Systematic Urokinase-Activated Anthrax Toxin Therapy Produces Regressions of Subcutaneous Human Non–Small Cell Lung Tumor in Athymic Nude Mice

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Abstract

The novel recombinant anthrax toxin, PrAgU2/FP59, composed of the urokinase-activated protective antigen and a fusion protein of *Pseudomonas* exotoxin and lethal factor was tested for anti–lung cancer efficacy in an in vivo human tumor model. Male athymic nude mice (age 4–6 weeks) were inoculated s.c. with 10 million H1299 non–small cell lung cancer (NSCLC) cells in the left flank. When tumor volumes reached 200 mm³ (6–8 days), i.p. injection of 100 µL saline or different ratios and doses of PrAgU2/FP59 in 100 µL saline were given every 3 days for four doses and an additional dose at day 29. Animals were monitored twice daily and tumor measurements were made by calipers. The maximum tolerated doses of PrAgU2/FP59 differed dependent on the ratios of PrAgU2 to FP59 over the range of 3:1 to 25:1, respectively. At ed doses of PrAgU2/FP59 differed dependent on the ratios of PrAgU2 to FP59 over the range of 3:1 to 25:1, respectively. At tolerated doses, tumor regressions were seen in all animals. Complete histologic remission lasting 60 days occurred in 30% of animals. PrAgU2/FP59 showed dramatic anti-NSCLC efficacy and warrants further clinical development for therapy of patients with advanced NSCLC. [Cancer Res 2007;67(7):3329–36]

Introduction

Lung cancer is the leading cause of cancer-related mortality in the United States, of which most cases are non–small cell lung cancer (NSCLC; 1). More than three quarters of all patients of NSCLC present with locally advanced or widespread metastatic disease and are incurable with surgery, radiotherapy, or chemotherapy (2). A novel therapeutic approach for these patients is immunotoxins, peptide toxins coupled to antibodies or ligands reactive with NSCLC cells. Mesothelin and erbB-2 targeted immunotoxins have been tested in tissue culture and animal models of NSCLC (3, 4). We chose to examine another molecule overexpressed in NSCLC-urokinase plasminogen activator (uPA).

uPA is a protease overexpressed on a significant number of solid tumors, including NSCLC (5). Its presence is associated with increased tumor tissue invasiveness and metastatic potential (6). The urokinase receptor (uPAR) is also overexpressed in NSCLC and recruits uPA to the tumor cell microenvironment (7). Up-regulation of uPA/uPAR in tumors and general absence on normal cells make the uPA/uPAR system an attractive target for cancer therapy. Several inhibitors of uPA/uPAR have been designed and tested clinically yielding only limited tumor-static effects (8–10). Immunotoxins have also been synthesized, which target uPAR. These have included recombinant proteins with the NH₂ terminus of uPA fused to saporin and diphtheria toxin and have yielded antitumor activity both in vitro and animal models (11, 12). Our laboratory took another approach to target uPA and uPAR on NSCLC tumor cells by using the protease activity of the uPA/uPAR complex to activate a different potent catalytic and cytolytic peptide toxin, anthrax lethal toxin.

Anthrax lethal toxin is a binary protein that consists of protective antigen (PrAg) and lethal factor (LF). PrAg binds to ubiquitously distributed anthrax receptors, tumor endothelial marker-8 and capillary morphogenesis gene-2 associated with the coreceptor, low density lipoprotein receptor–related protein 6 (13–15). After binding, PrAg is cleaved by furin on the cell surface, and the 63-kDa receptor-bound PrAg fragments spontaneously heptamize and bind up to three copies of LF via the LF NH₂-terminal domains. The complexes internalize from lipid rafts into acidic endosomes where membrane-spanning pores facilitate the escape of unfolded LF molecules to the cytosol (16, 17). After refolding, the LF cleaves the mitogen-activated protein kinase kinases, which leads to cell dysfunction or cell death (18).

