Mesenchymal Stem Cell Delivery of TRAIL Can Eliminate Metastatic Cancer

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Abstract
Cancer is a leading cause of mortality throughout the world and new treatments are urgently needed. Recent studies suggest that bone marrow–derived mesenchymal stem cells (MSC) home to and incorporate within tumor tissue. We hypothesized that MSCs engineered to produce and deliver tumor necrosis factor–related apoptosis-inducing ligand (TRAIL), a transmembrane protein that causes selective apoptosis of tumor cells, would home to and kill cancer cells in a lung metastatic cancer model. Human MSCs were transduced with TRAIL and the IRES-eGFP reporter gene under the control of a tetracycline promoter using a lentiviral vector. Transduced and activated MSCs caused lung (A549), breast (MDAMB231), squamous (H357), and cervical (Hela) cancer cell apoptosis and death in coculture experiments. Subcutaneous xenograft experiments confirmed that directly delivered TRAIL-expressing MSCs were able to significantly reduce tumor growth [0.12 cm³ (0.04-0.21) versus 0.66 cm³ (0.21-1.11); P < 0.001]. We then found, using a pulmonary metastasis model, systemically delivered MSCs localized to lung metastases and the controlled local delivery of TRAIL completely cleared the metastatic disease in 38% of mice compared with 0% of controls (P < 0.05). This is the first study to show a significant reduction in metastatic tumor burden with frequent eradication of metastases using inducible TRAIL-expressing MSCs. This has a wide potential therapeutic role, which includes the treatment of both primary tumors and their metastases, possibly as an adjuvant therapy in clearing micrometastatic disease following primary tumor resection. [Cancer Res 2009;69(10):4134-42]

Introduction
Cancer remains one of the biggest causes of mortality and morbidity throughout the world (1). Present therapy focuses on varying combinations of surgery, chemotherapy, and radiation treatment. Despite healthcare improvements, metastatic disease remains poorly responsive to conventional therapy and a new modality of treatment is urgently needed.

Bone marrow–derived mesenchymal stem cells (MSC) are stromal cells that reside within the adult bone marrow. They are characteristically able to differentiate into bone, cartilage, and fat and have roles in the differentiation of hematopoietic cells. Recent studies have shown an ability of these cells to migrate to and incorporate within the connective tissue stroma of tumors (2–7). This property of MSCs can be used to directly targeting antitumor agents to tumor cells and their micrometastases with improvement in murine tumor models of glioma (4, 8), melanoma (6), and breast (5) and colon (7) cancers.

Tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) is a type 2 transmembrane death ligand that causes apoptosis of target cells through the extrinsic apoptosis pathway. TRAIL is a member of the tumor necrosis factor superfamily, which includes tumor necrosis factor and Fas ligand (9). The expression of tumor necrosis factor and Fas ligand leads to the damage of normal tissues in addition to their proapoptotic effect on transformed cells (10, 11), limiting their clinical applications. Conversely, TRAIL is able to selectively induce apoptosis in transformed cells but not in most normal cells (9, 12, 13), making it a promising candidate for tumor therapy. Intravenous delivery of recombinant TRAIL has, however, met with problems including a short pharmacokinetic half-life (12), necessitating frequent and high doses to produce the desired effect. The use of MSCs as a delivery vector promises to provide both targeted and prolonged delivery of this death ligand.

In this study, we express TRAIL in MSCs using a lentivirus conditionally activated by doxycycline. This system allows a mixed cell and gene therapy approach for metastatic cancers that can be activated and deactivated. We show that MSCs can be infected at high efficiency using the lentivirus system and delivery of TRAIL causes apoptosis of cancer cells through the extrinsic death pathway. In vivo models confirm a predilection of engraftment of MSCs within metastatic lung tumors with activation of TRAIL resulting in a significant reduction in metastasis number and complete clearance in 38% of mice.

Materials and Methods

Cell culture. Tissue culture reagents were purchased from Invitrogen unless otherwise stated. All cells were obtained from Cancer Research UK, London Research Institute, and cultured in DMEM and 10% fetal bovine serum unless otherwise stated. Human adult MSCs were purchased from Tulane University and cultured in α-MEM with 16% fetal bovine serum. Adipogenic and osteogenic differentiation of MSCs was done as described previously (14, 15).

