Table 2. Effect of substance P and D–substance P on synoviocyte proliferation. Synoviocytes were cultured in the presence of substance P and D–substance P ($10^{-8}M$) for 72 hours. For the last 6 hours, 5-bromo-2′-deoxyuridine (10 μM) and thymidine (32 μM) were added to the cultures. Cells were then dislodged with trypsin. After being washed with cold phosphate-buffered saline, the cells were fixed with 70% ethanol at 0°C for 30 minutes and spun onto microscope slides. DNA was denatured with 0.07M NaOH at room temperature for 2 minutes. Slides were then incubated with monoclonal antibody to BrdUrd (1:500). Bound antibodies were visualized with fluorescein isothiocyanate–labeled antibody to mouse immoglobulin. The cells were analyzed with a Leitz OrthoLux II microscope. Results from four experiments performed in triplicate are expressed as the percentage of fluorescence positive cells ± SEM.

Substance P (M)	Cells stained with antibody to BrdUrd	
	Alone	In presence of D–substance P
0	8.3 ± 2.3	
10^{-6}	18.3 ± 3.4	
10^{-7}	24.8 ± 3.9	
10^{-8}	29.6 ± 3.8	13.6 ± 2.8
10^{-9}	19.8 ± 3.2	
10^{-10}	14.4 ± 2.9	

release substance P into the joint tissues. From the present results it appears that long-term exposure of synoviocytes to substance P could contribute to the development of several pathological findings in RA. By stimulating synoviocyte proliferation, substance P can enhance the formation of pannus, which represents excessive growth of synovial tissue over the joint surface. This hypothesis is consistent with its known stimulation of skin fibroblast proliferation (*17*). The basis for the effects of substance P on these cells may be the amino acid sequence homology between substance P and acidic fibroblast growth factor (*18*).

The augmentation of collagenase release and PGE_2 generation from synoviocytes activated by substance P suggests additional roles for this neuropeptide in RA. Through release of collagenase, substance P may stimulate loss of cartilage and development of lesions in the adjacent bone. Through PGE_2 release, substance P may provide a signal to perpetuate the inflammatory process in the arthritic joint. The two other known activators of synoviocytes, IL-1 and TNF-α, are both products of the reticuloendothelial system. An interaction of the nervous and reticuloendothelial system involving substance P has been proposed (*9*).

In summary, these observations define a specific pathway by which substance P, a nervous system–derived peptide, can contribute to the pathogenesis of RA. Similar effects of substance P on connective tissue remodeling and destruction may be relevant also in the response of other organs to inflammatory or traumatic injury, as well as inflammation in other diseases.

REFERENCES AND NOTES

1. J. H. Vaughan and M. Lotz, in *Immunological Diseases*, M. Samter, Ed. (Little, Brown, Boston, 1986).
2. S. B. Mizel, J. M. Dayer, S. M. Krane, S. E. Mergenhagen, *Proc. Natl. Acad. Sci. U.S.A.* **78**, 2474 (1981); J. M. Dayer, B. Beutler, A. Cerami, *J. Exp. Med.* **162**, 2163 (1985).
3. D. M. Mitchell and J. F. Fries, *Arthritis Rheum.* **25**, 481 (1982).
4. M. Thompson and E. G. L. Bywaters, *Ann. Rheum. Dis.* **25**, 370 (1962).
5. G. H. B. Baker, *Psychother. Psychosom.* **38**, 173 (1982).
6. B. Wyke, *Clin. Rheum. Dis.* **7**, 223 (1981).
7. B. Pernow, *Pharmacol. Rev.* **35**, 85 (1983).
8. F. Lembeck and P. Holzer, *Naunyn. Schmiedebergs. Arch. Pharmacol.* **310**, 175 (1979).
9. H. P. Hartung, K. Wolters, K. V. Troyka, *J. Immunol.* **136**, 3856 (1986); Z. Bar-Shavit *et al.*, *Biochem. Biophys. Res. Commun.* **90**, 1445 (1980); W. A. Marasco, H. J. Showell, E. L. Becker, *ibid.* **99**, 1065 (1981).
10. J. D. Levine *et al.*, *Science* **226**, 547 (1984).
11. J. M. Dayer, J. Bréard, L. Chess, S. M. Krane, *J. Clin. Invest.* **64**, 1386 (1979).
12. K. Folkers, J. Horig, S. Rosell, U. Bjorkroth, *Acta Physiol. Scand.* **111**, 505 (1981).
13. B. Johnson-Wint, *Anal. Biochem.* **104**, 175 (1980).
14. P. E. Auron *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **81**, 7907 (1984).
15. R. D. Inman, B. Chin, K. W. Marshall, *Arthritis Rheum.* **29**, 59 (1986).
16. F. Lembeck, J. Donnerer, F. C. Colpaert, *Neuropeptides* **1**, 175 (1981).
17. J. Nilsson, A. M. von Euler, C.-J. Dalsgaard, *Nature (London)* **315**, 61 (1985).
18. G. Gimenez-Gallego *et al.*, *Science* **230**, 1385 (1985).

