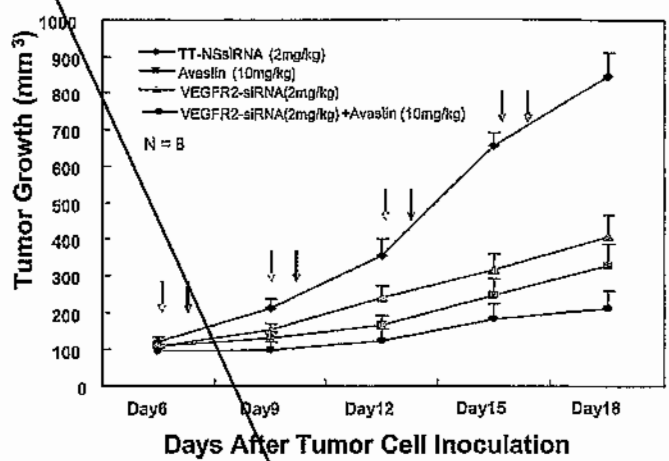


Figure 1. Stronger anti-tumor efficacy has been observed using a combination cancer therapeutics with VEGFR2-siRNA inhibitor and Avastin (Bevacizumab) in the same treatment regimen, in a human colon carcinoma (DLD-1) xenograft tumor model.

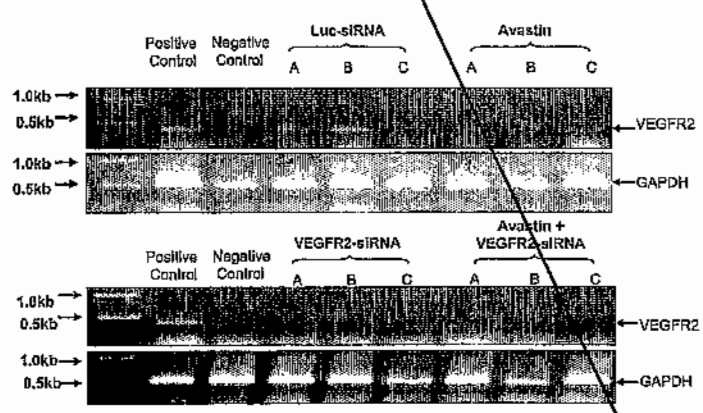


Figure 2. VEGFR2-siRNA nanoparticle targeting neovasculature through systemic delivery demonstrated potent efficacy in colon carcinoma xenograft mouse model (DLD-1 tumor) after four repeated administrations every three days. RT-PCR results illustrate the knockdown of VEGFR2 gene expression at mRNA level.

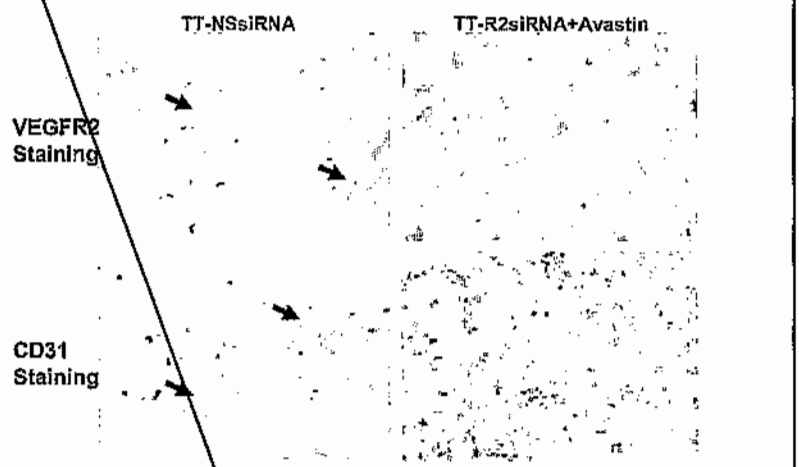


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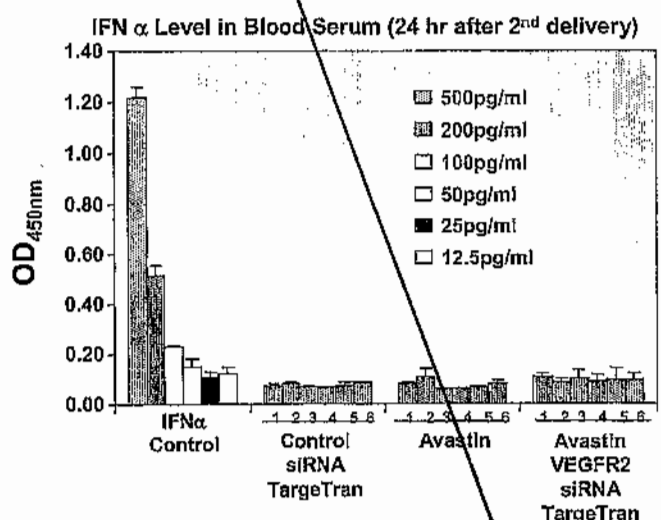


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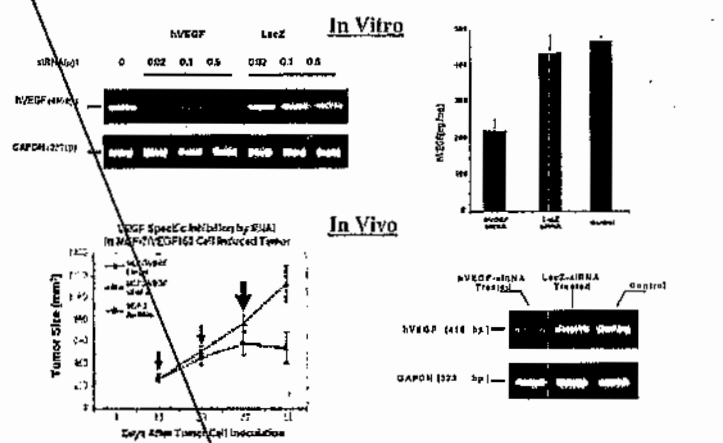


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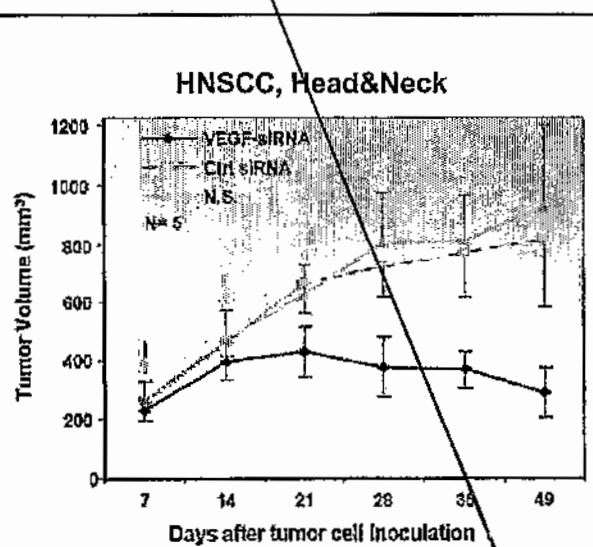


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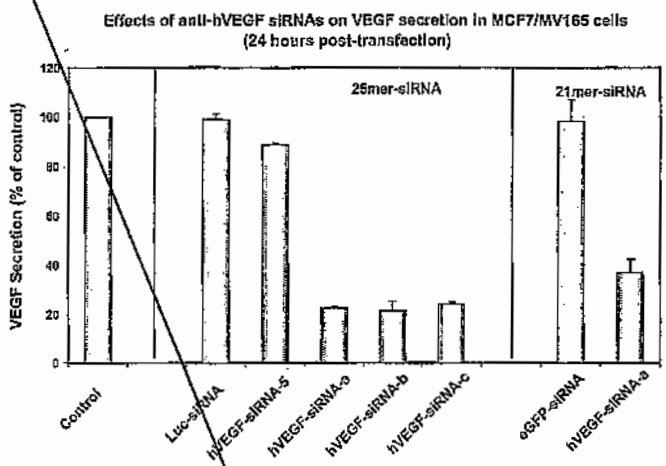


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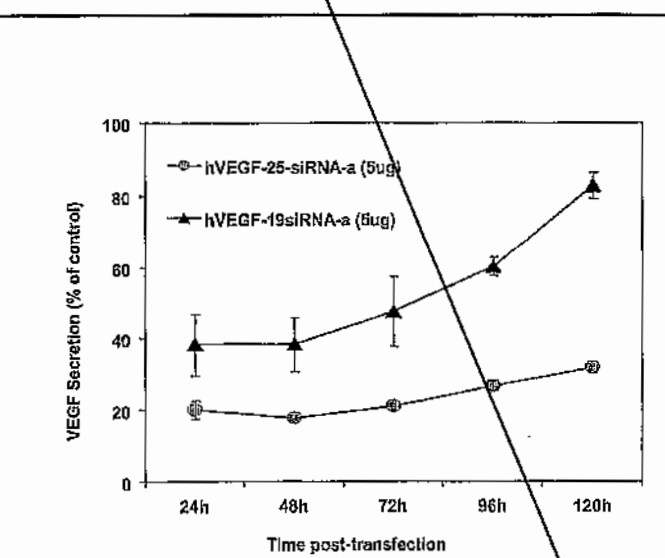


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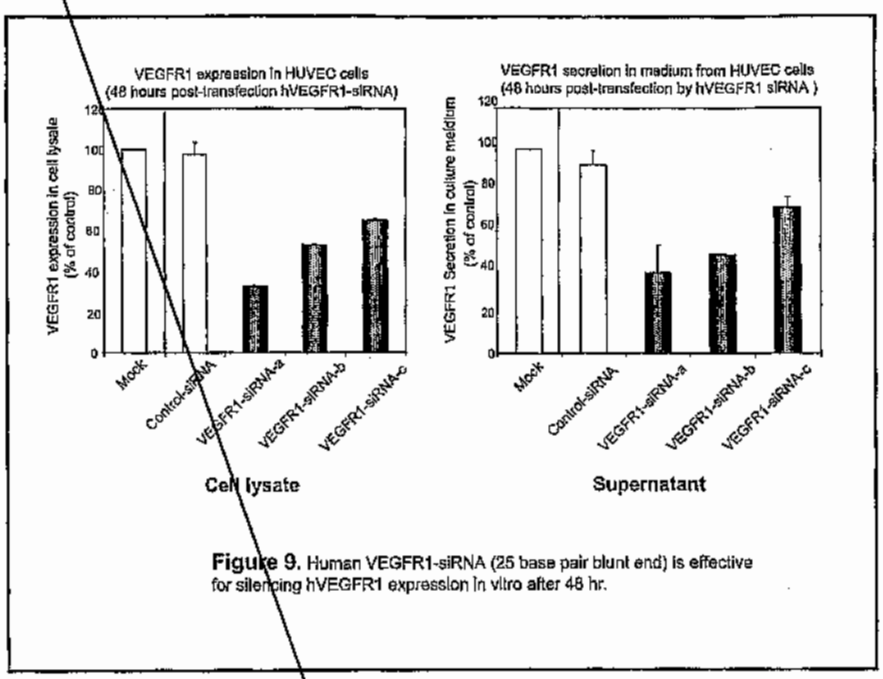


Figure 9. Human VEGFR1-siRNA (25 base pair blunt end) is effective for silencing hVEGFR1 expression in vitro after 48 hr.

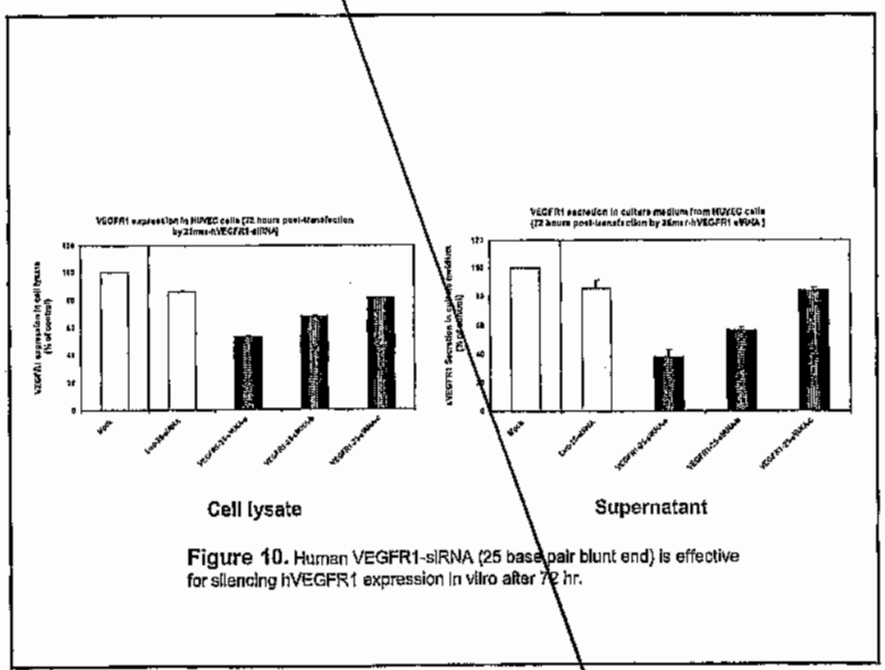


Figure 10. Human VEGFR1-siRNA (25 base pair blunt end) is effective for silencing hVEGFR1 expression in vitro after 72 hr.

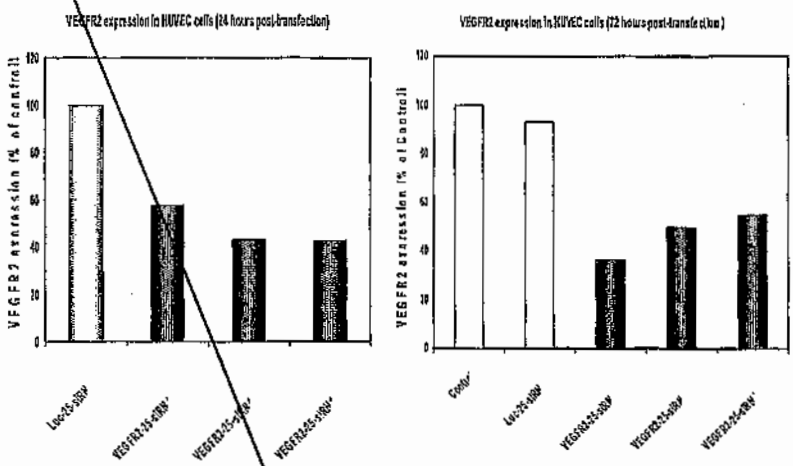


Figure 11. Human VEGFR2-siRNA (25 base pair blunt end) is effective for silencing hVEGFR2 expression in vitro at two different time points.

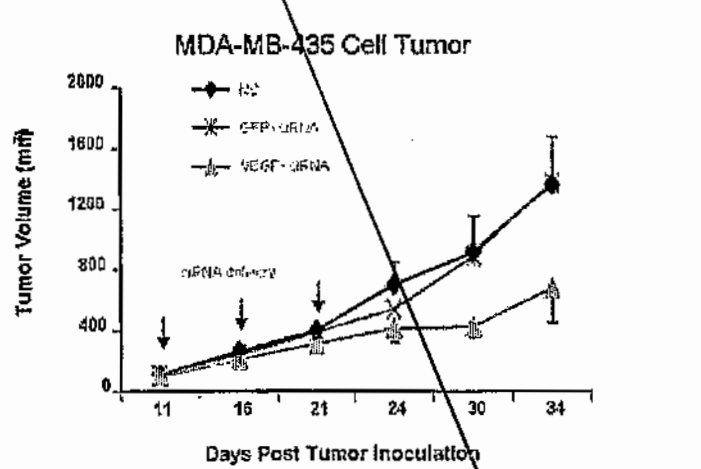


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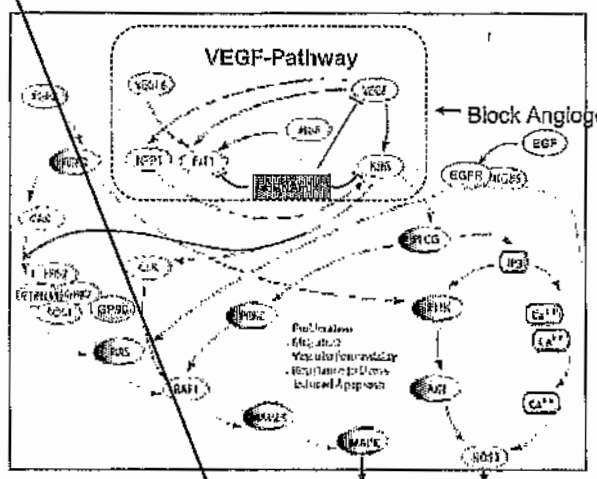


Figure 13. Concept framework for using siRNA cocktail targeting VEGF, VEGFR1 and VEGFR2 in the same treatment to block the angiogenesis pathway.

