

# Innovative Polymer siRNA Carrier Development

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## 1 Introduction

In 1998, Drs. Mello and Fire, whose research was awarded a Nobel Prize in 2006, published research findings in *Nature* demonstrating that a particular form of ribonucleic acid or RNA - the cellular material responsible for the transmission of genetic information - can silence targeted genes. The form in question, known as siRNA, is a double-stranded complex of small interfering RNAs that is around 21 nucleotides in length. siRNA technology offers astounding potential for understanding and manipulating the cellular basis of human disease and is now the state-of-the-art method used by scientists to 'knock out' the expression of specific genes and thereby determine their biological functions. At the same time, siRNA medicine offers a revolutionary approach to the treatment of previously intractable diseases not susceptible to conventional medical technologies. A major bottleneck in the development of siRNA medical technology, however, is the delivery of siRNA to the desired cell type. Although several siRNA delivery systems have been reported in animal studies, including lipid-, polymer-, and peptide-based carrier systems, there are still no truly effective *in vivo* carriers available.

## 2 NDT Polymer siRNA Delivery Technologies

An innovative lipopolymer-based siRNA carrier has been successfully developed at Nitto Denko Technical Corporation (NDT). This new technology combines the advantages of polymer and lipid carriers, which both demonstrate great effectiveness in *in vitro* and *in vivo* siRNA delivery. The interaction of our novel lipopolymer with siRNA in aqueous environments leads to the formation of spherical nanoparticles exhibiting three distinct layers (Fig. 1A). One strength of our system is that it is environmentally responsive in the body, which means that the carrier will show different physical and functional properties in different environments within the body (e.g. in the blood circulation, migration to the target cells, and in the cell organelles).

### (1) Excellent Delivery Performance

The carrier shows efficient delivery of siRNA to cultured cells, resulting in significantly stronger gene inhibition and lower toxicity *in vitro* than the current leading siRNA carrier on the market (Fig. 1B). We have also developed a truly unique siRNA delivery product by pre-coating the bottom of the individual wells of cell culture plates with our lipopolymer material. In *in vivo* delivery studies, the NDT siRNA carrier shows efficient delivery of siRNA to the liver and significant inhibition of the apoB gene (up to 70% according to real-time PCR analysis) with long-lasting inhibitory effect (two weeks) after a single injection (Fig. 1C). This data on

the gene inhibition efficacy and duration of NDT's siRNA carrier is highly promising for the eventual translation to clinical siRNA therapeutics.

### (2) Delivery Specificity

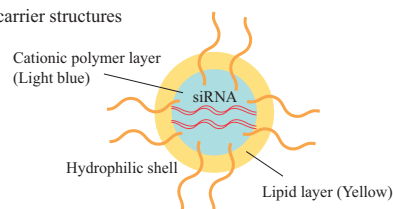
One of the most attractive features of current polymer carrier systems is the flexible ability to functionalize the material for very specific applications through facile attachment of functional groups, which gives it a very wide range of applications.

### (3) Safety

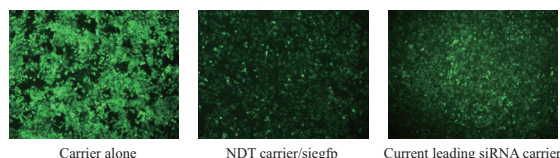
Red blood cell lysis assay indicated no lysis, while the therapeutic dose of siRNA/carrier was only one sixth of the ID50, indicating that the carrier will be safe for *in vivo* applications.

NDT siRNA delivery technology is a flexible platform for siRNA delivery. Tailoring the polymer matrix by controlling the ratio of hydrophobic and hydrophilic components, the molecular weight, and cation density has enabled us to produce self-assembling polymer-siRNA nanoparticles of defined size. This exceptional degree of control is expected to provide us with the ability to deliver siRNA to various desired organs, tissues, and cells for a wide variety of therapeutic applications.

A: Schematics of carrier structures



B: *In vitro* siRNA delivery efficiency



C: *In vivo* siRNA delivery efficiency

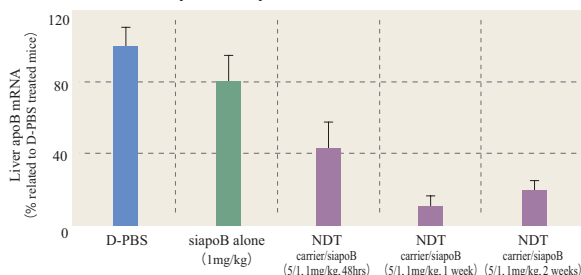


Fig.1 Innovative polymer siRNA carrier development