

July 2, 2015



# **Macrophage Therapeutics Reports Data Demonstrating a Manocept™ Drug Conjugate Induces Apoptosis in CD206 Positive Kaposi's Sarcoma and Tumor Associated Macrophages**

- *Results demonstrated programmed cell death in KS tumor cells and anti-HIV activity -*
- *Reinforces therapeutic potential of targeting activated macrophages via the CD206 receptor -*

DUBLIN, Ohio--(BUSINESS WIRE)-- Macrophage Therapeutics, Inc., a subsidiary of Navidea Biopharmaceuticals, Inc. (NYSE MKT: NAVB), today announced that preclinical results in Kaposi's Sarcoma (KS) demonstrated that a cytotoxic drug, doxorubicin, linked to Manocept™ was targeted to and dose-dependently taken up in CD206+ KS tumor cells and tumor associated macrophages (TAMs) and caused apoptotic death of the KS tumor cells and TAMs. The results are being presented at the 18<sup>th</sup> International Workshop on Kaposi's Sarcoma Herpesvirus (KSHV) and Related Agents in Hollywood, Florida by Michael S. McGrath, M.D., Ph.D., Professor, Departments of Laboratory Medicine, Pathology, and Medicine at the University of California, San Francisco (UCSF). The study also shows that Cy3-Manocept and a Cy3-Manocept-doxorubicin conjugate quantitatively permitted the evaluation of tumor burden, tissue uptake of Manocept and tumor response to therapy in vitro and ex vivo, supporting the potential for the Manocept platform to be used not only diagnostically but as a precision targeted molecule to deliver payloads to tumor sites throughout the body.

"Advances in the treatment of cancer such as the recently approved PD1 and PDL1 inhibitors demonstrate the benefit of disrupting the communication signals between tumors and immune cells," said Frederick O. Cope, Ph.D., FACN, Chief Scientific Officer of Macrophage Therapeutics. "Based on the role tumor associated macrophages are thought to play in the progression of cancer, there exists a strong rationale that targeting CD206 represents a therapeutic pathway that is highly likely to exist across tumor types, and which reverses the immunosuppressive effects of cancer cells."

"In my experience, the impressive loss of TAMs demonstrated in these Manocept studies is unique and potentially extremely relevant clinically," said Dr. McGrath. "The results from data in primary human KS tissue, which provides the closest experimental model to human patients, showed not only selective killing of only CD206+ KS tumor cells and macrophages, but demonstrated through a biomarker that the Manocept conjugate induced programmed cell death in tumor cells and exhibited unprecedented anti-HIV activity which could eventually



address a broad unmet need for patients with Kaposi's sarcoma and other tumor types."

The preclinical studies included use of Human peripheral blood mononuclear cells (PBMCs) to measure the time course of Manocept uptake in CD206+ macrophages. Flow cytometry studies identifying CD206+ cells allowed quantitation of the amount of Cy3-Manocept bound to and internalized into the CD206+ cells and also verified Cy3-Manocept-doxorubicin internalization. Confocal microscopy was used with KS biopsies that were cultured overnight with Cy3-Manocept or Cy3-Manocept-doxorubicin and showed that all cells within the KS tissue including macrophages and spindle cells were CD206+ and incorporated the Cy3-Manocept with and without doxorubicin. In KS organ cultures, immunofluorescence assays for the detection of antibodies against latent nuclear antigen (IFA-LANA) and Annexin V were performed. Inhibition studies showed Cy3-Manocept-doxorubicin exhibited anti-HIV activity in HIV infected macrophage culture. In summary, the data presented include evidence that:

- KS tissue based cells take up Cy3-Manocept or Cy3-Manocept-doxorubicin into both KS tumor cells and TAMs.
- Manocept conjugate uptake is dose and time dependent in CD206+ macrophages
- Cy3-Manocept and Cy3-Manocept-doxorubicin bind to CD206 positive macrophages equivalently indicating that the linkage of a drug conjugate did not lessen the CD206 binding ability
- Manocept-doxorubicin killed CD206 expressing macrophages. After 24 hours, Cy3-Manocept-doxorubicin killed 70% of CD206 positive macrophages in tissue cultures. Doxorubicin alone showed no toxicity.
- KS organ culture treated with Manocept-doxorubicin resulted in the loss of macrophages and induced programmed tumor cell death and apoptosis in KS HHV8+ spindle cells, and showed anti-HIV activity in HIV infected macrophage cultures.

"We are very encouraged that our Manocept platform, with its unique ability to seek out activated macrophages, may selectively deliver a therapeutic that can kill tumor cells, tumor support cells and virus contained in the macrophage. This activity was seen with a therapeutic that without our delivery system would not be effective on the tumor, the TAM's or either of the viruses. This data suggests that targeting the activated macrophage is a viable strategy for attacking cancers that have TAM's. It is well established that depleting TAM's makes the tumor more susceptible to chemotherapy, radiation therapy and many of the new and emerging immune therapy drugs. In addition the effect of this agent with no known anti-viral properties on killing both HIV and HHV8 suggests a novel anti-viral strategy that will not require development of specific tailored drugs to a given virus," said Michael M. Goldberg, M.D., CEO of Macrophage Therapeutics and Director of Navidea. "We look forward to advancing development of our broad therapeutic platform through animal testing this summer in a number of solid tumor models as well as explore the potential of our technology in CNS diseases, viral diseases and animal models of auto-immune disease. Our goal is to seek strategic collaborations with industry leaders to enable rapid development. Finally, we will host an investor day at the end of the summer where we will review the accumulated data being generated."