To achieve uPA/uPAR targeting and enhance the catalytic potency, the furin cleavage fragment of PrAg 164RKKR167 was substituted with a urokinase cleavage sequence 164SGRSA168 termed PrAgU2. LF residues 1 to 254, which bind the PA63 receptor, were fused with the 38-kDa ADP-ribosylation catalytic domain of *Pseudomonas aeruginosa* exotoxin A to form FP59 (19). PrAgU2 together with FP59 constitutes a potent prodrug that is delivered into cyttoplasm through PA-LF interaction, where the *Pseudomonas* exotoxin A ADP-ribosylation domain catalyzes ADP attachment to the diphthamide residue of elongation factor 2 and blocks protein synthesis. PrAgU2/FP59 has potent and selective cytotoxicity to uPA/uPAR–expressing NSCLC with 14 of 20 NSCLC lines showing EC₅₀ <40 pmol/L (20). Intratumoral injection of PrAgU2/FP59 given to Lewis lung carcinoma–bearing mice induced transient (1 week) tumor growth inhibition (21). A pilot study of systemically administered in PrAgU2/FP59 in Lewis lung carcinoma–bearing mice showed modest tumor growth inhibition lasting 1 week at doses causing 33% lethality (22). We now want to determine accurately the safety and efficacy of systemically administered PrAgU2/FP59 in an *in vivo* athymic nude mice model of human NSCLC.
Materials and Methods

Cells. H1299 and H1703 were purchased from the American Type Culture Collection (Manassas, VA) and cultured in RPMI 1640 with 2 mmol/L L-glutamine adjusted to contain 1.5 g/L sodium bicarbonate, 4.5 g/L glucose, 90% HEPES, 1.0 mmol/L of 90% sodium pyruvate, 10% fetal bovine serum, and 1% penicillin/streptomycin.

Toxins. Both PrAgU2 and FP59 were expressed and purified as described above (23, 24).

Animals. Male BALB/c and athymic nude mice (nu/nu). 4 to 6 weeks old, were purchased from Charles River Laboratories (Wilmington, MA) and maintained in a ventilated rack system. Irradiated food and autoclaved water were provided ad libitum. The mice were allowed to adjust to their environment for 1 week before the initiation of experiments.

Maximum tolerated dose studies. BALB/c mice (six per group) were injected s.c. in the left flank with 10^7 H1299 cells in 100 μL medium. Three groups of mice (10 mice per group) were then treated i.p.

Antitumor efficacy studies. Athymic nude mice (nu/nu) were injected i.p. with 75 μg of a rat anti-mouse asialo GM1 antibody (Wako Chemical Co., Richmond, VA) to reduce natural killer cells. Injections were done on days −4 and −2 before the injection of H1299 cells. At day 0, mice were injected s.c. in the left flank with 10^7 H1299 cells in 100 μL serum-free medium. Three groups of mice (10 mice per group) were then treated i.p. with one of two different doses of PrAgU2/FP59 (0.36 mg/kg PrAgU2/0.06 mg/kgFP59 and 0.5 mg/kg PrAgU2/0.05 mg/kg FP59 in 100 μL PBS) or with vehicle alone (PBS) in combination with 15 mg/kg dexamethasone, every 3 days for four total injections starting at day 7 post-tumor inoculations, with one additional injection at day 29. Animals were observed twice daily and tumor size was measured twice weekly with calipers, based on the formula L x W^2 where L is the length and W is the width of the tumor. Moribund mice and mice whose tumor burdens exceeded 20% of their body weight were euthanized as described above. All mice were euthanized at day 60 post-tumor inoculation following institutional regulations.

Tumor tissues were removed, fixed in 10% buffered formaldehyde, and dehydrated and embedded in paraffin. Sections were stained with H&E and subjected to microscopic analysis. All surviving mice were euthanized at day 60 postinjection.

Histologic analysis. The organs (liver, spleen, heart, lung, kidney, testis, small intestine, and brain) and tumors were fixed for 24 h in 10% buffered formaldehyde and dehydrated and embedded in paraffin. Sections were stained with H&E and subjected to microscopic analysis.

Immunohistochemical analysis. Tumors from vehicle- and PrAgU2/FP59–treated animals were harvested, fixed for 24 h in 10% buffered formaldehyde, dehydrated and embedded in paraffin, sectioned, rehydrated, blocked with 10% goat serum, and reacted with mouse anti-human uPA (NeoMarkers/LabVision, Fremont, CA) or mouse anti-uPAR (Zymed, San Francisco, CA). Immunostaining was done with a Vectastain avidin-biotin complex method kit (Vector Laboratories, Burlingame, CA), with 3,3’-diaminobenzidine as chromogenic substrate using horseradish peroxidase–conjugated goat anti-mouse IgG.

