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Effect of Recombinant Human Interferon-alpha In Vitro and In Vivo on Mitogen-Induced Lymphocyte Blastogenesis in Cats*

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ABSTRACT

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The effect of recombinant human interferon-alpha (rHuIFN-α) in vitro and in vivo on mitogen-induced lymphocyte blastogenesis was evaluated in specific-pathogen-free cats. Pre-incubation of isolated feline peripheral blood lymphocytes (PBL) in vitro with either 10^4 or 10^3 International Units (U) of rHuIFN-α for 24 h significantly suppressed ($P<0.001$ and 0.01, respectively) blastogenic responses to the phytomitogens concanavalin A (Con A) and pokeweed mitogen (PWM). Lower doses of IFN (range, 10–10^{-3} U/ml) neither suppressed nor enhanced mitogenesis. In the absence of phytomitogens, incubation of PBL with 10^4–10^2 U ($P<0.001$) or 10 U ($P<0.05$) of rHuIFN-α/ml resulted in a significant decrease in incorporation of [methyl-^{3}H] thymidine into newly synthesized cellular DNA. Cultures of PBL exposed continuously for 4 days to rHuIFN-α doses of 10^4 U/ml or less did not demonstrate specific reductions in cell viability, indicating that the observed antiproliferative actions of IFN apparently were independent of any direct cytotoxic effects.

To investigate the dose-response effects of rHuIFN-α in vivo on lymphocyte blastogenesis, individual groups of cats were evaluated on 3 consecutive days before and then 24 h after each cat was inoculated intramuscularly with either a high dose (10^6 U/kg), moderate dose (10^4 U/kg), or a relatively low dose (10^2 U/kg) of rHuIFN-α. Cats inoculated with 10^6 U of rHuIFN-α/kg had significantly reduced ($P=0.037$) blastogenic responses to Con a at 24 h postinoculation compared to preinoculation values; mean PWM responses were also decreased, but this effect was not statistically significant. In contrast, inoculation of cats with either 10^4 or 10^2 U of rHuIFN-α/kg significantly enhanced ($P=0.05$ or 0.008, respectively) Con A-induced blastogenesis and had no discernible effect on PWM responses. These findings suggest that very high doses of rHuIFN-α given parenterally may be associated with suppression of certain T-cell responses in cats; conversely, much lower doses may be immunoenhancing.

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INTRODUCTION

Interferons (IFN) are a group of cellular proteins that inhibit viral replication, modulate immune responses, inhibit normal cellular division and have antitumor activity (Borden and Ball, 1981). There are several classes of IFN (α, β and γ) which differ on the basis of their antigenic, biological and physicochemical properties (Mannering and Deloria, 1986). Because IFN (particularly human IFN-α) has antiviral and immunomodulatory activities that cross species lines (Pallikoff et al., 1962; Desmyter et al., 1968; Gresser et al., 1974; Krakowka et al., 1988) and because recombinant DNA-produced human IFN is now available in relatively large quantity, the use of human IFN in veterinary medicine has increased. Human IFN-α has been used clinically in cattle afflicted with respiratory diseases (Roney et al., 1985; Cummins and Hutcheson, 1986), in cats infected with either feline leukemia virus (FeLV) (Cummins et al., 1988) or feline infectious peritonitis virus (FIPV) (Weiss and Cox, 1989), and in dogs infected with canine parvovirus (Dr. J. Cummins, unpublished data, 1986). Dosages of IFN used clinically in domestic animals have been empirical and extrapolated largely from studies in persons or mice using interferon preparations that can differ in purity and potency. Unfortunately, studies of the immunological effects of homologous or heterologous IFN in domestic animals have been lacking; the effects of human IFN-α in vitro on canine immune responses, however, have recently been reported (Krakowka et al., 1988).

Our interest in studying IFN is related to its application clinically as an antiviral and immunomodulating drug in cats with viral diseases. The effects of heterologous IFNs on feline immune responses in general are not known. Resistance to diseases such as FIP is associated with effective cell-mediated immunity (CMI) (Pedersen and Floyd, 1985; Weiss and Cox, 1989); cats infected with other viruses like FeLV may have severely impaired T-cell responses (Rojko and Olsen, 1984). Obviously, an understanding of the relationship between IFN dosage and modulation of CMI is necessary prior to recommending IFN as treatment for viral diseases where stimulation of CMI is required. Mitogen-induced lymphocyte blastogenesis, which is a widely used in vitro assay for evaluation of CMI (Oppenheim and Schechter, 1976), has been used previously in cats to assess alterations in CMI induced by immunomodulating agents such as cyclosporin (Gregory et al., 1987). In the studies reported here, the effects of doses of human IFN-α in vitro and in vivo on lymphocyte blastogenesis in normal cats was investigated.

