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# Systemic Treatment with a Recombinant erbB-2 Receptor-specific Tumor Toxin Efficiently Reduces Pulmonary Metastases in Mice Injected with Genetically Modified Carcinoma Cells

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## ABSTRACT

**Receptor-mediated targeted tumor therapy is an important applied consequence of the studies on the genetic causes of cancer. These therapy concepts have to be evaluated in novel animal models that reflect the molecular aberrations found in human tumors. Here we introduce an animal model that allows the evaluation of drugs directed against a surface receptor that is frequently altered in primary human adenocarcinomas. Tumor toxins are polypeptides in which a tumor cell-specific recognition domain and a toxic effector domain have been joined by DNA recombination *in vitro*. Tumor cell recognition is contributed by a single-chain antibody domain specific for the extracellular domain of the erbB-2 receptor [scFv(FRP5)] and cytotoxicity by the enzymatically active domain of a bacterial exotoxin (exotoxin A from *Pseudomonas aeruginosa*). The erbB-2 receptor is overexpressed in many primary human cancer cells and is a favorable target for directed tumor therapy. The fusion protein scFv(FRP5)-exotoxin A has previously been shown to be able to efficiently and specifically kill erbB-2 receptor-expressing tumor cells. We have investigated the potential of this tumor toxin to detect and eliminate metastasizing tumor cells upon systemic administration. Murine renal carcinoma cells genetically modified with human erbB-2 receptor and bacterial β-galactosidase genes form large pulmonary metastases when injected into the tail vein of BALB/c mice. Administration of the tumor toxin over a 10-day time period starting 1 day after tumor cell transplantation totally suppressed the formation of metastases. The treatment of animals 11 days after tumor cell transplantation, allowing the establishment of many pulmonary metastases, led to a drastic reduction in their number and size.**

## INTRODUCTION

The identification of the genetic changes that underlie cellular transformation and the biochemical consequences that result from structurally changed or inappropriately expressed genes are being used as a vantage point for the development of new anticancer agents (1). A promising strategy originates with the preferential recognition of tumor cells by the therapeutic agent when compared with normal cells. This can be achieved when the therapeutic agent is able to bind to a cell surface component that exhibits enhanced expression levels in tumor cells. This is frequently the case for the erbB-2 receptor (2). The erbB-2 receptor is a member of the type I/erbB receptor tyrosine kinase family (3) and is overexpressed in many primary human tumor cells of epithelial origin including those of the breast, ovaries, stomach, and lung. erbB-2 receptor expression in normal adult cells is low; the molecule is extracellularly accessible and causally involved in the process of malignant transformation (2). These aspects have made the erbB-2 receptor a suitable target for directed tumor therapy (4–6).

Tumor toxins are bifunctional polypeptides designed to recognize antigens overexpressed on the surface of tumor cells and to kill target cells via a cytotoxic effector domain (7–9). We previously described the fusion of a single-chain antibody fragment [scFv(FRP5)] that provides recognition specificity for the extracellular domain of the erbB-2 receptor (10, 11) to the enzymatically active portion of ETA[2] from *Pseudomonas aeruginosa* (9). This recombinant fusion protein, scFv(FRP5)-ETA, specifically and efficiently kills human erbB-2-expressing tumor cells *in vitro* and inhibits the growth of s.c. tumors *in vivo* (4, 9, 12).

The treatment of disseminated metastases by the systemic application of antitumor agents is still a most difficult task for the medical oncologist. In a novel mouse model, we investigated the systemic engagement of the erbB-2 receptor-specific tumor toxin in the prevention of formation and in the reduction of established pulmonary metastases. For this purpose, we genetically modified a murine renal carcinoma cell line, Renca, (13–16) with the human erbB-2 gene to confer sensitivity toward the recombinant toxin and with the bacterial β-galactosidase gene to provide for a sensitive means to detect tumor cells and quantitate metastasis formation. These genetic alterations did not affect the potential of the Renca cells to efficiently cause pulmonary metastases when injected i.v. into syngeneic BALB/c mice. The therapeutic efficacy of scFv(FRP5)-ETA on pulmonary metastases was investigated. When animals were systemically treated, starting 1 day after tumor cell inoculation, with 20 μg of tumor toxin for 10 consecutive days, the establishment of pulmonary metastases was completely suppressed. When treatment was started 11 days after tumor cell inoculation, upon formation of many metastatic nodules in the lung, the tumor toxin drastically reduced the number and size of the pulmonary metastases. Our experiments show that the systemic application of scFv(FRP5)-ETA has a very favorable therapeutic effect.

