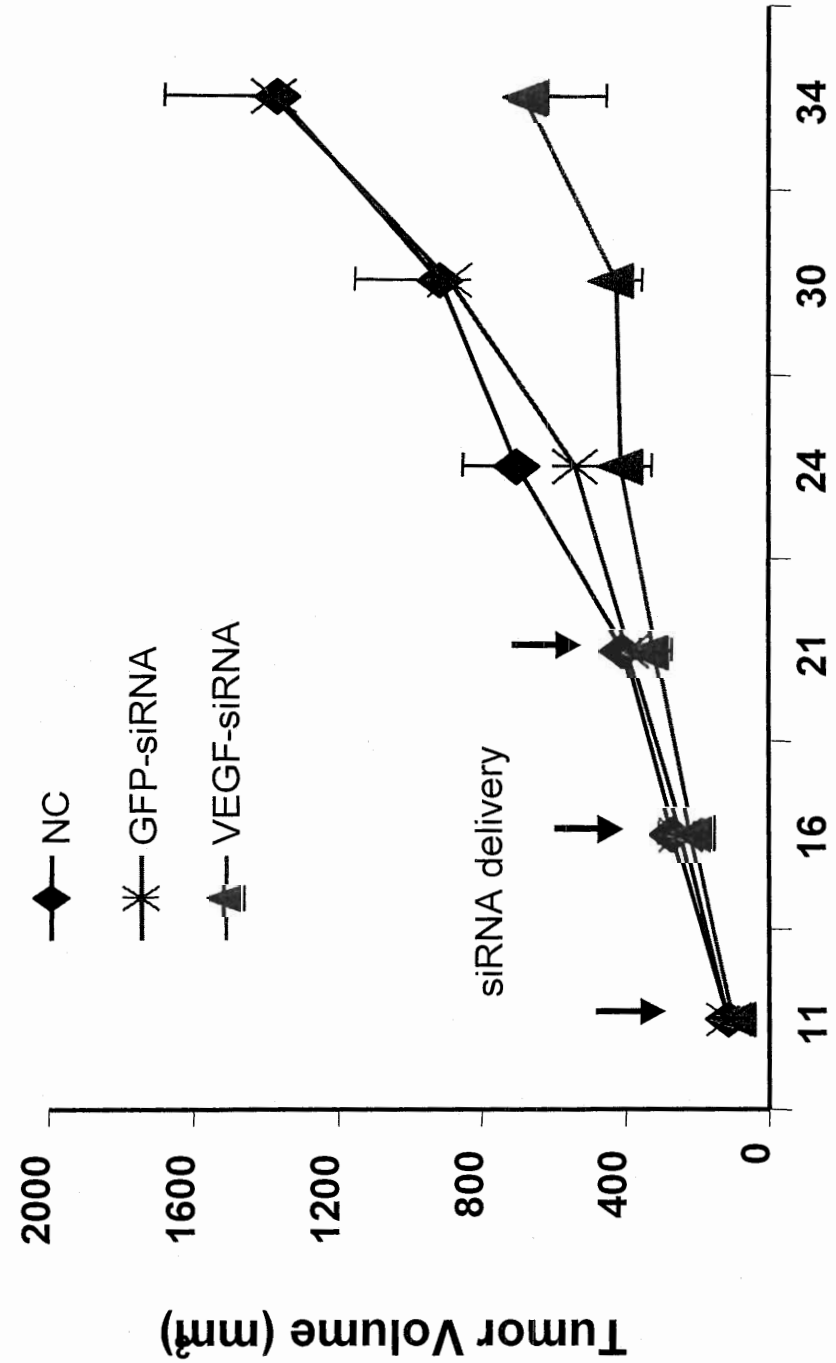


Figure 12. Human VEGF-siRNA (25 base pair blunt end) is effective for silencing hVEGF expression in vivo resulting in tumor growth inhibition, with a MDA-MB-435 breast carcinoma cell line.

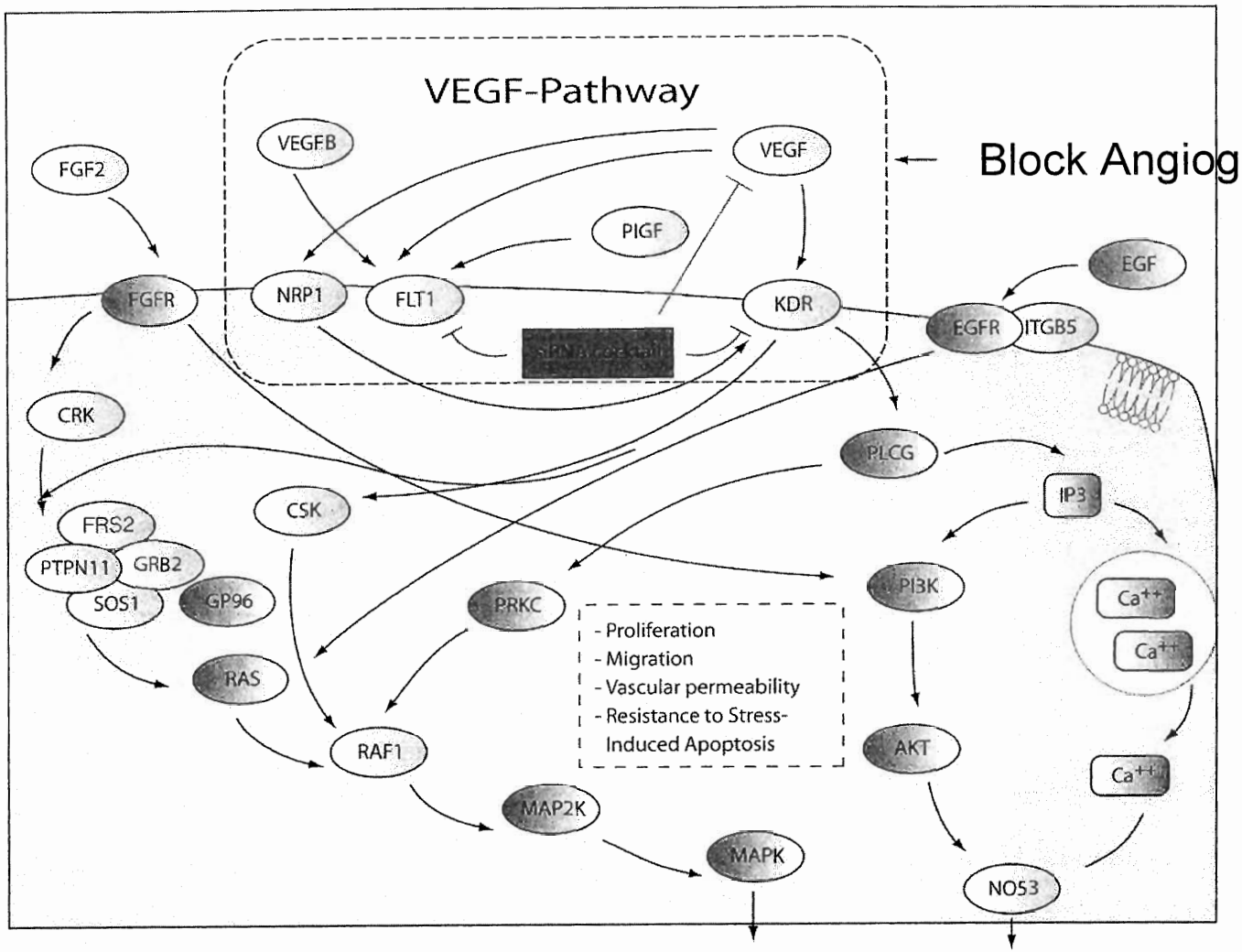


Figure 13. Concept framework for using siRNA cocktail targeting VEGF, VEGFR1 and VEGFR2 in the same treatment to block the angiogenesis Pathway.

