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# Clinical Use of Interferon-γ

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## Abstract

Interferon gamma (IFN-γ), a pleotropic cytokine, has been shown to be important to the function of virtually all immune cells and both innate and adaptive immune responses. In 1986, early clinical trials of this cytokine began to evaluate its therapeutic potential. The initial studies focused on the tolerability and pharmacology of IFN-γ and systematically determined its antitumor and anti-infection activities. In the 20-plus years since those first trials, IFN-γ has been used in a wide variety of clinical indications, which are reviewed in this article.

### Keywords

Interferon-γ; Actimmune; HuZaf

## Introduction

Interferon gamma (IFN-γ), a cytokine with diverse roles in the innate and adaptive immune responses, was discovered in 1965. IFN-γ function has been strongly conserved throughout evolution and across multiple species. T cells, NK cells, and NKT cells are the primary producers of IFN-γ, and it has a myriad of effects in both host defense and immune regulation, including antiviral activity, antimicrobial activity, and antitumor activity. Experimental models in which IFN-γ production has been disrupted have resulted in an increase in autoimmune diseases (reviewed in Ref. 1).

IFN-γ has been shown to be important to the function and maturation of multiple immune cells. IFN-γ is essential for Th1 immune responses and regulates T cell differentiation, activation, expansion, homeostasis, and survival. Killing of intracellular pathogens requires IFN-γ production by T cells. T regulatory cell (Treg) generation and activation requires

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Given the large number of publications on IFN-γ, it is inevitable that some authors may believe that their work was not properly cited or included in this review. The authors of this review apologize to those investigators whose work was not cited as any exclusion of relevant work was not intentional.

Conflicts of Interest

The authors declare no conflicts of interest.

IFN-γ. IFN-γ stimulates dendritic cells and macrophages to upregulate major histocompatibility complex (MHC) molecules, enhances antigen presentation, and increases expression of costimulatory molecules. IFN-γ stimulated macrophages also produce reactive nitrogen intermediates. NK cells secrete IFN-γ early in host infection, facilitating immune cell recruitment and activation. IFN-γ also activates NK cells, enhancing their cytotoxicity and cell mediatedimmune responses. During a viral infection, IFN-γ mediates IgG2a isotype class switching in B cells. IFN-γ recruits neutrophils, stimulates them to upregulate chemokines and adhesion molecules, and triggers rapid superoxide production and respiratory burst (reviewed in Ref. 1). Due to the pleiotrophic effects of IFN-γ on the immune system, it was thought to have great promise as an immunomodulatory drug.

It was not until 1986 that early clinical trials of this cytokine were first conducted.[2] The initial studies were focused on side effects and dose escalation, and then later trials systematically determined its therapeutic potential against cancers and infections. In subsequent years, IFN-γ has been used in a wide variety of clinical indications. The most common adverse therapeutic events occurring with IFN-γ1b therapy are “flu-like,” such as fever, headache, chills, myalgia, or fatigue. Other common side effects include rash, injection site erythema or tenderness, diarrhea and nausea, and leukopenia.[3–8]

IFN-γ clinical trials have been conducted using recombinant derived protein (IFN-γ1b, Actimmune), adenovirus vectors which express IFN-γ cDNA (TG-1041, TG-1042), and neutralizing antibodies against IFN-γ (HuZaf and AMG811). Actimmune has been used to treat a wide variety of diseases, including cancer, tuberculosis, hepatitis, chronic granulamotous disease, osteopetrosis, scleroderma, among others. Adeno-IFN-γ has been used to treat cutaenous lymphoma and malignant melanoma. HuZaf has been used against autoimmune diseases, including rheumatoid arthritis and multiple sclerosis. Promising results have been seen with all agents and are reviewed here.

