Antitumor Activity of Intraperitoneal Immunotoxins in a Nude Mouse Model of Human Malignant Mesothelioma

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ABSTRACT

Immunotoxins directed against human transferrin receptor have been evaluated in a nude mouse model of human malignant mesothelioma. Immunotoxins were constructed by linking ricin A chain to murine monoclonal antibodies reactive with the human transferrin receptor. A chain was obtained either by isolation from the parent toxin or by recombinant DNA techniques. These immunotoxins acted as potent in vitro cytotoxins against human malignant mesothelioma cells (H-MESO-1) (ID_{50}, 2 × 10^{-7} M). Cytotoxic potency and kinetics of cell kill were potentiated in vivo by the carbonyl isononole mnnosine. For in vivo trials, nude mice were injected i.p. with 6–9 × 10^6 human malignant mesothelioma cells 24 h prior to the start of i.p. immunotoxin treatments. The survival of tumor-bearing mice was extended by 149–404%, representing a probable cell kill of 2–4 logs. Specificity of this antitransferrin receptor immunotoxin response was confirmed by the ineffectiveness of irrelevant control immunotoxins and blockade of specific immunotoxin action by excess free antibody. Monensin showed limited in vivo potentiation of immunotoxin effect, but a derivative formed by esterification of monensin with linoleic acid gave improved survival times over treatment with immunotoxin alone.

Immunotoxins constructed with ricin A chain have significant tumoricidal activity in this model of regional antitumor therapy. These results may have direct relevance for treatment of i.p. malignancy in clinical settings.

INTRODUCTION

Human malignant mesothelioma is a neoplasm arising from the serosal surfaces of the body (1). This cancer is frequently associated with exposure to asbestos. Its incidence may be on the rise in the last decade. The disease is commonly treated by surgery, radiation, chemotherapy, or a combination of these therapies. With conventional therapy, however, this type of cancer is difficult to cure. The clinical behavior of human malignant mesothelioma is characterized by growth on serosal surfaces with progressive encasement of heart and visceria, and the concomitant development of malignant effusions. Blood borne metastases to other organs occur late in the natural progression of this malignancy. Because of this distinctive pattern of contained growth, malignant mesothelioma may be a candidate for regional therapy.

We have had a long interest in the use of monoclonal antibodies to deliver toxic agents directly to tumor cells. In particular, we have used monoclonal antibodies directed against human cell surface antigens conjugated to the enzymatically active A chain of ricin (2–6). Such immunotoxins have proven potent inhibitors of protein synthesis and highly selective cytoxins when tested on human cell lines in vitro. Their cytotoxic potency and kinetics of action are greatly improved in the presence of carboxylic ionophores (7). We have now employed these immunotoxins either alone or in conjunction with carboxyl isononole mnnosine for regional i.p. therapy in a nude mouse model of malignant mesothelioma. For these studies a human malignant mesothelioma of the pleura was established as a malignant peritoneal effusion in genetically athymic mice (8). Subcultures derived from this ascitic tumor model and passaged in vitro were shown to be highly sensitive to ricin A chain immunotoxins directed against the human transferrin receptor. These highly selective agents were tested for the ability to prolong the survival of mice bearing human malignant mesothelioma. Their lack of cross-reactivity with normal mouse tissues circumvents complications due to adverse toxicity or depletion. These immunotoxins alone produced specific antitumor effects in this nude mouse model of human peritoneal malignancy, and improved responses were seen in the presence of ionophores. The results may have relevance to the future use of immunotoxins for the clinical treatment of peritoneal malignancy.

MATERIALS AND METHODS

Chemicals. Monensin was purchased from Sigma Chemical Co. (St. Louis, MO) and a fatty acid derivative was constructed by esterification of its primary alcoholic function with linoleic acid. Each ionophore was prepared as a 10^{-5} M stock solution in ethanol and diluted to an appropriate final concentration in 0.14 M NaCl, 0.01 M NaHPO_4, pH 7.4.