19. We thank the BCR word processing team for preparation of the manuscript. This is publication number 4525BCR from the Research Institute of Scripps Clinic, La Jolla, CA. Supported by a grant from the Rheumatic Diseases Research Foundation and by NIH grants AM 25443, AM 21175, and RR 00833. R. Convery, University of California Medical Center, San Diego, kindly provided the synovial tissue specimens. We thank F. E. Bloom, Scripps Clinic, for helpful discussions.

22 September 1986; accepted 6 January 1987

Recombinant Interferon Enhances Monoclonal Antibody–Targeting of Carcinoma Lesions in Vivo

JOHN W. GREINER, FIORELLA GUADAGNI, PHILIP NOGUCHI, SIDNEY PESTKA, DAVID COLCHER, PAUL B. FISHER, JEFFREY SCHLOM

Heterogeneity in the expression of tumor-associated antigens, as defined by the binding of monoclonal antibodies, is a characteristic common to most, if not all, human carcinoma cell populations. Antigen-negative cells within the population can escape detection and therapy by their failure to bind the appropriate antibody. Therefore, the extent of antigenic heterogeneity is an important consideration when designing protocols for the management of cancer by administration of monoclonal antibodies. One approach to counteracting the effect of antigenic heterogeneity is the use of clone A of recombinant human leukocyte interferon (Hu-IFN-αA). Administration of Hu-IFN-αA in vivo effectively increased the amount of tumor antigen expressed by a human colon xenograft in situ and augmented the localization of a radiolabeled monoclonal antibody to the tumor site. Concomitant administration of Hu-IFN-αA and monoclonal antibody may thus be effective in overcoming the antigenic heterogeneity of carcinoma cell populations and in enhancing the efficacy of monoclonal antibodies in the detection and treatment of carcinoma lesions.

HETEROGENEITY OF ANTIGEN EXpression is characteristic of human carcinoma cell populations (*1*). This phenomenon has far-reaching implications for the use of monoclonal antibodies (mAbs) in diagnosis or therapy. Rendering a human tumor cell population more homogeneous for the expression of an antigen could result in an augmentation of mAb binding and, thus, more efficient diagnostic or therapeutic results.

Human natural and recombinant interferons, in addition to eliciting antiviral and antiproliferative actions, can alter the surface antigenic phenotype of various human target cells in vitro (*2–6*). The level of expression of class I and II histocompatibility antigens as well as of certain tumor-associated antigens can be modulated by recombinant human interferons (*2, 4–6*). Recombinant human leukocyte interferon (Hu-IFN-α) can enhance the expression of histocompatibility antigens (HLA) and of several mAb-defined tumor antigens on the surface of human breast and colon carcinoma cells (*5, 7*). We reported recently that of eight different recombinant species of Hu-IFN-α,

J. W. Greiner, F. Guadagni, D. Colcher, J. Schlom, Laboratory of Tumor Immunology and Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.
P. Noguchi, Office of Biologics, National Center for Drugs and Biologics, Food and Drug Administration, Bethesda, MD 20892.
S. Pestka, Department of Molecular Genetics and Microbiology, Rutgers Medical School, Piscataway, NJ 08854.
P. B. Fisher, Department of Urology, Cancer Center/Institute of Cancer Research, Columbia University, College of Physicians and Surgeons, New York, NY 10032.