Navidea and Macrophage Therapeutics plan a webcast to provide investors with a complete look at the data being presented at the International Workshop on Kaposi's Sarcoma Herpesvirus (KSHV) and Related Agents conference on July 7, 2015 at 1:00 pm EDT.



Webcast details will be available on the Navidea website.

### **About Manocept CD206 Targeting Platform for Therapeutics Development**

Manocept™ CD206 Targeting Platform is a proprietary mannose-containing, receptor-directed technology platform designed to engineer novel, synthetic receptor targeted imaging agents and therapeutics for cancer and other diseases. Manocept's unique structural and molecular properties enable the design of novel immuno-constructs that selectively target and bind to CD206 (mannose receptor) and other C-type Lectins found on activated, disease-associated macrophages and tumor associated macrophages (TAMs). The Manocept CD206 Targeting Platform provides a novel and valuable approach to the design of drug molecules targeting CD206 disease-associated macrophages for therapeutic purposes.

### **About Kaposi's Sarcoma**

Kaposi sarcoma (KS) is a cancer that develops from the cells that line lymph nodes or blood vessels. It usually appears as tumors on the skin or on mucosal surfaces such as inside the mouth, but tumors can also develop in other parts of the body, such as in the lymph nodes (bean-sized collections of immune cells throughout the body), the lungs, or digestive tract. The abnormal cells of KS form purple, red, or brown blotches or tumors on the skin. These affected areas are called lesions. The skin lesions of KS most often appear on the extremities, trunk and face. AIDS-related KS is the most common type of KS in the United States which develops in people who are infected with HIV, the virus that causes AIDS. KS can also develop in people whose immune systems have been suppressed after an organ transplant and is called transplant-related KS.<sup>1</sup>

### **About Navidea**

Navidea Biopharmaceuticals, Inc. (NYSE MKT: NAVB) is a biopharmaceutical company focused on the development and commercialization of precision diagnostics, therapeutics and radiopharmaceutical agents. Navidea is developing multiple precision-targeted products and platforms including Manocept™ and NAV4694 to help identify the sites and pathways of undetected disease and enable better diagnostic accuracy, clinical decision-making, targeted treatment and, ultimately, patient care. Lymphoseek® (technetium Tc 99m tilmanocept) injection, Navidea's first commercial product from the Manocept platform, was approved by the FDA in March 2013 and in Europe in November 2014. Navidea's strategy is to deliver superior growth and shareholder return by bringing to market novel radiopharmaceutical agents and therapeutics, and advancing the Company's pipeline through global partnering and commercialization efforts. For more information, please visit [www.navidea.com](http://www.navidea.com).

### **About Macrophage Therapeutics**

Macrophage Therapeutics, Inc., a newly created subsidiary of Navidea Biopharmaceuticals, Inc. (NAVB), is developing therapeutics using the patented Manocept immunotherapy platform licensed from Navidea to target over-active macrophages implicated in cancer, cardiovascular, central nervous system, autoimmune, antiviral, and skin diseases. Manocept specifically targets CD206, or the mannose receptor prevalent on over-active macrophages. The technology enables highly specific targeted delivery of active (either existing or yet to be developed) agents that can modulate the activity of over-active macrophages that have been



implicated in many diseases. Targeted delivery should significantly enhance a given compound's efficacy and safety.

*The Private Securities Litigation Reform Act of 1995 (the Act) provides a safe harbor for forward-looking statements made by or on behalf of the Company. Statements in this news release, which relate to other than strictly historical facts, such as statements about the Company's plans and strategies, expectations for future financial performance, new and existing products and technologies, anticipated clinical and regulatory pathways, and markets for the Company's products are forward-looking statements within the meaning of the Act. The words "believe," "expect," "anticipate," "estimate," "project," and similar expressions identify forward-looking statements that speak only as of the date hereof. Investors are cautioned that such statements involve risks and uncertainties that could cause actual results to differ materially from historical or anticipated results due to many factors including, but not limited to, the Company's continuing operating losses, uncertainty of market acceptance of its products, reliance on third party manufacturers, accumulated deficit, future capital needs, uncertainty of capital funding, dependence on limited product line and distribution channels, competition, limited marketing and manufacturing experience, risks of development of new products, regulatory risks and other risks detailed in the Company's most recent Annual Report on Form 10-K and other Securities and Exchange Commission filings. The Company undertakes no obligation to publicly update or revise any forward-looking statements.*

<sup>1</sup> American Cancer Society web accessed 22May2015.

<http://www.cancer.org/cancer/kaposisarcoma/detailedguide/kaposi-sarcoma-what-is-kaposi-sarcoma>

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