Reported homologies between the IL-6 receptor, ciliary neurotrophic factor receptor (*16*), and the natural killer cell stimulatory factor (*17*) indicate possible interactions of these molecules with gp130. By contrast, the G-CSF receptor, which is structurally similar to both gp130 and the LIF receptor, binds G-CSF and transduces a signal (as a homodimer) independently of gp130 (*18*). Thus, gp130 as well as KH97 in a separate but parallel system might be focal points of signal transduction for a variety of cytokines, providing an explanation for the functional redundancy of those cytokines.

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19. After DEAE-dextran–mediated transfection (*1*), COS-7 cells were replated on fresh dishes on day 1 and removed from the dishes with nonenzymatic cell-dissociation solution (Sigma) on day 2. Binding experiments were performed essentially as described (*4*). Cells were incubated at 1.6×10^6 cells per milliliter and the appropriate concentration of ^{125}I-ligand in a total volume of 150 μl at 25°C for 2 hours. A 200-fold molar excess of unlabeled ligand was used to determine nonspecific binding. At the end of the incubation, duplicate 60-μl portions were removed, and bound and free ^{125}I-labeled ligands were separated on phthalate oil columns as described (*4*). Scatchard analysis of binding isotherms (*20*) was done with the program RS/1 (Bolt, Beranek and Newman, Boston, MA). The hLIF and hOSM were expressed in yeast, purified, and ^{125}I-labeled with Enzymobeads (Bio-Rad) to 2×10^{15} and 5×10^{15} cpm/mmol, respectively (*1*). The cDNA clone encoding hOSM was isolated from a human T cell cDNA library with an oligonucleotide based on the published sequence (*21*). Purified hIL-6 (H. Sassenfeld, Immunex) was ^{125}I-labeled to a specific activity of 10^{15} cpm/mmol.
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22. Binding assays were done essentially as above (*19*) except that cells were incubated at 1.6×10^7 cells/ml. A 200-fold molar excess of unlabeled ligand was used to determine nonspecific binding and competition assays were done with unlabeled ligands at a final concentration of 2 μg/ml. Murine IL-6 (R+D Systems, Minneapolis, MN) was ^{125}I-labeled to 4×10^{15} cpm/mmol. The number of low-affinity hLIF receptors expressed on these B9-hLIFR cells is lower than that described (*4*) although the number of high-affinity LIF and OSM binding sites has remained approximately constant. During the course of the transfection and selection procedure the B9-hLIFR cells (and control cells) lost their requirement for IL-6 (*4*).

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Inhibition of Development of Kaposi's Sarcoma–Related Lesions by a Bacterial Cell Wall Complex

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In vitro and in vivo model systems for the study of human immunodeficiency virus (HIV)–associated Kaposi's sarcoma (KS) were used to evaluate compounds for their potential as therapeutic agents. A sulfated polysaccharide–peptidoglycan compound (SP-PG) produced by bacteria controlled the in vitro growth of acquired immunodeficiency syndrome (AIDS)–associated, KS-derived spindle-shaped cells (AIDS-KS cells) at noncytotoxic concentrations. Angiogenesis induced by AIDS-KS cells in the chicken chorioallantoic membrane assay was blocked by SP-PG, which also inhibited the vascular hyperpermeability response and the angiogenesis associated with the induction of KS-like lesions that develop after subcutaneous inoculation of AIDS-KS cells into nude mice. Suramin, pentosan polysulfate, and interferon α, which are currently in use for therapy of KS, were either less effective than SP-PG or much more cytotoxic, or both.

KAPOSI'S SARCOMA (KS) IS CHARACTERIZED by microvascular proliferation (angiogenesis) in the initial stage of lesion development that is soon followed by the presence of proliferating spindle cells, edema, and infiltration by multiple cell types (*1*). We developed in vitro systems for the long-term culture of AIDS-KS cells and in vivo systems that simulate the formation of KS-related lesions (*2, 3*). AIDS-KS cells induce vascularization on chicken chorioallantoic membranes (CAM), and when transplanted into nude mice they induce vascular hyperpermeability and resultant edema (*4*), angiogenesis, and the development of KS-like lesions of murine origin (*3*).

