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Multi-tiered strategy for an optimization of therapeutic siRNA compositions and their delivery

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Silencing of gene expression by small interfering RNA (siRNA) is promising for drug target discovery and as a therapy. However, there are a number of impediments to the practical use of this technology, namely, an off-target effects of siRNA through its less-than perfect but still detrimental binding to partially matching mRNAs, an instability of siRNAs in the bloodstream due to their susceptibility to nucleases and undesired effects on immune system. To address these restrictions, we developed multi-tiered strategy of optimization of therapeutics siRNA compositions and their delivery. First, we designed Tree-SORT algorithm capable of top-down prediction of the human siRNA with minimized off-target hybridization and pre-computed a list of the best siRNA locations within each human gene ("siRNA seats"). To efficiently deliver siRNA, we designed a novel DNA/albumin-based vehicle that forms a "basket" surrounding the siRNA and provides both steric separation of siRNA from nucleases and local excess of the substrate for nuclease action. Importantly, basket-forming DNA molecules may be modified to stimulate an antioxidant response in target tissue that is achieved by increase in its 8-oxo-dG or GC content that is known to stimulate TLRs that could be desirable when treating certain human disorders. To study effects of these modifications to the standard siRNA delivery protocols further, we chose relatively uncomplicated model of substantial clinical value - a perfusion of isolated human organs before transplantation. Our preliminary data imply that DNA baskets may be a promising technology for further development as the delivery vehicle for siRNA therapeutics.

Biography

Ancha Baranova, a specialist in the area of functional genomics of complex human diseases, is an Associate Professor in the School of Systems Biology, College of Science, George Mason University in Fairfax, Virginia, USA. Dr. Baranova's major academic contributions are in the field of functional genomics, with emphasis on cancer and metabolic syndrome-related disorders. A significant part of Dr. Baranova's efforts is dedicated to *in silico* analysis of the publicly available genomics and proteomics databases. Dr. Baranova directs a team of postgraduate and graduate associates that employs a multidisciplinary approach in order to broaden research perspective in the genetics of complex human diseases. Dr. Baranova has published about 50 manuscripts in international journals including Genomics, Hepatology, Clinical Cancer Research, FASEB Journal, FEBS Letter, Bioinformatics, Leukemia and Lymphoma, Oncogene, and others.

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