Malignant epithelial cancers, the major cause of cancer morbidity and mortality, arise in organs composed of both epithelial and mesenchyme-derived stromal cells, such as fibroblasts, myofibroblasts, endothelial cells, pericytes, smooth muscle, and hematopoietic cells. During disease progression, the stroma of primary, invasive lesions as well as distant metastases changes in architecture, gene expression, secretion of soluble mediators, and extracellular matrix deposition; in turn, the malignant epithelial cells can undergo reversible epithelial-mesenchymal transitions (1–5). The fibroblast response in several types of human cancer is characterized by the induction of an integral cell surface protein, fibroblast activation protein-α (FAPα; refs. 6, 7), a serine protease (8–11) with highly restricted expression in developing organs, wound healing, and head and neck cancers with no signs of intolerability. Analysis of chemically distinct conjugates, resistance models, and biomarkers implicates a unique mode of action, with mitotic arrest and apoptosis of malignant epithelial cells coupled to disruption of fibroblastic and vascular structures.

Conclusions: We show that mAb FAP5-DM1 combines excellent efficacy and tolerability and provides a first assessment of the mode of action of a novel drug candidate for tumor stroma targeting, thus encouraging further development toward clinical testing of this treatment paradigm.
With this testing scheme in place, we have developed specific, high-affinity mAbs that bind shared epitopes of mouse, human, and monkey FAPα and generated immunoconjugates with distinct maytansine derivatives and diverse linker moieties. We show that these stroma fibroblast-targeted immunoconjugates combine excellent efficacy and tolerability and provide a first assessment of their mode of action.

Materials and Methods

Cell lines and tumor tissues. FaDu (human squamous cell carcinoma; ATCC HTB-43), HT1080 (human fibrosarcoma; ATCC CCL-121), and HT1080 v1.33 and HT1080 13.8 (human fibrosarcoma cell lines expressing recombinant human and mouse FAPα, respectively) cultures were maintained in RPMI 1640 supplemented with 10% heat-inactivated fetal bovine serum and 1% glutamine. In addition, the recombinant cell lines were kept in 200 μg/mL G418. The human tumor xenografts CXF158 (colon carcinoma), LXF629 (non-small cell lung adenocarcinoma), and PAXF739 (pancreatic adenocarcinoma) were established at Oncotest, by s.c. implantation of surgical tumor specimens in immunodeficient mice, and were maintained by serial passaging (20).

Antibody generation and characterization. The mAb FAP5 was generated after immunization of BALB/c FAPα−/− mice with recombinant murine CD8-FAPα fusion protein (10) by hybridoma technology. Reactivity of mAb FAP clone 5 to recombinant human (9), mouse (10), and cynomolgus FAPα was tested by ELISA and fluorescence-activated cell sorting using the FAPα-negative human fibrosarcoma cell line...
HT1080 and cloned derivatives expressing human and mouse FAPs. Recombinant His-tagged cynomolgus monkey FAPs for ELISA was generated by amplification of the cDNA (amino acids 27-760) by PCR with primers derived from the human sequence and cloning into the expression vector pSecTag2. The protein was expressed by transient transfection of HEK293 freestyle cells (Invitrogen) and purified on Ni-columns.

**Affinity determination by surface plasmon resonance.** Anti-mouse IgG antibody (≈200 resonance units) was immobilized using the amine coupling kit on a CM5-biosensor chip in a Biacore 2000 (Biacore AB, Uppsala, Sweden). mAb FAP5 was bound to the sensor chip (5.2 μg/mL for 3 min). Association and dissociation of recombinant human, mouse, and cynomolgus FAPs were measured for 5 min at concentrations from 3.7 to 300 nmol/L. Affinity variables were calculated using the separate cure fit algorithm of the BIAevaluation software version 4.1 (Biacore).

**Immunoconjugates.** The mAb FAP5-maytansinoid conjugates mAb FAP5-5P-DM1 (here designated mAb FAP5-DM1), mAb FAP5-SPDBDM4 (mAb FAP5-DM4), and mAb FAP5-SMCC-DM1 were prepared at Immunogen following published procedures (23–25).

