RNA Interference (RNAi) and Making Drugs out of Small Interfering RNAs (siRNAs)

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Synthetic small interfering RNAs (siRNAs) act as therapeutic agents through the RNA interference (RNAi) pathway and are specific and potent inhibitors of gene expression. These agents may be designed to target disease pathways previously considered “undruggable”. Numerous proof-of-concept studies both in animal models of human disease and in clinical trials demonstrate the broad potential and therapeutic value of RNAi therapeutics. The major challenge for the successful development of systemically delivered RNAi therapeutics had been the efficient delivery into organs or tissues and cells of interest to elicit RNAi mediated knockdown of faulty genes and effective translation of these approaches into clinic.

At Alnylam, we have advanced two delivery platforms for RNA interference (RNAi) based human therapeutics for liver-based disease molecular targets. The first one is lipid nanoparticles (LNPs) formulation containing siRNAs and used for intravenous administration. The second one, in which siRNAs are conjugated to trivalent GalNAc sugar to target asialoglycoprotein receptor (ASGPR) of hepatocytes are emerging as a potential new class of medicine supporting a broad clinical pipeline across multiple therapeutic targets by subcutaneous administration. Furthermore, we have been able to continuously optimize the siRNA chemical modifications and design resulting in the Enhanced Stabilization Chemistry (ESC) platform exhibiting improved efficacy and extended duration lasting for several months. Our progress and applications will be presented.