## MATERIALS AND METHODS

**Cell Culture.** Mouse renal carcinoma cells (Renca cells) and transfected cell clones Renca-lacZ and Renca-lacZ/erbB-2 were grown in RPMI 1640 supplemented with 10% FCS, 2 mM L-glutamine, 100 units/ml penicillin, 100 μg/ml streptomycin, 0.25 mg/ml Zeocin (for Renca-lacZ and Renca-lacZ/erbB-2), and 0.48 mg/ml G418 (for Renca-lacZ/erbB-2).

**Transfection of Renca Cells.** Renca cells were transfected with vector pZeoSV2/lacZ encoding for β-galactosidase (Renca-lacZ) and were subsequently cotransfected with the plasmids pSV2erbB-2N and pSV2neo (Renca-lacZ/erbB-2) using the calcium phosphate precipitation method. Stable transfectants were selected in medium containing Zeocin (Renca-lacZ) or Zeocin and G418 (Renca-lacZ/erbB-2).

**β-Galactosidase-dependent Staining of Stably Transfected Cells.** The medium was removed from the cell culture plates, and the cells were fixed with 0.05% glutaraldehyde for 5–10 min in PBS. The fixative solution was removed, and the cells were washed with PBS before staining with X-Gal solution containing 5 mM $K_3Fe(CN)_6$, 5 mM $K_4Fe(CN)_6 \times 3H_2O$, 1 mM $MgCl_2$, and 1 mg/ml X-Gal. The cells were incubated for 6 h at 37°C.

**X-Gal Staining and Quantitation of Pulmonary Metastases.** Excised lungs were fixed overnight at 4°C in PBS containing 2% formaldehyde and 0.2% glutaraldehyde. The fixative solution was removed, and the lungs were

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[2] The abbreviations used are: ETA, exotoxin A; mAb, monoclonal antibody; FACS,

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washed with PBS. Staining with X-Gal solution was performed as described above at 37°C in the dark for 10–12 h. Metastatic surface nodules were counted under a dissecting microscope.

**Immunoblotting.** Cell extracts were prepared by lysis of $5 \times 10^5$ cells in 700 μl of a buffer containing 1% NP40, 150 mM NaCl, 50 mM Tris-HCl (pH 7.5), and 5 mM EDTA. Proteins were separated by SDS-PAGE and electroblotted onto polyvinylidene difluoride membranes (Millipore, Bedford, MA). The erbB-2 receptor was visualized by incubation of the membranes with c-neu antibody (mAb 3; reactive with the mouse and human receptors; Calbiochem), followed by incubation with a horseradish peroxidase-coupled antimouse antibody (Sigma) and chemiluminescent detection with the enhanced chemiluminescence kit (Amersham, Aylesbury, United Kingdom).

**FACS Analysis.** Cells ($5 \times 10^5$) were incubated for 45 min with the erbB-2-specific antibody FRP5 and subsequently incubated with a FITC-labeled antimouse IgG (Serotec) according to the manufacturer's recommendations. Stained cells were washed twice in PBS supplemented with 5% FCS, and fluorescence was measured by FACScan (Becton Dickinson).

**Bacterial Expression and Purification of scFv(FRP5)-ETA Tumor Toxin.** The erbB-2-specific antibody toxin scFv(FRP5)-ETA was expressed and purified under denaturing conditions as described previously (12, 17). Purified recombinant proteins were renatured by dialysis against PBS containing 400 mM L-arginine and subsequently renatured by dialysis against PBS.

**Cell Viability Assay.** Cells were seeded in 96-well plates at a density of $10^4$ cells/well in growth medium. Various concentrations of scFv(FRP5)-ETA were added to triplicate samples, and the cells were incubated for 40 h. Ten μl of 10 mg/ml 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (Sigma) in PBS were added to each well, and the cells were incubated for another 3 h. Cells were lysed by the addition of 90 μl of 20% SDS in 50% dimethyl formamide (pH 4.7). The absorbance of each sample at 590 nm was determined in a microplate reader as a measure of the relative amount of viable cells in comparison to the number of cells grown without the addition of recombinant protein.

