Basic Fibroblast Growth Factor Enhancement of Adenovirus-mediated Delivery of the Herpes Simplex Virus Thymidine Kinase Gene Results in Augmented Therapeutic Benefit in a Murine Model of Ovarian Cancer

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ABSTRACT
A number of preclinical and human clinical gene therapy trials using adenoviral vectors have shown that the number of viral particles necessary to give adequate levels of gene transfer can be associated with significant vector-related toxicity. In an effort to reduce the number of adenoviral particles required for a given level of gene transfer, we sought to redirect adenoviral infection via a receptor that is highly expressed on the target cells. By using basic fibroblast growth factor (FGF2) as the targeting ligand, adenovirus-mediated gene transfer to the human ovarian cancer cell line SKOV3.ip1 was significantly enhanced, permitting the transduction of a greater number of target cells to be achieved by a given dose of virus. In a murine model of human ovarian carcinoma, an FGF2-redirected adenoviral vector carrying the gene for herpes simplex virus thymidine kinase (AdCMVHSV-TK) was shown to result in a significant prolongation of survival compared with the same number of particles of unmodified AdCMVHSV-TK. In addition, equivalent survival rates were achieved with a 10-fold lower dose of the FGF2-redirected AdCMVHSV-TK compared with the unmodified vector. To our knowledge, this is the first report demonstrating that strategies to enhance the efficiency of in vivo transduction of adenoviral vectors will be of clinical utility.

INTRODUCTION

In the various human clinical gene therapy approaches using toxin genes, the disease stage considered most suitable has been locoregional, whereby tumor is contained within an anatomical compartment. This situation potentially allows vector concentrations favoring optimal tumor cell transduction. In addition, vector containment within the compartment theoretically limits vector dissemination, thereby preventing the deleterious consequences of non-tumor cell transduction. In this regard, recombinant adenoviral vectors have shown the greatest vector utility for toxin gene delivery, demonstrating significant antitumor effects in animal models of glioma, mesothelioma, carcinoma of the ovary, and disseminated breast carcinoma based upon high levels of in situ tumor cell transduction (1–4).

Human adenoviral vectors of serotypes 2 (Ad2) and 5 (Ad5) have been widely used to deliver genes to a range of cell types in vivo (5). However, human clinical studies have demonstrated host inflammatory and immunological responses to the vectors resulting in limited vector efficiency and treatment-related toxicity (6, 7). Most importantly, these studies have demonstrated relatively low efficiencies of tumor cell transduction at the magnitudes of the adenoviral vectors used (8). In addition, the number of adenoviral particles necessary to give adequate in vivo levels of gene transfer can be associated with significant vector-related toxicity (9–11).

It would therefore be advantageous to reduce the number of adenoviral particles required for optimal levels of gene transfer. We hypothesized that an enhancement in the efficiency of infection could be achieved by redirecting the adenovirus to receptors that are highly expressed on the target cells. We have demonstrated previously the feasibility of such an approach in in vitro and in vivo experiments using reporter genes (12–14). However, none of these was designed to evaluate the therapeutic efficacy of redirected adenoviral vectors in animal models so that this approach could be translated into a clinical context. In
this report, we thus compare the *in vitro* and *in vivo* efficacy of native and modified adenoviral vectors by using basic fibroblast growth factor (FGF2) as the tumor cell targeting ligand and the prodrug activating the HSV-TK/GCV system as the therapeutic agent in a xenograft mouse model of human ovarian carcinoma. Our results suggest that strategies to redirect and enhance the efficiency of infection of adenoviral vectors will be of clinical utility and are worth pursuing.

**MATERIALS AND METHODS**

**Cells and Adenoviruses.** The human ovarian carcinoma cell line SKOV3.ip1 was obtained from Janet Price (Baylor University, Houston, TX). 293 cells (15) were purchased from the American Type Culture Collection (Rockville, MD). All cells were maintained in DMEM/Ham’s F-12 medium. The medium was supplemented with 10% heat-inactivated FCS, 2 mM glutamine, 100 units/ml penicillin, and 100 µg/ml streptomycin, and the cells were propagated at 37°C in a 5% CO₂ atmosphere. FCS was purchased from HyClone Laboratories (Logan, UT), and media and supplements were from Mediatech (Herndon, VA).

