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# Magic Bullet and Immunotherapy against Metastasis

**Abstract**

Cancer is uncontrolled cell proliferation. Apoptosis controls the cells from inside while immune system controls the cells from outside. Cancer breaks both controls. To treat cancer one need to restore these controls. Apoptosis can be fixed with targeted chemotherapy (magic bullet) and immune tolerance can be reversed by immunotherapy. Both actions can be done with alpha-fetoprotein (AFP)-toxin drugs. AFP can naturally deliver the toxin through AFP receptors to cancer and powerful immune suppressive cells - myeloid-derived suppressor cells (MDSC). MDSC depletion with AFP-toxin drugs releases both innate and adaptive immunity. By this way activated immune system, together with targeted chemotherapy could effectively erase primary cancer cells and/or metastases.

**Keywords:** Targeted chemotherapy; Immunotherapy; Apoptosis; Metastasis; Alpha-fetoprotein receptor-mediated endocytosis; Embryogenesis; Oncofetal proteins; MDSC

Mini Review

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**Abbreviations:** AFP: Alpha-Fetoprotein; AFPR: Alpha-Fetoprotein Receptor; MDSC: Myeloid-Derived Suppressor Cells; NK: Natural Killers; DNA: Deoxyribonucleic Acid; CEA: Carcinoembryonic Antigen; Hcg: Human Chorionic Gonadotropin

## Introduction

More than 100 years of attempts to beat cancer with magic bullet only did not bring a solution. Today, more than 90% of cancer patients die from metastasis. Cancer cells/metastasis develops from a single cell and abnormally grow to form the whole tumor. The similar process can be observed during embryogenesis: the whole body grows from a single cell. Embryo cells theoretically have half the father's genes/proteins that should be rejected by the mother's immune system that rarely happens. The mechanisms that protect embryo cells from the mother's immune system during embryogenesis are aberrantly re-used by cancer cells and involve oncofetal proteins. The well-known oncofetal protein AFP [1,2] originated from embryo yolk sac and liver can grab small molecule essential nutrients into its hydrophobic pocket [3,4] and specifically deliver them into the AFP receptor-positive cells in a shuttle manner [5]. Alpha-fetoprotein receptor (AFPR) is another oncofetal protein present on majority of cancer cells. Receptor-positive embryo and cancer cells have definite benefits of targeted nutrient delivery (Figure 1). That is why AFP loaded with the different toxins was used for the targeted chemotherapy [6,7]. The AFP receptor detection on the major immune suppressive cells - MDSC - was very promising [8,9]. The mechanism of immune tolerance to the embryo and in cancer cells now could be explained by AFP-nutrient stimulation of MDSC and subsequent local suppression of the immune system (Figure 1). On the contrary, AFP-toxin drugs not only deplete cancer cells but host MDSC too (Figure 2). MDSC was announced a perspective therapeutic target in cancer treatment because its depletion removes "brakes" from both innate and adaptive immunity activation [10-12]. Compared to adaptive immunity innate immunity activation against cancer cells is more important as it does not need time and critical cell numbers to develop. The AFP-toxin drugs immunotherapy and targeted chemotherapy united anti-cancer action was successful in cancer patients [13-15].

## Magic Bullet

The magic bullet must be double targeting; not only the cancer cell, but also the optimal intracellular target [16]. Intracellular targets are not equal. As a matter of fact, many toxins are directed to proliferation-associated targets such as, DNA, tubulin, phosphokinases, etc. that rely on healthy apoptosis in the subsequent step. In my opinion the toxins that are associated with apoptosis executive action should have a priority. It is due to p53, elephants, for example, have a low cancer rate than humans [17]. In majority of human cancers, mutations in the p53 gene prevent apoptosis. To overcome this issue the target for the toxin should be not DNA or the non-functional p53 but, for example mitochondrion, that is directly involved in the intrinsic apoptosis pathway after p53 [18]. The damage of mitochondrion, lysosome, endoplasmic reticulum or peroxisome membrane is fatal for any cell because membrane is a boundary between life and death. Like cell membrane damage, organelle membrane damage cannot be repaired and leads to the whole cell death by apoptosis or auto digestion. So, the toxins that destroy organelle membranes do not rely on p53, and lead to inevitable cancer cell death are preferable for the magic bullet [6]. The only problem for organelles toxins is to be internalized specifically by cancer cells. Targeted delivery to cancer cells and organelle toxin internalization can be organized with different artificial nano-vehicles but we used natural AFP [6].

