In vivo screening of modified siRNAs for non-specific antiviral effect in a small fish model: number and localization in the strands are important

Small interfering RNAs (siRNAs) are promising new active compounds in gene medicine but the induction of non-specific immune responses following their delivery continues to be a serious problem. With the purpose of avoiding such effects chemically modified siRNAs are tested in screening assay but often only examining the expression of specific immunologically relevant genes in selected cell populations typically blood cells from treated animals or humans. Assays using a relevant physiological state in biological models as read-out are not common. Here we use a fish model where the innate antiviral effect of siRNAs is functionally monitored as reduced mortality in challenge studies involving an interferon sensitive virus. Modifications with locked nucleic acid (LNA), altitol nucleic acid (ANA) and hexitol nucleic acid (HNA) reduced the antiviral protection in this model indicative of altered immunogenicity. For LNA modified siRNAs, the number and localization of modifications in the single strands was found to be important and a correlation between antiviral protection and the thermal stability of siRNAs was found. The previously published sisiRNA will in some sequences, but not all, increase the antiviral effect of siRNAs. The applied fish model represents a potent tool for conducting fast but statistically and scientifically relevant evaluations of chemically optimized siRNAs with respect to non-specific antiviral effects in vivo.

General information
Publication status: Published
Organisations: National Veterinary Institute, Division of Poultry, Fish and Fur Animals, Section of Fish Diseases, Aarhus University, University of Southern Denmark
Pages: 4653-4665
Publication date: 2012
Peer-reviewed: Yes

Publication information
Journal: Nucleic Acids Research
Volume: 40
Issue number: 10
ISSN (Print): 0305-1048
Ratings:
BFI (2012): BFI-level 2
Web of Science (2012): Impact factor 8.278
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
Original language: English
Electronic versions:
8A574d01.pdf
DOIs:
10.1093/nar/gks033

Bibliographical note
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.
Source: dtu
Source-ID: n:oai:DTIC-ART:highwire/365094979::16535
Research output: Contribution to journal › Journal article – Annual report year: 2012 › Research › peer-review