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Targeting Trends

Reporting the latest news in Molecular Surgery

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ADVANCED TARGETING SYSTEMS

Safety Studies Begin for Chronic Pain Therapeutic

Early last month (March 2001), Advanced Targeting Systems (ATS) received funding from the National Institute of Mental Health (NIMH) to begin toxicology/safety studies of Substance P-Saporin (SP-SAP), a potential therapeutic for the treatment of chronic pain. The studies will be completed under the direction of three scientists who are experts in their respective fields.

Dr. Douglas Lappi (President and Chief Scientific Officer of ATS) is principal investigator for the project and will oversee the various aspects of the studies. He is an expert in the design, construction and testing of targeted toxins. His laboratory will be producing the drug and performing quality control assays throughout the project.

Dr. Tony Yaksh (Professor of Anesthesiology and Pharmacology at the University of California, San Diego School of Medicine) will direct the administration of the drug. He is the leading expert in spinal cord delivery of experimental agents. The dog is one of the species routinely used to satisfy most regulatory requirements for drug safety evaluation. The studies will assess safety from four points: 1) intrathecal dose ranging to determine the maximum tolerated dose, 2) kinetics of cerebral spinal fluid to determine how the drug penetrates spinal tissue, is redistributed and eliminated, 3) histopathology to determine impact of drug on organs and tissue, and 4) spinal GLP safety studies to determine physiological (heart and respiratory rate, blood pressure) and behavioral (arousal, muscle tone, coordination) impacts of drug administration (4).

Dr. Patrick Mantyh (Professor, University of Minnesota, Minneapolis) has established the efficacy of SP-SAP in rats and is internationally acclaimed for his immunohistochemical analysis. His laboratory will measure parameters involving the efficacy and specificity of the SP-SAP treatment. Immunohistochemistry will help in determining where the drug travels and what impact, if any, it has on spinal cord neurons *(See Figure)*.

The development of SP-SAP was first published in 1997 (1) by Drs. Ronald G. Wiley and Douglas Lappi, two of the founders of ATS. Their collaboration with Dr. Patrick Mantyh led to two publications in the journal *Science* (2, 3). These three articles describe the results of experiments with SP-SAP in the rat.

SP-SAP is a targeted toxin that permanently eliminates cells that bear the Substance P

(continued on page 6)

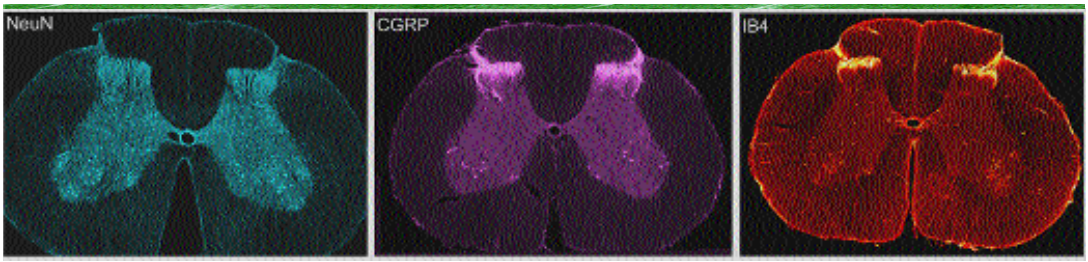

Figure Legend: This figure shows the staining of NeuN, CGRPand IB4 in the canine spinal cord. Immunostaining is one of the tests that will be used for determination of specificity and evaluation of bystander effects by SP-SAP. Confocal photomicrographs show the pattern of immunohistochemical labeling of the neuronal nuclear marker, NeuN, a peptidergic sensory nerve fiber marker, CGRP, and the non-peptidergic sensory nerve fiber marker, IB4, in the dog spinal cord. The NeuN staining is distributed throughout the entire gray matter, while the staining for the sensory fibers (CGRP, IB4) is localized to the dorsal horn (Photo supplied by Dr. Patrick Mantyh).