



Two Novel Lilly Molecules Target Genetic Mutations That Can Lead to Cancer

Research on Malfunctioning JAK2 and Hedgehog Pathways Focus of AACR Presentations

ORLANDO, Fla., April 4, 2011 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) announced results today from two preclinical studies of molecules that target genetic mutations and disable specific signaling pathways that can lead to cancer. The studies evaluated two unique molecules — a JAK2 inhibitor and a Hedgehog inhibitor — with results presented during the American Association for Cancer Research (AACR) 102nd Annual Meeting in Orlando, Fla.

Signaling pathways within cells regulate genes that underlie crucial biological processes including cell division, embryonic development and immunity. When these networks of proteins misfire, many types of cancer can result. At AACR, data from Lilly showed how these pipeline molecules target out-of-control signaling pathways.

"Lilly is focused on developing therapies tailored for an individual patient's needs — such as a cancer treatment that targets a specific genetic mutation," said Jonathan M. Yingling, Ph.D., vice president of oncology research at Lilly. "We believe beginning this evaluation early in the preclinical stage, as we have with these two studies, may lead to more focused, efficient clinical trials and, in turn, speed drug discovery."

LY2784544: JAK2 Inhibitor (Abstract # 2820)

Research presented at AACR's New Small Molecule Therapeutics mini-symposium suggested that the investigational compound LY2784544, a small-molecule JAK2 inhibitor, blocks a specific, difficult-to-isolate, signaling pathway that can lead to the development of cancer cells.

Specifically, Lilly researchers chose to study inflammatory breast cancer (IBC) cells because these cells support their own survival by secreting chemicals known as growth factors, which allow them to break away from the primary tumor, multiply and then cluster together into tumor spheres — ultimately metastasizing, or spreading.

Lilly scientists focused on a growth factor called IL-6, which latches onto receptors on the surface of cells and triggers the IL-6—JAK—STAT3 signaling pathway, promoting formation of the deadly IBC cell clusters by activating the STAT3 protein, which then turns on the genes that encourage IBC cells to stick together.

Researchers hypothesized that short-circuiting the IL-6—JAK—STAT3 pathway could prevent the formation of tumor cell clusters. The scientists first cultured the tumor spheres in medium containing IL-6. As expected, IL-6 activated STAT3, the cells proliferated, and the tumor spheres grew. Furthermore, expression of IL-6 by the spheres themselves increased by 50-fold; and secretion of intracellularly produced IL-6 activated STAT3, and prevented cell death in the tumor spheres.

But when Lilly's JAK2 inhibitor was added to the medium containing the tumor spheres, the scientists found that it inhibited STAT3 activation in a dose-dependent manner and that blocking this signaling pathway induced cell death in the tumor spheres. The IL-6—JAK—STAT3 pathway may serve as a "molecular signature" of IBC and as a potential therapeutic target.

Lilly's JAK2 inhibitor is currently being evaluated in Phase I clinical trials for the treatment of myeloproliferative neoplasms, or diseases of the blood and bone marrow, called polycythemia vera, essential thrombocythemia and myelofibrosis.

LY2940680: Halting Abnormal Signaling via the Hedgehog Pathway (Abstract # 2819)

Lilly scientists have identified an orally administered anti-cancer agent, LY2940680, which, in preclinical studies, disrupted the abnormal signaling of a key regulator of embryonic cell development. Data was also presented at AACR's New Small Molecule Therapeutics mini-symposium.

This novel molecule has been shown to affect a cancer cell signaling pathway initiated by the Hedgehog (Hh) protein, which is essential for regulating normal cell differentiation and proliferation. Abnormal Hh signaling has been implicated in several types of cancer, including brain, lung, breast, prostate and skin cancers. Abnormal Hh pathway activation can result from genetic mutations in the pathway's protein components.

One such protein component, known as Smoothed (Smo), is a key regulator of the Hh signaling pathway and is seen as a potential target for therapies aimed at treating cancer by halting abnormal Hh signaling.

Lilly scientists have identified that Lilly's Hedgehog inhibitor is a small molecule antagonist of Smo, binding to it and inhibiting Hh signaling in a human medulloblastoma tumor cell. (Medulloblastoma is the most commonly diagnosed form of brain tumor in children, but is rare in adults.(1)) In addition, when the compound was orally administered to transgenic mice that spontaneously develop medulloblastoma, it improved animal survival.

Lilly's Hedgehog inhibitor is currently being studied in Phase I clinical trials for solid tumors.

About Preclinical Data

The compounds discussed in this press release are investigational. Their safety and efficacy in humans have not been established.

About Lilly Oncology

For more than four decades, Lilly Oncology, a division of Eli Lilly and Company, has been dedicated to delivering innovative solutions that improve the care of people living with cancer. Because no two cancer patients are alike, Lilly Oncology is committed to developing novel treatment approaches. To learn more about Lilly's commitment to cancer, please visit www.LillyOncology.com.

About Eli Lilly and Company

Lilly, a leading innovation-driven corporation, is developing a growing portfolio of pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers — through medicines and information — for some of the world's most urgent medical needs.

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This press release contains forward-looking statements about the potential of LY2784544 and LY2940680 and reflects Lilly's current beliefs. However, as with any pharmaceutical compound, there are substantial risks and uncertainties in the process of development and commercialization. There is no guarantee that either compound will be approved by the relevant regulatory authorities or prove to be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's filings with the United States Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

(1) Brandes AA, Ermani M, Amista P, et al.: The treatment of adults with medulloblastoma: a prospective study. Int J Radiat Oncol Biol Phys 57 (3): 755-61, 2003.

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