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Luxeptinib Preclinical Data Extend Potential Applications from Oncology to Inflammation

Three Recent Peer-reviewed Journal Articles Reflect Distinctive Properties of Luxeptinib

SAN DIEGO and TORONTO, May 02, 2022 (GLOBE NEWSWIRE) -- Aptose Biosciences Inc. (“Aptose” or the “Company”) (NASDAQ: APTO, TSX: APS), a clinical-stage precision oncology company developing highly differentiated oral kinase inhibitors to treat hematologic malignancies, today highlighted recent publications of preclinical data for luxeptinib (CG-806) in three peer-reviewed scientific journals. Luxeptinib, Aptose’s oral, dual lymphoid and myeloid kinome inhibitor, is an investigational drug currently in two Phase 1 a/b trials: one in patients with relapsed or refractory B cell malignancies, and separately in patients with relapsed or refractory acute myeloid leukemias (AML) or high-risk myelodysplastic syndromes (MDS).

Recent Journal Articles:

Luxeptinib disables NLRP3 inflammasome-mediated IL-1β release and pathways required for secretion of inflammatory cytokines IL-6 and TNFα *Biochemical Pharmacology (2022)195 114861* (link)

Luxeptinib is an orally bioavailable kinase inhibitor with potency against select kinases including BTK. Aberrant activation of inflammasomes act as drivers of pathological complications observed during autoimmune and inflammatory disorders, metabolic syndromes, and cancer; and inhibiting the inflammasome-induced activation of pro-inflammatory cytokines has shown beneficial effects in human disease models. BTK and certain other kinases serve as an integral components or influence functions of the NLRP3 inflammasome complex. The aim of this study was to determine if luxeptinib interferes with the release of IL-1β, IL-6 and TNFα from THP-1 monocytes and bone marrow-derived macrophages following endotoxin exposure and priming of the NLRP3 inflammasome.

Key findings:

- Luxeptinib inhibits NLRP3 inflammasome function in THP-1 monocytes and bone marrow-derived macrophages.
- Mechanistically, luxeptinib prevents the release of cleaved IL-1β from THP-1 cells by inhibiting the ability of the NLRP3 inflammasome to proteolytically cleave caspase-1 to its active form.
- Luxeptinib does not impede the assembly of the NLRP3-ASC complex but does potently inhibit three kinases phosphorylated in response to endotoxin.

Phosphorylation and nuclear translocation of transcription factor NF-κBp65 was inhibited by luxeptinib.
- Luxeptinib also inhibits the release of TNFα and IL-6 in response to activation of the TLR pathway without affecting the TLR/IRAK/MyD88 proteins.
- These studies provide novel insights into the mechanisms by which luxeptinib interferes with the NLRP3 inflammasome and endotoxin-induced inflammatory signaling pathways, along with its protective effects against inflammation-induced toxicity in murine models.
- The ability of luxeptinib to inhibit inflammatory pathways at concentrations which are well-tolerated in patients makes it a potential clinical candidate for the treatment of inflammatory diseases and inflammation-associated resistance in cancer.

Dual BTK/SYK inhibition with CG-806 (luxeptinib) disrupts B-cell receptor and Bcl-2 signaling networks in mantle cell lymphoma *Cell Death & Disease - Nature (2022)13:246* (link)

Small molecules BTK inhibitors like ibrutinib are approved for the treatment of mantle cell lymphoma, or MCL, a rare subtype of non-Hodgkin's lymphoma (NHL). Nevertheless, median duration of response is less than two years, and MCL patients who develop therapeutic resistance have poor outcomes. Resistance to BTK inhibitors is not clearly understood and a number of alternative mechanisms have been implicated. Luxeptinib, previously known as CG-806, inhibits LYN, SYK, and BTK activation, potently inhibiting both wildtype and C481S mutant BTK, and is expected to have activity in settings where resistance to BTK inhibitors is driven by these mutations. In a Phase 1 trial in patient with chronic lymphocytic leukemia (CLL) and NHL, treatment with luxeptinib resulted in decreased phosphorylation of SYK and BTK in the circulating malignant cells within eight hours of administration. This current pre-clinical study investigates mechanism and efficacy of luxeptinib in MCL.

Key findings:

- Luxeptinib induced apoptosis in ibrutinib-resistant MCL cell lines, and in primary MCL cells luxeptinib downmodulated anti-apoptotic proteins Mcl-1 and Bcl-xL and reversed stromal cell survival effects.
- Luxeptinib, but not ibrutinib, blocked SYK and BTK signaling and inhibited ERK phosphorylation in MCL cell lines and primary MCL cells.
- Dual suppression of BTK/SYK activation with luxeptinib demonstrated efficacy in a PDX MCL model, where efficacy was accompanied by downmodulation of Bcl-2 family proteins and NFκB.
- Luxeptinib induced metabolic reprogramming toward a glycolytic shift in MCL cells, accompanied by mitochondrial depolarization and induction of mitophagy that eliminates dysfunctional mitochondria and leads to cell death.
- Luxeptinib Inhibits BTK/SYK/ERK signaling and is a potentially promising new therapy in MCL and NHL.