TRAIL lentivirus construction and transfection of MSCs. A lentiviral plasmid (pPRL-cPPT-hPGK-mcs-WPRE) into which the Tet-On system elements had been introduced (ref. 16; a kind gift from O. Danos, University College London) was used as a backbone for the incorporation of TRAIL DNA. The existing reporter gene, MuSEAP, was excised using the MluI and EcoRV restriction sites. The IRES-eGFP sequence (from pENTR1A) was amplified and restriction sites were introduced by PCR and then inserted into the plasmid in place of MuSEAP. Subsequently, human TRAIL (amino acids 1-281; RZPD) was similarly amplified and restriction sites were introduced by PCR and then cloned into the lentivirus plasmid, via MluI
and BstXI restriction sites, next to the IRES-eGFP. The plasmid constructs were confirmed by DNA sequence analysis (Cogenics).

The lentivirus was produced by transfecting 293T cells with 15 mL Opti-Mem plus 10 mL of a solution made by mixing 3.6 mL polyethylenimine (Sigma-Aldrich) and 56.4 mL Opti-Mem to 600 μg TRAIL plasmid, 450 μg of the packaging construct pCMV-dR8.74, and 150 μg of a plasmid producing the VSV-G envelope, pMD.G2, and 60 mL Opti-Mem (both pCMV-dR8.74 and pMD.G2 were a kind gift from A. Thrasher, University College London). The lentivirus was concentrated by ultracentrifugation at 18,000 rpm (SW28 rotor, Optima LE80K Ultracentrifuge, Beckman) at 4°C and stored at −80°C before use.

Human MSCs were transduced with a multiplicity of infection of 10 virus particles for each cell and 4 μg/mL polybrene (Sigma-Aldrich).

Human TRAIL expression was verified by ELISA (R&D Systems) as per manufacturer’s instructions and by Western blot.

Western blots. Supernatants were centrifuged and cells were lysed in radioimmunoprecipitation assay buffer (PBS, 1% Igepal Ca-630, 0.5% sodium deoxycholate, 0.1% SDS; Sigma) supplemented with complete protease inhibitor cocktail (Complete-mini; Roche Diagnostics). Samples were denatured, resolved with a 10% SDS-polyacrylamide gel, and transferred using a semidry transfer method (Novablot; Pharmacia LKB).

Blots were then incubated with anti-TRAIL (1 μg/mL; H257 rabbit polyclonal antibody; ref. 17; Santa Cruz Biotechnology) or anti-actin (0.24 μg/mL; Sigma) antibodies and detected using enhanced chemiluminescence (GE Healthcare) as per manufacturer’s instructions.

Coculture experiments. Human MSCs permanently transduced with the full-length TRAIL plasmid (MSCFLTs) were plated with target cells. A total of 100,000 cells were plated in each 6-well plate. The following day, doxycycline or other active agents were added to the cocultures and left for 48 h. Staining of target cells was done with the fluorescent dye, DiI, as per manufacturer’s instructions (Invitrogen).

Apoptosis and cell death was assessed by flow cytometry (FACSCalibur or LSRII machines; Becton Dickinson). This was done on floating and adherent cells from cocultures using Annexin V-647 antibody (Invitrogen) and 5 μg/mL propidium iodide (PI; Sigma). 4’,6-Diamidino-2-phenylindole (DAPI; 2 μg/mL; Sigma) was used instead of PI when cancer cells were stained with DiI. Annexin V+/PI− cells were judged to be nonapoptotic. Annexin V+/PI+ cells were considered to be apoptotic. Annexin V+/PI+ cells were recorded as being dead.

The following compounds were used in coculture experiments: the pan-caspase inhibitor zVADfmk (1 μg/mL; Sigma), a soluble recombinant TRAIL (200 ng/mL; R&D Systems), and a neutralizing TRAIL antibody (250 ng/mL; R&D Systems).

Production of dominant-negative Fas-associated death domain cancer cells. Phoenix packaging cells were transiently transfected with
retroviral vector for the dominant-negative Fas-associated death domain (dnFADD)/GFP construct (18) or empty vector and the virus containing supernatant was added to infect AM12 packaging cells as described previously (19). The AM12 cell supernatant was added to Hela cells (30% confluence) with 5 μg/ml polybrene and the cells were selected with 1 μg/ml puromycin (20).

