



# Role of Alpha-Fetoprotein and Derived Peptides in Remission of Autoimmune Diseases During Pregnancy: A Proposed Mechanism of Action

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## Abstract

Multiple Sclerosis is a debilitating neurological Autoimmune Disorder (AD) which produces self-antibodies against the myelin-coating of axons in the Central Nervous System (CNS). Because this neuroinflammatory disorder is three times more prevalent in women of childbearing age, the occurrence of MS during pregnancy is commonly reported. Interestingly, most MS pregnant patients undergo a period of remission in the late second and the third trimester of pregnancy. However, a relapse of the MS disease occurs in the mother in the postpartum period accompanied by the return of maternal MS disorder symptoms. The clinical remission observations of MS during pregnancy have been reported by obstetricians since the 1980s. The mode of action of the remission has largely been attributed to the full-length Alpha-Fetoprotein (AFP) molecule in contrast to other serum biomarkers. Recently, the presence of a functional variant form of AFP has been reported which results in a stress/shock-induced transformational changed version of the full-length AFP molecule. However, the precise active amino acid segment of the AFP polypeptide responsible for change has never been identified. In the present report, the active amino acid site causing remissions during pregnancy has been determined to be a short amino acid fragment stretch buried within the full-length tertiary-folded AFP molecule.

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**Keywords:** Alpha-Fetoprotein; Autoimmunity; Multiple sclerosis; Remission; Peptides; Cell immunity; Immune system; Pregnancy

## Introduction

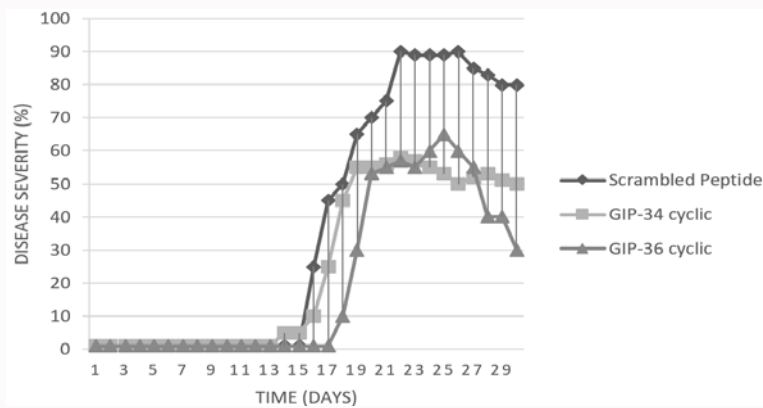
### A) General: Multiple sclerosis as an autoimmune disease

Multiple Sclerosis (MS) is a chronic autoimmune neurological disorder that produces antibodies directed against the myelin sheath of CNS neurons. The AD is acquired during emerging adulthood between the ages of 20 and 30 [1,2]. At least 400,000 people in the United States and 1 to 2 million people worldwide exhibit the MS disease [1,3]. This autoimmune neuroinflammatory disorder is three times more prevalent in women of child-bearing age; hence, its occurrence during pregnancy is frequently reported [4-6]. MS is the most prevalent de-myelinating disease of the CNS and is a potentially disabling disease [2]. Although, no single gene or gene cluster is known to manifest the multiple sclerosis disorder, recent evidence suggests a connection to an HLA-DR15 haplotype [7,8]. The disease is highly influenced during pregnancy by growth factors, cytokines, and anti-inflammatory agents which are thought to function as neuroprotective factors in the immune induction and effector stages of this autoimmune disease [9,10]. Changes in soluble circulating factors (steroids, AFP, etc.) have been proposed to provide protective effects against the immunoneurological damage that underlies MS pathology [6,9].

## Impact of Multiple Sclerosis (MS) on Pregnancy

### A) Multiple sclerosis during pregnancy

During pregnancy, MS disease produces two major clinical manifestations of interest; a period of profound reduction of MS symptoms (remission) in the late second and third trimester followed by an exacerbation of disease (relapses) in the postpartum period before returning to the mother's pre-pregnancy disease state [5,11]. Past and present data support the conclusion that progression of MS is not worsened but may actually be lessened or reduced during pregnancy. In a large study of pregnancy in women with MS, relapses occurred in 50% of patients during the postpartum



**Figure 1:** The effect of Growth Inhibitory Peptides (GIP) on EAE Clinical Course Cyclic Peptide Configuration. (All graphs were provided in collaboration with Prof/ Dr. Talma Brennen; Hadassah Hospital, Jerusalem, Israel).

period, while less than 10% relapses occurred in the second and third trimesters of pregnancy [12,13]. Investigators found a notable reduction of relapses in late pregnancy, in contrast to a high increase of relapses in the first 3 months postpartum [5,13,14]. Thus, there appears to be soluble immuno-protective factors (*i.e.*, AFP) produced during pregnancy that seem to be capable of suppressing cell-mediated and humoral immune responses in MS during pregnancy [15] (Table 1).