Kaposi's sarcoma is currently treated with cytotoxic agents such as vinblastine, bleomycin (*5, 6*), and suramin (*7*), or with cytokines like interferon α (IFN-α) (*8*). Both of these forms of therapy may effect multiple cell types and many cell functions. An angiostatic compound, pentosan polysulfate (*9, 10*), has also been used, but many potential angiostatic compounds (*11–16*) still remain to be clinically tested. One of these is SP-PG, a naturally occurring sulfated polysaccharide–peptidoglycan produced by a specific species of the bacterium *Arthrobacter* sp. (strain AT-25, Daiichi Pharmaceutical). Although SP-PG has not yet been purified to homogeneity, the most active fraction has a molecular size of 30 kD (*17*) and inhibits the growth of subcutaneously inoculated solid tumors (which require angiogenesis for their growth), while not affecting growth of ascites tumor cells of the same origin (*18*). Although subcutaneous tumor growth is inhibited by SP-PG, in vitro growth of these tumor cells is not inhibited; however, SP-PG does inhibit growth of vascular endothelial cells in vitro (*19*).

The AIDS-KS cells were more sensitive to SP-PG than normal endothelial cells

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(Fig. 1). The IC_{50} (concentration at which 50% inhibition was obtained) was 0.1 μM (*20*) for AIDS-KS cells and 0.8 μM for normal human vascular endothelial cells prepared from umbilical vein (H-UVE). Skin fibroblasts, however, remained unaffected at all concentrations tested. Hydrocortisone, which augments the growth of AIDS-KS cells in the presence of activated T cell–conditioned medium (*21*), increased the IC_{50} of SP-PG on AIDS-KS cells to 0.4 μM (Fig. 1). Growth of fibroblasts was not affected by a combination of SP-PG and hydrocortisone (*22*). Pentosan polysulfate also inhibited the growth of AIDS-KS and H-UVE cells, but only at higher concentrations (the IC_{50} for AIDS-KS cells was 2 μM and that for H-UVE cells was 8 μM). Neither suramin (IC_{50}, 33 μM) nor IFN-α (IC_{50}, 1.6 nM) specifically inhibited growth of AIDS-KS or H-UVE cells (Fig. 1).

CAM assays were used to evaluate the effect of SP-PG on new blood vessel formation. New vessel formation was suppressed by addition of SP-PG (*18*) [ID_{50} (dose at which 50% inhibition was obtained) evaluated by Probid analysis was 156 ng (*18*)]. The sensitivity to SP-PG was augmented by tetrahydrocortisone (0.1 μg), giving an ID_{50} value of 4 ng. The formation of halo-like angiogenic lesions (*3*), induced by AIDS-KS cells (1×10^5), which normally reach 1 to 1.5 cm in diameter in 4 days (Fig. 2), was inhibited by treatment with SP-PG. When SP-PG [25 μg in 30 μl of phosphate-buffered saline (PBS)] was added to the CAM with the AIDS-KS cells and SP-PG alone was then added once a day for 4 days thereafter, the angiogenic lesion diminished in size to about 0.5 cm. This result was reproduced in six independent experiments. Higher concentrations (100 μg in 30 μl) produced more dramatic suppression of growth and the only visible evidence of angiogenesis was in close proximity to the AIDS-KS cells themselves (Table 1). In contrast to

Table 1. A summary of the effects of SP-PG on AIDS-KS cell–induced angiogenesis in CAM assay.

Treatment	Peripheral lesions (cm)*	Histology	CAM assays (no.)
PBS	1–1.5	Angiogenesis and edema were observed. Proliferative lesion resulted in thickening of CAM. (Fig. 2A)	16
SP-PG (25 μg)	~0.5	Proliferative lesion and thickness of CAM were similar to PBS control.	6
SP-PG (100 μg)	<0.3	Angiogenesis and edema were inhibited. Thickness of CAM also decreased.	4
SP-PG + hydrocortisone (25 μg + 20 μg)	<0.3	Angiogenesis and edema were inhibited. Lesion degenerated and the thickness of CAM decreased. (Fig. 2B)	4

*Size of the area of added AIDS-KS cells on CAM on day 1 was 0.2 to 0.3 cm.