**Cell migration assay.** An *in vitro* cell migration assay was done to determine the tropism of MSCs for tumor cells according to previously described methods (4, 7, 21). One hundred fifty thousand cancer cells or 293T cells were plated in 800 μL medium on the bottom well of a Transwell plate (8 μm pore membrane; Becton Dickinson) for 24 h before 40,000 MSCs in 300 μL of the same medium were added to the top well. MSCs were allowed to migrate across the membrane for 24 h at 37°C. The cells attached to the top side of the membrane were removed, and the migrated cells on the bottom side were fixed, stained using a Rapid Romanowsky staining kit (Raymond Lamb), and counted (5 fields per well, triplicate wells) at ×10 magnification (Olympus BX40).

**Xenograft cancer models.** All animal studies were done in accordance with British Home Office procedural and ethical guidelines. Six-week-old NOD/SCID mice (Harlan) were kept in filter cages.

Subcutaneous tumors were obtained by the injection of 2 million MDAMB231 cells in 200 μL PBS subcutaneously into the left flank with a 29 gauge needle. Tumors were measured every 3 to 5 days with calipers, and the volume was calculated as \( \frac{4}{3} \pi r^3 \), where \( r \) is the radius. Metastatic lung tumors were produced by the intravenous delivery of 2 million MDAMB231 in 200 μL PBS into the lateral tail vein.

**In vivo use of TRAIL-expressing MSCs.** In the subcutaneous models, MSCFLTs labeled with CM-DiI (Invitrogen) as per manufacturer’s instructions were either delivered concurrently with the cancer cells; 2 million MDAMB231 with 0.75 million MSCFLT in 200 μL PBS, or after tumors had become established; 1 million MSCFLTs were injected into...
established subcutaneous tumors. In metastatic models, 0.75 million MSCFLTs were cocultured with Hela cells even at low 1:16 ratios compared with untreated controls. B, induced cell death and apoptosis is higher using MSCFLTs than with recombinant TRAIL (rhTRL) and can be partially blocked with blocking antibody (Ab), a pan-caspase inhibitor, is used compared with the control (con). *** P < 0.001; **, P < 0.01; *, P < 0.05.

Results

Characterization and TRAIL transduction of MSCs. Fully characterized MSCs were purchased from Tulane University and were shown to differentiate into fat and bone in differentiation assays and have the expected colony-forming efficiency ± SD (48 ± 2.83%; Fig. 1A). MSCs were stably transduced with our lentivirus expressing TRAIL and GFP under the control of doxycycline at different multiplicities of infection. A multiplicity of infection of 10 was used for further experiments producing 82.13 ± 0.40% successful transduction (GFP expression) at day 7 (Fig. 1B) while limiting the number of dead cells 4.8 ± 1.83%.

MSCFLTs were examined for TRAIL and GFP expression using flow cytometry, Western blots, and ELISA. Flow cytometry showed <0.5% GFP expression before activation with doxycycline, whereas, 48 h after doxycycline addition to the medium, this increased to 74.7 ± 2.5% (Fig. 1B). Withdrawal of doxycycline, after the cells had been exposed for 5 days, led to a fall in GFP expression with 12.2 ± 1.0% of cells weakly positive at day 7 (Fig. 1B; Supplementary Fig. S1).

ELISA and immunoblotting for TRAIL showed that it was only produced when the transgene was activated by doxycycline (Fig. 1C and D). Western blots showed TRAIL protein expression in MSCFLTs lysates was maximal after 2 days of doxycycline stimulus (Fig. 1D), but very little TRAIL protein remained after the doxycycline stimulus had been removed for 1 day, following a preceding doxycycline stimulus of 5 days (Fig. 1D).
dead cells increased significantly when doxycycline was added. This effect was observed with lung cancer (A549; apoptotic and dead cells increased from 3.1 ± 0.1% to 19.6 ± 0.8%; t = 0.001, t test; with the addition of doxycycline), breast cancer (MDAMB231; 15.4 ± 1.7-37.7 ± 6.5%; t = 0.001, t test), squamous cell cancer (H357; 12.5 ± 0.3-34.5 ± 1.0%; t = 0.001, t test), and cervical cancer (Hela; 6.7 ± 1.0-36.1 ± 3.5%; t = 0.0001, t test) cells (Fig. 2D). These apoptosed and dead cells were shown to come specifically from the cancer cell population by labeling the cancer cells with the fluorescent dye (DiI). Thus, 50.7 ± 2.7% of the Hela cell population were dead or apoptotic compared with only 8.3 ± 4.6% of the MSCFLT population (t < 0.0001, t test; Fig. 2D).

