**[S1-6] [10/17/2002 (Thurs) 12:30~12:50/Hall A]**

## Targeting of Large-molecule Radiopharmaceuticals across the Blood-brain Barrier Using Endogenous Transport Systems

Hwa Jeong Lee

*Department of Pharmaceutics, College of Pharmacy, Ewha Womans University, Seoul 120-750*

Drug targeting to the central nervous system (CNS) is the limiting factor in CNS drug development because most of drug do not cross the brain capillary endothelial wall, which forms the blood-brain barrier (BBB) in vivo. One strategy for drug targeting to the brain is to use endogenous BBB transport systems. Drug delivery to the brain is possible with peptidomimetic monoclonal antibodies (MAbs) that undergo receptor-mediated transcytosis through the BBB. These peptidomimetic MAbs act as brain drug delivery vectors and are generally species-specific. The murine 83-14 MAb to the human insulin receptor (HIR) was genetically engineered to form a chimeric antibody (TAYD), where most of the immunogenic murine sequences were replaced by human antibody sequence. The murine 83-14 MAb and chimeric TAYD MAb have identical reactivity with the HIR produced from CHO cells based on both Western blotting and immunoradiometric assay. The [$^{111}$In]-chimeric TAYD MAb was administered intravenously to an anesthetized Rhesus monkey, and the 2 hour brain scan showed avid uptake of the chimeric antibody by the primate brain in vivo. The availability of the chimeric TAYD MAb may allow for future drug targeting of neurodiagnostics or neurotherapeutics to the human brain. The emergence of transgenic mouse models to investigate the pathogenesis of disease creates the need for brain drug-targeting vectors in this species. Two rat MAbs to the mouse transferrin receptor, 8D3 MAb and RI7-217 MAb were evaluated with OX26 MAb, a murine MAb to the rat transferrin receptor. The brain uptake of the OX26 MAb in mouse was negligible because this antibody did not recognize the mouse transferrin receptor. Both the 8D3 MAb and RI7-217 MAb had comparable permeability-surface area products at the mouse BBB in vivo. The mouse brain uptake of the 8D3 MAb was two times higher than that of RI7 MAb at 60 minutes after i.v. injection due to a higher area under the curve (AUC). The RI7-

217 MAb was more selective for brain because this antibody was not measurably taken up by liver and kidney. The capillary depletion analysis demonstrated transcytosis of the RI7-217 MAb through the mouse BBB in vivo. These studies indicate that rat MAbs to the mouse transferrin receptor may be used for brain drug delivery studies in the mouse, including transgenic mouse models.

The accumulation of Aβ amyloid plaque in the brain is a specific neuropathologic hallmark of Alzheimer's disease (AD). $A\beta^{1-40}$ pepetide radiopharmaceuticals can be used to image the brain Aβ amyloid of AD in vivo. However, these CNS amyloid imaging agents do not cross the BBB in vivo. The BBB transport of $[^{125}I]$-$A\beta^{1-40}$ in a transgenic mouse model was enabled by conjugation to the 8D3 MAb, rat antibody to the mouse transferrin receptor. The $A\beta^{1-40}$-8D3 MAb conjugate is a bifunctional molecule that binds to both the BBB transferrin receptor and Aβ amyloid plaque in the brain. $App^{sw}$/Psen1 double-transgenic and littermate control mice were administered either unconjugated $[^{125}I]$-$A\beta^{1-40}$ or the $[^{125}I]$-$A\beta^{1-40}$-8D3 MAb conjugate intravenously, and brain scans were obtained 6 hours later. Immunocytochemical analysis showed abundant Aβ immunoreactive plaques in the brains of the $App^{sw}$/Psen1 double-transgenic mice. There was a selective retention of radioactivity in the brains of the double-transgenic mice at 6 hours after i.v. injection of the conjugate. In contrast, there was no selective sequestration either of the unconjugated $A\beta^{1-40}$ in transgenic mouse brain or of the conjugate in littermate control mouse brain. These results suggest that it is possible to image the Aβ amyloid burden in the brain in vivo with an amyloid imaging agent, which is conjugated to the brain drug-targeting system.