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Review

# Here, there, and Everywhere: Alpha-fetoprotein in Cancer Immunotherapy

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## Abstract

Alpha-fetoprotein (AFP) delivers nutrients in a shuttle manner to immature cells through AFP receptor (AFPR)–mediated endocytosis. A small population of immature myeloid-derived suppressor cells (MDSCs) act as key regulators of immune tolerance during pregnancy, cancer, and other conditions. MDSCs, low doses of AFP, and AFP-binding ligands can modulate the innate and adaptive immune response. MDSC decreases excessive immune activation, while their depletion can cancel immune suppression. The reduction of MDSCs by AFP and toxins reactivates natural killer (NK) cells, macrophages, and cytotoxic lymphocytes (CTLs), strengthening both innate and adaptive immune responses. AFP with apoptosis-inducing toxins specifically destroy MDSCs and cancer cells without pro-inflammatory byproducts. AFP-toxin complexes or chemical conjugates demonstrate high efficacy, low toxicity, defined mechanism of action, cost-effectiveness, and are not personalized. AFP combinations with drugs or traditional medicines represents a targeted immune/chemotherapy approach for cancer prevention and treatment.

**Keywords:** cancer immunotherapy, myeloid-derived suppressor cells, Alpha-fetoprotein receptor, targeted chemotherapy, drug repurposing.

## 1. Introduction

Cancer remains one of the leading causes of mortality. Many treatments try to destroy tumor cells directly. On the other hand, the immune system erases them on a regular basis. In cancer the immune system is tolerant to the malignant cells. Reactivating the immune system is a physiological strategy able to recognize and eliminate any “wrong” cells.

The immunology of pregnancy and cancer is similar, where the primary cells find mechanisms to evade immune attack [1,2]. Myeloid-derived suppressor cells (MDSCs) are immature myeloid progenitors released from the bone marrow or spleen during pregnancy, under chronic inflammatory conditions such as cancer, and other diseases. MDSCs includes two major subsets based on their phenotypic and morphological features: monocytic MDSC (M-MDSC) and polymorphonuclear MDSC (PMN-MDSC, or former G-MDSC) [3]. Normally rare, they expand in cancer and demonstrate suppressive functions on both innate and adaptive immunity [4]. MDSCs are essential for maternal–fetal tolerance during pregnancy [5,6], and used by tumors also. Their presence in cancer creates an immunosuppressive tumor microenvironment (TME) [7].

MDSCs inhibit natural killer (NK) cell [8]– and macrophage-mediated clearance of embryonic or tumor cells. They also promote the expansion of regulatory T cells (Tregs), thereby suppressing T and B cell responses. Over months to years of tumor development, an immune system composed of ~1.8 trillion cells (approximately 1.2 kg of immune biomass) [9] cannot eradicate small populations of cancer cells once MDSCs impair immune recognition, effectively rendering the host immune system "blind" and preventing a functional antitumor response (Fig.1).

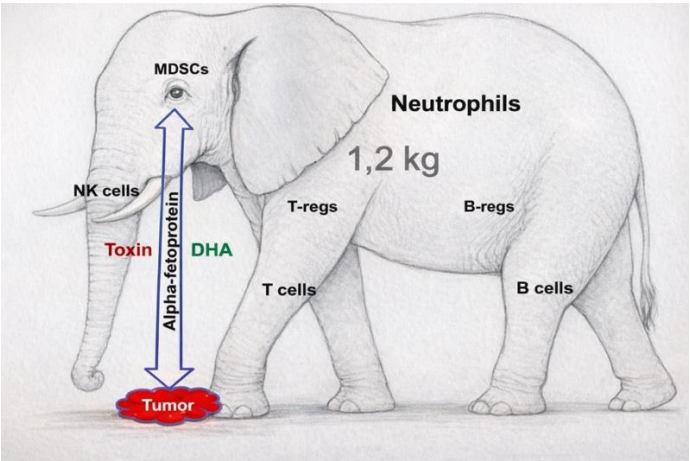


**Figure 1.** 1.2 kg of immune cells cannot smash a small tumor. Myeloid-derived suppressor cells (MDSCs) and tumor cells can be stimulated by alpha-fetoprotein (AFP) and docosahexaenoic acid (DHA). In contrast, AFP conjugated with a toxin function as a targeted immunotherapy against MDSCs and as a targeted chemotherapeutic agent against tumor cells.

Reflecting their central importance, more than 8,600 PubMed-indexed publications now address MDSCs in cancer, yet only a small fraction investigate the interplay among MDSCs, oncofetal alpha-fetoprotein (AFP), and AFP-binding ligands.

AFP supports fetal growth by transporting nutrients and promoting immune tolerance. In healthy adults, AFP expression is minimal, however, it reappears in several malignancies, most notably hepatocellular carcinoma (HCC) [10], germ cell tumors, and certain gastrointestinal cancers [11]. Elevated AFP often correlates with tumor burden, aggressiveness, and poor prognosis. Tumors exploit the same immunoregulatory pathways used during pregnancy to maintain tolerance to semi-allogeneic fetal tissue, thereby dampening immune responses [12]. AFP transports nutrients and drugs through AFP receptor (AFPR), thereby modulating immune regulatory cells' activity. The AFPR is found on human T-lymphocytes during blast-transformation, on human monocytes, primary macrophages, and cancer cells [13-16]. The AFPR structure has not yet been elucidated, and several other AFP-binding proteins have been identified, including chemokine, mucin, and scavenger receptors, as well as metastasis-related and intracytoplasmic proteins [17,18]. This article focuses on AFPR-mediated endocytosis of AFP bound with toxins. When AFP selectively delivers toxins into the $AFPR^{+}$ regulatory immune and cancer cells it helps cancer immunotherapy and cancer prevention [19].