**Metastatic Growth of Transplanted Renca-lacZ and Renca-lacZ/erbB-2 Cells in BALB/c Mice.** Renca-lacZ or Renca-lacZ/erbB-2 cells ($10^5$) in 100 μl of PBS were injected into the lateral tail vein of female 4–6-week-old BALB/c mice. Five animals/group were sacrificed at weekly intervals for up to 4 weeks after tumor cell injection, and the lungs were excised. The number of pulmonary metastases was determined as described above.

**Antitumor Activity of scFv(FRP5)-ETA.** Female BALB/c mice (five mice/group) at 4–6 weeks of age were injected i.v. with $10^5$ Renca-lacZ or Renca-lacZ/erbB-2 cells in 100 μl of PBS at day 0. ScFv(FRP5)-ETA was administered systemically through the tail vein at a dose of 20 μg in 100 μl of PBS/day from either days 1–10 or days 11–20 after tumor cell injection. Control animals received PBS. Four weeks after tumor cell injection, all animals were sacrificed, and the lungs were excised and stained with X-Gal for visualization of the pulmonary metastases.

**Histology.** Tissues were fixed for histological analysis in 4% buffered formalin, embedded in paraffin, and sectioned at 4 μm. The sections were stained with H&E and examined for pathological findings.

## RESULTS

**Establishment of a scFv(FRP5)-ETA-sensitive Metastasis Model.** Mouse renal carcinoma cells (Renca) were established from a spontaneously arising kidney tumor in BALB/c mice. These cells efficiently form metastases in the lung upon transplantation into BALB/c mice through the tail vein (13, 18). We have based our experimental approach on this extensively characterized and widely used metastasis model. No reactivity of a mAb specific for the mouse or human erbB-2 receptor (mAb 3) was found when receptor expression was probed by Western blot or FACS analysis [Fig. 1, *A* (*Lane 1*) and *B*]. In accordance with this result, we found that parental Renca cells are insensitive to the action of the recombinant tumor toxin scFv(FRP5)-ETA. The function of this toxin is dependent on the binding to the extracellular domain of the human erbB-2 receptor, receptor-mediated internalization, and the inhibition of cellular protein synthesis through ADP ribosylation of elongation factor EF-2 (19, 20).

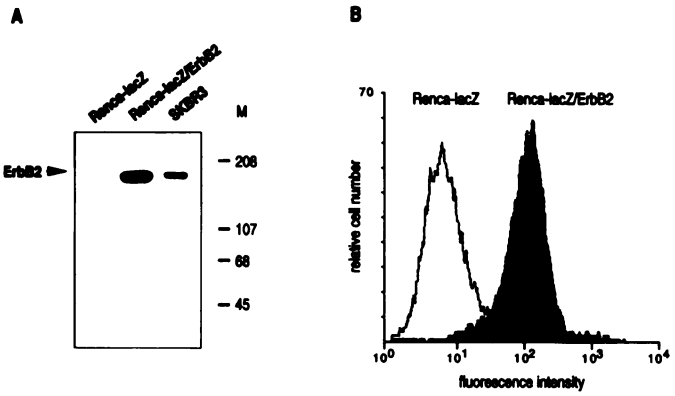


Fig. 1. Expression of erbB-2 receptor in renal carcinoma (Renca) cells. *A*, immunoblot analysis of cell extracts from Renca-lacZ (*Lane 1*) and Renca-lacZ/erbB-2 (*Lane 2*). SKBR3 human breast carcinoma cells served as a control (*Lane 3*). erbB-2 protein was detected with an anti-c-neu antibody (mAb 3; Calbiochem). The position of the 185-kDa erbB-2 molecule is indicated by an *arrow*. *B*, FACS analysis of Renca-lacZ and Renca-lacZ/erbB-2 cells. erbB-2 surface expression was measured with erbB-2-specific mAb FRP5 and subsequent incubation with a FITC-labeled antimouse IgG (Serotec).

Stable transfection of Renca cells with an expression vector encoding the human erbB-2 receptor yielded genetically modified cell clones which persistently express the receptor of 185 kDa on their cell surface (Fig. 1*A*, *Lane 2* and Fig. 1*B*). These cells are very sensitive toward the tumor-toxin. An $IC_{50}$ of 6 ng/ml was found and the cells loose their viability entirely upon 40 h of exposure to 100 ng/ml (Fig. 2). The cytotoxic activity of scFv(FRP5)-ETA was suppressed when a 100-fold molar excess of the parental mAb FRP5, which gave rise to the scFv domain, was included in the incubation (data not shown). The introduction of a second gene into the Renca cells, the lacZ gene encoding β-galactosidase, enabled us to conveniently and quantitatively visualize the tumor cells in culture (Fig. 3) or in organs upon staining with an appropriate substrate.