Monoclonal Antibodies and Immunotoxins. The 7D3 monoclonal antibody (IgG_1) directed against the human transferrin receptor (aTfR) was produced in mice by injection of cultured human leukemia CEM cells. The anti-CEA murine monoclonal antibody (Ab-1, also IgG_1) was a gift of Abbott Laboratories. Native ricin A chain (A) was disulfide coupled to these antibodies after modification with N-succinimidyl-3-(2-pyridyldithio)propionate reagent (5) to produce both an anti-transferrin receptor immunotoxin aTfR-A and an anti-CEA immunotoxin (aCEA-A). Recombinant ricin A chain (A) produced in Escherichia coli has an amino acid sequence identical to the A chain of native ricin but is not glycosylated. It was disulfide linked to a 2-iminocarbonyl ionophore derivatized mouse monoclonal IgG_1 antibody (454A12) directed against the human transferrin receptor to produce a recombinant-based immunotoxin (aTfR-A). MOPC-21, a nonspecific murine monoclonal immunoglobulin, was similarly conjugated to produce a control immunotoxin (MOPC-A). These two conjugates made with recombinant DNA-derived ricin A chain were provided by Cetus Corporation.

Characterization of the Human Malignant Mesothelioma Cell Line H-MESO-1. Fragments of a malignant mesothelioma, obtained from a pleural biopsy of a 42-year-old man with heavy exposure to asbestos, were serially passaged in genetically athymic mice. After one year's...
serial passage as a s.c. tumor, minced samples of the growing tumor were propagated as a malignant peritoneal effusion. Malignant cells obtained from the ascites of mice inoculated with this tumor showed pathologic characteristics of human malignant mesothelioma, with epithelioid cells in nests, multiple mitotic figures, and autophagocytosis. Mice inoculated with 6–9 × 10^6 malignant cells died reproducibly from malignant ascites, 20–40 days after i.p. injection. Malignant cells stained strongly with antibodies directed against intermediate size cytoskeletons, but were negative for CEA, consistent with mesothelial origin. Description of H-MESO-1 growth in genetically athymic mice has been previously reported (8).

Cytotoxicity Assay of Immunotoxins. Human mesothelioma cells were cultured in tissue culture flasks in RPMI 1640 medium containing 10% fetal calf serum. RPMI 1640 was removed and the cells were treated with 1 ml of 0.05% trypsin 0.02% EDTA for 2 min. After 2 min almost all of the trypsin-EDTA solution was removed, leaving only a thin coating on the cells for an additional 8 min. After all the cells had become round and detached from the surface of the flask, 10 ml of RPMI 1640 was added to the cells. Using a 10-ml syringe with a 22 × 1–1.5 needle (Becton-Dickinson, Rutherford, NJ) the cells were aspirated and expelled several times in order to attain a single cell suspension. The cells were then seeded into microtiter wells (Becton-Dickinson Labware, Oxnard, CA), 31,000 cells in a final volume of 200 µl/well. The cells were incubated in the microtiter wells overnight 15 h at 37°C in 5% CO₂. The cells were further incubated with phosphate buffered saline alone (control) and specific additions of αTR-A, immunotoxin 2.5 x 10⁻⁴ M, 2.5 x 10⁻¹⁴ M, 2.5 x 10⁻¹⁸ M, 2.5 x 10⁻¹⁰ M, for 6 h at 37°C in 5% CO₂. Similar experiments were performed for the other designated immunotoxins. The medium was then removed and replaced with leucine-free medium supplemented with [¹⁴C]leucine (New England Nuclear Corp., Boston, MA; Amersham Corporation, Arlington Heights, IL) at concentrations of 0.4 µCi per well in 200 µl. Following a 2-h incubation at 37°C in 5% CO₂ the radioactive medium was removed and the cells were treated with 0.05% trypsin 0.02% EDTA (100 µl/well) for 10 min. The cells were then collected onto glass fiber filters with a Mash II cell harvester. Incorporation of [¹⁴C]leucine into cellular protein was measured by scintillation counting of the glass fiber discs.

