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Preparation and Anti-Viral Activity of Oligoribonucleotides Containing 5-Fluorouridine W. H. Gmeiner, P. Sahasrabudhe, N. Schulte, P.L. Iversen, S. Rhode Contribution from the Eppley Cancer Institute, University of Nebraska Medical Center, Omaha, NE USA

Oligoribonucleotides consisting solely of FUrd have been prepared. Such oligoribonucleotides when taken up by cells release FUMP that is converted by cellular kinases into FUTP. FUTP is a substrate for viral and cellular RNA polymerases. We hypothesized that cellular uptake of oligoribonucleotides that contain FUrd into virally infected cells would result in efficient incorporation of FUrd into viral RNA. Viruses that utilize highly structured RNA molecules in their replicative processes may be prone to miscode proteins or be otherwise less efficient when FUrd is incorporated into viral RNA. To test this hypothesis we have prepared four oligomeric compounds that contain FUrd or FdUrd. Compound (1) contains six FdUrd and is a deoxynucleotide. Compound (2) is identical to compound (1) but contains a phosphorothioate backbone. Compound (3) is an oligoribonucleotide containing two FUrd in a 10 nucleotide oligomer. Compound (4) is an oligoribonucleotide containing eight FUrd residues. The oligomeric FUrd and FdUrd compounds (1) - (4) were tested for anti-viral activity against the parvovirus H-1. They all reduced virus yields with compounds (1), (2), and (3) reducing titers by 1.75 +/- 0.25 x 10-2 and compund (4) reducing titers by 10-3. Addition of deoxythymidine (dT) at 10-5 M reduced the inhibition of compounds (3) and (4) by a factor of 10 suggesting a TS independent mechanism. In addition, compound (4) had a dramatic effect on the morphology of infected or uninfected human kidney cells with or without the added dT. The treated cells assumed a more rounded shape within 24 hours of exposure to the drug. We will further discuss the cytoxic and antiviral effects of these and related compounds.

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Preparation of Enantiomerically Pure Branched DNA for Shape Specific Binding of RNA Hairpin Loops W.H. Gmeiner[1], Yin Zhong[1], Richard T. Pon[2] Contribution from the [1]Eppley Cancer Institute University of Nebraska Medical Center and the [2]Regional DNA Synthesis Laboratory, University of Calgary

The synthesis of branched DNA molecules (br-DNA) that are chiral at the point of branching and are prepared in optically pure form is described. The starting materials for these compounds are (D)- and (L)-aspartic acid that are reduced to the diol form. The 2-amino group is reacted with allyl chloride to leave a terminal double bond for attachment of a third strand of DNA. The 4-hydroxyl is tritylated with 4,4' dimethoxytrityl chloride and the 1-hydroxyl is reacted with phosponamidic chloride to form a reactive phosphoramidite. We have incorporated the resulting species into the interior of the DNA strand AGCT(br)TCGA by solid-phase synthesis. These branched DNA (br-DNA) molecules may have binding affinity for specific RNA hairpin loops. The br-DNA are being used to explore the requirements for stereospecificity at the point of branching for binding to hairpin loops from viral RNA. The spatial requirements for forming multiple hydrogen bonding and hydrophobic contacts with RNA hairpin loops will also be explored with these compounds.