Strong immune response to new siRNA drugs in development may cause toxic side effects

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Small synthetic fragments of genetic material called small interfering RNA (siRNA) can block production of abnormal proteins; however, these exciting new drug candidates can also induce a strong immune response, causing toxic side effects. Understanding how siRNA stimulates this undesirable immune activity, how to test for it, and how to design siRNA drugs to avoid it are critical topics explored in a timely review article published online ahead of print in *Oligonucleotides*, a peer-reviewed journal published by Mary Ann Liebert.

siRNAs are duplex structures comprised of short oligonucleotide sequences. The discovery that naturally occurring and synthetic siRNAs can effectively prevent expression of a disease gene sparked intense interest in developing siRNAs as drugs. However, depending on the structure and sequence of a siRNA and how it is delivered, it may induce a potent innate immune response in humans, stimulating the release of inflammatory chemicals such as cytokines and interferons.

Exploring the possibility of designing synthetic siRNAs and developing novel delivery methods that would exploit the drug-like capabilities of siRNA while preventing toxic side effects, researchers are working to understand the mechanism by which siRNA stimulates the immune system. In the article entitled, "siRNA and Innate Immunity," Marjorie Robbins, Adam Judge, and Ian MacLachlan, from Tekmira Pharmaceuticals (Burnaby, British Columbia, Canada), describe the different possible mechanisms for siRNA-mediated immune activation in various cell types, present preferable siRNA sequences and strategies

for chemically modifying the siRNA to minimize its immunostimulatory effects, and suggest experimental methods for studying the safety of siRNA therapeutics.

The authors conclude, "We are confident that through the judicious application of well-informed siRNA design and the use of increasingly effective delivery systems, demonstrations of systemic siRNA in human subjects will soon be realized."

"This is perhaps the most comprehensive review on siRNAs and innate immunity to date and a must read for anyone using siRNAs therapeutically," says John Rossi, PhD, Co-Editor-in-Chief of *Oligonucleotides* and Professor in the Department of Molecular Biology, Beckman Research Institute of the City of Hope (Duarte, CA).

More information: The article is available free online at www.liebertpub.com/oli

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