MATERIALS AND METHODS

Animals

The cats used in these studies were healthy, 10–12-month-old specific-path-

ogen-free (SPF) males and females, weighing approximately 3.5 kg. The cats were purchased from a commercial breeder (Liberty Laboratories, Liberty Corners, NJ) and were FeLV test-negative (by ELISA) and feline coronavirus antibody-negative prior to the studies. The cats were housed separately in cages located in the Scott-Ritchey Animal Isolation Facility and were tested and cared for according to humane standards as set forth in the "Guide for the Care and Use of Laboratory Animals" (Publication No. 85-23, National Institutes of Health, Bethesda, MD). All experimental protocols were approved by an independent animal welfare committee prior to the studies.

Interferon

The recombinant DNA-derived (Bgl-II restriction endonuclease-specified) human leukocyte (alpha) hybrid (subtypes A/D) IFN (rHuIFN-α), lot no. RO-23-1740, was kindly supplied by Dr. Richard Cordts, Hoffman LaRoche, Nutley, NJ. The IFN was stored lyophilized (at a concentration of 50×10^6 International Units (U)/vial) at $-80°$C prior to use. The IFN was diluted before use in Hank's balanced salt solution (HBSS; pH 7.2) and was sterile-filtered through a 0.2 μM cellulose acetate membrane (Nalge Co, Rochester, NY). The biological activity of the rHuIFN-α (expressed in U/ml of antiviral activity) was determined in the manufacturer's laboratory, using an international reference standard for human leukocyte IFN.

Preparation of feline peripheral blood lymphocytes

Cats were lightly anesthetized with an intramuscular injection of ketamine hydrochloride (Vetalar; Parke, Davis & Co, Detroit, MI) and blood collected by jugular venipuncture into glass syringes containing heparin (10 units/ml of blood). Peripheral blood lymphocytes (PBL) were isolated and prepared as previously described (Cockerell et al., 1975; Tham et al., 1982). Briefly, PBL were separated by Ficoll-diatrizoate (Histopaque-1077; Sigma Chemical Co, St Louis, MO) gradient separation and the interface mononuclear cells collected and washed in HBSS. The washed cells were resuspended to 2×10^6 viable cells/ml in tissue culture growth medium (GM) consisting of RPMI-1640 (Gibco, Grand Island, NY) supplemented with 10% heat-inactivated fetal bovine serum, 100 U of penicillin/ml and 100 μg of streptomycin/ml along with 1.0 mM L-glutamine and 25 mM HEPES.

Lymphocyte blastogenesis assay

For the in vitro IFN studies, PBL (2.0×10^5 cells, 0.1 ml) were pipetted into wells of sterile 96-well flat-bottom microtitration plates (Corning Glass Works, Corning, NY) and then incubated with GM containing varying amounts of rHuIFN-α or GM only (0.1 ml/well) for 24 h at 37°C in humidified air containing 5% CO_2. For the in vivo studies, preincubation of PBL with IFN was omitted. The cell suspensions were then cultured 72 h with either concanavalin A (Con A) (0.6 μg/well) or pokeweed mitogen (PWM) (0.5 μg/well), or they

