COINS Seminar #10

Chemistry of Therapeutic Oligonucleotides: An Overview

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日程：2015 年 11 月 27 日（金）14：30～15：15
会場：ナノ医療イノベーションセンター（iCONM）3001 会議室
交流会：同日 16:00～18:00 会費 500 円
定員：40 名
申込：メール事前登録制、「氏名」「ご所属」「お役職」「交流会参加有無」「メールアドレス」を COINS 支援事務局宛にメールでお申込みください。
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—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.

*主催: JST　COI プログラム
「スマートライフケア社会への変革を先導するものづくりオープンイノベーション拠点（COINS）
研究統括　片岡一則　（川崎市産業振興財団 ナノ医療イノベーションセンター　センター長）
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別紙

＜会場へのアクセス＞

住所：

〒210-0821　神奈川県川崎市川崎区殿町 3-25-14

交通：

電車の方は　京急川崎駅から 京急大師線 「小島新田」下車 乗車時間約 10 分　 徒歩約１５分

バスの方は

「JR 川崎駅 東口ターミナル」

■20 番のりば

・川 02「殿町」行き乗車（臨港バス）乗車時間約 30 分「殿町」下車　徒歩約３分

・急行　快速「浮島橋」行き乗車（臨港バス）乗車時間約 20 分「キングスカイフロント入口」下車　徒歩約５分

■16 番のりば

・川 03「浮島バスターミナル」行き乗車（臨港バス　又は　川崎市営バス）乗車時間約 30 分「キングスカイフロント入口」下車　徒歩約５分

川崎生命科学・環境研究センター（LiSE）の隣です。