A Medical Device Strategy
To Inhibit HER2+ Breast Cancer Progression

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James A. Joyce
Chairman & CEO, Aethlon Medical, Inc
jj@aethlonmedical.com

Last week, we introduced HER2osome™ as a therapeutic strategy to maximize the ability of the immune system and established drug therapies to combat HER2+ breast cancer, which is characterized by aggressive growth and poor prognosis resulting from the over-expression of HER2 protein. HER2osome™ is a novel medical device, whose goal is to inhibit HER2+ breast cancer progression by reducing the circulatory presence of HER2 protein and breast cancer exosomes, which increasingly have become recognized as playing a pivotal role in the development and progression of breast cancer. Researchers have reported that breast cancer exosomes suppress the immune response, stimulate angiogenesis, contribute to the spread of metastasis, and inhibit the therapeutic benefit of Herceptin® (trastuzumab), a leading monoclonal antibody treatment against the HER2+ breast cancer. As an adjunct therapeutic candidate, HER2osome™ offers to fill an unmet medical need and enhance the benefit of Herceptin and standard of care chemotherapies without adding drug toxicity or interaction risks.

HER2some™ therapy has evolved from our Aethlon ADAPT™ system, which is an adaptable dialysis-like affinity platform technology that provides the foundation for an entirely new class of device-based therapeutics. Products developed from the Aethlon ADAPT™ system target the selective clearance of harmful agents from the entire blood volume within clinically relevant time frames and without the loss of essential blood components. The Aethlon ADAPT™ system overcomes the historic limitation of extracorporeal strategies that indiscriminately adsorb or remove particles solely by

molecule size. In function, the device platform allows the immobilization of single or multiple affinity agents in the outer-capillary space of plasma filtration membrane technology as a means to provide rapid real-time clearance of corresponding targets. In the case of HER2osome™, the immobilization of a HER2 antibody and an exosome targeted affinity agent provides a mechanism to clear both targets from the circulatory system of HER2+ breast cancer patients. Like all ADAPT™ derived therapies, HER2osome™ will operate dialysate free, will not require replacement fluids, and can be utilized on dialysis machines or CRRT systems already located in hospitals and clinics worldwide.

The multi-faceted pro-cancer mechanisms of tumor-secreted exosomes and disappointing response rates to HER2+ drug therapy provide a compelling rationale for the clinical advancement of HER2osome™. In this regard, the therapeutic objective of HER2osome™ will be to address three unmet medical needs.

1. To provide a synergistic device mechanism that works in concert with drug therapies to improve HER2 protein clearance.
2. To reduce drug resistance associated with exosome proliferation.
3. To eliminate immunosuppressive and pro-cancer exosomes from circulation.

The following sections entitled; HER2 Protein and Breast Cancer; The Implication of Breast Cancer Exosomes in Drug Resistance; and The Role of Exosomes in Breast Cancer Progression detail supporting scientific rationale for HER2osome™ therapy.

HER2 Protein and Breast Cancer

Breast cancer is the most common form of cancer in women, accounting for 20% of cancer deaths with approximately 180,000 women diagnosed annually in the United States (Merrill, R. M., and A. Sloan. 2011. Risk-adjusted female breast cancer incidence rates in the United States. *Cancer Epidemiol*.). Over-expression of the human epidermal growth factor receptor 2 (HER2; ErbB2) gene occurs in approximately 25% of breast cancers and has been linked to poor prognosis (Slamon, D. J., G. M. Clark, S. G. Wong,

W. J. Levin, A. Ullrich, and W. L. McGuire. 1987. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 235:177-182).

HER2 is a receptor tyrosine kinase, member of the EGF receptor family, which possesses proliferative and anti-apoptotic activities. The standard of treatment for women diagnosed with HER2+ breast cancer includes the humanized monoclonal antibody trastuzumab (marketed as Herceptin®) directed against the extracellular domain of HER2. Trastuzumab binding to HER2 mediates direct growth inhibition of tumor cells and induces antibody-dependent cell cytotoxicity (ADCC), a major anti-cancer mechanism by which natural killer (NK) cells lyse antibody-coated tumor cells (Nahta, R., D. Yu, M. C. Hung, G. N. Hortobagyi, and F. J. Esteva. 2006. Mechanisms of disease: understanding resistance to HER2-targeted therapy in human breast cancer. *Nat Clin Pract Oncol* 3:269-280).