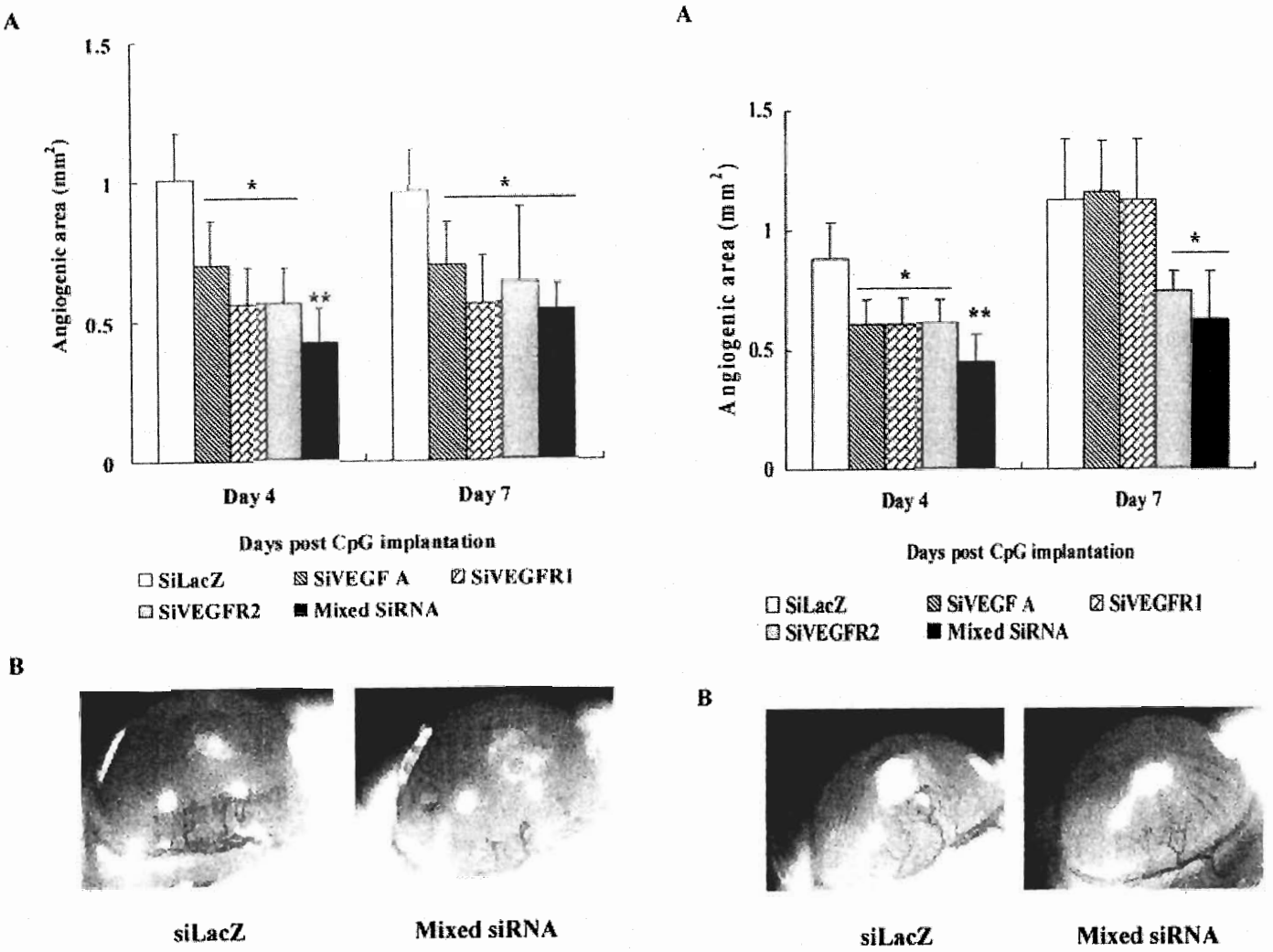


Figure 14. siRNA cocktail targeting VEGF, VEGFR1 and VEGFR2 is more effective than any single siRNA targeting individual gene at the same Dosage tested in the HSV induced ocular angiogenesis mouse model, with Either local(left) or systemic (right) deliveries.