**Pulmonary Metastasis Formation by Renca-lacZ and Renca-lacZ/erbB-2 Cells.** The tumorigenic properties of Renca cells and their potential to induce metastatic growth after transplantation into mice have been well established (13, 16). To ascertain that the genetically modified derivatives Renca-lacZ and Renca-lacZ/erbB-2 maintain the properties of parental Renca cells, we investigated their ability to form metastases in BALB/c mice. For this purpose, $10^5$ Renca-lacZ or Renca-lacZ/erbB-2 cells were injected into the lateral tail vein of mice at 4–6 weeks of age. In four weekly intervals after the injection of the tumor cells, five animals/group were sacrificed, and the lungs were excised, fixed, and stained with X-Gal solution to visualize the disseminated tumor foci. Tumors on the surface of the lungs can be easily recognized and counted under a dissecting microscope.

The number of tumor nodules detected on the lung surface at 1, 2, 3, and 4 weeks after tumor cell injection is shown in Fig. 4. After 2 weeks, ~150 (Renca-lacZ) and ~200 (Renca-lacZ/erbB-2) metastases were detected. The numbers increased to approximately 280 and 320 after 3 weeks and increased to approximately 320 and 350 after 4 weeks. Histopathological analysis did not reveal metastasis formation in any other major organ (data not shown). We also analyzed the sera of the mice for the presence of antibodies directed against the human erbB-2 receptor or the bacterial β-galactosidase protein. No humoral immune responses against these proteins were found (data not shown). We conclude that the Renca-lacZ and Renca-lacZ/erbB-2 cells retain their potential for organ-specific metastasis formation.

**Systemic Treatment of BALB/c Mice with scFv(FRP5)-ETA Prevents the Establishment of Metastases.** Renca-lacZ/erbB-2 cells are able to metastasize in BALB/c mice, and they are sensitive to the action of scFv(FRP5)-ETA *in vitro*. These prerequisites enabled us to

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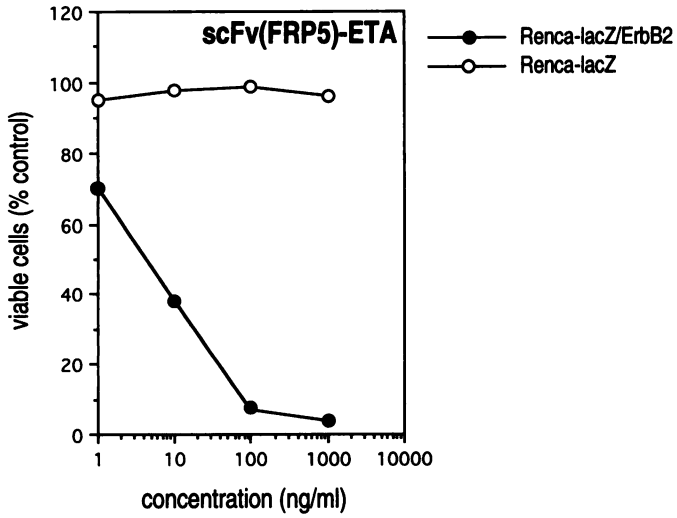


Fig. 2. *In vitro* cytotoxicity of scFv(FRP5)-ETA toward Renca-lacZ or Renca-lacZ/erbB-2 cells. The cells were incubated for 40 h with the indicated concentrations of erbB-2-specific toxin scFv(FRP5)-ETA. The relative number of viable cells was determined using an enzymatic assay as described previously.

