siRNA Carrying Targeted Nanoparticles as a New Class of Rationally-Designed Anti-Cancer Therapeutics

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Computational modeling and simulation have increasingly become integral to scientific discovery, and significant advances in computational modeling and simulation are driven by increases in computing power. Advances in computational tools, access to supercomputers with unprecedented computational powers and recent development of dynamic algorithms that allow rapid analysis of publicly available datasets directly relevant to oncology now and provide a unique opportunity for a biomedical revolution that can provide the foundation for therapeutic innovations aimed at more effective treatment of cancer patients. A large number of gene expression profiling studies have been curated for further secondary data analyses in Gene Expression Omnibus (http://www.ncbi.nlm.nih.gov/geo/) and in cancer specific interrogating tools provided by Oncomine. This highly data rich knowledge environment is poised to provide high genetic and molecular resolution for various cancer types and help identify key target genes for therapeutic gene knockdown efforts using RNA interference (RNAi) therapeutics [1,2].

RNA interference (RNAi) has emerged as an attractive technology for silencing the expression of specific genes in human cells. In the physiological RNA interference pathway of gene silencing, double stranded RNAs are processed into small interfering RNAs (siRNA) by the Rnase enzyme Dicer. These siRNAs are incorporated into a RNA-induced silencing complex (RISC), that is capable of identifying and degrading mRNA that is complementary to the antisense strand of the siRNA thereby causing “gene silencing” [2]. However, sequence-specific gene knockdown via RNAi can also be triggered by a variety of synthetic double-stranded siRNA species that are capable of serving as Dicer substrates and are therefore being developed as potential RNAi therapeutics candidates [1]. Several formidable obstacles exist for the development of siRNA as RNAi therapeutics, including their rapid degradation by nuclease in the blood, poor cellular uptake, and requirements for endosomal escape after cellular uptake, off-target effects due to their microRNA-like activity profile, and their inflammatory effects [1,3,4]. It remains to be seen if specific formulation strategies or structural modifications in the synthetic siRNA molecules can effectively overcome these obstacles or prevent inflammatory acute immune responses, including activation of innate immune receptors and/or the complement system and release of proinflammatory cytokines.

Nanotechnology-enabled delivery of anti-cancer therapeutics is an area of intense translational research [5,6]. Rationally designed biotargeted anti-cancer nanomedicines have the potential to substantially improve the therapeutic index of their “payload” by (1) increasing their potency via a (a) selective delivery to target cancer cells as well as (b) improved cellular pharmacokinetic/pharmacodynamics (PK/PD) features that avoid the multi-drug resistance associated drug efflux pumps and (2) reducing their systemic toxicity and undesired off-target effects. Several non-targeted nanomedicine candidates are being evaluated in clinical trials or have been given FDA approval, including biocompatible micellar, liposomal, and polymeric formulations of standard chemotherapy drugs. Several biotargeting moieties are being explored in pre-clinical studies including small molecules, antibodies/antibody fragments, affibodies, cell penetrating peptides, cytokines, avimers and aptamers. Current research efforts in several laboratories are aimed at overcoming the barriers that limit the effective tumor delivery and penetration of the nanomedicine candidates as anti-cancer therapeutics, including: [1] heterogeneous tumor circulation caused by abnormal and irregular architecture of the tumor vasculature, [2] intratumoral vascular hyperpermeability contributing to increased interstitial pressure in the targeted tumor that substantially reduces the convective transport of nanoparticles and [3] impaired diffusion in the context of an abnormal and highly dense extracellular collagen matrix in the tumor microenvironment.

Nanoparticles represent particularly attractive delivery systems for siRNA and may provide the foundation for rational design and formulation of RNAi-triggering nanomedicines. siRNA can be delivered with a therapeutic intent using lipid-based delivery platforms such as stable nucleic acid lipid particles (SNALP) with a lipid bilayer containing cationic as well as fusogenic lipids and a diffusible PEG-lipid coat, polymers, cationic complexes, recombinant fusion proteins, conjugates, or polyconjugates [1-3, 7-24]. Several investigators have reported preclinical and early clinical proof of concept studies demonstrating that systemic delivery of a siRNA nanoparticle targeting a specific gene transcript can elicit anti-tumor responses [10]. Davis et al. reported siRNA-loaded multifunctional nanoparticles that consist of a cyclodextrin-based synthetic polymer, a transferring receptor ligand for active targeting, and polyethylene glycol as a hydrophilic polymer for nanoparticle stability [19]. Afonin et al. developed self-assembling functional nanoparticles for siRNA delivery using two complementary nanoscaffold designs (nanoring and nanocube), which serve as carriers of multiple siRNAs [12]. Lee et al. [9] recently reported the synthesis of RNAi-microsponges as a novel nanoscale delivery vehicle in which RNAi polymers that self-assemble into nanoscale pleated sheets of hairpin RNA, which in turn form sponge-like microspheres. The RNAi-microsponges are processed to siRNA only after cellular uptake. Sakurai et al. reported the use of a fusogenic peptide to modify liposomes to enhance the endosomal escape of the encapsulated siRNA delivered as the payload against cancer cells [16]. Polymeric vectors such as polyethylenimine (PEI) have also been used for siRNA delivery.

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In recent years, several recombinant fusion proteins that consist of a cell surface targeting moiety (e.g. an antibody fragment or ligand) and an oligonucleotide complexation moiety (e.g. truncated protamine) have been designed for targeted delivery of siRNA [21-23]. These nanoscale delivery platforms offer several theoretical and practical advantages over more traditional lipid-based nanoparticle formulations [21]. Song et al. reported the preclinical proof of concept that such fusion proteins can selectively deliver effective doses of siRNA to cancer cells both in vitro and in vivo [22]. Further preclinical and clinical development of the most promising nanoscale delivery platforms for selective delivery of siRNA may provide the foundation for much needed therapeutic innovations against various forms of cancer, especially those that do not respond to contemporary chemotherapy or radiation therapy regimens.

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