Kinetics Assay. Human mesothelioma cells were released from the tissue culture flask using trypsin-EDTA ( Gibco) and resuspended in RPMI 1640 medium plus 10% fetal calf serum. These cells were then pelleted by centrifugation and resuspended at 5 x 10⁶ cells/ml in leucine free minimal essential medium (Gibco) supplemented with L-glutamine and penicillin-streptomycin. This cell suspension was added to tissue culture flask using trypsin-EDTA ( Gibco) and resuspended in a thin coating on the cells for an additional 8 min. After all the cells had become round and detached from the surface of the flask, 10 ml of RPMI 1640 was applied to the cells. Using a 10-ml syringe and a 22-gauge needle a 22 × 1–1.5 needle (Becton-Dickinson, Rutherford, NJ) the cells were aspirated and expelled several times in order to attain a single cell suspension. The cells were then seeded into microtiter wells (Becton-Dickinson Labware, Oxnard, CA), 31,000 cells in a final volume of 200 µl/well. The cells were incubated in the microtiter wells overnight 15 h at 37°C in 5% CO₂. The cells were further incubated with phosphate buffered saline alone (control) and specific additions of αTR-A, immunotoxin 2.5 x 10⁻⁴ M, 2.5 x 10⁻¹⁴ M, 2.5 x 10⁻¹⁸ M, 2.5 x 10⁻¹⁰ M, for 6 h at 37°C in 5% CO₂. Similar experiments were performed for the other designated immunotoxins. The medium was then removed and replaced with leucine-free medium supplemented with [¹⁴C]leucine (New England Nuclear Corp., Boston, MA; Amersham Corporation, Arlington Heights, IL) at concentrations of 0.4 µCi per well in 200 µl. Following a 2-h incubation at 37°C in 5% CO₂ the radioactive medium was removed and the cells were treated with 0.05% trypsin 0.02% EDTA (100 µl/well) for 10 min. The cells were then collected onto glass fiber filters with a Mash II cell harvester. Incorporation of [¹⁴C]leucine into cellular protein was measured by scintillation counting of the glass fiber discs.

RESULTS

In Vitro Cytotoxicity and Kinetics of Cell Kill. Upon entry into the cytosol, ricin A chain irreversibly damages ribosomes, and the resulting inhibition of protein synthesis accurately reflects its lethal effect on cells. Dose-response curves were generated by testing the inhibitory effects of various immunotoxins on the protein synthesis capacity of H-MESO-1 cells in culture (Fig. 1). The transferrin receptor specific immunotoxin (αTR-A) was a potent cytotoxin against H-MESO-1 cells, in contrast to the MOPC-A control immunotoxin. In a 6-h assay, the concentration of αTR-A, required to inhibit protein synthesis by 50% was 1 nM, assuming a molecular weight of 200,000 for the immunotoxin. At the highest concentration of αTR-A, a 6-h treatment was sufficient to inhibit nearly all protein synthesis. Furthermore, the ID₅₀ was substantially reduced using longer incubation times.

The aTR-A immunotoxin produced with native ricin A chain gave an identical ID₅₀ value as the recombinant based conjugate for H-MESO-1 cells. In addition the ID₅₀ value of both immunotoxins was reduced 100-fold (to 1 x 10⁻¹⁰ M) in the

Fig. 1. Cytotoxicity of specific and control immunotoxin on H-MESO-1 cells. H-MESO-1 cells were incubated with specific or control immunotoxin at the designated concentrations for 6 h before measuring [¹⁴C]leucine incorporation. Values, mean of triplicate determinations expressed as the % control mean ± SD.
presence of $10^{-7}$ m monensin or monensin linolate (data not shown). In contrast, these ionophores had no effect on the inactivity of the control MOPC-A immunotoxin. Moreover, the human directed αTIR-A immunotoxin alone or in the presence of monensin, produced no toxicity for NS-1 murine cells at concentrations up to $10^{-7}$ m (data not shown).

The time course for inhibition of cellular protein synthesis by immunotoxins was examined using H-MESO-1 cells (Fig. 2). In the presence of either the αTIR-A or αTIR-A, immunotoxin these cells lost their capacity for protein synthesis in a log-linear manner with a $t_{50}$ value of 150 min. This pattern changed radically upon inclusion of the carboxylic ionophore monensin during exposure to immunotoxin (Fig. 2). Both the native and recombinant based A chain conjugates displayed biphasic kinetics characterized by a 45-min lag and subsequent rapid decline in protein synthesis having a $t_{50}$ value of 10 min.

