



**A MEDICAL DEVICE STRATEGY TO IMPROVE THE BENEFIT  
OF CANCER TREATMENT REGIMENS**

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The Aethlon Hemopurifier<sup>®</sup> is an FDA designated “Breakthrough Device” therapy related to the depletion of circulating exosomes in cancer patients. In recent years, tumor-derived exosomes have been discovered to suppress the immune system and promote the growth and spread of tumors in cancer patients. Beyond addressing this significant unmet need in global health, a reduced presence of cancer-promoting exosomes would likely augment the benefit of both standard-of-care and emerging immuno-oncology treatment regimens. The rationale underlying this promising medical device strategy is described in this white paper.

## **Tumor-Derived Exosomes are Unaddressed Targets in Oncology**

Exosomes are a part of a communication system that conveys signals to near or distant target cells and reprograms their functions<sup>[1]</sup>. Exosomes are membrane-bound vesicles similar in size to viruses (30-150nm), and are present in the systemic circulation where they are distributed throughout the body. Exosomes carry a broad variety of membrane-associated biologically-active molecules, including cell adhesion molecules necessary for exosome uptake by recipient cells via phagocytosis, endocytosis, fusion with the membrane, or receptor-mediated uptake <sup>[2]</sup>. Compared to normal cells, cancer cells release tumor-derived exosomes (TEX) in exponentially greater quantities [3]. TEX are associated with cancer progression [4], down-regulation of anti-tumor immune responses [5] and chronic inflammation promoting cancer development [6]. TEX re-program immune cells by initiating signaling cascades that activate endogenous molecular pathways. TEX deliver inhibitory signals to the surface of effector immune cells responsible for anti-tumor activity and deliver oncogenic proteins to recipient cells [7]. Exosome-associated inhibitory molecules can interact directly with their target cells and activate cellular inhibitory pathways, reprogramming the functions of immune-competent cells [8]. Overall, hundreds of studies indicate that TEX are immunosuppressive elements in cancer, thus establishing TEX as relevant therapeutic targets.

## **Mechanisms by which Aethlon's Hemopurifier® selectively captures exosomes from the bloodstream**

The mechanism of action of the Hemopurifier® (also an FDA designated “Breakthrough Device” related to the treatment of life-threatening viruses) is based on the convergence of plasma membrane separation technology with affinity chromatography to establish a specificity to capture glycan shielded nanoparticles [9, 10] from the entire circulatory system. The technology separates particles below 200 nm away from blood cells and delivers them to an immobilized affinity matrix that has a specificity to bind a unique glycan structure that cloaks the surface of viruses and exosomes from the surveillance of the immune system. Cellular components that are not bound by the affinity matrix are returned to circulation. The resulting mechanism establishes the Hemopurifier® as a therapeutic candidate to address cancer-promoting exosomes, which would fulfill a significant unmet need in global health.

The Hemopurifier® affinity matrix incorporates galanthus nivalis agglutinin (GNA) lectin, which exhibits specificity for glycoprotein moieties on the outer surface of exosomes. Exosomes have lipid bilayer membranes that express glycoprotein signatures analogous to those found on enveloped viruses, which serve the purpose of allowing these particles to exist “under the radar” of the immune system [11]. Lectin microarray analysis of exosomes isolated from a battery of cancer cell lines revealed enrichment for high mannose surface epitopes [12, 13]. Previous studies confirm that exosomes can be captured by GNA *in vitro* [11, 14]. These highly glycosylated surface structures disguise disease-mediating cargo from immune surveillance, and allow TEX to act as stable messengers of oncogenic functional proteins and genetic material [15], and to prime the metastatic niche at locations remote from the original tumor [16]. Accordingly, TEX concentrations measured in plasma correlate with patients’ disease status [17]. These lines of evidence support the strategy of capturing TEX from the circulatory system using a GNA lectin affinity mechanism.

## **Rationale for Applying the Hemopurifier® to Target Exosomes in Cancer Patients**

The administration of Hemopurifier® therapy to reduce circulating exosome load is anticipated to lead to improved efficacy of existing therapies, including immunotherapeutic antibodies, adoptively transferred T cells, and chemotherapeutic agents. For example, by delivering

Hemopurifier® therapy prior to administration of an immunotherapeutic agent (ie: an immune checkpoint inhibitor drug) would inhibit several deleterious influences of exosomes and augment the patient immune response, resulting in improved responses to cancer therapies.

