Tumor-specific Targeting Polymeric Gene Delivery Carriers

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Since the first cancer gene therapy trial in 1991, a number of different approaches have been performed for cancer treatment and they may be categorized into two basic concepts: (1) directly killing tumor cells by boosting host immune system, inducing drug-sensitivity to tumor cells, or modulating tumor-related genes, and (2) inhibiting tumor growth/metastasis by destroying tumor vasculature that supplies tumor cells with oxygen and nutrients (anti-angiogenesis).

For the first concept, a leukemia-specific polymeric gene delivery carrier was developed by conjugating the cationic polymer, polylysine (PLL) with the leukemia T cell-targeting anti-JL1 antibody. Anti-JL1 antibody has been proven to bind to JL1 antigen and subsequently be internalized into human leukemia T cells, demonstrating that anti-JL1 antibody has the potential as a targeting ligand for leukemia-specific gene transfer. As shown in Figure 1, anti-JL1 antibody was modified with the heterobifunctional crosslinker, PDPH, at carbohydrate sites and conjugated to thiolated poly-L-lysine (PLL) via disulfide bridges. The composition and antigen binding affinity of antibody–PLL conjugates were analyzed by the amino acid analysis and the flow cytometry, respectively. In the experiments with human leukemia T cells (Figure 2), anti-JL1 antibody-PLL/DNA complexes were efficiently internalized into the cytoplasm and exhibited significantly higher transfection efficiency than DNA/PLL complexes and DNA/Lipofectin formulation. This high efficiency might result from the targeting effect of anti-JL1 antibody and following receptor-mediated endocytosis.

As the anti-angiogenic approach, an angiogenic endothelial cell-targeting polymeric gene carrier was synthesized by conjugating $\alpha v\beta 3/\alpha v\beta 5$ integrin-binding RGD peptide (ACDCRGDCFC) with polyethyleneimine (PEI) using a polyethylene glycol (PEG) linker (Figure 3). The incorporation of PEG into PEI improved poor physicochemical properties of DNA/PEI complexes; however, the extensive grafting of PEI with PEG inhibited DNA condensation process, significantly decreasing transfection efficiency. In transfection experiments (Figure 4), PEI-PEG-RGD exhibited the high specificity to angiogenic endothelial cells, as compared with normal endothelial cells, with a five-fold increase in

transfection efficiency over PEI homopolymer. This high efficiency specificity to angiogenic endothelial cells was confirmed with nontargeting PEI-PEG-RAE and in angiostatic endothelial cells.

These results demonstrated that the modification of polymeric gene delivery vector with tumor-specific ligands may make it possible to selectively transfer therapeutic genes into tumors with low cross-reactivity in normal tissue, which is one of important criteria to be considered in cancer gene therapy.