## Immunotherapy

Immunotherapy is a different approach from chemotherapy or radiation. The latter attack cancer cells itself, while immunotherapy aims to empower the immune system to kill them. The immune system could prove a strong weapon against many cancers and offer long-term protection with reduced

side effects. Two types of immunotherapy appeared recently: checkpoint inhibitors, which remove "brakes" from the immune system, allowing it to see and erase cancer cells [19]; and more sophisticated CAR T-cell therapy [20]. Both use T-cells that belong to adaptive immunity and have moderate efficacy. To potentiate the efficacy of these immunotherapies they are combined with a lot of other chemotherapies. Immunotherapy goal is to shift the balance of activating/suppressing T-cells to favor the ability of activating ones to overcome suppressors. On the other hand, to restore the natural full size immune response to cancer cells it could be helpful to use additionally immunotherapy that activates also innate immunity [21]. The example of the full immune response and its local suppression can be seen in pregnancy. Dr. Govallo has found the similarities between immune suppression in pregnancy and cancer. During pregnancy, the mother's immune system is generating anti-embryo response, which is neutralized by the embryo-secreted proteins leading to immune tolerance. Being "the embryo's evil twin" a tumor generates the anti-cancer immune response, but it is suppressed by the factors secreted by cancer cells. Dr. Govallo has shown that a protein extract of human placenta effectively blocks all expressions of cell immunity. To remove "brakes" from the immune system he immunized cancer patients with placental proteins. Placental protein injections lead to elimination of immune tolerance to the tumor, reduction of the tumor mass and decreased production of immune blocking factors. Statistics in his book show a 77.1% 5-year survival rate in the group of 35 patients with metastases of different cancers [22]. The "brakes" removal therapy of cancer through the use of placental/oncofetal proteins provides a new type of immunotherapy. Hence, immunization with the mixture of AFP, AFPR, CEA, hCG and other oncofetal proteins is likely responsible for the reversal of immune tolerance to tumor [23]. The individual proteins of the extract yet should be identified but AFP is the major one of them [24]. Embryo secreted AFP penetrates into the mother's blood and together with the sex hormones [25] participates in immune tolerance to the embryo [26]. AFPR was detected on the powerful immune suppressive cells - MDSC [8,9,27,28]. By delivering nutrients to MDSC, AFP stimulates their suppressive activity (Figure 1). MDSC may be the major "brakes" of the immune system and are responsible for immune tolerance to the embryo and cancer cells. Hence, to reverse tolerance to cancer cells AFP was loaded with the toxin. AFP-toxin drug following the natural way was internalized by MDSC and depleted them [9]. The magic bullet targeted to MDSC became a new type of immunotherapy. MDSC-targeted immunotherapy removes "brakes" from both innate and adaptive immunity and has a great potential [29-31] (Figure 2). AFP-mitochondrion toxin drug in a very low dose effectively erased liver metastasis [14] (Figure 3).