were not treated with mitogens (6 replicates/treatment). Previous titrations in feline PBL indicated that the concentrations of mitogen used were optimal for our assay. To each well, 0.5 μCi (0.025 ml) of [methyl-^{3}H]thymidine (specific activity 6.7 Ci/mmol) (Dupont, NEN Research Products, Boston, MA) was added for the last 20 h of incubation. The cultures were then stored at $-80°$C until harvested. Cells were harvested using a semi-automatic multiple cell microharvester (Bellco Glass, Vineland, NJ) so that the cellular proteins were collected onto glass fiber filter paper strips (Bellco). The paper strips were dried at 60°C for 30 min and the filter discs transferred to scintillation vials into which 5 ml of toluene base cocktail (Scinti Verse II; Fischer Scientific, Fairlawn, NJ) was added. The incorporation of [methyl-^{3}H]thymidine into newly synthesized cellular DNA was quantitated in a liquid scintillation spectrometer (LKB-Wallac Oy, Turku, Finland) using channels ratio method of quench correction. The net counts per minute (c.p.m.) of a total of 6 wells for each variable were averaged to obtain the mean c.p.m. The stimulation index (s.i.) was determined by dividing the mean c.p.m. of the mitogen-stimulated (or rHuIFN-α-stimulated only) cells by the mean c.p.m. of unstimulated (media control) cells. Stock solutions of IFN, thymidine and fetal calf serum were prepared from the same lots, respectively, prior to the studies and only fresh reagents were used.

Cell viability assay

To determine the potential cytotoxic effect of rHuIFN-α on feline PBL, lymphocytes were isolated from eight normal cats as described before and were exposed to varying amounts of rHuIFN-α continuously for several days. Briefly, freshly isolated PBL (2.0×10^5 cells, 0.1 ml) were cultured with GM (0.1 ml/well) containing rHuIFN-α (ranges, 10^4–1.0 U/ml) or GM only for 96 h at 37°C in 96-well microtitration plates (6 replicates/dose). The nonadherent cells were aspirated from a total of 6 wells for each IFN dose; the number of viable cells, determined by trypan blue dye exclusion, were counted in duplicate using a Neubauer hemocytometer. Results were expressed as mean viable cell density (number of viable cells/ml) in rHuIFN-α-treated or medium control cultures.

In vivo studies

A study was designed to evaluate the effects of giving varying amounts of rHuIFN-α parenterally on lymphocyte blastogenesis in cats. Cats were randomly assigned to one of three experimental groups and were treated as follows: a high-dose IFN group ($n=10$ cats) received a single injection i.m. of rHuIFN-α at a dosage of 10^6 U/kg; a moderate-dose IFN group ($n=4$ cats) likewise received 10^4 U of rHuIFN-α/kg; and a low-dose IFN group ($n=4$ cats) similarly received 10^2 U of rHuIFN-α/kg. Three additional cats were inoculated similarly with HBSS (diluent controls). Cats were evaluated by

lymphocyte blastogenesis in response to phytomitogens at 24 h postinoculation. In order to minimize normal diurnal variation in test results, all cats were evaluated by lymphocyte blastogenesis at 24-h intervals on 3 successive days preceding inoculation and then 24 h postinoculation. For each group of cats, a single preinoculation mean Con A or PWM response (3-day average) was determined and then compared statistically against the corresponding postinoculation group mean. Each group of cats was evaluated separately on alternate weeks.

Statistics

The one-tailed Student's *t* test was used to determine statistical significance between groups. All data analysis was performed using a computerized statistical analysis program (Abstat; Anderson-Bell, Canon City, CO). A conservative number of degrees of freedom was used (i.e., one for each animal rather than one for each well). *P* values of $\leqslant 0.05$ were considered significant.

RESULTS

Effect of rHuIFN-α in vitro on mitogen-induced lymphocyte blastogenesis

Incubation of normal feline PBL with doses of rHuIFN-α in vitro suppressed lymphocyte proliferative responses to Con A and PWM (Table 1). Suppression of blastogenesis was dose-dependent; significant inhibition occurred at relatively high in vitro doses of rHuIFN-α (10^4 or 10^3 U/ml). Doses of 10^2 U of rHuIFN-α/ml also decreased mean Con A or PWM responses, but this effect was not statistically significant. Lower doses of rHuIFN-α (10.0–10^{-3} U/ml) neither suppressed nor enhanced mitogenesis.

Effect of rHuIFN-α on incorporation of [methyl-^{3}H]thymidine in unstimulated feline PBL

Incorporation of [methyl-^{3}H]thymidine into newly synthesized cellular DNA in the absence of phytomitogens was significantly inhibited in feline PBL cultures exposed to rHuIFN-α doses of 10^4–10.0 U/ml compared to untreated PBL (Table 2). Mean thymidine incorporation (c.p.m.) in cultures treated with 10^4–10^2 or with 10.0 U/ml was approximately 14% or 50%, respectively, of the thymidine incorporation measured in untreated cells.