### B) Historical: Multiple sclerosis and alpha-fetoprotein

The early studies of MS and AFP can be attributed to the meticulous research by the Israeli team of Orams and Brenner from 1979 to 2009 [13,16-23]. Studies were performed using animal models of the MS disease termed "Experimental Allergic Encephalomyelitis (EAE)." The experimental MS disease that was induced in mice, guinea pigs, and rabbits was accomplished by immunization with Myelin BASIC protein (MBP) into the animals [18,19]. The daily administration of AFP in test animals was employed which were later found to be inhibited by both the cell mediated immune response to MBP and the binding of MBP antibody-to-antigen in the host animal [19]. In the years to follow, this same scientist team reported that human pregnancy-derived AFP was capable of delaying both the occurrence and the onset of EAE (MS) in the various animal models [21,22].

In 1985, the same Israeli team of scientists showed that purified Human AFP (HAFP) (50 µg) was able to suppress rabbit EAE following the onset of neurological signs and that AFP further improved the clinical scores of the affected animals [17,19,21,23]. These researchers reported that pregnancy (tested *via* HAFP) protected the animals from developing EAE following the induction and alteration stages in the host humoral and cellular immune systems; such results occurred as long as AFP was present during the postpartum and neonatal stages [3,23]. MS is an unpredictable, disabling condition in humans; hence, the amelioration of MS symptoms during pregnancy is highly indicative that soluble factors, such as AFP and possibly other biomarker related factors, could affect the disease symptoms to be less severe [21-23]. A clinical case report of a pregnant woman with reduced striated muscle strength added credence to the predicted immuno-protective role of AFP in the progression of human MS disease [6,8,17].

### Objectives

As described in prior published reports regarding Alpha-Fetoprotein (AFP) in MS pregnancies, AFP has been deemed a major

factor in contributing to patient's remissions during autoimmune affected pregnancies. Although past experiments and trials have demonstrated that full length AFP, in contrast to other biomarkers, was a necessary and major component in producing such remissions during pregnancy. In addition, the full-length AFP polypeptide was effective in reducing both the humoral and cellular immune responses in pregnant women while affecting a reduction in symptoms in the severity of autoimmune disease. However, the precise mechanism of action regarding the AFP-induced remissions has never been fully explained. It is the objective of the present report to: A) describe the relationship of AFP to autoimmune diseases during pregnancy using Multiple Sclerosis (MS) as one example; B) to illuminate the relationship and describe the impact of AFP affecting the remission of MS in pregnancy; and C) to seek out the mechanism of action of AFP by use of its derived peptides in producing a reduced severity of MS symptoms in the animal models. Such findings could possibly apply to explaining the alleviation of MS symptoms in pregnant patients and providing the potential for developing treatment in the non-pregnant population.

### How is Alpha-Fetoprotein Involved in MS and other Autoimmune Disease (AD) Remissions?

**A) Removal of AFP from pregnancy fluids:** (*i.e.*, serum and amniotic fluids) was shown to nullify the effects of AD autoantibodies during animal model pregnancies. Purified AFP had been reported to inhibit the experimental Phytohemagglutinin (PHA) mitogen reaction induced in the proliferative responses employing MS-derived lymphocytes in AD cell culture models [15,23]. During normal human pregnancy, maternal serum AFP levels are known to gradually increase and ultimately peak in the 30 to 32 gestational-week period of the third trimester; afterwards, AFP levels decline. The third trimester is the gestational age in which 50% of AD patients are known to undergo disease remission. Thereafter, maternal serum AFP levels decrease to low nanogram levels at postpartum where most patient relapses were found to occur. A transitory AD occurs in some neonates following delivery, when AFP levels abruptly decrease in both the maternal serum and in newborn serum levels [5,14].

