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New antisense inhibitors of hepatitis C virus

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Background: Antisense technology is one of the most straightforward approaches for suppressing unwanted gene expression. It can be applied as a treatment for the largest variety of disorders including cancer and infectious diseases. Various modifications of deoxyribose/ribose sugar backbone have greatly improved the efficiency, bioavailability and increased *in vivo* half-life of these compounds.

Method: Our technology is based on oligonucleotide analogs that contain specifically modified DNA bases and that are bound to organic complexes with highly selective nuclease activity. The structure of such compounds has been optimized using computer predictions, cell culture and *in vivo* activity assays.

Results: Two LNA-gapmer oligonucleotides, targeting genomic RNA of hepatitis C virus (HCV), were selected. These compounds contained three modified nucleobases (either 5-OH-dC or 8-oxo-dG) and had effective concentration 50 in HCV replicon cell line assay in low nanomolar range. They were equally efficient against the parental HCV-1b replicons and the replicons, containing mutations (T54A or T54S+A156S in NS3) associated with resistance against protease inhibitors. The catalytic activity of the compounds conjugated with artificial nuclease leaded to the further lowering of the effective concentration of the compounds. Importantly, the compounds were also highly active in mice model where a single dose (5 microgram/kg) of compound resulted in ca 50% reduction of targeted marker gene expression.

Conclusions: The oligonucleotides with nucleobase modifications are much more potent antiviral inhibitors than oligonucleotides without such modifications.

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Biography

Andres Merits has completed his Ph.D at the age of 26 years from Moscow State University (Russia) and postdoctoral studies from Institute of Biotechnology, University of Helsinki (Finland). He is group leader of RNA virus studies and the professor of Applied virology in Institute of Technology, University of Tartu. The main areas of research include molecular biology of RNA viruses (alphaviruses and HCV), development of systems and tools of virus-based bio- and gene technology and novel antiviral compounds. He has published more than pre-reviewed 50 papers in reputed journals.