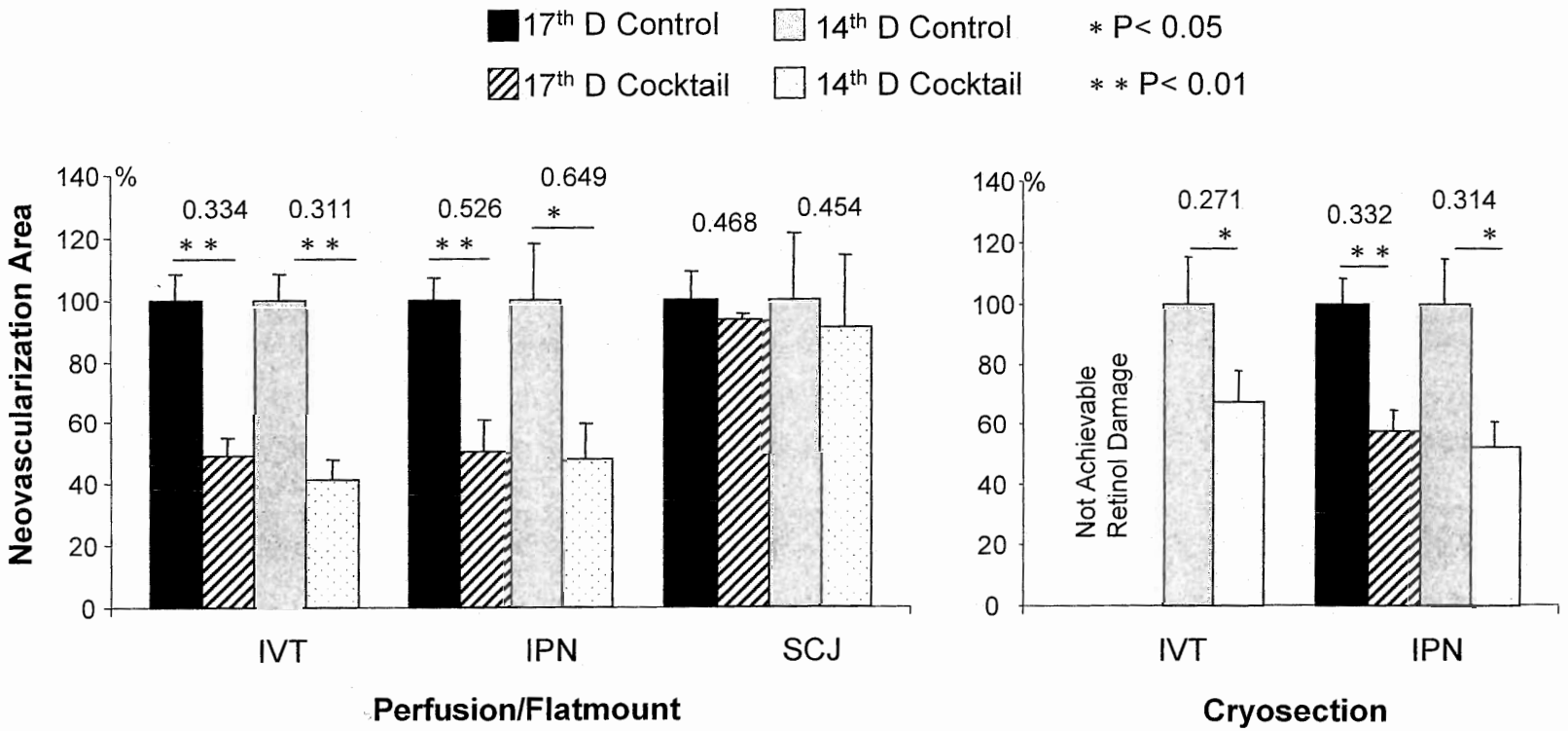


Figure 15. Inhibition of angiogenesis by administration of VEGF pathway siRNA cocktail on Day 17 or day 14 after induction of disease in ocular tissues of a murine model of retinal angiogenesis in a perfusion/flamount measurement

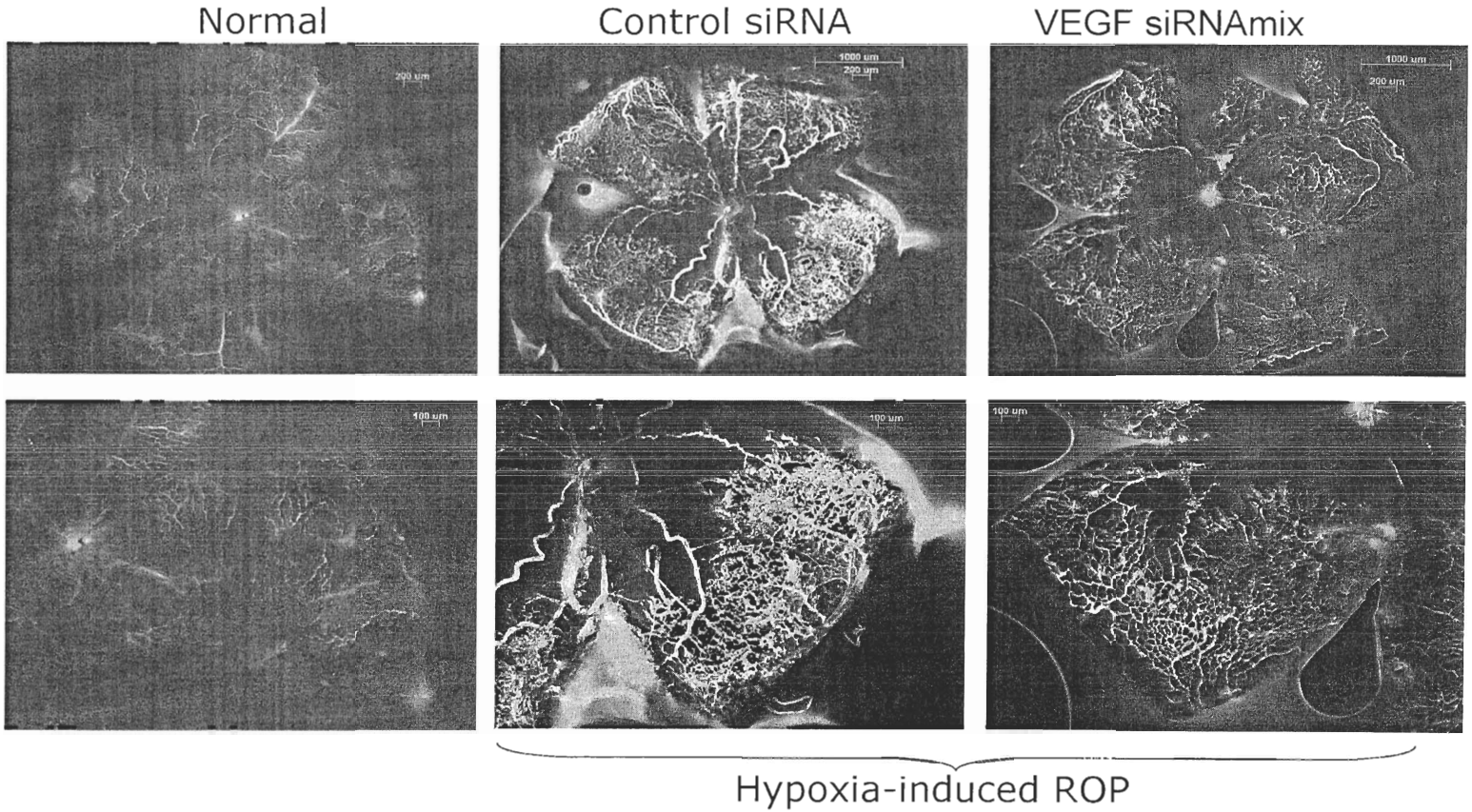


Figure 16. siRNA cocktail targeting VEGF, VEGFR1 and VEGFR2 demonstrates very effective anti-angiogenesis activity in the retinopathy of prematural (ROP) mouse model induced by Hypoxia

