Differential Effects of Recombinant Human Leukocyte Interferons on Cell Surface Antigen Expression

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ABSTRACT

Human leukocyte (α) interferon (IFN-α) is composed of a multigene family within which at least eight different species have been expressed in Escherichia coli, isolated, and shown to exert a wide range of biological activities on different human target cells. This study involved eight species of IFN-α (A, B, C, D, F, I, J, and K) and investigated their respective capabilities to alter the proliferation of a human breast carcinoma cell line (MCF-7). The antigens studied were all constitutively expressed on the MCF-7 cell surface: the M, 180,000 carcinoembryonic antigen; a high molecular weight (>10^6) glycoprotein, termed tumor-associated glycoprotein 72; and a major HLA histocompatibility antigen. The level of expression of each antigen was measured by the binding of monoclonal antibodies B1.1, B72.3, and W6/32, respectively. A high degree of diversity was found among the various IFN-α species with respect to their ability to enhance antigen expression and inhibit MCF-7 cell growth. The two most potent species, IFN-αA and IFN-αB, were found to increase the expression of tumor antigens as well as the HLA determinant by 2-5-fold. In contrast, IFN-αD and IFN-αJ were virtually inactive in altering antigen expression but did inhibit the growth of MCF-7 cells. The remaining IFN-α species, −αC, −αF, −αI, and −αK, exerted an intermediate range of activities for both antigen enhancement and inhibition of MCF-7 cell growth. The relative ability of each species of IFN-α to inhibit MCF-7 cell growth appeared to be independent of their effectiveness in augmenting antigen expression. IFN-αD and IFN-αJ, the two species that failed to alter tumor antigen expression, did, however, seem to interact with the interferon receptor since they inhibited MCF-7 cell growth and competed with other IFN-α species for the increase in carcinoembryonic antigen, tumor-associated glycoprotein 72, or HLA expression. A comparison of the concentrations of each IFN-α necessary to enhance antigen expression revealed that the surface HLA determinant was approximately 10-fold more sensitive to enhancement than was the tumor antigen, carcinoembryonic antigen. The individual members of the IFN-α family thus differ extensively in their ability to alter the level of antigen expression on the surface of MCF-7 breast carcinoma cells. The differential response of these cells to the IFN-α species, which share a high degree of sequence homology and bind to the same cell membrane receptor, suggest that these biologically related compounds may differ in the biochemical and molecular signals induced distal to binding to the surface interferon receptor.

INTRODUCTION

Human IFN-α2 consists of a family of individual species with amino acid residues that have been shown to differ by as much as 20% (1–8). At least eight different species of leukocyte interferons have been expressed in Escherichia coli and purified and their biological activities have been compared (6, 9, 10). Besides the difference in amino acid composition of these interferons, several studies have found significant differences with respect to their biological actions. Interferons are generally regarded as having antiviral, antiproliferative, differentiation-modulatory, and immunomodulatory activities. Studies have shown substantial quantitative differences among these species of recombinant leukocyte interferon in their varied biological and biochemical effects on a range of target cells (9–17). Other studies have demonstrated that the individual species of leukocyte interferon can elicit different antigrowth effects on the same target cell (9, 11, 15, 16–19). It was also shown that a single leukocyte interferon species was an effective antiviral agent yet was completely inactive in boosting human natural killer activity (10). Therefore, as originally observed with the various natural leukocyte interferon species (15) there seem to exist quantitative and qualitative differences with respect to their abilities to regulate a variety of biological properties of target cells.