Hu-IFN-αA was the most potent in augmenting the binding of mAbs to defined cell surface human tumor antigens (*8*). The increased surface antigen expression, as determined by a radioimmunoassay (RIA), cytofluorometry, and immunohistochemical analysis, was a result of (i) an increase in the amount of surface tumor antigen per cell and (ii) a higher percentage of antigen-positive cells providing a more homogeneous antigen-expressing tumor cell population.

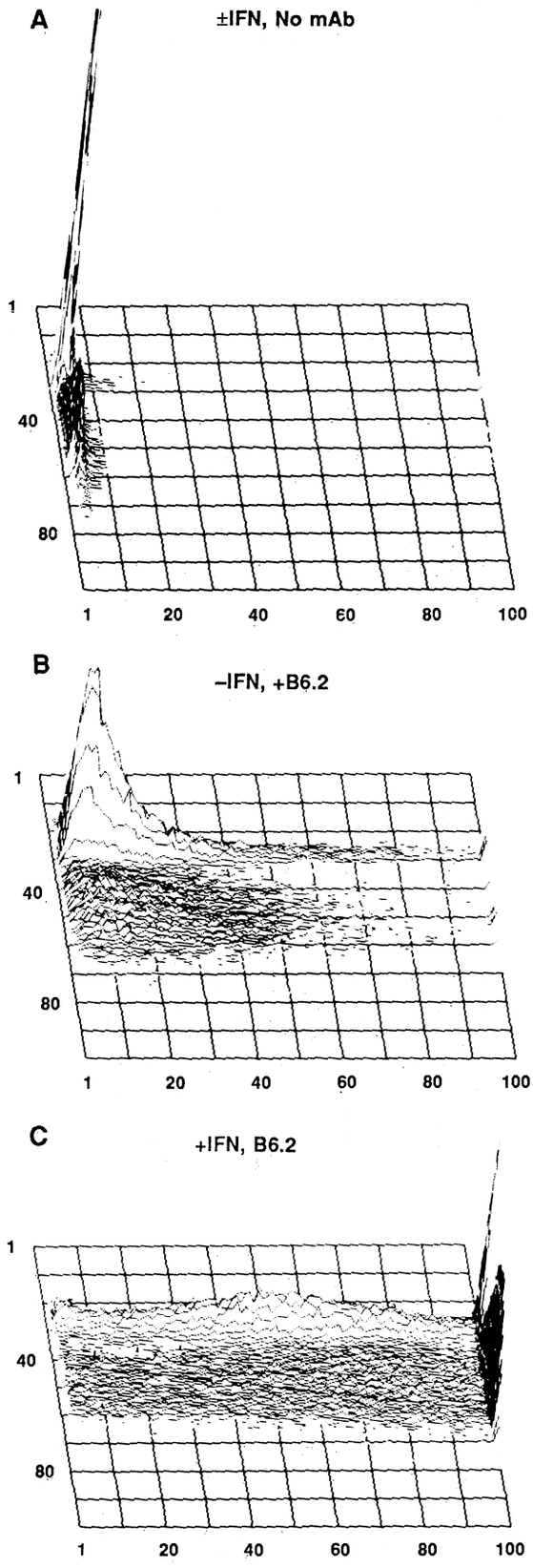

Fig. 1. Fluorescence-activated cell sorter (FACS) analysis of mAb B6.2 binding to the surface of human colon carcinoma cells: effect of Hu-IFN-αA. An Ortho Cytofluorograf System 50H with blue laser excitation of 200 mW at 488 nm was used for flow cytometric analysis. WiDr cells were incubated for 24 to 36 hours in growth medium with or without Hu-IFN-αA at 850 antiviral units per milliliter, harvested, and incubated in culture medium containing 2 μg of mAb B6.2 per 10^6 cells for 30 minutes at 4°C. The cells were then washed thoroughly with Ca^{2+}, Mg^{2+}–free Dulbecco's phosphate-buffered saline and then treated with fluorescinated sheep antibody to mouse IgG (1:30 dilution) for 30 minutes at 4°C. The cells were washed; excess antibody was removed; and the cells were resuspended at a concentration of 10^6 cells per milliliter and stained with propidium iodide (18 μg/ml) and ribonuclease A (2000 unit/ml) for 4 hours at room temperature. Under these conditions, fluorescence of propidium iodide bound to nuclear DNA is red, whereas surface immunofluorescence bound to the 90-kD tumor antigen is green (*5*). Data from 25,000 cells were stored on a computer system (Ortho model 2150) and were used to generate each three-dimensional isometric display, showing DNA content on the *y* axis; fluorescence intensity—that is, cell surface expression of the B6.2-reactive 90-kD tumor antigen on the *x* axis; and the number of cells on the *z* axis. (**A**) WiDr cells stained for DNA content, but no mAb B6.2. (**B**) WiDr cells stained for nuclear DNA and B6.2 binding. (**C**) WiDr cells treated with Hu-IFN-αA (850 antiviral units for 24 to 36 hours) and stained as in (B).

