



Contact: Leonard Borrmann
President & CEO
Insert Therapeutics, Inc.
lbormann@insertt.com
626.683.7200

Marty Tullio
Investor Relation Resources
Marty@investorRR.com
949.566.9860

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**INSERT THERAPEUTICS DESCRIBES *IN VIVO* PERFORMANCE AND
VERSATILITY OF DRUG DELIVERY PLATFORM**

Preclinical results demonstrate successful intracellular delivery of a broad range of therapeutics

PASADENA, CA – Jul 22, 2003 – **Insert Therapeutics, Inc.** President and Chief Executive Officer, Leonard R. Borrmann, Pharm.D., presented data today demonstrating the flexibility and distinct advantages of the company's proprietary Cyclosert™ drug delivery technology. First, Cyclosert provides a solution to the diverse challenges of systemic delivery for small-molecule drugs that, without delivery enhancement, have limited clinical effectiveness or unacceptable toxicity. Second, Cyclosert can be used to formulate, protect and systemically deliver nucleic acids, including plasmid DNA, RNA and oligonucleotides, into targeted cells with subsequent expression.

In a poster presented at the Controlled Release Society Annual Meeting in Edinburgh, Scotland on behalf of Insert's founder, Mark Davis, Ph.D. and Insert's scientific staff, Dr. Borrmann discussed *in vivo* data on the company's lead development candidate. The candidate is a Cyclosert conjugate of the anticancer agent camptothecin (CPT), a potent topoisomerase I inhibitor with broad-spectrum anticancer activity. Although camptothecin analogues have been approved for treatment of cancer, camptothecin itself has not been commercialized due to its poor solubility, unfavorable pharmacokinetics, rapid hydrolysis and high plasma protein binding.

In tests recently completed by a leading contract research laboratory, Insert's Cyclosert-CPT formulation was compared against placebo, camptothecin alone, and irinotecan, a camptothecin analogue currently marketed for cancer treatment, in athymic nude mice bearing a single subcutaneous LS-174t human colon carcinoma tumor. Animals were treated with Cyclosert-CPT, camptothecin alone or placebo every four days beginning on Day 1 for three doses, or with irinotecan once weekly beginning on Day 1 for three doses.

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 weight of 1,500 mg) over the 114-day study, was superior for Cyclosert-CPT treated animals compared to the other three treatment groups. The high molecular weight Cyclosert-CPT (97 kDa) produced the greatest anti-tumor activity as measured by tumor growth delay (79.1 days and 227%). In addition, the median tumor burden for Cyclosert-CPT treated animals at the completion of the study was extremely low (256 mg), further supporting the protracted tumor suppressive effects of high molecular weight Cyclosert-CPT. By comparison, tumor growth delay and tumor burden for the irinotecan group were 33.8 days (97%) and 1,152 mg, respectively.

"The remarkable finding from this initial *in vivo* evaluation of the anti-tumor efficacy of Cyclosert-CPT is that a brief course of treatment (only 3 doses over 9 days) with our high molecular weight Cyclosert-CPT conjugate resulted in very protracted antitumor activity, with essentially static tumor growth out to 114 days," commented Dr. Borrmann. "On the strength of these significant results, we are moving forward with Cyclosert-CPT to complete necessary preclinical studies, file an IND and initiate human clinical trials."

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Dr. Borrmann also stressed Cyclosert's applicability in nucleic acid delivery. Results of preclinical studies demonstrate the significant progress made by the company in overcoming the limitations of other non-viral vectors. The Cyclosert non-viral delivery platform self assembles with nucleic acids to form highly stable DNA-containing nanoparticles. *In vitro* and *in vivo* results have confirmed that the fully formulated Cyclosert-DNA polyplexes are non-toxic and non-immunogenic even upon continuous intravenous administration.

The Cyclosert system allows for high concentration formulations of nucleic acids to circulate *in vivo* and to target specific tissues and cell types by addition of cell surface receptor ligands. *In vivo* results have shown that surface modification of the Cyclosert non-viral delivery system significantly enhances passive distribution of the p53 gene to tumor cells in tumor-bearing mice following tail vein injection. Furthermore, the modification of the Cyclosert polyplexes to include the targeting protein, transferrin, results in p53 transgene expression in tumor, as measured by p53 RNA.

"Our preclinical data indicate that targeting plays a significant role in the intracellular delivery and expression of therapeutic genes administered systemically using non-viral delivery systems," said Dr. Borrmann. "The flexibility to customize the Cyclosert non-viral delivery system to include components that protect the DNA from degradation and that recognize and bind to specific cell or tissue types has the potential to be a significant advancement in delivery of nucleic acids for treatment of cancer and other diseases throughout the body."

"We believe that Cyclosert provides unparalleled flexibility to design and create new customized polymer drug products that address specific drug delivery challenges and therapy requirements of small molecules and nucleic acids," continued Dr. Borrmann. "We intend to leverage this technology by building a pipeline of delivery-enhanced products and pursue strategic collaboration with pharmaceutical and biotechnology companies whose marketed products or proprietary development compounds could benefit from Cyclosert."

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.

INSERT THERAPEUTICS, INC.

Insert Therapeutics, Inc., a privately held biopharmaceutical delivery company, is using its proprietary and entirely new 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 drug delivery 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.

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