Exosomes carry a broad variety of membrane-associated biologically-active molecules, including cell adhesion molecules necessary for exosome uptake by recipient cells via phagocytosis, endocytosis, fusion with the membrane or receptor-mediated uptake [2]. Compared to normal cells, cancer cells release exosomes in exponentially greater abundance [3]. TEX are associated with cancer progression [4], down-regulation of anti-tumor immune responses [5] and chronic inflammation promoting cancer development [6]. TEX re-program immune cells by initiating signaling cascades that activate endogenous molecular pathways. TEX deliver inhibitory signals to the surface of effector immune cells responsible for anti-tumor activity and deliver oncogenic proteins to recipient cells [7]. Exosome-associated inhibitory molecules can interact directly with their target cells and activate cellular inhibitory pathways, reprogramming the functions of immune-competent cells [8]. Overall, TEX are therapeutically relevant targets as hundreds of studies reveal that TEX are major immunosuppressive elements in cancer.

Further rationale as to why cancer-promoting exosomes are important therapeutic targets is detailed below. These examples demonstrate that exosomes derived from patients with many tumor types exert immunosuppressive functions and additionally counteract the actions of many therapeutic drug agents as well as immunotherapeutic regimens. In addition to the summary below, Table 1 outlines a summary of cancer therapies that have reported to be inhibited by TEX.

1. *Tumor-derived exosomes inhibit tumor-reactive T cells, and may present barriers to the efficacy of adoptive T cell therapies for c*

TEX from many cancer types deliver suppressive or apoptosis-inducing signals to activated T cells and to other immune cells responsible for eradicating tumors in response to therapies [15]. Suppression of T cell function is mediated by exosomes isolated from the plasma of cancer patients but not by exosomes isolated from plasma of healthy individuals [18].

Research studies have demonstrated how exosome depletion would affect the subsequent functions of immune cells. Exosomes from ovarian cancer can inhibit T cell functions, however, subsequent physical removal of TEX *in vitro* has been shown to allow T cells to regain their functions and become activated. This research supports the concept that TEX targeting strategies could prevent the functional arrest of therapies involving adoptively transferred T cells or chimeric antigen receptor (CAR) T cells used for immunotherapy [19].

In another study, plasma from patients with refractory/relapsed acute myeloid leukemia was found to contain elevated levels of immunosuppressive exosomes that interfered with the anti-leukemia functions of immune cells [20]. These *in vitro* studies support the conclusion that TEX may limit the expected therapeutic benefits of adoptive cell therapies.

2. *Tumor-derived exosomes act as decoys that directly inhibit the actions of monoclonal antibodies that are used for cancer immunotherapy.*

Several proof-of-concept studies have shown that TEX interfere with the actions of monoclonal antibodies that are FDA approved cancer treatment drugs. In tumors that over-express the human epidermal growth factor receptor 2 (HER2), which include 25-30% of breast cancers, TEX also express HER2 in addition to other tumor growth-promoting proteins. These proteins allow exosomes to directly engage in signaling for tumor cell proliferation [21, 22] and also to bind to mAb that are used for therapies. HER2-expressing TEX bind to and sequester the therapeutic mAb trastuzumab (Herceptin®; anti-HER2 mAb), leading to a decreased drug concentration and attenuated interaction of the drug with its intended targets, HER2+ cancer cells [21]. The targeted removal of HER2-expressing exosomes using the Hemopurifier® may therefore improve the bioavailability of Herceptin®, thereby improving its clinical benefits or possibly addressing drug resistance.

In another example, lymphoma cells were found to release exosomes that carry the CD20 molecule on their surfaces and thereby bind to therapeutic anti-CD20 mAb, rituximab. This in turn protected target tumor cells from antibody attack [23]. Pharmacological blockade of the exosome biogenesis pathway *in vitro* improves the anti-tumor activity of rituximab. These findings delineate a specific role for TEX in shielding tumor cells from immunotherapeutic agents. Also, the study supports a rationale for Hemopurifier<sup>®</sup>-mediated removal of circulating TEX prior to treatment with therapeutic antibodies to mitigate the known problem of resistance to rituximab [24].

Exosomes have also been shown to activate vascular endothelial growth factor (VEGF) signaling to promote tumor angiogenesis, which is required to support tumor growth. A unique form of VEGF is expressed by TEX that is biologically active yet possesses a weak affinity for the therapeutic monoclonal antibody bevacizumab. Hence, TEX have a means to circumvent the actions of the drug. *In vitro* tests also showed that sensitivity to bevacizumab was restored by preventing the actions of exosomal VEGF [25].