We now report that Hu-IFN-αA can augment the binding of a mAb to human carcinoma cells in vivo. Monoclonal antibody B6.2 reacts with a 90-kD glycoprotein found in 75% to 80% of breast carcinomas and more than 90% of colon carcinomas (*9*). We showed earlier that mAb B6.2 can be labeled with a radionuclide while maintaining its immunoreactivity and can efficiently localize human carcinoma xenografts in athymic mice (*10*). Heterogeneity for the expression of the B6.2-reactive 90-kD antigen within these human colon carcinoma cells has been established (*5, 9*). We investigated the possibility that Hu-IFN-αA treatment of athymic mice bearing human colon carcinoma xenografts can enhance the level of expression of the 90-kD tumor antigen and can augment the localization of labeled mAb B6.2 to the colon tumor mass. For controls we used mAb W6/32, which recognizes histocompatibility antigens HLA-A, B, and C (*11*), and MOPC-21, an immunoglobulin G1 (IgG1) produced by a murine myeloma (*10*).

We used the colon carcinoma cell line WiDr and the normal fibroblast cell line WI-38 to investigate the effects of Hu-IFN-αA on the expression of the B6.2-reactive 90-kD tumor antigen and the histocompatibility antigens. We reported earlier that the binding of mAb B6.2 to the surface of human breast and colon carcinoma cells can be enhanced in a dose-dependent manner by Hu-IFN-αA (*5*). In the present study, treatment of the WiDr cells with 2000 units of Hu-IFN-αA for 24 to 36 hours resulted in a 2.7-fold increase in the binding of B6.2 to the WiDr cell surface (13,810 as opposed to 5,080 count/min per 5×10^4 cells). The binding of mAb W6/32 to HLA was also increased threefold after Hu-IFN-αA treatment. For comparison, we studied the effects of the Hu-IFN-αA on the expression of these same antigens on the surface of the normal human WI-38 fibroblasts. The WI-38 fibroblasts expressed HLA constitutively; however, these cells do not express the 90-kD tumor antigen either before or after IFN-αA treatment and thus fail to react with mAb B6.2. Neither cell type demonstrates any reactivity with the MOPC-21 antibody. As reported by others (*2, 4*), Hu-IFN-αA can increase the expression of HLA on the surface of normal human cells. HLA expression on the WI-38 cell surface was increased 34% with the addition of Hu-IFN-αA; moreover, treatment with higher doses or longer time intervals failed to further boost W6/32 binding to the WI-38 cell surface. Such observations are particularly important for the analysis of the kinetics of B6.2