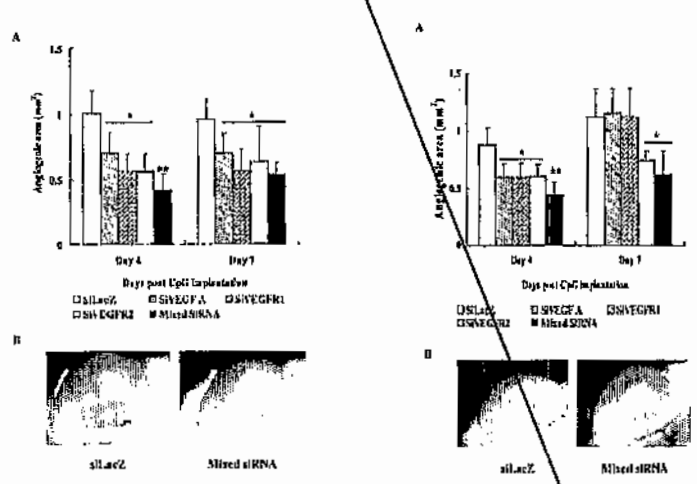


Figure 16. siRNA cocktail targeting VEGF, VEGFR1 and VEGFR2 is more effective than any single siRNA targeting individual gene at the same dosage tested in the HSV induced ocular angiogenesis mouse model, with either local (left) or systemic (right) deliveries.

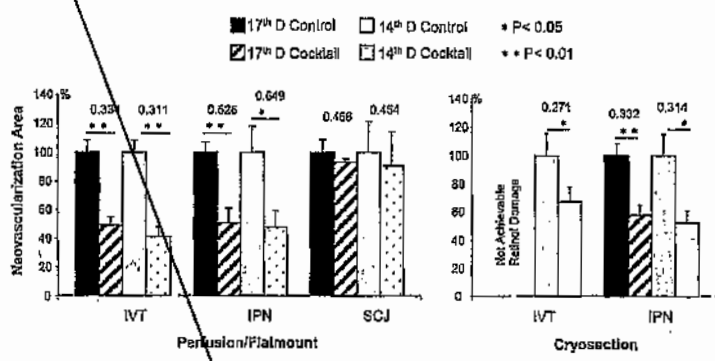


Figure 19. Inhibition of angiogenesis by administration of VEGF pathway siRNA cocktail on day 17 or day 14 after induction of disease in ocular tissues of a murine model of retinal angiogenesis in a perfusion/flatmount measurement.

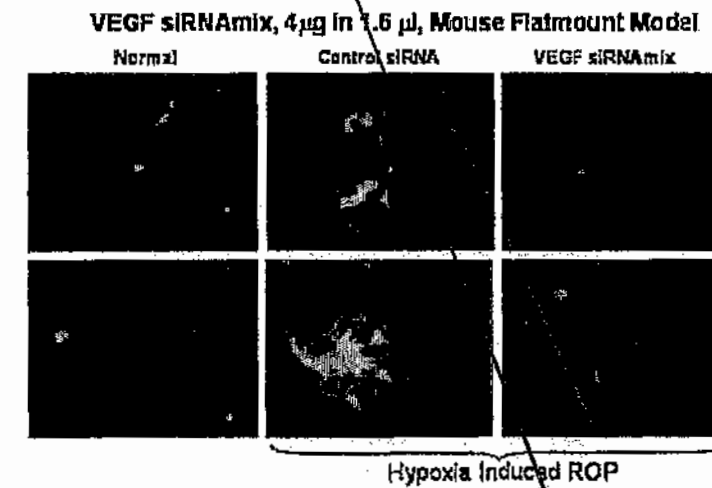


Figure 20. siRNA cocktail targeting VEGF, VEGFR1 and VEGFR2 demonstrates very effective anti-angiogenesis activity in the retinopathy of prematural (ROP) mouse model induced by Hypoxia.

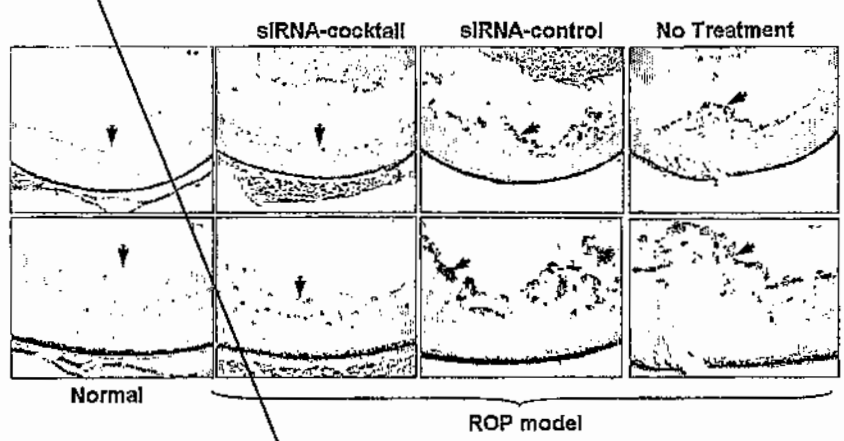


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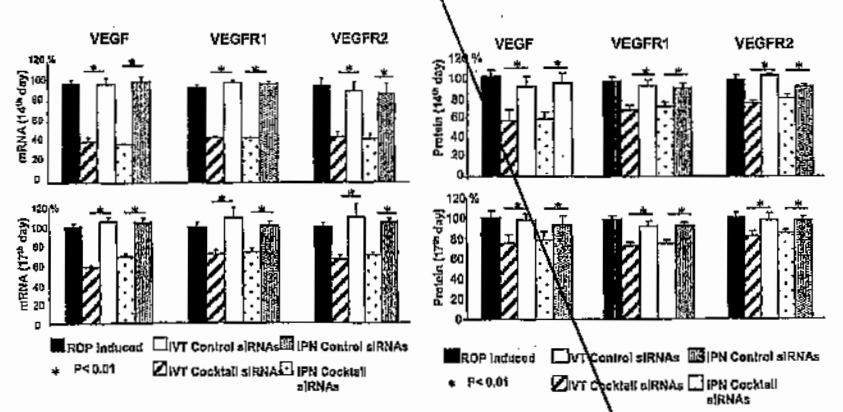


Figure 22. siRNA cocktail targeting VEGF, VEGFR1 and VEGFR2 inhibits ocular angiogenesis significantly with different routes of administration with different carriers. IP delivery was mediated by a ligand-directed nanoparticle. siRNA Cocktail Mediated Knockdowns of VEGF Pathway Factors RT-PCR Detection of mRNA Levels with ROP Model

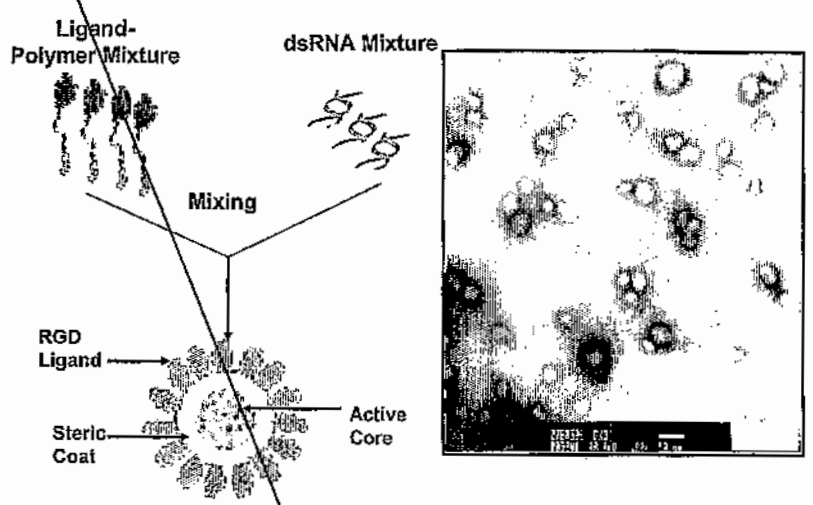


Figure 23. Self-assembled nanoparticle for siRNA delivery. When the pre-made RGD-PEG-PEI conjugate mixture is mixed with the siRNA mixture, the nanoparticles will be self-assembled with a relatively homogenous size.

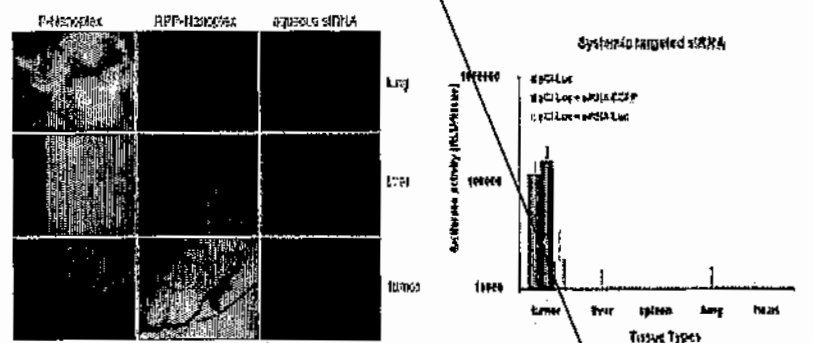


Figure 24. siRNA nanoparticle targeting neovasculature demonstrated tumor targeting properly using labeled siRNA payload (left) and plasmid payload expressing Luciferase reporter gene (right).

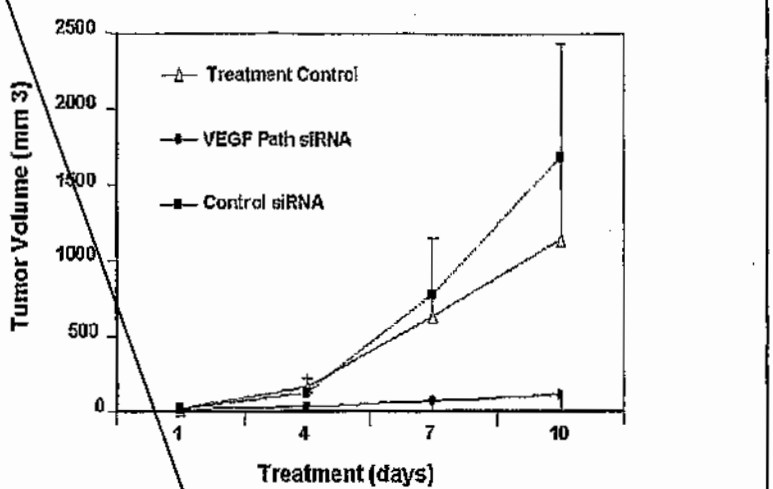


Figure 25. VEGFR2-siRNA nanoparticle targeting neovasculature demonstrated potent efficacy in neuroblastoma syngenic mouse model (N2A tumor) after four repeated administrations every three days.

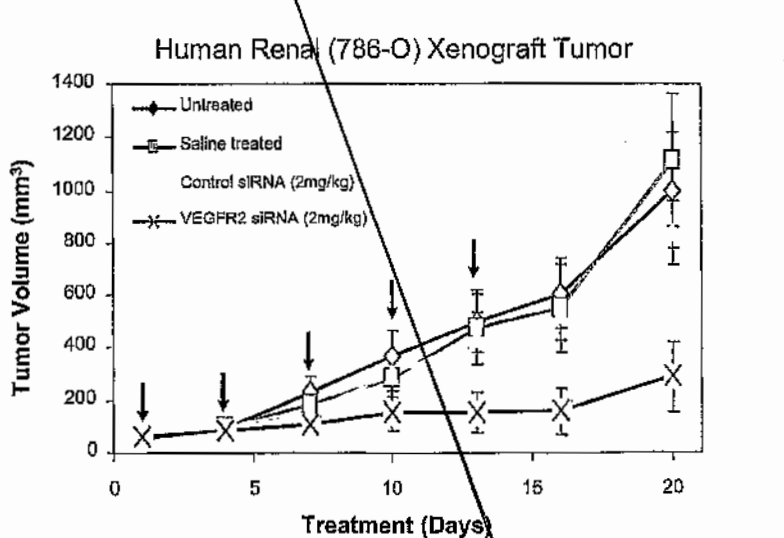


Figure 26. VEGFR2-siRNA nanoparticle targeting neovasculature demonstrated potent efficacy in renal carcinoma xenograft mouse model (786-O tumor) after five repeated administrations every three days.

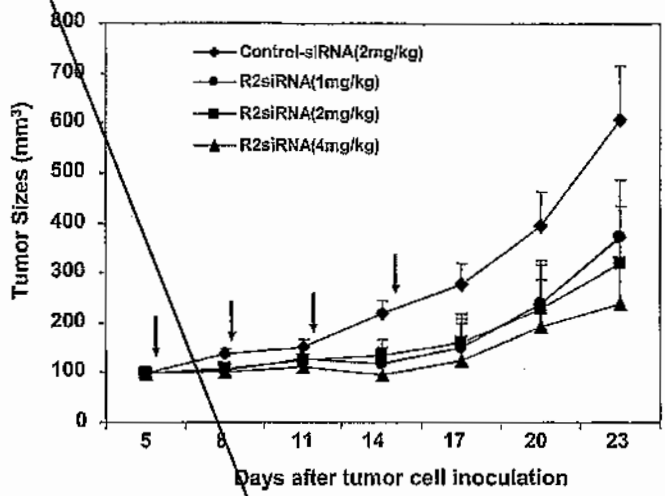


Figure 27. VEGFR2-siRNA nanoparticle targeting neovasculature demonstrated potent efficacy in colon carcinoma xenograft mouse model (DLD-1 tumor) after four repeated administrations every three days. Three different dosages were used in the study.

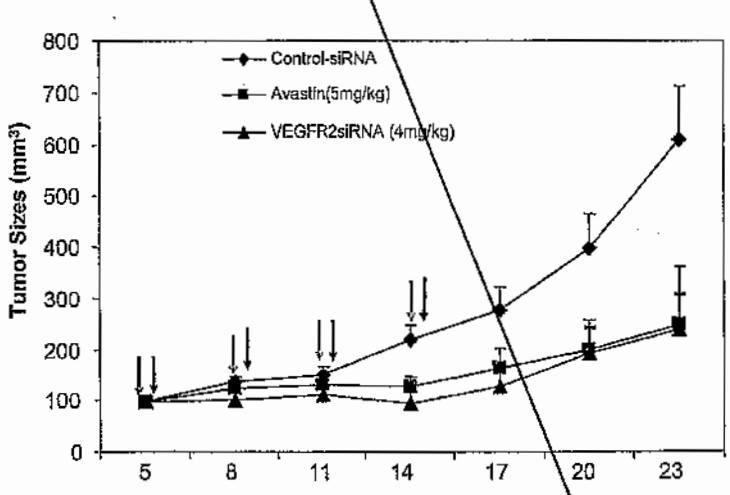


Figure 28. VEGFR2-siRNA nanoparticle targeting neovasculature demonstrated potent efficacy in colon carcinoma xenograft mouse model (DLD-1 tumor) after four repeated administrations every three days. Four mg per kilo of VEGFR2 dosing resulted in the same anti-tumor efficacy as 5 mg per kilo.

