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Novel therapeutic strategies in virology: Cancer terminator viruses and innovative delivery approaches

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Although in principle, genetically engineered viruses, particularly type 5 adenoviruses (Ad5), hold significant promise as therapeutics, this potential has not been realized. Several factors contribute to lack of clinical translation. Systemic administration of Ad5 results in sequestration in the liver and neutralization by the immune system. Additionally, replication competence is not sufficient to elicit objective clinical responses. We have created improved therapeutic viruses and approaches to circumvent liver entrapment and immune recognition. Using the promoter region of progression elevated gene-3 (PEG-Prom), which displays cancer-specific expression, we have developed conditionally replication competent adenoviruses that selectively replicate in cancer cells. To enhance the efficacy of these viruses as therapeutics, we engineered the cancer-specific apoptosisinducing cytokine gene melanoma differentiation associated gene-7/Interleukin-24 (*mda*-7/IL-24) in these adenoviruses. These novel Cancer Terminator Viruses (*CTV*) have potent "bystander" activity and selectively kill both primary and distant cancers in animal models of human cancer. Since Ad5 enters cells through Coxsackie Adenovirus Receptors (CAR), and these receptors are frequently reduced in primary human cancers limiting infection, we created a tropism-modified serotype 5 and serotype 3 chimeric *CTV* (Ad.5/3-*CTV*) with enhanced infectivity and anti-cancer activity in CAR-deficient cancer cells, while retaining activity in CAR positive cells, thereby increasing its potential applications for cancer therapy. To avoid liver trapping and immune clearance, and to provide target-specific delivery, we developed a stealth approach for delivering the *CTV* by microbubbles combined with ultrasound to release the viruses in the tumor milieu. This approach is paradigm shifting and offers potential for enhancing systemic cancer therapy using viruses.

Biography

Dr. Paul B. Fisher is Professor and Chairman, Department of Human and Molecular Genetics and Director, VCU Institute of Molecular Medicine, Virginia Commonwealth University School of Medicine, Richmond, Virginia. Research focuses on three broad areas; cancer, neurodegeneration and infectious diseases. A primary aim is to move discoveries made in the laboratory into the clinic, the concept of "bench-to-bedside." He is among the top 5% of NIH funded investigators over the past 25 years, published over 400 primary papers and review articles, serves on many US government and private review panels and has over 55 issued US and numerous international patents.