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Targeted delivery of generic chemotherapeutic agents to solid tumors via systemic nanotetrac (nano-diamino-tetrac)

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Covalently bound to a poly (lactic-co-glycolic acid) (PLGA) polymer via a linker, tetraiodothyroacetic acid (tetrac) as Nano-diamino-tetrac (NDAT) targets a specific cell surface receptor on the extracellular domain of integrin αvβ3. αvβ3 is primarily expressed by cancer cells and rapidly dividing endothelial cells relevant to tumors. Conjugation of tetrac and linker to a 120 nm PLGA nanoparticle limits cell entry of the compound and offers an opportunity to load the nanoparticle with a generic cancer chemotherapeutic agent for tumor-targeted delivery. Even without a payload, NDAT has anticancer and anti-angiogenesis properties. We established xenografts of human urinary bladder cancer (263JBV) cells and of human pancreatic cancer (SUIT-2) cells in nude mice and tumor growth and tumor content of cisplatin (263JBV xenografts) and of paclitaxel (SUIT-2 xenografts) were compared in multiple animal cohorts. These included: 1) untreated xenografted controls; 2) controls treated with void PLGA nanoparticles (NPs), 3) daily standard treatment with chemotherapeutic agent (cisplatin, 1 mg/kg, doxorubicin, 1 mg/kg or paclitaxel, 0.3 mg/kg), alone, 4) daily treatment with NDAT, alone, at a concentration with low anticancer activity, 5) daily treatment with chemotherapeutic agent encapsulated into PLGA NPs (no tetrac), and 6) daily treatment with chemotherapeutic agent loaded into NDAT. The dose of NDAT in groups 4 and 5 was 0.3 mg tetrac/kg. Daily drug treatments were continued for 3 weeks after establishment of xenografts in nude mice. Urinary bladder tumor weight at animal sacrifice decreased insignificantly vs. controls in animals that received cisplatin or cisplatin + PLGA. Submaximal dosing of NDAT, alone, induced a small, but significant, decreased in tumor weight. Tumors in animals treated with NDAT bearing a payload of cisplatin decreased in weight by 50% ($P < 0.01$) and mean cisplatin content (LC/MS/MS) of tumors (ng/gm of tissue) was 5-fold more than in animals treated with cisplatin, alone, and 3-fold more than in animals treated with PLGA NPs with encapsulated/adsorbed cisplatin. Animals receiving cisplatin, alone, developed neurotoxicity (inability to use the hind limbs). In pancreatic cancer xenografts, paclitaxel encapsulated into PLGA NPs, NDAT, alone, and NDAT bearing a payload of paclitaxel caused significant decreases in tumor weight. The greatest reduction in tumor weight (60%, $P<0.01$) was in animals exposed to NDAT bearing a drug payload and mean concentration of paclitaxel in these tumors (ng/gm tissue) exposed to an NDAT/paclitaxel payload was 5-fold more than in xenografts exposed to paclitaxel, alone, or paclitaxel encapsulated into PLGA NPs. Thus, the payload capacity of NDAT for cancer chemotherapeutic agents and tumor-specific delivery of cancer chemotherapeutic agents significantly increased bladder and pancreatic cancer content of, respectively, cisplatin and paclitaxel. Enhanced tumor size reduction and deceased systemic toxicity were achieved with this targeted approach.

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 textbook chapters and he has edited three medical textbooks.

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