AdCMVLuc (16), an E1-, E3-deleted AdS vector that expresses firefly luciferase under the control of the CMV promoter, was provided by Robert D. Gerard (University of Leuven, Leuven, Belgium). AdCMVLacZ, an E1-deleted AdS vector that expresses a nuclear-localized form of *Escherichia coli* β-galactosidase from the CMV promoter, was obtained from De-chu Tang (University of Alabama at Birmingham, Birmingham, AL). AdCMVHSV-TK has been described previously and is an E1-deleted AdS vector that expresses HSV-TK from the CMV promoter (17). The recombiant adenoviral vectors were propagated on the permissive 293 cell line and purified according to standard techniques (18).

**Generation and Characterization of Fab-FGF2 Conjugate.** The Fab-FGF2 conjugate was constructed by conjugating the Fab fragment of 1D6.14, a neutralizing monoclonal antibody directed against the Ad5 knob (12), with an FGF2 mutein as described (19). The FGF2 mutein is a 155-amino acid protein that expresses HSV-TK, mice were separated into 10 groups, each containing 10 animals, except for the Animal Program (Frederick, MD). To study the effects on ovarian tumor cells were infected with AdCMVLacZ. Sixteen hours before infection, SKOV3.ip1 cells were seeded in six-well plates at a density of 3 × 10⁵ cells/well. AdCMVLacZ (5 × 10⁶ pfu) was preincubated with or without Fab-FGF2 (1.94 µg) in 20 µl of HBS for 30 min at room temperature. The vector or vector complexes were then diluted in infecting medium, and 24,000 SKOV3.ip1 cells in 24-well plates were infected at an MOI of 50 pfu/cell in a final volume of 100 µl. Inhibition experiments were performed by adding a polyclonal anti-FGF2 antibody (Sigma Chemical Co., St. Louis, MO) to the AdCMVLacZ-Fab-FGF2 complex prior to infection. Cell lysates were assayed for luciferase activity 24 h after infection. The protein concentration of the lysates was determined to permit normalization of the data. An overall comparison of the groups was performed using ANOVA at the 5% significance level. Pairwise comparisons were made using Tukey’s HSD method with a family error rate of 5% and an individual error rate of 1.26%.

To quantitate the number of transduced cells, SKOV3.ip1 ovarian tumor cells were infected with AdCMVLacZ. Sixteen hours before infection, SKOV3.ip1 cells were seeded in six-well plates at a density of 3 × 10⁵ cells/well. AdCMVLacZ (5 × 10⁶ pfu) was preincubated with or without Fab-FGF2 (1.94 µg) in 20 µl of HBS for 30 min at room temperature. The vector or vector complexes were then diluted in infecting medium and incubated with the cells at an MOI of either 5 or 50 pfu/cell in a final volume of 200 µl. After 1 h at 37°C, the infecting medium was aspirated and replaced with complete medium. After incubation for an additional 24 h at 37°C, the cells were lysed, and extracts were assayed for luciferase activity by a chemiluminescent assay (Promega Corp., Madison, WI). The protein concentration of the lysates was determined to permit normalization of the data. The lowest dose of Fab that blocked infection was used in subsequent experiments. In addition, because the molar ratio of Fab to FGF2 in the conjugate was known to be 1:1, this value was used to calculate the optimal dose of Fab-FGF2 to be used in subsequent retargeting experiments.

To determine the ability of the Fab-FGF2 conjugate to enhance adenovirus-mediated gene delivery, AdCMVLuc (5 × 10⁷ PFU) was preincubated with the optimal dose of the Fab fragment (1.44 µg) or Fab-FGF2 conjugate (1.94 µg) in 20 µl of HBS for 30 min at room temperature. The vector or vector complexes were then diluted in infecting medium, and 24,000 SKOV3.ip1 cells in 24-well plates were infected at an MOI of 50 pfu/cell in a final volume of 100 µl. Inhibition experiments were performed by adding a polyclonal anti-FGF2 antibody (Sigma Chemical Co., St. Louis, MO) to the AdCMVLacZ-Fab-FGF2 complex prior to infection. Cell lysates were assayed for luciferase activity 24 h after infection. The protein concentration of the lysates was determined to permit normalization of the data. An overall comparison of the groups was performed using ANOVA at the 5% significance level. Pairwise comparisons were made using Tukey’s HSD method with a family error rate of 5% and an individual error rate of 1.26%.