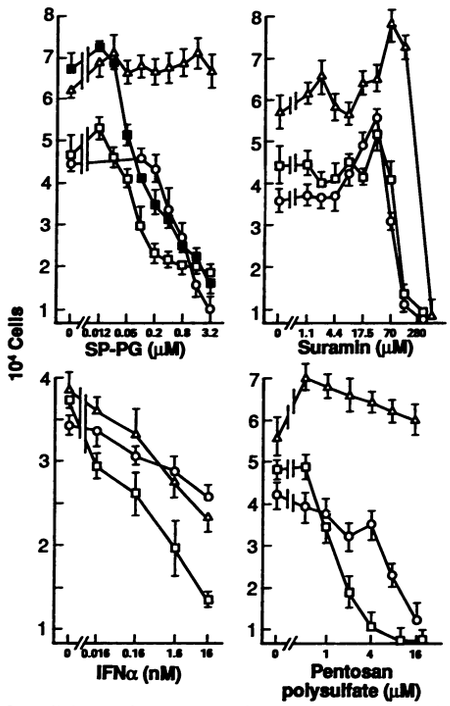


Fig. 1. Effects of SP-PG, IFNα, suramin, and pentosan polysulfate on the in vitro growth of AIDS-KS cells, H-UVE cells, and human fibroblasts. AIDS-KS3 cells (3×10^3) (*2*) were cultured in RPMI 1640 medium supplemented with fetal calf serum (FCS) (15%) (Inovar, Gaithersburg, Maryland), activated CD4 positive T cell–derived conditioned medium (T cell CM) (12.5%) (□), or T cell CM with 1 μM hydrocortisone (■) (Hydrocorton, Merck, Sharp & Dohme, West Point, Pennsylvania). H-UVE cells (5×10^3) (○) (*2*) were cultured in RPMI 1640 medium supplemented with fetal calf serum (15%), endothelial cell growth supplement (30 μg/ml) (Collaborative Research, Lexington, Massachusetts), and heparin (45 μg/ml) (Sigma, St. Louis, Missouri). Cells in 0.5 ml of medium were plated in gelatinized 24-well tissue culture dishes. Human skin fibroblasts (HSF) (3×10^3) (△) were cultured in Dulbecco's modified Eagle's medium (DMEM) (ABI, Silver Spring, Maryland) supplemented with FCS (10%). Cells were plated in ungelatinized tissue culture dishes in 0.5 ml. These cultures were incubated with or without 0.012, 0.025, 0.05, 0.1, 0.2, 0.4, 0.8, 1.6, and 3.2 μM SP-PG (Daiichi Pharmaceutical, Tokyo); 1.1, 2.2, 4.4, 8.8, 17.5, 35, 70, 140, and 280 μM suramin (FBA Pharmaceutical Division, Mobay Chemical Corporation, New York); 0.016, 0.16, 1.6, and 16 nM human recombinant IFN-α (3×10^8 U/mg, provided by A. Rashidbaigi, University of Medicine and Dentistry of New Jersey); and 0.5, 1, 2, 4, 8, and 16 μM pentosan polysulfate (Bering Werke, Germany). Compounds and media were replaced every 2 days for H-UVE cells and every 3 days for KS cells and fibroblasts. Cells at day 6 of culture were trypsinized and counted in a Coulter particle counter (*2*).