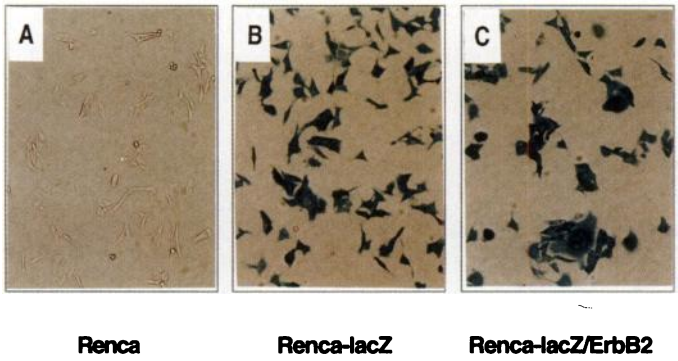


Fig. 3. Expression of β-galactosidase activity in transfected Renca cells *in vitro*. Untransfected Renca cells (*A*), lacZ-transfected Renca cells (*B*), or lacZ/erbB-2-transfected Renca cells (*C*) were fixed and incubated with X-Gal as a substrate (magnification, ×50).

investigate the antitumor activity of scFv(FRP5)-ETA *in vivo*. BALB/c mice (five animals/group) were injected i.v. with $1 \times 10^5$ Renca-lacZ or Renca-lacZ/erbB-2 cells. Treatment with scFv(FRP5)-ETA was started 1 day after the tumor cell injection. A total of 20 μg/day were administered in 100 μl of PBS by injection through the tail vein. Injections were repeated at daily intervals for 10 days. Control animals were treated for the same time period with PBS.

Twenty-eight days after tumor cell inoculation and 18 days after termination of treatment, the animals were sacrificed, their lungs were excised and stained with X-Gal, and surface pulmonary metastases were counted. Animals inoculated with Renca-lacZ or Renca-lacZ/erbB-2 cells and treated with PBS exhibited ~360 pulmonary metastases (Fig. 5*A*). The treatment of animals inoculated with Renca-lacZ cells served as a control for the toxin specificity. In this case, treatment with scFv(FRP5)-ETA did not influence the number of detectable metastases. In sharp contrast, four of five animals inoculated with Renca-lacZ/erbB-2 cells and treated with scFv(FRP5)-ETA were completely free of pulmonary metastases (Fig. 5*A*). Only two very small tumor foci were found in the lungs of the fifth animal. Lungs from each treatment group stained with X-Gal are shown in Fig. 5*B*. These results show that systemic administration of the tumor toxin efficiently prevents the establishment of metastases by Renca-lacZ/erbB-2 cells in the lungs. When the follow-up period of the nontreated

treated animals died within 6 weeks, whereas more than 50% of the treated animals survived longer than 44 weeks.

**Regression of Established Metastases by Treating BALB/c Mice with scFv(FRP5)-ETA.** We also tested the efficacy of treatment with the erbB-2-specific tumor toxin upon establishment of metastases. For this purpose, animals were inoculated with $10^5$ Renca-lacZ or Renca-lacZ/erbB-2 cells. The animals were left alone for 10 days to provide time for the tumor cells to establish lung metastases. At this time, ~150–200 metastases had formed (Fig. 4). Treatment with 20 μg/day scFv(FRP5)-ETA commenced on day 11 and continued to day 20 after tumor cell injection. At day 28, surface lung metastases were quantitated. Treatment with the tumor toxin caused a strong reduction in the number of pulmonary metastases in the mice inoculated with Renca-lacZ/erbB-2 cells. Only 85 tumor nodules were counted on the lung surface as compared with 380 tumor nodules found in mice inoculated with Renca-lacZ cells and treated with scFv(FRP5)-ETA in an identical fashion (Fig. 5*C*). Lungs from each treatment group stained with X-Gal are shown in Fig. 5*D*.

The lungs of the animals in the different treatment groups were also evaluated by histopathological examination (Fig. 6). A section through the lung of a noninoculated untreated control animal is shown in panel Fig. 6*A*. In the lungs of the Renca-lacZ/erbB-2-inoculated mouse treated with PBS from days 1–10, a large number of tumors can be seen (Fig. 6*B*). No tumors can be detected in the section from the mouse inoculated with Renca-lacZ/erbB-2 and treated with scFv-(FRP5)-ETA from days 1–10 after inoculation (Fig. 6*C*). The lungs of the mouse inoculated with Renca-lacZ cells not expressing the erbB-2 receptor and treated with scFv(FRP5)-ETA from days 1–10 after inoculation (Fig. 6*D*) showed the same number and size of metastases as the PBS-treated controls (Fig. 6*B*). Fewer and smaller tumor nodules are present in the lungs of animals treated from days 11–20 after inoculation of the tumor cells (Fig. 6*E*) when compared with those of the control animals treated with PBS during the same time period (Fig. 6*F*). We also compared the appearance of metastases before the onset of treatment with the situation found in animals treated from days 11–20. A larger number of metastases were found in the lungs of untreated animals 14 days after tumor cell inoculation (Fig. 6*G*) than in the animals treated from days 11–20 with scFv-