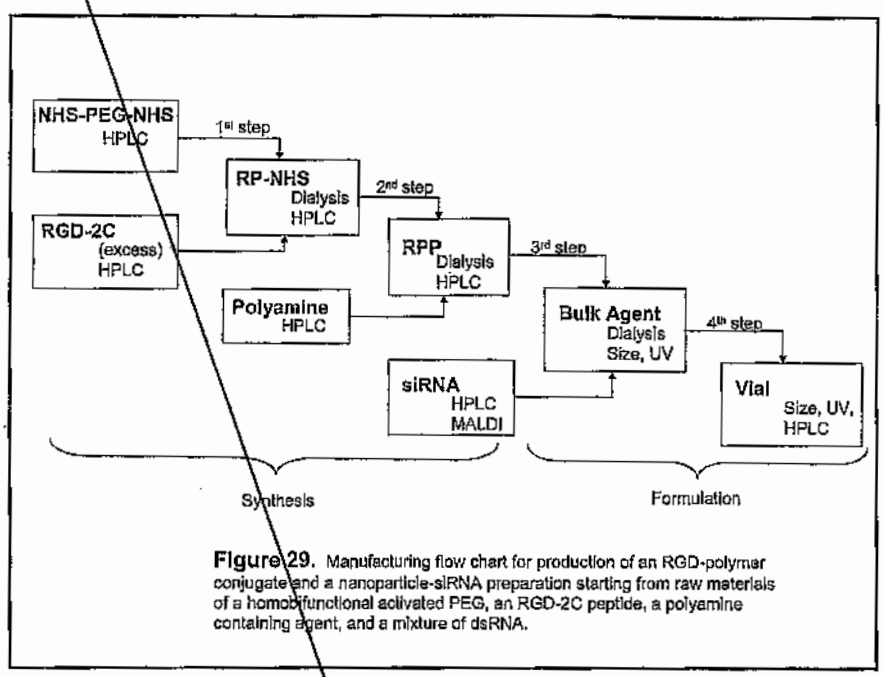


Figure 29. Manufacturing flow chart for production of an RGD-polymer conjugate and a nanoparticle-siRNA preparation starting from raw materials of a homobifunctional activated PEG, an RGD-2C peptide, a polyamine containing agent, and a mixture of dsRNA.

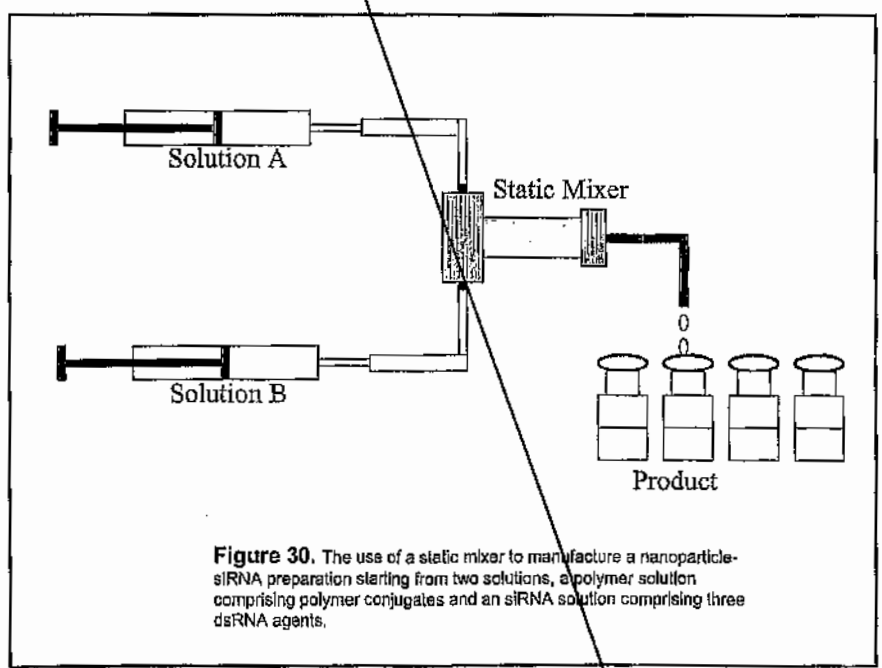


Figure 30. The use of a static mixer to manufacture a nanoparticle-siRNA preparation starting from two solutions, a polymer solution comprising polymer conjugates and an siRNA solution comprising three dsRNA agents.

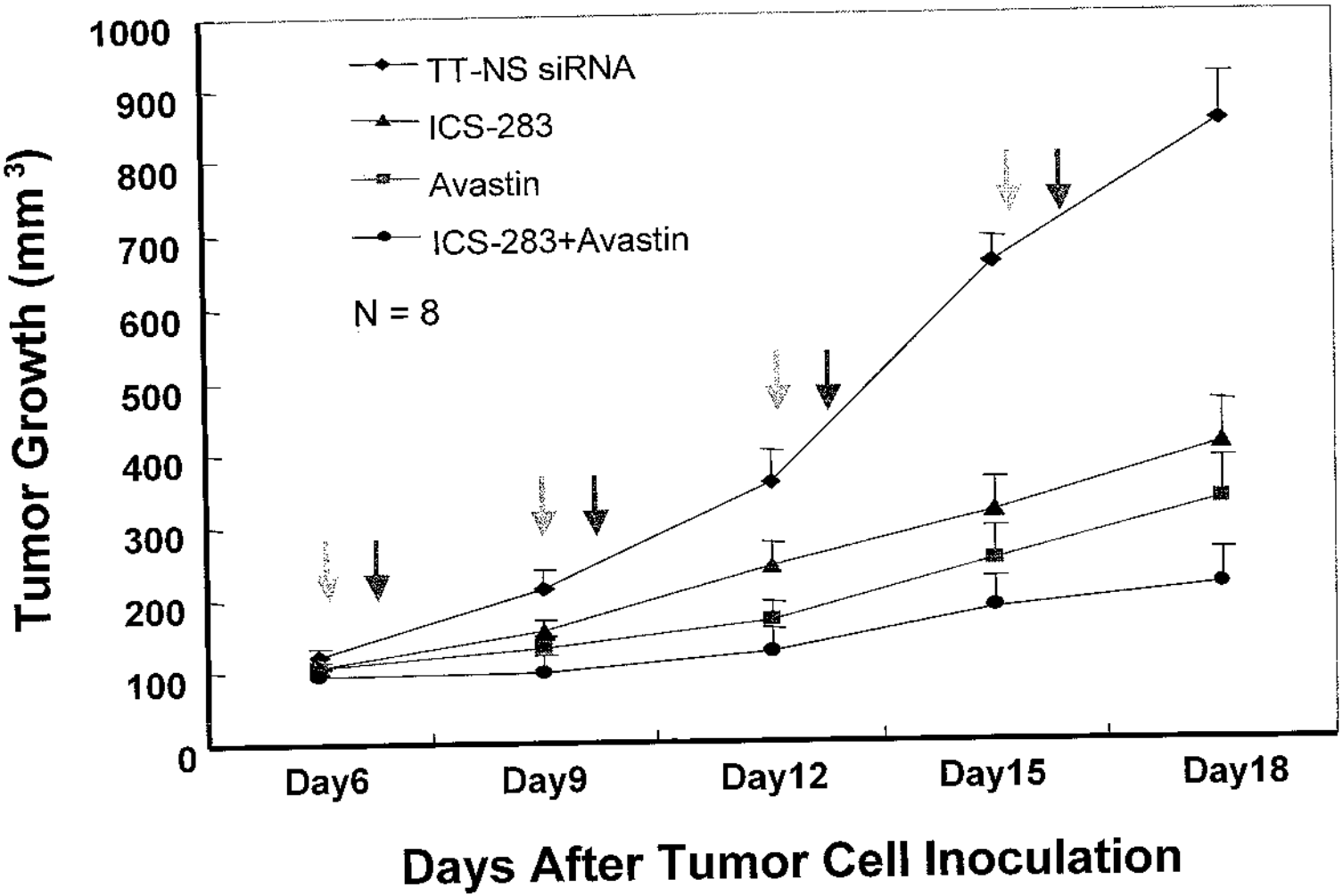


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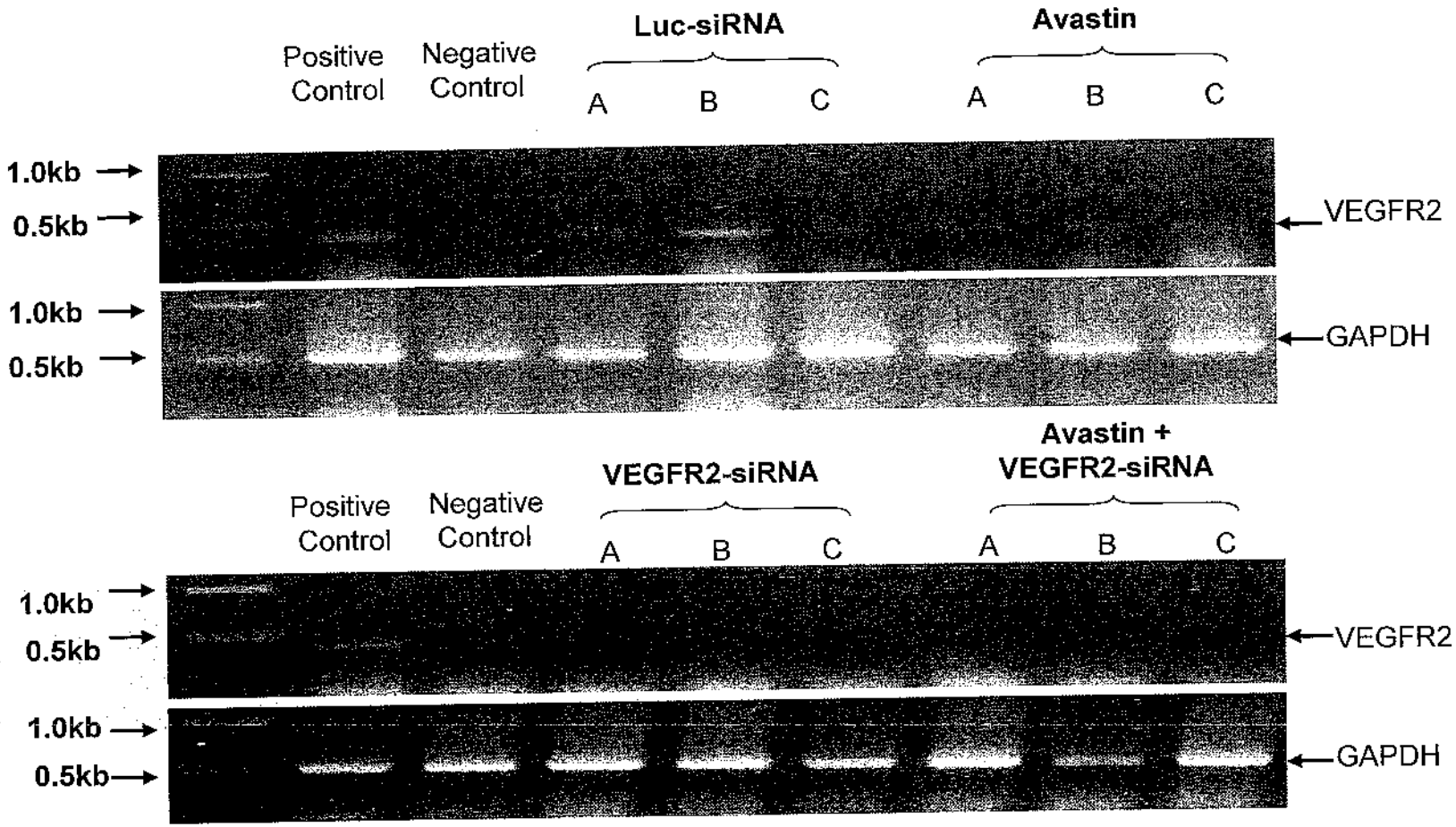


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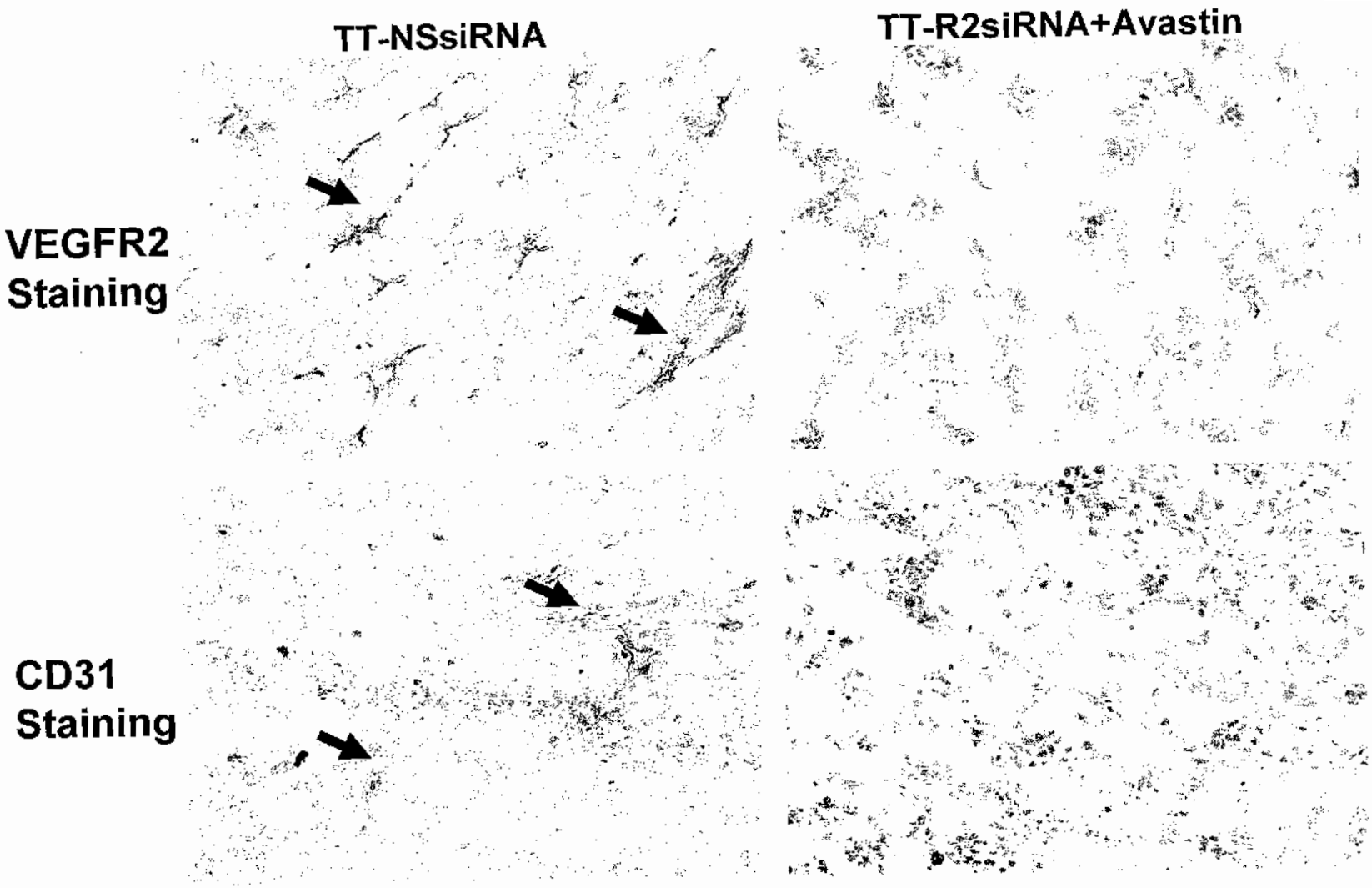