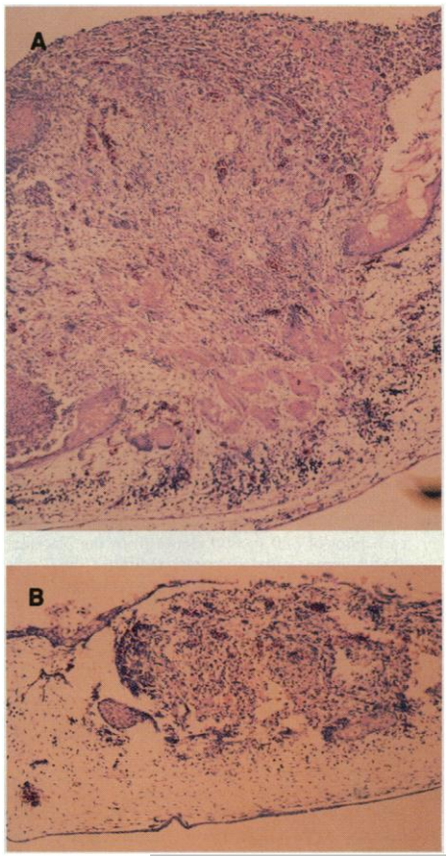


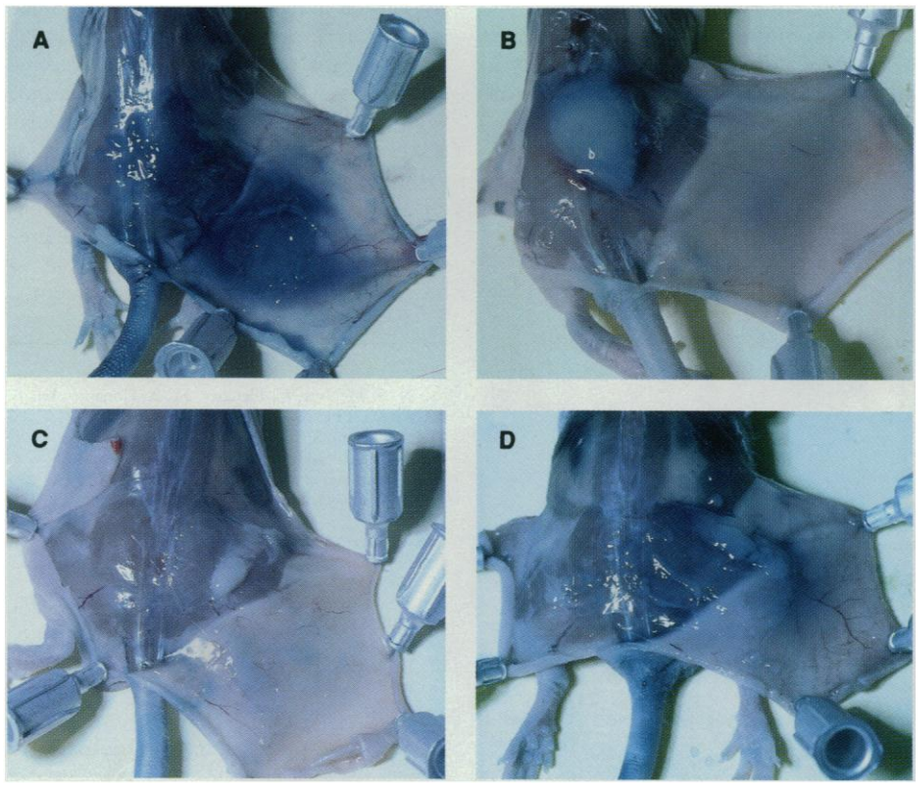
Fig. 2. Angiogenesis induced by AIDS-KS cells on chick chorioallantoic membranes (CAM) is inhibited by SP-PG. One day after fertilized eggs were cracked and embryos were transferred into 10-cm culture dishes and incubated at 37°C, in a CO_2 incubator with 70% humidity. After 9 days of culture, CAM of well-developed embryos were selected for angiogenesis experiments. AIDS-KS3 cells (1×10^5) were placed on the CAM, and new blood vessel formation was observed for the next 4 days. AIDS-KS cells and SP-PG alone or SP-PG with hydrocortisone (in 30 μl) were added simultaneously to the CAM, and subsequently SP-PG alone or SP-PG with hydrocortisone was applied to the CAM daily for 4 days. Halo-like angiogenesis of the peripheral regions was observed under low magnification in a biocular microscope, and the CAM was fixed with paraformaldehyde (4%) and stained with Giemsa. The response in the center of the lesion was evaluated by histologic examination and is summarized in Table 1. (**A**) Control only with PBS. (**B**) SP-PG (25 μg) and hydrocortisone (20 μg).

the in vitro effects on cell growth, a synergistic effect was observed when a combination of SP-PG and hydrocortisone (25 μg + 20 μg, respectively, in 30 μl) was used in this assay (Table 1 and Fig. 2). IFN-α (up to 10,000 U in 30 μl) did not inhibit angiogenesis in the CAM assay. Suramin and pentosan polysulfate were not tested in CAM assays because of prior toxicity in nude mouse assays (see below).

