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TITLE

CHALLENGES IN SIRNA/ SHRNA DELIVERY AND DEVELOPMENT OF RNAI THERAPEUTICS FOR CANCER

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Although small interfering RNA (siRNA) treatment holds great promise for the treatment of cancers, the field has been held back by the availability of suitable delivery system. Unmodified, naked siRNAs are relatively unstable in blood and serum as they are rapidly degraded by endonuclease and exonucleases, thereby having very short in vivo half-life. The administered siRNA, should be suitably internalized by the target cell, must avoid endosomal uptake & errant siRNA compartmentalization for exerting gene silencing activity. Selection and formulation of siRNA with an appropriate biocompatible and possibly "genocompatible" delivery system is necessary for improving biological stability, targeted cell uptake, and pharmacokinetics of siRNA. Inappropriate selection of a delivery vector can thereby reduce gene-silencing activity and even enhance off-target effects. Delivery systems can also alter the pharmacokinetics of siRNA by altering their molecular and physical size so as to reduce excretion via the kidneys and thereby prolong in vivo half-life. Targeting to diseases cell is necessary for efficient gene silencing. Once inside the cell, siRNA has to escape compartmentalization into cell organelles such as endosomes and lysosomes, be intracellularly bioavailable, and interact with its intended mRNA targets in the cytosol to effect highly potent and sequence-specific gene-silencing activity. Strategies for delivering siRNA to specific tissue/organ in vivo following systemic administration involves hydrodynamic intravenous injection, cationic liposomes, cationic polymer and peptide based delivery systems, local in vivo delivery systems, etc. The success of RNAi therapeutics for cancer lies in formulating siRNA/shRNA involving a suitable delivery system, which can overcome these challenges.