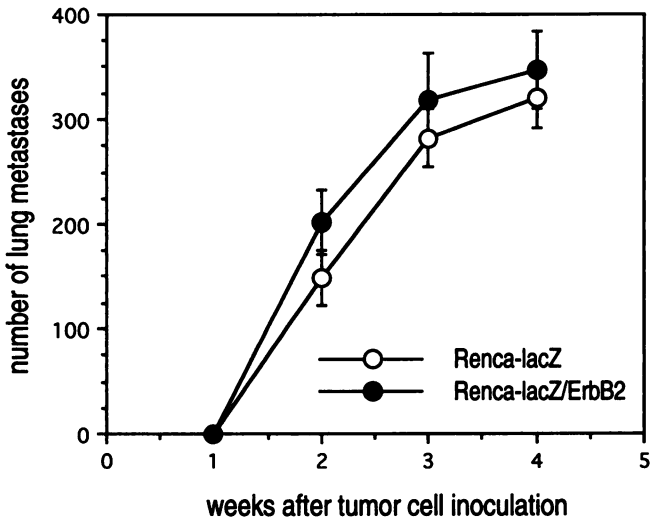


Fig. 4. Kinetics of pulmonary metastasis formation by Renca cells in BALB/c mice. Renca-lacZ or Renca-lacZ/erbB-2 cells ($10^5$) were injected into the lateral tail vein of each animal. At weekly intervals, up to 4 weeks after tumor cell injection, five mice from each group were sacrificed, and the lungs were excised. After fixation and incubation of the organs with X-Gal solution, tumor foci on the organ surface were counted as described

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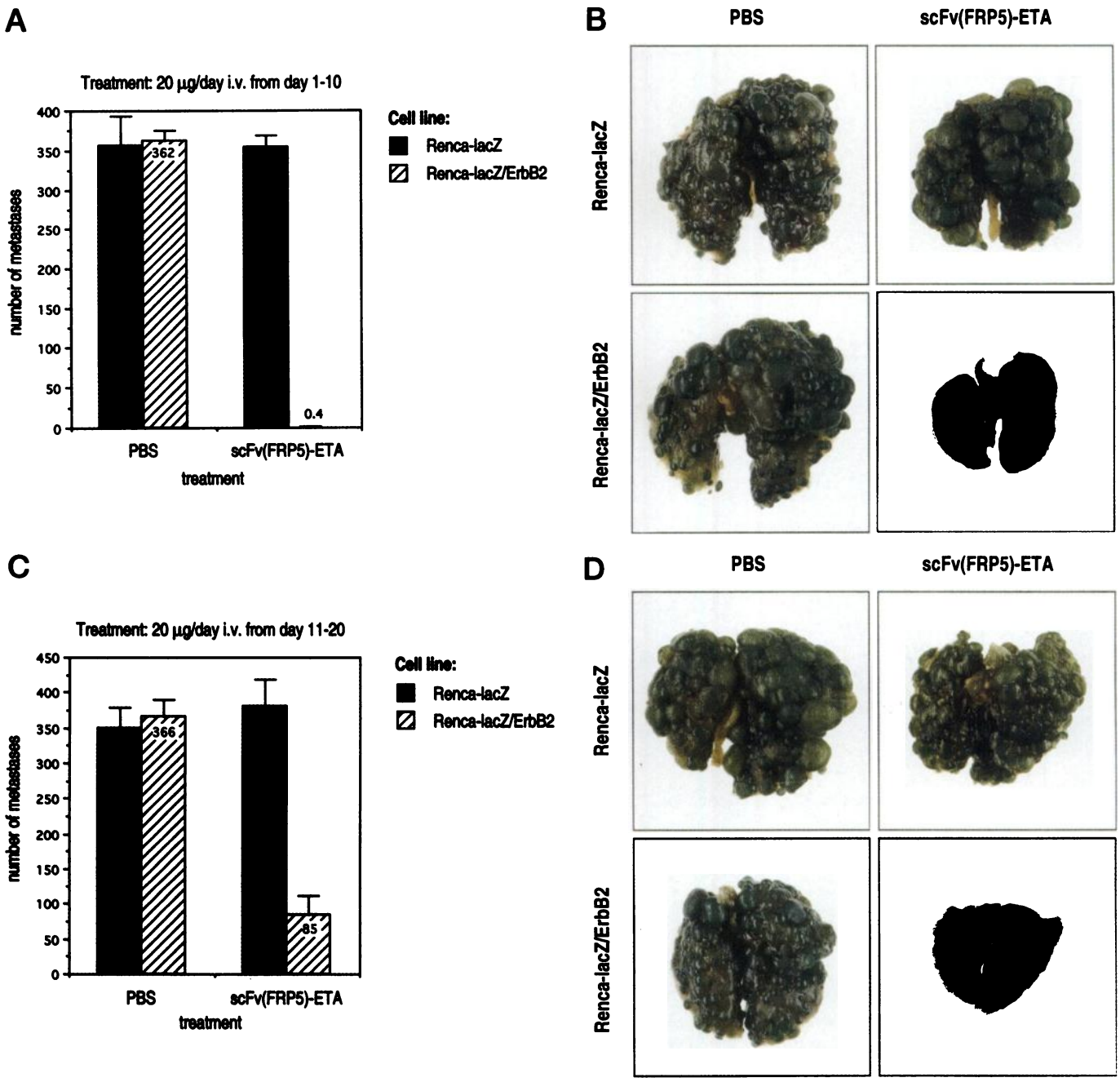