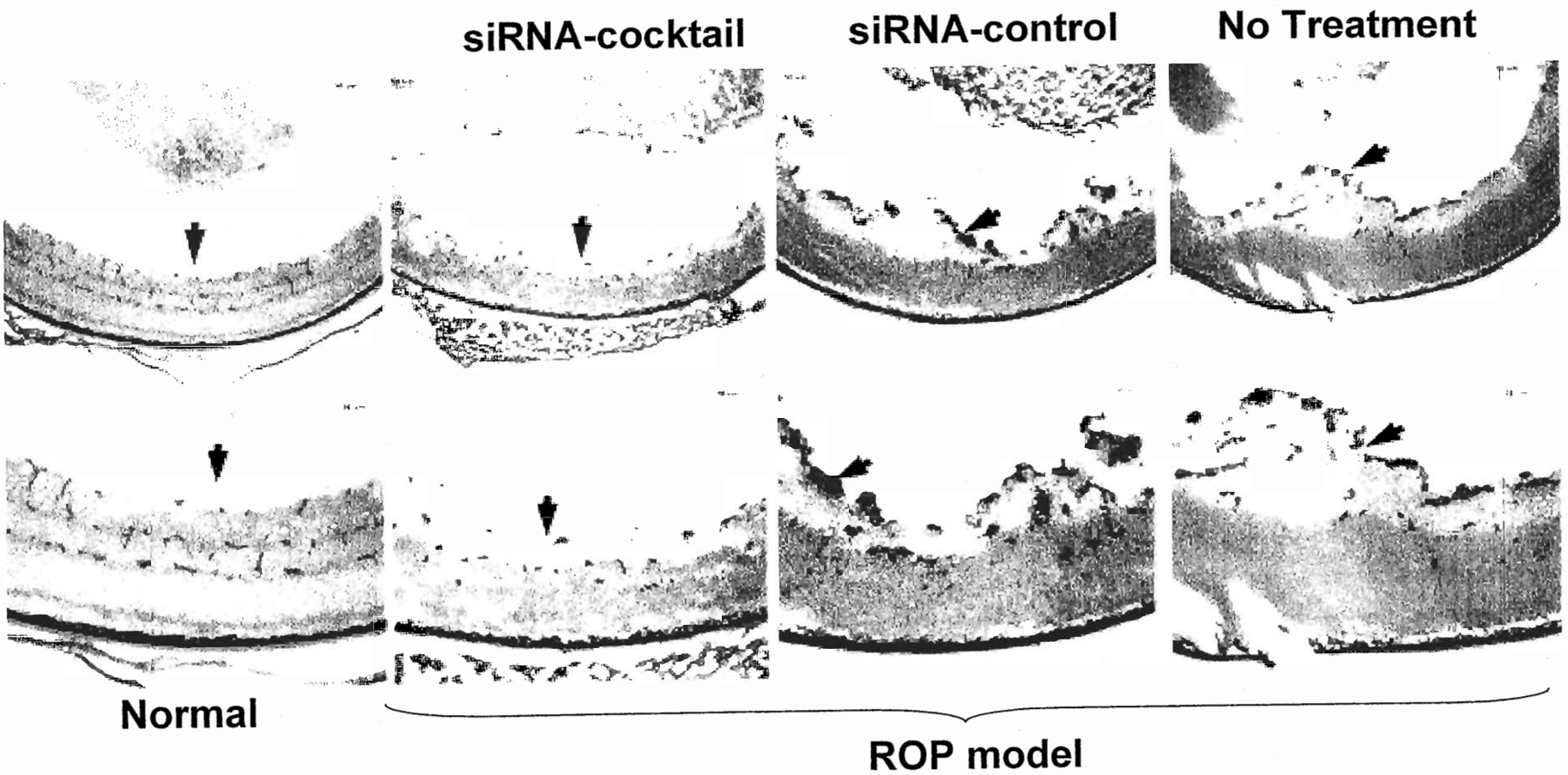


Figure 17. siRNA cocktail targeting VEGF, VEGFR1 and VEGFR2 demonstrates very effective anti-angiogenesis activity in the retinopathy of prematural (ROP) mouse model induced by Hypoxia.

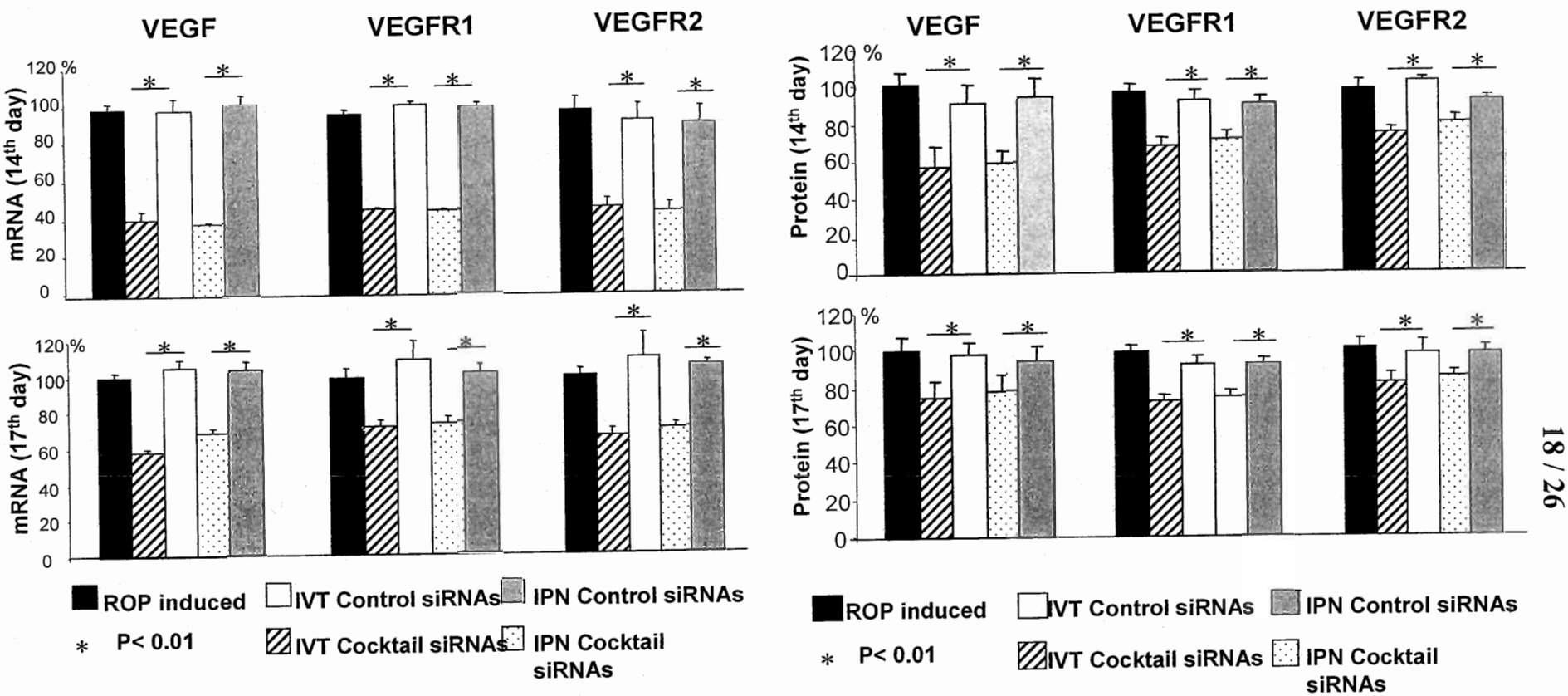


Figure 18. siRNA cocktail targeting VEGF, VEGFR1 and VEGFR2 inhibits ocular angiogenesis significantly with different routes of administration with different carriers. IP delivery was mediated by a ligand-directed nanoparticle. siRNA Cocktail Mediated Knockdown of VEGF PathwayFactors RT-PCR Detection of mRNA levels with ROP Model