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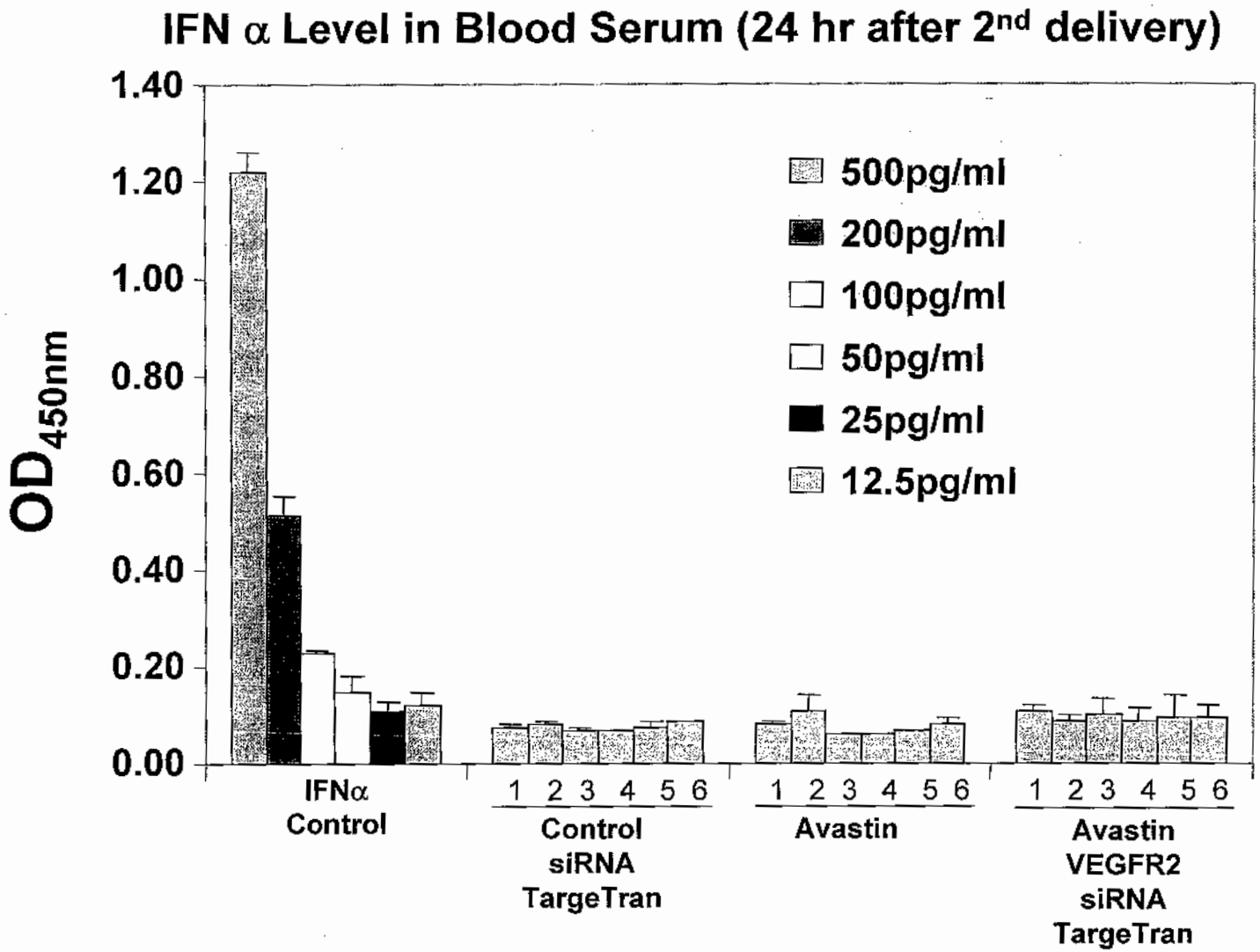


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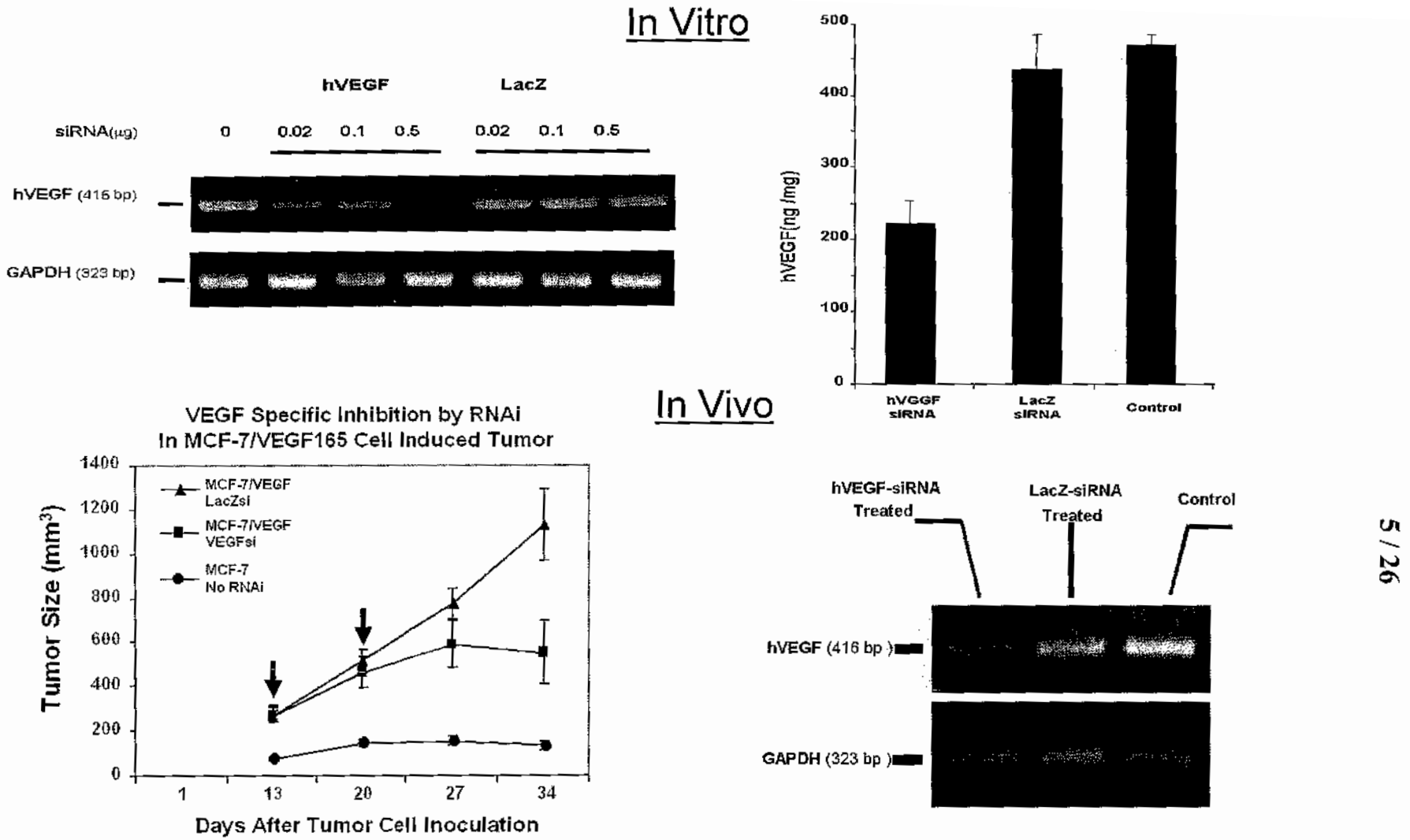


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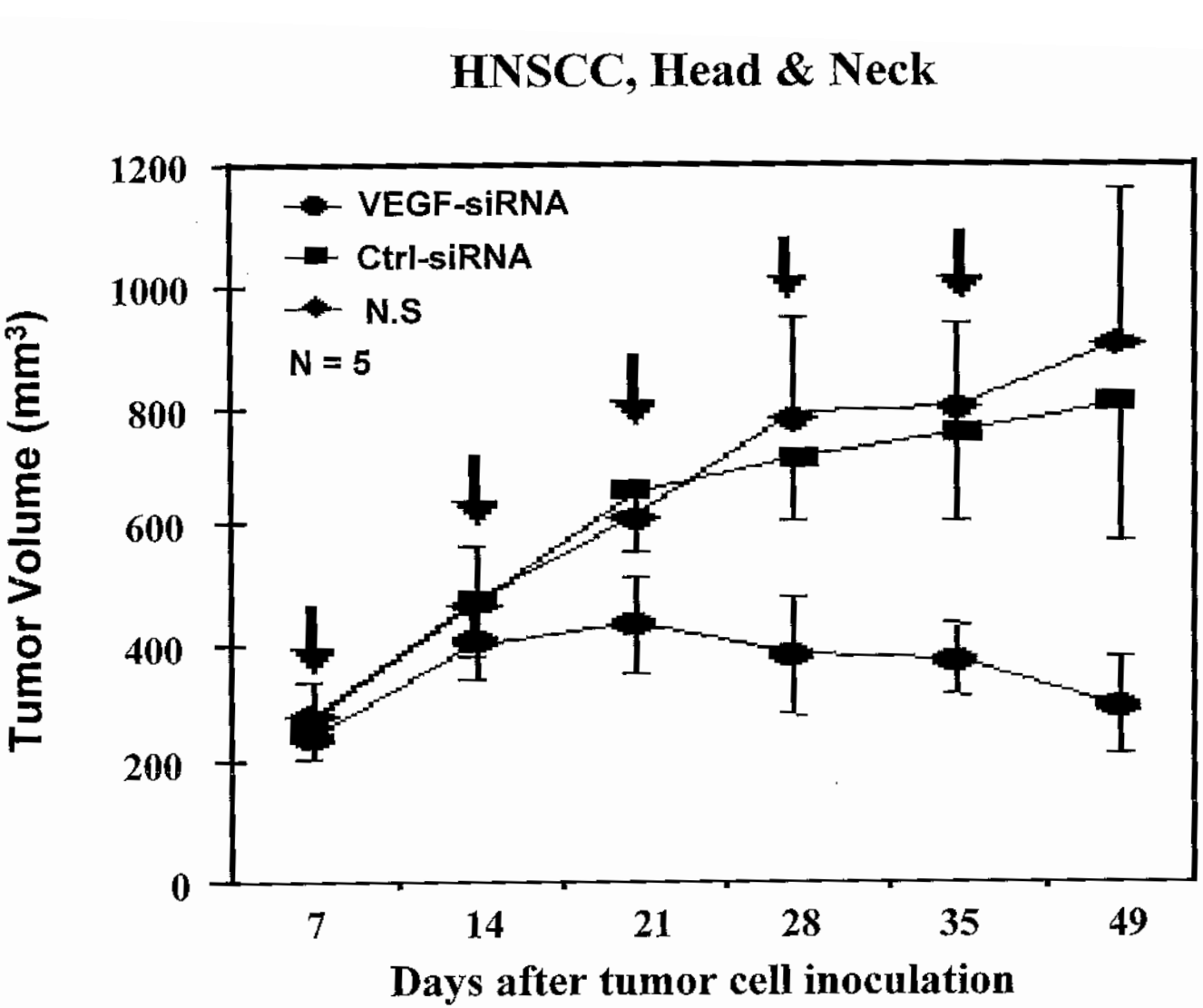


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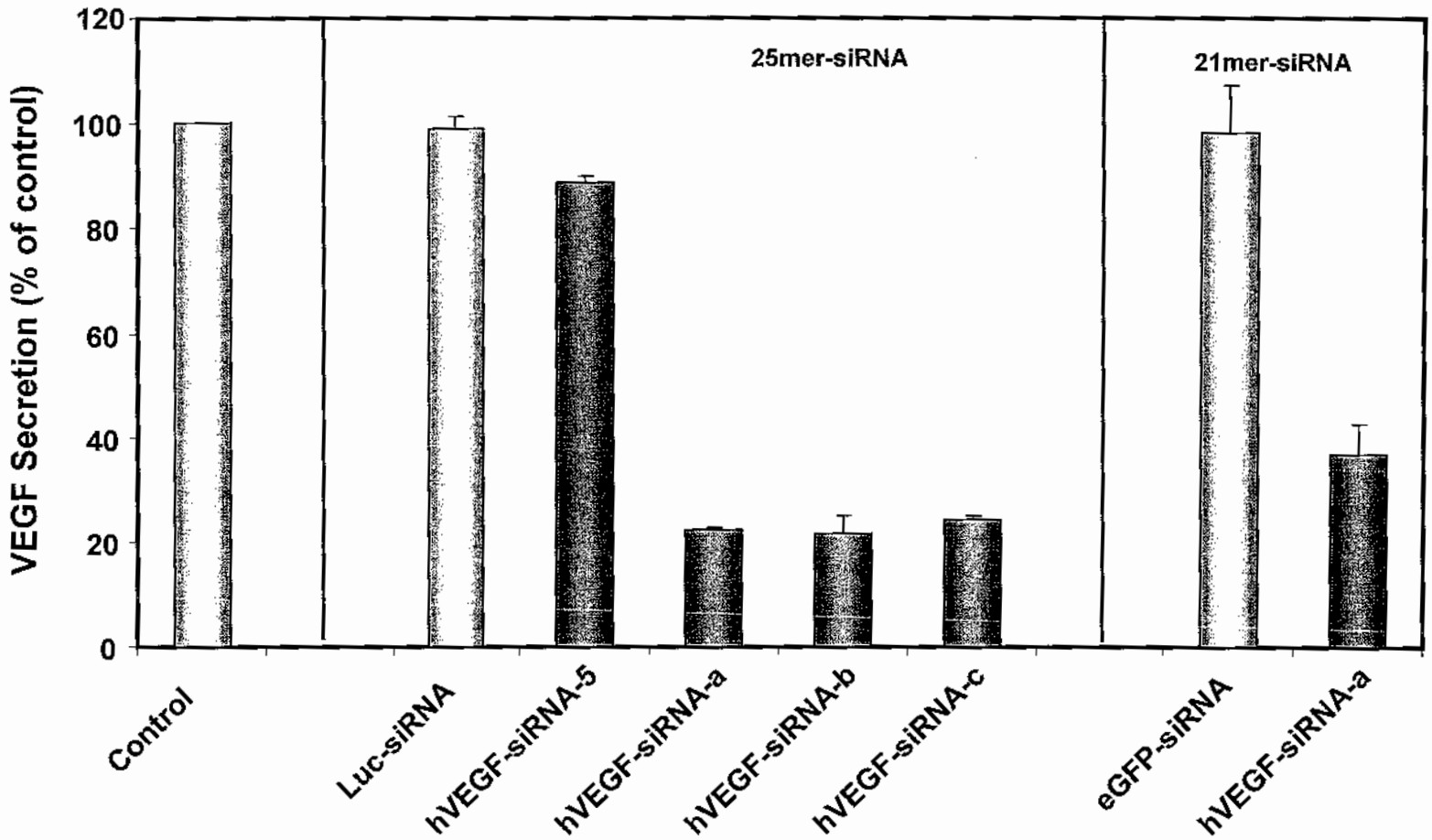


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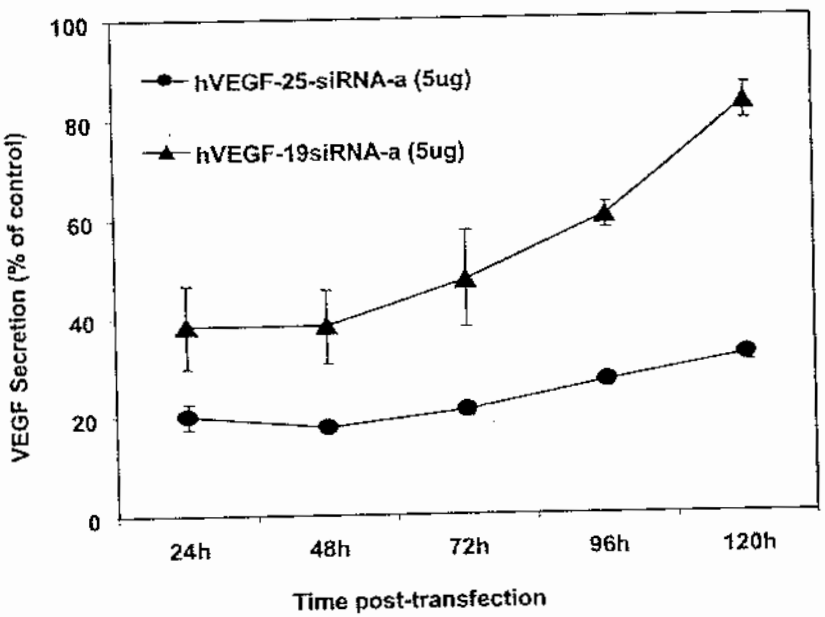
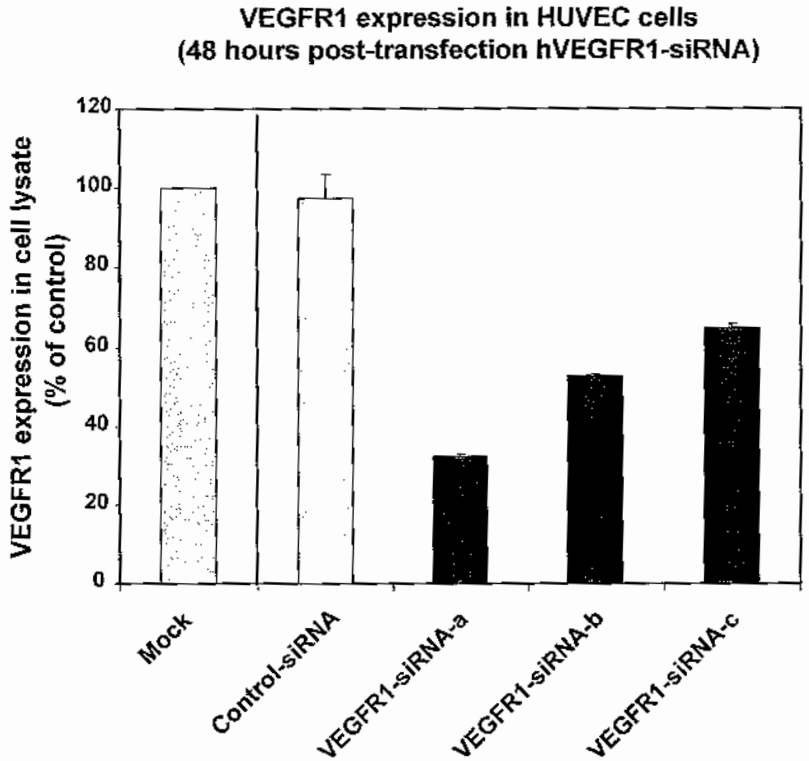
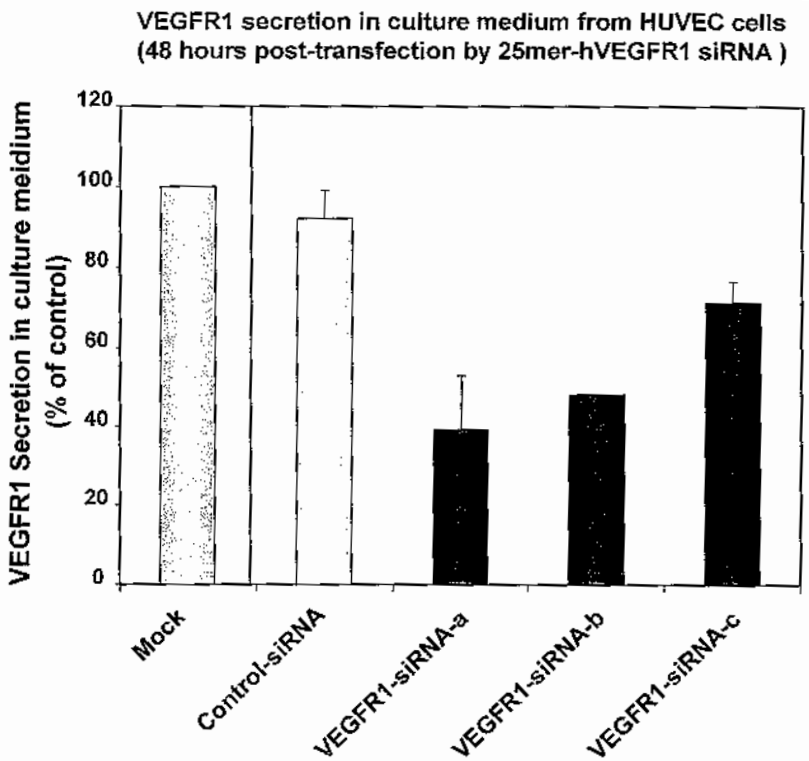


