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Gene Delivery Systems (GDS) and Molecular Trojan Horses

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Global expression of exogenous genes throughout the entire brain is possible with an intravenous (IV) administration of a non-viral Gene Delivery System (GDS). The plasmid DNA is encapsulated in the interior of 100 nm liposomes, which have a net anionic charge. The surface of the liposome is covered by several thousand strands of 2000 Dalton polyethyleneglycol (PEG). The tips of 1-2% of the PEG strands are conjugated with receptor-specific molecular Trojan horses to form a pegylated immunoliposome (PIL) with the DNA encapsulated inside the liposome. The molecular Trojan horse is a peptidomimetic monoclonal antibody (MAb) to the transferrin receptor (TfR) or the insulin receptor. Both of these receptors are expressed on both the brain capillary endothelial wall, which forms the blood-brain barrier (BBB), and on the brain cell membrane (BCM). The molecular Trojan horse binds BBB and BCM receptors to trigger receptor-mediated transcytosis across the BBB and receptor-mediated endocytosis across the BCM. Gene transfer to the brain with the PIL gene delivery system has yielded the following results:

- Global expression of reporter genes throughout the entire brain of mice, rats, and Rhesus monkeys following an IV injection of low doses of DNA, e.g. 10 µg/kg. Real time PCR assays show this dose of DNA delivers 5-10 plasmid DNA molecules per brain cell.
- Tissue-specific gene expression in brain when tissue specific gene promoters are incorporated in the plasmid DNA.
- 100% normalization of striatal tyrosine hydroxylase (TH) gene expression in rats with experimental Parkinsons disease treated IV with PILs carrying a TH expression plasmid.
- 100% increase in survival time in mice with intracranial brain cancer with weekly IV injections of PILs carrying an expression plasmid encoding antisense RNA against the human epidermal growth factor receptor (EGFR).
- The first, and thus far only, demonstration of an increase in survival time in experimental cancer with RNA interference (RNAi) therapy. Mice with intracranial brain cancer were treated with weekly IV injections of PILs carrying an expression plasmid encoding a short hairpin RNA (shRNA) against the EGFR mRNA.

Profile: Dr. Pardridge received the M.D. degree from Pennsylvania State University, and trained in internal medicine at Boston University Hospital, and Endocrinology & Metabolism at UCLA. He is Professor of Medicine at UCLA, and has been working on the blood-brain barrier since 1970.