**Cell proliferation assay.** The cytotoxic activity of the DM1 and DM4 conjugates was tested on untransfected and human FAPs-transfected HT1080 cells using a MTS staining system. The absorbances were read at 490 nm to determine the concentration of the antibody conjugate needed to achieve 50% inhibition of tumor cell growth (IC50). The four-variable logistic curve-fit algorithm of the GraphPad Prism software version 3.03 (GraphPad) was used.

**Human xenograft tumor models in mice.** Female athymic NMRI nude mice (Taconic) ages 6 to 8 weeks were inoculated s.c. with FaDu cells (1 × 106/100 μL PBS) in the right flank. For the lung, pancreas, and colon carcinoma models, mice were grafted with tumor fragments in the right flank. Tumor growth was measured three times a week and the tumor volume was determined using the formula: π/6 × larger diameter × (smaller diameter)2. Studies were terminated when tumors reached a size of 1,500 mm3 or when tumors were judged to adversely affect the well-being of the animals. Treatment was administered i.v. to groups of six or eight mice and commenced when tumors reached an average size of 1,500 mm3 or when tumors were judged to adversely affect the well-being of the animals. Treatment was administered i.v. to groups of six or eight mice and commenced when tumors reached a size of 100 to 250 mm3. Body weights were monitored three times per week. All animal experiments were done according to the legal requirements in Austria as well as to the guidelines of the American Association for Laboratory Animal Science.

**Immunohistochemistry.** Frozen-fresh tumor samples were analyzed using the avidin-biotin complex immunoperoxidase procedure as described previously (7). For the analysis of FAPs expression in mouse tissues and biomarker modulation in tumor xenografts, NMRI nude mice were grafted s.c. with the human tumors as described above. Mean tumor volume at the start of the experiment was ~100 mm3. Tumors were then excised either before treatment or 48 h, 72 h, and 5 days after i.v. administration of the compounds and at the end of the experiment. For FAPs detection in mice tissues, mAb FAP5 was biotinylated and detected with the avidin-biotin complex method as before. The binding of the antibodies was visualized with 3,3′-diaminobenzidine solution. Slides were then dehydrated and counterstained with Harris’ hematoxylin. For double immunostaining of tumor cells and stroma components, an indirect immunofluorescence method was used. Apoptosis was determined by a terminal nucleotidyl transferase–mediated dUTP nick end labeling assay using the ApopTag Fluorescein In situ Apoptosis Detection Kit (Chemicon International) and analyzed by fluorescence microscopy.

**Antibodies.** Primary antibodies used included anti-human/mouse FAPs/mb FAP5, anti-cytokeratin 18 (clone DC10; DAKO), anti-smooth muscle actin (DAKO), anti-collagen type IV (Chemicon), anti-mouse endothelial marker Meca32 (BD Pharmingen), antibody to Ser10-phosphorylated histone H3 (Upstate Biotechnology), anti-mouse CD11b (Bioscience), and anti-pan-macrophage marker F4/80 (Bioscience). Alexa-conjugated secondary antibodies were obtained from Molecular Probes.

### Results

**Generation of FAPα-specific, species cross-reactive antibodies.** FAPα-/- mice (26) were used to generate antibodies that recognize an epitope shared by human FAPs and its close orthologues in the mouse and cynomolgus monkey. The lead antibody, mAb FAP5, binds to recombinant human, cynomolgus monkey, and mouse FAPs with affinities of 5, 4, and 0.6 nmol/L, respectively, as determined by surface plasmon resonance assay. The pattern of FAPs expression in normal human and mouse tissues as well as tumor tissues has been defined previously in considerable detail by immunohistochemistry and RNA analysis (7, 12–14, 16, 27). For mAb FAP5, we confirmed the restricted antigen expression in a panel of normal adult human tissues, normal mouse tissues, and a series of epithelial cancers. As predicted, mAb FAP5 reacts with tumor stromal fibroblasts in colorectal, breast, head and neck, and pancreatic carcinomas, whereas epithelial cancer cells and stromal fibroblasts of normal tissues lack FAPs expression, with the known exception of fibroblasts in the uterus and scattered dermal fibroblasts (6, 16, 28). Likewise, analysis of human tumor xenografts grown in nude mice revealed staining of activated stromal fibroblasts of mouse origin, but no immunoreactivity was observed with human tumor cells (Fig. 1). In fluorescence-activated cell sorting assays, mAb FAP5 binds to HT1080 cells transfected with human and mouse FAPα cDNA, respectively, but not to the FAPα-negative parental cells (Fig. 2A).