Traditional medicine provides many bioactive compounds with cytotoxic, anti-inflammatory, and immune-modulating properties. Many of them shows anticancer activity while also enhancing immune function [20,21]. When delivered by AFP, such compounds may

gain selective access to MDSCs and tumor cells, potentially increasing efficacy while reducing systemic toxicity.

This paper proposes a novel immunotherapeutic concept. Delivering nutrients or drugs, AFP may suppress hyperactive immune responses, whereas AFP complexed with toxic compounds from traditional medicine may selectively deplete MDSCs, restore immune effector functions, and directly destroy tumor cells. Such an approach offers a universal, non-personalized, and low-toxicity strategy for cancer prevention and treatment. By modulating immune activity, this therapy enables the body's own immune cells to recognize and eliminate malignant cells.

## 2. Alpha-Fetoprotein: Structure, Function, and Biological Role

The structure, biochemical properties, and clinical roles of AFP have been thoroughly reviewed in the literature [22-27].

AFP is a 70 kDa oncofetal glycoprotein predominantly synthesized by the fetal liver, yolk sac, and gastrointestinal (GI) tract during embryonic development and is well recognized as an immunosuppressive protein [28]. AFP is used as a pregnancy marker [29]. Elevated AFP levels correlate with pregnancy disorders, or poor tumor prognosis [30].

AFP is a globular protein with 3-5% glycosylation, with a flexible hydrophobic pocket capable of accommodating fatty acids, bilirubin, steroids, xenobiotics, drugs, and other small molecules, enabling AFP to function as a natural shuttle carrier protein. During the laboratory testing, the saturated palmitic C16:0 and stearic C18:0 fatty acids were extracted from 4 binding sites of AFP [31]. Naturally, AFP's hydrophobic cavity fits 1-2 molecules of polyunsaturated fatty acids (PUFAs) like C22:6 docosahexaenoic acid (DHA) (Fig. 2).

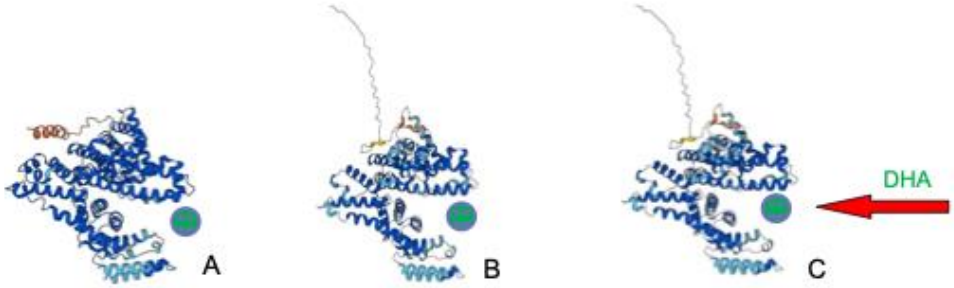


Figure 2. Serum albumin (A), human (B) and porcine (C) AFP 3D structures (https://alphafold.ebi.ac.uk). The structure (B) is confirmed by the Cryo-EM structure generated with PDB ID 8X1N [31]. DHA: docosahexaenoic acid.

Like the conformational change of haemoglobin upon oxygen binding, DHA binding alters AFP's conformation [32], shifts its isoelectric point, increases binding affinity, and stabilizes AFP: ligand complexes [33,34]. During its 3–5-day half-life, AFP naturally shuttles dozens of essential ligands into embryo and other $AFPR^+$ cells.

Receptor-mediated endocytosis of AFP-ligand complexes in occur placenta, in cancer cells, human B-lymphoma and T-leukemia cells, and peripheral blood mononuclear cells (PBMC) [35-38].

The specific AFPR-mediated endocytosis by the small PBMC fraction - M-MDSCs (~1%) - was discovered by the following experiment. The AFP–daunorubicin conjugate eliminated ~60% of M-MDSCs, compared with ~8% cell death induced by daunorubicin alone. In contrast, G-MDSCs exhibited only minimal changes in viability (~18% versus ~20%, respectively). Notably, non-MDSC populations remained viable following treatments [39].

This discovery was particularly significant, expanding the relevance of AFP-based delivery to a major immunosuppressive cell's population.

AFP crosses the three cellular layers of the hemochorial placenta due to the AFPR found in the normal human placenta [35], and/or the neonatal Fc receptor (FcRn) [40], and returns with nutrients. AFP affinity for the essential PUFA DHA is 54 times stronger than that of albumin [41], and binds it even in a massive excess of albumin in the mother's blood (35–55 mg/mL) compared to AFP (~150 ng/mL). Interestingly, AFP: DHA complexes remain stable even during chromatography or electrophoretic procedures. The preferential binding of a ligand to AFP over albumin causes a significant enhancement of its fetal uptake. Thus, over 70% of estrone and estradiol injected into the rat's maternal circulation have been subsequently found to be associated with AFP in the fetus. Unlike AFP, rodent AFP binds strongly to these hormones, while artificial estrogens with low binding affinity do not concentrate in the rat fetus [42]. The AFP pocket can accommodate dioxin or diethylstilbestrol, providing a mechanistic explanation for their known embryotoxicity [43,44]. Nevertheless, as mutagens and carcinogens, these toxins cannot be used for cancer treatment. On the other hand, cyclophosphamide, doxorubicin, bleomycin, vincristine, and etoposide do not bind AFP strong enough. They may be given safely to a woman in need during any trimester of pregnancy, as they do not hurt the child or the mother [45].

Porcine AFP (pAFP) shares extensive amino acid and functional homology with AFP (Fig. 3). Unlike AFP, which has several glycosylated isoforms, mono-glycosylated pAFP serves both nutrient delivery and immunosuppression functions. PAFP binds ~2.6 moles of DHA and arachidonic acid per mole of protein [46]. Notably, pAFP transports nutrients and ligands across the six cellular layers of the epitheliochorial placenta, highlighting its exceptional transcytosis efficiency and evolutionary specialization for high-binding capacity ligand delivery [47].

