COINS Seminar #10

Chemistry of Therapeutic Oligonucleotides: An Overview

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Date: November 27, 2015

Time: 2:30pm ~ 3:15pm

Venue: #3001, Innovation Center of Nanomedicine (iCONM)

Capacity: 40 people

Research Mixer:16:00-18:00(Fee:JPY500)

Registration: By E-mail (jimukyoku-coins@kawasaki-net.ne.jp)

Please send your "name" and "Affiliation"and"
Division"and"Attendance of Research Mixer"and"E-Mail"

—Abstract—

Since the commercial inception of oligonucleotide-based therapeutics in 1987, various therapeutic strategies based on multiple mechanisms have evolved. These strategies involve (not in any order) single-stranded oligonucleotides, like antisense oligonucleotide "gapmers" that mediate RNase H cleavage of messenger RNA, oligonucleotides that modulate mRNA splicing, and anti-microRNAs ("antagomirs"). RNA interference-based short interfering RNAs (siRNAs) and microRNA (miRNA) mimics are duplexes. Apart from such direct nucleic acid-targeting mechanisms, approaches involving direct interactions with proteins are also of therapeutic interest; these nucleic acid-based protein mediators include aptamers and immune modulators. In a recent development, entire mRNAs have been created to enable expression of protein-based therapeutics. Numerous chemical modifications have been designed, synthesized, and evaluated to confer "drug-like" properties on various classes of therapeutic oligonucleotides. The chemistries developed include pentofuranose sugar-based modifications (2′-*O*-Me, 2′-F, 2′-*O*-MOE, LNA, *S*-c-Et BNA, UNA, FANA, tricyclo-NA, and L-nucleotides), linkage modifications such as phosphorothioate (P=S), sugar-phosphate backbone replacements (phosphoramidates, PNA, PMO, and analogs), and nucleobase modifications (5-Me-C). Among the linkage modifications, the P=S linkage is unique as it provides metabolic stability and for single-stranded mechanisms, broad biodistribution advantages. Simple conjugate modifications with cholesterol and lipophilic molecules enhance biodistribution and cell-permeation properties. Polyethylene glycols (PEGs) have been conjugated to aptamers to improve pharmacokinetic properties. Recently, siRNAs conjugated to trivalent GalNAc ligand targeting the asialoglycoprotein receptor (ASGPR) expressed on liver hepatocytes have shown clinical success in multiple RNAi-based therapeutic applications. This conjugate strategy is being evaluated for other single-stranded oligonucleotide therapeutics as well. Packaging oligonucleotides into lipid nanoparticles (LNPs) constructed with ionizable lipids is effective for siRNAs and is being extended to mRNAs. Molecular inclusion complexes and polymer conjugates are also being evaluated for delivery of siRNAs. This presentation will provide an introduction to various clinically tested oligonucleotide motifs and delivery chemistries and their relative virtues and limitations.

＊Organizer: Center of Innovation (COI program) by JST

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<Venue access>

Name: Innovation Center of Nanomedicine (iCONM)

Address: 3-25-14, Tonomachi, Kawasaki-ku, Kawasaki 210-0821, JAPAN

Access by train:

Keikyu-Kawasaki Sta. to Kojima-Shinden Sta. by Keikyu-Daishi Line (ride time about 10 minutes) and Walk about 15 minutes to iCONM (See below access map)

Access by bus

"Bus stop on East Terminal at JR Kawasaki Sta."

1) No. 20 bus stop (KAWASAKI TSURUMI RINKO BUS Co.,LTD)

川 (kawa) 02 line; Tonomachi terminal, to "Tonomachi" bus stop (ride time about 30 minutes), walk about 3 minutes to iCONM from the bus stop

2) No. 20 bus stop (KAWASAKI TSURUMI RINKO BUS Co.,LTD)

川 (kawa) 02 line; Ukishima-Bashi terminal, to "King Sky Front Irigchi" (ride time about 20 minutes), walk about 5 minutes to iCONM from the bus stop

3) No. 16 bus stop (KAWASAKI TSURUMI RINKO BUS Co.,LTD)

川 (kawa) 03 line; Ukishima-bus terminal, to "King Sky Front Irigchi" (ride time about 30 minutes), walk about 5 minutes to iCONM from the bus stop

Access Map