**Design of mAb FAP5-maytansinoid immunoconjugates as therapeutic agents.** We determined that unmodified mAb FAP5, at concentrations up to 50 μg/mL, has no detectable effect on survival or proliferation of HT1080-FAPα cells in vitro. Moreover, we established that bound mAb FAP5 is rapidly internalized in HT1080-FAPα cells at 37°C. We therefore endowed mAb FAP5 with a de novo antimitotic function through covalent linkage with DM1, a tubulin-binding maytansinoid with picomolar antimitotic activity (23–25, 29). Using SPP as a linker, we generated a mAbFAP5-DM1 drug candidate (Fig. 2B) with desired specificity and activity. This chemical modification did not alter the binding specificity and the affinity of the parental mAb FAP5 as determined by direct binding and competitive ELISA (data not shown). Unlike mAb FAP5, the mAb FAP5-DM1 immunoconjugate showed remarkably high potency in proliferation assays with HT1080-FAPα cells (EC50 50 pmol/L), with ≥100-fold selectivity against FAPα-negative control cells (Fig. 2C).

**Immunoconjugate mAb FAP5-DM1 is highly efficacious in cancer xenograft models.** The in vivo efficacy of mAb FAP5-DM1 given once weekly by i.v. injection was tested in four human cancer xenograft models (pancreatic, non-small cell lung, colorectal, and head and neck squamous cell carcinomas) grown s.c. in immunodeficient mice. For each model, prescreening had established a histotypic arrangement of epithelial and stromal components consistent with the human disease, and the mouse-derived tumor stromal fibroblasts show distinct FAP expression before initiation of therapy (Fig. 3A, untreated). Furthermore, we observed that, following treatment of the responsive pancreas and lung cancer models, the nonprogressing tumors consist of bands of collagenized stroma, with scattered fibroblasts, small capillaries, microcalcifications, diffuse inflammatory infiltrates, and only minute...
foci of malignant epithelial cells (Fig. 3A, end of treatment); the same post-treatment pattern is seen for the head and neck cancer model (data not shown). As expected, the resistant colorectal cancer model shows no histologic changes after therapy (Fig. 3A). The treatment schedule consisted of once weekly i.v. injections of mAb FAP5-DM1 at three dose levels, adjusted to 100, 200 and 400 μg/kg DM1, respectively, with four to five consecutive treatment cycles (Fig. 3B). In the pancreas, lung, and head and neck carcinoma models, a prominent antitumor effect was observed, including complete tumor regressions (3 of 6 animals in the pancreatic and head and neck cancer models and 5 of 6 animals in the lung cancer models in the high-dose groups). After discontinuation of therapy (days 20-27), a large proportion of animals remained free of palpable tumors or showed no further growth during an extended observation period (3-4 weeks). Remarkably, strong and long-lasting tumor regressions in the pancreas cancer model were seen even with a single i.v. administration of mAb FAP5-DM1 at the high dose (see below). In all treatment groups, the animals showed no evidence of toxicity or impaired weight gain when compared to control mice. The colorectal cancer model was selected based on high MDR1 multidrug resistance gene expression and in vivo unresponsiveness to treatment with taxanes. In this model, mAb FAP5-DM1 showed no therapeutic effect (Fig. 3B).