Specific immunotoxin constructed with either native ricin A chain or with recombinant ricin A chain were both potentiated to the same degree by monensin (Fig. 2). Importantly, ionophore improved the kinetics of the recombinant conjugate preparation, which obviates any possibility of even slight ricin B chain contamination. Therefore, in the transferrin receptor system, monensin potentiation of the immunon conjugate did not require the presence of B chain, as has been suggested for ammonium chloride potentiation in other target systems (9).

**In Vivo Trials of Immunotoxin.** The survival curves of genetically athymic mice implanted with H-MESO-1 and treated with vehicle or specific immunotoxins is shown in Fig. 3. The median survival of mice treated with various control proteins as well as specific immunotoxins is listed in Table 1. Only treatment with antitransferrin receptor reactive immunotoxins prolonged survival. Unmodified anti-human transferrin receptor antibody (αTfR), anti-CEA immunotoxin (αCEA-A) and control MOPC immunotoxin (MOPC-A), in the presence or absence of ionophore, had little or no effect on the survival of tumor-bearing mice (Tables 1 and 2). The majority of mice died of massive malignant ascites. However, for the specific immunotoxin-treated mice the cause of death was frequently extra-peritoneal tumor. Similar but less marked results were seen when injections with specific immunotoxins started on day 6, and continued with the same dose and schedule (increased survival of treated mice 140–180%).

Monensin induced a 15-fold faster rate of immunotoxin mediated cell kill in vitro (Fig. 2) therefore ionophores were used in combination with these immunotoxins in an effort to improve the survival times of tumor-bearing mice. While monensin itself gave no improvement over immunotoxin treatment alone, its fatty acid derivative monensin linolate did provide a substantial prolongation of survival (Fig. 3C). Furthermore, the number of long-term survivors (>100 days) was also increased.

To demonstrate that the increased survival produced by specific immunotoxin treatment was mediated via interaction with the transferrin receptor we performed an antibody block in vivo. Specific immunotoxin was injected along with an excess of uncoupled antitransferrin receptor antibody, to preoccupy the target epitope on the receptor. Survival of mice treated with this combination was similar to that of the vehicle controls (Fig. 3D).

The appearance of malignant ascites and eventual death of mice treated with immunotoxins might be explained by the emergence of cells selected for resistance to anti-transferrin receptor antibody immunotoxin. To address this question, on two occasions malignant ascites was obtained from immunotoxin-treated mice which had greatly prolonged survival (200% increase in length of survival). This ascites was reintroduced into tissue culture. In vitro dose-response curves, determined as described above, showed that sensitivity to anti-human transferrin immunotoxin was retained (ID$_{50}$ 1–2 × $10^{-9}$ m), indicating that emergence of resistant cells was not responsible for the appearance of tumor ascites.

**Lethality Titration Results.** Having demonstrated increased survival for immunotoxin treated mice, we attempted to determine the log cell kill by performing a lethality titration. Control mice were injected with serial dilutions of mesothelioma cells and survival was determined. Mice injected with $1 \times 10^6$ cells had a median survival of 34.5 days, while mice injected with $1 \times 10^5$ cells had a median survival of 85 days. Table 3 shows the median survival times corresponding to the titrated innocula of malignant cells. Since mice injected with $6 \times 10^6$ cells and treated with immunotoxin (α-TIR-A$_2$) had a median survival of 84 days, it can be inferred that the immunotoxin treatment produced a biological effect equivalent to 3–4 log tumor cell kill (or elimination of >99.9% of H-MESO-1 cells).

**DISCUSSION**

There remains considerable interest in the clinical applications of monoclonal antibodies to selectively deliver toxic agents to cancer cells. One of the challenges in the use of such immunotherapy is to develop a method for insuring that the administered immunoconjugates will be able to reach the site of tumor growth. This aspect of immunotherapy is especially challenging for advanced disseminated cancer where therapy is required in multiple anatomical locations and organs. Depending on the location of the tumor, numerous factors may influence the effectiveness of the administered immunon conjugates. Various aspects of pharmacokinetic behavior including sites of metabolism and elimination by components of the host immune system may be obstacles to this approach (10–12). We have therefore decided to evaluate the effectiveness of immunotoxins in a regional model of tumor therapy. For logistical reasons the peritoneal cavity is the most practical site for experimental studies of tumors in mice and may provide the best location for regional therapy in humans. Therefore, we have adapted a human tumor for growth in the peritoneal cavity as a model to obtain basic information about the in vivo efficiencies of immunotoxins as regional antitumor agents.
INTRAPERITONEAL IMMUNOTOXINS

Fig. 3. Effect of immunotoxin treatment on survival of tumor-bearing mice. A and B, effect of α-TfR-A and α-TfR-A, on mouse survival; C, monensin linoleate effect on prolongation of survival produced by immunotoxin; D, reversal of immunotoxin prolongation of survival by excess unconjugated antibody.

