

## **Paloma Pharmaceuticals Presents at the American Association for Cancer Research**

**-- Presentations highlight Palomid 529 as an anti-angiogenic, anti-tumor Akt/mTOR inhibitor --**

Jamaica Plain, MA, Apr 15, 2008 /PRNewswire/ --Paloma Pharmaceuticals, Inc. today announced it has presented three presentations at the 2008 annual meeting of the American Association for Cancer Research describing cancer drug Palomid 529 (P529).

P529 is a non-steroidal, synthetic, small molecule dual acting anti-angiogenic and direct anti-tumor agent created through computational design, synthetic and medicinal chemistry, the result of three generations of Palomid design work. Palomid's broad activity as an anti-angiogenic agent and anti-tumor agent is shown to reside in its ability to target and inhibit the PI3K/Akt/mTOR signal transduction pathway as a TORC1/TORC2 inhibitor.

The first of the three presentations, "Palomid 529, a Dual Acting Anti-angiogenic and Direct Anti-tumor Agent Affecting the PI3K/Akt/mTor Pathway", was be given by Dr. David Sherris, President and CEO of Paloma Pharmaceuticals. The second presentation, "Palomid 529 (P529) inhibits tumor angiogenesis and selectively inhibits the Akt but not MAPK signaling pathways", was given by the laboratory of Dr. Laura E. Benjamin of the Department of Pathology and Center for Vascular Biology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA. The last presentation, "Enhancement of radiotherapy in prostate cancer by the dibenzo[c]chrom-6-one derivative P529" was given by the laboratory of Dr. Alfonso Calvo of the Division of Oncology, Center for Applied Medical Research, University of Navarra, Pamplona, Spain.

"mTOR and the protein complexes mTORC1 and mTORC2 are excellent targets for cancer therapy because they provide important signaling links to tumor and stromal pathways dysregulated in many cancers," said Dr. Benjamin whose work has helped to understand the mechanism of action of P529.

"We have shown in a series of prostate cancer models that P529 enhances anti-tumor activity caused by radiation therapy. If P529 allows the radio-oncologist to use lower levels of radiation due to the radio-sensitizing effect of P529, this could translate into a reduction of side effects seen by radiation treatment including urinary tract dysfunction, impotence and an increase in rectal cancer," said Dr. Calvo.

"P529 is a potent inhibitor of angiogenesis and tumor growth", said Dr. Sherris. "Taken together, these presentations describe P529 as a broad acting anti-angiogenic and anti-tumor agent. Since tumor cells are known to release a large number of pro-angiogenic factors initiating tumor angiogenesis, to effectively inhibit angiogenesis one needs to inhibit not just one but if possible all of the factors. Single agent anti-cytokine therapy, such as anti-VEGF, has shown efficacy in the clinic but is limited by its ability to only target one pro-angiogenic factor. P529 has the ability to inhibit a range of disparate pro-angiogenic cytokines by

inhibiting the pro-angiogenic factor's ability to transmit its signal through the cell as well as inhibiting the synthesis of pro-angiogenic factors through inhibition of HIF-1 $\alpha$ , a known regulator of the synthesis of pro-angiogenic cytokines by tumor cells. As P529 is shown to inhibit all tumor cell lines of the National Cancer Institute's 60 cell screen, and is shown here to inhibit multiple human tumor mouse xenograft models, P529 displays broad tumor cell activity. Furthermore, we show that P529 augments radiation therapy both in the test tube and in animal models. Such a response may result in lowering the dose of radiation used in radiotherapy thus reducing radiation side effects or perhaps potentiate radiotherapy efficacy. We believe all of these results are due to P529's ability to inhibit the PI3K/Akt/mTOR pathway through TORC1/TORC2 inhibition."

### About Angiogenesis

Cancer, less than a few millimeters in size, utilizes nearby normal vessels to provide nutrients and oxygen. However, above this critical size, cancers utilize angiogenesis to create additional vascular support. Normally, angiogenesis is kept in check by the body naturally creating angiogenic inhibitors to counteract angiogenic factors. However, the cancer cell changes this balance by producing angiogenic growth factors in excess of the angiogenic inhibitors, thus favoring blood vessel growth. Cancer cell induced angiogenesis utilizes common pathways of angiogenesis observed during normal vessel growth. Angiogenic factors pass from the cancer cell to the normal endothelium, binding the endothelial cell, activating it and inducing endothelial signaling events leading to endothelial cell proliferation. Endothelial tubes begin to form, homing in toward the tumor with the formation of capillary loops. Capillaries then undergo a maturation process to stabilize loop structure, but the resulting vessels formed tend to be leaky, structurally aberrant, inefficient and fragile. When formed aberrantly, capillaries induce or promote a variety of pathological conditions in addition to cancer. For example, aberrant neovasculature is found in ocular diseases (such as macular degeneration, diabetic retinopathy and retinopathy of prematurity), arthritis and psoriasis. Under normal conditions, angiogenesis occurs during such conditions as wound healing, repair after myocardial infarction and the female reproductive cycle (generating endometrium forming the corpus luteum and during pregnancy to create the placenta).

### About Paloma Pharmaceuticals

Paloma Pharmaceuticals, Inc. is an early stage drug development company focusing on pathologies with a vascular component including cancer, ocular diseases (macular degeneration and diabetic retinopathy), arthritis, fibrotic diseases (pulmonary fibrosis) endometriosis, osteoporosis 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.

SOURCE: Paloma Pharmaceuticals, Inc.

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