Cleavable linkers are essential for potent in vivo efficacy. We compared the efficacy of mAb FAP5-DM1 to similar constructs that differ in the chemical stability of the linker (24) and the metabolic fate of the conjugates in tumor tissues and following cellular uptake. Two analogues of mAb FAP5-DM1 were constructed (Fig. 2B): mAb FAP5 conjugated to DM4 by the disulfide linker SPDB (mAb FAP5-DM4; ref. 30) and mAb FAP5 conjugated to DM1 by the thioether linker SMCC (mAb FAP5-SMCC-DM1; ref. 24). Both analogues were profiled in vitro and in vivo as described for mAb FAP5-DM1, and two key findings emerged. First, each of these compounds was highly active against HT1080-FAPα cells in vitro, with EC50 values of 29 and 22 pmol/L, respectively, and 100- to 1,000-fold less active on the HT1080 wild-type cells (Table 1). Second, mAb FAP5-DM4 showed impressive in vivo antitumor activity, similar to mAb FAP5-DM1, whereas mAb FAP5-SMCC-DM1 was inactive in the pancreas cancer model and only marginally active in the lung and head and neck cancer models (Fig. 4A-C). Previous studies with antiepithelial cancer
Fig. 3. A, histopathologic analysis of tumor xenografts treated with mAb FAP5-DM1. Sections from tumor xenografts before treatment stained with H&E. Moderately to well-differentiated adenocarcinomas of pancreas, lung, and colon. Adjacent sections stained with mAb FAP5 show prominent expression of FAPα by the activated tumor stromal fibroblasts in all three cases (avidin-biotin complex method). Morphologic changes following treatment in the pancreatic and lung carcinoma models. Small tumor nodules composed of a collagenized stroma with scattered fibroblasts, inflammatory infiltrates (arrowheads), and a minute cluster of tumor cells (arrow). The resistant colorectal cancer model showed no histologic changes after treatment. Bar, 50 μm. B, efficacy of mAb FAP5-DM1 in human cancer xenograft models. Nude mice bearing established PAXF736 (pancreas), LXFA629 (lung), and CXF158 (colon) tumors were treated i.v. with either vehicle control (PBS; green, filled square), mAb FAP5-DM1 at doses of 200 μg/kg DM1 (red, filled circle), 400 μg/kg DM1 (blue, open square), and unconjugated antibody (orange, open triangle) for four to five cycles. Tumor sizes are represented as median of six or eight mice. Arrows, treatment days.

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antibodies (29) have shown that the respective immunoconjugates do not differ significantly in their general pharmacokinetic properties in vivo but are quite distinct in their metabolic fate after cellular uptake. Thus, mAb FAP5-DM1 and mAb FAP5-DM4 contain linkers with disulfide bonds that are readily cleaved on internalization, whereas the SMCC linker contains a noncleavable thioether bond. Accordingly, the pattern we observed with our three compounds in vitro (similar potency) versus in vivo (dramatic differences in efficacy) are suggestive of a marked bystander effect in the xenograft models. No evidence of toxicity or impaired weight gain when compared with control mice was observed (Fig. 4D).

**Changed architecture during tumor stromal fibroblast therapy.** Histologic and immunological biomarker analyses were carried out to map the changes in tissue architecture during the course of mAb FAP5-DM1 therapy.

Focusing on the lung cancer xenograft model (Fig. 5), we confirmed that, before therapy, the FAPα-expressing tumor stromal fibroblasts are chiefly located at the interface of tumor

<table>
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<th>Conjugate</th>
<th>Linker/bond</th>
<th>Drug</th>
<th>In vitro efficacy EC50 (pmol/L)</th>
<th>Selectivity factor EC50 ratio: HT1080 wild-type/HT1080-FAPα+</th>
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<tbody>
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<td>SPP/disulfide</td>
<td>DM1</td>
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<td>540</td>
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<td>SMCC/thioether</td>
<td>DM1</td>
<td>22</td>
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**Table 1.** Cytotoxic activity of the mAb FAP5-maytansinoid conjugates

**Fig. 4.** In vivo efficacy and tolerability of mAb FAP5-maytansinoid conjugates in different carcinoma xenograft models. A, nude mice bearing PAXF736 tumors were treated with a single i.v. dose of either vehicle, mAb FAP5-DM1, mAb FAP5-DM4, or mAb FAP5-SMCC-DM1 at 800 µg/kg maytansinoid. The tumor volume of each treatment group at day 45 is shown. B, FaDu tumor-bearing mice treated once with 600 µg/kg maytansinoid. Tumor volumes at day 19 are shown. C, nude mice bearing LXFA629 tumors treated with three weekly doses of the conjugates indicated above at 400 µg/kg maytansinoid. Tumor volumes at day 41 are shown. Columns, median tumor volume of each group. D, average body weight change (in percentage) of mice bearing the LXFA629 tumors during treatment.
capillaries and malignant epithelium (Fig. 5, pretherapy). Further analyses were carried out on tumors excised 2, 3, or 5 days after therapy. At day 2 post-therapy, the tumor nodules show histologic evidence of necrosectes and a marked inflammatory cell infiltrate, evidence of a mitotic spindle poison in malignant epithelial cells with cell cycle arrest as evidenced by the phospho-histone H3 marker and apoptosis shown by terminal nucleotidyl transferase–mediated dUTP nick end labeling staining (Fig. 5, 48 h post-therapy). In addition, we determined that the inflammatory cell infiltrate consists predominantly of CD11b/F4/80+ macrophages, dispersed small capillaries indicative of tumor capillary damage, and isolated nests of tumor cells.