Table 1 Survival of mice bearing H-MESO-1 as i.p. ascites following treatment with specific or control proteins

<table>
<thead>
<tr>
<th>Test</th>
<th>Median survival (days) test/control</th>
<th>% Control survival</th>
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</thead>
<tbody>
<tr>
<td>αTfR-A</td>
<td>84.0/20.8</td>
<td>404</td>
</tr>
<tr>
<td>αTfR-A</td>
<td>65.8/29.7</td>
<td>224</td>
</tr>
<tr>
<td>αTfR-A</td>
<td>35.0/20.8</td>
<td>168</td>
</tr>
<tr>
<td>αTfR-A</td>
<td>44.5/29.7</td>
<td>149</td>
</tr>
<tr>
<td>αTfR-A</td>
<td>60.0/31.0</td>
<td>192</td>
</tr>
<tr>
<td>αTfR-A</td>
<td>24.1/27.1</td>
<td>89</td>
</tr>
<tr>
<td>αCEA-A</td>
<td>30.0/27.1</td>
<td>111</td>
</tr>
<tr>
<td>MOPC-A</td>
<td>28.0/29.7</td>
<td>94</td>
</tr>
<tr>
<td>PBS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* PBS, phosphate buffered saline.

Table 2 Survival of mice bearing H-MESO-1 as i.p. ascites following treatment with specific or control proteins and carboxylic ionophores

<table>
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<tr>
<th>Test</th>
<th>Median survival (days) test/control</th>
<th>% Control survival</th>
</tr>
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<tr>
<td>Monensin</td>
<td>34.0/34.0</td>
<td>100</td>
</tr>
<tr>
<td>Monensin linoleate</td>
<td>32.0/34.8</td>
<td>96</td>
</tr>
<tr>
<td>αTfR-A + monensin</td>
<td>22.8/27.1</td>
<td>84</td>
</tr>
<tr>
<td>αTfR-A + monensin</td>
<td>64.0/20.8</td>
<td>308</td>
</tr>
<tr>
<td>αTfR-A + monensin</td>
<td>66.9/29.7</td>
<td>225</td>
</tr>
<tr>
<td>αTfR-A + monensin</td>
<td>41.0/20.8</td>
<td>197</td>
</tr>
<tr>
<td>αTfR-A + monensin</td>
<td>31.0/27.1</td>
<td>114</td>
</tr>
<tr>
<td>αTfR-A + monensin</td>
<td>30.0/27.1</td>
<td>111</td>
</tr>
<tr>
<td>MOPC - A + monensin</td>
<td>24.0/29.7</td>
<td>81</td>
</tr>
<tr>
<td>αTfR-A + monensin</td>
<td>65.1/29.7</td>
<td>219</td>
</tr>
<tr>
<td>αTfR-A + monensin</td>
<td>110.0/31.0</td>
<td>355</td>
</tr>
<tr>
<td>Monensin linoleate</td>
<td></td>
<td>183</td>
</tr>
</tbody>
</table>

Table 3 Lethality titration experiment

<table>
<thead>
<tr>
<th>Group no.</th>
<th>No. Survivors/total</th>
<th>Treatment code</th>
<th>Median survival (days)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1/5</td>
<td>10⁶ cells</td>
<td>35.5</td>
</tr>
<tr>
<td>2</td>
<td>0/5</td>
<td>10⁶ cells</td>
<td>38.5</td>
</tr>
<tr>
<td>3</td>
<td>0/5</td>
<td>10⁵ cells</td>
<td>47.5</td>
</tr>
<tr>
<td>4</td>
<td>2/5</td>
<td>10⁵ cells</td>
<td>88.0</td>
</tr>
<tr>
<td>5</td>
<td>4/5</td>
<td>10⁵ cells</td>
<td>&gt;90.0</td>
</tr>
</tbody>
</table>