Coculture experiments were repeated with decreasing numbers of MSCFLTs. A significant increase in apoptosis and death of the cancer cells was achieved at all concentrations of MSCFLT used (t < 0.001 at ratio MSCFLT/Hela cells of 1:16, ANOVA). There was a cell ratio-dependent effect (Fig. 3A). This experiment underestimates the true killing capacity of MSCFLT cells as the seeding ratios do not account for any proliferation of cancer cells compared with MSCFLTs before the addition of doxycycline.

TRAIL-expressing MSCs kill cancer cells by TRAIL induction of the extrinsic apoptosis pathway. A TRAIL antibody with some ability to neutralize the bioactivity of TRAIL was added to the MSCFLT and Hela cell cocultures. The antibody was used at a dose to give maximal neutralizing effect (250 ng/mL; ref. 23). The amount of MSCFLT-induced death and apoptosis was significantly reduced with this antibody (38.03 ± 0.49% compared with 50.67 ± 3.8%; t < 0.001, ANOVA) but not back to baseline (11.48 ± 1.49%; Fig. 3B). We found that our doxycycline-induced MSCFLTs were potent inducers of death and apoptosis of Hela cells, with a larger proportion of apoptotic and dead cells in comparison with maximal doses (200 ng/mL) of recombinant soluble TRAIL (50.67 ± 3.8% compared with 27.50 ± 0.70%; t < 0.001, ANOVA; Fig. 3B).

The caspases are a family of closely related enzymes crucial to apoptosis. zVADfmk is a cell permeable, pan-caspase inhibitor. Application of this compound to the 1:1 cocultured MSCFLTs and Hela cells caused a 51.6% reduction in death and apoptosis (26.5 ± 0.7% compared with a DMSO-treated control 54.8 ± 1.0%; t < 0.001, t test) confirming the importance of caspases in the mechanism of TRAIL-induced cell death (Fig. 3C).

To confirm that the mechanism of MSCFLT-induced cancer cell death is via the extrinsic pathway, Hela cancer cells were retrovirally transduced with a dnFADD construct or an empty vector (18). The dnFADD consists of the death domain that binds to the TRAIL receptor but not the domain responsible for caspase-8 recruitment and the triggering of apoptosis. We observed a significant reduction (t = 0.018, t test) in death and apoptosis of Hela cells transduced with dnFADD after coculture with activated MSCFLTs (Fig. 3C). This data present strong evidence that MSCFLT cells induce apoptosis via the extrinsic pathway.

MSCs migrate toward some tumor cells. In vitro Transwell experiments showed the ability of MSCs to home toward tumors. A549, MDAMB231, and Hela cancer cell cultures were used to attract MSCs, with benign fibroblast 293T cells and medium alone used as controls. There was significantly increased migration to the MDAMB231 cells: 250.4 ± 0.8 cells per field compared with 98.6 ± 9.3 cells to 293T and 57.6 ± 7.6 toward the medium (t < 0.001, ANOVA). There was no significantly increased migration toward the A549 (92.0 ± 7.1) and Hela (81.0 ± 2.1) cells (Fig. 4A).

To examine if MSCFLTs could be traced to metastatic tumors, we used a lung metastasis model. Intravenously injected MDAMB231 cells produced lung metastases in all of 20 NOD/SCID mice. These tumors were visible at day 10 post-injection and grew to large metastases by day 30 (Fig. 4B). Dil-stained MSCFLTs were injected at day 10 and shown histologically to preferentially localize to lung tumor metastases by day 30 (Fig. 4C).
metastases (Fig. 4C). Dil-stained fibroblasts were not detected in the tumors or in the lungs 10 days after injection (data not shown). These histologic data show that MSCFLTs preferentially engraft and are maintained in the in vivo tumor environment compared with surrounding lung parenchyma, whereas fibroblasts are not.