Fig. 5. Systemic treatment of BALB/c mice injected with Renca cells with the erbB-2-specific tumor toxin scFv(FRP5)-ETA. Mice of 4–6 weeks of age (five mice/group) were injected with $10^5$ Renca-lacZ or Renca-lacZ/erbB-2 cells in the lateral tail vein at day 0. Animals were treated i.v. with 20 µg/dose of the erbB-2-specific antibody toxin scFv(FRP5)-ETA either from days 1–10 or from days 11–20. Control animals were treated with PBS. All mice were sacrificed at day 28, the lungs were excised, and pulmonary metastases were visualized and counted under a dissecting microscope. *A*, the number of pulmonary metastases in mice treated with scFv(FRP5)-ETA or PBS from days 1–10 after tumor cell injection. *B*, lungs of animals treated with scFv(FRP5)-ETA or PBS from days 1–10 after tumor cell injection. *C*, the number of pulmonary metastases in mice treated with scFv(FRP5)-ETA or PBS from days 11–20 after tumor cell injection. *D*, lungs of animals treated with scFv(FRP5)-ETA or PBS from days 11–20 after tumor cell injection.

(FRP5)-ETA. We conclude that the majority of the metastases that have been established at the onset of treatment at day 11 are eliminated by the tumor toxin. The residual tumor cells that remain after the termination of treatment at day 20 probably expand into the metastases seen in Fig. 6*E*.

## DISCUSSION

Surgery and radiotherapy are effective means to treat primary tumor lesions and result in the cure of more than 50% of cancer patients (21). However, not all tumors can be efficiently operated upon. In particular, metastatic disease is still difficult to treat and remains the primary cause of death. For this reason it is mandatory to improve on antitumor agents that can be administered systemically and are able to detect and eliminate distant metastases. We have been developing targeted antitumor agents that are able to distinguish between normal cells and tumor cells and have previously shown that these agents are effective in model systems *in vitro* and *in vivo* (9, 22–26). We now extend the investigation of the usefulness of an erbB-2 receptor-specific tumor toxin to its effect on distant metastases.

Mouse renal carcinoma cells have been used extensively in the study of agents that might influence metastatic growth and survival after transplantation into animals (16, 27, 28). We improved this