Luxeptinib (CG-806) targets FLT3 and clusters of kinases operative in acute myeloid leukemia *Molecular Cancer Therapeutics (2022), Mol. Cancer Ther.* molcanther.0832.2021 (link)

AML cells survive via dysregulation of multiple pathways, including FLT3 mutations that

occur in approximately 30% of AML patients and are associated with increased risk of relapse and poor survival. Luxeptinib, currently in a Phase 1a/b clinical trial for the treatment of AML, potently inhibits both FLT3 and many of the kinases that participate in rescue pathways that contribute to relapsed and refractory disease. In this study, researchers investigated the range of kinases it inhibits, its antiproliferative landscape *ex vivo* with AML patient samples, and its *in vivo* efficacy in xenograft models.

Key findings:

- Luxeptinib, an oral non-covalent kinase inhibitor, potently suppresses wild type and mutant forms of FLT3 and select clusters of kinases that can participate in rescue pathways.
- Oral luxeptinib demonstrated strong antitumor activity in preclinical *in vivo* AML xenograft models but no myelosuppression or evidence of tissue damage in acute toxicology studies.
- Importantly, luxeptinib does not inhibit the TEC, EGFR, or ERBB2 kinases that can be associated with cardiac, skin and bleeding adverse events.
- Ex vivo profiling of luxeptinib against 186 AML fresh patient samples demonstrated greater potency relative to other FLT3 inhibitors, including cases with mutations in FLT3, IDH1/2, ASXL1, NPM1, SRSF2, TP53 or RAS.
- A combination of venetoclax and luxeptinib enhanced cell killing of the majority of AML samples relative to either drug alone.
- Luxeptinib retained activity against FLT3 mutants that render cells resistant to quizartinib, gilteritinib, and crenolanib FLT3 inhibitors.

“These publications contribute to the wealth of preclinical data demonstrating luxeptinib’ s unique activity as a lymphoid and myeloid kinome inhibitor, and now as an inflammation kinome inhibitor, and support its continued clinical development in several therapeutic areas,” said William G. Rice, Ph.D., Chairman, President, and Chief Executive Officer. “Luxeptinib is a clinical-stage compound, currently in Phase 1 a/b studies in AML and B-cell malignancies. We look forward to reporting on our progress in the upcoming months.”

About Aptose

Aptose Biosciences is a clinical-stage biotechnology company committed to developing personalized therapies addressing unmet medical needs in oncology, with an initial focus on hematology. The Company's small molecule cancer therapeutics pipeline includes products designed to provide single agent efficacy and to enhance the efficacy of other anti-cancer therapies and regimens without overlapping toxicities. The Company has two clinical-stage investigational products under development for hematologic malignancies: HM43239, an oral, myeloid kinome inhibitor in an international Phase 1/2 trial in patients with relapsed or refractory acute myeloid leukemia (AML); and luxeptinib, an oral, dual lymphoid and myeloid kinome inhibitor in a Phase 1 a/b trial in patients with relapsed or refractory B-cell malignancies who have failed or are intolerant to standard therapies, and in a separate Phase 1 a/b trial in patients with relapsed or refractory AML or high risk myelodysplastic syndrome (MDS). For more information, please visit www.aptose.com.

Forward Looking Statements

This press release contains forward-looking statements within the meaning of Canadian and U.S. securities laws, including, but not limited to, statements regarding the clinical potential

and development, favorable properties and extended potential application of luxeptinib, upcoming reports on progress and statements relating to the Company's plans, objectives, expectations and intentions and other statements including words such as "continue", "expect", "intend", "will", "hope" "should", "would", "may", "potential" and other similar expressions. Such statements reflect our current views with respect to future events and are subject to risks and uncertainties and are necessarily based upon a number of estimates and assumptions that, while considered reasonable by us, are inherently subject to significant business, economic, competitive, political and social uncertainties and contingencies. Many factors could cause our actual results, performance or achievements to be materially different from any future results, performance or achievements described in this press release. Such factors could include, among others: our ability to obtain the capital required for research and operations; the inherent risks in early stage drug development including demonstrating efficacy; development time/cost and the regulatory approval process; the progress of our clinical trials; our ability to find and enter into agreements with potential partners; our ability to attract and retain key personnel; changing market and economic conditions; inability of new manufacturers to produce acceptable batches of GMP in sufficient quantities; unexpected manufacturing defects; the potential impact of the COVID-19 pandemic and other risks detailed from time-to-time in our ongoing current reports, quarterly filings, annual information forms, annual reports and annual filings with Canadian securities regulators and the United States Securities and Exchange Commission.

Should one or more of these risks or uncertainties materialize, or should the assumptions set out in the section entitled "Risk Factors" in our filings with Canadian securities regulators and the United States Securities and Exchange Commission underlying those forward-looking statements prove incorrect, actual results may vary materially from those described herein. These forward-looking statements are made as of the date of this press release and we do not intend, and do not assume any obligation, to update these forward-looking statements, except as required by law. We cannot assure you that such statements will prove to be accurate as actual results and future events could differ materially from those anticipated in such statements. Investors are cautioned that forward-looking statements are not guarantees of future performance and accordingly investors are cautioned not to put undue reliance on forward-looking statements due to the inherent uncertainty therein

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