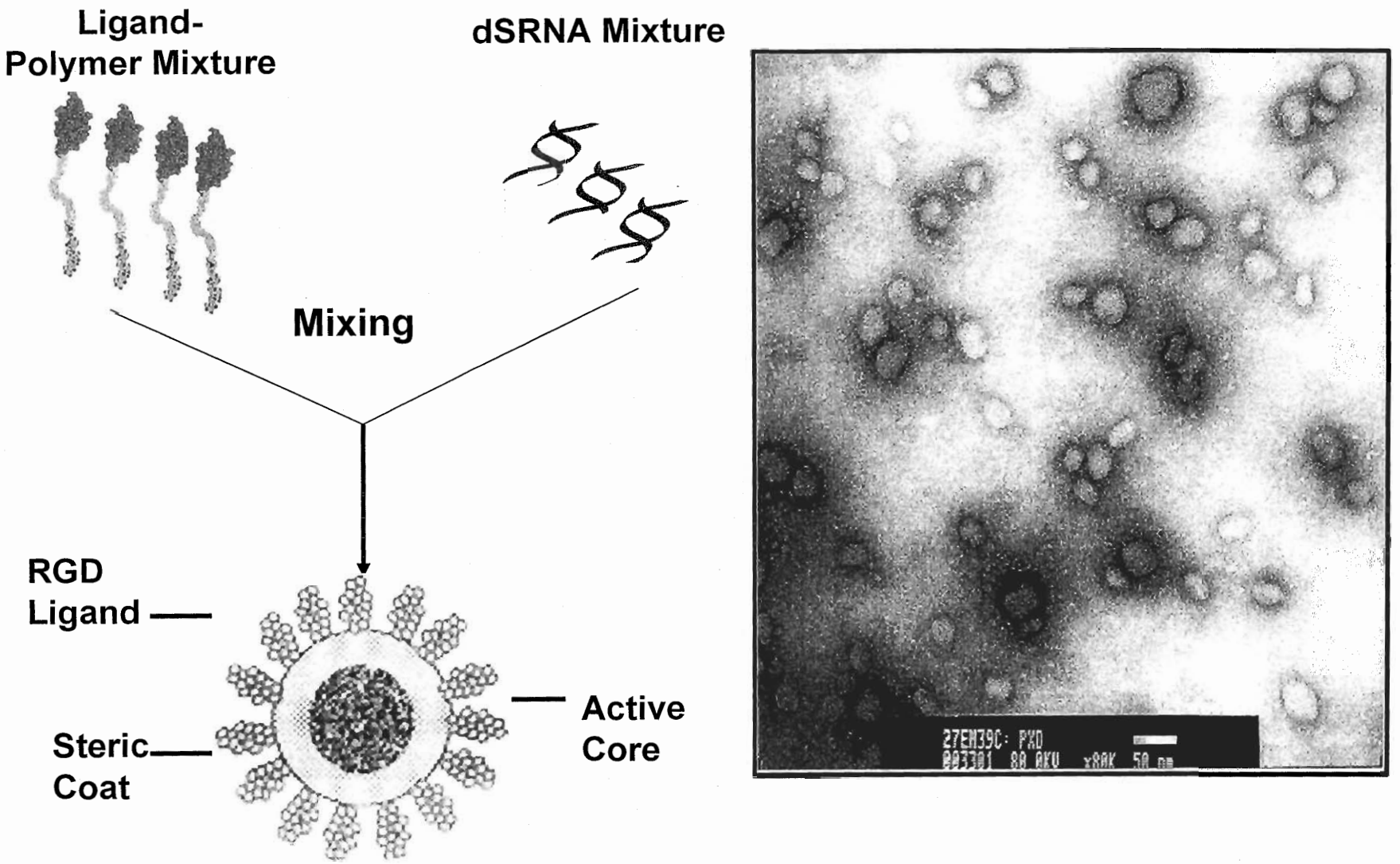


Figure 19. Self-assembled nanoparticle for siRNA delivery. When the pre-made RGD-PEG-PEI conjugate mixture is mixed with the siRNA mixture, the nanoparticles will be self-assembled with a relatively homogenous size.

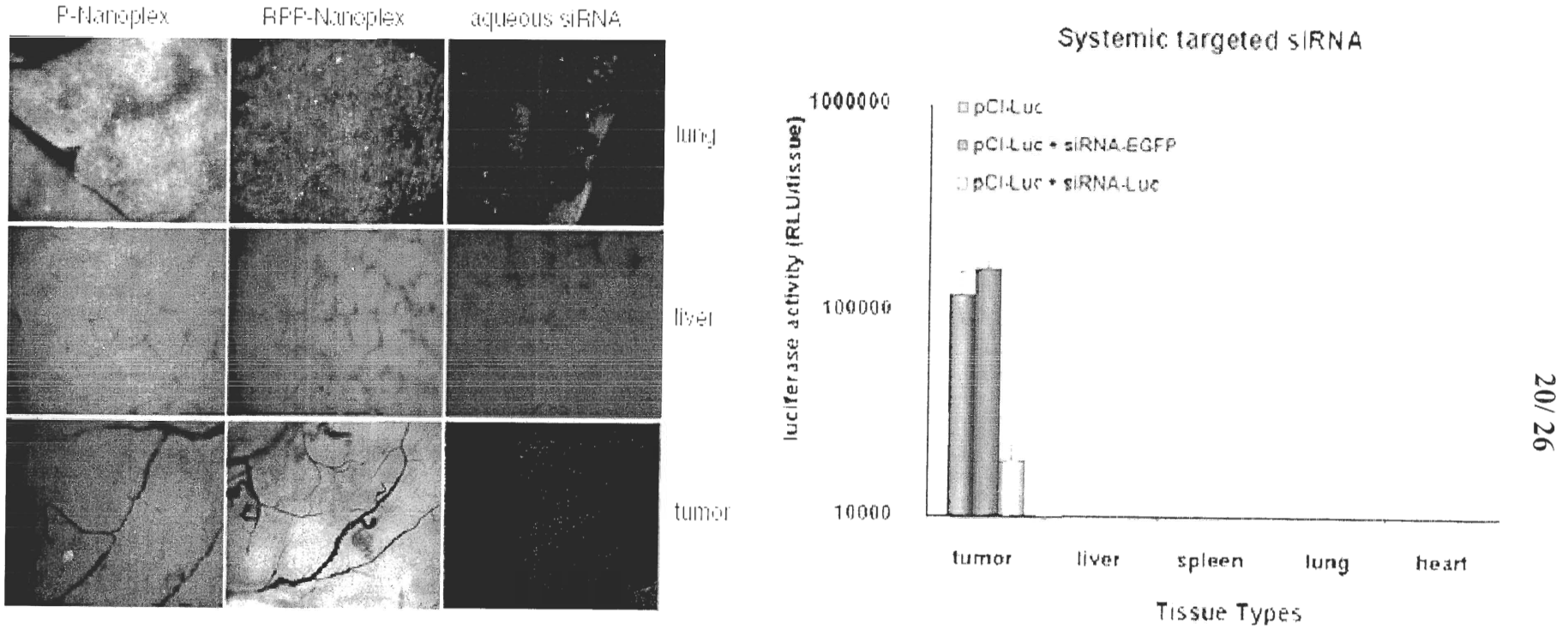


Figure 20. siRNA nanoparticle targeting neovasculature demonstrated tumor targeting property using labeled siRNA payload (left) and plasmid payload expressing Luciferase reporter gene (right).