Cell viability studies

Varying amounts of rHuIFN-α (10^4–1.0 U/ml) were added to PBL cultures to determine whether direct cytotoxic effects from the IFN itself may have contributed to the dose-related suppression of blastogenesis observed in vitro. Differences in mean viable cell density between untreated PBL cultures and those treated with IFN, however, were not observed. (Fig. 1).

TABLE 1

The effects of pre-incubation with varying amounts of recombinant human interferon-alpha (rHuIFN-α) upon feline peripheral blood lymphocyte proliferative responses to phytomitogens[a]

Units of rHuIFN-α/ml[b]	Phytomitogen added	
	Con A[c]	PWM[c]
10^4	29.1 ± 7.8*	20.4 ± 4.7*
10^3	57.7 ± 21.1**	37.3 ± 3.6*
10^2	119.5 ± 34.0	65.5 ± 6.5
10	142.4 ± 28.8	81.8 ± 7.5
1	151.7 ± 32.3	80.8 ± 8.8
10^{-1}	156.8 ± 31.7	78.1 ± 10.7
10^{-2}	157.8 ± 34.1	82.6 ± 11.2
10^{-3}	147.2 ± 31.6	80.3 ± 8.4
Media	143.3 ± 29.7	83.8 ± 8.0

[a]Cells were incubated with rHuIFN-α or medium, 24 h, 37 °C, and cultured with mitogens Con A and PWM 51 h prior to radiolabelling.
[b]Final concentration in well.
[c]Data expressed as the group mean ± s.e.m. ($n = 14$ cats) stimulation index where the stimulation index of each cat was calculated as the mean c.p.m. (counts per minute) of mitogen-treated cultures divided by the mean c.p.m. of media control cultures (6 replicates each).
*$P < 0.001$; **$P < 0.020$ vs media alone.

TABLE 2

The effects of pre-incubation with varying amounts of recombinant human interferon-alpha (rHuIFN-α) upon [methyl-^{3}H]thymidine incorporation by feline peripheral blood lymphocytes[a]

Units of rHuIFN-α/ml[b]	[methyl-^{3}H]thymidine incorporation (c.p.m.)[c]	Stimulation index[c]	P value[d]
10^4	119.6 ± 18.7	0.21 ± 0.05	0.0002
10^3	118.3 ± 12.4	0.22 ± 0.06	0.0001
10^2	144.9 ± 26.2	0.22 ± 0.04	0.0002
10	423.0 ± 122.1	0.50 ± 0.06	0.0278
1	634.3 ± 128.0	0.80 ± 0.07	0.1637
10^{-1}	818.3 ± 159.2	1.00 ± 0.07	0.4461
10^{-2}	805.9 ± 193.3	0.94 ± 0.07	0.4326
10^{-3}	927.9 ± 290.9	1.01 ± 0.10	0.4109
Media	850.6 ± 174.1	-	-

[a]Cells were incubated with rHuIFN-α or medium in the absence of phytomitogens for 75 h at 37 °C and then were radiolabelled with [methyl-^{3}H]thymidine for an additional 20 h prior to harvesting.
[b]Final concentration in well.
[c]Data expressed as the group mean ± s.e.m. ($n = 14$ cats) counts per minute (c.p.m.) or stimulation index where the stimulation index of each cat was calculated as the mean c.p.m. of rHuIFN-α-treated cultures divided by the mean c.p.m. of media control cultures (6 replicates each).
[d]Mean c.p.m. in rHuIFN-α-treated cultures vs media control.

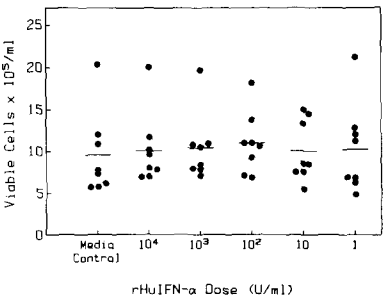

Fig. 1. Effect of rHuIFN-α in vitro upon viability of feline peripheral blood lymphocytes (PBL). The PBL were cultured in media containing varying amounts of IFN or in media lacking IFN. Cells were evaluated for viability after 4 days in culture. Each data point represents the mean viable cell density in PBL cultures ($n=6$) from each cat. Horizontal bars indicate the mean viable cell density ($n=8$ cats) in control or IFN-treated cultures.