Advanced tumor therapy with PrAgU2/FP59. Thirty days after antitumor efficacy study, five mice bearing tumors (mean ± SE, 1,398 ± 127 mm^3) from PBS-treated group were treated i.p. with PrAgU2/FP59 (0.36 mg/kg PrAgU2/0.06 mg/kgFP59 100 μL PBS) in combination with 15 mg/kg dexamethasone every 5 days for two total injections. Animals were observed twice daily and tumor size was measured once weekly as described above. On day 11, animals were euthanized following institutional regulations and tumors were harvested and processed as above. Apoptosis was visualized by terminal deoxynucleotidyl transferase–mediated dUTP nick end labeling (TUNEL) by using Apoptag kit (Serologicals, Norcross, GA), proliferating cells were tested by staining of sections with mouse anti–Ki-67 antibody (NeoMarkers/LabVision), and angiogenesis was visualized by staining with mouse anti–CD34 antibodies (NeoMarkers/LabVision) Immunostaining was done as introduced above.

Statistics. Survival was analyzed by Kaplan-Meier method. For comparison of tumor volume and EC50s, a Mann-Whitney or Kruskall-Wallis test was used. Significance of differences was measured at P < 0.05. Statistical analyses were done with GraphPad Prism software (GraphPad Software, San Diego, CA).

Results

PrAgU2/FP59 is cytotoxic to uPA/uPAR–expressing NSCLC cell. Two different human NSCLC cells, H1299 and H1703, were tested for their sensitivities to PrAgU2/FP59. Cytotoxicity assays of PrAgU2/FP59 on H1299 yielded an EC50 of 3.5 pmol/L after 48 h incubation. H1703 cells had an EC50 >10,000 pmol/L under the same treatment condition (Fig. L). H1299 but not H1703 expressed high level of cell surface uPA as shown by immunofluorescent staining. uPAR was expressed on both cell lines (Fig. 1A).

Maximum tolerated dose and dose-limiting toxicity of PrAgU2/FP59. PrAgU2/FP59 is composed of two protein moieties. We therefore needed to evaluate the effects of different ratios of PrAgU2 and FP59 in in vivo toxicity. As shown in Fig. 2A, the maximum tolerated doses (MTD) of PrAgU2/FP59 in combination with 15 mg/kg dexamethasone i.p. injected every 3 days for eight doses were 0.30±0.06, 0.50±0.05, and 1.0±0.04 mg/kg for the increasing ratios of PrAgU2 to FP59 over the range of 3:1, 6:1, 10:1, and 25:1, respectively. No deaths were observed at the MTD of all 24 animals (four groups of six). In contrast, animals that received 0.45±0.15 mg/kg (ratio 3:1), 0.60±0.2 mg/kg (ratio 3:1), 0.45±0.075 mg/kg (ratio 6:1), 0.60±0.1 mg/kg (ratio 6:1), 0.80±0.08 mg/kg (ratio 10:1), and 1.25±0.05 mg/kg (ratio 25:1) had mortalities of 67%, 50%, 50%, 33%, 50%, and 67%, respectively. Figure 2F showed the relationship between the ratios of PrAgU2 to FP59 versus the concentration of FP59. Values in the shadow area were associated with no mortality.

Concurrent administration of dexamethasone significantly reduced the dose-limiting toxicity (DLT) and reduced animal mortality related to PrAgU2/FP59 treatment. As shown in Fig. 3B, two i.p. injections of 0.36±0.06 mg/kg PrAgU2/FP59 every 3 days
without concurrent administration of dexamethasone caused >80% animal death and the rest of the animals became moribund with fur ruffling and loss of activity by day 9. Necropsies of dead or terminal ill animals showed profound histologic damage to kidney, liver, and heart with vessels displaying severe angiectasis, vascular stasis, and hemorrhaging (Fig. 3B). Lung and kidney also showed dramatic vacuolization that might be a result of cell necrosis induced by this toxin (Fig. 3B). The spleen, brain, small intestine, and testis were not affected by PrAgU2/FP59 treatment showing no sign of histologic toxicity (Supplementary Data). Concurrent administration of 15 mg/kg dexamethasone, instead, kept all animals alive with no outward signs of toxicity (Fig. 3A). Necropsies of animal showed no sign of histologic cytotoxicity on all major organs, including kidney, liver, heart, lung, spleen, brain, small intestine, and testis (Fig. 3B).