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**In Vivo Survival Experiment.** Female CB17 SCID mice of ages 6–8 weeks were obtained from the National Cancer Animal Program (Frederick, MD). To study the effects on survival of FGF2-modified *versus* unmodified AdCMVHSV-TK, mice were separated into 10 groups, each containing 10 animals, except for the 2 control groups which contained only 5 mice each. The groups were as follows: tumor cells only; tumor cells + GCV; tumor cells + 2 × 10⁸ pfu AdCMVHSV-TK; tumor cells + 2 × 10⁷ pfu AdCMVHSV-TK + GCV; 2 × 10⁸ pfu FGF2-AdCMVHSV-TK; 2 × 10⁷ pfu FGF2-AdCMVHSV-TK + GCV; 2 × 10⁸ pfu AdCMVHSV-TK + GCV; 2 × 10⁹ pfu FGF2-AdCMVHSV-
TK; and 2 × 10^9 pfu FGF2-AdCMVHSV-TK + GCV. On day 0, all of the mice of all groups received an i.p. injection of 2 × 10^7 SKOV3.ip1 cells. On day 5, the treated groups were injected i.p. with a dose of 2 × 10^9 or 2 × 10^8 pfu of AdCMVHSV-TK alone or AdCMVHSV-TK complexed with Fab-FGF2. The Fab-FGF2 modification of AdCMVHSV-TK vector was done as described earlier with the exception that the protocol was scaled up for the total pfu required for all animals, and the volume was adjusted so that each mouse received a total of 2 × 10^9 or 2 × 10^8 pfu in 0.5 ml. Unmodified AdCMVHSV-TK was subjected to the same treatment but in the absence of the Fab-FGF2 conjugate. Forty-eight h after administration of vectors, half of the treated groups were administered every day with an i.p. injection of GCV (50 mg/kg body weight) for 14 consecutive days. The mice were then monitored daily for survival. Survival differences between control and experimental groups were then compared, and the statistical significance was analyzed using the log-rank test. All animal protocols were approved by the University of Alabama at Birmingham and were in compliance with the standards established by the NIH.

RESULTS

We first performed binding studies with 125I-labeled FGF to confirm that the target ovarian cancer cell line, SKOV3.ip1, possessed FGF receptors (data not shown). AdCMVLuc, an E1-, E3-deleted Ad5 vector that expresses firefly luciferase (16), was then premixed with the unconjugated anti-knob Fab fragment or the Fab-FGF2 conjugate prior to infection of SKOV3.ip1 cell monolayers at an MOI of 50 pfu/cell. Expression of luciferase activity in infected cells was determined 24 h after infection; this value is directly proportional to the number of infecting virus particles. As shown in Fig. 1, when AdCMVLuc was premixed with the Fab-FGF2 conjugate, the level of luciferase activity was more than 9-fold greater than that achieved by the unmodified vector. This enhancement of infection was specifically mediated by FGF2 because gene delivery by the Ad-Fab-FGF2 complex was inhibited by anti-FGF2 antibody. ANOVA demonstrated an overall difference between the groups (P < 0.0001). There was no statistical difference between the Ad, Ad + Fab, and Ad + Fab-FGF2 + anti-FGF2 groups. However, there was a significant difference between the Ad + Fab-FGF2 group and all other groups. These results thus demonstrated that FGF2 redirection of an adenoviral vector allows more efficient gene transfer to SKOV3.ip1 cells in vitro.

We next sought to investigate whether this FGF2-mediated enhancement in gene expression was due to transduction of a greater percentage of target cells or to more gene copies per transduced cell. SKOV3.ip1 cell monolayers were infected at different MOIs with an E1-deleted Ad5 vector carrying the β-galactosidase reporter gene, AdCMVlacZ, in the presence or absence of Fab-FGF2. Twenty-four h after infection, the cells were stained with X-gal to demonstrate the expression of β-galactosidase (Fig. 2). It was found that the Fab-FGF2 conjugate mediated adenoviral infection of a greater percentage of target cells than the native virus, permitting the transduction of a given number of target cells to be achieved by a lower dose of virus.