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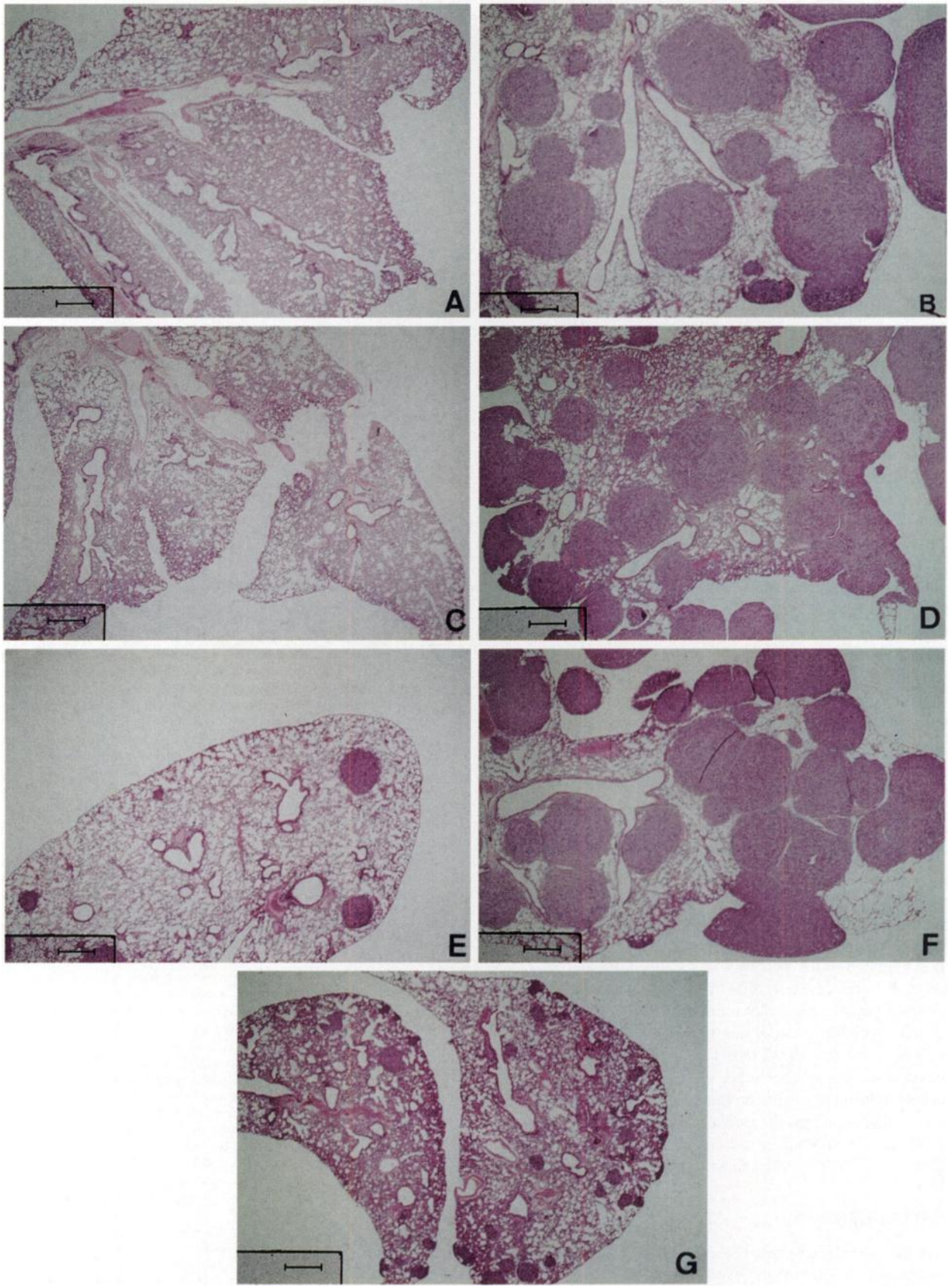


Fig. 6. Histopathological analysis of the lungs of mice injected with Renca cells and treated with scFv(FRP5)-ETA. Sections of lung tissue 28 days after tumor cell injection (*A–F*) from: *A*, an untreated control animal; *B*, a Renca-lacZ/erbB-2-injected mouse treated with PBS from days 1–10 after tumor cell injection (multiple, extensive metastases of an undifferentiated carcinoma); *C*, a Renca-lacZ/erbB-2-injected mouse treated with scFv(FRP5)-ETA from days 1–10 after tumor cell injection (normal lung, no microscopically detectable tumor cells); *D*, a Renca-lacZ-injected mouse treated with scFv(FRP5)-ETA from days 1–10 after tumor cell injection (multiple, extensive metastases); *E*, a Renca-lacZ/erbB-2-injected mouse treated with scFv(FRP5)-ETA from days 11–20 after tumor cell injection (few metastases); *F*, a Renca-lacZ/erbB-2-injected mouse treated with PBS from days 11–20 after tumor cell injection (multiple, extensive metastases). *G*, an untreated Renca-lacZ/erbB-2-injected mouse. The lungs were excised 14 days after tumor cell injection (multiple, dispersed metastases). *Scale bar*, 200 μm.

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