
INSERT THERAPEUTICS DESCRIBES *IN VIVO* PERFORMANCE AND VERSATILITY OF LEAD ANTICANCER COMPOUND

Preclinical results demonstrate efficacy over a broad range of cancer types

PASADENA, CA – April 17, 2005 – **Insert Therapeutics, Inc.** Chief Scientific Officer, Thomas Schlupe, Sc.D., presented data today demonstrating the improved biodistribution and preclinical efficacy *in vivo* of its lead anticancer compound, IT-101. Insert Therapeutics, a majority-owned subsidiary of Arrowhead Research Corporation (NASDAQ: ARWR), is progressing towards a broad-based Phase I clinical trial for IT-101, a combination of Insert's patented polymer technology, Cycloset™, and the anti-cancer compound camptothecin. Subject to the filing by Insert of an Investigational New Drug application with the US Food and Drug Administration, and upon clearance of regulatory requirements, Phase I/II human safety and efficacy trials are scheduled to begin at The City of Hope (COH) Medical Center in late 2005.

In a presentation at the American Association of Cancer Research Annual Meeting in Anaheim, CA, on behalf of Insert's scientific staff, the Chemical Engineering at Caltech and Children's Hospital Los Angeles, Dr. Schlupe discussed *in vivo* efficacy data of IT-101 in rodent models of various human cancers, including colon cancer, breast cancer, lung cancer, pancreatic cancer and Ewing's sarcoma, a rare cancer primarily affecting children and young adults.

Discovered in the 1960s, camptothecin is a naturally occurring, water-insoluble alkaloid that has established potent activity against a broad spectrum of cancer types. Although analogues of camptothecin (e.g., irinotecan and topotecan) continue to realize nearly \$1 billion in worldwide sales annually, camptothecin itself has not been commercialized due to its poor solubility and unfavorable pharmacokinetics. In animal studies conducted by Insert, treatments with IT-101 result in protracted anti-tumor activities that are substantially more effective at significantly lower doses than all other treatment groups, including irinotecan.

In studies recently completed by a leading contract research laboratory, pharmacokinetics, biodistribution and antitumor efficacy of IT-101 were evaluated in rodents. Plasma pharmacokinetic studies were performed after intravenous injection of the polymer-camptothecin conjugate in rats. The polymer conjugates showed favorable pharmacokinetics compared to the free CPT in that (A) the mean half-life ($t_{1/2}$) for polymer bound camptothecin was 17-20 hrs compared to 2.6-8.0 hrs for free camptothecin, and (B) the area under the curve (AUC) for free camptothecin was at least 100-fold less than the AUC for polymer bound camptothecin. A long $t_{1/2}$ is of potential benefit, because CPT is known to have a cell-cycle dependent mechanism and the prolonged exposure could result in increased anti-tumor activity while the low AUC for free camptothecin may provide a potential safety benefit, since high plasma AUCs for free camptothecin were correlated to increased side effects.

Biodistribution was determined in tissues of nude mice bearing subcutaneous colon cancer xenografts. After intravenous injection, IT-101 distributed to all major organs tested, including tumor, within 24 hrs of administration. A single dose of IT-101 resulted in high camptothecin concentration in the tumor when compared to other tissue tested and at doses where camptothecin alone showed negligible tumor concentration. These results support the hypothesis that IT-101 is escaping the blood circulation through the leaky tumor vasculature leading to an accumulation of the drug within the tumor tissue.

Efficacy studies were performed in a disseminated model of Ewing Sarcoma and subcutaneous xenograft models of breast, colon, pancreatic, small-cell lung, and non small-cell lung cancer. Anti-tumor activity, as measured by median tumor size and tumor growth delay (difference between treatment group and placebo in the time required for the tumor to reach a predetermined weight) was superior for IT-101

treated animals compared to irinotecan in all tumor models tested. In mice with Ewing sarcoma and non-small-cell lung cancer complete tumor remission was achieved. In these two studies, animals remained tumor free throughout the duration of the 90-day study.

“The remarkable finding from this *in vivo* evaluation of the anti-tumor efficacy of IT-101 is that a brief course of treatment (only 3 doses over 14 days) with our polymer-camptothecin conjugate resulted in very protracted antitumor activity and in a fair number of long-term tumor free animals” commented Dr. Schlupe. “On the strength of these significant results, we are moving forward with IT-101 to complete necessary preclinical studies, file an IND and initiate human clinical trials.”

Cyclosert™ Technology

Insert's proprietary Cyclosert delivery system is based on small cyclic repeating molecules of glucose called cyclodextrins. Using modified cyclodextrins as building blocks, Insert has developed an entirely new proprietary class of materials called linear cyclodextrin-containing polymers. Cyclosert polymers can be made biodegradable and animal studies have confirmed that they are non-toxic and non-immunogenic, even after repeated administration.

Cyclosert polymers have been synthesized at molecular weights ranging up to 100 kD, allowing for systemic drug delivery with the potential to slow renal clearance, enhance circulation time and improve passive accumulation of active drug at the target tissue. Additionally, Cyclosert polymers can be tuned to be neutral, positively charged or negatively charged. This feature is unique to Cyclosert technology and provides great flexibility for formulation and delivery. When modified with the addition of transferrin ligands, Cyclosert can achieve targeted intracellular delivery of drugs. Transferrin was chosen as a targeting agent based on the observation that the transferrin receptor is up regulated on the surface of many tumor cells.

About Insert Therapeutics, Inc.

Insert Therapeutics, Inc., a majority-owned subsidiary of Arrowhead Research Corporation (NASDAQ: ARWR), is using its proprietary, nanoscale, polymeric delivery system, Cyclosert™, to design, develop and commercialize drug-delivery-enhanced small-molecule therapeutics and nucleic acids. Cyclosert uses cyclodextrins as building blocks to create an entirely new class of biocompatible materials – linear cyclodextrin-containing polymers that are nontoxic and nonimmunogenic at therapeutic doses. 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.insertt.com.

Contact

John G. Petrovich, President
Telephone: 626.683.7200
Email: jpetrovich@insertt.com

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