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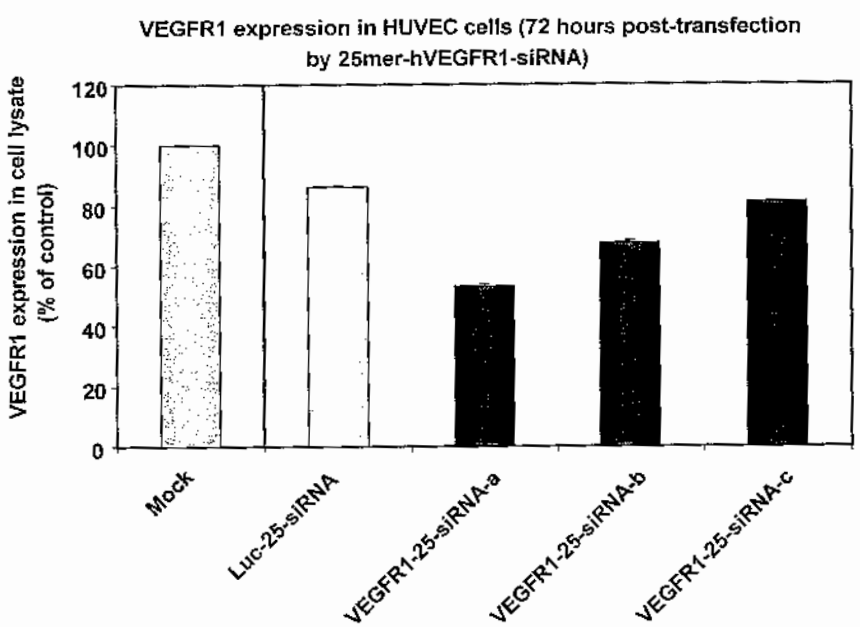


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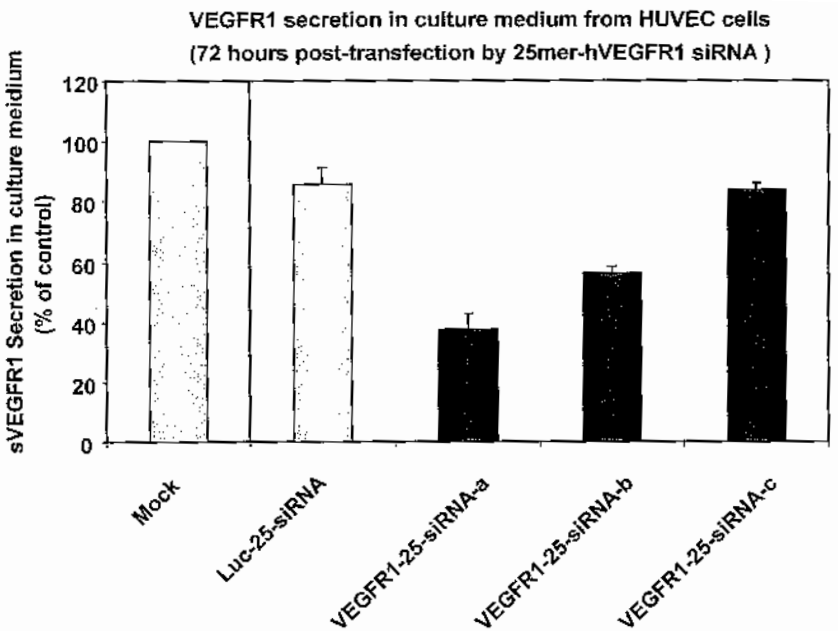


Supernatant

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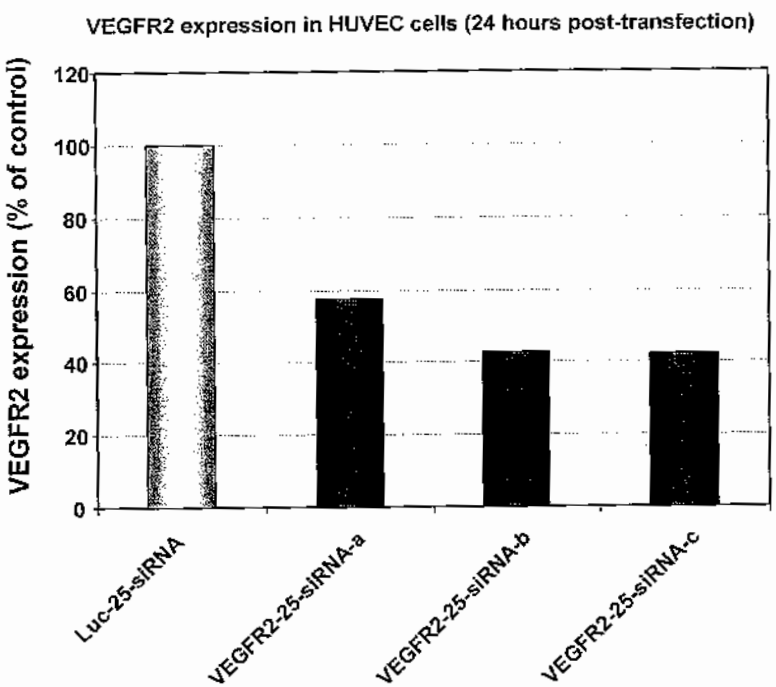


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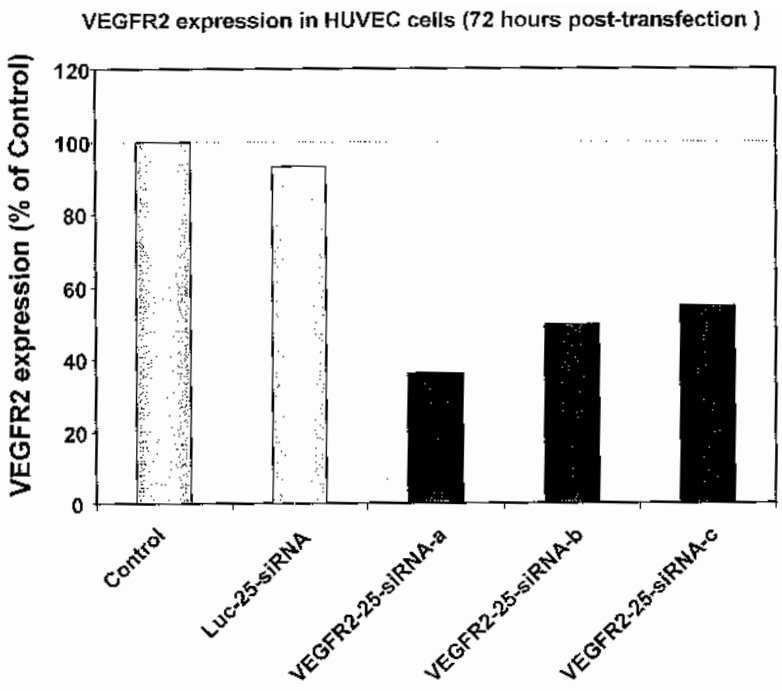


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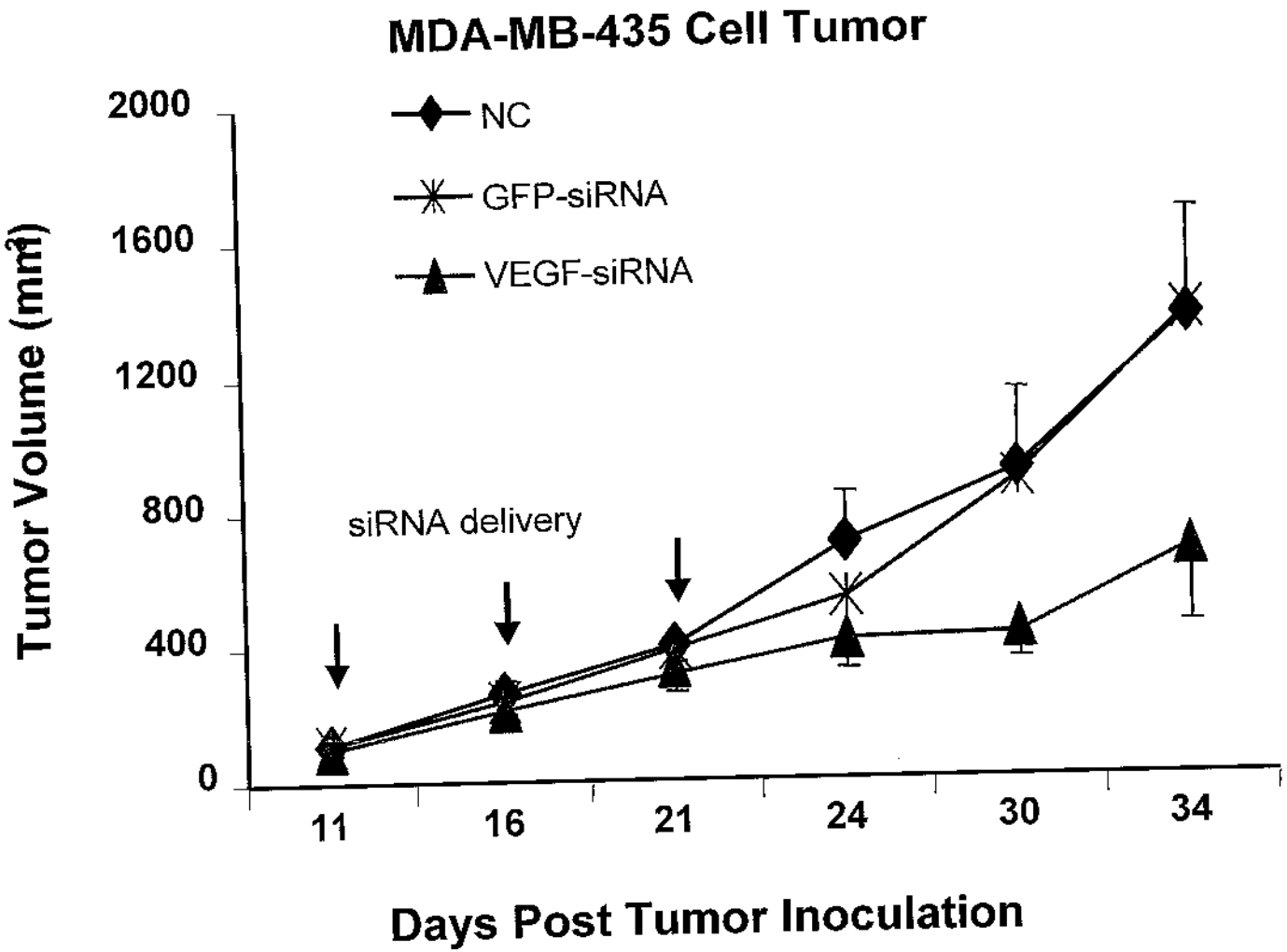


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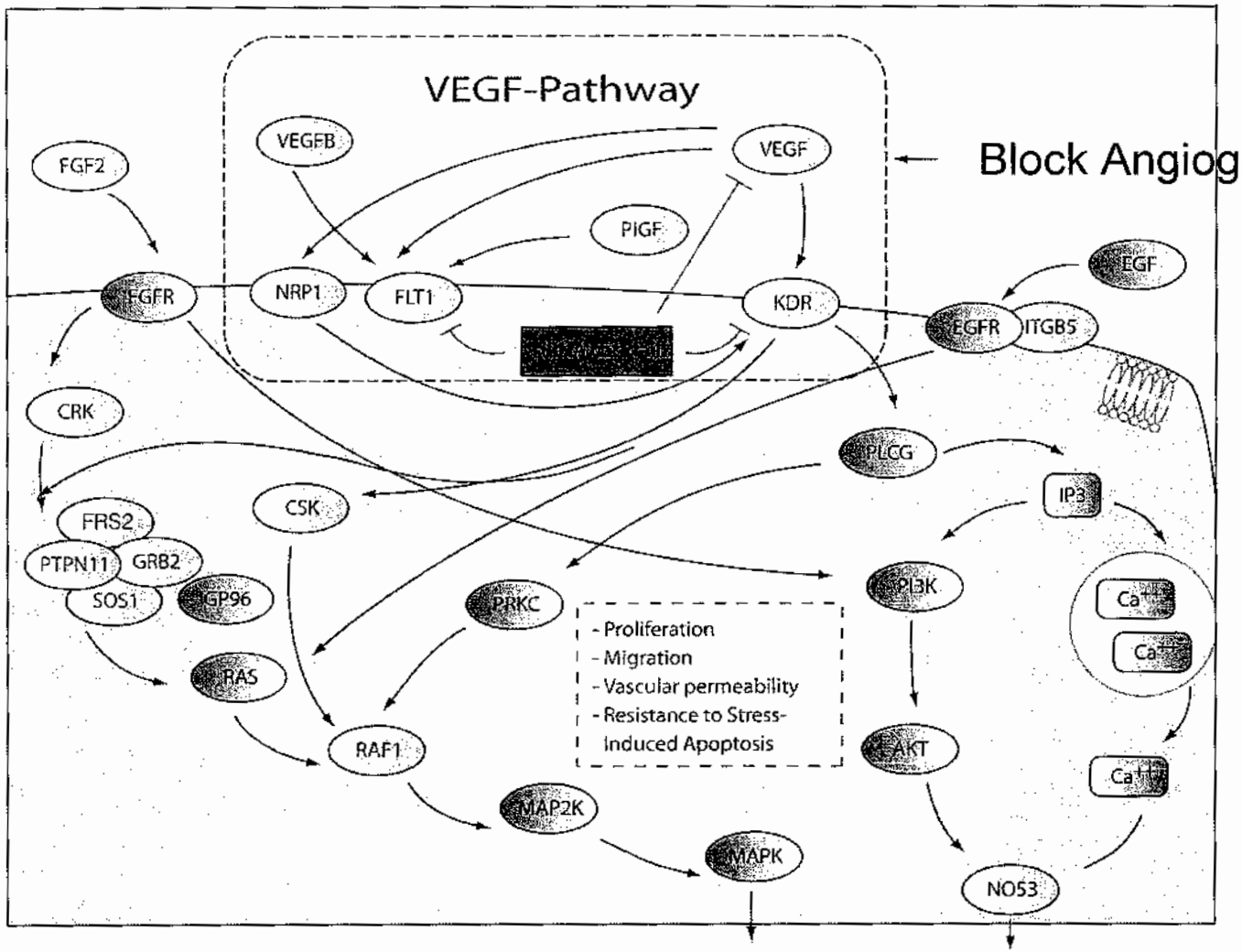