## Actimmune

The majority of the clinical trials involving IFN-γ have been performed using Actimmune (InterMune) or IFN-γ1b, a genetically engineered form of human IFN-γ. The naturally occurring IFN-γ produced by human peripheral blood leukocytes (PBLs) has the same primary structure as IFN-γ1b.[9,10] However, these two cytokines differ in that: (1) IFN-γ is glycosylated and IFN-γ1b is not, (2) IFN-γ1b is 140 amino acids long while IFN-γ has 143 amino acids, and (3) IFN-γ has blocked pyroglutamate residue N-termini, whereas recombinant IFN-γ1b has methionine at the N-terminus.[9–11]

### Cancer

The role of IFN-γ in the host response to cancer has been the subject of numerous research studies. Studies have shown that IFN-γ is vital to tumor surveillance by the immune system and a high correlation between IFN-γ production and tumor regression has been seen in immunotherapy. IFN-γ also has direct antitumor effects, as it is anti-angiogenic, inhibits proliferation, sensitizes tumors cells to apoptosis, upregulates MHC class I and II expression, and stimulates antitumor immune activity. There have been mixed results as to the efficacy of IFN-γ in the clinical treatment of various cancers.

In a study of recurring superficial transitional bladder carcinoma, it was shown that intravesicle instillations of IFN-γ were effective against cancer recurrence.[12] There were significant increases in T cells, NK cells, ICAM-1$^+$ B cells, and HLA-DR$^+$ cell infiltrating the tumor. Strong IFN-γ-induced expression of *HLA-DR* has been correlated with improved prognosis in colorectal cancer patients.[13]

Ovarian cancer is a leading cause of cancer death and is an ideal target for cytokine targeted treatment.[14–16] The presence of intratumoral IFN-γ producing CD3$^+$ T cells is associated with better prognosis.[17] The standard treatment is platinum-based chemotherapy. IFN-γ is synergistic with platinum chemotherapeutics *in vitro* at inhibiting ovarian cancer cell proliferation and inducing apoptosis.[18] Intraperitoneal IFN-γ has been shown to achieve antitumor responses against ovarian cancer.[19] In a recent randomized phase III trial, administration of subcutaneous IFN-γ and cisplatin to patients improved complete response rates from 56% to 68%[20] and prolonged progression-free survival. Another study showed that IFN-γ with carboplatin and paclitaxel is safe as a first-line treatment of patients with advanced ovarian cancer. Conversely, a phase III clinical trial was ended prematurely in 2006. Ovarian cancer and peritoneal carcinoma patients were treated with carboplatin/paclitaxel chemotherapy alone or with IFN-γ 1b subcutaneously. In the second interim analysis, it was found that patients treated with IFN-γ and carboplatin/paclitaxel had a significantly shorter survival rate and more adverse events as compared to patients receiving chemotherapy alone. 39.7% of the IFN-γlb and chemotherapy group had died, in contrast to 30.4% of patients in the chemotherapy only group.[21]

IFN-γ is an approved treatment for adult T cell leukemia (ATL) in Japan. There are several reports which claim that intralesional injections of IFN-γ can induce lasting remissions.[22] IFN-γ treatment was first developed and approved in Japan for treatment of Mycosis fungoides (MF).[23]

Several clinical trials are underway using IFN-γ as an adjuvant for vaccine therapies and chemotherapies (NCT00428272, NCT0049-9772, NCT00824733, NCT00004016).

## Tuberculosis

Tuberculosis (TB), a result of infection with *Mycobacterium tuberculosis*, primarily affects the respiratory system, and the emergence of multidrug resistant strains (MDR-TB) has led to the need for new therapeutic agents. IFN-γ activates alveolar macrophages, which are important in host immunity against *M. tuberculosis*.[24] Condos *et al.* performed a clinical trial examining the effects of an IFN-γ aerosol on MDR-TB. Stabilization or an increase in bodyweight was observed in all IFN-γ treated patients. Furthermore, sputum smears became negative, and a decrease in the mycobacterial burden was seen. Two months after cessation of treatment, a reduction in cavitary lesion sizes was observed in all patients.[25] Another trial found that co-administration of IFN-γ and anti-TB drugs to tuberculosis patients, resulted in increased levels of *STAT1, IRF-1*, and *IRF-9* in BAL cells from lung segments. IFN-γ actively stimulated signal transduction and gene expresion in alveolar macrophages in TB patients, thus providing a basis for potential use as an adjuvant therapy in this disease.