Considerable attention has been focused on the ability of the interferons to modulate surface antigens on a variety of human cells (reviewed in Ref. 18). Partially purified as well as recombinant leukocyte interferon can enhance the expression of class I histocompatibility antigens on both normal and transformed human cells (18, 20–26). Our laboratories have reported that IFN-αA can increase the binding of MAbs to the surface of human breast and colon carcinoma cells (27, 28). We have shown that such an increase is a result of the enhanced expression of tumor antigens, such as the M, 180,000 CEA and the high molecular weight (>10^6) mucin, TAG-72, which react with MAbs B1.1 and B72.3, respectively (18, 24, 26). The anti-CEA and TAG-72 MAbs are currently being used in several areas in the management of human cancers, including (a) serum assays for the detection of antigen; (b) immunohistochemical assays for the detection of occult tumor cells in pleural effusions, ascites, and fine needle aspirate biopsies (29–31); and (c) the detection of in situ occult tumors by radiolabeled MAbs (32, 33). The use of recombinant interferon to augment tumor antigen expression and thereby enhance detection by MAbs for diagnosis and treatment in each of the above situations merits consideration. The present study was carried out to evaluate the different species of IFN-α for their abilities to alter cell proliferation and modulate the level of cell surface antigen expression. The antigens monitored were the M, 180,000 CEA, a high molecular weight (>10^6) mucin termed TAG-72, and HLA, all of which are constitutively expressed by the human breast carcinoma cell line, MCF-7. The levels of expression of these antigens were measured by the binding of MAbs B1.1, B72.3, and W6/32, respectively (Table 1).

MATERIALS AND METHODS

Recombinant Human Leukocyte Interferons. The isolation, expression, and purification of eight different clones of human leukocyte interferon have been described (2, 5–7, 11). The interferons were prepared and purified as described (8, 9, 11, 34). Unless otherwise noted, the specific activity of the preparations on MDBK cells was 1–
5 x 10^4 antiviral units/mg protein with respect to the human IFN-α reference standard. Preparations with specific activities ≥1 x 10^5 units/ml were at least 90% homogeneous as determined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (34). IFN-αB represented about 75% of the total protein. IFN-αF was a crude bacterial extract. The interferons were diluted with RPMI 1640 containing 25 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid and 1% bovine serum albumin and stored at −70°C. Periodically an aliquot of each IFN-α species was rechecked for antiviral activity which remained virtually unchanged with storage at −70°C. Prior to use an aliquot of each was thawed, diluted, and added to the growth medium at the indicated antiviral titers.

Hybridoma Methodology. The details of the generation and characterization of the MAbs B1.1 and B72.3 have been reported (26–28). Briefly, B1.1 is an IgG2a that recognizes a Mr 180,000 CEA, whereas B72.3 is an IgG1 that reacts with a high molecular weight (>10^6) glycoprotein antigen complex termed TAG-72. B1.1 has been shown to react primarily with human breast and colon carcinoma cells, while some reactivity has been found with melanomas and selected normal tissues. B72.3 has a more restrictive range of reactivity that includes primarily human breast, colon, and ovarian carcinoma tissues (29, 35, 36). The W6/32 monoclonal antibody is IgG2a that recognizes the ABC loci of the HLA major histocompatibility complex (37) and was purchased from Cappell Laboratories (Malvern, PA).

Cells and Growth Inhibition Assay. The MCF-7 cell line was generated from a pleural effusion of a primary breast cancer patient and was purchased from Cappell Laboratories (Malvern, PA). B72.3 has a more restrictive range of reactivity that includes primarily human breast, colon, and ovarian carcinoma tissues (29, 35, 36). The W6/32 monoclonal antibody is IgG2a that recognizes the ABC loci of the HLA major histocompatibility complex (37) and was purchased from Cappell Laboratories (Malvern, PA).

To assess the antiproliferative actions of the recombinant leukocyte interferons, the MCF-7 cells were seeded at a density of 5 x 10^4 cells/T-25 flask in complete growth medium. The cells attached and grew for 48 h at which time the complete growth medium was removed and medium with and without the appropriate titers of the different recombinant interferons was added. After 5 additional days the cells were trypsinized, resuspended in serum-free RPMI 1640, and counted with a hemocytometer. Each control and interferon-treated group consisted of at least four T-25 flasks.

