Optimization of *in Vivo* Gene Transfer by Regulating Biological Response to Vectors

○Makiya Nishikawa (Grad. Sch. of Pharm. Sci., Kyoto Univ.)

Because the spatio-temporal distribution of transgenes determines the therapeutic efficacy of *in vivo* gene transfer approaches, intensive efforts have been made to optimize the distribution by developing novel vectors with better gene delivery and transfer properties and by exploring proper administration methods for vectors. In this pursuit, however, not only the level of the expression, but also the duration and cell-specificity of the expression, and the number of transfected cells, should be evaluated. Upon administration, vectors encounter with target cells, antigen presenting cells, serum proteins and other biological components; this would affect the transgene expression profile. Although plasmid DNA is less immunogenic than viral vectors, it would induce the release of inflammatory cytokines, due mainly to the presence of unmethylated CpG dinucleotides, or CpG motifs, in plasmid DNA. In this presentation, I will discuss how to optimize *in vivo* gene transfer by regulating the biological responses to nonviral vectors. An intravenous injection of plasmid DNA/cationic liposome complex, or lipoplex, resulted not only in the induction of inflammatory cytokines such as tumor necrosis factor, but also in the activation of NF-κB, a transcription factor, in the lung. Based on the latter finding, additional NF-κB binding sequences were inserted into a conventional plasmid DNA to obtain a high transgene expression in the lung. Separately, the number of the CpG motifs in plasmid DNA was reduced in an attempt to achieve long-term expression. Sustained gene expression of interferons was effective for inhibiting experimental pulmonary metastasis in mice.