In further studies, lab animals receiving intravenous injections of purified AFP failed to induce animals to develop experimental MS following disease induction stages [24]. Also, animals with already established experimental MS disease showed clinical improvements

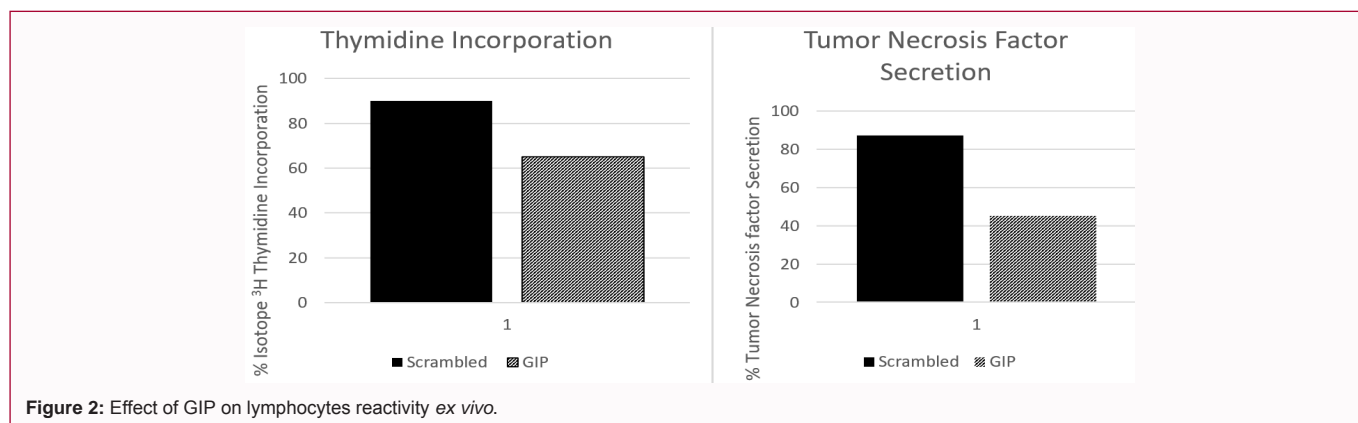


Figure 2: Effect of GIP on lymphocytes reactivity *ex vivo*.

in response to purified AFP injections in which antigen-induced autoantibody production was suppressed [24-26]. Rats immunized with autoantigens develop AD and show both early acute and late phase chronic autoimmune disease symptoms similar to humans with ADs; in these instances, both clinical phases can be prevented by prior injections of purified AFP [27]. Not only did purified AFP treatments result in reduced clinical manifestations, such AFP injections also decreased the serum autoantibody titers directed against the BMP autoantigen (68). In a similar manner, the absence of fetal symptoms of autoimmune disease and the delayed onset of worsening in clinical neonates with MS might partially be attributed to the low serum levels of fetal and neonates AFP levels in infants following birth [28]. In the instance of premature and Small-for-Gestational Age (SGA) infants, the serum levels of AFP remain high as compared to newborns with average birthweights. Moreover, premature and SGA newborns appear to be more common in patients with autoimmune disorders than in normal pregnancy populations.

Although the remission of autoimmune multiple sclerosis during pregnancy has largely been attributed to full length AFP compared to other pregnancy biomarkers, the precise mechanism of MS remission has remained unsolved. It is tempting to propose that a well-published AFP-derived peptide fragment might be the causative factor involved. This AFP-derived peptide fragment has been named the "Growth Inhibitory Peptide" (GIP) [29-33]. It is further germane to this study to suggest that a proposed structural alteration (transformation) in the full-length AFP molecule during pregnancy appears to be a first step involved in the clinical remissions of AFP. As described in prior published biomedical reports, the full-length AFP molecule has been reported to undergo a transitional conformational change when exposed to various stress and shock environments that occur in the fetus during pregnancy [30,31]. Such stress/shock environments result from osmotic factors, oxygenated species, ion presence, pH changes, and high concentrations of estrogens, fatty acids, steroids, and growth factors. The conformational changes produce a denatured intermediate (molten globular) form of full-length AFP that lies buried in an encrypted amino acid segment region within the inner cell membrane bilayer of the unfolded AFP molecule [33,34].

#### B) The transformed version form of alpha-fetoprotein:

This intermediate (unfolded) form of circulating full-length AFP during pregnancy has been referred to as "Transformed Alpha Fetoprotein" (TAFP) in the biomedical literature [35]. The TAFP has been identified and assayed in both fetal and maternal serum as a pregnancy variant biomarker form in multiple clinical pregnancy studies [36,37]. The AFP variant (TAFP) has been confirmed to be a

transient unfolded version of the compacted tertiary-folded structure of the full-length AFP polypeptide [34]. Hence, full-length TAFP has since been employed as a clinical biomarker for predicting adverse outcomes in third trimester pregnancies as well as in perinatal stages [37]. Such late term outcomes have encompassed late-term clinical complications such as intrauterine growth retardation, threatened pre-term labor, fetal distress, chronic hypoxic stress, and fetal hemodynamic redistribution [36-38].