AFP-bound cytotoxic compounds are selectively internalized by cancer cells via AFPR-mediated endocytosis. Electron microscopy has been used to follow AFP conjugates with horseradish peroxidase after specific endocytosis. AFP has been reported within coated pits of the plasma membrane, and tracked to vesicles, endosomes, and a tubular vesicular network localized in the Golgi-centrosphere region adjacent to the nucleus [48]. Once inside the cell, toxins can destroy organelles, and induce apoptosis, autodigestion or other regulated forms of cell death. For example, AFP delivers glycoside atractyloside (ATR) [49] into the $AFPR^{+}$ cells, where ATR induces mitochondrion damage and consequent apoptosis, road of no return (Fig. 3) [50].

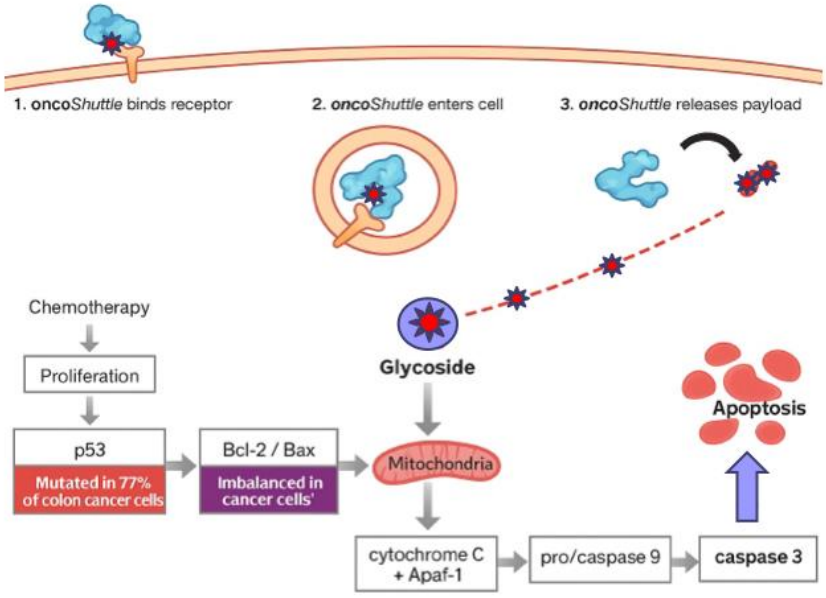


Figure 3. AFP specifically delivers glycoside atractyloside to AFPR$^+$ cancer cells. Glycoside targets mitochondria, inducing cell apoptosis undependable of p53 conditions.

## 3. AFP as an Immunomodulator

Physiological AFP concentrations—approximately 5–10 ng/mL in healthy adults and 10–150 ng/mL during pregnancy—help maintain immune tolerance. Moderately elevated AFP levels (>7 ng/mL) in otherwise healthy individuals have been associated with protective metabolic phenotypes, including reduced hepatic steatosis, myosteatosis, and sarcopenia [51]. AFP administration increased muscle strength and endurance in humans and mice; it enhanced the relative mass of immunotropic organs, improved survival at advanced age mice, and reduced their auto-aggressive behaviour [52,53]. The AFP effects on immune cells are summarized in the Table 1 [54-62].

| Immune Cell Type / Process | AFP Effect | Functional Outcome | References |
|---|---|---|---|
| Monocytes | Downregulates major histocompatibility complex class II (MHC II) expression | Reduced antigen presentation capacity | [54] |
| Macrophages | Promotes polarization toward an M2-like phenotype | Immunosuppressive, pro-tumor macrophage profile | [55] |
| NK cells | Suppression | Decreased NK-mediated cytotoxicity | [56,58] |
| DCs | Inhibits DC function | Suppression of NK cell cytotoxicity | [57] |
| Human mononuclear leukocytes | Modulates differentiation and functional activity | Broad immunoregulatory effects | [59] |
| Tregs | Inhibition | Decreased number | [60] |
| T helper cells | Influences conversion of naïve T helpers into memory T cells | Modulation of adaptive immune responses | [61] |

| Immune Cell Type / Process | AFP Effect | Functional Outcome | References |
|---|---|---|---|
| MDSCs | Modulates differentiation and functional activity | Broad immunoregulatory effects | [62] |

Table 1. The AFP effects on immune cells.

Fetal-derived AFP (4 µg/kg/day) produced complete clinical responses in inflammatory bowel disease (IBD), enabling mucosal healing and steroid administration reduction [52]. Recombinant not glycosylated AFP (rAFP) was used in patients with active rheumatoid arthritis [63]. Newer rAFP formulation (ACT-101) surpassed anti-tumor necrosis factor alpha antibodies in preclinical colitis models, improved symptoms in myasthenia gravis and IBD [64-66].

AFP transport nutrients, and modulate the immune response via immature myeloid cells. The AFP properties depend on its ligands [67]. Hence, MDSC is a "double-edged sword," playing protective or pathological roles depending on AFP deliveries. This trio mediate immune protection in autoimmune diseases—including multiple sclerosis, rheumatoid arthritis, IBD—as well as in allergic conditions and organ transplantation. On the other hand, they promote the progression of cancers [68,69]. When bound to cytotoxic ligands, AFP becomes a targeted delivery system that addresses MDSCs and tumor cells, enabling a dual therapeutic effect: a comprehensive approach to cancer immunotherapy and direct cytotoxicity [70].