Determination of Cell Surface Antigen Expression. The MCF-7 cells were maintained in T-75 flasks. Subconfluent cells were harvested with 0.1% trypsin-0.05 mM EDTA; then 5 x 10^4 MCF-7 cells in 0.1 ml complete medium with and without interferon were seeded in each well of at least four T-25 flasks. The interferons were added. After 5 additional days the cells were harvested and pelleted by centrifugation at 1000 x g. The cell pellet was resuspended and homogenized for 2–3 min on ice in 10 ml Tris-HCl (pH 7.2)-0.2 mM CaCl2 (10 g wet weight/100 ml). The homogenate was further disrupted with a cell bomb (Parr Instrument Co., Moline, IL) for 5 min at 1000 lb/in². The disrupted homogenate was sonicated on ice for 1–2 min and centrifuged at 10,000 x g for 10 min. The protein concentration of the supernatant (i.e., cell extract) was determined by the method of Lowry et al. (40). The cell extracts were diluted to 1 mg/ml in Dulbecco’s phosphate-buffered saline containing calcium and magnesium (pH 7.2); then 50 μl were added to each well of a 96-well microtiter plate and dried. The solid phase RIA was carried out essentially by the same procedure outline for the surface antigen expression (40). The radiolabeled goat anti-mouse IgG was added at a concentration of 75,000 cpm/25 μl of phosphate-buffered saline containing 1% BSA. After the 1-h incubation the plates were washed and the bound cpm were determined by cutting the wells and measuring the radioactivity in a gamma counter.

RESULTS

Fig. 1 shows the results of a representative experiment in which the relative effect of the various species of IFN-α on the growth of MCF-7 cells were compared. IFN-αA, -αB, -αD, and -αJ were chosen because the IFN-αA and -αB clones were among the most potent while the IFN-αD and -αJ clones were the least effective leukocyte interferons in inhibiting the growth of MCF-7 cells (see Table 2). All four IFN-α species exhibited a dose-dependent relationship showing demonstrable inhibition of MCF-7 cell growth with 10 antiviral units of interferon. IFN-αB was substantially more effective than the other three IFN-α species in inhibiting MCF-7 cell growth at low (<100 units) antiviral titers. For example, 10 units of IFN-αB reduced MCF-7 cell growth by more than 40%, whereas the same antiviral titer of IFN-αA, -αD, or -αJ resulted in a reduction of cell growth by approximately 10%. At higher antiviral titers the IFN-αA clone was as effective as the IFN-αB clone in suppressing MCF-7 cell growth. Incubation with either of these two IFN-α species at antiviral titers greater than 1000 units reduced MCF-7 cell growth by 50–55%. In contrast, the IFN-αD and -αJ species were clearly less effective in reducing MCF-7 cell growth. Maximum growth inhibition with IFN-αD and IFN-αJ was obtained with 500–1000 antiviral units and any additional increase in dose did not result in a further significant reduction of growth. Table 2 summarizes the antiviral titers of each IFN-α species required to achieve a 25% reduction in MCF-7 cell growth. There was a greater than 100-fold range in the antiproliferative capabilities of these eight IFN-α species. As

### Table 1. Characteristics of monoclonal antibodies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Antigen</th>
<th>Isotype</th>
<th>Reactivity</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>W6/32</td>
<td>M, 43,000 HLA-ABC loci</td>
<td>IgG2a</td>
<td>All human cells, except RBC</td>
<td>37</td>
</tr>
<tr>
<td>B1.1</td>
<td>M, 180,000 carcinoembryonic antigen (TAG-72)</td>
<td>IgG2a</td>
<td>Human breast and colon carcinomas, some melanomas</td>
<td>26–28</td>
</tr>
<tr>
<td>B72.3</td>
<td>M, &gt;10^6 glycoprotein complex</td>
<td>IgG1</td>
<td>Human breast, ovarian, and colon carcinomas; no reactivity to normal human cells</td>
<td>26, 27, 29, 35</td>
</tr>
</tbody>
</table>
DIVERSITY AMONG HUMAN IFN-α FOR ANTIGEN AUGMENTATION

Fig. 1. Effects of different IFN-α species on the in vitro growth kinetics of the MCF-7 cells. An in vitro growth inhibition assay was used to assess the effects of IFN-αA, -αB, -αD, and -αJ on MCF-7 cell growth. The assays were carried out as outlined in “Materials and Methods.” MCF-7 cells were transferred to T-25 flasks (5 x 10^6 cells/flask) and grown in complete medium for 2 days. The complete medium was then changed to medium containing various antiviral titer of the different IFN-αs. The cells were grown for an additional 5 days at which time cells from each group were harvested and counted with a hemocytometer. The mean number of cells per group was determined from 4 flasks. The range of cell number for the untreated MCF-7 flasks was 4.4-6.1 x 10^6 cells/flask. The data are presented as the means of triplicate experiments.