Table 1. Reactivity of mAbs to human colon tumor extracts isolated from athymic mice after Hu-IFN-αA treatment. Human colon carcinoma xenografts from WiDr cells were grown as subcutaneous tumors in female athymic mice. When the tumor diameter averaged 0.5 to 0.8 cm, the mice were divided into an Hu-IFN-αA–treated group that received twice daily intramuscular injections of either 0.25×10^5 or 1.25×10^5 antiviral units of Hu-IFN-αA and a control group that received phosphate-buffered saline (PBS) containing 1% bovine serum albumin. After 5 days of treatment the mice were killed and, bled by cardiac puncture; plasma Hu-IFN-αA levels were measured by means of MDBK cells infected with vascular stomatitis virus. The amount of binding of ^{125}I-labeled B6.2 or MOPC-21 was measured as counts per minute per 5 μg of tumor extract in extracts prepared from the WiDr tumors (*8*). Each ^{125}I-labeled mAb was added at a concentration of 75,000 count/min per 25 μl to each well of a 96-well plate containing dilutions of tumor extract ranging from 20 μg per well to 0.3 μg per well. Values in parentheses represent the range of mAb binding, where the mean amount of each mAb bound is calculated from three to five experiments. Each experiment consisted of 25 to 40 control and IFN-αA–treated tumor-bearing mice. NSB, no significant binding.

Hu-IFN-αA treatment (antiviral units)	Plasma Hu-IFN-αA level (antiviral unit/ml)	Amount of mAb bound to tumor tissue (count/min per 5 μg)	
		B6.2	MOPC-21
	75 (<30	5,460 (3,680 to 7,240)	NSB*
+50,000	75 (<40 to 90)	7,890 (5,810 to 12,890)	NSB
+250,000	310 (160 to 540)	18,460 (7,890 to 24,410)	NSB

*Less than 500 count/min above background.

reactivity to nontumor cells. In this regard, we found that incubation of the WI-38 and other normal human cells with as much as 10,000 antiviral units of Hu-IFN-αA did not result in the initiation of expression of this, or any other, tumor antigen. These results have shown that a noncarcinoma human cell population which does not constitutively express a particular surface tumor antigen remains antigen-negative even after treatment with high levels of Hu-IFN-αA.

The data from the RIA established that Hu-IFN-αA treatment can increase the overall level of surface antigen expression within a cell population (*5, 8*). It is possible, however, that the increase induced by the interferon could be a result of the enhanced expression of the B6.2-reactive antigen within a subpopulation of cells or a preferential expansion of a population that exhibits a constitutively high level of B6.2 reactivity. WiDr cells were treated with Hu-IFN-αA for 36 hours and the binding of B6.2 was analyzed by cytofluorometry. Cell sorter analysis of the untreated and Hu-IFN-αA–treated WiDr cells, but with no mAb B6.2 added, is shown in Fig. 1A. The addition of mAb B6.2 to the WiDr cell population results in 40% to 50% of the cell population binding the B6.2 (Fig. 1B). Treatment of the WiDr cells with Hu-IFN-αA for 36 hours followed by the addition of mAb B6.2 (Fig. 1C) results in more than 90% of the population being positive for the 90-kD antigen and a two- to threefold increase in the fluorescence intensity. These findings indicate that in addition to the overall increase in tumor antigen expression within the cell population, Hu-IFN-αA treatment results in an increase in the percentage of antigen-positive cells within that population (from approximately 50% to more than 90%). The results argue against a preferential expansion of a high antigen-expressing cell population and suggest enhanced synthesis of the surface antigen as a possible mechanism.

Experiments were conducted to determine whether Hu-IFN-αA was capable of enhancing tumor antigen expression and subsequent mAb binding in vivo. WiDr cells were grown as subcutaneous tumors in athymic mice. The mice were untreated or were treated with 50,000 or 250,000 units of Hu-IFN-αA daily for 5 days. The mean plasma Hu-IFN-αA levels for the mice treated with 50,000 or 250,000 units were 75 and 310 antiviral units per milliliter, respectively (Table 1). When the mice were killed, the human colon tumors were removed from each of the individual mice, extracts were prepared (*9*), and the binding of ^{125}I-labeled B6.2 was measured. The data indicate that the administration of either 50,000 or 250,000 antiviral units of Hu-IFN-αA to athymic mice bearing WiDr tumors can significantly increase the amount of B6.2-reactive 90-kD tumor antigen in the tumor extracts. The mean level of binding of ^{125}I-labeled B6.2 to the WiDr tumor extracts prepared from mice that received 50,000 units of Hu-IFN-αA per day for 5 days was approximately 45% higher than that measured in WiDr tumor extracts prepared from the untreated mice (7890 as opposed to 5460 count/min per 5 μg of tumor protein extract). Increasing the Hu-IFN-αA daily dose to 250,000 antiviral units resulted in an increase in the circulating interferon plasma levels. The mean level of binding of ^{125}I-labeled B6.2 to those WiDr tumor extracts was more than threefold higher than for the control WiDr tumors (18,460 as opposed to 5,460 count/min per 5 μg of tumor protein extract). An analysis of WiDr tumor extracts prepared from individual mice treated with 250,000 antiviral units Hu-IFN-αA per day revealed that the level of expression of the