Nude mice can be used to study the increased vascular permeability and angiogenesis that are hallmarks of the KS tumor. When AIDS-KS3 cells (2×10^6 to 4×10^6) were subcutaneously injected into the backs of the nude mice, or administered intraperitoneally (i.p.), a biphasic vascular permeability response was observed (*4*). The first phase was histamine-dependent and nonspecific and occurred approximately 30 min after inoculation. The prolonged AIDS-KS cell–induced phase was histamine-independent and occurred later, approximately 12 hours after inoculation (*4*). In addition, angiogenesis was induced in these subcutaneous lesions; the growth of spindle-shaped cells of murine origin was observed within 5 to 6 days after transplantation of the cultured human AIDS-KS cells (*3*).

BALB/c athymic nude mice were simultaneously inoculated with AIDS-KS cells (subcutaneously) and injected with either SP-PG, IFN-α, or pentosan polysulfate intravenously (i.v.) or given suramin i.p. (Table 2). The drugs were administered again after 6 hours. All drugs were tested with or without the addition of 1 mg (50 mg/kg) of oral tetrahydrocortisone in 0.1 ml of peanut oil (5 to 18 mice for each experiment). SP-PG, with or without the administration of tetrahydrocortisone, had no effect on the early, nonspecific, histamine-dependent phase of hyperpermeability induced by AIDS-KS cells (Fig. 3, A through C and E). In contrast, it inhibited the induction of the late phase in a dose-dependent manner, beginning at a dose as low as 0.05 mg (2.5 mg/kg). The oral administration of tetrahydrocortisone did not affect this response. A high dose of IFNα (10,000 U, i.v.) (5×10^5 U/kg) only partially inhibited the late response (Fig. 3D), but either suramin (5 mg, i.p.) (250 mg/kg) or a high dose of pentosan polysulfate (2 mg, i.v.) (100 mg/kg) alone or in combination with tetrahydrocortisone had no effect (Table 2).

To evaluate the effect of SP-PG on AIDS-KS cell–induced angiogenesis, experiments were done in a similar manner as for the vascular permeability response stud-



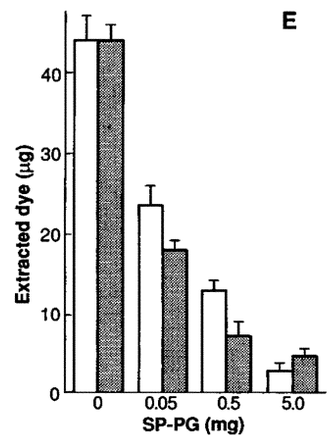


Fig. 3. Effect of various concentrations of SP-PG and IFN-α on the vascular permeability response induced by AIDS-KS cells. Eight-week-old female BALB/c nu/nu athymic nude mice (NIH Cancer Research Facility, Frederick, Maryland) were used in all experiments (body weight about 20 g). After the mice were treated with various compounds (summarized below and Table 2) with or without initial peroral administration of tetrahydrocortisone (1 mg) in peanut oil (Sigma), AIDS-KS3 cells (2×10^6) were injected subcutaneously. The resulting late phase vascular permeability response was observed 12 hours after injection as described (*4*). At that time 100 μl of Evans blue (5 mg/ml) (Sigma) was injected into the tail vein, and 15 min later the animals were killed. The KS-like visible lesion (approximately 1.5 cm in diameter) was excised and minced with scissors, and the dye was extracted by overnight incubation in PBS at 4°C. The total amount of dye exuded into the extracellular space was determined spectrophotometrically after subtracting the optical density of an extract from an adjacent but uninvolved area, which was similarly excised, minced, and extracted (E). The appearance of the lesion was also photographically recorded (**A** through **D**) (*4*). (**E**) Dose response of SP-PG. Administration with (shaded bars) or without (open bars) tetrahydrocortisone. Each value is the mean of measurements on six mice; the result was reproduced in ten separate experiments (SD ranged from 1.0 to 3.2). (A through D) Inhibition of the AIDS-KS–related vascular permeability by SP-PG. (A) Control, PBS; (B) SP-PG (0.5 mg); (C) SP-PG (5 mg); (D) IFN-α (10,000 U).