Table 2. Comparison of the antiproliferative properties of the different recombinant leukocyte interferons on a human breast carcinoma cell

<table>
<thead>
<tr>
<th>IFN-α</th>
<th>MCF-7 cell growth inhibition (IC50) (antiviral units/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>38 (25-60)</td>
</tr>
<tr>
<td>B</td>
<td>2 (0.5-12)</td>
</tr>
<tr>
<td>C</td>
<td>60 (40-110)</td>
</tr>
<tr>
<td>D</td>
<td>250 (180-410)</td>
</tr>
<tr>
<td>F</td>
<td>33 (25-80)</td>
</tr>
<tr>
<td>I</td>
<td>92 (80-125)</td>
</tr>
<tr>
<td>J</td>
<td>75 (60-95)</td>
</tr>
<tr>
<td>K</td>
<td>38 (45-70)</td>
</tr>
</tbody>
</table>

* MCF-7 (5 x 10^6 cells) cells were added in complete medium to T-25 flasks. After 48 h 10-2000 antiviral units of each recombinant species of leukocyte interferon were added. After 5 days in the interferon-containing growth medium, the cells were removed by trypsinization and counted with a hemocytometer. IC50 represents the approximate antiviral titer for each leukocyte interferon which resulted in a 25% inhibition of cell growth.

Fig. 2. Effects of IFN-αA, -αB, and -αD on the expression of CEA (A) and HLA (B) on the MCF-7 cell surface. MCF-7 (5 x 10^6/well) were added to 96-well microtiter plates in growth medium alone (•) or containing 1000 antiviral units of IFN-αA (A), -αB (α), or -αD (α). After a 24-36-h treatment the binding of MAb B1.1 and W6/32 was measured as a function of antibody concentration. Data presented are the means of 3-5 determinations for each species of IFN-α.

αB. It should be noted that the increase in HLA expression (i.e., W6/32 binding) (4-5-fold) in the cell extracts from interferon-treated MCF-7 cells was much greater than that detected on the cell surface (Table 3). Other IFN-α species, in particular -αC, -αF, -αI, and -αK, were also found to augment the level of expression of CEA, TAG-72, and HLA on the MCF-7 cell surface. For example, treatment with 1000 units of IFN-αK enhanced B1.1, B72.3, and W6/32 binding to the MCF-7 cell surface by 1.7-, 1.7-, and 2.4-fold, respectively. Of the eight IFN-α species tested, IFN-αD and -αJ, which were among the least effective for inhibiting MCF-7 cell growth, were relatively ineffective in enhancing HLA expression and even less effective in altering the level of tumor antigen expression. Whereas other IFN-α species enhanced cell surface HLA expression at least 2-fold, IFN-αD and -αJ at antiviral titers of greater than 1000 units/ml could boost HLA expression by only 30% (Fig. 2B; Table 2). Similarly, analysis of whole cell extracts from the same IFN-αD- or -αJ-treated cells also revealed a modest 30-60% enhancement of W6/32 binding. As noted above, these two IFN-α species (-αD and -αJ) were found to be inactive for increasing the expression of CEA or TAG-72. Analysis of the reactivity of both MABS B1.1 and B72.3 to the MCF-7 cell surface (Fig. 2; Table 3) and whole cell extracts (Table 3) revealed little or no change in the level of B1.1 or B72.3 binding following incubation with 2000-5000 antiviral units of either IFN-αD or IFN-αJ.

The molecular weights and specific activities (i.e., 1-5 x 10^6

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antiviral units/mg protein) are known for each purified species of IFN-α. Data on the antigrowth and antigen augmentation of the various IFN-α species have been presented in terms of antiviral units of interferon. The data are shown as AE50 in Table 4. Table 4 permits a more reliable comparison among the various IFN-α species for their enhancement of surface antigen expression. The AE50 for HLA expression requires substantially less IFN-α than for a similar increase in the expression of CEA. For example, 10 times more interferon molecules per cell are required to induce a 50% increase in B1.1 (CEA expression) binding with IFN-αA or IFN-αB than to elicit the same increase in W6/32/32 binding. In addition, there is a wide range of potencies within the different species of IFN-α with respect to their abilities to increase HLA and CEA expression. IFN-αA and -αB were the most effective in increasing HLA expression by 50% following the binding of 1.2 x 10^4 and 3.6 x 10^4 molecules/cell, respectively. IFN-αD and -αJ were virtually inactive in enhancing the expression of CEA so that their AE50 for HLA and CEA were greater than 350- to 600-fold higher than the values for IFN-αA and -αB. The overall ranking of the eight different IFN-α species for enhancement of both HLA and CEA expression was A = B > I > F > C = K >> J, D. This ranking represents the relative potencies of the IFN-α species for the enhancement of both the HLA antigen and the tumor antigen, CEA.

