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## **Arrowhead Publishes First Ever Cholesterol-siRNA Mediated Gene Knockdown in Primates and Novel DPC Co-Injection Strategy**

PASADENA, Calif. — November 27, 2012 — Arrowhead Research Corporation (NASDAQ: ARWR), a targeted therapeutics company, today announced the publication of data demonstrating that high level target gene knockdown with low doses of cholesterol-siRNA is possible in non-human primates using the company's Dynamic Polyconjugate (DPC) delivery system and a novel co-injection strategy. This new delivery approach dramatically increases the efficacy of cholesterol-siRNA and, together with the co-injection strategy, simplifies the manufacturing process to enable a commercially scalable delivery vehicle for RNAi therapeutics. The company is using this strategy and a next generation DPC polymer in ARC-520, its hepatitis B clinical candidate. The paper titled, "Co-injection of a targeted, reversibly masked endosomolytic polymer dramatically improves the efficacy of cholesterol-conjugated siRNAs *in vivo*," was published online ahead of print in the journal [Nucleic Acid Therapeutics](#) to be featured in the December issue (Nucleic Acid Therapeutics, December 2012, 22(6): 380-390).

The publication describes an important advance in DPC technology. Specifically, the requirement for siRNA attachment to the DPC polymer is replaced by conjugating a cholesterol to the siRNA and co-injecting it with the DPC polymer. Uptake of the DPC in the target cells and subsequent unmasking of the polymer's endosomolytic properties enables release of the cholesterol-siRNA from the endosome to the cell's cytoplasm where it can elicit RNAi. This delivery strategy produces over 500-fold increase in efficiency in mice compared to injection of cholesterol-siRNA alone and is the first delivery system to demonstrate cholesterol-siRNA mediated gene knockdown in monkeys. Long duration silencing was observed after administration of a single dose with maximal protein reduction sustained until day 30. Further, unlike other siRNA delivery platforms, the co-injection method does not require complex formation of the siRNA to the delivery vehicle, which eliminates potentially complicated and costly manufacturing steps. This represents a seminal advance in the siRNA delivery field.

"The main drawback of cholesterol-conjugated siRNAs is that their delivery is highly inefficient, and extraordinarily high doses would be needed to achieve even minimal amounts of target gene silencing," said Bruce Given, MD, Arrowhead's COO and Head of R&D. "Our strategy and the DPC platform enable much higher levels of gene silencing at dramatically lower doses of cholesterol-siRNA. Moreover, the ability to simply co-inject the cholesterol-siRNA with the DPC polymer without having to attach them together simplifies manufacturing and has facilitated our use of next generation polymers. This co-injection strategy and a next generation polymer are being used in our HBV clinical candidate, ARC-520."

### **About Arrowhead Research Corporation**

Arrowhead Research Corporation is a clinical stage targeted therapeutics company with development programs in oncology, obesity, and infectious disease. The company leverages its platform technologies to design and develop peptide-drug conjugates (PDCs) which specifically home to cell types of interest while sparing off-target tissues, creates targeted drugs based on the gene silencing RNA interference (RNAi) mechanism, and works with partners to create improved versions of traditional small molecule drugs.

For more information please visit <http://www.arrowheadresearch.com>, or follow us on Twitter [@ArrowRes](#). To be added to the Company's email list to receive news directly, please send an email to [ir@arrowres.com](mailto:ir@arrowres.com).

### **Safe Harbor Statement under the Private Securities Litigation Reform Act:**

This news release contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties, including our ability to finance our operations, the future success of our scientific studies, our ability to successfully develop drug candidates, the timing for starting and completing clinical trials, rapid technological change in our markets, and the enforcement of our intellectual property rights. Arrowhead Research Corporation's most recent Annual Report on Form 10-K and subsequent Quarterly Reports on Form 10-Q discuss some of the important risk factors that may affect our business, results of operations and financial condition. We assume no obligation to update or revise forward-looking statements to reflect new events or circumstances.

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