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# Activity of nanoparticulate tetrac (nanotetrac) on models of glioblastoma

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Glioblastoma multiforme (GBM) is an aggressive brain tumor with a less than 10% 5-year survival rate. The tumor is relatively chemo- and radioresistant and, despite its vascularity, has shown disappointing clinical responses to anti-angiogenic management. Nanoparticulate tetrac (Nanotetrac) is anti-cancer/anti-angiogenic agent that acts exclusively at a thyroid hormone-tetrac receptor on plasma membrane integrin αvβ3 and does not gain entry to cells. In the formulation, tetrac is covalently bound via a linker to poly(lactic-co-glycolic acid) (PLGA) nanoparticles. From the integrin, the agent disorders a panel of tumor cell defense pathways by downstream actions on expression of differentially regulated genes and is pro-apoptotic by several mechanisms. In the C6 rat subcutaneous glioma xenograft in the mouse, standard clinical GBM chemotherapy with temozolomide (TMZ) at 10 mg/kg was wholly ineffective (tumor volumes) at 14 d, as was subtherapeutic Nanotetrac at 0.3 mg/kg. Added to TMZ, Nanotetrac at 0.3 mg/kg reduced tumor volume by 53% at 14 d. In the subcutaneous human U87MG (U87-luc) GBM xenograft, Nanotetrac at 1 mg/kg injected with implanted cells inhibited tumor growth by 79% at 16 d. Luminescent scanning revealed no viable cells in the Nanotetrac-exposed tumors, with full viability in the void PLGA-injected lesions. Systemic (s.c.) Nanotetrac at 1 mg/kg reduced subcutaneous tumor U87MG xenograft volume by 46% at 10 d. All Nanotetrac results were significant at $p < 0.05$. Studied in vitro, U87MG cells proliferated in response to physiological concentrations of free L-thyroxine (T4) and supraphysiological levels of 3,5,3,-triiodo-L-thyronine (T3). The T4 effect was associated with activation of mitogen-activated protein kinase (pERK1/2), but not phosphatidylinositol 3-kinase. Taken together, these studies indicate that 1) GBM is a thyroid hormone-responsive tumor, consistent with clinical observations of the action of induced hypothyroxinemia on GBM and 2) Nanotetrac systemically or intratumorally is effective in reducing GBM xenograft volumes/weights and reducing tumor cell viability.

## Biography

Davis is a graduate of Harvard Medical School and had his postgraduate medical training at Albert Einstein College of Medicine and the NIH. His academic positions have included Chair, Department of Medicine, Albany Medical College. He has served as President, American Thyroid Association, as a member of the Board of Directors of the American Board of Internal Medicine and he is Co-Head, Faculty of 1000 – Endocrinology. He serves on multiple Editorial Boards of His scientific interests include molecular mechanisms of actions of nonpeptide hormones, particularly, thyroid hormone. He and his colleagues described the cell surface receptor for thyroid hormone on integrin avb3 that underlies the pro-angiogenic activity of the hormone and the proliferative action of the hormone on cancer cells. He has co-authored more than 200 original research articles and 30 text book chapters and he has edited three medical textbooks.

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