Table 2. Comparison of the relative effects of SP-PG and various other agents on the vascular hyperpermeability induced by AIDS-KS cells.

Compound (dose)	Mice tested (no.)	Injection mode	Inhibition of exuded dye* (%)
SP-PG			
0.05 mg (2.5 mg/kg)	10	i.v.	48
0.5 mg (25 mg/kg)	10	i.v.	70
5.0 mg (250 mg/kg)	18	i.v.	94
IFN-α			
10,000 U (5×10^5 U/kg)	5	i.v.	52
Suramin			
5.0 mg (250 mg/kg)	5	i.p.	2
Pentosan polysulfate			
2.0 mg (100 mg/kg)	5	i.v.	4

*Late phase vascular permeability (12 hours) was induced by subcutaneous injection of AIDS-KS cell (4×10^6) into athymic nude mice and measured by Evans blue dye exudation as described in the text and legend to Fig. 3. Inhibition of vascular permeability response after treatment with various compounds was determined by measuring the amount of exuded dye, expressed as a percent of the total amount of dye exuded in the untreated KS-like lesion (44.7 μg per lesion).

ies but were continued for 6 days to induce an observable effect. In summary, athymic nude mice were simultaneously inoculated with AIDS-KS cells (subcutaneous) and SP-PG (i.v.) and then injected with SP-PG daily for 5 days. SP-PG was tested with or without the addition of oral tetrahydrocortisone (1 mg). Although 0.05 mg (2.5 mg/kg) of SP-PG did not affect angiogenesis (with or without tetrahydrocortisone), 0.5 mg (25 mg/kg) of SP-PG led to degeneration of newly formed vascular lesions, and 5 mg (250 mg/kg) of SP-PG completely inhibited vascularization. Unlike the vascular permeability response, the effect on angiogenesis was even more pronounced when SP-PG (5 mg) was combined with tetrahydrocortisone (1 mg) (Fig. 4). All mice remained healthy and active. Histological examination of the lesions in the nude mice demonstrated degenerated vascular structures and fewer blood vessels, less bleeding, and only a few spindle-shaped cells, compared to untreated control animals (Fig. 4). In similar experiments, suramin (5 mg, 250 mg/kg) had no inhibitory effect on vascular permeability induced by AIDS-KS cells and was toxic; two of five nude mice died during these experiments, and the remaining mice showed evidence of lethargy and weakness. IFN-α (10,000 U, 5×10^5 U/kg) had only a limited effect and pentosan polysulfate (2 mg, 100 mg/kg) had no inhibitory effect on the development of these angiogenic lesions (*22*).

The present study suggests that SP-PG may be promising for KS therapy because of its low cytotoxicity and its efficiency in limiting AIDS-KS cell growth and development of KS-like lesions. Classical inhibitors of angiogenesis, such as protamine sulfate (*13*) and heparin or heparin analogs (*13, 14*) with angiostatic steroids (*15*) have been tested on CAM or tumor-associated angiogenic systems. However, these compounds have shown toxicity or induced bleeding. Recently, other angiostatic agents have also been described such as platelet factor 4 (*16*), cartilage-derived inhibitor (*23*), and a fungal product or its analog (*24*), which remain to be tested in our systems.

In our in vitro and in vivo systems, two components of KS lesion development, vascular hyperpermeability and angiogenesis, can be independently evaluated. Since vascular hyperpermeability (perhaps an efficient means for new lesions to receive cellular as well as extracellular factors), vascular proliferation, and other vascular responses are involved in a variety of pathological situations, such as tumorigenesis, inflammation, and diabetic retinopathy, the development of methods to prevent or reverse their effects could have broad implications for disease treatment.