This study used immunotoxins directed against human transferrin receptor. The transferrin receptor is a cell surface protein whose expression is clearly linked to cell proliferation (13). Not only is the expression of this receptor greatly increased in proliferating normal and malignant cells, but induction of the receptor appears to require cellular proliferation. Antibody to the receptor can inhibit cell growth in some instances (14, 15). The receptor appears to be the recognition site for natural killer cells (16, 17), although this has been disputed in some studies (18). The tumor-promoting phorbol esters induce hyperphosphorylation of the transferrin receptor with concomitant reduction of its cell surface levels (19). Increased surface transferrin receptor expression is seen on cells with pleiotropic drug resistance to chemotherapeutic drugs (20). Transferrin receptors therefore are a suitable model as a tumor associated antigen for experimental studies of immunotoxins.

A number of other investigators have characterized immunotoxins composed of anti-transferrin receptor antibodies and ricin A chains or A chain-like inhibitors of ribosomes or other components of protein synthesis. Trowbridge and Domingo (14) described an anti-transferrin receptor antibody-ricin A chain conjugate which was highly cytotoxic to cultured leukemia CEM cells. Ramakrishnan and Houston demonstrated that the cytotoxicity of a pokeweed antiviral protein-containing immunotoxin directed against transferrin receptor could be potentiated by chloroquine and other lysosomotropic amines (21). Bjorn et al. (22) developed a monoclonal antibody-ricin A chain immunotoxin active against MCF-7 breast cancer carcinoma cell line in vitro. Fitzgerald et al. (23) and Pirker et al. (24, 25) described immunotoxins composed of anti-transferrin receptor antibody conjugated to pseudomonas exotoxin. These were potent in vitro cytotoxins and markedly inhibited growth of human ovarian cancer in a nude mouse model. Studies in our laboratory7 have shown anti-transferrin receptor immunotoxins to be highly active against pancreas and colorectal tumor cell lines. Therefore these immunotoxins seem to act as general antitumor cytotoxins.

The distribution of transferrin receptor on normal tissues will be crucial to the clinical utility of this immunotoxin.

7 T. W. Griffin, unpublished data.
Transferrin receptors are found on a limited number of normal tissues. In particular, proliferating tissues such as gastrointestinal epithelium, erythroid myeloid precursors in bone marrow, and the endometrial epithelium show moderate reactivity with anti-transferrin receptor monoclonal antibody in immunoperoxidase assays. Other tissues, such as alveolar macrophages, brain capillaries, or placental synciotrophoblasts, may express transferrin receptor by immunohistochemistry (26). Various monoclonal antibodies to the transferrin receptor show different tissue binding patterns, which may be due to varying reactivity for different epitopes (27, 28). None of the monoclonal antibodies would be expected to bind extensively to normal human peritoneal mesothelium. Thus, local peritoneal irritation should not be produced by anti-transferrin receptor antibody-toxin conjugates.

Monensin is a carboxylic ionophore which catalyzes ion fluxes across cell membranes. It has been reported to potentiate the cytotoxic activity of ricin A chain immunotoxins directed against a variety of tumor-associated antigens (7, 29–31). Carboxylic ionophores greatly speed the kinetics of immunotoxin action apparently by facilitating the divergence of these toxins from endocytotic pathways, so that they can contact and inactivate ribosomes (31). This study has shown that monensin elevates the in vitro activity of antitransferrin receptor immunotoxins on H-MESO-1 mesothelioma cells, both in terms of cytotoxic potency and speed of action. Previous studies have shown that this enhancement by ionophores is also manifested by a greatly increased extent of in vitro cell kill when measured by clonogenic assays (31). The limited in vivo effect of monensin in this model system is surprising, but may be due to rapid extraperitoneal transit or tissue uptake of this lipophilic drug. Monensin and its linoleic acid derivative are equivalent in action apparently by facilitating the divergence of these toxins to different tissue binding patterns, which may be due to varying reactivity for different epitopes (27, 28). None of the monoclonal antibodies would be expected to bind extensively to normal human peritoneal mesothelium. Thus, local peritoneal irritation should not be produced by anti-transferrin receptor antibody-toxin conjugates.

REFERENCES

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