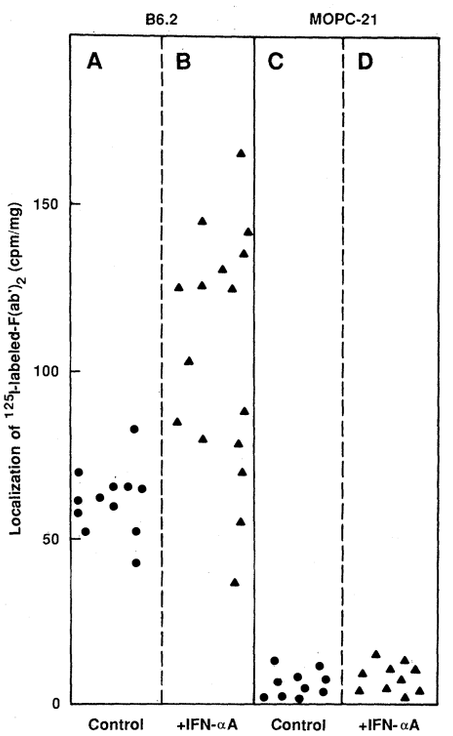

Fig. 2. Comparison of the localization of (**A** and **B**) ^{125}I-labeled B6.2 F(ab')$_2$ and (**C** and **D**) ^{125}I-labeled MOPC-21 to WiDr tumors grown in athymic mice with and without Hu-IFN-αA treatment. The B6.2 IgG was purified from ascites fluid obtained from pristane-primed BALB/c mice inoculated intraperitoneally with 10^7 hybridoma cells (*12*). F(ab')$_2$ fragments were prepared by pepsin digest without any pretreatment with dithiothreitol or iodoacetamide. MOPC-21, a mouse myeloma IgG1 was purchased from Litton Bionetics (Rockville, Maryland). The B6.2 F(ab')$_2$ and MOPC-21 antibodies were labeled with Na^{125}I with the use of iodogen as described earlier (*12*). The iodination protocol yielded labeled IgG and fragments with a specific activity of 15 to 50 μCi/μg, with up to 60% of the ^{125}I bound to the protein. Four-week-old female athymic mice were inoculated subcutaneously with 2×10^6 WiDr cells (in 0.2 ml), and after 18 to 32 days tumors with average diameters of 0.8 to 1.5 cm had appeared. In this representative experiment the WiDr tumor-bearing athymic mice were divided into two groups: controls and those treated with Hu-IFN-αA at 250,000 units per day. Hu-IFN-αA–treated mice received intramuscular injections twice daily for 5 days and the control, untreated animals received PBS containing 1% bovine serum albumin. Approximately 2 hours after the final Hu-IFN-αA injection all mice received, via the tail vein, 1.5 μCi (0.1 μg) of iodinated B6.2 F(ab')$_2$ or ^{125}I-labeled MOPC-21 in PBS. The mice were killed 24 hours later, the tumors were excised and weighed, and the radioactivity was measured in a gamma counter.

Table 2. Binding of ^{125}I-labeled B6.2 F(ab′)$_2$ to WiDr tumors grown in athymic mice. F(ab′)$_2$ fragments of mAb B6.2 were produced and labeled with Na^{125}I (*12*). Mice were injected with 2×10^6 count/min (approximately 0.1 μg of protein) of the radiolabeled B6.2 F(ab′)$_2$ and killed 24 hours later; the percentage of the injected dose per gram was determined for each of the tissues (*12*). Control animals received either a single injection of 0.9% NaCl or ^{125}I-labeled MOPC-21 mouse myeloma antibody. The growth of WiDr tumors in athymic mice and the administration of 250,000 units of Hu-IFN-αA were as described in Table 1.