The active site causing AD remission within the TAFP molecule has since been identified, isolated, purified, sequenced, and biologically/biochemically characterized [30-32]. The active site is a 34 to 36 amino acid fragment of AFP that lies buried in the third domain structure of AFP. This amino acid fragment (named Growth Inhibitory Peptide) was isolated from full length AFP and has been determined to be a cell bioregulator of both growth and immune responses [29-31]. Hence, the GIP segment is an alpha-fetoprotein derived peptide which is produced during human pregnancy; AFP gradually disappears following childbirth in both the woman and later (9 months) in the newborn [39]. Following a stress-induced conformational change in the AFP polypeptide, GIP is revealed on the unfolded AFP molecular surface; the peptide emerges from a concealed occult site on the unfolded full-length AFP [31]. The exposed 34 to 36 amino acid GIP peptide was reported to target, block, and suppress malignant growth in the mammalian body. GIP can further assist in preventing blood clotting, arresting growth *via* the cytoplasmic growth cycle, suppressing tumor blood vessel angiogenesis, and inhibiting circulating cancer cell derived metastatic cells. In further studies, GIP was shown to suppress growth in numerous human breast and other cancer cell lines in addition to mouse tumor implants and xenografts [30-33]. Furthermore, GIP was found to suppress and inhibit cancer growth and regulate the immune response in both *in vitro* and *in vivo* preclinical studies [40]. Thus, GIP is not only capable of inhibiting cancer growth but also is capable of regulating and enhancing both the humoral and cellular arm of the body's immune system [31]. This relevance to humoral and cellular immunity could serve to explain the ability of AFP derived GIP to induce the state of remission observed in autoimmune diseases such as Multiple Sclerosis as well as other ADs.

#### C) A proposed mechanism of action of pregnancy remission:

A possible mechanism of action of AFP-derived GIP to induce the remission of autoimmune Multiple Sclerosis (MS) symptoms could be explained from experiments derived from using an *in vivo* mouse model of MS (EAE) treated with GIP. As shown in Figures 1 & 2 (unpublished data), the treatment of GIP for 30 days in a mouse

**Table 1:** Molecular docking and protein interaction sites on alpha-fetoprotein derived Growth Inhibitory (GIP) were identified. Such sites were localized by means of proprietary computer software (peptide Discovery Platform). See legend below. \*

A. Alpha-fetoprotein derived Growth Inhibitory Peptide (GIP) sequence and polypeptide number	B. Name of GIP interacting protein	C. Function of Interacting Protein	D. Protein data bank accession number
1) <sub>458</sub> ADIIIGHL <sub>465</sub>	1. Chemokine-CCL1 Receptor (CCR8)	Receptor expressed on monocytes, T-Lymphocytes	AAI07153
	2. CD11 leucocyte adhesion molecule	PMN neutrophils, innate immunity, acute inflammation	NP000623
	3. Chemokine Receptor CXCR4	Broadly expressed in the immune system	CAA12166
2) <sub>462</sub> IGHLCIRH <sub>470</sub>	1. Tubulin (heterodimers)	Microtubule function, key cytoskeletal element	NP001060
	2. Ceruloplasmin	Cooper binding protein (blood)	NP000087
	3. Glial Fibrillary acid protein	Expressed in the brain by astrocytes oligodendroglia, and astroglia cells	AAB22581
	4. Interferon-B2 IL-6 (interleukin-6)	Modulates alpha-1-antitrypsin in monocytes phagocytes	NP00091
	5. Factor-8 (expressed in arteries)	Platelet-derived protein corrects ischemic-impaired wound healing	AAK30167
	6. Chemokine receptor (CCR3)	G-coupled receptor on eosinophils, basophils, and TH1, Th2 cells	NP847899
3) <sub>466</sub> CIRHEMTP <sub>473</sub>	1. Ephrin tyrosine kinase	Development of angiogenesis and cardiovascular development	P54764
	2. C-reactive protein (member of pentraxin family)	Acute inflammatory protein, acute phase protein	CAAA39671
	3. Peptidyl Peptidase	A cell surface peptidase, an endopeptidase, a leukocyte differentiation antigen-CD26	AAB60646
	4. Tumor necrosis factor receptor superfamily 9	Regulates immune responses via reverse signal transduction, ligand is CD137 on activated T-cells	Q07011
4) <sub>470</sub> EMTPVNPG <sub>477</sub>	1. Peptidyl peptidase	Carboxyl peptidase, cell surface peptidase	AAB60646
	2. Ferritin	Iron storage protein, iron binding protein	AAA35832
5) <sub>474</sub> VNPGVGQC <sub>481</sub>	1. Interferon-B2 (Interleukin-6)	Signal protein, immunomodulatory proteins, antiviral protein	NP00091
	2. Factor-B (complement involved factor)	Complement activation against C1q factor, Brain injury	AAK30167