**Fig. 5.** Mechanism of action of mAb FAP5-DM1 in human epithelial cancer xenograft models. Histologic and immunophenotype analysis of tumor samples obtained during treatment. **Pretherapy:** histologic appearance of LXFA629 tumors from control mice with an abundant fibroblastic stroma with prominent FAPα expression (red arrow) and a well-developed network of tumor capillaries (EC). 48 h post-therapy: changes in tumor morphology 48 h after second i.v. administration of mAb FAP5-DM1. Clusters of enlarged tumor cells surrounded by extensive inflammatory infiltrates. The tumor cells show cytologic abnormalities consistent with mitotic spindle poisoning; some of these cells are arrested in mitosis (pH3, phospho-histone H3 staining), whereas others showed signs of cell death by apoptosis (green, fluorescence terminal nucleotidyl transferase–mediated dUTP nick end labeling assay). The inflammatory infiltrates consist mostly of CD11b+ tissue macrophages (MΦ; green, CD11b+ macrophages; red, DNA counterstaining propidium iodide). A loss of collagen type IV marker protein indicative of a disruption of the basement membrane is seen in the treated tumors (white arrows) compared with the untreated tumors (BM; inset, red) where the basement membrane directly surrounds the clusters of tumor cells stained with cytokeratin 18 (green). **Late effects,** at the end of the experiment (day 45), the remaining nodules are composed of an acellular, collagenized stroma, with microcalcifications (asterisk), dispersed small capillaries indicative of tumor capillary damage, and isolated nests of tumor cells.
with loss of collagen type IV marker protein (white arrows) compared with the preserved basement membrane in untreated control tumors (inset). When tumors were analyzed at the end of the experiment (day 45), we observed minute s.c. nodules with an acellular, collagenized stroma, with microcalcifications, isolated nests of tumor cells, and disruption of the blood vessel network in which remaining vessels were of small caliber and showed less uniform distribution in the tissue (Fig. 5, late effects).

Discussion

Novel therapeutic principles (31), such as imatinib or rituximab, have had a strong effect on objective response rates and survival in patients with certain leukemias and lymphomas (32–34). By comparison, targeted approaches for solid cancers have shown lower response rates and less survival benefits (35, 36), which may reflect highly disparate and redundant genetic aberrations accumulated during epithelial carcinogenesis, pathway activation less amenable to drug discovery, or confounding patterns of tissue invasion and metastasis.

Along with notable advances in some indications (37), there has been a remarkable attrition for antibodies against solid tumors that appeared promising in preclinical testing but failed in clinical trials. In our preclinical testing, we focused on three aspects.

First, for antibody-based drugs, the selectivity of target antigen expression in cancer versus normal tissues remains the defining characteristic (38–40). We selected a unique antigen, FAPα, based on its preferential expression in cancer tissues (6, 7, 16, 27), and radiolabeled anti-FAPα antibodies have shown in vivo tumor targeting in cancer patients (17, 19). FAPα is distinctive in its cancer distribution, as it is not expressed by the malignant epithelial cells but rather by the nontransformed, activated stromal fibroblasts.

Second, particular care was taken to design antibodies that cross-react with human and mouse FAPα to avoid the limited relevance of human-mouse xenograft studies for antibodies binding exclusively to human-specific epitopes.

Third, we ensured that the tissue architecture of our xenograft models is consistent with the corresponding human carcinomas. The histotypic models used here recapitulate the hallmark of human carcinomas. Of note, advances in the purification of CD133+ human colon cancer-initiating cells from surgical specimens should now allow routine generation of xenograft models that reproduce the histomorphologic features of the original cancers (21, 22).