We then sought to determine whether Fab-FGF2-mediated enhancement of adenoviral infection could be exploited for therapeutic advantage. To do so, a murine model of human ovarian cancer was established, as described previously, by i.p. injection of SCID mice with SKOV3.ip1 cells (20, 21). Five days later, the treated mice were injected i.p. at two doses (2 × 10^8 or 2 × 10^9 pfu), either with AdCMVHSV-TK, an E1-deleted Ad5 vector that expresses the prodrg-activating HSV-TK gene, or with AdCMVHSV-TK premixed with the Fab-FGF2 conjugate. Two days later, mice were then treated for 14 days with 50 mg/kg of the prodrug GCV or with an equivalent volume of serum-free medium. Ten animals were studied in each group with the exception of the control groups containing 5 mice each. The animals were monitored daily, and the length of survival of each mouse was recorded (Fig. 3).

As expected, no significant increase in duration of survival over the group of untreated mice with tumors was observed for those animals treated with GCV alone (median survival, 32 days). Nor was a survival advantage conferred in the absence of GCV by injection of either AdCMVHSV-TK or AdCMVHSV-TK premixed with Fab-FGF2. However, when comparing treatment with GCV, injection of the mice with AdCMVHSV-TK premixed with Fab-FGF2 was shown to result in a significant prolongation of survival compared with injection with the same number of particles of unmodified AdCMVHSV-TK. Thus, when a viral dose of 2 × 10^8 pfu was used, the median survival of mice injected with AdCMVHSV-TK premixed with Fab-FGF2 was 37 days, compared with 35 days
observed for the native virus \((P = 0.0025)\). Similarly, at a viral dose of \(2 \times 10^6\) pfu, median survival was increased from 36 to 44 days when the efficiency of adeno viral infection was enhanced by Fab-FGF2 \((P = 0.0070)\). Of note, equivalent survival rates were achieved with a 10-fold lower dose of the redirected AdCMVHSV-TK compared with the unmodified vector \((37\) days for \(2 \times 10^5\) pfu AdCMVHSV-TK complexed with Fab-FGF2 versus \(36\) days for \(2 \times 10^6\) pfu AdCMVHSV-TK: \(P = 0.3760)\). In all groups, tumor burden seemed to be the cause of death, and no sign of treatment-associated toxicity was noticed in the treated groups. These results thus demonstrated that, at a given dose, an FGF2-redirected adenoviral vector is more efficient than an unmodified vector in achieving a therapeutic benefit. Moreover, a lower dose of FGF2-redirected adenoviral vector can be administered to achieve a given therapeutic benefit.

**DISCUSSION**

In this report, we compared the efficacy of an FGF2-redirected adenovirus to that of a native adenovirus for achievement of a molecular chemotherapy approach for treatment of carcinoma of the ovary. This strategy of rerouting adenoviral vectors was shown to enhance gene delivery *in vitro* by transducing a greater number of tumor cells. More importantly, the enhanced transduction efficacy of an FGF2-redirected adenoviral vector encoding the *HSV-TK* gene resulted in an augmented therapeutic benefit when compared with the unmodified adenoviral vector in a xenograft mouse model of human ovarian carcinoma. To our knowledge, this represents the first demonstration of enhanced therapeutic benefit using a redirected adenoviral vector and suggests that strategies to augment the efficiency of infection of adenoviral vectors *in vivo* will be of clinical utility.

To date, human clinical studies using adenoviral vectors have demonstrated relatively low efficiencies of tumor cell transduction at the vector concentrations presently used (8). In addition, it is well known that adenoviral vectors produce a dose-dependent inflammatory response in rodents and primates, and that vector-associated toxicity has also been observed in human clinical trials (6, 7). These problems thus threaten to prevent the adenovirus from realizing its full potential as a vector for human gene therapy (9). To this end, several studies have focused on the development of adenoviral vectors with altered tropism in an attempt to augment *in vivo* efficacy of gene transfer. Such studies have either expanded or limited adenovirus tropism. Expanding the tropism of adenoviral vectors allows transduction of cells that are not ordinarily susceptible to adenovirus infection, i.e., do not express at sufficient levels the requisite cellular receptors (13, 22–25). Meanwhile, limiting adenoviral tropism permits specific transduction of target cells, thus preventing a dilution effect due to transduction of non-target cells (12, 22, 25). The optimal adenoviral vector would have a greater efficiency of gene transfer compared with the native adenoviral vector and would specifically transduce the intended target cells.

