

## **PRO-PHARMACEUTICALS ANNOUNCES SIGNIFICANT ADVANCE IN DEFINING DAVANAT®'s MECHANISM OF ACTION BASED ON EXPERIMENTS DONE AT THE UNIVERSITY OF MINNESOTA AND THE LUDWIG INSTITUTE IN BRUSSELS, BELGIUM**

### **Studies Demonstrate DAVANAT® Binds To Galectin-1 and Galectin-3 Receptors That Control Angiogenesis and the Tumor's Ability To Evade the Immune System**

**Newton, MA – December 17, 2009 – Pro-Pharmaceuticals, Inc. (OTC: PRWP)**, a developer of Galectin-targeting, carbohydrate therapeutic compounds to treat cancer and fibrosis, today announced it has made significant advances in determining the mechanism of action for its lead drug DAVANAT®. Recent studies conducted by Dr. Kevin Mayo at the University of Minnesota demonstrate DAVANAT® binds to Galectin-1, a receptor that controls angiogenesis of cancer tumors. Angiogenesis, the ability to form new blood vessels, represents a critical step in tumor development through which the tumor establishes an independent blood supply, consequently facilitating tumor growth.

Galectin-3 can modulate immune response and, therefore, plays a key role in helping tumors to escape immune surveillance. Galectin-1 also regulates the supply of oxygen, nutrients, and host-derived regulators through angiogenesis. In the 1970's, it was discovered that tumor growth depends on angiogenesis; however, only within the last several years have a series of experiments implicated Galectin-1 as one of the major components in this process.

In the 1980's, it was discovered that tumor cells can be recognized by cytolytic T lymphocytes (CTL), an important component of the immune system, which recognizes antigens on tumor cells and kills them without harming normal tissues. Therapeutic vaccines, containing such tumor antigens, are expected to increase CTL responses, hence, increase the efficiency of its anti-cancer action. However, this effect is hampered by tumor resistance, gained in the process of the tumor development. This explains the poor effectiveness of most cancer vaccines.

As was shown by Dr. Pierre van der Bruggen and his team from the Ludwig Institute for Cancer Research in Brussels, Belgium, one of the possible resistance mechanisms involves Galectin-3, which inhibits T cell function. Specifically, Galectin-3 appears to diminish the mobility of functional T cell receptors (TCR) in such a way that CTL becomes non-functional (anergic). Importantly, the function of CTL is restored when anergic T cells are incubated with Galectin-3 inhibitors such as the disaccharide N-acetyllactosamine. However, this low-molecular disaccharide is rapidly eliminated by the human body. Therefore, the Ludwig Institute turned to Pro-Pharmaceuticals, whose lead polysaccharide DAVANAT® binds to Galectin-3. Researchers at the Ludwig Institute in Brussels found that DAVANAT® can be added in culture of anergic CTL and human tumor-infiltrating T lymphocytes and effectively restore the function of these T lymphocytes. DAVANAT® is under clinical investigation in several types of solid malignancies for its ability to inhibit Galectins and to improve the efficacy and reduce serious side effects, such as Mucositis, of chemotherapy drugs.

Studies indicate that Galectin-1 regulates the formation of the capillary vessels in a tumor, which is critical for tumors' continuous growth. Galectin-1 also provides a gateway for the dissemination of malignant cells. There is sufficient evidence that Galectin-1 is required for tumor angiogenesis and outgrowth of tumors and that decreasing the expression of Galectin-1 in tumor cells impairs angiogenesis. Galectin-1 is up-regulated in capillaries associated with carcinoma cells. Researchers suggest that Galectin-1 is a target for a novel treatment of a range of devastating cancers, and concluded that "Galectin-1 regulates tumor angiogenesis and is a target for angiostatic cancer therapy," (quote from "GALECTINS" Chapter 3, John Wiley & Sons, 2008).