**TRAIL-expressing MSCs reduce subcutaneous tumor growth in mice.** Two million MDAMB231 cells were coinjected with 0.75 million MSCFLT cells and the TRAIL transgene was activated with the addition of doxycycline at day 0 or 25 or never, with tumors harvested at day 42. A recent study has shown that coculture of MSCs with MDAMB231 cells did not alter the tumor growth (24). In our study with transduced MSCs, activation at day 0 resulted in a significantly reduced tumor size (0.12 ± 0.12 cm³ versus 0.66 ± 0.49 cm³; P < 0.001, two-way ANOVA) and weight (0.07 ± 0.06 g versus 0.33 ± 0.33 g; P < 0.05, Kruskal-Wallis); however, there was no change in the tumor growth when TRAIL was activated after the tumor had already become established at day 25 (Fig. 5A and B). TUNEL staining of excised tumors showed areas of apoptosis colocalized with Dil-labeled MSCFLT cells (Fig. 5C). The subcutaneous tumors were excised and digested to a single-cell suspension. Confocal microscopy of the ex vivo single-cell digestion and culture showed Dil-positive (red) cells with MSC morphology that costained with vimentin (green; DAPI, blue). Bar, 3 μm.

**Systemic delivery of TRAIL-expressing MSCs reduces and can eliminate lung metastases.** Intravenously injected MDAMB231 cells were used to produce lung metastases in NOD/SCID mice. MSCFLTs were then used as an intravenous combined cellular and gene therapy with delivery at days 7, 14, 21, and 28 (Fig. 6A). At day 35, tumor metastases were found in all mice (8 of 8) without MSCFLT and all mice with MSCFLT without the use of doxycycline (8 of 8). In the MSCFLT plus doxycycline arm, 3 of 8 mice were tumor-free (P = 0.032, χ²; Fig. 6B). In addition to the elimination of metastases with MSCFLT plus doxycycline, the lung weight (P < 0.01, ANOVA), which serves as a correlate for metastases load, was also significantly reduced in all of these mice. Similar results were achieved when metastases numbers per lung area was used as an endpoint (P < 0.001, ANOVA; Fig. 6C). Three mice had to be excluded from this latter analysis as the lungs did not inflate during the fixation procedure. MSCFLT cells delivered to control mice without doxycycline were unable to clear the metastases in any mice but did have less metastases per area (P < 0.001, ANOVA) and a lower lung weight (P < 0.05, ANOVA) than the untreated mice. Doxycycline treatment, however, produced a further significant reduction (P < 0.05, ANOVA; Fig. 6B and C). In a subsequent experiment, TRAIL and GFP were both shown to be expressed in vivo by MSCFLT with immunohistochemistry when mice were harvested 2 days after treatment with MSCFLT and doxycycline (Fig. 6D; primary antibody controls showed no staining; data not shown). TRAIL mRNA derived from the lungs of these mice was also increased (Fig. 6D).

**Discussion**

The ability of TRAIL to lead to tumor apoptosis and death without affecting normal cells makes it an extremely exciting molecule for tumor therapy. Here, we have shown that MSCs can be engineered to express TRAIL under the sensitive control of the Tet-On inducible system. These cells were able to kill cancer cell lines in vitro via the extrinsic death pathway to a higher degree than recombinant protein. In vivo, we show that TRAIL-expressing MSCs reduce the growth of early subcutaneous tumors, whereas, in a systemically delivered metastasis model, these cells reduced...
metastases but most significantly eliminated metastases in three mice.

We used MSCs as vectors of delivery due to observations that they appear to home to, or at least engraft preferentially, within tumors. MSCs also make an attractive therapeutic tool as they are widely acknowledged to be immunoprivileged. Theoretically, future cell therapies using allogenic MSCs could be used in patients without the use of prior immunomodulation (25). Alternatively, with the ease of harvest, culture, and infection of MSCs, the use of autologous cells may also be realistic.

It is important to consider the possible direct effects that MSCs may have on disease. Some studies have suggested intrinsic anti-neoplastic properties of these cells, with improvements in Kaposi’s sarcoma (2) and subcutaneous breast tumor models (26). Various mechanisms have been proposed for these effects, including Akt inhibition (2), nuclear factor-κB down-regulation (27), and the Wnt pathway (26). Conversely, MSCs have also been associated with a tumor-promoting effect in certain models, including increased growth and metastasis in colonic (28) and breast (24) subcutaneous tumor models. In our subcutaneous tumor model, we did not see an increase in lung metastases when the tumor cells were co-injected with MSCs. Furthermore, MSCs in our lung metastasis model appeared to have an antineoplastic effect.