## 4. Targeting AFP-receptor–positive cells.

The pore-forming anti-fungal antibiotic amphotericin B (AmB) disrupts organelles' membranes, sparing membrane of the cell, leading this cell to autodigestion. Patients with stage IV malignancies, were infused with AFP (75–300 µg) which can bind AmB in the blood. Infusions frequently triggered acute-phase reactions—transient chills and fever. Notably, no signs of endotoxicity related to rapid tumor lysis were observed. By the end of treatment, three patients demonstrated 30–40% reductions in primary tumor mass and metastatic burden. Two patients with lung cancer experienced continued metastatic regression for up to three months post-therapy. A patient with cerebral metastases showed marked neurological improvement, including recovery of swallowing and hand mobility, along with resolution of pleural carcinomatosis. Pain abated in three patients and did not recur for up to four months. Three patients gained more than 5 kg, and one maintained a stable weight. Overall, AFP: AmB infusions produced objective clinical responses in six of eight treated patients [71,72].

## 5. MDSC and Cancer Immune Evasion

MDSCs is a small heterogeneous cell population of immature myeloid progenitors of granulocytes, macrophages, and dendritic cells (DCs) generated from a common hematopoietic stem cell [73,74]. MDSCs expand under both physiological and pathological conditions, including cancer, chronic inflammation, autoimmunity, bacterial, viral, and parasitic infections, sepsis, obesity, trauma, and psychological stress [75]. Currently, no unique markers or signalling pathways definitively identify MDSCs, possibly because these immature cells occupy a transitional stage within the continuum of suppressive myeloid cell differentiation [76,77].

MDSCs are the key immune suppression cells, above Tregs, they exert activity through multiple mechanisms inhibiting both innate and adaptive responses (Fig. 4) [78]. Their accumulation correlates with tumor progression, metastasis, and poor clinical outcomes [79].

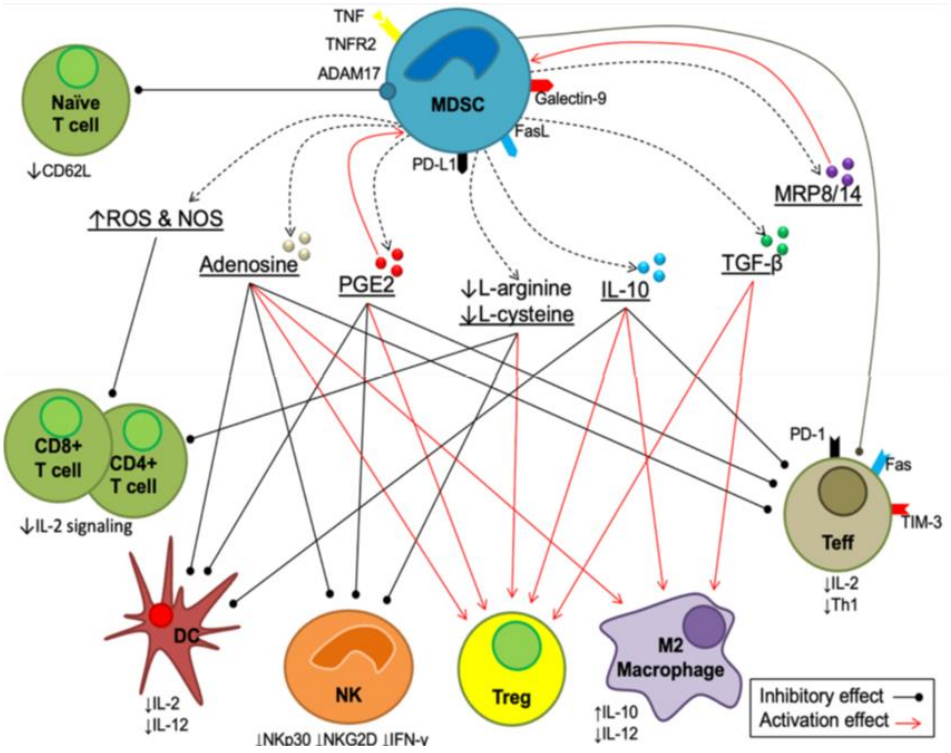


Figure 4. MDSC suppress the immune response by different mechanisms. Adapted from [78].

## 6. MDSC as Therapeutic Targets

The DC's and MDSC's suppressive function are stimulated by AFP and PUFAs [80,81]. MDSCs regulate maternal–fetal tolerance, they support implantation and fetal survival [5,6]. On the opposite, MDSC depletion in mice leads to pregnancy loss due to decidual NK cells activation [82,83]. Similarly, MDSC depletion in cancer by AFP: toxin unleashes NK cell and cytotoxic lymphocytes (CTLs) and leads to tumor elimination.

Cancer can be detected 3-5 years before clinical diagnosis [84,85], and the immune system could theoretically be "awakened" at any stage of tumor evolution by timely MDSC depletion. Like a pregnancy prevention, a cancer preventive/therapeutic MDSC-depletion vaccine can be applied to protect from cancer or improve patient outcomes.

MDSC targeting is a promising strategy in cancer immunotherapy [86-89]. Depleting MDSCs or blocking their suppressive pathways enables NK cells, macrophages, and CTLs to effectively recognize and eliminate malignant cells. Importantly, the absolute number of MDSCs—both systemically and within the PBMC compartment—is relatively small (~1%), meaning that effective MDSC-depleting therapies may require significantly lower doses compared to traditional cytotoxic chemotherapies.

MDSC and Treg levels are prognostic factors in cancers [90,91]. For example, in preoperative patients with MDSC levels >1.0% of total PBMCs, the overall survival of patients with stage IV breast cancer was significantly shorter compared with other disease stages, and was also significantly shorter compared with patients with MDSC levels <1.0% of total PBMCs [92].