The combination of weak antiproliferative and relatively ineffective tumor antigen-enhancing activities by IFN-αD, in particular, might be explained by inefficient binding of this IFN-α species to the MCF-7 surface interferon receptor. This hypothesis was tested by preincubating MCF-7 cells in the presence of IFN-αD (1000 units/ml) followed by the addition of IFN-αA (1000 units/ml). As shown previously, 1000 units IFN-αA/ml resulted in a significant increase in B1.1 binding to CEA (approximately 2-fold) on the surface of MCF-7 cells. A 2-h preincubation with IFN-αD or -αJ completely blocked the IFN-α-induced increase in B1.1 binding (Fig. 3, IFN-αD data shown). These findings indicate that IFN-αD can interact with the MCF-7 cell membrane and block the enhancement of tumor antigen expression induced by IFN-αA. It was also observed...

<table>
<thead>
<tr>
<th>Leukocyte interferon species</th>
<th>Concentration (units/ml)</th>
<th>HLA expression (AE50)*</th>
<th>CEA expression (AE50)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antiviral titer (pg/ml)</td>
<td>No. of molecules/cell</td>
<td>Antiviral titer (pg/ml)</td>
</tr>
<tr>
<td>A</td>
<td>10</td>
<td>18.9</td>
<td>94</td>
</tr>
<tr>
<td>B</td>
<td>7</td>
<td>58.3</td>
<td>90</td>
</tr>
<tr>
<td>C</td>
<td>90</td>
<td>900</td>
<td>860</td>
</tr>
<tr>
<td>D</td>
<td>&gt;5000</td>
<td>&gt;3 x 10^4</td>
<td>&gt;5000</td>
</tr>
<tr>
<td>F</td>
<td>46</td>
<td>511</td>
<td>1250</td>
</tr>
<tr>
<td>J</td>
<td>&gt;3000</td>
<td>&gt;3 x 10^4</td>
<td>&gt;5000</td>
</tr>
<tr>
<td>K</td>
<td>141</td>
<td>117</td>
<td>480</td>
</tr>
</tbody>
</table>

* A 50% increase in the expression of HLA or CEA as measured by the binding of MAbs W6/32 and B1.1 was considered significant. Therefore, the antiviral titer of each leukocyte interferon required to boost each antigen expression by 50% is termed the AE50. Calculations were performed as described previously (11, 13, 14).
The results of the present and previous studies (21, 23, 24) suggest that the mechanisms by which interferon enhances HLA expression and the expression of tumor antigens are different. Cell-sorting experiments indicate that W6/32 binds to approximately 100% of the human breast and colon carcinoma cells and, therefore, that the IFN-α-induced HLA expression is a result of more antigen expressed per cell or an increased antigen production by a subset of responsive cells (24). These observations are in accordance with those of other investigators who have shown that the interferon-mediated increase in surface HLA may be a result of an increased synthesis of this surface antigen (20, 21, 23). The augmentation of tumor antigen expression by IFN-α is different from the enhancement of HLA in several aspects. (a) MAb B1.1 reacts with 40–60% of the MCF-7 cells, but following IFN-α treatment more than 90% of the cell population is CEA positive. This is a result of recruitment of antigen-negative cells to become antigen positive, resulting in a more homogeneous cell population with respect to the expression of that particular tumor antigen. (b) Analysis of single cell subclones of the MCF-7 cell line indicate that three different classes of cells exist (41): cells expressing either high or low levels of constitutive tumor antigen expression which are enhanced following IFN-α treatment; cells that express a constitutive level of antigen but do not respond with increased expression by IFN-α treatment; and cells that are negative for a particular tumor antigen either before or after interferon treatment. These results suggest that the parental MCF-7 cell line consists of a heterogeneous population of cells which vary in their capacity to respond to IFN-α with increased tumor antigen expression. (c) The data presented indicate that IFN-αD and -αJ can induce a modest increase in HLA expression, whereas both species are unable to alter tumor antigen expression. Because of the previous lack of availability of homogeneous IFN-α preparations of known specific activity, it was possible only to evaluate IFN-α enhancement of tumor antigen and HLA antigen expression using antiviral titers. However, with the advent of recombinant DNA techniques and improved biochemical purification procedures homogeneous preparations of various IFN-α species are available (6, 8) and permit an evaluation of the functional and molecular activities of these biological agents. Such data can demonstrate in absolute terms whether tumor antigens expressed by human carcinoma cells are more susceptible to enhancement by the IFN-α than the normal HLA surface antigen. A comparison of IFN-αA and -αB for increasing the expression of the two tumor antigens, CEA and TAG-72, and HLA indicated that the AE50 for expression of the normal cell surface determinant could be achieved by the administration of 10-fold less IFN-α than required for the same level of enhancement of either tumor antigen. Therefore, these observations coupled with the dissociation of tumor antigen-enhancing activities from that of the HLA antigen-enhancing activities for IFN-αD and -αJ suggest that multiple, if not different, mechanisms are responsible for the interferon-mediated increase in tumor-associated than those modulating the expression of normal cell surface antigens.