To our knowledge, this is the first study that uses MSCs as a vector for a lentiviral delivery of a gene therapy for cancer. We used a lentivirus in view of their significant advantages over other vector systems. Adenoviral vector expression is transient and often produces a significant host immune response, whereas retroviruses may cause incorporation errors. Lentiviral vectors are less likely to cause insertional mutagenesis as the promoter can be modified extensively. Furthermore, they have the ability to stably transduce both dividing and quiescent cells (29), which is a further significant advantage when using stem cells that are often quiescent or slow-growing. Finally, our construct incorporates the Tet-On system allowing us to both turn on and, through withdrawal of doxycycline, off the protein expression, attractive in the view of possible

Figure 6. TRAIL-expressing MSCs reduce the growth of lung metastases. A, 2 million MDA MB231 cells were injected intravenously at day 0 followed by delivery or no delivery of MSCFLT cells at days 7, 14, 21, and 28 with or without doxycycline. B, representative histology of lung lobes in the three experimental groups. Metastases remained, but were reduced, after injection of MSCFLT without activation of the TRAIL construct, whereas TRAIL activation of MSCFLTs eliminated metastases in 3 of 8 mice (*P = 0.03). C, reduction in lung weight and metastases (met) number per lung area with the use of MSCFLTs both with and without doxycycline treatment. There was a further significant reduction between activated MSCFLTs compared with inactivated. ***, P < 0.001; **, P < 0.01; *, P < 0.05. D, immunohistochemistry showing cells expressing GFP (bar, 5 μm) and TRAIL (bar, 10 μm) and consecutive immunofluorescence sections showing these cells also express Dil. There is an increase in TRAIL mRNA from lung digests treated with MSCFLT and doxycycline. *, P < 0.05.
longevity of using stem cells as delivery vehicles in disease. Clinically, treatment could be timed to chemotherapy or radiotherapy regimens, with the expression turned off in between courses.

TRAIL is thought to operate physiologically in the immunosurveillance against tumors. Administration of a neutralizing anti-TRAIL antibody or the use of TRAIL knockout mice showed the increased susceptibility of TRAIL deficient mice to TRAIL-sensitive tumors and metastases (30–32). TRAIL-expressing MSCs in this study may act in a similar way, replacing the deficient immunosurveillance systems in the NOD/SCID mice leading to tumor cell destruction and prevention of metastasis. The property of metastasis prevention would be ideal as an adjuvant therapy in the treatment of many patients with solid organ tumors, who remain at significant risk of future metastatic disease despite primary tumor resection and chemotherapy and radiotherapy. Identifying these patients is now becoming a reality with the use of highly sensitive and specific molecular and cytologic techniques, which allow the detection of very small numbers of circulating tumor cells in the blood and bone marrow (33, 34), which could be amenable to MSC-directed TRAIL therapy.

The use of targeted TRAIL therapy could be widely applicable to many different cancers. Despite some cancers being resistant to the effects of TRAIL, an additive effect has been shown with the concomitant use of TRAIL with other antineoplastic agents that act at different positions in either intrinsic or extrinsic apoptotic pathways. For example, the down-regulation of Bcl-2 (35) or the DNA damage caused by chemotherapy can increase the effects of TRAIL therapy in various in vivo models (36–39).

One of the limitations of our study is the model used for the in vivo experiments. With the aim of future translational therapeutics, we used human cancer xenograft models, human MSCs, and human TRAIL constructs. It is important to consider that human TRAIL has only 65% homology to murine TRAIL (9), and there are also differences in the receptors in mice and humans. In the mouse, only one death-inducing receptor with homology to DR5 has been discovered in addition to two decoy receptors (mdsTRAILr1 and mdsTRAILr2; ref. 40). Consequently, the effects of TRAIL on the normal mouse cells may be different to the response of normal human cells.

In summary, we describe, for the first time to our knowledge, the use of TRAIL-expressing MSCs for the reduction and, in some cases, elimination of metastatic disease in a murine lung metastasis model. We believe that this therapy may have an important future therapeutic role in preventing metastatic recurrence in patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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