Other approaches have evaluated IFN-γ as an adjuvant therapy in addition to a chemotherapeutic cocktail. Saurez-Mendez *et al.* found that intramuscular injection of IFN-γ for 6 months as an adjuvant to chemotherapy led to reduced lesion sizes, negative sputum smears and cultures, and increased body mass index.[4]

**Mycobacterium avium Complex (MAC)—**Atypical mycobacteria infections have been rising, especially among older women. MAC infection leads to progressive chronic pneumonia and lung disease. Atypical mycobacteria survive and proliferate within host macrophages. Treatment of MAC pulmonary infections is difficult because of high drug resistance. IFN–γ has been shown to be a critical cytokine in the resistance of infected macrophages. Thirty-two patients were treated with either intramuscular IFN-γ and chemotherapy or chemotherapy and placebo. The overall response in the IFN-γ group was significantly better than those treated with chemotherapy alone (72.2% vs. 37.5% complete responders). During the study, 35.7% of the control group died compared to 11.1% of the IFN-γ treated group.[26]

**Idiopathic Pulmonary Fibrosis—**Currently, there is no FDA approved drug treatment for idiopathic pulmonary fibrosis (IPF). IPF is the most frequent of the idiopathic interstitial pneumonias and has the worst prognosis.[27] IPF is a chronic condition characterized by progressive scarring, loss of lung function, progressive limitation, and eventual death.[28] Alveolar epithelial cells release fibrogenic cytokines, such as TGF-β, PDGF, TNF-α, IL-1, insulin-like growth factor-1, and basic fibroblast factor, in response to injury. The release of these cytokines causes fibroblast proliferation, migration to the lung, and fibroblast differentiation.[29,30] Traditional therapies have been ineffective, and new agents are required to halt the progression of disease. IFN-γ therapy of IPF has been explored, as IPF is characterized by an IFN-γ deficit. It was hypothesized that treatment with IFN-γ might halt the progression of IPF.

Unfortunately, the results from IPF studies with IFN-γ treatment are mixed. In an initial randomized clinical trial[31] of IPF patients, IFN-γ treatment in combination with prednisolone resulted in increased total lung capacity and increased resting and maximal exertion values of partial pressure of arterial oxygen, compared to prednisolone alone. In a retrospective study of qualified IPF patients, IFN-γ had beneficial effects on forced vital capacity and single breath diffusing capacity for $CO_2$.[28] Furthermore, these effects were most pronounced in patients with advanced disease.

Conversely, in a large (330 patients) one year placebo-controlled clinical trial, subcutaneous IFN-γ administration did not affect progression-free survival or pulmonary function.[32] The time to death or disease progression was not significantly altered. However, subgroup analyses, which are at best hypothesis generating, showed a possible survival benefit for patients with mild-to-moderate impairment.[33]

The results of a double-blind clinical trial of the molecular effects of subcutaneous IFN-γ1b in IPF patients were published in 2004.[34] After IFN-γ1b treatment, expression of the immunomodulatory chemoattractant CXCL11 was increased in bronchoalveolar lavage fluid (BALF) and plasma. Levels of neutrophil activating CXCL5, PDGFA (platelet derived

growth factor A), and type 1 procollagen were lower in BALF. Gene expression studies showed increases in *CXCL11*, type III procollagen, and *PDGFB* in transbronchial biopsy samples. A decrease in elastin was also seen. These changes suggested that IFN-γ 1b would be an effective treatment for IPF via multiple pathways.[34]

In March of 2007, the INSPIRE trial of Actimmune for treating IPF (NCT00075998) was forced to end prematurely. INSPIRE was a randomized, double-blind, placebo-controlled Phase 3 study designed to evaluate the safety and efficacy of Actimmune in IPF patients with mild to moderate impairment in lung function. The primary endpoint was survival time. An interim analysis showed that patients who received Actimmune did not benefit. Approximately 14.5% of patients treated with Actimmune died compared to 12.7% of placebo treated patients (NCT00075998).