Mouse	Plasma Hu-IFN-αA (unit/ml)	Percentage of injected dose per gram of tissue			
		Tumor	Blood	Liver	Spleen
		Control			
1	<30	2.68	0.52	0.52	0.30
2	<30	2.16	0.79	0.44	0.32
3	<30	2.60	0.85	0.77	0.43
4	<30	2.81	0.68	0.69	0.44
5	<30	4.61	1.03	0.68	0.53
6	<30	4.40	0.78	0.73	0.53
		Hu-IFN-αA–treated			
1	128	7.24	0.70	0.80	0.38
2	64	3.47	0.96	0.68	0.33
3	196	8.23	0.85	0.76	0.36
4	128	6.19	0.60	0.74	0.43
5	196	9.37	0.90	1.22	0.49
6	64	12.89	1.03	1.04	0.69
7	196	12.55	1.15	0.98	0.63

90-kD tumor antigen was six- to sevenfold higher than that found in comparable tumors in the untreated group.

To determine whether the IFN-αA–mediated increase in tumor antigen content included the cell surface component of the antigen, we carried out in vivo localization studies with the ^{125}I-labeled B6.2 F(ab′)$_2$ fragment. In an earlier study of human tumors in athymic mice (*12*), a comparison of the radiolocalization indices for the intact B6.2 IgG and related fragments showed that the F(ab′)$_2$ fragment of B6.2 was capable of eliciting higher ratios of tumor to tissue than the other forms of the antibody. Therefore, we decided to compare the localization of ^{125}I-labeled B6.2 F(ab′)$_2$ in athymic mice carrying WiDr tumor with and without Hu-IFN-αA treatment (Fig. 2, A and B). Hu-IFN-αA treatment of WiDr tumor-bearing athymic mice resulted in a substantial enhancement of the ^{125}I-labeled B6.2 F(ab′)$_2$ localization index as measured by the amount of ^{125}I bound per milligram of tumor weight—a 93% increase in the mean amount of ^{125}I bound (104 as opposed to 54 count/min per milligram of tumor weight). In addition, the WiDr-bearing athymic mice that received Hu-IFN-αA exhibited a fivefold range for the localization of ^{125}I-labeled B6.2 F(ab′)$_2$; this finding suggests differing sensitivities or plasma interferon levels (or both) among the individual mice of the interferon-treated group. Again, analysis of individual mice revealed that Hu-IFN-αA treatment can result in a fourfold increase in the localization of the F(ab′)$_2$ fragment of B6.2 to the WiDr tumor mass. The control, MOPC-21 antibody, did not react with either control or Hu-IFN-αA–treated WiDr tumor-bearing mice (Fig. 2, C and D). Furthermore, interferon treatment did not alter the in vivo growth of the WiDr tumors during this study.

Table 2 is a summary of the difference in the percentage of the injected dose of ^{125}I-labeled B6.2 F(ab′)$_2$ localized in untreated and Hu-IFN-αA–treated WiDr tumor-bearing mice. In untreated WiDr tumor-bearing mice, 2.1% to 4.6% of the amount of injected ^{125}I-labeled mAb was localized after 24 hours. The percentages of injected ^{125}I-labeled B6.2 F(ab′)$_2$ localized in the WiDr tumor of athymic mice treated with Hu-IFN-αA were considerably higher, with values up to 12.9% of the injected dose per gram. Untreated WiDr tumor-bearing athymic mice consistently failed to exhibit plasma Hu-IFN-αA levels that were greater than the minimum level (30 unit/ml) of detection for the assay. In general, there is a linear relation between the circulating plasma levels of Hu-IFN-αA and the amount of localization of ^{125}I-labeled B6.2 F(ab′)$_2$ to WiDr tumors in situ (Table 2). However, the wide range of plasma interferon may reflect differences in the rate of clearance of Hu-IFN-αA by the individual mice, development of antibodies to interferon, differential release of Hu-IFN-αA from the site of injection, or any combination of these or other factors.

