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Localized regulated expression of IL-12 as a gene therapy approach to cancer immunotherapy

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Tumors escape the immune system through the process of immunoediting. Thus, restoration of the immune system's ability to detect the tumor should result in an improved treatment outcome. Localized IL-12 administration elicits antitumor activity mediated by direct tumor cell cytotoxicity and enhancement of immuno-regulatory activities. We have developed an adenoviral vector, Ad-RTS-mIL-12, administered intratumorally under the control of the RheoSwitch Therapeutic System® expression platform. Gene expression and subsequent IL-12 production is tightly controlled by the oral administration of the activator ligand veledimex. We have shown on mechanism biologic activity and safety with this system in syngeneic mouse models of melanoma and breast cancer. Ad-RTS-mIL-12 (1x1010)+ veledimex elicited a dose-related increase in tumor IL-12mRNA and IL-12 protein leading to increased tumor influx of natural killer, CD4+ and CD8+ T cells with corresponding reduction in tumor growth. A return to baseline IL-12mRNA and IL-12 protein was observed on veledimex withdrawal. Approximately 1% of veledimex crosses the blood brain barrier in naive mice and cynomolgus monkeys increasing to 6% in orthotopic mice. In the orthotopic mouse model Ad-RTS-mIL-12+veledimex demonstrated a dose-related increase in survival devoid of adverse safety effects. At Day 100 (study termination) ~50% of the Ad-RTS-mL-12+veledimex 450mg/m2/day (Qdx14) survived. Survival correlated with marked decreases in tumor stem cells. In ongoing Phase 2 clinical trials in melanoma and breast cancer we have observed immune responses and biologic activity. In summary, this novel regulated immunotherapeutic approach could potentially be translated into an effective clinical regimen for the treatment of melanoma, breast and glioblastoma.

Biography

John A Barrett has completed his PhD from Saint John's University, NY. He is presently Vice President of R&D and Head of Translational Research at Ziopharm Oncology with a research focus in immunotherapy, oncology, targeted radiopharmaceuticals and biomarkers. During his career, he was responsible for numerous IND's and NDA's and has authored 45 papers in peer review journals.

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