Cyclacel & Dartmouth researchers report novel mechanism of action for seliciclib at AACR

- Certain lung cancer cells overexpress Cyclin E and are targeted by seliciclib -

Denver, CO – April 21, 2009 – Cyclacel Pharmaceuticals, Inc. (NASDAQ: CYCC, NASDAQ: CYCCP) announced that scientists from Dartmouth Medical School and Cyclacel reported today preclinical evidence that certain lung cancer cells overexpress Cyclin E and are targeted by seliciclib, Cyclacel's CDK (cyclin dependent kinase) inhibitor which is currently in Phase 2 development for lung cancer. The data was presented at "Biological Mechanisms and Molecular Markers of Prevention," a symposium at the American Association of Cancer Research (AACR) Annual Meeting taking place here.

The report also suggests a novel mechanism of action for seliciclib resulting from its targeting of the CDK2/cyclin E complex: induction of anaphase catastrophe, a defect during cell division that results in apoptosis or death of cancer cells. Pending successful clinical and regulatory outcomes, lung cancers found to overexpress cyclin E may prove particularly vulnerable to molecularly targeted treatment with CDK inhibitors such as seliciclib.

Separately, Cyclacel scientists reported the discovery of novel derivatives of seliciclib with improved potency and pharmacologic properties. The novel CDK inhibitors, currently in IND-directed development, were presented at "Mechanisms of Drugs Targeting Cell Cycle Controls," a symposium at the AACR Annual Meeting.

Cyclacel scientists also reported synergistic anticancer effects on Acute Myeloid Leukemia cell lines of combinations of Cyclacel's sapacitabine with three approved drugs inhibiting either HDAC or methyltransferase enzymes. The data were presented at "Agents Targeting Histone Deacetylases and DNA Methyltransferase" a poster session at the AACR Annual Meeting.

Details of the presentations referring to specific Cyclacel programs are as follows:

Sapacitabine

Simon R. Green, Ruth H. MacKay, David E. MacCallum, Jean Melville, Sheelagh Frame, Ian N. Fleming. Cyclacel, Ltd., Dundee, United Kingdom. "Synergistic interactions between sapacitabine (CYC682) and inhibitors of either histone deacetylase or methyltransferase in Acute Myeloid Leukemia cell lines"
In: *Proceedings of the 100th Annual Meeting of the American Association for Cancer Research*; 2009 Apr 18-22; Denver, CO. Philadelphia (PA): AACR; 2009. Abstract nr. 4552.

The combination of sapacitabine's primary metabolite CNDAC and the HDAC inhibitor vorinostat was evaluated in acute myeloid leukemia (AML) cells *in vitro* as was the combination of CNDAC with the DNA methyltransferase inhibitors azacitidine or decitabine. All combinations resulted in a synergistic induction in apoptosis leading to increased cellular cytotoxicity in the combinations compared to single agent treatments. The vorinostat-sapacitabine combination was explored *in vivo* in a MV4-11 AML model and demonstrated significantly improved efficacy, including tumor regression, at doses that had limited single agent activity. At the doses evaluated there was no increased toxicity in the combination groups compared to single agent treatment. An increase in apoptotic markers from tumor samples taken during the first week of dosing was observed in the combination groups compared to single agent treatment.

Seliciclib

Fabrizio Galimberti, Sarah Thompson, Xi Liu, Simon R. Green, Vincent Memoli, Duane Compton, Ethan Dmitrovsky. Dartmouth Medical School, Hanover, NH, Cyclacel Ltd., Dundee, United Kingdom. "Targeting the cyclin E-Cdk2 complex represses lung cancer growth by triggering apoptosis and anaphase catastrophe", In: *Proceedings of the 100th Annual Meeting of the American Association for Cancer Research*; 2009 Apr 18-22; Denver, CO. Philadelphia (PA): AACR; 2009. Abstract nr. 4784.

Overexpression of cyclin E leads to tumor growth *in vivo*. This study explored the consequences of targeting the CDK2/cyclin E complex in lung cancer cell lines. Targeting CDK2/cyclin E either genetically with small interference RNA or pharmacologically with seliciclib resulted in the inhibition of cellular proliferation of cells that appear to be "addicted" to high levels of CDK2/cyclin E. Inhibition of CDK2/cyclin E-driven tumors was observed *in vivo* after seliciclib treatment which also reduced the levels of proliferation markers in established tumors and the number of lung lesions in animals following intravenous injection of lung cancer cells overexpressing cyclin E two weeks prior to the start of seliciclib treatment. Molecular analysis in cell lines overexpressing cyclin E indicated that seliciclib treatment increased mitotic defects leading to anaphase catastrophe and

apoptosis. These effects were enhanced by combination treatment of seliciclib with the taxanes paclitaxel or docetaxel suggesting that such combinations could be molecularly targeted in the clinic in patients with lung cancers found to overexpress cyclin E.