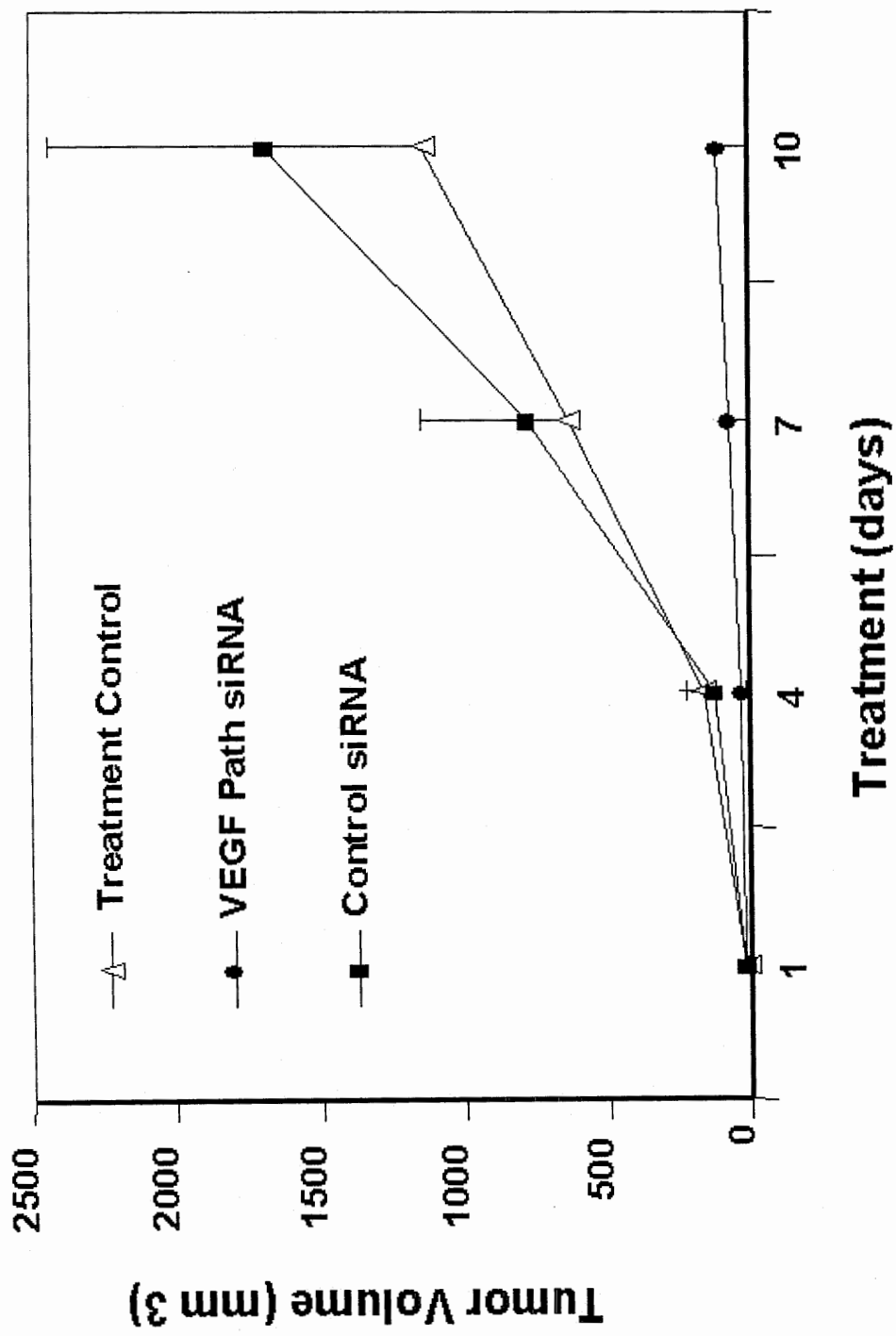


Figure 21. VEGFR2-siRNA nanoparticle targeting neovasculature demonstrated potent efficacy in neuroblastoma syngenic mouse model (N2A tumor) after four repeated administrations every three days.

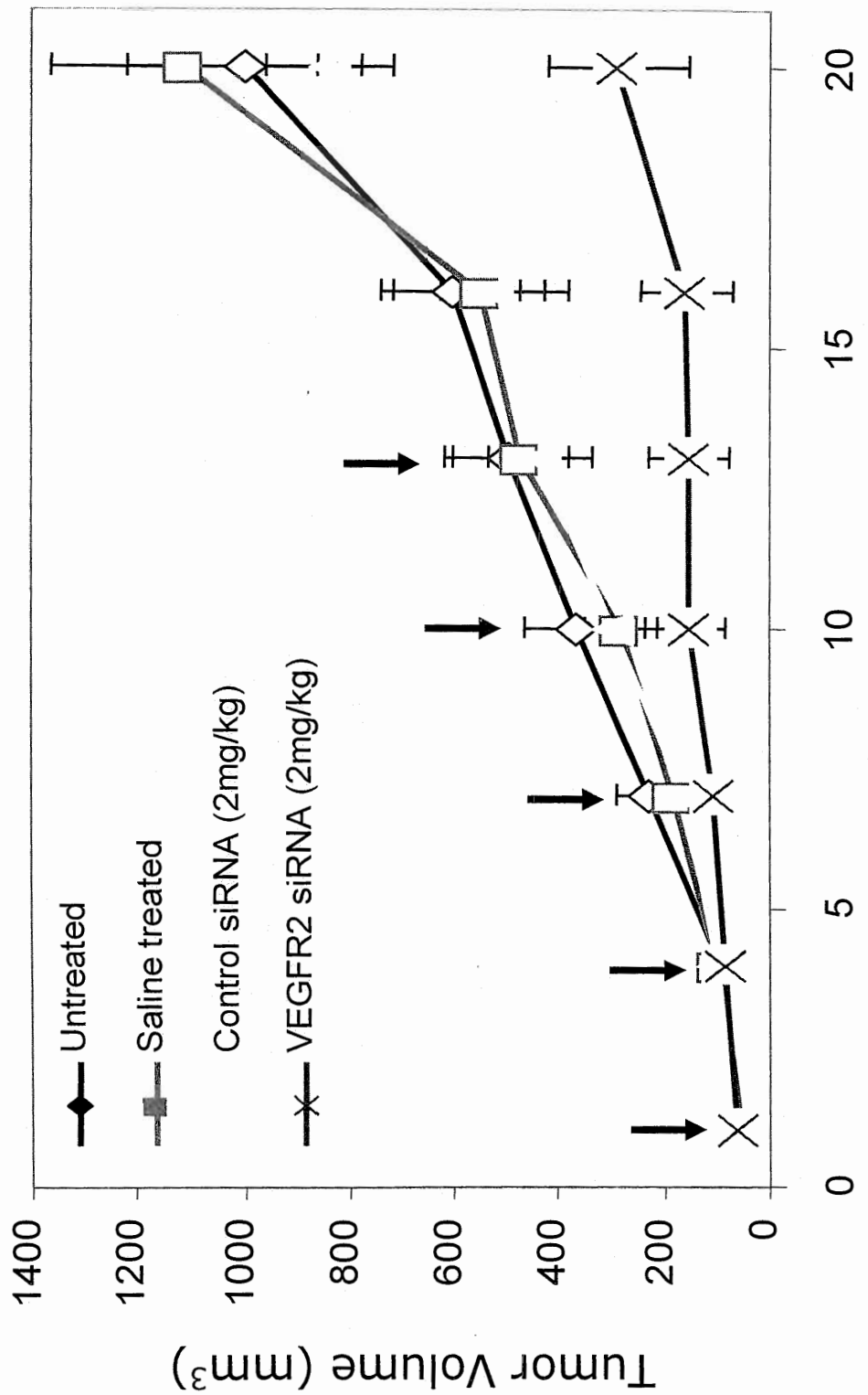


Figure 22. VEGFR2-siRNA nanoparticle targeting neovasculature demonstrated potent efficacy in renal carcinoma xenograft mouse model (786-O tumor) after five repeated administrations every three days.