**Human NSCLC tumor growth in athymic nude mice.** Athymic nude mice (n = 10) treated with anti-asialo GM1 antibody were inoculated with 10^7 H1299 cells. After a long lag phase, s.c. tumors had rapid tumor growth. Mean ± SE tumor volume was ~200 mm^3 after 22 days, then doubled in volume to 430 ± 53 mm^3 by day 29, and then doubled again (794 ± 154 mm^3) by day 33. The mean tumor volume continued to double with a doubling time of ~4 days until animals were sacrificed on day 36 (1,768 ± 356 mm^3). With 10 animals per group and the observed SD, we detected a 50% tumor growth inhibition, with two-sided type I error of 5% and a power 0.9. Pathology of the tumor confirmed the malignant histology.

**Anti-NSCLC in vivo efficacy of PrAgU2/FP59.** Beginning on day 7 post–tumor cell inoculation, cohorts of 10 animals received treatment systemically with PrAgU2/FP59 every 3 days for a total of four doses. Treatments were 0.18±0.03 mg/kg (PrAgU2/FP59), 0.25±0.025 mg/kg (PrAgU2/FP59), or saline in combination with 15 mg/kg dexamethasone (Fig. 4A). On day 29, the saline control tumors were 430 ± 53 mm^3. The two groups of the PrAgU2/FP59–treated tumors were only 34 ± 8 mm^3 (PrAgU2/FP59, 6:1; P = 0.0008 versus control) and 75 ± 17 mm^3 (PrAgU2/FP59, 10:1; P = 0.0002 versus control), respectively. On day 29, both PrAgU2/FP59 groups received one additional treatment at the same dose and ratio. On day 33, the PBS–treated tumors were 794 ± 155 mm^3, and the PrAgU2/FP59–treated tumors were 27 ± 12 mm^3 (PrAgU2/FP59, 6:1 compared with PBS-treated; P = 0.0008) and 47 ± 15 mm^3 (PrAgU2/FP59, 10:1 compared with PBS treated; P = 0.0002), respectively. By day 58, 3 of 10 (30%) from 6:1 ratio group and 3 of 9 (33%) from 10:1 ratio group PrAgU2/FP59–treated mice remained in complete remission by both gross and histologic examination.

NSCLC cells harvested from relapsing tumors and tumors of PBS–treated group were examined for their sensitivities in tissue culture to PrAgU2/FP59. Relapsed tumor cells remained sensitive to PrAgU2/FP59 with EC50s of 1.6 pmol/L (PrAgU2/FP59, 6:1) and 3.6 pmol/L (PrAgU2/FP59, 10:1), respectively, versus 1.9 pmol/L for PBS–treated tumor cells (Fig. 4B). Immunohistochemical staining showed that both relapsing tumors and tumors of PBS–treated group retained uPA and uPAR expressions (Fig. 4C).

**Tumoricidal activity of PrAgU2/FP59 on established tumor.** We evaluated the therapeutic efficacy of PrAgU2/FP59 on established H1299 NSCLC tumors. Nude mice bearing solid s.c. tumor nodules constituting 1.5% to 3% of the total body mass on day 36 post-tumor inoculation were treated with two i.p. injections of PrAgU2/FP59 (0.36±0.06 mg/kg) in combination with 15 mg/kg dexamethasone at 5 days interval (Fig. 4A). The tumors were highly.