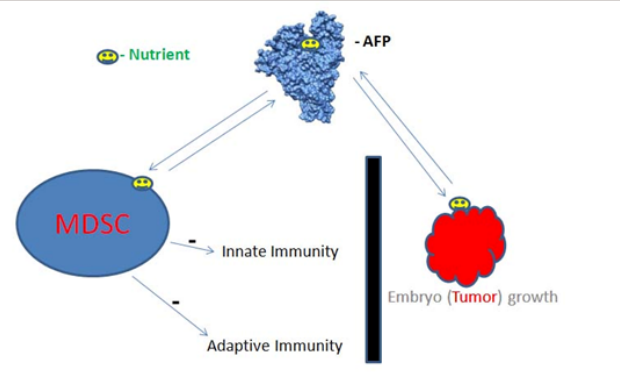


**Figure 1:** Delivering nutrient to MDSC and cancer cells through AFPR-mediated endocytosis AFP stimulates accordingly immune tolerance and tumor growth.

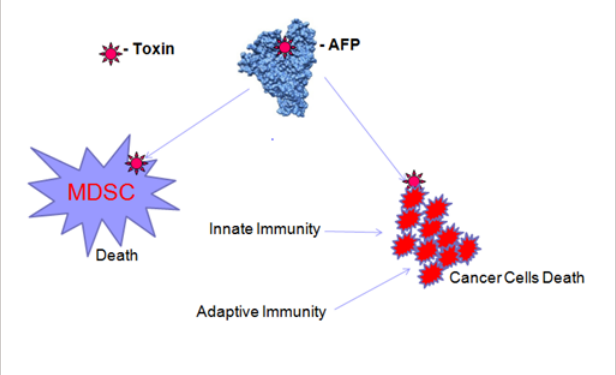


**Figure 2:** AFP-toxin drug depletes cancer cells and MDSC that in its turn removes "brakes" from innate and adaptive immunity to kill cancer cells.

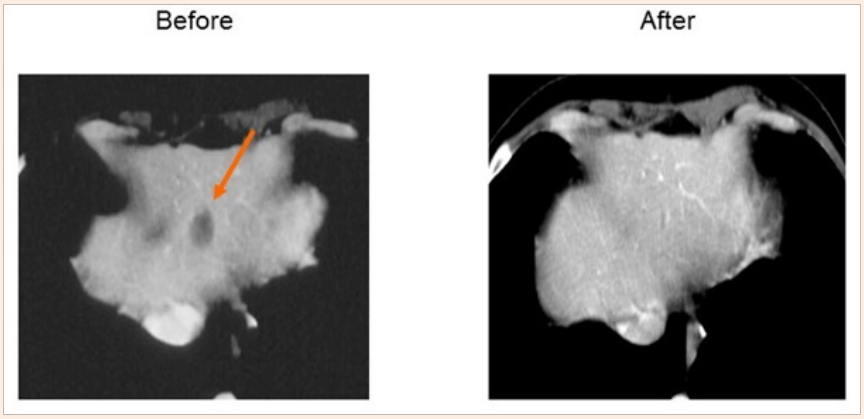


**Figure 3:** CT scan with liver metastasis (arrow) and its elimination in 8 weeks with AFP-toxin drug.

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## Conclusion

The magic bullet is not enough to beat cancer. The united action of both targeted chemotherapy and immunotherapy is a rational way to treat cancer. Adaptive immunity can be activated with e.g., checkpoint inhibitors, but oncologists need also innate immunity activators. Innate immunity can destroy the primary cancer cells/metastasis while adaptive immunity needs a bigger cell number and time in order to develop specific response. MDSC - targeted immunotherapy has a great potential. MDSC controls both innate and adaptive immunity and are involved in immune tolerance to cancer and autoimmune diseases. They demonstrate AFPR and can be specifically targeted by AFP-toxin drug. This drug can deplete MDSC, thus immune tolerance to cancer cells will be broken. Activated NK and T- cells effectively erase metastasis. Natural delivery vehicle AFP loaded with the toxin plays dual role in metastasis depletion: as targeted chemotherapy and immunotherapy where the second one is more important and dominating with low doses (Figure 2). Low doses make it possible to combine AFP-toxin therapy with any other therapies for better patients' outcomes. Other oncofetal proteins should be tested on immune modulation.

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