Simon R. Green, Sheelagh Frame, Sian Anderson, Morag Hogben, David E. MacCallum, Gavin Wood, Stuart Wilson, Paul Workman, Edward McDonald, Daniella Zheleva. Cyclacel, Ltd., Dundee, United Kingdom, The Institute of Cancer Research, London, United Kingdom. “Derivatives of seliciclib with improved potency both in vitro and in vivo as novel cyclin dependent kinase (CDK) inhibitors”, In: *Proceedings of the 100th Annual Meeting of the American Association for Cancer Research*; 2009 Apr 18-22; Denver, CO. Philadelphia (PA): AACR; 2009. Abstract nr. 3863.

A library of compounds was synthesized to identify derivatives of seliciclib with increased potency and improved pharmaceutical properties. These molecules have a similar target inhibitory profile to seliciclib (CDK2/cyclin E, CDK2/cyclin A and CDK9) but have enhanced activity against their target kinases. This improved potency is reflected in their cellular cytotoxicity properties where the compounds demonstrated increased activity up to 40-fold compared to seliciclib. Detailed cellular analysis demonstrated that the molecules maintain a very similar mechanism of action to seliciclib. Metabolism studies indicated that both primary and secondary metabolism of the follow-on compounds has been improved over that of seliciclib. In xenograft models with a once a day oral dosing regimen these compounds exhibited significant anticancer activity achieving up to 90% tumor growth inhibition.

The abstracts are available online at www.aacr.org.

About Cyclacel Pharmaceuticals, Inc.

Cyclacel is a biopharmaceutical company dedicated to the discovery, development and commercialization of novel, mechanism-targeted drugs to treat human cancers and other serious disorders. Three orally-available Cyclacel drugs are in clinical development. Sapacitabine (CYC682), a cell cycle modulating nucleoside analog, is in Phase 2 studies for the treatment of acute myeloid leukemia in the elderly, myelodysplastic syndromes, cutaneous T-cell lymphoma and lung cancer. Seliciclib (CYC202 or R-roscovitine), a CDK (cyclin dependent kinase) inhibitor, is in Phase 2 for the treatment of lung cancer and nasopharyngeal cancer. CYC116, an Aurora kinase and VEGFR2 inhibitor, is in Phase 1 in patients with solid tumors. Cyclacel’s ALIGN Pharmaceuticals subsidiary markets directly in the U.S. Xclair® Cream for radiation dermatitis, Numoisyn® Liquid and Numoisyn® Lozenges for xerostomia. Cyclacel’s strategy is to build a diversified biopharmaceutical business focused in hematology, oncology and other therapeutic areas based on a portfolio of commercial products and a development pipeline of novel drug candidates.

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Risk Factors

This news release contains certain forward-looking statements that involve risks and uncertainties that could cause actual results to be materially different from historical results or from any future results expressed or implied by such forward-looking statements. Such forward-looking statements include statements regarding, among other things, the efficacy, safety, and intended utilization of Cyclacel's product candidates, the conduct and results of future clinical trials, plans regarding regulatory filings, future research and clinical trials and plans regarding partnering activities. Factors that may cause actual results to differ materially include the risk that product candidates that appeared promising in early research and clinical trials do not demonstrate safety and/or efficacy in larger-scale or later clinical trials, the risk that Cyclacel will not obtain approval to market its products, the risks associated with reliance on outside financing to meet capital requirements, and the risks associated with reliance on collaborative partners for further clinical trials, development and commercialization of product candidates. You are urged to consider statements that include the words "may," "will," "would," "could," "should," "believes," "estimates," "projects," "potential," "expects," "plans," "anticipates," "intends," "continues," "forecast," "designed," "goal," or the negative of those words or other comparable words to be uncertain and forward-looking. These factors and others are more fully discussed under "Risk Factors" in the Annual Report on Form 10-K for the year ended December 31, 2008, as supplemented by the interim quarterly reports, filed with the SEC.

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