## Cystic Fibrosis

Cystic fibrosis (CF) is an inherited disorder caused by a mutation in a chloride channel, the cystic fibrosis transmembrane conductance regulator gene. CF is characterized by chronic endobronchial infection and inflammation, destruction of lung tissue, and eventual respiratory failure in 90% of patients. CF patients have inefficient pulmonary clearance of thick secretions and defects in production of nitric oxide resulting in chronic bacterial infections with a thick bacterial biofilm. Bacterial biofilms resist opsonins, phagocytes, antibiotics, and cause chronic neutrophil inflammation. Production of elastase by neutrophils contributes to lung damage. Due to the ability of IFN-γ to activate macrophages, correct deficiencies in NO production *in vitro*, and inhibit the proliferation of Th2 clones, and based on clinical data showing IFN-γ deficiencies in PBMCs from cystic fibrosis patients,[35,36] it was thought to have great potential as a treatment for cystic fibrosis. Sixty-six cystic fibrosis patients received 50 μg–1000 μg aerosolized IFN-γ1b or placebo three times a week for 12 weeks.[37] No statistically significant differences were seen in the primary endpoints of the trial, $FEV_1$ (forced expiratory volume in 1 s) and sputum bacterial density over the entire study. At 4 weeks, a slight, but significant reduction was seen in the $FEV_1$ of the 1000 μg IFN-γ treated group versus placebo, and a significant reduction was also seen in bacterial density between the 1000 μg IFN-γ treated group versus placebo. No significant statistical differences were seen in levels of neutrophils, IL-8, elastase, myeloperoxidase, or DNA in the sputum of either IFN-γ or placebo treated patients.

## Hepatitis

Liver cirrhosis and hepatocellular carcinoma arise primarily as a result of chronic hepatitis infection.[5,38] The current regimen for the treatment of chronic hepatitis B (HBV) and C (HCV) is pegylated IFN-α (peginterferon-α) and ribavirin with a response rate of only 50–60%.[6] In light of the large number of non-responders, IFN-γ has been evaluated as a potential alternative treatment. In chronic HBV trials, IFN-γ1b alone was not found to have any significant impact on viral infection but did modulate the immune system.[7] Treatment of HCV with IFN-γ1b has also proven generally unsuccessful[8,39] but pretreatment with IFN-γ prior to IFN-α treatment resulted in enhanced immunologic activity in HCV patients. The enhanced immunological activity is speculated to enhance IFN-α-mediated viral clearance.[40]

Fibrosis accounts for the majority of the complications associated with chronic hepatitis. IFN-γ has been shown to have antifibrotic effects and is efficacious against fibrosis in HBV patients.[41] In a recent study, the antifibrotic activity of IFN-γ1b in HCV patients was examined.[8] Although no overall reduction in fibrosis was seen, select patients had significant fibrosis reductions.

## Chronic Granulomatous Disease

In 1991, IFN-γ1b was FDA approved for the treatment of chronic granulomatous disease (CGD). CGD is an inherited disorder of leukocyte function, caused by a defect or the absence of reduced nicotinamide adenine dinucleotide phosphate oxidase. This enzyme is essential for microbiocidal activity and superoxide generation in phagocytes. Consequently, CGD patients suffer recurrent life-threatening bacterial and fungal infections. As IFN-γ is known to enhance the respiratory burst of human phagocytic cells, it was hoped that IFN-γ would reverse the immunological defects observed in CGD patients. In clinical trials, IFN-γ1b reduced the frequency and severity of serious infections in CGD patients.[11]

Marciano *et al.* examined the long-term effects of IFN-γ1b administration to CGD patients.[42] 76 patients were enrolled in an uncontrolled study to assess long-term safety and efficacy of IFN-γ1b therapy. Patients were followed for up to 9 years and received IFN-γ1b subcutaneously thrice weekly. This study concluded that IFN-γ prophylaxis for CGD appears to be effective and well tolerated over a prolonged period of time. Actimmune product literature claims that treatment with their product leads to a 67% reduction in the relative risk of serious infections, 53% fewer primary infections, 64% fewer infections overall, and 67% fewer inpatient hospital days.

## Osteopetrosis

Congenital osteopetrosis (OP) is a rare osteosclerotic bone disease caused by a defect in osteoclast function and bone resorption.[43] Severe, malignant OP is characterized by an overgrowth of body structures which results in infection, anemia, thrombocytopenia, blindness, deafness, and ultimately early death.[44–46] The granular leukocytes of OP patients are defective in superoxide production,[47,48] resulting in frequent, severe infections. As IFN-γ1b reduces infection in CGD patients by increasing neutrophil superoxide production, Key *et al.* hypothesized that IFN-γ1b might stimulate osteoclasts in a similar manner.[49] IFN-γ1b administration to OP patients significantly increased osteoclastic bone resorption, increased superoxide production in PBLs, and reduced infection.[50] *In vitro* studies with OP patient blood cultures, have shown that IFN-γ1b enhances osteoclast generation and normalizes superoxide production.[45] Presently, the only effective treatment for osteopetrosis is hematopoietic stem cell transplant (HSCT), which has high treatment related morbidity and mortality.[51]