Inoculation of MDSC from donor mice supported tumor growth in recipient animals [93]. In murine models, a single AFP dose increased MDSC numbers, reduced NK cell activity by ~20%, and accelerated tumor growth by ~60% [94]. Through MDSC, AFP indirectly

suppresses NK cell cytotoxicity and CTL responses while promoting Treg differentiation. AFP plays a pivotal role in MDSC biology, acting as a complementary and synergistic regulator of these cells. AFP and MDSC levels correlate with response to immune checkpoint inhibitors in cancers [95-97]. HCC cells produce tumor AFP (tAFP), which binds and transports nutrient to $AFPR^+$ cells, promoting tumor growth and metastasis. The AFP and tAFP isoforms differ only at one glycosylation carbohydrate. tAFP inhibited differentiation of a monocyte-like DCs, which produced less of inflammatory mediators, and cancelled T cell responses. The tAFP immunosuppressive activity dependents on impurities bound with tAFP in both tumor and nontumor cell lysates. tAFP serves as a delivery protein for small molecules, deteriorating DC differentiation and function [57,58]. The lipid uptake by AFP is known as a key of TME composition and immune response [80,81].

The high level of AFP accumulation was detected in the tumor tissue, reaching 6% of the injected amount per 1 g of tissue [98]. So, both AFP: PUFA and tAFP: small molecules suppress the immune response in cancer, while the opposite result can be achieved by AFP: toxin.

The replacement of PUFA with toxin for the AFP-mediated delivery was first introduced in 1983. PUFA–daunomycin conjugate bound tAFP and exhibited potent cytotoxicity against rat hepatoma cells both *in vitro* and *in vivo* [99]. On the other hand, toxins that directly bind tAFP or AFP can be administered separately or as pre-formed non-covalent complexes. Alternatively, AFP–toxin conjugates can be manufactured by chemical coupling [100,101]. Each strategy enables selective delivery to MDSCs and cancer cells.

Bioactive constituents from traditional medicines provide an additional means of modulating MDSCs activities [102]. As a result, many MDSC-dependent diseases may be sensitive to AFP-based immunotherapeutic intervention [103-110].

## 7. AFP–Toxin Immunotherapy Versus Conventional Chemotherapy

Chemotherapy Abraxane delivers albumin + 100 mg paclitaxel to cancer cells [111]. In contrast, sub-cytotoxic doses of AFP: toxins, that function primarily through immune reactivation rather than bulk tumor cell killing, selectively deplete MDSC, restore NK- and T-cell activity, and generate robust antitumor responses with minimal systemic toxicity.

The elimination of metastases observed during AFP: AmB infusions cannot be fully explained by direct cytotoxicity against $AFPR^+$ cancer cells, given the extremely low doses of AFP (1–4 μg/kg) and AmB used (<17 mg) [71,72]. Several clinical observations support an immune-mediated mechanism:

1. Transient monocytopenia: Treatment briefly reduced circulating monocytes, while the peripheral blood lymphocyte-monocyte ratio (LMR) is closely associated with the prognosis of many tumors [112,113].
2. Infusion-associated fever and chills: These acute-phase reactions preceded tumor regression and resembled the mild cytokine release syndrome associated with rapid MDSC death and subsequent immune activation.
3. Durable responses after therapy cessation: Clinical improvements continued for up to three months after a one-month treatment course, indicating sustained immune-mediated tumor control rather than a short-lived direct cytotoxic effect.

4. New tactile awareness of metastases: Some patients reported sensation or discomfort in metastatic sites post-treatment, consistent with renewed immune recognition of previously immunologically "silent" lesions.

Together, these findings suggest that AFP: AmB infusions produce dual therapeutic benefits: (1) immunomodulation via MDSC depletion and immune reactivation, and (2) targeted chemotherapy delivery to cancer cells.

The superiority of AFP: toxin therapy is most apparent in immunocompetent systems. Nude mice require substantially higher doses than immunocompetent mice or human patients, underscoring that therapeutic benefit depends on an intact capacity for immune restoration.

Because of its low-dose, and immune-rebalancing mechanism, AFP: toxin therapy holds promise for prevention, early-stage cancers, metastatic disease, and for use in combination with other anticancer modalities.

## 8. Safety and Risks Considerations

Safety and risks of AFP: toxin cancer immunotherapy are summarized in the Table 2 [52, 114].

| Aspect | Key Point | Safety Implication / Outcome | References / Notes |
|---|---|---|---|
| AFP dosing and physiological exposure | AFP administered at doses known to be safe; cancer incidence comparable between pregnant and non-pregnant women | Low intrinsic oncogenic risk | [52] |
| Clinical use of natural AFP | Natural AFP registered and used in Russia for autoimmune diseases and cancer (4 μg/kg/day) | Established safety and therapeutic efficacy | [52] |
| Recombinant AFP (rAFP) | Biosimilar rAFP (ACT-101) enables delivery of AFP-binding toxins | Expands therapeutic options with maintained safety | [114] |
| Toxin dose and binding | Sub-cytotoxic toxin doses non-covalently bound to AFP (2:1) | No damage to normal cells | — |
| Toxin selection | Toxins are non-mutagenic and non-carcinogenic; act as direct apoptosis inducers | Reduced long-term cancer and genetic risks | Fig. 3 |
| Drug repurposing | AFP-binding embryotoxic or teratogenic drugs may be repurposed | Facilitates clinical translation using registered drugs | — |
| Target cell abundance | Regulatory immune cells are less abundant than effector cells | Lower drug doses required, improved treatment safety | — |
| MDSC depletion in circulation | Depletion associated with fever and chills preceding tumor regression | Predictable, manageable immune-related effects | — |
| MDSC localization | Bone marrow–resident MDSCs not exposed to AFP: toxin complexes | Limits excessive myeloid depletion | — |

| Aspect | Key Point | Safety Implication / Outcome | References / Notes |
|---|---|---|---|
| Contraindications | Like pregnancy and breastfeeding | Clear and familiar clinical exclusion criteria | — |
| AFP–toxin chemical conjugates | Prevent toxin release outside cancer cells in acidic TME | Enhanced safety compared to non-covalent complexes | — |
| AFP growth-stimulating effects | Covalent conjugation eliminates AFP-mediated tumor stimulation | Improves therapeutic specificity | — |
| Preclinical efficacy (ACT-903) | AFP–maytansine conjugate induced complete tumor regression in COLO-205 xenografts | Strong anti-tumor efficacy | [114] |
| Systemic toxicity (ACT-903) | No systemic toxicity at 20–40 mg/kg/day | Favorable safety profile | [114] |
| Cancer models | Efficacy demonstrated in colorectal and ovarian cancer xenografts | Supports clinical advancement | [114] |
| Potential risks | Broad MDSC depletion and risk of autoimmunity | Requires careful immune monitoring | — |
| Risk mitigation | Adverse effects may be managed via treatment adjustments | Improves clinical controllability | — |

Table 2. Safety and risks of AFP–toxin cancer immunotherapy.

