

## Paloma Pharmaceuticals Presents at the 101<sup>st</sup> Meeting of the American Association of Cancer Research

-- Presentation highlights Palomid 529 along with radiation increasing survival in an orthotopic (cancer directly implanted into brain) mouse brain cancer model--

Jamaica Plain, MA, Apr. 19, 2010 -- Paloma Pharmaceuticals, Inc. announced it will give a presentation today at the annual meeting of American Association of Cancer Research (AACR), "Palomid 529, a PI3K/Akt/mTOR dual TORC1/2 inhibitor, is a radiosensitizer with effect in both subcutaneous and orthotopic U251 glioblastoma tumor xenograft models" by Dr. Stephen S. Yoo, Ph.D. of the Molecular Radiation Therapeutics Branch, Radiation Research Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute/National Institutes of Health, Rockville, MD.

Glioblastoma (GBM) is the most common malignant brain tumor of adults and is one of the most lethal cancers. Radiotherapy and temozolomide followed by temozolomide alone is the standard of care for nearly all patients with newly diagnosed glioblastoma. However, the prognosis for GBM patients remains dismal with about one year survival after diagnosis. Due to a set of defined molecular lesions and signal transduction pathway disruptions, GBMs are well suited for molecular targeted therapy. Signaling through the PI3Ks is frequently activated in GBMs due to gain-of function mutations in PIK3CA or loss of PTEN. Palomid 529 (P529) is a dibenzochomene small molecule drug with a molecular weight of 406 Daltons, a first-in-class dual TORC1 and TORC2 inhibitor of the PI3K/Akt/mTOR pathway. P529 causes the dissociation of both the TORC1 and TORC2 complexes. P529 inhibits pro-angiogenic cytokines such as VEGF, IGF and bFGF along with anti-proliferative activity against tumor cells *in vitro*. P529 has previously shown activity in a variety of subcutaneous (ectopic) xenografts. The objective of the study here was to investigate whether P529 has activity as a radiosensitizer in murine models of glioblastoma.

"Palomid 529 delayed the growth of U251 tumors with irradiation compared to irradiation alone, indicating a radiation-enhancing efficacy of Palomid 529. Treatment of xenografted U251 tumors in mice with Palomid 529 inhibited phosphorylation of S6RP, suggesting inhibition of PI3K activation in U251 along with good radiation enhancing efficacy. Survival of mice intracranially implanted with U251 was prolonged when treated with Palomid 529 plus irradiation compared to irradiation with statistical significance," said Dr. Yoo.

"Dr. Yoo's work has great implications for P529 as a successful therapeutic agent in human cancer patients. His work shows efficacy in a clinically relevant model of cancer where cancer cells are directly implanting into the brain of animals and showing significant survival compared to control animals", said Dr. Sherris.

About the PI3K/Akt/mTOR Pathway

The PI3K/Akt/mTOR pathway has been implicated in a wide variety of biological responses and is considered a major therapeutic target in cancer. Activation of this signaling pathway, via direct or indirect mutagenic events, is common in many types of human cancer resulting in deregulation of PI3K/Akt/mTOR pathway in cancer. Thus, agents capable of inhibiting the PI3K/Akt/mTOR pathway are attractive targets for therapeutic intervention in cancer. Central within the signalling pathway are two distinct protein complexes, one of which regulates growth through the signal transduction protein S6K, TORC1, and the other that regulates cell survival through Akt, TORC2. These complexes define both rapamycin-sensitive and insensitive branches of the PI3K/Akt/mTOR pathway. Inhibition of the TORC2 pathway suppresses the formation of tumors driven by the loss of the PTEN tumor suppressor, a gene which when lost contributes to carcinogenicity. Inhibitors of TORC2 may then have beneficial effects as anti-cancer agents without toxicity to normal tissues since loss of TORC2 through genetic alteration does not appear to affect normal tissue. TORC1 antagonists as rapamycin and other such rapalogs have shown activity in both animal models of cancer and in human clinical trials. As inhibition of both TORC1 and TORC2 should result in more complete inhibition of PI3K/Akt/mTOR signaling up-regulated in cancer, dual inhibitors are of active interest for pharmaceutical development.

#### About Paloma Pharmaceuticals

Paloma Pharmaceuticals, Inc. is an early stage drug development company utilizing its PI3K/Akt/mTOR inhibitors focusing on cancer, ocular diseases (macular degeneration and diabetic retinopathy), CNS (epilepsy, Parkinson's disease, Alzheimer's disease), fibrotic diseases (pulmonary and renal fibrosis), antiviral (HIV, HCV) and skin diseases (psoriasis and atopic dermatitis). Paloma owns the intellectual property relating to a library of novel, proprietary, small molecule drugs created through an integrated design platform incorporating proprietary, customized and industry standard computational tools that has therapeutic potential for the treatment of the foregoing diseases.

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