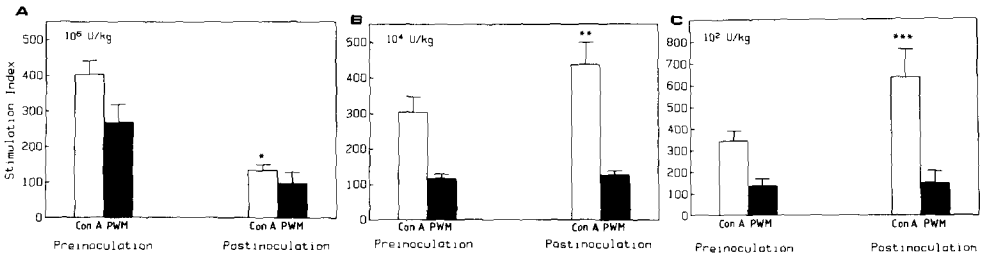

Fig. 2. Lymphocyte proliferative responses to phytomitogens (expressed as mean stimulation index ± s.e.m.) in cats before and 24 h after receiving a single intramuscular inoculation of rHuIFN-α. (A) High-dose (10^6 U/kg); $n=10$ cats. (B) Moderate-dose (10^4 U/kg); $n=4$ cats. (C) Low-dose (10^2 U/kg); $n=4$ cats. Cats were tested every 24 h for 3 consecutive days preceding IFN treatment and a single preinoculation mean (averaged over 3 days) was determined for each group and then compared against the postinoculation group mean. Separate groups of cats were evaluated on alternate weeks.
Significant difference vs preinoculation; $^*P=0.037$, $^{**}P=0.05$, $^{***}P=0.008$.

Effect of rHuIFN-α administration in cats on lymphocyte blastogenesis

To determine the effects of varying amounts of rHuIFN-α in vivo on mitogen-induced blastogenesis, cats in each of three groups were given a single injection of either a high (10^6 U/kg), moderate (10^4 U/kg), or relatively low dose (10^2 U/kg) of rHuIFN-α and then evaluated 24 h later. To minimize normal diurnal variation in responses, a 3-day average of daily mean responses was determined preinoculation for each group. Day-to-day variation in blastogenic responses of individual cats evaluated on 3 consecutive days of the same week was not significant ($P>0.05$, $n=18$; data not shown). Cats inoculated with a single high dose of rHuIFN-α had a significant suppression ($P=0.037$) in Con A-induced lymphocyte blastogenesis 24 h postinoculation compared to preinoculation values (Fig. 2A). Mean PWM responses were also decreased, but this effect was not statistically significant. In contrast to the

cats inoculated with a high dose of rHuIFN-α, cats given 10^4 or 10^2 U of rHuIFN-α/kg had significantly enhanced ($P=0.008$ or 0.05, respectively) blastogenic responses to Con A; PWM responses, however, were unaffected (Fig. 2B and C). Inoculation of cats with HBSS alone had no significant effect on mitogen-induced blastogenesis 24 h postinoculation (data not shown).

DISCUSSION

The effects of IFN in vitro or in vivo on the immune system are manyfold and sometimes apparently contradictory. Overall, it appears that IFN can either stimulate or suppress various arms of the immune response, depending on the timing of administration and dosage (Epstein, 1977). IFN in general seems to inhibit immunologic responses when given prior to an immunogen but enhances responses if given some days later (White and Fenner, 1986). Moreover, high doses of IFN can produce opposite effects or annul the responses obtained with much lower doses. For example, very low doses of IFN-α in vitro or in vivo may stimulate development of antibody-forming spleen cells in mice, whereas high doses are immunosuppressive (Braun and Levy, 1972; Epstein, 1977). The addition of low doses of IFN (10 or 100 units/ml) in the primary mixed lymphocyte reaction increases the cytotoxic response in mice severalfold, but larger doses (10^4 units/ml) depress the response (Fradelizi and Gresser, 1982). Similarly, low doses of IFN can enhance lymphocyte blastogenesis in mice or persons, whereas large doses are suppressive (Miorner et al., 1978; Taylor-Papadimitriou, 1980). Depending on the timing of administration, extremely low doses of IFN-α, β (2×10^{-10} U) in mice significantly increase the number of antibody-secreting cells in spleen and strongly stimulate cytotoxic activities of allospecific T-cells (Daurat et al., 1988).