In this study, we have used a method that ablates native adenoviral tropism while conferring new tropism. This was achieved through the use of the neutralizing Fab fragment of an anti-knob antibody conjugated to FGF2 to redirect the adenoviral vector to FGF receptors on ovarian tumor cells *in vitro* and *in vivo*. Our study has established key concepts with respect to the efficacy of FGF2-redirected adenoviral vectors for gene therapy of ovarian carcinoma. FGF2-mediated adenoviral gene transfer was specifically achieved in the human ovarian carcinoma cell line SKOV3.ip1. The redirection of the adenoviral vector was specifically mediated through FGF2 because gene transfer was inhibited in presence of FGF2 antibody. In addition, when redirecting the adenoviral vector with FGF2, an enhancement in gene transfer efficacy was observed *in vitro*. This enhancement of gene transfer accomplished by the FGF2-redirected adenoviral vector was shown to be due to transduction of a greater number of tumor cells.

Direct modifications of adenoviral capsid proteins could result in decreased infectivity of the vector. However, in our strategy, preformed and titered adenoviral vectors were modified by incubation with the retargeting conjugate at room tem-

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*Fig. 2* FGF2-mediated enhancement of adenoviral gene expression is the result of infection of a greater percentage of target cells. AdCMVLacZ \((5 \times 10^5\) pfu) was preincubated with or without Fab-FGF2 \((1.94 \mu g)\) in 20 \(\mu l\) of HBS for 30 min at room temperature. The vector or vector-Fab-FGF2 complexes were then diluted in DMEM/0.1% FCS, and SKOV3.ip1 cells were infected at an MOI of 5 or 50 pfu/cell. Expression of \(\beta\)-galactosidase was determined 24 h after infection by staining with the chromogenic substrate X-gal \(\times 100\). a, AdCMVLacZ, MOI = 5; b, AdCMVLacZ-FGF2, MOI = 5; c, AdCMVLacZ, MOI = 50; d, AdCMVLacZ-FGF2, MOI = 50.
per temperature for 30 min. Preliminary experiments showed that a control incubation performed in the absence of the retargeting conjugate does not induce any change in viral particle number or particle/pfu ratio. We thus believe that the incubation conditions do not affect the infectivity of the modified vector and that the enhancement in adenovirus-mediated gene transfer is therefore due to redirection of adenoviral infection.

In our study, the enhancement of gene transfer observed in the SKOV3.ip1 cells was specifically mediated by the FGF2 ligand because an anti-FGF2 antibody could abrogate gene transfer. We have subsequently established the basis for the enhanced gene transfer efficacy of FGF2-redirected adenoviral vectors. In this regard, we have demonstrated that the FGF2 redirection of adenoviral vectors to a panel of cell lines, including SKOV3.ip1, is accomplished specifically through the high affinity FGF receptors, and that low affinity receptors (heparan sulfate proteoglycans) are not required.

Our in vitro results using reporter genes suggested that FGF2 redirection of a therapeutic adenoviral vector would augment its clinical efficacy for gene therapy of ovarian cancer because of its ability to achieve enhanced gene transfer. This hypothesis was tested using an adenoviral vector encoding the HSV-TK gene in a xenograft mouse model of human ovarian carcinoma. The fact that the Fab-FGF2 conjugate enhanced adenoviral infection by permitting infection of a greater percentage of cells rather than by producing more copies of the gene per cell is relevant to the choice of HSV-TK as the therapeutic gene in this study. It has been reported that the antitumor effect of the HSV-TK/GCV system cannot be augmented simply by increasing the HSV-TK enzyme levels per cell (26). In a study by Yee et al. (27) exploring adenovirus-mediated gene delivery of HSV-TK in a murine ascites model of human breast cancer, a 3-fold higher viral dose was used in an attempt to increase survival. However, they instead found that the higher dose led to substantial toxicity and more deaths. In contrast, we were able to augment the efficiency of the HSV-TK/GCV system by increasing the number of cells expressing the enzyme. Our results showed that for a given dose of FGF2-modified or unmodified adenoviral vector, the FGF2-redirected adenoviral vector significantly increased survival of treated mice compared with native adenoviral vector, thus establishing the rationale for using FGF2-redirected adenoviral vector for gene therapy of ovarian carcinoma. We have recently reported that FGF2 redirection of an adenoviral vector carrying the luciferase reporter gene resulted in enhanced in vivo gene transfer to SKOV3.ip1 cells in the context of the same murine xenograft model of ovarian cancer. Moreover, the redirected adenoviral vector displayed preferential gene transfer to the tumors relative to the mesothelial lining (14). Therefore, we believe that the basis of increased survival in the present study is clearly related to enhanced in vivo tumor transduction.