In 2000, the FDA approved Actimmune for delaying the time to disease progression in patients with severe malignant OP. In a 1999 phase III clinical trial, 15 osteopetrosis patients received either Actimmune or control vitamin D. The length of time to disease progression was significantly delayed in patients treated with Actimmune (165 days) compared to

patients treated with the control (65 days). Evidence of increased bone resorption, enhanced bone marrow activity, and a reduction in serious infections was observed.[50]

### Scleroderma

Scleroderma is a connective tissue disease that affects multiple organ systems, including skin, heart, lungs, and kidneys.[52] The mechanisms of fibrosis in scleroderma are not fully understood. It is known that soluble mediators, such as TGF-β, PDGF, IL-4, IL-6, and TNF-α, can affect the behavior of fibroblast growth, proliferation, collagen synthesis, and chemotaxis.[52–54] IFN-γ has been used in the treatment of scleroderma because of its antifibrotic activity, its ability to reduce collagen production *in vitro*, and to inhibit fibroblast cell proliferation. In most clinical trials, either subcutaneous or intramuscular administration of IFN-γ to scleroderma patients has resulted in modest improvements.[55–58]

### Invasive Fungal Infections/Immunosuppressed Patients

Invasive fungal infections are an increasing problem, especially in immunocompromised patients, such as leukemia patients, HIV patients, and transplant patients. The most common infectious agents are candida and aspergillus. There are several new drugs available to treat fungal infection, including triazoles and immunotherapeutics, such as colony stimulating factors, granulocyte transfusions and IFN-γ. GM-CSF and IFN-γ are given in combination to treat patients with serious refractory fungal infections and non-neutropenic infections. It has been demonstrated that IFN-γ increases the anti-fungal activity of macrophages and neutrophils.[26] (ISRCTN70900209)

*Cryptococcus neoformans* is responsible for the most common central nervous system infection in HIV patients, acute cryptococcal meningitis, and is the most common cause of fungal meningitis worldwide. In a double-blind clinical trial, patients received either 100 or 200 μg of IFN-γ1b or placebo in addition to standard anti-fungal therapy. (NCT00012467) Among 75 patients, 13% of placebo patients, 36% of 100 μg IFN-γ1b, and 32% of 200 μg IFN-γ1b had fungus clean cerebrospinal fluid cultures after 2 weeks.[59]

The efficacy of IFN-γ1b to reduce opportunistic infections in advanced HIV was tested in a 12-month double-blind phase III trial of HIV patients on antiretroviral drugs. Eighty-four patients were treated with either IFN-γ or placebo subcutaneously for 48 weeks. Patients on placebo had an average of 3.45 opportunistic infections in the first 48 weeks, while patients with IFN-γ1b therapy had an average of 1.71. Three-year survival in the IFN-γ arm was 28% compared to 18% in the placebo group, although this difference was not statistically significant. IFN-γ1b treatment was especially effective against candida, herpes, and cytomegalovirus infections.[60]

## Adeno-IFN-γ

### Cutaneous B and T Cell Lymphomas

Primary cutaneous lymphomas (CL) are characterized by an accumulation of clonal T or B lymphocytes in the skin. Typically, CLs are chronic indolent diseases. TG-1042, or adeno-IFN-γ, was investigated in a phase I trial, where patients with advanced primary cutaneous

B or T CL were repeatedly injected intratumorally with TG-1042.[61,62] TG-1042 is a nonreplicating adenovirus vector containing a human IFN-γ cDNA insert. Five of nine treated patients had local clinical responses. Three patients had complete responses with the clearance of non-injected skin lesions. Two patients had partial responses. IFN-γ from TG-1042 message was detected in injected lesions in seven patients after the first treatment cycle and remained detectable for several cycles. Humoral antitumor immune responses were also detected. Adeno-IFN-γ is now being tested in a phase II trial (NCT00394693) against chronic BCL.[61]