### 3. TEX act as immune checkpoints that suppress T cell responses.

FDA has approved several immune checkpoint inhibitor drugs for oncology; specifically, pembrolizumab (anti-PD-1 mAb; advanced melanoma, advanced non-small cell lung cancer, Hodgkin's lymphoma, head and neck cancer, microsatellite instability-high cancer, advanced gastric cancer, advanced cervical cancer, advanced urothelial bladder cancer, primary mediastinal B cell lymphoma), ipilimumab (anti-CTLA-4 mAb; advanced melanoma), nivolumab (anti-PD-1 mAb; metastatic colorectal cancer, advanced renal cell carcinoma, unresectable or metastatic melanoma, late-stage melanoma, hepatocellular carcinoma, advanced non-small cell lung cancer), and atezolimumab (anti-PD-L1 mAb; metastatic non-small cell lung cancer, locally advanced or metastatic urothelial carcinoma). Combinations of these drugs are also FDA approved for advanced or metastatic cancers.

Immune checkpoint inhibitors address the over-expression of the checkpoint receptors and ligands on tumor cells and immune cells in cancer patients. The most widely studied immune checkpoint inhibitors are directed against CTLA-4, PD-1, and anti-PD-L1, which are involved in pathways that inhibit T cell function (reviewed in [26]). The administration of antibodies against these receptors induces objective clinical responses in approximately 20-40% of patients with various types of cancer (reviewed in [27]). When using anti-CTLA-4 and anti-PD-1 monoclonal antibodies in combination, approximately half of patients exhibit resistance and disease progression [28]. In instances where combinations of checkpoint inhibitors have been administered, positive outcomes for patients may also occur at the expense of safety concerns, i.e. autoimmunity [29-31]. Thus, there exists a strong rationale for evaluating novel means for improving the safety and efficacy of immune checkpoint inhibitors.

TEX in the circulatory system of cancer patients will express immunosuppressive molecules, including the immune checkpoint molecules, PD-L1 and CTLA-4 (reviewed in [32, 33]). The levels of PD-L1 expressed by exosomes correlate with patients' disease activity and lymph node status in head and neck squamous cell carcinoma [34]. TEX expressing PD-L1 are actively involved in suppressing T cells, as demonstrated *in vitro*, which is an effect that is blocked by anti-PD-1 mAb [34, 35]. It is therefore conceivable that depletion of circulating exosomes could improve the efficacy of checkpoint inhibitor antibodies without introducing additional drug toxicities.

#### 4. Tumor-derived exosomes interfere with the activity of chemotherapeutic drugs.

There is evidence that TEX can interfere with the activity of certain chemotherapeutic drugs. TEX can confer drug resistance between chemotherapy-resistant breast cancer cells to chemosensitive cells through varied mechanisms [36]. Tumor cells can also reportedly export chemotherapeutic drugs in TEX, thereby reducing the intracellular drug concentrations and rendering the cells drug

resistant [37]. Blockade of exosome secretion from cancer cells using a non-specific agent (ketotifen; a mast cell stabilizer) sensitized the cells to the chemotherapeutic agent doxorubicin *in vitro* [38]. In another study, TEX biogenesis was inhibited using GW4869, a neutral sphingomyelinase inhibitor that prevents exosome formation in cells. This reduced the rate of proliferation of highly chemoresistant triple negative breast cancer cells [39]. These results provide more evidence that Hemopurifier<sup>®</sup> therapy would be anticipated to improve responsiveness to certain chemotherapy drugs. Table 1 lists other chemotherapeutic agents that are adversely affected by TEX.

### **Potential Implementation of Hemopurifier<sup>®</sup> Therapy for Exosome Depletion in Cancer.**

The Hemopurifier<sup>®</sup> is a candidate to be deployed as an adjunct to immunotherapy and chemotherapy treatments for patients with advanced or metastatic tumors. By reducing the presence of TEX in peripheral blood, Hemopurifier<sup>®</sup> therapy may augment the immune response against cancer and improve patients' responses to drug treatments. It would not be expected or even necessary for the Hemopurifier<sup>®</sup> to clear all TEX out of the circulatory system. By affording a reduction in the numbers of TEX, Hemopurifier<sup>®</sup> therapy might provide a window of opportunity for improved benefits of systemically delivered drugs. To address these possibilities, current efforts at Aethlon are being directed toward evaluating the capabilities of the Hemopurifier<sup>®</sup> for capturing TEX and defining the cancer-promoting activities of the Hemopurifier<sup>®</sup>-captured material.

