



**PRESS RELEASE**  
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**FOR IMMEDIATE RELEASE**

**CALANDO PHARMACEUTICALS DELIVERY TECHNOLOGY ACHIEVES  
TUMOR KNOCKDOWN WITH TARGETED siRNA**

*Systemic administration inhibits growth of metastatic Ewing's sarcoma*

**DUARTE, CA** – April 20, 2005 – **Calando Pharmaceuticals Inc.** CEO John Petrovich announced today that collaborators using Calando's proprietary siRNA delivery technology have generated preclinical data that demonstrate sequence-specific gene inhibition in tumors from the systemic administration of targeted formulations of siRNA. Calando, a privately held biopharmaceutical company funded by Arrowhead Research Corporation (OTCBB: ARWR), was formed earlier this year to develop and commercialize proprietary technologies that will lead to the therapeutic use of RNA interference, or "RNAi."

Siwen Hu-Lieskovan, MD, PhD, of Children's Hospital Los Angeles (CHLA), presented the findings on behalf of workers in the laboratories of Mark Davis in Chemical Engineering at Caltech and Timothy Triche at CHLA in a mini-symposium at the American Association of Cancer Research (AACR) Annual Meeting in Anaheim, CA.

Researchers at Caltech and CHLA 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-FLI1 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-FLI1, anti-EWS-FLI1 siRNA and anti-EWS-FLI1 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 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.

"These data are the first to show evidence for the safety of targeted, non-viral siRNA delivery in animals," said Dr. Hu-Lieskovan, speaking at a press conference sponsored by the AACR. "Our study shows that siRNA delivered by this non-viral system does not induce detectable immune responses or any changes in mouse physiology."

"To our knowledge, this is the first study to show that systemic, non-viral administration of siRNA can inhibit disseminated tumor growth in a sequence-specific manner," Petrovich said. "The results are particularly significant since the effects were conclusively shown to be due to the inhibition of the EWS-FLI1 protein that is known to play a significant role in tumorigenesis of Ewing's sarcoma, and not due to side effects. Additionally, the route of administration and the dosage levels of siRNA used in this study will translate well to the clinic."

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### ***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.

### ***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).

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