**Figure 1.** The cytotoxic activity of PrAgU2/FP59 on NSCLC is dependent on the expression of uPA on cell surface. A, H1299 cells were sensitive to PrAgU2/FP59 treatment with an EC50 of 3.5 pmol/L, whereas H1703 cells had >75% survival under the same treatment with EC50 >10,000 pmol/L. B, immunofluorescent staining of uPA and uPAR on H1299 and H1703 cells. uPA was tested with biotinylated mouse anti-human uPA monoclonal antibody (mAb) and visualized with Oregon green–conjugated streptavidin; uPAR was tested with mouse anti-human uPAR mAb and visualized by Alexa 594–conjugated goat anti-mouse IgG.
susceptible to PrAgU2/FP59 treatment. The first and second treatment caused 56% and 78% reduction in the size of H1299 NSCLC tumors compared with the size of tumor before treatment, respectively. Immunohistologic analysis of tumor tissues revealed dramatic tumor cell cytotoxicity after PrAgU2/FP59 administration. Tumor cells underwent massive necrotic cell death with predominant cession of Ki-67 and H&E staining (Fig. 5B). Moreover, tumor cell apoptosis was manifested by TUNEL staining 24 h after drug administration, showing apparent cytoplasmic shrinkage and nuclear condensation (Fig. 5B). Previous study suggested that

Figure 2. MTD of PrAgU2/FP59. A, Kaplan-Meier curves of six BALB/c mice (ages 4–6 wks) i.p injected with PrAgU2/FP59 at different ratios in combination with 15 mg/kg dexamethasone every 3 days for eight total doses. The increasing ratios of PrAgU2 to FP59 are over the range of 3:1 to 25:1. At a ratio 3:1, animals received 0.3:0.1, 0.45:0.15, and 0.6:0.2 mg/kg; at a ratio 6:1, animals received 0.36:0.06, 0.45:0.075, and 0.6:0.1 mg/kg; at a ratio 10:1 animals received 0.5:0.05 and 0.8:0.08 mg/kg; and at a ratio 25:1, animals received 1:0.04 and 1.25:0.05 mg/kg. B, the relationship between the ratios of PrAgU2 to FP59 and the concentration of FP59. The values above shadowed area are the doses resulting in mortality under given ratio of PrAgU2 to FP59.
PrAgU2/FP59 produces tumor endothelial cell damage (21). However, in current assay, we did not observe any histologic damage to tumor blood vessel endothelial cells by CD34 staining (Fig. 5B).

**Discussion**

In the current study, we have investigated the anti-NSCLC activity of PrAgU2/FP59 fusion toxin. We observed remarkable anti-NSCLC efficacy both in tissue culture and in s.c. nude mouse xenograft with the uPA/uPAR–positive H1299 cell line. Importantly, direct tumor killing rather than growth inhibition was found. Further studies will be needed to extend these findings to other NSCLC cell lines and other models, such as orthotopic lung cancer models (25).

Higher ratios of PrAgU2 to FP59 produced greater animal toxicity. Time of death and histopathology were similar in all treated animals. Because PrAgU2 is required for toxin delivery, higher ratios likely enhance the uptake of FP59 by particular normal tissues leading to toxicity.

The DLT of PrAgU2/FP59 seemed to be the multiorgan endothelial damage with vascular injury to the kidney, liver, lung, and heart. Epithelial vacuolization was also seen in the lung and kidney. The spleen, brain, small intestine, and testis were not affected by PrAgU2/FP59 treatment showing no sign of histologic toxicity. These findings are consistent with the distribution anthrax toxin receptors on endothelial cells in multiple organs (13–15). At high dose, nonspecific activation of the toxicity may have occurred in tissues. Incubation *in vitro* of PrAgU2/FP59 with mouse serum did not lead to activation, suggesting that the drug is not activated in the bloodstream but at tissue sites. 4

Dexamethasone reduced toxicity of PrAgU2/FP59 *in vivo*. Our *in vitro* studies also showed that dexamethasone attenuates the

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4 Unpublished data.
cytotoxic effect on human vascular endothelial cells. The mechanism for this protection is unknown but may involve antiapoptotic effects in endothelial cells as has been observed with endothelial serum deprivation (26). Dexamethasone has been shown previously to reduce vascular leak with other immunotoxins, including DAB389IL2, BR96-Pseudomonas exotoxin, and BR96-doxorubicin without impairing antitumor efficacy (27–29). Alternatively, steroids may decrease uPA/uPAR expression in normal cells. Normal mammary epithelial, renal cells, and macrophages had reduced uPA and uPAR expression after dexamethasone incubation (30–32).