In our search for more effective drugs to treat epithelial cancers, we have developed an experimental paradigm for tumor stromal fibroblast-targeted therapy. As the major finding from our study, mAb FAP5-DM1 shows an impressive level of therapeutic benefit, with rapid onset of action, complete responses, and long-lasting suppression of tumor growth. In all three xenograft models, the treatment was exceptionally well tolerated considering the cross-reactivity with endogenous mouse FAPα. Considering that only a small fraction of the tumor mass in these models represents the stromal compartment with FAPα+ activated fibroblasts, it is tempting to speculate about the potent mode of action of the drug. Several steps may be considered along the known sequence (38) of in vivo targeting, cell membrane binding and internalization, lysosomal activation, intracellular modification, cellular release, and microtubule disruption and apoptosis.

The initial targeting of mAb FAP5-DM1 to FAPα+ tumor stromal fibroblasts in vivo is likely to be fast and efficient, because we have shown that these target cells surround tumor capillaries and this proximity should lower diffusion barriers faced by antibodies targeting the malignant cells. Previous studies with the human epitope-specific mAb F19 and sibrotuzumab in patients have shown selective tumor detection (17, 19, 41). Cell culture studies have suggested that cell surface binding of drugs with the general structure mAb-SPP-DM1 (like mAb FAP5-DM1) leads to antigen-dependent endocytosis of the immunon conjugate and lysosomal degradation with intracellular release of a lysine derivative, lysine-Nc-SPP-DM1, which binds microtubules and causes mitotic arrest and apoptosis. Subsequently, a further metabolite, the neutral, lipophilic S-methyl-DM1, can convey bystander effect by crossing cell membranes and reentering target cells with high potency as an antimitotic agent (24). This process of intracellular immunon conjugate activation and tumor cell apoptosis is straightforward when the drug binds to the highly proliferative cancer cells directly, reflecting a mode of “suicide prodrug activation.” The process is more intriguing for tumor stromal fibroblast targeting, because activated fibroblasts are generally quiescent, not actively proliferating within tumors as seen by low mitotic index (data not shown). Thus, whereas mAb FAP5-DM1 binding, internalization, and generation of lysine-Nc-SPP-DM1 and S-methyl-DM1 likely occur in the FAPα+ tumor stromal fibroblasts, these cells do not attempt to enter mitosis and undergo apoptosis. Instead, they perform a “transit activation” step for the prodrug, remain viable for repeat activation cycles, and presumably release the uncharged, lipophilic S-methyl-DM1 as the essential antimitotic moiety into their microenvironment. At present, no methods exist to measure this release in cancer models in situ, but our histologic and biomarker studies indeed identify malignant epithelial cells adjacent to fibroblastic stroma as early responders, with mitotic spindle arrest phenotypes, up-regulation of the phospho-histone H3 marker, and apoptosis induction solely in epithelial clusters rather than ablation of the stromal compartment. In line with this sequence, the multidrug-resistant CXF158 model shares a distinct, FAPα+ fibroblastic stroma with the three responsive tumor models but is unresponsive to mAb FAP5-DM1 therapy; we postulate that transit activation with release of S-methyl-DM1 occurs in this model also, but S-methyl-DM1 is a substrate for the multidrug resistance efflux transporters in this model (42).

Further confirmation comes from the fact that the uncleavable mAb FAP5-SMCC-DM1 analogue of mAb FAP5-DM1 has no in vivo antitumor activity in our models despite its potent, direct effect on FAPα-transfected HT1080 cells. The thioether-linker in this compound, SMCC, is not cleaved inside cells, and the major metabolite generated by lysosomal degradation, lysine-Nc-SMCC-DM1, is not converted to the cell-permeable and highly potent derivative, S-methyl-DM1, the essential active principle in our concept of stromal-fibroblast targeted therapy.

In conclusion, we have developed a novel experimental paradigm for tumor therapy based on maytansinoid
immunoconjugates targeting stromal fibroblasts. In view of the substantial therapeutic efficacy and excellent tolerability seen with our lead compound, mAb FAPS-DM1, in animal models, combined with the feasibility of safety assessments in commonly used animal species due to cross-reactivity with autologous target proteins, this concept may be poised for a rapid transition to clinical development. If successful, stroma-directed therapy may provide clinical benefits in a broad spectrum of indications, based on the consistent presence and, sometimes, remarkable abundance of stromal compartments in human carcinomas.

References


Disclosure of Potential Conflicts of Interest

The authors declare that they have no competing financial interests.

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Effective Immunoconjugate Therapy in Cancer Models
Targeting a Serine Protease of Tumor Fibroblasts


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