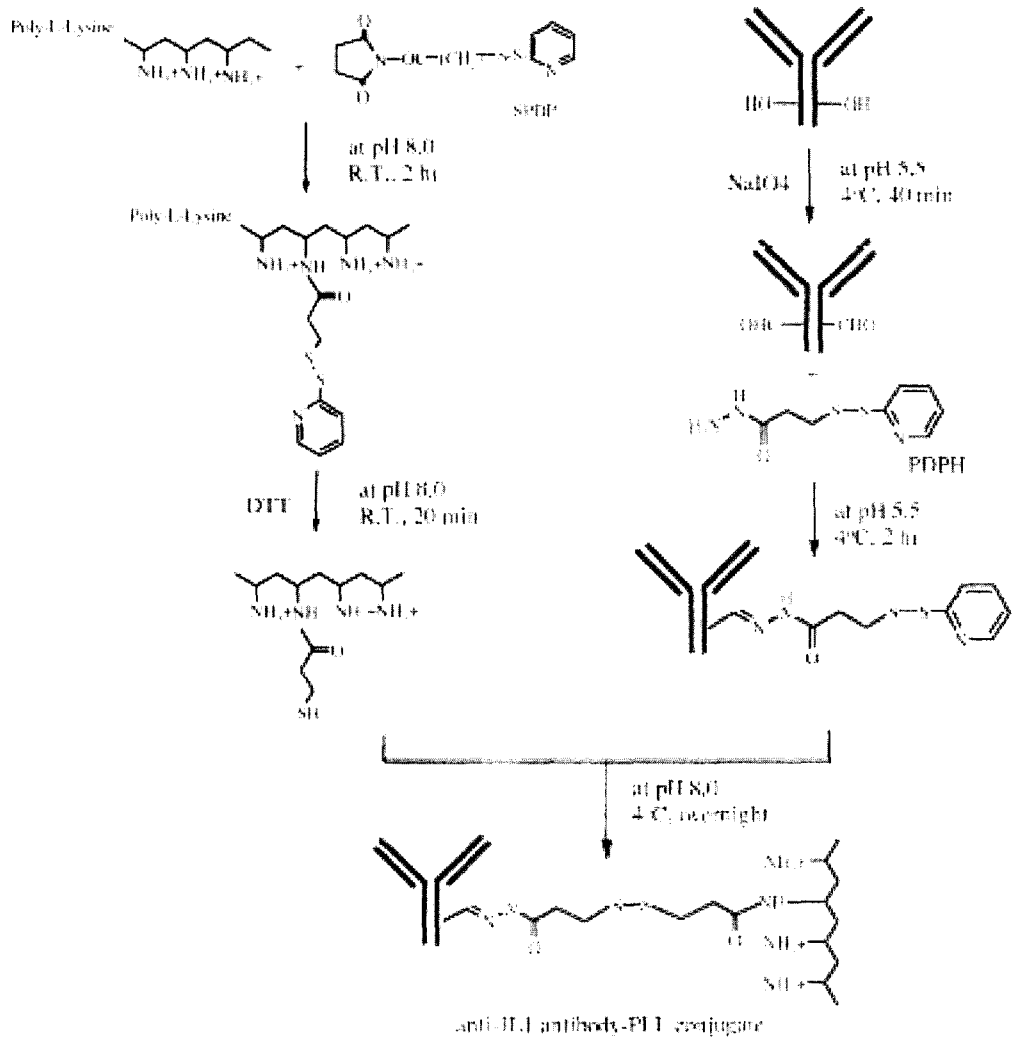

Figure 1. Synthesis scheme of anti-JL1 antibody-PLL conjugates

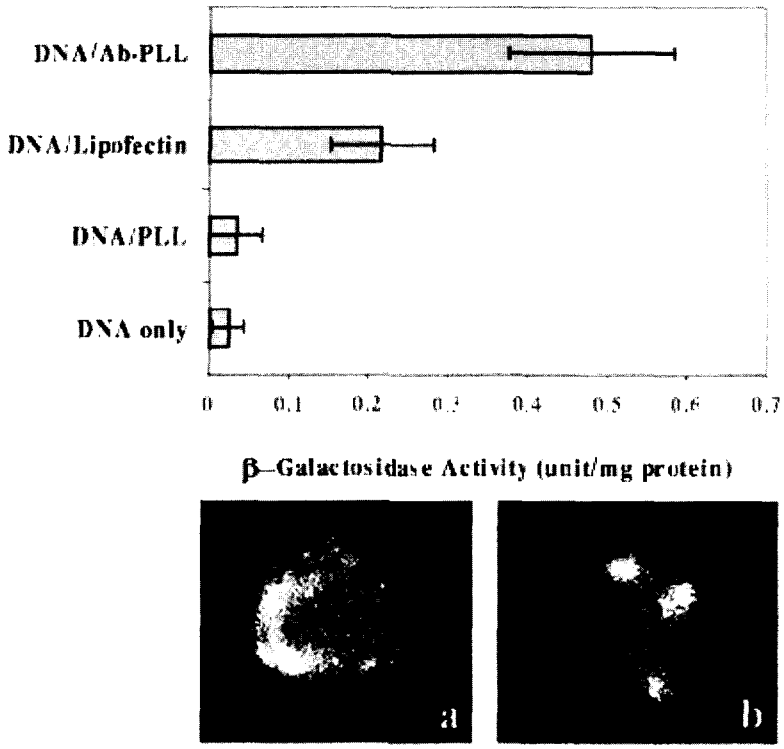

Figure 2. anti-JL1 antibody-mediated gene transfer into Molt 4, human leukemia T cells.

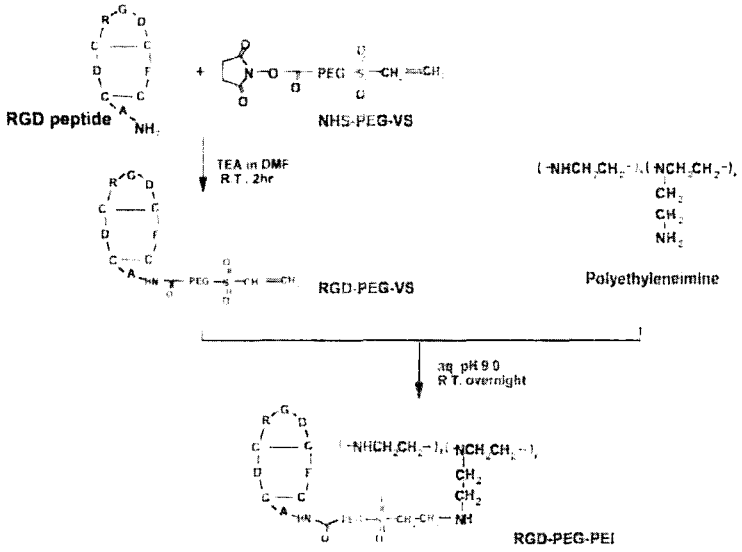

Figure 3. Synthesis scheme of PEI-g-PEG-RGD conjugates

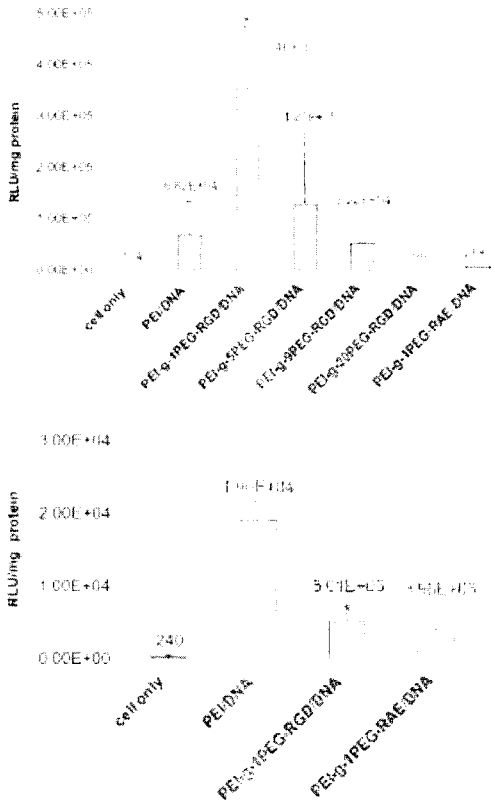

Figure 4. αvβ3/αvβ5 Integrin-mediated gene transfer into angiogenic endothelial cells