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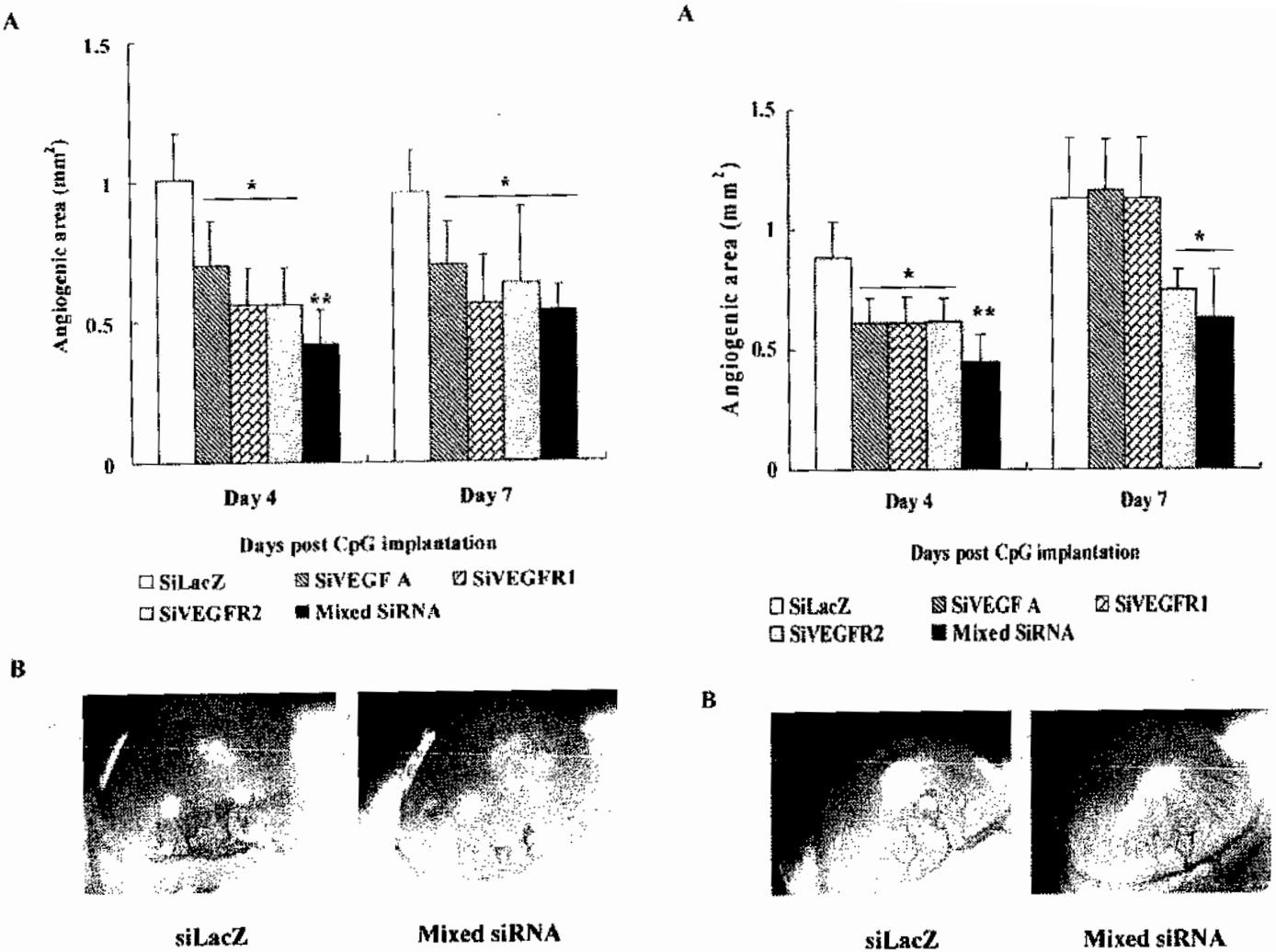


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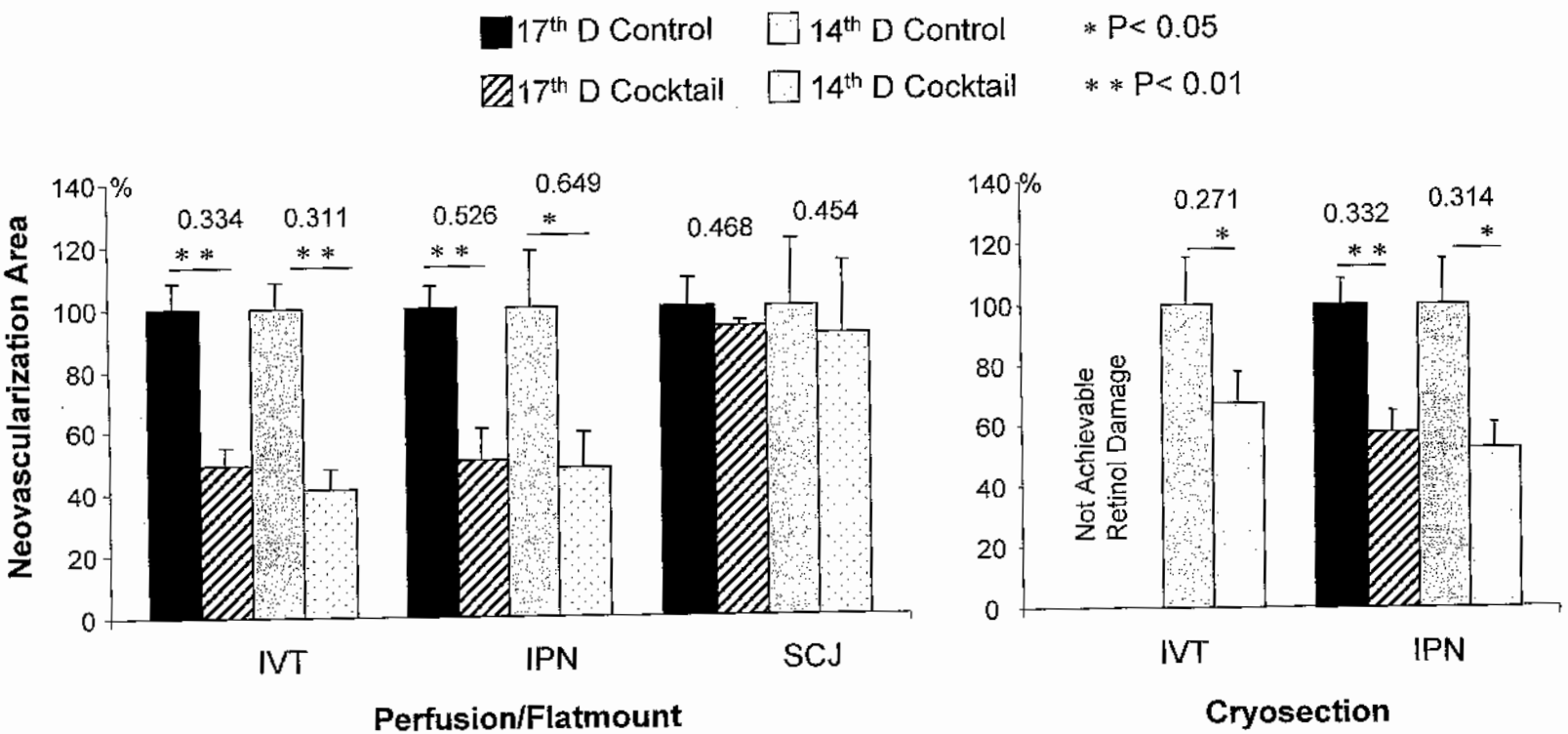


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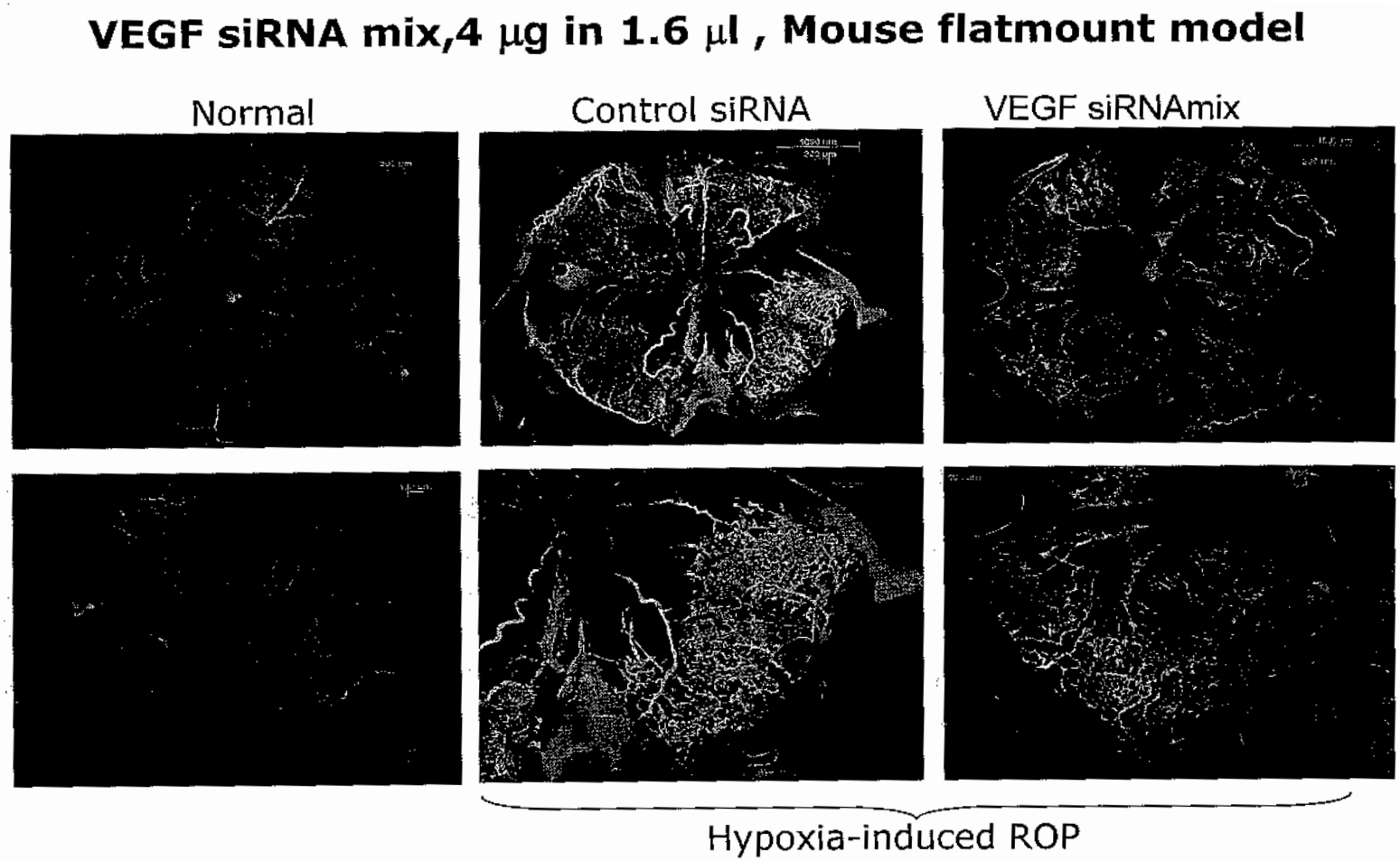


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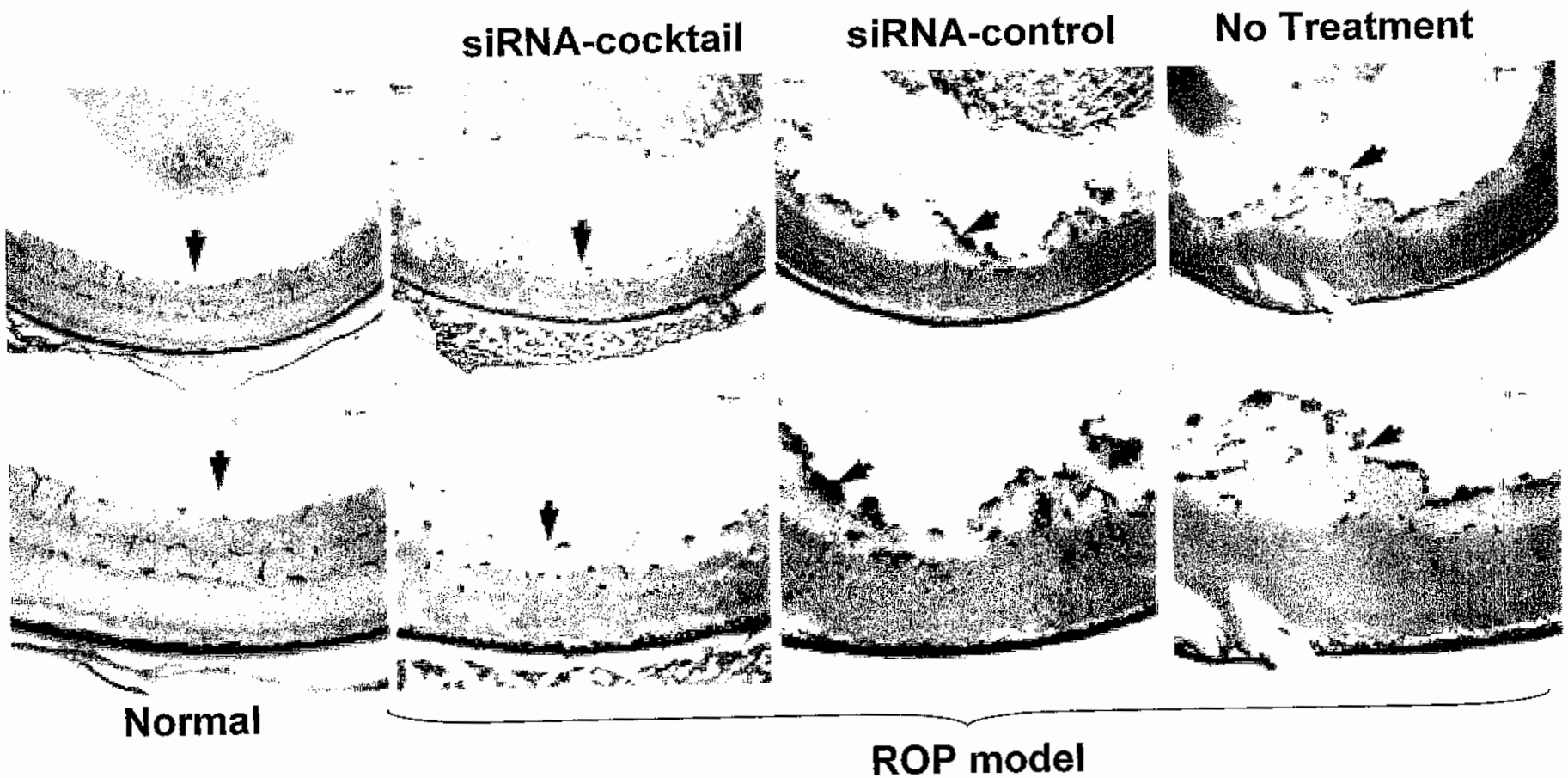


Figure 17. siRNA cocktail targeting VEGF, VEGFR1 and VEGFR2 demonstrates very effective anti-angiogenesis activity in the retinopathy of prematural (ROP) mouse model induced by Hypoxia.