In Chapter 6, from "GALECTINS", the role that Galectins play in the regulation of immunity is defined. A leading researcher in the field, Professor Fu-Tong Liu of the University of California, Davis School of Medicine, summarized the experimental results, "Galectin-1, through induction of apoptosis and suppression of the immune cell response, is immunosuppressive, and Galectin-1 secreted by tumor cells induces apoptosis of activated human immune cells targeting the cancer cells, which makes it a cancer tumor protector. This was shown in particular using Galectin-1 null mutant (gal-1-) mice, and confirmed by recent studies". The review concludes that current information suggests that inhibitors of some Galectins also may be useful for treatment of other diseases.

"We believe that these studies explain our encouraging results in the Phase I and Phase II human trials," said Anatole Klyosov, Ph.D. Chief Scientist, Pro-Pharmaceuticals. "We now have additional, convincing data from the recently published Nuclear Magnetic Resonance (NMR) studies which link DAVANAT® as an anti-angiogenic agent via its interaction with Galectin-1. This

interaction of DAVANAT® with Galectin-1 was described in detail in the June 2009 issue of the journal "GLYCOBIOLOGY".

"The experiment data and human clinical trial results were found to be complementary. DAVANAT® prevented side effects and increased longevity of human patients treated with 5-FU, a chemotherapy drug known for its severe side effects. DAVANAT® effectively binds to Galectin-1, and Galectin-1 is well established as a receptor responsible for the angiogenesis of cancer tumors. These results suggest that DAVANAT® is an anti-angiogenic agent. In the course of the research, it also was found that DAVANAT® binds to a site on Galectin-1, which, we believe, is involved in the angiogenic functions of Galectin-1. Therefore, DAVANAT® is indicated as an inhibitor which suppresses the action of Galectin-1 and its role in angiostatic cancer pathways," stated Dr. Klyosov.

DAVANAT® has proven to be a non-toxic and effective drug when co-administered with chemotherapy treatments. Results from Phase I and Phase II clinical trials indicate that co-administration of DAVANAT®, with the chemotherapeutic agent 5-FU, increased patient survival, increased the length of time 5-FU circulated in the patients' blood, while reducing the number and severity of chemotherapy side effects. Pre-clinical data indicated that co-administration of DAVANAT® with 5-FU increased the amount of 5-FU in the tumor by more than 50%. Based on these results, the Company is designing a Phase III study for the treatment of late stage colorectal cancer patients.

### **About DAVANAT®**

DAVANAT®, the Company's lead product candidate, is a carbohydrate polymer that targets Galectin receptors on cancer cells. Current research indicates that Galectins affect cell development and play important roles in cancer, including tumor cell survival, angiogenesis and tumor metastasis. To date, DAVANAT® has been administered to approximately 100 cancer patients. Data from a Phase II trial for end-stage colorectal cancer patients showed that DAVANAT® in combination with 5-FU extended median survival to 6.7 months with significantly reduced side effects, as compared to 4.6 months for best standard of care as determined by the patients' physicians. These clinical trials also showed that patients experienced fewer serious adverse side effects of the chemotherapy and required less hospitalization.

### **Pro-Pharmaceuticals, Inc.**

Pro-Pharmaceuticals, OTCBB: PRWP, is engaged in the discovery, development and commercialization of carbohydrate therapeutics that target galectin receptors for advanced treatment of cancer and fibrosis. Initially, the product pipeline is focused on increasing the efficacy and decreasing the toxicity of chemotherapy drugs. The Company is headquartered in Newton, Mass. Additional information is available at [www.pro-pharmaceuticals.com](http://www.pro-pharmaceuticals.com).

**FORWARD LOOKING STATEMENTS:** Any statements in this news release about future expectations, plans and prospects for the Company, including without limitation statements containing the words "believes," "anticipates," "plans," "expects," and similar expressions, constitute forward-looking statements as defined in the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These forward-looking statements are based on management's current expectations and are subject to a number of factors and uncertainties, which could cause actual results to differ materially from those described in such statements. We caution investors that actual results or business conditions may differ materially from those projected or suggested in forward-looking statements as a result of changing conditions. Readers should not place undue reliance on forward-looking statements. The forward-looking statements represent the Company's views as of the date of this news release and should not be relied upon to represent the Company's views as of a subsequent date. While the Company anticipates that subsequent events may cause the Company's views to change, the Company disclaims any obligation to update such forward-looking statements.

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