## 9. Lessons from Traditional Fertility Control

Some traditional medicines historically used as contraceptives may also exert anticancer effects, reflecting shared reliance on immune-tolerance pathways in both pregnancy and tumor development. Natural agents can reduce or modulate MDSC populations and display antitumor activity that may be partially mediated through AFP-based transport to cancer and $AFPR^+$ immune cells. Silphium—an extinct herbal contraceptive—has been speculated to influence HCC, where tAFP levels are elevated [19]. Artemisinin, used in antiquity as a contraceptive and now known for its potent antimalarial activity, also exhibits anticancer effects and downregulates MDSC [115]. Its affinity for AFP suggests that its modern oncologic potential may echo its historical role in reproductive modulation. Withaferin A, from *Withania somnifera* (Ashwagandha), similarly suppresses MDSC activity and induces apoptosis in tumor cells [116]. Most medical guidance recommends avoiding ashwagandha during pregnancy.

AFP-binding embryotoxic and teratogenic compounds may be used for cancer therapy. In combination with AFP or pAFP, agents such as warfarin [117], retinoids [118,119], glycyrrhizic acid [120], thalidomide, isotretinoin, etc., may prevent or treat cancer.

Many women benefit from oral contraceptives that can reduce women's risk with some cancers [121,122]. For example, pregnancy-preventing drug mifepristone (RU486) inhibits embryonic implantation and modulates macrophage-regulated NK cell activity, enhancing their cytotoxicity and migration in a dose-dependent manner [123]. Mifepristone

induces apoptosis through mitochondrial protein imbalance, and has shown promise in treating various cancers, including metastatic lung cancer resistant to immune checkpoint inhibitors [124]. A pregnancy prevention mechanism can be not only blocking the hormone progesterone, but also both the decrease of MDSC activity and the toxin direct action on embryo cells. Hence, like oral mifepristone prevents pregnancy, AFP: mifepristone can possibly prevent cancer.

AFP increases ligand stability, reducing renal clearance, and prolonging circulating half-life. Such AFP-bound compounds retain selective uptake by $AFPR^+$ cells and can be administered orally, leveraging gut-associated lymphoid tissue (GALT) for systemic immune modulation.

## 10. AFP Potentiates Traditional Medicine–Derived Compounds in Immunotherapy

Natural compounds and functional foods are often regarded as safer alternatives to synthetic drugs. Many traditional medicines contain ingredients that have demonstrated immunotherapeutic potential, that selectively "feed" key regulatory immune cells thereby shaping the immune response [125]. As of late 2024, 125 natural products and their derivatives were in clinical trials or the registration phase [126]. Herbal agents can influence MDSC through several mechanisms, including blocking AFP–MDSC interactions, reducing MDSC suppressive activity, altering the ligand carried by AFP, or directly depleting MDSCs. MDSCs are "here, there, and everywhere", acting not only in pregnancy and cancer [127]. Consequently, AFP also participate in immune balance regulation. The interaction among MDSCs, AFP, and AFP-bound ligands forms an immunoregulatory trio that operates in both physiological and pathological contexts [128].

In oncology, robust antitumor responses can be achieved by administering sufficient AFP to act as a shuttle together with moderate toxins, by delivering preformed AFP: toxin complexes, or AFP-toxin chemical conjugates.

The moderate anticancer agents genistein, curcumin, artemisinin, and resveratrol suspensions in oil show improved absorption and enhanced cytotoxicity [129]. These agents can also bind tAFP or AFP. Through these binding botanical compounds are targeted to MDSCs and become immunomodulators. Thus, curcumin suppresses MDSC expansion and promotes immune activation; genistein, resveratrol, and artemisinin exhibit similar effects. Curcumin and genistein bound to rAFP, demonstrate elevated antitumor activity [130].

1′-S-1′-Acetoxychavicol acetate (ACA) from *Alpinia* species has anticancer properties [131]. When complexed with AFP at a 1:1–3 ratio, ACA demonstrated potent antitumor activity [132]. As a food, ACA may possibly support immunity through AFP-mediated shuttling during lifetime.

At a conventional 15 mg/kg dose, paclitaxel from Taxus species has demonstrated direct cytostatic or cytotoxic effects on melanoma cells. In contrast, paclitaxel in low non-cytotoxic concentrations (1 mg/kg, weekly × 3) significantly decreased the accumulation and immunosuppressive activities of tumor infiltrating MDSCs. It has also reversed immunosuppression and chronic inflammation. In low non-cytotoxic doses, paclitaxel is unable to directly suppress tumor cell proliferation, induce apoptosis, or alter the bone marrow hematopoiesis, but it modulates the functions of MDSCs in primary skin tumors and lymphoid organs, affect the production of mediators of chronic inflammation and T cell activities in the TME, prolong mice survival, and reduce the melanoma burden. The low non-cytotoxic paclitaxel doses have also been used for enhancing the efficacy of accompanying anti-cancer therapies [133]. So, immunotherapeutic impact outweighs paclitaxel's cytotoxic one. When complexed with AFP at a 1:2 molar ratio, paclitaxel becomes water-soluble, gains an extended

half-life, and selectively targets the AFPR$^+$ cells. The AFP: paclitaxel complex (ACT-901) improves survival and reduces toxicity compared to high-dose paclitaxel [134].