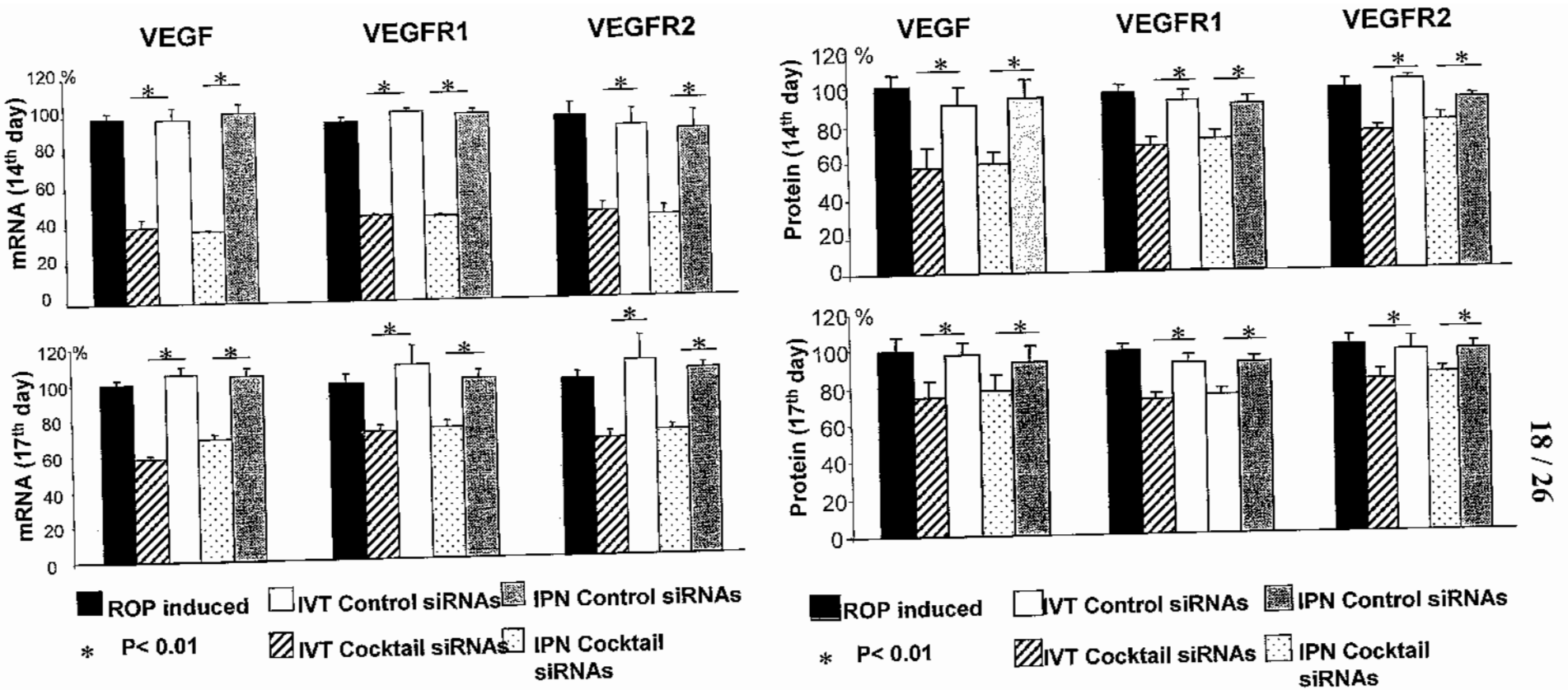


Figure 18. siRNA cocktail targeting VEGF, VEGFR1 and VEGFR2 inhibits ocular angiogenesis significantly with different routes of administration with different carriers. IP delivery was mediated by a ligand-directed nanoparticle. siRNA Cocktail Mediated Knockdown of VEGF PathwayFactors RT-PCR Detection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

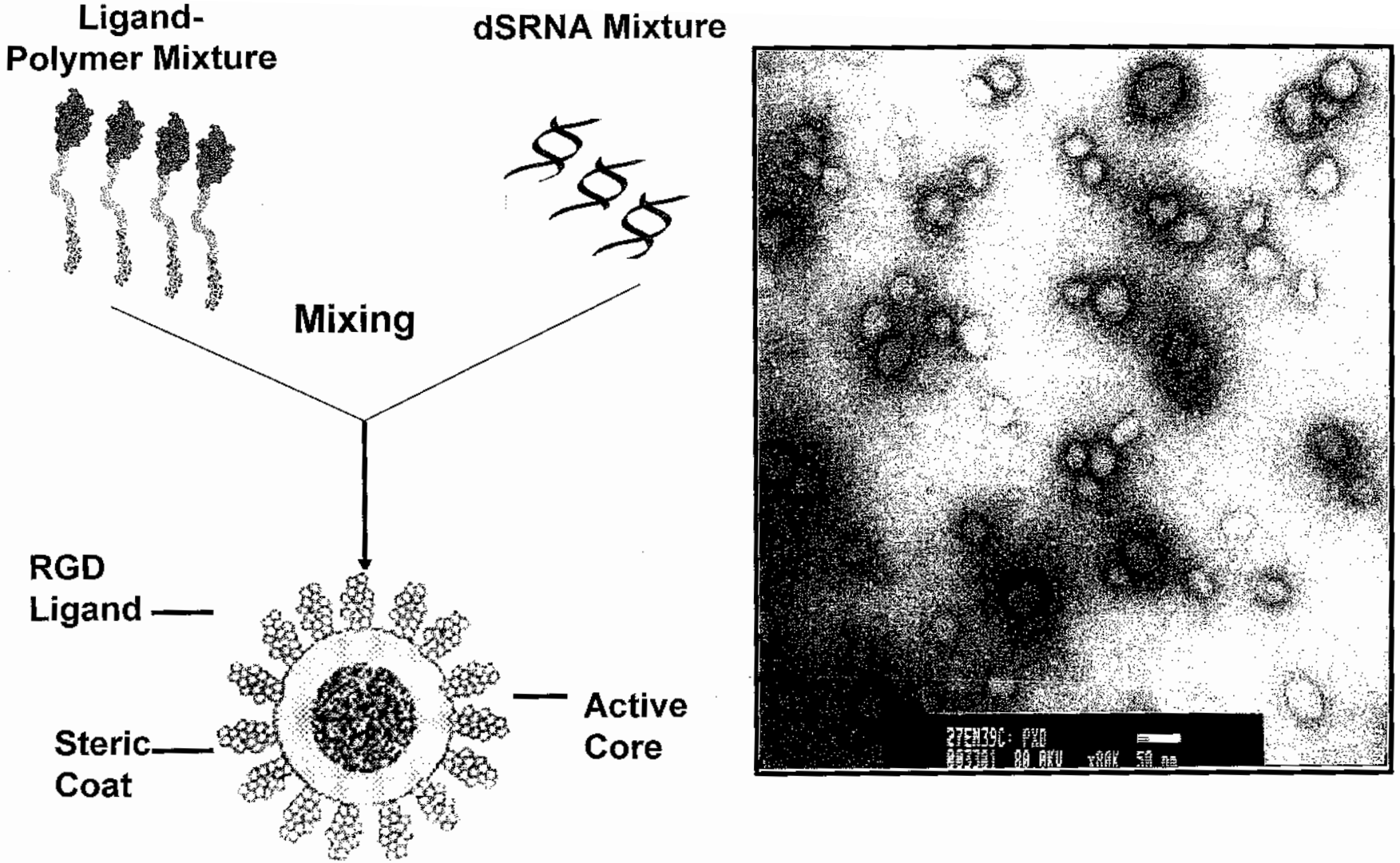


Figure 19. Self-assembled nanoparticle for siRNA delivery. When the pre-made RGD-PEG-PEI conjugate mixture is mixed with the siRNA mixture, the nanoparticles will be self-assembled with a relatively homogenous size.

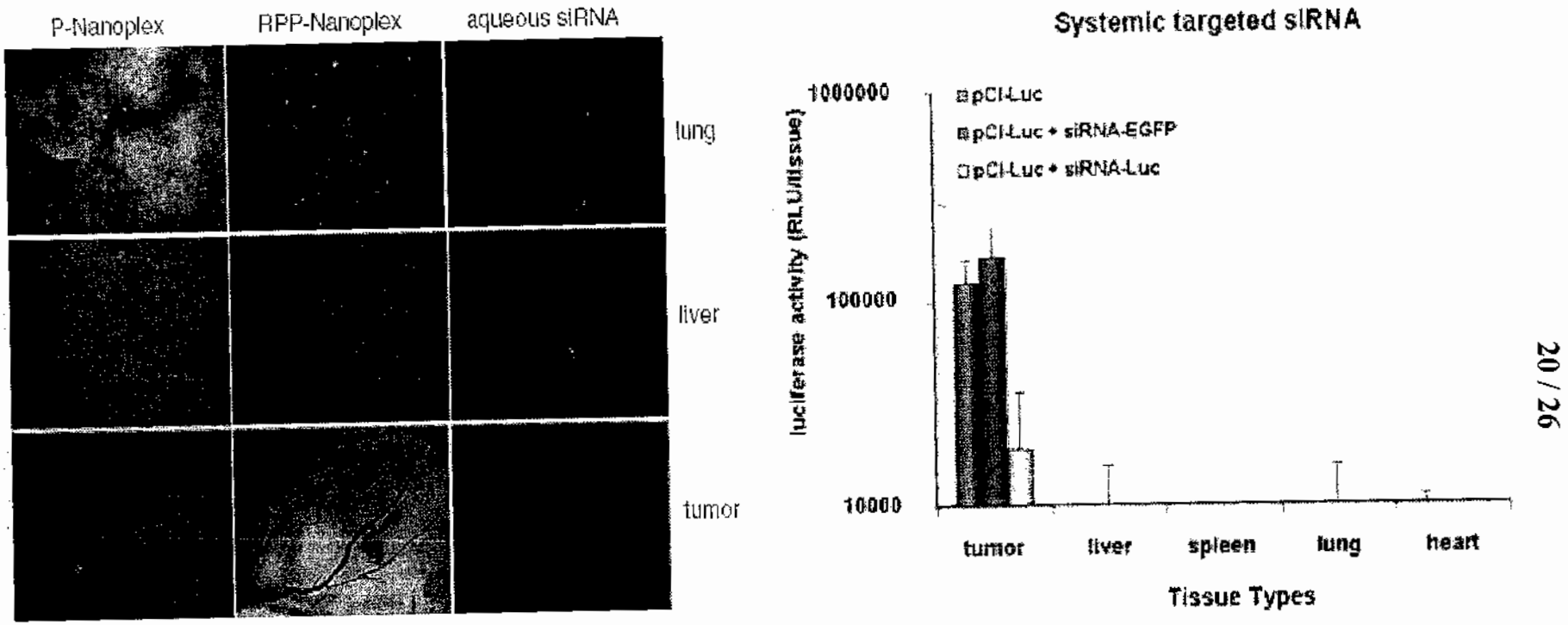


Figure 20. siRNA nanoparticle targeting neovasculature demonstrated tumor targeting property using labeled siRNA payload (left) and plasmid payload expressing Luciferase reporter gene (right).

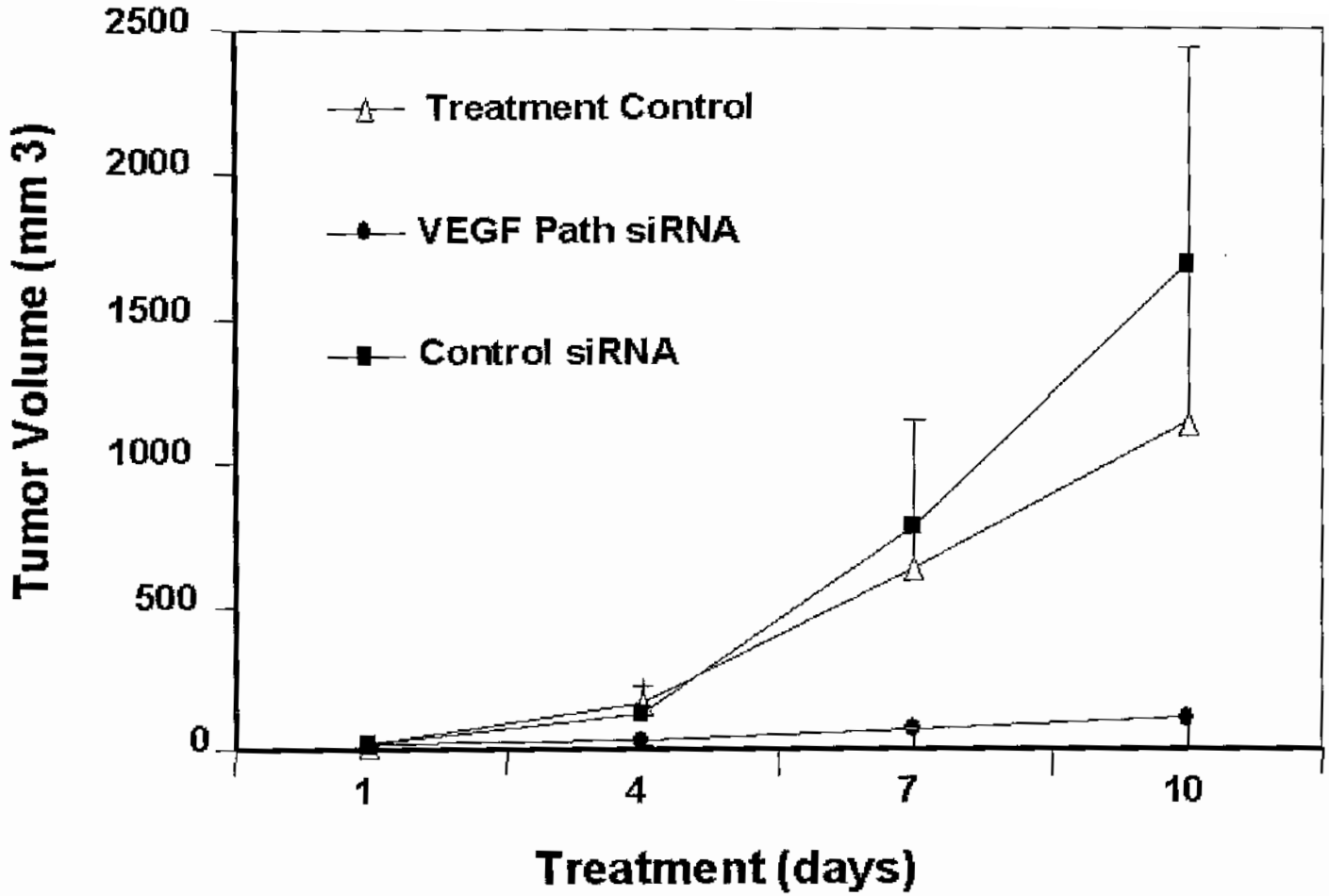


Figure 21. VEGFR2-siRNA nanoparticle targeting neovasculature demonstrated potent efficacy in neuroblastoma syngenic mouse model (N2A tumor) after four repeated administrations every three days.