A large number of preclinical studies have been done testing anti-NSCLC agents in athymic mice bearing human tumor xenografts. Single-agent therapy showed tumor growth inhibition of 34%, 50%, 72%, 82%, 84%, and 85% for cetuximab, radiation therapy, gefitinib, erlotinib, gemcitabine, and cisplatin, respectively (33–35). In contrast, PrAgU2/FP59 produced complete tumor regressions and a 30% apparent histologic cure rate. Because each of the listed treatments are currently used for NSCLC patients and have shown clinical benefit, we expect that PrAgU2/FP59 will also have a favorable therapeutic index in NSCLC patients. Because direct comparisons were not made with the established cytotoxic agents in our experiments, we cannot compare accurately efficacy.

Relapsed tumors retained uPA/uPAR expression and PrAgU2/FP59 sensitivity, suggesting incomplete penetration of the drug during the initial treatment. We observed regression on retreatment of previously treated tumors, suggesting that such a strategy may be useful clinically. Moreover, an orthotropic NSCLC animal model might be better in predicting the therapeutic effect of i.v. administered PrAgU2/FP59, which is our future study in plan. Because of the likely immunogenicity of these nonhuman proteins similar to other immunotoxins (36), methods will need to be developed to reduce the humoral immune responses. Moreover, pharmacokinetics with respect of drug distribution and metabolism will have to be investigated to establish the optimal administration for treatment of human malignancies.

Combination therapy of PrAgU2/FP59 with other NSCLC drugs leads to tumor cell death by different mechanisms and should produce improved antitumor efficacy in patients. Previous experiences of monoclonal antibodies (mAb) in combination with chemotherapy for lymphoma and breast cancer suggested the usefulness of this approach (37, 38). We have also observed previously the synergy of immunotoxin with DNA-damaging cytotoxic drugs (39–41).

The remarkable antitumor activity of PrAgU2/FP59 on late established tumor was unexpected and portends well for the behavior of this drug in patients with large advanced NSCLC tumor or significant metastatic disease. Necrotic cytotoxicity seems to be

![Figure 4](https://example.com/figure4.png)

**Figure 4.** A, H1299 NSCLC s.c. tumor size in athymic nude mice treated i.p. every 3 d starting at day 7 post-tumor inoculation: PBS (■), a 6:1 ratio of PrAgU2/FP59 at 0.18:0.03 mg/kg (○), or a 10:1 ratio of PrAgU2/FP59 at 0.25:0.025 mg/kg (△); all treatments were in combination with concurrent administration of 15 mg/kg dexamethasone. Filled arrows, treatment times. Points, mean; bars, SE.  B, tumor cells harvested from PBS-treated tumor and relapsed tumors after either 0.18:0.03 or 0.25:0.025 mg/kg PrAgU2/FP59 treatments were sensitive to PrAgU2/FP59 treatment in vitro, with EC50s of 1.9, 1.6, and 3.6 pmol/L, respectively. C, tumors treated with PBS or relapsed after 0.18:0.03 mg/kg PrAgU2/FP59 treatment still express uPA and uPAR.
the predominant tumoricidal activity of PrAgU2/FP59, although it also induces massive apoptosis within 24 h of drug administration. The infrequent apoptotic cells observed in PBS-treated tumors could only be a result of natural cell death. We are not sure if the antiangiogenesis is a major mechanism for PrAgU2/FP59. The CD34 staining suggested that there is no angiogenic difference between PrAgU2/FP59–treated and untreated tumors. However, the dexamethasone administered along with PrAgU2/FP59 might alienate the drug-related endothelial damage. A more detailed study on the angiogenic effect of this drug is now under investigation. In summary, PrAgU2/FP59 is a potent anti-NSCLC agent in vivo and warrants further development for therapy for NSCLC patients.

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Figure 5. Potent tumoricidal activity of PrAgU2/FP59. A, athymic nude mice bearing established H1299 NSCLC tumors were injected i.p. with 0.36:0.06 mg/kg PrAgU2/FP59 in combination with 15 mg/kg dexamethasone twice every 5 d. The tumor size was measured at days 5 and 10. B, tumors collected from PrAgU2/FP59– or PBS-treated mice were detected by Ki-67, H&E, and CD34 staining. TUNEL assay of tumor tissues 24 h after one single i.p. injection of either PBS or 360:60 mg/kg PrAgU2/FP59.

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