A novel CDC25B promoter-based oncolytic adenovirus inhibited growth of orthotopic human pancreatic tumors in different preclinical models

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Purpose: We decided to construct a novel oncolytic adenovirus whose replication was driven by the CDC25B promoter for its use in preclinical models of pancreatic cancer. Experimental Design: We placed the essential E1A gene under control of the CDC25B promoter. Based on preliminary data, we pseudotyped the adenovirus with a chimeric fiber of serotypes 5/3. We investigated the in vitro lytic effect and the in vivo therapeutic efficacy in combination with gemcitabine on human pancreatic tumor xenografts orthotopically growing in nude mice and in tumors growing in Syrian hamsters. We also assessed biochemical markers of hepatic toxicity and CA19.9 levels. Results: AV25CDC exhibited a strong in vitro lytic effect on pancreatic cancer cells. In vivo administration of AV25CDC combined with gemcitabine in mice harboring subcutaneously growing SW1990 pancreatic tumors almost abrogated tumor growth. Nude mice harboring 15-day-old orthotopic tumors, treated intratumorally or systemically with AV25CDC combined with gemcitabine, exhibited 70% to 80% reduction in tumor size compared with control mice that lasted for at least 60 days. Chemovirotherapy treatment induced a return to normal levels of biochemical parameters of hepatic toxicity; these mice exhibited more than 90% reduction in CA19.9 serum levels compared with

control. Chemovirotherapy efficacy was confi rmed in mice harboring Mia PaCa-2 tumors and in Syrian hamster harboring HaP-T1 tumors.Weobserved that viral treatment disrupted tumor architecture and induced an increase in MMP-9 activity that might facilitate gemcitabine penetrability. Conclusion: These data demonstrate that AV25CDC is an effective oncolytic agent candidate for pancreatic cancer chemovirotherapy combination.