The lack of antigen-enhancing ability of the IFN-αD and -αJ species may be a result of: (a) preferential inactivation of these IFN-α species by the MCF-7 target cell; (b) the inability of the cell surface interferon receptor to recognize these compounds leading to ineffective binding to the receptor; and/or (c) their binding to a component of the interferon receptor which cannot elicit the required transmembrane signals to ultimately evoke alterations in cell surface tumor antigen expression. The data in this paper demonstrating that both IFN-αD and -αJ can
inhibit the growth of MCF-7 cells as well as reduce the antigen enhancement induced by IFN-αA or -αB suggest that the -αD and -αJ species can competitively interact with the interferon receptor. The third possibility, which requires further experimentation, is suggested by the observations that various IFN-α preparations differ in their ability to induce a number of interferon-related properties, including antiviral, antiproliferative, differentiation-modulating, and antigen-enhancing effects. Because of the differences in the structures of IFN-αD and -αJ versus active IFN-α species (reviewed in Ref. 8), it is possible that the primary amino acid sequence or the tertiary structures of these molecules which allows for binding and/or activation of only a portion of the cell membrane IFN-α/β receptor, i.e., the region which regulates antiviral (IFN-αD and -αJ), antiproliferative (IFN-αD and -αJ), natural killer cell (IFN-αD), and HLA expression (IFN-αD and -αJ), but not the receptor domain required for modulating tumor antigen expression may be responsible for the observed varied effects. Different IFN-α species, as a result of structural dissimilarities, could then exhibit a high, intermediate, or low affinity for specific binding domains within the interferon receptor which are required to elicit the appropriate biological and biochemical responses after interferon binding. These observations provide additional support for the hypothesis that the interferon receptor contains multiple trigger sites that regulate specific subsets of biochemical pathways distal to receptor occupancy (8).

The discovery that the multiple species of IFN-α have distinct functional properties suggests that preferential expression of the different IFN-α species might occur in response to different environmental stimuli. Evidence has been presented indicating that the complementary DNA clones of IFN-αA and -αD occur more frequently in the library prepared from the Sendai-induced myeloblastoid cell line KG-1 (7). Furthermore, the major IFN-α species present in the lymphoblastoid Namalwa cell line closely resembles IFN-αF (42). An attempt to correlate any functional differences reported for the various IFN-α species with their known structural differences failed to reveal any obvious relationships. A more detailed understanding of the relationship between the structure and the function of specific IFN-α species may lead to the development of an IFN-α molecule that exerts significant enhancement of tumor antigen expression on a population of human tumor cells in vivo while lacking some of the clinical side effects such as pyrogenicity. Such a natural or designed species of IFN-α would be useful as an adjuvant for the detection and/or therapy of human carcinomas by therapeutically conjugated MAbs. Testing these hypotheses is integral to the development of combination therapies which include a biological response modifier and monoclonal antibody.

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REFERENCES


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