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Research Seminar

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Micelles and Lipid Nanoparticles: Catalysis and Biomedical Applications

Abstract

Part I of this presentation focuses on the synthesis and applications of PS-750-M, an environmentally benign surfactant developed to form aqueous micelles with polar cores. The application of PS-750-M in (a) Suzuki-Miyaura couplings of unactivated quinoline systems in water;[1] and (b) sulfonylation of polyfluoroarenes[2] and a-arylation of alkyl nitro compound[3] will be described. PS-750-M contains both the hydrophobic and hydrophilic chains that are linked to a proline fragment. When dissolved in water, PS-750-M instantaneously forms micelles with slightly polar inner cores. PS-750-M functions as a green solvent that mimics toxic dipolar-aprotic solvents, such as DMF, DMAc, NMP, and 1, 4-dioxane. An aqueous micellar reaction medium derived from PS-750-M is recyclable.

Part II will focus on the use of cationic lipids as delivery agents for RNAi therapeutics.[4, 5] We first explored in vivo utility of hydroxylated oxime ether lipids (OELs). Our studies show that the surface modification of formulations of one analog, OEL4, was essential for tumor accumulation in mice bearing human lung cancer xenographs.[6] The surface-modified OEL4 formulations were developed by inclusion of a PEG lipid polymer (distearoylphosphatidylethanolamine (DSPE)) carrying varying degrees of PEG molecules. The resulting PEGylated OELs formed stable vesicles and retained the ability to associate with DsiRNA duplexes.[6] However, vesicle stability and gene knock-down potential depended on the type of PEG lipid used. OEL4 containing DSPE-PEG 350 and DSPE-PEG1000 promoted gene silencing (eGFP & luciferase) in cell culture assays, whereas OEL4-DSPE2000 formulations impaired the gene silencing.[6] In vivo studies were conducted in mice bearing human lung cancer (A549-luc2) tumors following intravenous injections. The fluorescent lipid probe DiR was included in the formulations to measure tissue biodistribution. The data show that OEL4 vesicles formulated using 3 mol% DSPE-PEG350 accumulate in tumors with high efficiency as compared to industry control formulations and provided beneficial tumor to liver ratios.[6] The vesicles also showed a statistically significant luciferase signal reduction in tumors as compared to untreated mice. Taken together, the OEL4/DSPE-PEG50 formulation serves as a novel candidate for delivery of RNAi therapeutics.

Boron-modified lipids have been envisaged to enhance the tumor-targeting ability of derived lipid-RNA complexes by increasing their retention time at tumor sites due to boron complexation with characteristic cell surface features of tumors. Preliminary cell culture experiments of a novel cationic boron-based lipid will be presented that show addition of the boronated lipid to OEL-complexed anti-eGFP DsiRNA duplexes improves eGFP down-regulation.

References

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