Thapsigargin (TG), a highly potent toxin from *Thapsia garganica*, is unsafe when administered systemically [135], but rAFP (ACT-101): TG at a 1:2 ratio (ACT-902) induces ~32% MDSC death *in vitro* (versus 5% in controls) and, at 0.15 mg/kg, produced complete tumor regression in five of six nude mice within seven days [114]. Notably, nude mice are deficient in T cells, which play a critical role in the immune response. Consequently, immunocompetent mice are expected to demonstrate improved outcomes at lower doses. Oral pAFP: TG formulations have also demonstrated strong anticancer activity in mice [72].

Rodenticide rotenone, a botanical mitochondrial inhibitor ($IC_{50}$: 0.8–4 nM), is moderately toxic in humans at high doses (oral $LD_{50}$ ~300–500 mg/kg). Gavage with pAFP: rotenone has shown significant inhibition of tumor growth in mice [72].

Overall, the potency of pAFP: toxin complexes correlate with toxin strength: TG, ATR, rotenone > betulinic acid [136], ajoene [137]> tocotrienol, vitamin $D_3$ [138], while adjunctive betulinic acid or ajoene further improve therapeutic outcomes [72].

## 11. Oral Delivery

“Let food be thy medicine, and let medicine be thy food.” (Hippocrates)

The poor GI absorption, and low bioavailability usually prevents the oral protein-based drugs administration [139]. Nevertheless, AFP or pAFP are candidates for oral formulations [140].

The FcRn-mediated transcytosis through placenta and GI enterocytes is known for immunoglobulin G: antigen and albumin: ligand complexes [141]. AFP: ligand also crosses several cell layers of placenta, and AFP has an even stronger binding affinity to FcRn [142]. That possibly allows AFP: ligand complexes to reach FcRn$^+$ and/or AFPR$^+$ regulatory immune cells in the mucosa and regional lymph nodes.

At 5–7 μM (350–490 μg/mL), full-length AFP induce apoptosis in HCC cells. The main role was attributed the AFP molecule, but not to its ligands [143].

A peptide mimicking the anti-estrogenic, anti-breast-cancer active site of AFP was isolated and developed into a nine–amino acid cyclic peptide (~1.2 kDa). This peptide inhibited the development and growth of mammary tumors in rodent models. In non-human primates, intravenous (IV) administration at 4 mg/kg achieved peak plasma concentrations of ~13 μg/mL. This exposure exceeds, on a molar basis, the concentrations of full-length AFP (70 kDa) reported to induce apoptosis (350-490 μg/mL), reflecting the substantially lower molecular weight of the peptide (70 kDa vs. 1.2 kDa). So, the peptide, like a full-length AFP, can induce apoptosis in cancer cells. An oral peptide administration resulted in minimal systemic exposure, with plasma levels of approximately 0.03 μg/mL, corresponding to an estimated oral bioavailability of ~0.23%. AFP peptide at concentrations ≥0.1 μg/mL was sufficient to inhibit tumor xenografts in mice [144].

Nevertheless, AFP-toxin non-covalent complexes or conjugates are more potent than full-length AFP or AFP peptides, as they additionally deliver cytotoxins (e.g., 1:5.9 molar ratio in ACT-903) [100,101]. Moreover, partial MDSC depletion is sufficient to “tip” the immune system toward activation, enabling endogenous effector cells to eliminate tumors.

Glycoside ATR (Fig. 3), the major bioactive constituent of *Callilepis laureola*—used in Zulu medicine as a decoction for gastrointestinal and reproductive disorders [145], that

allows to test it as an oral medicine in cancer too. The oil-based ATR formulations have demonstrated antitumor activity in mouse models [146]. In high doses, ATR inhibits the development, as well as the metastasis, of colon cancer, and is under active investigation as a TME modulator [49]. Aimpila is a 1:2 molar complex of pAFP: ATR, it is an example of an oral cancer immunotherapy. In Ca-755 breast adenocarcinoma models, gavage of mice with Aimpila significantly extended survival without observable toxicity [72].

Clinical observations are consistent with preclinical data supporting the efficacy and safety of AFP: ATR therapy. Aimpila delivers 0.012 mg ATR/day—orders of magnitude below known toxicity thresholds, given that the oral $LD_{50}$ of ATR in rodents ranges from 25 to 100 mg/kg. In an initial study of 16 patients with advanced solid tumors (colon, stomach, breast, and liver), administration of two Aimpila capsules/day (containing 0.3 mg pAFP and 0.006 mg ATR) for one month resulted in approximately 20% improvements in Karnofsky indexes. No adverse events were reported [72].

12 patients with liver-metastatic colorectal cancer (mCRC) received two Aimpila capsules per day for two months. Computer tomography before and after eight weeks of therapy showed responses in six of the twelve patients. Two achieved complete disappearance of small metastases, one exhibited a 73% reduction in metastatic burden, and three achieved disease stabilization. Tumor-growth inhibition and regression occurred without notable toxicity. Two of the responders had previously undergone chemotherapy, suggesting that Aimpila may help overcome multi-drug resistance (Fig.3). Serum carcinoembryonic antigen levels declined from 816 to 268 ng/mL in a patient with complete response, and from 1,243 to 638 ng/mL in a patient with stable disease. Two patients survived more than five years, exceeding the ~9-month median survival for mCRC [147,148].

A woman with stage IV ovarian cancer received 6.0 mg pAFP + 0.12 mg ATR daily and survived more than 10 years post-diagnosis [72].