In patients with metastatic breast cancer undergoing chemotherapy, treatment with trastuzumab augments overall response rates and increases median survival time by 25% (Baselga, J. 2001. Clinical trials of Herceptin® (trastuzumab). *Eur J Cancer* 37 Suppl 1:18-24). However, response rates to trastuzumab range from 12% to 34% with median duration of 9 months due to development of resistance. Despite co-treatment with other HER2 targeting therapies (e.g. the tyrosine kinase inhibitor lapatinib) and chemotherapy, patients with metastatic breast cancer experience a limited duration of benefit; therefore, novel treatment strategies that act synergistically or overcome drug resistance are urgently needed (Sachdev, J. C., and M. Jahanzeb. 2011. Blockade of the HER Family of Receptors in the Treatment of HER2-Positive Metastatic Breast Cancer. *Clin Breast Cancer*).

The Implication of Breast Cancer Exosomes in Drug Resistance

Although trastuzumab (Herceptin®) has significantly altered the standard of care for HER2 over-expressing breast cancer, resistance remains a significant obstacle, with only 30% responses achieved on monotherapy and average responses lasting 9 months (Nahta, R., D. Yu, M. C. Hung, G. N. Hortobagyi, and F. J. Esteva. 2006. Mechanisms of disease:

understanding resistance to HER2-targeted therapy in human breast cancer. *Nat Clin Pract Oncol* 3:269-280.). Tumor-secreted exosomes play a role in directly accelerating tumor progression through stimulation of angiogenesis and ECM remodeling, as well as indirectly by causing immune suppression (Taylor, D. D., and C. Gercel-Taylor. 2011. Exosomes/microvesicles: mediators of cancer-associated immunosuppressive microenvironments. *Semin Immunopathol*.). Exosomes have been shown to directly bind agents such as trastubuzumab and rituximab, potentially decreasing efficacy (Ciravolo, V., V. Huber, G. C. Ghedini, E. Venturelli, F. Bianchi, M. Campiglio, D. Morelli, A. Villa, P. D. Mina, S. Menard, P. Filipazzi, L. Rivoltini, E. Tagliabue, and S. M. Pupa. 2011. Potential role of HER2-overexpressing exosomes in countering Trastuzumab-based therapy. *J Cell Physiol*; and Aung, T., B. Chapuy, D. Vogel, D. Wenzel, M. Oppermann, M. Lahmann, T. Weinhage, K. Menck, T. Hupfeld, R. Koch, L. Trumper, and G. G. Wulf. 2011. Exosomal evasion of humoral immunotherapy in aggressive B-cell lymphoma modulated by ATP-binding cassette transporter A3. *Proc Natl Acad Sci U S A* 108:15336-15341).

The Role of Exosomes in Breast Cancer Progression

Exosomes are 30-100 nm microvesicles shed by many cell types, serving as "messengers" that mediate intercellular transport of proteins and genetic material or interact directly with target cells. Tumor-derived exosomes express tumor antigens and immune inhibitory molecules that mirror their tumor of origin and are produced in increasing quantities during tumor progression (Taylor, D. D., K. S. Lyons, and C. Gercel-Taylor. 2002. Shed membrane fragment-associated markers for endometrial and ovarian cancers. *Gynecol Oncol* 84:443-448). Tumor-derived exosomes bind and sequester tumor-reactive antibodies, thereby potentially inhibiting the ability of immune effector cells to mediate ADCC (Battke, C., R. Ruiss, U. Welsch, P. Wimberger, S. Lang, S. Jochum, and R. Zeidler. 2011. Tumour exosomes inhibit binding of tumour-reactive antibodies to tumour cells and reduce ADCC. *Cancer Immunol Immunother* 60:639-648). Exosomes secreted by breast cancer cells express HER2 and effectively sequester trastuzumab. Functional assays revealed that HER2+ exosomes suppress trastuzumab's

ability to inhibit tumor cell proliferation. Cancer exosomes release ECM remodeling enzymes that promote metastasis, and pro-angiogenic factors for tumor growth. Hence, breast cancer patients can benefit from therapeutic strategies that counter the systemic immune suppression and tumor growth-promoting activities of exosomes.

Conclusion

HER2osome™ therapy provides a novel strategy to improve treatment outcomes of HER2+ breast cancer through the improved clearance of HER2 protein and removal of circulating exosomes that contribute to cancer progression and drug resistance. The HER2osome™ mechanism of action offers to improve patient responsiveness to current and future drug therapies without adding drug toxicity or interaction risks.

About Aethlon Medical

The Aethlon Medical mission is to create innovative medical devices that address unmet medical needs in cancer, infectious disease, and other life-threatening conditions. Aethlon's ADAPT™ platform provides the technology foundation for a new class of therapeutics that target the selective removal of disease enabling particles from the entire circulatory system. The Aethlon ADAPT™ product pipeline includes the Hemopurifier®, a first-in-class medical device with broad-spectrum capabilities against exosomes that contribute to the progression of cancer and infectious viral pathogens such as HIV and Hepatitis C. For more information, please visit www.aethlonmedical.com.

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