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Targeting Trends

Reporting the latest news in Molecular Surgery

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ADVANCED TARGETING SYSTEMS

CBF Lesioning in Rabbits

contributed by Dr. Thomas Beach

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Our hypothesis, developed through our own human and animal studies[1-6] and the cell culture work of others (beginning with Nitsch[7]), is that the normal, age-related loss of cortical cholinergic innervation leads to Aβ deposition and Alzheimer's disease. To test this hypothesis, we have been using a saporin-conjugated antibody to lesion the cholinergic basal forebrain (CBF) of rabbits. The antibody is the ME20.4 monoclonal[8] against the low affinity nerve growth factor receptor, also known as the p75 neurotrophin receptor (p75NTR). This approach had already been shown to result in an effective and specific lesion in rats, but we wished to use an animal with an Aβ sequence identical to that of humans (the rat sequence differs by 3 amino acids), since we considered that, because of this difference, rats may be less likely to produce Aβ deposits. As the IgG192 anti-p75NTR antibody used for rats does not recognize rabbit CBF neurons, we tested the ME20.4 antibody

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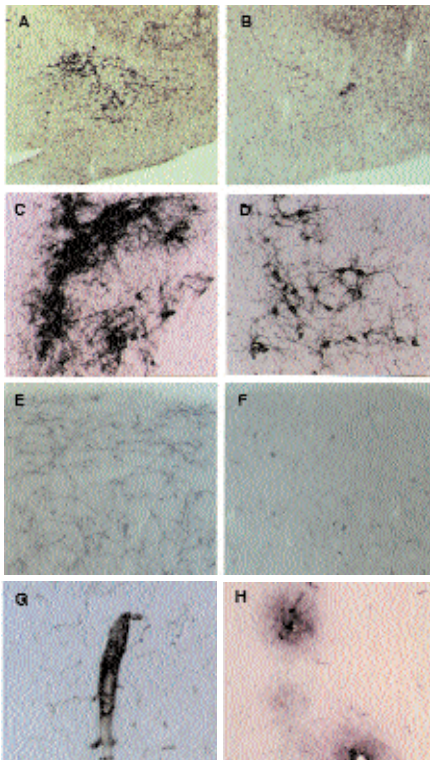

Fig 1 Histologic demonstration of the nbm lesion and resultant Aβ deposition. A,B: rabbit nbm area in control (A) and immunotoxin-treated animals (B), stained for AChE. Note the marked depletion of nbm neurons in the latter. C,D: rabbit nbm in control (C) and treated (D) animal, stained immunohistochemically for p75 NTR. Note the depletion of neurons in the treated animal. E,F: frontal cortex from control (E) and treated (F) animals, stained for AChE. Note eradication of cholinergic fibers in the latter. G,H: Aβ deposition in cerebral cortex of lesioned animals. Aβ is deposited in blood vessel walls (G) and in the perivascular neuropil (H).

Chronic Pain Therapeutic

In April of this year ATS applied for funding from the National Institute for Mental Health (NIMH) for the toxicology studies of Substance P-Saporin (SP-SAP). This $674,000 supplement to a previous NIMH Small Business Innovative Research grant will cover one of the FDA-required safety and toxicology studies and will bring us closer to clinical trials in humans. On August 14, ATS received notice of the reviewers' score of these studies. ATS is pleased with the reviewers' assessment and is optimistic about funding. Collaborating with ATS on this grant are two scientists who are experts in their fields: Dr. Tony Yaksh (UCSD, Dept. of Anesthesiology) who will be heading the toxicology/safety experiments in animals, and Dr. Patrick Mantyh (Univ. Minnesota), who will provide analysis and

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