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Volkmar Weissig

Midwestern University Glendale, USA
Pennsylvania State University, USA
Pennstate Hershey Cancer Institute, USA

DQAsome-based delivery of phosphorothioate gapmer antisense oligonucleotides as therapy for *Clostridium difficile*

Statement of the Problem: *C. Difficile* Infection (CDI) is a major healthcare burden due its prevalence, its communicable nature within healthcare settings, its frequent need for multiple rounds of conventional antibiotics and its predilection for severe forms of colitis. Unpredictable responses associated with conventional antibiotics have raised significant interest in designing alternative CDI therapies, among which "antisense antibiotics" able to prevent the expression of bacterial genes through posttranscriptional mechanisms appeared of particular interest to us. The purpose of this study was to test DQA some like cationic nanovesicles composed of bolaamphiphiles as a delivery system for 2'-O-methyl phosphorothioate gapmer antisense oligonucleotides (ASO) in order to target the expression of essential genes of *C. difficile*.

Methodology: The ASO were assessed for their ability to inhibit mRNA translation using luciferase reporter and *C. difficile* protein expression plasmid constructs in a coupled transcription-translation system. Bolasomes were prepared as described and characterized by particle size distribution, zeta potential and oligonucleotide binding capacity. Anaerobic *C. difficile* log phase cultures were treated with serial doses of nanocomplexes obtained from incubating the cationic bolasomes with ASO's.

Results: Antisense gapmers for four chosen gene targets achieved nanomolar minimum inhibitory concentrations for *C. difficile*. No inhibition of bacterial growth was found in treatments at matched dosages of scrambled gapmers or plain oligonucleotide-free bolasomes compared to untreated cultures.

Conclusion & Significance: Cationic bolasomes originally developed for the delivery of biologically active molecules to mammalian mitochondria can successfully be used to deliver ASOs into bacteria. We also report the first successful *in vitro* antisense treatment to inhibit growth of *C. difficile*. The efficient delivery of antisense molecules via DQAsome-like nanovesicles into bacteria will allow the advantageous targeting of virulence functions essential for infection, disease, and recurrence.

Biography

Volkmar Weissig, is a Tenured Full Professor of Pharmacology and Chair of the Department of Pharmaceutical Sciences and Co-Director of the Nanomedicine Center of Excellence in Translational Cancer Research at Midwestern University Glendale, AZ, USA. He holds 16 patents and has published over 100 research papers, review articles and book chapters, mostly in the area of nano drug delivery systems. He also edited and published 8 books. Since the late 1990s, he has pioneered the development of vesicular nanocarriers for the delivery of biologically active molecules to mitochondria within living mammalian cells *in vitro* and *in vivo*. In 2009, he was inducted into the World Technology Network as a Fellow, and in 2014, he was elected as Inaugural President of the World Mitochondria Society.

vweiss@midwestern.edu

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