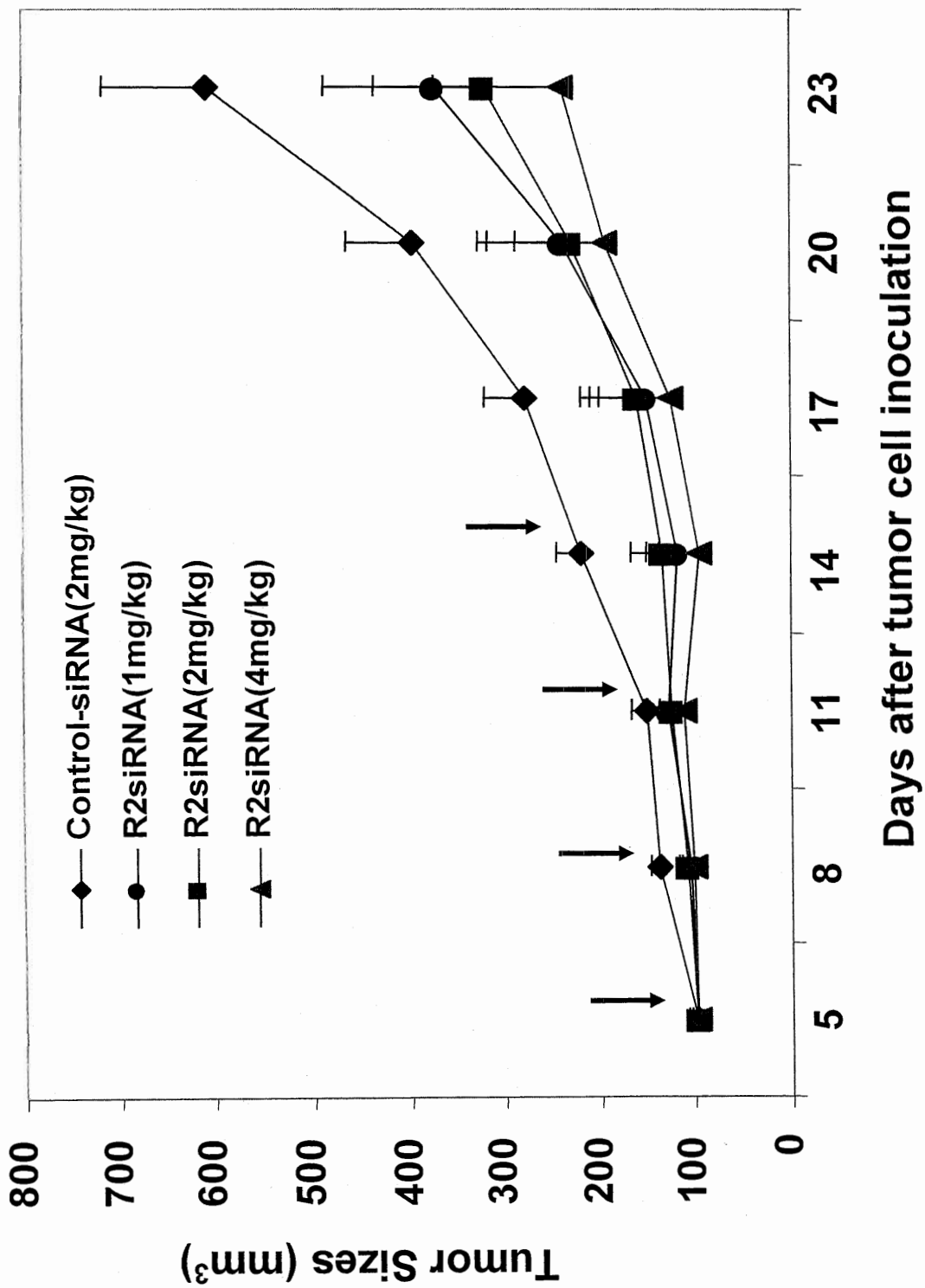


Figure 23. VEGFR2-siRNA nanoparticle targeting neovasculature demonstrated potent efficacy in colon carcinoma xenograft mouse model (DLD-1 tumor) after four repeated administrations every three days. Three different dosages were used in the study.

