



Calithera Presents Data Highlighting Discovery of Novel Series of Promising Synthetic Lethal Compounds

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Findings presented today at AACR Annual Meeting detail Calithera discovery of VPS4A inhibitors and their potential as a therapeutic approach in numerous solid tumor cancers

VPS4A and VPS4B are gene paralogs that show strong synthetic lethal interaction

SOUTH SAN FRANCISCO, Calif., April 08, 2022 (GLOBE NEWSWIRE) -- Calithera Biosciences, Inc. (Nasdaq: CALA), a clinical-stage, precision-oncology biopharmaceutical company, shared new data today from the company's preclinical synthetic lethality program. The findings, which are now available as an e-poster and will be presented live on April 11 at the American Association for Cancer Research (AACR) Annual Meeting 2022 (Abstract #1816), validate the synthetic lethal interaction between the gene paralogs vacuolar protein sorting-associated protein 4A (VPS4A) and 4B (VPS4B), and provide the first preclinical evidence supporting a newly discovered series of compounds designed to target these proteins for cancer treatment.

"Synthetic lethality is a promising area of cancer therapy that we believe has the potential to address major unmet needs in oncology. Our discovery of a novel series of VPS4A inhibitors is an important validation of our platform," said Susan Molineaux, chief executive officer of Calithera. "We are now advancing these inhibitors through lead optimization."

Synthetic lethal interaction between genes occurs when inhibition of either gene alone does not alter cell viability, but simultaneous inhibition of both genes induces cell death. Calithera is building a preclinical pipeline of synthetic lethality targets with a focus on paralog genes, which are pairs of genes that play redundant roles in essential cellular functions. In the context of cancer therapy, inhibiting one of the paralogs when there is an existing loss-of-function alteration in the other paralog can be lethal to cancer cells.

In the AACR presentation, Calithera researchers describe how they mined CRISPR genetic loss-of-function data and associated molecular datasets from the Cancer Dependency Map Project Datasets to identify pairs of gene paralogs, which they then prioritized for potential drug targets. This work resulted in the identification of VPS4A and VPS4B as promising targets. The researchers then conducted multiple studies to validate the paralog gene pair, demonstrating that cells with VPS4B homozygous or heterozygous loss are sensitive to VPS4A knock down while cells without VPS4B loss are not. In addition, simultaneously knocking down VPS4A and VPS4B consistently resulted in cell death.

"The paralog gene pair VPS4A/B stood out to us as promising synthetic lethal therapeutic targets given the strong interdependence between these genes," said Molineaux. "Additionally, by mining data from about 11,000 human tumor samples in the Pan Cancer Atlas studies, we confirmed that up to 60 percent of certain tumor types harbor heterozygous VPS4B loss of function, including colorectal cancer, pancreatic ductal adenocarcinoma, ovarian, esophageal, and head and neck cancers."

Utilizing the VPS4A and VPS4B paralog genes as targets, Calithera researchers identified a novel series of small molecule inhibitors. Among the findings shared today at AACR are data detailing the performance of one inhibitor of VPS4A and VPS4B ATPase activity, which outperformed previously reported VPS4 inhibitors. Calithera is currently advancing multiple inhibitors in the series through lead optimization.

These data are now available to meeting registrants as an e-poster on the [AACR Annual Meeting 2022 website](#) and will be presented live in the "Experimental and Molecular Therapeutics: Drug Targets" session on Monday, April 11 from 1:30 – 5:00 p.m. PT, the poster will also be available on the [Calithera website](#).

About Calithera

Calithera Biosciences is a clinical-stage, precision oncology biopharmaceutical company developing targeted therapies to redefine treatment for biomarker-specific patient populations. Driven by a commitment to rigorous science and a passion for improving the lives of people impacted by cancer and other life-threatening diseases, Calithera is advancing a robust pipeline of investigational, small molecule oncology compounds with a biomarker-driven approach that targets genetic vulnerabilities in cancer cells to deliver new therapies for patients suffering from aggressive hematologic and solid tumor cancers for which there are currently limited treatment options.

Calithera is headquartered in South San Francisco, California. For more information about Calithera, please visit www.calithera.com.

Forward Looking Statements

Statements contained in this press release regarding matters that are not historical facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Words such as "may," "will," "expect," "anticipate," "estimate," "intend," "poised" and similar expressions (as well as other words or expressions referencing future events, conditions, or circumstances) are intended to identify forward-looking statements. These statements include those related to the safety, tolerability and efficacy of Calithera's product candidates, the overall advancement of Calithera's product candidates in preclinical development and clinical trials, including the advancement of multiple synthetic lethality inhibitors through lead optimization, the unmet need in the treatment of patients with advanced disease, and Calithera's plans to continue development of its product candidates. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. The potential product candidates that Calithera develops may not progress through clinical development or receive required regulatory approvals within expected timelines or at all. In addition, clinical trials may not confirm any safety, potency or other product characteristics described or assumed in this press release. Such product candidates may not be beneficial to patients or be successfully commercialized. The failure to meet expectations with respect to any of the foregoing matters may have a negative effect on Calithera's stock price. Additional information concerning these and other risk factors affecting Calithera's business can be found in Calithera's periodic filings with the Securities and Exchange Commission at www.sec.gov. These forward-looking statements are not guarantees of future performance and speak only as

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