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Antiviral Potency of Small-Interfering RNA Complementary to the Conserved Region within the Enterovirus Coding Region

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RNA interference (RNAi) is a sequence-specific 'gene expression knock-down' process. The potential of RNAi as a platform technology to develop novel antiviral therapeutics has been intensively explored. However, the antiviral potency of siRNAs is limited in virus groups characterized by high sequence diversity and genetic instability. To overcome this drawback, we developed novel siRNA-designing software to readily select siRNA candidates, particularly targeting highly conserved regions, called CAPSID (Convenient Application Program for siRNA Design). Using CAPSID, user can easily extract conserved patterns optimized for siRNA design in multiple mRNA targets and filter them for the selection of highly potent siRNA candidates by hierarchical selection criteria.

Human enterovirus (EV) having positive strand RNA as a genome is the major causative agent of numerous human diseases, such as aseptic meningitis, encephalitis, myocarditis, cardiomyopathy, and diabetes. In spite of that EV is the major pathogen of a wide spectrum of human diseases, the development of effective therapeutics against them are largely limited by their genomic diversity. By applying CAPSID program, we enabled to readily design MET-2C, a siRNA that targets a multi-enteroviral region located in the 2C cis-acting replication element (CRE) of the viral genome. Treatment of Hela cells with MET-2C significantly down-regulated viral replication and viral cytotoxicity by a number of EV reference strains, as well as by various clinical isolates. Also, in contrast to a siRNA targeting a region of virus capsid protein VP1, MET-2C was highly resistant to the emergence of viable escape mutants resulting in persistent antiviral activity over time. Moreover, a siRNA targeting CRE region of other human enterovirus groups efficiently demolished detrimental cytopathic effects by viral replication.

These results strongly suggest that a siRNA designed by CAPSID exhibits universal antiviral effects against a variety of HEB serotypes. Plus, the data provides evidence that a siRNA properly designed from highly conserved virus genome region has a great advantage to achieve potent anti-viral activity. Finally,

we found that CAPSID is an improved method for siRNA design using highly conserved patterns and is expected to contribute to developing novel multi-mRNA-targeting siRNA agents such as universal antiviral therapeutics against highly divergent viral genomes.