Combinatorial Design of Multiantibody-Targeted Immunolipopolyplex Nanoparticles of Oligonucleotides for Leukemia Therapy

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Due to the sequence-specific hybridization and highly effective inhibiting translation of specific mRNA, oligonucleotides (ONs) such as antisense ODN and siRNA-based therapy has made considerable development and represented a new era of cancer therapy in the past several years. Unmodified ONs are vulnerable to exo- and endonucleases and are rapidly degraded *in vivo*. To address these drawbacks, polymeric and liposomal nanoparticles have been used as carriers to deliver ONs to down-regulate targeted mRNAs. Our group has successfully synthesized ON-containing immunolipopolyplex nanoparticles (ILPs) for the therapy of Chronic Lymphocytic leukemia (CLL), which is the most common adult leukemia in the world. To further improve the selectivity and specificity to target tumor cells and alleviate the side effects, multiantibody-conjugated ILPs were developed for B-CLL therapy through a combinatorial design. A microfluidics based antibody microarray with high throughput was used to study the combinatorial effects of antibodies for specific cell binding. Optical tweezer was applied to quantify the dynamic interactions and binding force of cell surface receptors and antibodies. The synergistic/additive cell internalization and bcl-2 down-regulation of ILPs targeted by selected antibody combination at different molar ratios were investigated by confocal microscopy, flow cytometry and Western blotting. Good agreement was observed between the microarray and ILPs results for both cell lines and patient cells.