**Table 1: Summary of FDA-Approved Oncology Drugs Reported Inhibited by Exosomes**

<b>Class of Drug</b>	<b>Name of Drug; Target</b>	<b>Oncology Indication for Use</b>	<b>References (www.pubmed.com)</b>	
Monoclonal antibodies	Bevacizumab (Avastin)	Advanced epithelial ovarian, fallopian tube or primary peritoneal cancer.	PMID: 28205552	
	Retuximab (Retuxin)	Non-Hodgkin's lymphoma, chronic lymphocytic leukemia.	PMID: 21873242	
	Trastuzumab (Herceptin)	HER2 overexpressing breast or metastatic stomach cancer.	PMID: 29209569 PMID: 21465472	
	Cetuximab (Erbix)	Colorectal cancer, head and neck cancer	PMID: 29160412	
Tyrosine kinase inhibitor	Erlotinib (Tarceva)	Non-small cell lung cancer, pancreatic cancer	PMID: 29961070	
	Imbrutinib (Imbruvica)	Chronic lymphocytic leukemia, small lymphocytic lymphoma, marginal cell lymphoma, mantle cell lymphoma	PMID: 28596280	
	Idelalisib (Zydelig)	Chronic lymphocytic leukemia, Non-Hodgkin's lymphoma	PMID: 28596280	
	Imatinib mesylate (Gleevec)	Chronic myelogenous leukemia	PMID: 29223442	
	Sunitinib (Sutent)	Renal cell sarcoma, gastrointestinal stromal tumors	PMID: 27117758	
	Sorafenib (Nexavar)	Renal cell sarcoma, liver cancer	PMID: 27716356	
	Gefitinib (Iressa)	Non-small cell lung cancer	PMID: 29928355	
	Bortezomib (Velcade)	Multiple myeloma	PMID: 24928860	
	Chemotherapy	Fludarabine (Fludara)	B cell chronic lymphocytic leukemia,	PMID: 28596280
		Venetoclax (Venclexta)	Chronic lymphocytic leukemia or small lymphocytic lymphoma	PMID: 28596280
Pemetrexed (Alimta)		Non-small cell lung cancer	PMID: 26095379	
Gemcitabine (Gemzar)		Breast cancer, ovarian cancer, non-small cell lung cancer, pancreatic cancer, and bladder cancer.	PMID: 28743280 PMID: 28152544 PMID: 28198398	
Docetaxel (Taxotere)		Breast cancer, non-small cell lung cancer, advanced stomach cancer, head and neck cancer, prostate cancer, others.	PMID: 25077924	
Doxorubicin (Adriamycin, Rubex)		Breast cancer, bladder cancer, Kaposi's sarcoma, lymphoma, and acute lymphocytic leukemia, gastric cancer, others.	PMID: 29244610	
Cisplatin (Platinol)		Testicular cancer, bladder cancer, ovarian cancer, osteogenic sarcoma, squamous cell carcinoma, malignant melanoma, oral cancer, anal cancer, others.	PMID: 29158318 PMID: 28910982	

## **About Aethlon Medical**

Aethlon Medical is focused on addressing unmet needs in global health. The Aethlon Hemopurifier® is a first-in-class therapeutic device designed for the rapid depletion of circulating viruses and cancer promoting exosomes. The United States Food and Drug Administration (FDA) has designated the Hemopurifier® as a Breakthrough Device related to the treatment of cancer and life-threatening viruses. TIME magazine named the Hemopurifier® a "Top 25 Invention" and one of the "Eleven Most Remarkable Advances in Healthcare."

*Certain of the statements within this report may be forward-looking and involve risks and uncertainties. Such forward-looking statements involve assumptions, known and unknown risks, uncertainties and other factors, which may cause the actual results, performance or achievements of Aethlon Medical to be materially different from any future results, performance, or achievements expressed or implied by the forward-looking statements. Such potential risks and uncertainties include, without limitation, the Company's ability to raise capital when needed, the Company's ability to complete the development of its planned products, the ability of the Company to obtain FDA and other regulatory approvals permitting the sale of its products, the Company's ability to manufacture its products and provide its services, the impact of government regulations, patent protection on the Company's proprietary technology, product liability exposure, uncertainty of market acceptance, competition, technological change, and other risk factors. In such instances, actual results could differ materially as a result of a variety of factors, including the risks associated with the effect of changing economic conditions and other risk factors detailed in the Company's Securities and Exchange Commission filings which can be accessed at [www.SEC.gov](http://www.SEC.gov).*

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