



**PRESS RELEASE**  
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**PUBLICATION IN *CANCER RESEARCH* SHOWS POTENTIAL OF THERAPEUTIC GENE SILENCING FOR A BROAD RANGE OF DISEASES**

DUARTE, California – October 4, 2005 – Calando Pharmaceuticals Inc., a therapeutic RNA interference (RNAi) company and majority-owned subsidiary of Arrowhead Research Corporation (NasdaqSC: ARWR), today announced that collaborators using Calando's proprietary siRNA delivery technology have published the first clear *in vivo* demonstration of sequence-specific gene inhibition in tumors from the systemic administration of targeted formulations of siRNA. The research, published in *Cancer Research*, represents a significant advance in the development of systemic RNAi therapeutics. Systemic delivery through the bloodstream enables RNAi therapeutics to target metastatic cancer located throughout the body, and raises the prospect for broad application of RNAi therapeutics to treat a wide range of cancers and other systemic diseases.

In the published research, Caltech and Children's Hospital Los Angeles investigators created a mouse model of Ewing's sarcoma that mimics the tumor localizations in humans and also provides for simultaneous, real time bioluminescence imaging of the disseminated tumors by using human Ewing's sarcoma cells engineered to express luciferase. Two groups of 10 mice each received sham injections and naked anti-EWS-FLII siRNA, respectively, and three additional groups of 10 mice each received various siRNA sequences formulated with Calando's proprietary cyclodextrin-containing polymer siRNA delivery system: siRNA with an unrelated sequence to EWS-FLII, anti-EWS-FLII siRNA and anti-EWS-FLII siRNA that did not contain the tumor targeting ligand. All injections were at 2.5mg/kg via the tail vein at normal venous pressure. The data show that only the targeted anti-EWS-FLII formulation provided any anti-tumor efficacy – control sequences and removal of the targeting ligand eliminated the anti-tumor effects. Additionally, no abnormalities in IL-12 and interferon-alpha, liver and kidney function tests, complete blood counts or pathology of major organs were observed. Of major significance is that the cyclodextrin-containing delivery system does not produce an interferon response like those obtained from lipid delivery of siRNA even when published immunostimulatory motifs are included in the siRNA.

"The results from the Caltech-CHLA collaboration conclusively show sequence-specific anti-tumor effects and the molecular targeting to and within tumor cells by the delivered siRNAs," said Dr. Mark Davis, professor of Chemical Engineering at Caltech and founder of Calando. "This study shows that the polymer system can deliver siRNA therapeutics by a route of administration and at a dose amenable to use in humans."

"It is important to recognize that these results were achieved with the delivery of natural RNA sequences. No chemical modifications are necessary for siRNAs delivered with Calando's polymeric system," said John Petrovich, Chief Executive Officer of Calando Pharmaceuticals. "We believe this will give us an easier regulatory path, and possibly result in reduced off-target effects." He noted that the delivery system is currently very well-characterized, and that considerable progress had been made in advancing the cGMP scale-up and preclinical development of the polymer.

## **About RNAi**

RNA interference, or RNAi, is a naturally occurring mechanism within cells for selectively silencing and regulating specific genes that is potentially the basis for a new class of therapeutic products. Since many diseases are caused by the inappropriate activity of specific genes, the ability to silence and regulate such genes selectively through RNAi could provide a means to treat a wide range of human diseases. The discovery of RNAi has been heralded by many as a major breakthrough, and the journal *Science* named RNAi the top scientific achievement of 2002, as well as one of the top ten scientific advances of 2003.

## **About Calando Pharmaceuticals Inc.**

Calando Pharmaceuticals Inc. is a privately held biopharmaceutical company funded by Arrowhead Research Corporation and located in a City of Hope research building immediately adjacent to the main campus. Calando is using its proprietary technologies to design and create new, targeted siRNA therapeutics. Calando combines proprietary technologies in targeted polymeric delivery systems and siRNA design to create effective therapeutics. The company is pursuing this goal through its internal research and development and also through collaborations and partnerships with pharmaceutical and biotechnology companies. For more information, visit [www.calandopharma.com](http://www.calandopharma.com).

## **Calando Technology**

Calando's cyclodextrin-containing polymers form the foundation for its two-part siRNA delivery system. The first component is a linear, cyclodextrin-containing polycation that, when mixed with small interfering RNA (siRNA) binds to the anionic "backbone" of the siRNA. The polymer and siRNA self-assemble into nanoparticles of approximately 50 nm diameter that fully protect the siRNA from nuclease degradation in serum. The siRNA delivery system has been designed for intravenous injection. Upon delivery to the target cell, the targeting ligand binds to membrane receptors on the cell surface and the RNA-containing nanoparticle is taken into the cell by endocytosis. There, chemistry built into the polymer functions to unpackage the siRNA from the delivery vehicle. In addition to targeting tumors, the targeting of liver cells has also been accomplished *in vivo*. Using anti-FAS siRNA, liver targeted delivery from tail vein injections in mice are able to provide FAS gene inhibition like that observed from a high pressure tail vein injection that is not clinically relevant.

## **Forward-Looking Statements**

*Various statements in this release concerning our future expectations, plans, prospects and future operating results constitute forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated by these forward-looking statements as a result of various important factors, including risks related to: our approach to discover and develop novel drugs, which is unproven and may never lead to marketable products; our ability to obtain additional funding to support our business activities; our dependence on third parties for development, manufacture, marketing, sales and distribution of our products; the successful development of products, all of which are in early stages of development; obtaining regulatory approval for products; competition from others using technology similar to ours and others developing products for similar uses; obtaining, maintaining and protecting intellectual property utilized by our products; our dependence on collaborators; and our short operating history; as well as those risks more fully discussed in the "Certain Factors That May Affect Future Results" section of our Form 10-Q filed with the Securities and Exchange Commission. In addition, any forward-looking statements represent our views only as of today and should not be relied upon as representing our views as of any subsequent date. We do not assume any obligation to update any forward-looking statements.*

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