Dose-dependent inflammatory responses and vector-associated toxicity have suggested that it would be advantageous to reduce the number of adenoviral particles required for a given level of gene transfer in vivo. Because the Fab-FGF2 conjugate allows transduction of a greater percentage of tumor cells, a lower dose of the FGF2-modified adenoviral vector should be required to achieve a given therapeutic benefit. We tested this

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Fig. 3 FGF2-enhancement of adenovirus-mediated expression of the HSV-TK gene augments therapeutic benefit in a survival experiment. A total of 95 female SCID mice of ages 6–8 weeks were inoculated i.p. with $2 \times 10^7$ SKOV3.ip1 cells on day 0. On day 5, some mice were injected i.p. with $2 \times 10^8$ or $2 \times 10^7$ pfu of AdCMVHSV-TK alone or AdCMVHSV-TK complexed with FGF2 (n = 20 mice per group). Forty-eight h later, half of the mice in each group (n = 10) were treated daily with an i.p. injection of GCV (50 mg/kg body weight) for 14 days. Control groups consisted of mice that received no virus or GCV (n = 5) or mice that were treated with GCV only (n = 10). The mice were monitored daily for survival. The percentage of animals surviving is plotted against the number of days after tumor cell inoculation.
hypothesis in our mouse model of ovarian cancer with the adenoviral vector encoding the HSV-TK gene. Our results demonstrated that a 10-fold lower dose of FGF2-modified adenoviral vector was as efficient as a high dose of native adenoviral vector in conferring a therapeutic benefit. These results thus suggest that FGF2 redirection of adenoviral vectors would allow us to administer lower doses of vectors and that could potentially reduce vector-related toxicities observed thus far in human studies (9). However, this latter issue could not be addressed in our study because we had to used immunocompromised SCID mice to xenotransplant the human tumor cells. In addition, Wilson's group has recently shown that the basis of the immunogenicity of adenoviral vectors is their ability to transduce dendritic cells (28). It is thus possible that our strategy to redirect adenoviral vectors, so that they preferentially transduce tumor cells, might prevent transduction of dendritic cells and therefore abrogate the basis for vector immunogenicity. On the other hand, it is also possible that FGF2-directed Ad construct could induce immunity due to new epitopes related to the Fab-FGF2 complex. However, Gu et al. (29) have reported recently that FGF2 redirection of adenoviral vectors decreases toxicity and immunogenicity in vivo. Nonetheless, more studies in immunocompetent animal models should be conducted to address vector-related toxicity and immunogenicity of redirected adenoviral vectors.

Other strategies are also being developed to increase the number of viral particles in situ. These strategies use conditionally replicative adenoviruses to achieve local amplification. In this regard, a mutant adenovirus deleted for the 55 kDa E1B protein has been shown to specifically replicate in and kill p53-null tumor cells in vitro and in vivo (30). We have developed a similar approach whereby the interleukin 6 autocrine loop of human tumor cells is responsible for tumor-specific adenovirus replication. In addition, other groups have engineered the replication of adenovirus by placing the EIA gene under the control of tumor-specific promoters such as prostate-specific antigen and α-fetoprotein (31, 32). In all of these schemas, the oncolytic property of the adenovirus is being used as the anticancer agent. In another approach, Dion et al. (33) have used the codelivery of the adenovirus EIA and EIB sequences with a recombinant adenoviral vector encoding the HSV-TK gene to achieve local amplification of the vector and obtain augmentation of the adenovirus-mediated therapeutic effect in vivo. These approaches are thus based on the induction of high local concentrations of adenovirus to avoid untoward toxicity. Our retargeting strategy is a complementary approach to the same problem.

Thus, by permitting therapeutically significant levels of gene transfer while minimizing the toxicity associated with high numbers of virus particles, our findings suggest that strategies to enhance the transduction efficiency of recombinant adenoviral vectors will be of general clinical utility.

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Basic fibroblast growth factor enhancement of adenovirus-mediated delivery of the herpes simplex virus thymidine kinase gene results in augmented therapeutic benefit in a murine model of ovarian cancer.

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