The results of this study showed that very high doses of rHuIFN-α either in vitro or in vivo suppressed mitogen-induced lymphocyte proliferative responses in cats. The rHuIFN-α also directly inhibited the in vitro incorporation of [methyl-^{3}H]thymidine into newly synthesized cellular DNA of unstimulated PBL and at much lower IFN concentrations than those required to suppress mitogen-induced blastogenesis. The inhibitory effects of various types of IFN on DNA synthesis and lymphocyte blastogenesis after mitogenic stimulation have been described previously in different species, including mice, cattle, and persons (Lindahl-Magnusson et al., 1972; Blomgren et al., 1974; Bielefeldt-Ohman and Babiuk, 1986; Kim et al., 1988; Roth and Frank, 1989). IFN has also been shown to directly inhibit thymidine incorporation into the DNA of normal cells, including both lymphoid and epithelial cells, in the absence of mitogenic stimulation (Brouty-Boye and Tovey, 1978; Stadler et al., 1986; Roth and Frank, 1989). Although the suppressive mechanism(s) associated with rHuIFN-α on DNA synthesis and lymphocyte blastogenesis were

not investigated in our study, it is possible that high doses of IFN in vitro enhanced lectin-binding on lymphocytes and stimulated suppressor cell activities. IFN can markedly enhance the binding of lectins to lymphocyte membranes (Miorner et al., 1978), and suppressor cells are activated by high doses of mitogen, particularly Con A (Piguet et al., 1976).

The IFN-mediated suppression of lectin-induced blastogenesis observed when feline PBL were preincubated 24 h with relatively high doses of rHuIFN-α was also seen 24 h after cats were inoculated i.m. with very high doses (10^6 U/kg) of rHuIFN-α. Significant decreases in blastogenic responses to T-cell mitogens (Con A) in particular were observed after parenteral administration of high-dose rHuIFN-α. Although responses to PWM (which acts both as a B- and T-cell mitogen) (Heegaard and Muller, 1988) were diminished, this effect was not statistically significant, suggesting that T-cell responses perhaps were somewhat more sensitive to the suppressive actions of high doses of IFN in vivo. Curiously, lower parenteral doses of rHuIFN-α (10^4–10^2 U/kg) significantly enhanced the blastogenic responses of PBL after stimulation with T-cell mitogens (this phenomenon, however, was not observed when low doses of IFN were incubated in vitro with PBL). An inverse relationship between IFN dose and lymphocyte proliferative responses similar to that which we observed in cats has been documented previously in vitro and in vivo in mice and persons (Miorner et al., 1978; Taylor-Papadimitriou, 1980; Kim, 1988). Seemingly, a mechanism associated with this phenomenon may have been IFN-induced activation of suppressor cells. Bielefeldt-Ohmann and Babiuk (1986) reported that in vitro treatment of bovine PBL with recombinant bovine IFN-gamma (rBoIFN-γ) induced suppressor cells which may have competed with interleukin (IL)-2; moreover, the suppression in lymphocyte blastogenesis after in vivo administration of high doses of rBoIFN-γ was found to be reversible by addition of human IL-2 to the lymphocyte cultures. Lower amounts of IFN, however, may actually enhance the cellular immune response by selectively blocking suppressor pathways (Knop et al., 1984). In support of this theory, Daurat et al. (1988) demonstrated enhanced cytotoxic activities of allospecific T-cells and enhanced cytotoxic responses of NK cells in mice inoculated several times with IFN-α, β at dosages as low as 2.0 or 2×10^{-10} U. The inverse dose-response effects of IFN, particularly its biologic activity at very low pharmacologic doses, has suggested a predominantly hormone-like action of IFN as a homeostatic regulator of immune functions (Daurat et al., 1988).

Undoubtedly, an understanding of the dose-response effects of IFN on normal feline immune responses is imperative when considering IFN therapy in cats with disease. Additional in vitro and in vivo studies on the effects of IFN on T- and also B-cell responses in cats will be required so that specific recommendations concerning the use of IFN in feline viral or other diseases rationally can be established.

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