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**Small Bioactive Lipoplex (SBL) Nanoparticles Self-Assembled at Elevated Temperature and Pressure**[1]

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Conventional lipoplex (cationic liposome/DNA complex) serves well for gene transfer in cultured cells. However, their *in vivo* gene delivery activity is limited due to its relatively large size ($\geq$100 nm). This is due to incomplete charge neutralization as a result of the steric hindrance during the complexation between DNA and liposomes. Behr et al hypothesized that monomolecular DNA condensate can be prepared if the DNA sees the cationic lipid as monomers. Indeed, small nanoparticles ($\sim$30 nm) were prepared by using a single-chain cationic amphiphile which has a high solubility at the physiological condition. To stabilize the monomolecular condensate, Behr has included a SH group in the cationic amphiphile which could be oxidized to form a dimer. Unfortunately, the stabilized nanoparticles showed no transfection activity when delivered into cells. We hypothesized that similar small lipoplex can be prepared by using a double-chain cationic amphiphile if both DNA and the amphiphile can be soluble in the same solvent. A hydrofluorocarbon HFC-152a is an excellent solvent for the cationic lipid DOTAP at an elevated temperature ($\sim$35 °C) and pressure ($\sim$300 atm). Since the solvent can accommodate small amounts of water, DNA or siRNA could be introduced into the system to allow lipoplex formation. The resulting Small Bioactive Lipoplex (SBL) is 30-50 nm in diameter and can transfect cultured cells. Freeze-fracture electron microscopy showed that SBL are solid nanoparticles without any lipid bilayer structure. Since plasmid DNA is fragile at elevated temperature and pressure, we have concentrated our effort in siRNA which is stable under the same conditions. The new formulation shows great promise as an *in vivo* delivery vector when small particles are required for efficient penetration into the tissues.

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