An important consideration in the design and implementation of mAbs for the detection and therapy of human carcinomas is the degree of tumor antigen heterogeneity within a human tumor cell population. Tumor cells that do not express antigen or cells with low surface antigen density might be undetected in immunodiagnostic or therapeutic procedures. We have presented evidence that Hu-IFN-αA can alter the biology of a human tumor cell population. Our in vitro studies revealed that the increase in tumor antigen expression as a result of Hu-IFN-αA treatment was due to an increased amount of antigen expressed per cell as well as an increase in the percentage of antigen-expressing cells within the population (*5, 7*). It is conceivable that the same events occurring in vivo can result in the increase in B6.2 reactivity to WiDr tumor extracts and the augmentation of ^{125}I-labeled B6.2 F(ab′)$_2$ localization at the WiDr cell surface. Numerous mAbs are being evaluated by different laboratories using both experimental models and clinical protocols to determine their usefulness in the management of human carcinomas. Some of the mAbs have been conjugated with radionuclides and used to localize occult tumor lesions in situ (*10, 12*), to detect antigen in serum (*13*), and to detect carcinoma cells in pleural effusions, ascites, and fine-needle aspirate biopsies (*14*). In an immunodiagnostic procedure, the ability to increase tumor antigen expression on tumor cells by a pretreatment with recombinant human interferon could result in a more accurate discrimination between tumor and nontumor tissue. In addition, mAbs can be used to deliver therapeutic doses of radionuclides, toxins, or effector cells to the tumor site. The use of recombinant interferon to augment tumor antigen expression in each of these situations merits consideration.

REFERENCES AND NOTES

1. P. Horan Hand, M. Nuti, D. Colcher, J. Schlom, *Cancer Res.* **43**, 728 (1983); P. Natali *et al., J. Immunol.* **130**, 1462 (1983); S. Fargion *et al., Cancer Res.* **46**, 2633 (1986).
2. M. Fellous, M. Kamoun, I. Gresser, R. Bono, *Eur. J. Immunol.* **9**, 446 (1979).
3. K. Imai, A-K. Ng, M. C. Glassy, S. Ferrone, *J. Immunol.* **127**, 505 (1981).
4. T. Y. Basham, M. F. Bourgeade, A. A. Creasey, T. C. Merigan, *Proc. Natl. Acad. Sci. U.S.A.* **79**, 3265 (1982).
5. J. W. Greiner *et al., Cancer Res.* **44**, 3208 (1984).
6. P. Giacomini, A. Aguzzi, S. Pestka, P. B. Fisher, S. Ferrone, *J. Immunol.* **133**, 1649 (1984).
7. J. W. Greiner *et al.*, in *Cancer Cells 4/The Transformed Phenotype*, A. J. Levine, G. F. Vande Woude, W. C. Topp, J. D. Watson, Eds. (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1984), pp. 265–291.
8. J. W. Greiner *et al., Cancer Res.* **46**, 4984 (1986).
9. M. Nuti *et al., Int. J. Cancer* **29**, 539 (1982); D. Stramignoni, R. Bowen, B. F. Atkinson, J. Schlom, *ibid.* **31**, 543 (1983).
10. D. Colcher *et al., Cancer Res.* **44**, 5744 (1984).
11. C. J. Barnstable *et al., Cell* **14**, 9 (1978).
12. D. Colcher *et al., Cancer Res.* **43**, 736 (1983).
13. A. J. Paterson, J. Schlom, H. F. Sears, J. Bennett, D. Colcher, *Int. J. Cancer* **37**, 659 (1986).
14. M. Nuti *et al., ibid.*, p. 193; W. W. Johnston, C. A. Szpak, S. C. Lottich, A. Thor, J. Schlom, *Cancer Res.* **45**, 1984 (1986).

15. We thank G. Davis, R. Cunningham, R. Riley, B. Kelder, and D. Simpson for technical assistance.

9 September 1986; accepted 31 December 1986