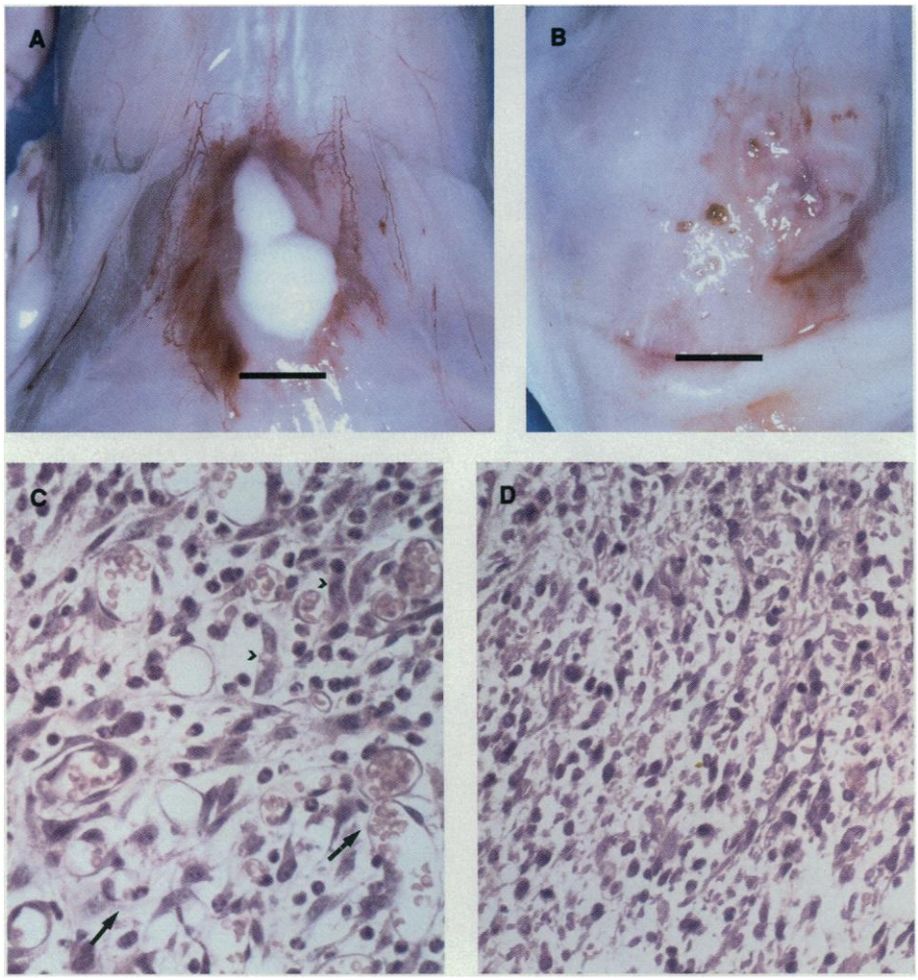


Fig. 4. SP-PG–induced inhibition of KS-like lesions in nude mice. AIDS-KS cells (4×10^6) were transplanted subcutaneously into BALB/c nu/nu athymic mice. At the same time SP-PG was given (i.v.) with oral tetrahydrocortisone (1 mg) suspended in peanut oil (0.1 ml) (Sigma). The administration of the drugs was continued daily for 5 days. Angiogenic lesions (observed on day 6) were fixed with paraformaldehyde (4%) and stained with hematoxylin-eosin. (>) Represents the spindle-shaped cells and (↑) the small vessels. (**A** and **C**) KS lesion in nude mouse after treatment with PBS (i.v.) and oral tetrahydrocortisone. (A) Gross appearance (bar = 1 cm); (C) histological section. (**B** and **D**) KS lesion in nude mouse after treatment with SP-PG (i.v., 5 mg) and oral tetrahydrocortisone. (B) Gross appearance (bar = 1 cm); (D) histological section.

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