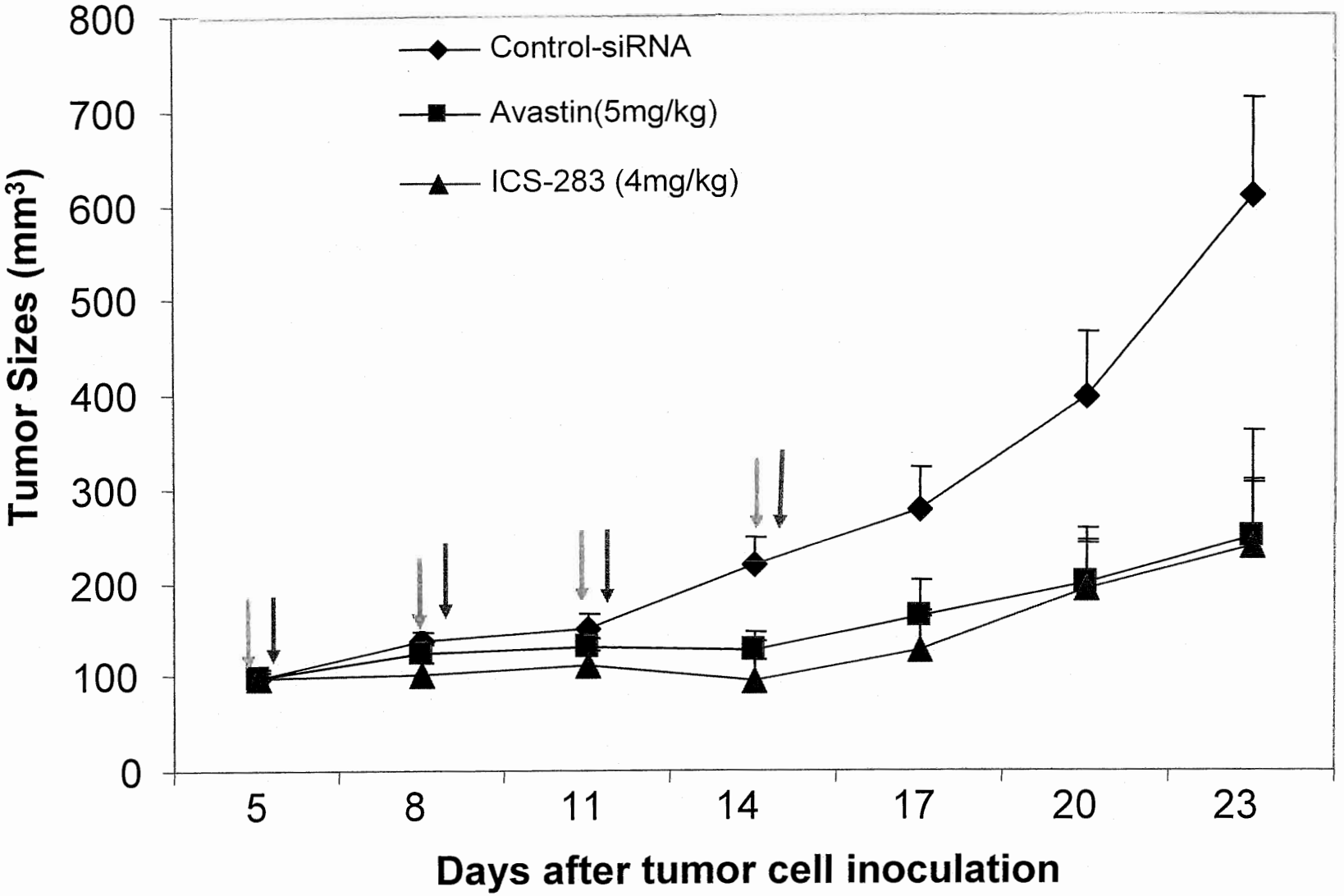


Figure 24. VEGFR2-siRNA nanoparticle targeting neovasculature demonstrated potent efficacy in colon carcinoma xenograft mouse model (DLD-1 tumor) after four repeated administrations every three days. Four mg per kilogram of VEGFR2 dosing resulted in the same anti-tumor efficacy as 5 mg per kilogram of Avastin.

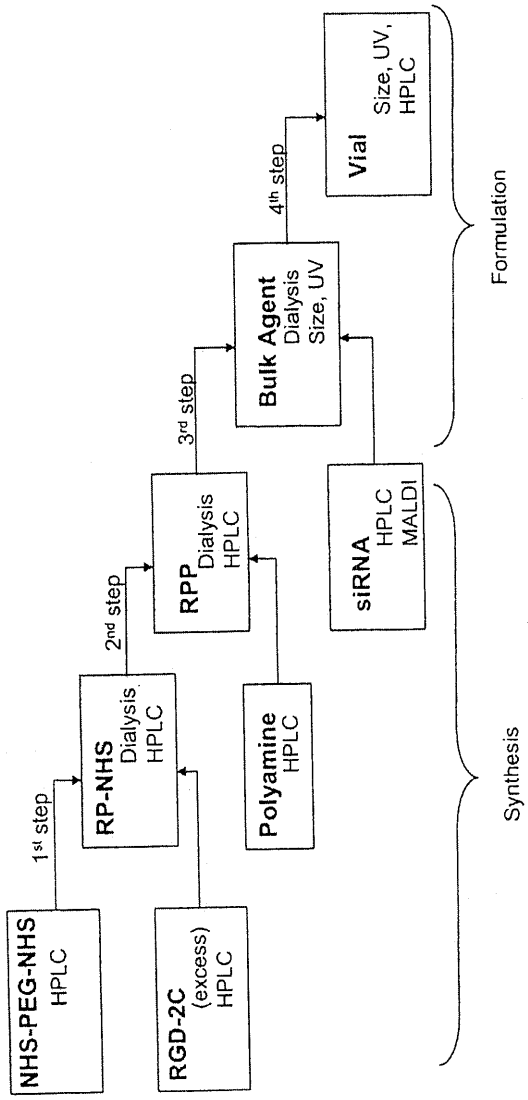


Figure 25. Manufacturing flow chart for production of an RGD-polymer conjugate and a nanoparticle-siRNA preparation starting from raw materials of a homobifunctional activated PEG, an RGD-2C peptide, a polyamine containing agent, and a mixture of dsRNA.

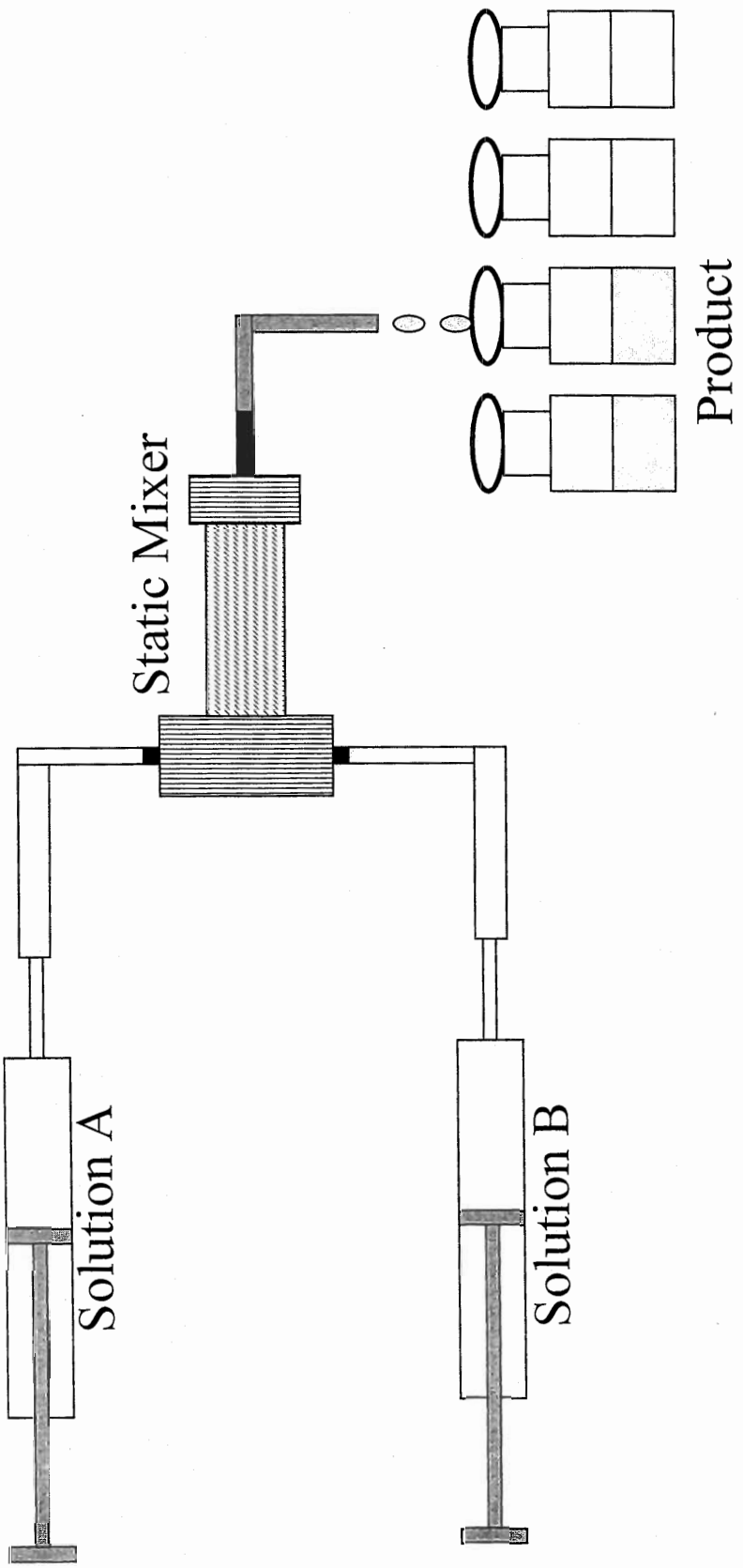


Figure 26. The use of a static mixer to manufacture a nanoparticle-siRNA preparation starting from two solutions, a polymer solution comprising polymer conjugates and an siRNA solution comprising three dsRNA agents.