AFP fragments have only ~0.23% oral bioavailability [144]. Hence, a dose of 0.6 mg pAFP in Aimpila is ~1.38 ng/mL in plasma, that is below cytotoxic AFP or AFP fragments concentrations (350–490 μg/mL, and ≥0.1 μg/mL accordingly). Nevertheless, therapeutic responses are consistently observed in both clinical and preclinical settings. This indicates that oral Aimpila act primarily through immunological modulation rather than direct systemic cytotoxicity. Supporting this, gavage of a pAFP: rotenone (1:2) complex in mice produced no detectable plasma levels of either component yet significantly suppressed tumor growth [72]. These findings suggest that activation of GALT and selective modulation or depletion of MDSCs and related immune populations is the principal mechanism of action.

Collectively, these data support a model in which oral AFP: ligand formulations act primarily as immune modulators. Their effects can be due to FcRn-mediated transcytosis and lymphatic trafficking and targeting of $AFPR^+$ immune cells. Rather than relying on plasma drug levels or direct tumor exposure, these complexes modulate systemic immunity from the intestinal immune system. Compared to injections, oral administration is more convenient and safer for patients, making AFP-toxin oral formulations an attractive cancer immunotherapy.

## 12. Clinical outcomes in cancer patients

Combining AFP with traditional medicine compounds offer a new way for cancer immunotherapy with minimal adverse effects. Human rAFP (ACT-101) is characterized clinically [114]. Pharmacokinetic advantages of intravenous (IV) or subcutaneous administration are improved bioavailability and prolonged circulation half-life. Unlike conjugates, AFP-shuttle can deliver dozens of toxins during its 3-5 days of half-life circulation. AFP: toxin therapy may complement existing treatments due to its reduced toxicity.

Because MDSCs and many solid and hematologic malignancies are AFPR$^+$, the preselection of patients for AFPR expression is unnecessary. Through coordinated depletion of MDSC and activation of effector immune cells, AFP: toxin therapies may restore immune competence and promote the memory. Summary of clinical outcomes in cancer patients are presented in Table 3.

| Patients | Treatment | Outcome | Ref. |
|---|---|---|---|
| 51 cancer pts | AFP 4 µg/kg/day | Anti-cancer effect on differentiated tumors | [52, p.273-287] |
| 8 cancer pts | AFP 4 µg/kg + AmB | 6/8 responses, 3 pts with 30-40% tumor inhibition/regression | [71,72] |
| 16 pts with advanced solid tumors | pAFP 0.6 mg + ATR 0.012 mg/day (oral) | ~20% ↑KPI | [72] |
| 12 mCRC pts | pAFP 0.6 mg + ATR 0.012 mg/day (oral) | 6/12 responses; tumor inhibition/regression; 2 OS > 5 yrs | [147,148] |
| 1 stage IV ovarian cancer pt | pAFP 6 mg + ATR 0.12 mg/day (oral) | OS > 10 yrs | [72] |

Table 3. Summary of clinical outcomes in cancer patients treated with AFP, pAFP, and AFP-toxin combinations. AFP, alpha-fetoprotein; pAFP, porcine AFP; ATR, atractyloside; AmB, amphotericin B; mCRC, metastatic colorectal cancer; KPI, Karnofsky Performance Index; OS, overall survival.

AFP: toxin complexes represent a novel immunotherapeutic approach. Studies on efficacy, safety, and ligand optimization will be essential to translate these discoveries into effective therapeutic and preventive tools.

## 13. Conclusions

AFP naturally delivers nutrients to immature AFPR$^+$ cells, including a small population of immunosuppressive MDSCs that orchestrate immune tolerance during pregnancy, cancer, and other conditions. The MDSCs, AFP, and AFP-bound ligands interaction generate a dynamic immune response “here, there, and everywhere”. Nutrients can stimulate MDSCs, thereby suppressing the activated immune system, while toxins with AFP selectively destroy MDSCs, providing a novel cancer immunotherapy that reactivate NK cells, macrophages, and cytotoxic T lymphocytes. Preliminary experiments have shown that AFP–toxin conjugates and non-covalent complexes combine selective cytotoxicity against MDSCs and malignant cells. The combined effects enhance natural antitumor immune response and possibly restore memory. The low doses of apoptosis-inducing toxins can eliminate targeted cells without generating pro-inflammatory byproducts. AFP: toxin complexes and conjugates are not personalized, they can be proposed as prophylactic agents and combined with other treatments. rAFP platforms like ACT-101 may streamline and accelerate clinical development of AFP-binding already-registered cytotoxic drugs, but they do not eliminate the need for clinical trials. Harnessing AFP’s natural biological functions alongside the pharmacological potency of traditional medicine active ingredients provide a biologically based, low-toxicity, and wide immunotherapy platform.

AFP: toxin non-covalent complexes or covalent conjugates injectable or oral formulations are mechanistically understood, highly efficacious, low in systemic toxicity, cost-effective, and patient-friendly. This approach offers a promising avenue toward durable cancer control and restoration of immune competence.

## Abbreviations

AFP Alpha-fetoprotein

pAFP Porcine AFP

rAFP Recombinant AFP

tAFP tumor-derived AFP

AFPR AFP receptor

AmB amphotericin B

ATR Atractyloside

mCRC metastatic colorectal cancer

CTL Cytotoxic T lymphocyte

DC Dendritic cell

DHA Docosahexaenoic acid

FcRn Neonatal Fc receptor

GALT Gut-associated lymphoid tissue

GI Gastrointestinal

KPI Karnofsky Performance Index

HCC Hepatocellular carcinoma

IBD Inflammatory bowel disease

IV Intravenous

$LD_{50}$ Median lethal dose

MDSC Myeloid-derived suppressor cell

NK Natural Killer

OS Overall survival

p53 Tumor protein 53

PBMC Peripheral blood mononuclear cells

PUFA Polyunsaturated fatty acid

TG Thapsigargin

Treg Regulatory T cell

TME Tumor microenvironment

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The author is solely responsible for conceptualization, investigation, writing – original draft, writing – review and editing, and visualization of the manuscript. The author has read and agreed to the published version of the manuscript.

## Conflicts of Interest

The author declares no conflicts of interest.

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