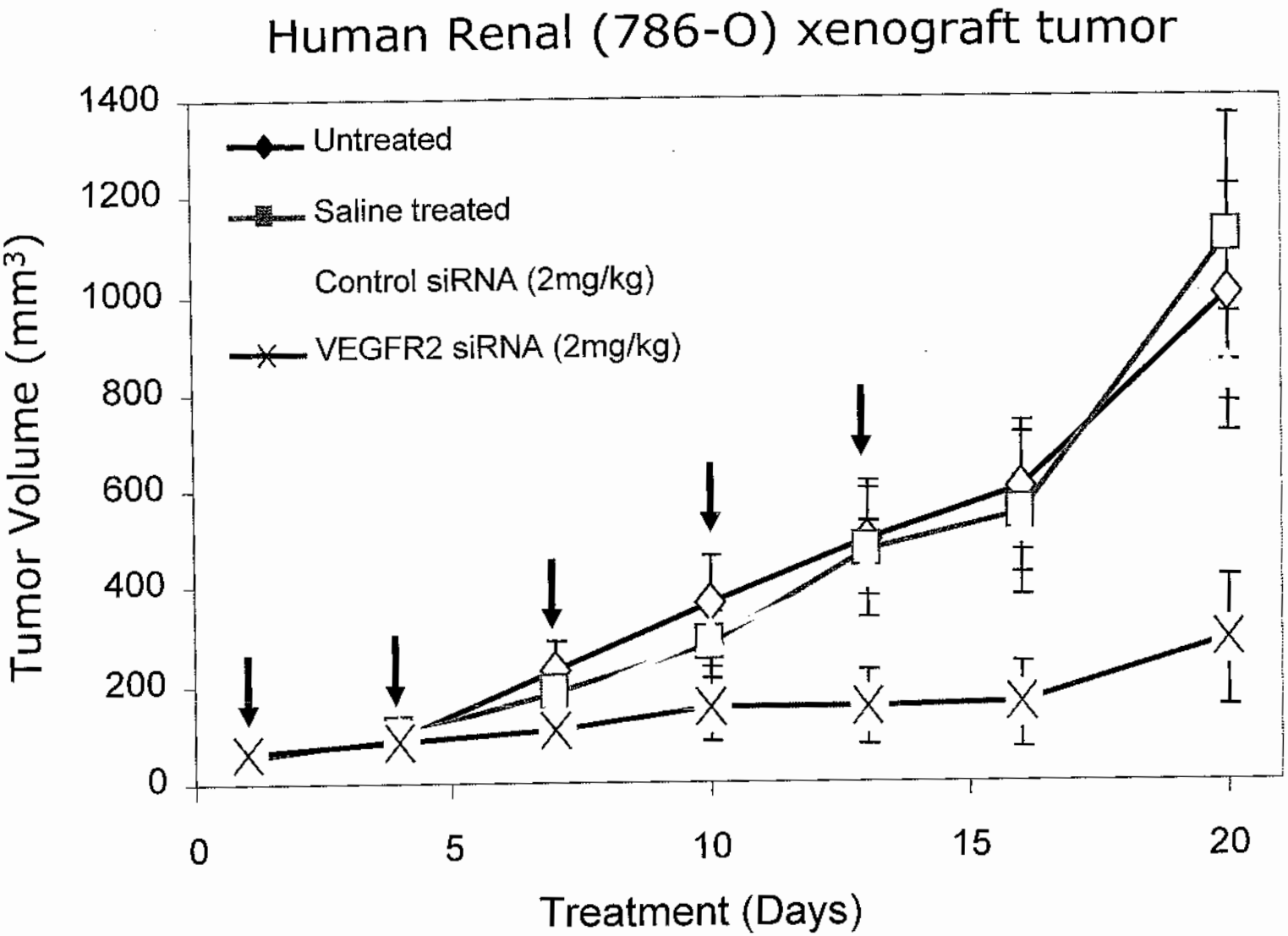


Figure 22. VEGFR2-siRNA nanoparticle targeting neovasculature demonstrated potent efficacy in renal carcinoma xenograft mouse model (786-O tumor) after five repeated administrations every three days.

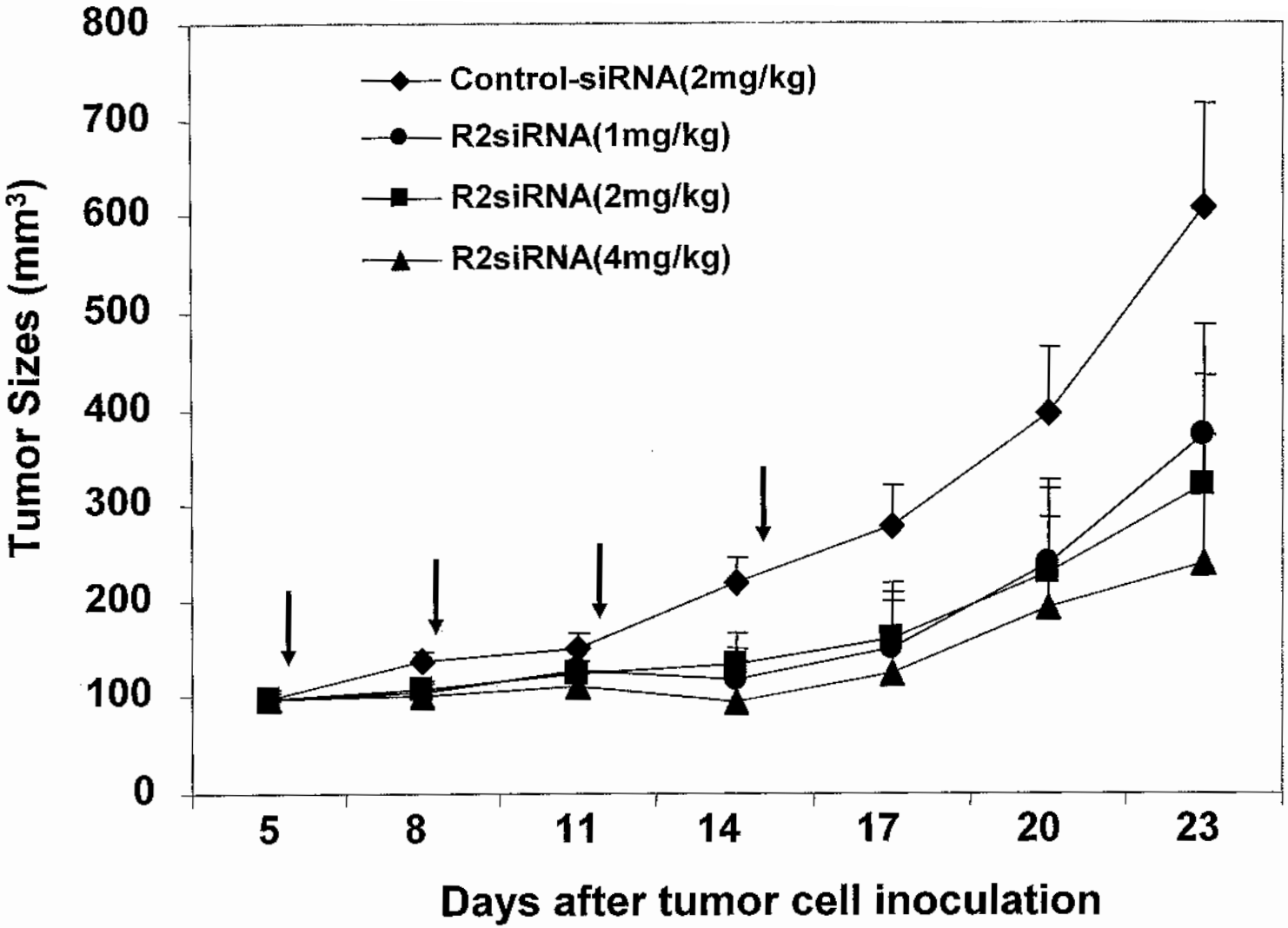


Figure 23. VEGFR2-siRNA nanoparticle targeting neovasculature demonstrated potent efficacy in colon carcinoma xenograft mouse model (DLD-1 tumor) after four repeated administrations every three days. Three different dosages were used in the study.

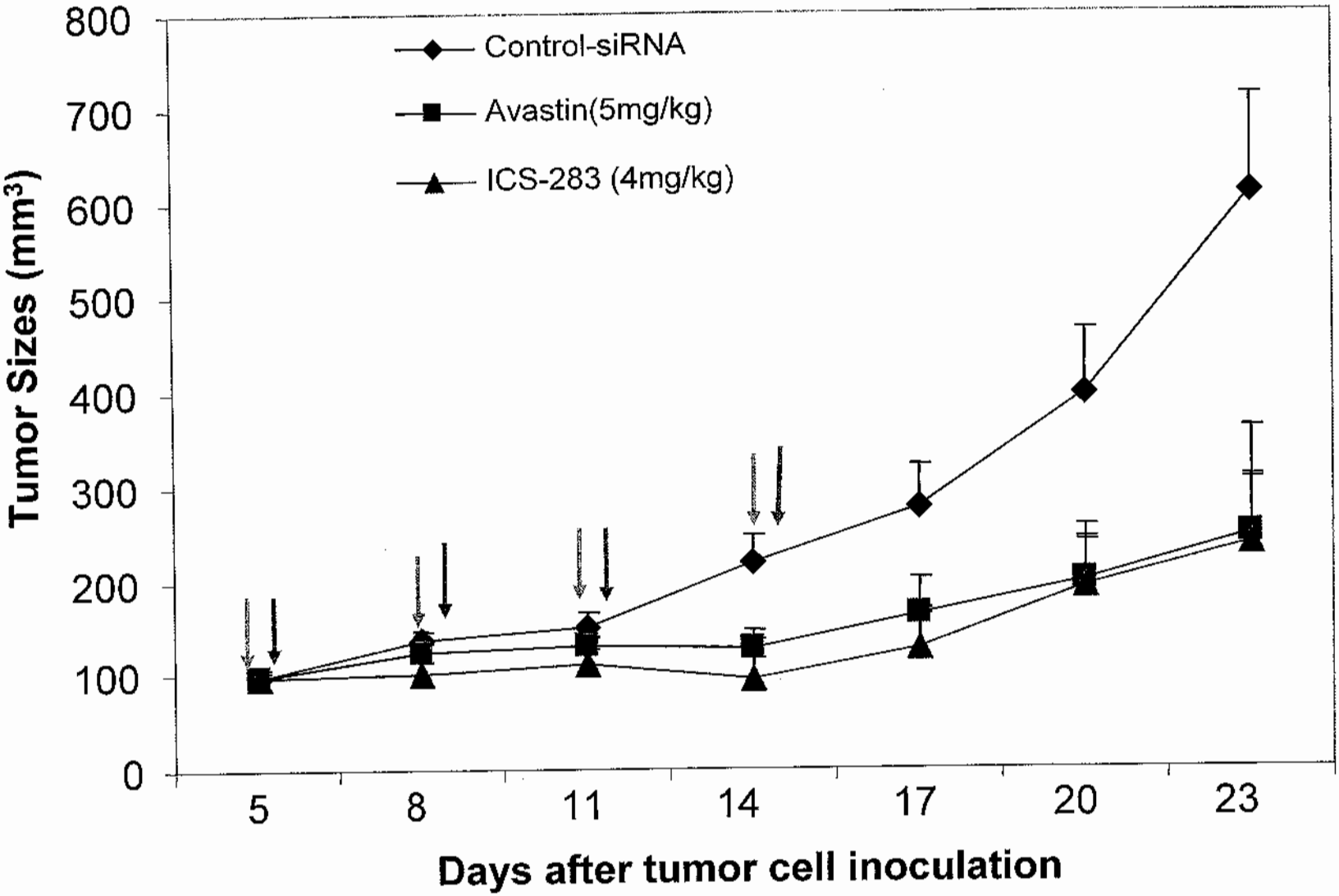


Figure 24. VEGFR2-siRNA nanoparticle targeting neovasculature demonstrated potent efficacy in colon carcinoma xenograft mouse model (DLD-1 tumor) after four repeated administrations every three days. Four mg per kilogram of VEGFR2 dosing resulted in the same anti-tumor efficacy as 5 mg per kilogram of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

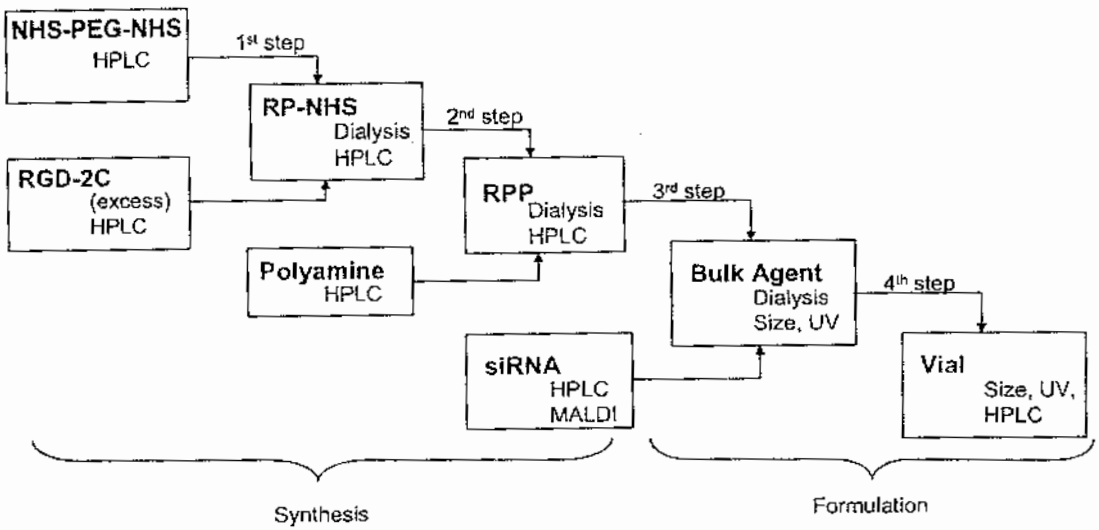


Figure 25. Manufacturing flow chart for production of an RGD-polymer conjugate and a nanoparticle-siRNA preparation starting from raw materials of a homobifunctional activated PEG, an RGD-2C peptide, a polyamine containing agent, and a mixture of dsRNA.

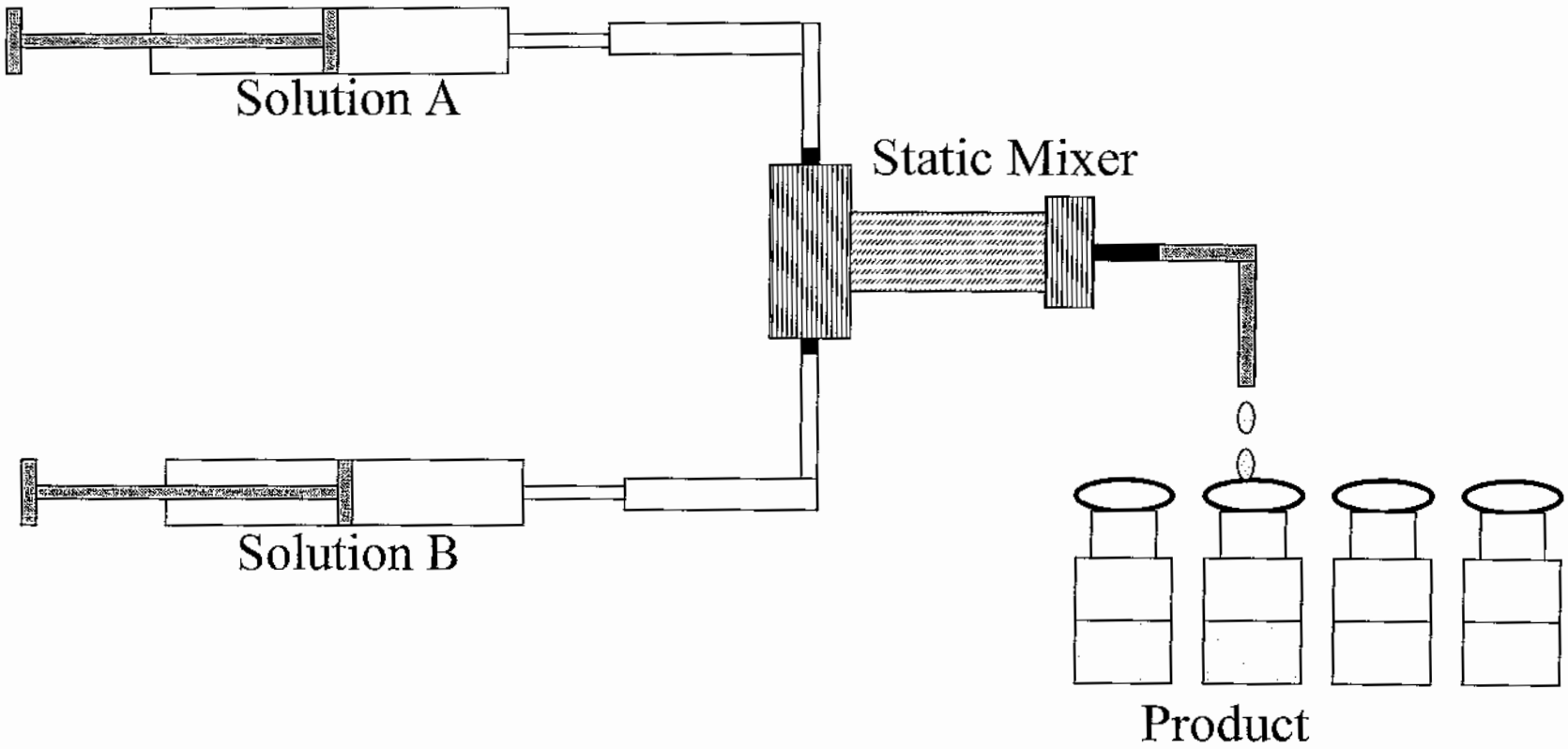


Figure 26. The use of a static mixer to manufacture a nanoparticle-siRNA preparation starting from two solutions, a polymer solution comprising polymer conjugates and an siRNA solution comprising three dsRNA agents.