\*Note: The computer software was developed and generously provided by the Serometrix LLC Biotech Co, Pittsford, New York, 14534 [46,47].

model of MS (EAE) clearly demonstrated that the GIP fragment of the AFP molecule is responsible for producing a 50% reduction in the clinical severity of the MS disease in mice. However, animal experiments were halted after 30 days to prevent further suffering in the animals from the MS disease. In additional conformations of the GIP action on the mouse MS disorder model, the *in vitro* immune reactivity of rat lymphocyte cell proliferation using titrated thymidine incorporation in cell proliferation studies were performed. The murine lymphocytes were isolated from host lymph nodes and used in the cell culture of lymphocytic cells treated with and without GIP. These *ex vivo* and *in vitro* studies clearly demonstrated alterations of cellular immune activities which contribute to causing the MS disease. The proliferation of the encephalitogenic mouse lymphocytes from MS-induced mice was decreased by 25% and the cytokine production and secretion of Tumor Necrosis Factor (TNF) following GIP treatment was reduced by 60%. These cellular immune cell data served to explain the reduction in the disease severity in the mouse model of MS as shown in Figure 1. Thymidine incorporation is a parameter to measure proliferation of cells which contribute to the encephalitogenic-induced activity; this is a part of the MS disease causative effects exhibited by the mouse sensitized lymphatic cells. Furthermore, the TNF cytokine production and secretion is a further measure of disease severity produced from the host lymphatic cells. In summation, Figure 1 & 2 demonstrate that mouse treatments with GIP demonstrated a direct causative effect on the reduced activity of the MS induction of immune sensitized cells of the murine MS disease. Overall, the above data can be summarized by stating that the MS disease induced mice were observed to be in a state of autoimmune disease "remission" mimicking that observed in pregnant women

suffering from the MS disease.

### Additional Computer Supporting Data: A Search for Pairing of Peptide-to-Protein Interactions

AFP and its derived peptides are bristling with matching amino acid segment sites from cytokines, chemokines, and immune system amino acid sequence identities which occur all over the AFP polypeptide molecule [41]. The protein-to-protein and peptide-to-protein pairing computer software from Serometrix revealed that the GIP peptide contained multiple matched allosteric amino acid pairing interaction sites with cellular immune-associated protein molecules; such proteins are the hallmark of diseases specific to MS. This software focused on the amino acid pairing of small amino acid fragments present on immune associated cells associated with MS disease. Such protein sites (amino acid segments) are potential targets for therapeutic changes [42,43]. Such pairing interactions could affect signal transduction pathways by inhibiting (or enhancing) receptor binding by blocking peptide-to-protein interactions. As shown in Table 1, the matched interacting sites with GIP included: A) Nerve cell (neuron) toxic proteins; B) Chemokine/receptor proteins; and C) Cytokine (immune associated hormone proteins). These targeted pinpointed interactions with proteins of the cellular immune response system might cause the autoimmune disorder to progress to the severe symptoms which are observed clinically in MS disease patients.

### Concluding Statements

Although the autoimmune neuroinflammatory MS disease

affects 1 to 2 million people worldwide, sufficient healing and treatment modalities have yet to be developed. The fact that MS and other autoimmune diseases go into remission during pregnancy have provided researchers a model with a multitude of clues. It has been reported that circulating soluble factors during pregnancy can interact with both the humoral and cell-mediated branches of the immune system. These factors may have contributed to the observed remissions of AD during pregnancy. The many circulating soluble factors were eventually narrowed down to Alpha-Fetoprotein (AFP) as a major contributing factor to the observed pregnancy remission. However, the precise mechanism of action of the AFP molecule has never been resolved. The experimental and computer pairing data presented in the present report indicated that an AFP derived peptide segment, buried in the internal molecular folds of AFP, appears to be an ideal interacting factor candidate as the active site agent inducing the clinically observed remissions. These data suggests that the AFP derived GIP peptide fragment is possibly a causative agent of the AD pregnancy remission. Such an observation suggests that such a treatment could be developed to treat AD in the non-pregnant patient population.

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