### Malignant Melanoma

A phase I clinical trial was conducted in 2003 using TG-1041, a recombinant adeno-IFN-γ vector to treat malignant melanoma. TG-1041 is a replication deficient adenovirus with the cDNA for IFN-γ inserted in the E1 region of the viral genome. Patients were given three intratumoral injections of adeno-IFN-γ. Out of 11 treated patients, no complete or partial responses were seen. However five patients had minor decreases in injected tumor nodules, eight patients had local inflammation, one patient had significant necrosis of the injected nodule, one patient had inflammation of distant nodules, and one patient had disease stabilization.[63]

## Anti-Interferon-γ Antibodies (HuZaf and AMG811)

Fontolizumab (HuZAF) is a humanized monoclonal antibody that binds IFN-γ and inhibits expression of IFN-γ regulated genes. Fontolizumab is being explored for the treatment of autoimmune diseases, such as Crohn's disease, lupus, rheumatoid a arthritis, and multiple sclerosis. Adverse side effects are generally mild and rare, and include abdominal pain, vomiting, headache, nausea, arthalgia, asthenia, and cough.[64,65] AMG811, a fully human monoclonal antibody that binds and neutralizes IFN-γ, is being evaluated by Amgen.

### Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune disorder where the immune system attacks the myelin sheath of the central nervous system. Disturbances in cytokine synthesis, particularly IFN-γ, play critical roles in the initiation and prolongation of MS.[66] IFN-β is currently used in the treatment of MS and may work via inhibition of IFN-γ-mediated immune activation. In a randomized study of patients with progressive MS, those patients who received a short course of neutralizing IFN-γ antibody had a significant delay in disability progression.[65] MRIs showed decreased numbers of active lesions. The cytokine profile produced by activated blood cells from treated patients changed, with decreased IL-1β, TNF-α, and IFN-γ and increased TGF-β. These data indicate that neutralizing IFN-γ may be a new treatment option for the management of progressive MS.

### Crohn's Disease

Recent studies have examined the safety and efficacy of HuZAF in the treatment of moderate to severe Crohn's disease (CD).[67] Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract. IFN-γ has been implicated in the inflammation observed in CD and increased levels are found in the mucosa.[64] In several models of experimental

colitis, increased mucosal IFN-γ levels were detected. In a randomized double-blind phase II clinical trial, 42 patients received one dose, and 91 patients received two doses of HuZAF.[67] There was no difference in response between HuZAF and placebo groups after a single dose. In contrast, those patients receiving two doses of fontolizumab had a doubled response rate at day 56 compared to placebo controls. Given the long half-life (18 days) and low immunogenicity, this study concluded that treatment of active CD with anti-IFN-γ antibody warrants further investigation.[67] Based on the results with Crohn's disease, HuZAF is being considered as a treatment for pediatric inflammatory bowel disease.

### Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by a predominant Th1-associated autoimmunity. Early clinical studies tested IFN-γ as a therapeutic for rheumatoid arthrititis. In these studies, 54 patients were treated with IFN-γ, while 51 received placebo in a double-blind study.[68] While greater improvement was seen in the IFN-γ treated group, it was not statistiscally significant. Recently, antibodies to IFN-γ have been found to be beneficial in the treatment of RA, in a randomized double-blind trial.[69] Thirty patients with active RA received intramuscular injections of either anti-IFN-γ, anti-TNF-α, or placebo. Based on a physical examination, nine patients receiving anti-TNF-α, seven receiving anti-IFN-γ and two receiving placebo, appeared to have an improvement of their condition.

### Lupus

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by self-reactive antibodies, often against nucleic acids, which form immune complexes and collect in body organs and joints. Because SLE patients have been shown to have increased levels of serum IFN-γ,[70] IFN-γ has been shown to exacerbate SLE,[71] and in mouse models, IFN-γ receptor is required for development of SLE.[72] Amgen has recently begun a phase Ib clinical trial, using AMG-811, a fully human monoclonal antibody that binds IFN-γ to treat SLE (NCT00818948). This trial will be focused on safety and pharmokinetics.

## Summary

IFN-γ has proven to be a key immunoregulatory molecule whose effects on immune system development, maturation and function is widespread, affecting a myriad of cell types. While IFN-γ affects numerous disease processes, the clinical applications of this important molecule are currently limited. Given the critical importance of IFN-γ in immunity, clinical use of IFN-γ will depend upon a more precise understanding of its basic biology and localized effects in order to better define how to use this molecule in the context of the disease setting.

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