Case study: HSP47 siRNA (Nitto Denko Technical Corporation)

Nitto Denko Technical Corporation (NDT) was established in the US in 2000 as a centre of excellence for R&D for its parent company Nitto Denko Corporation, Japan. NDT focuses on polymer based technologies and their applications in a broad range of fields including biomedical, optical and nanotechnology. NDT is one of the leading providers of oligonucleotide (OGN) synthesis products including solid phase supports for oligosynthesis (NittoPhase™). NDT has been actively engaged in the development of polymeric drug delivery systems for *in vivo* therapeutic applications.

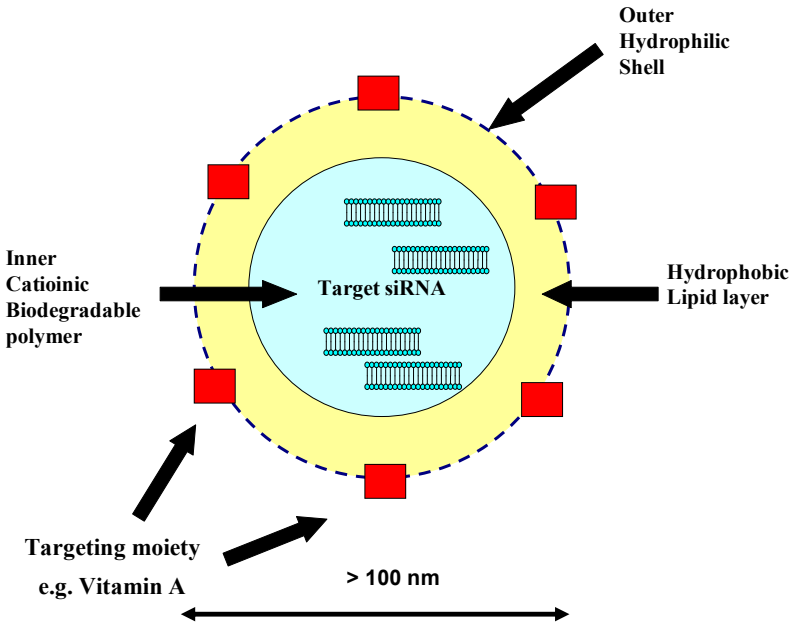
According to Dr Jain Krotz, Business Development at NDT the proprietary delivery platforms combine the key attributes of liposomes (self-aggregation, encapsulation) and polymers (biocompatibility, ease of manufacturing, stability and biodegradability). Furthermore, in designing the delivery platforms the company utilizes polymers, lipids and other molecules approved by the regulatory bodies to ensure safety of the final product. The company has developed a panel of delivery vehicles including liposomes, lipopolymers and nanomaterials.

NDTs delivery platforms have been applied to transport small molecules, genes and siRNA and can be formulated for a variety of delivery routes including oral, systemic and transdermal patches[i,ii]. For example, NDT has developed a novel, proprietary formulation of paclitaxel derived from self assembled nanoparticles of biodegradable polymers conjugated to paclitaxel. This novel formulation has shown excellent pre-clinical data (enhanced circulation time, dramatic reduction in toxicity of paclitaxel and significant improvement in efficacy compared to Abraxane®). This project is getting ready for Phase I, while the company is working with several major pharmaceutical companies worldwide to evaluate this novel drug delivery platform for various other oncology drugs.

In the siRNA therapeutics sector, NDT has been working on developing delivery systems for siRNA targeting various genes including ApoB for hypercholesterolemia and HSP47 for liver cirrhosis. HSP47 is a collagen-specific chaperone which

facilitates collagen secretion and has also been implicated in procollagen synthesis. Figure 44 is a schematic representation of a generic NDTs siRNA delivery platform.

Figure 44: NDT's siRNA delivery platform

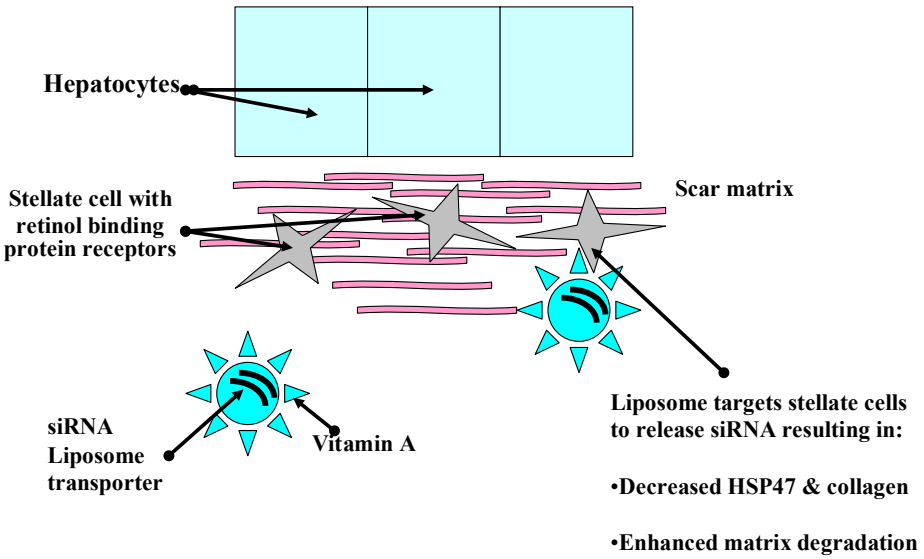


Source: PharmaVision.co.uk

In March 2008 Prof Niitsu and colleagues at the Sappro Medical University, Sapporo Japan published their groundbreaking research in Nature Biotechnology demonstrating that iv administration of siRNA encapsulated in vitamin-A coupled liposomes (VA-lip) could efficiently deliver siRNA gp46 (a rat homolog of HSP47) to hepatic stellate cells and cure liver cirrhosis in acute and chronic models of liver cirrhosis in rats. In liver fibrosis hepatic stellate cells become activated, proliferate and accumulate insoluble collagen, causing fibrosis (Figure 45).

The study showed that siRNA gp46 significantly suppressed gp46 expression and collagen secretion to cure liver cirrhosis and prolong animal survival.[iii] Importantly, relatively small amounts of siRNA (<0.75 mg/kg) were required for therapeutic effect, indicating that VA-lip delivery may provide a cost-effective method to minimize dose requirements. NDT has acquired this technology and Prof. Niitsu is working with NDT to develop and commercialize this product.

Figure 45: Mechanism of action of siRNA HSP47 in liver cirrhosis



Source: modified from Friedman, 2008

Meanwhile the company has been approached by miRNA companies and through numerous collaborations is assessing miRNA's potential in diagnostics with specific reference to identifying gene signatures associated with liver fibrosis.

Dr Mehrdad Tabrizi, VP, Business Development at NDT

"NDT is in a unique position. Through its expertise in chemistry, delivery, nanotechnology and manufacturing it has the ability to customize delivery vehicles for collaborators to transport any particular moiety from small molecules to siRNA. Whilst the company is focusing on systemic delivery it has the capacity to explore alternative delivery routes."

In our opinion NDT has considerable experience in developing delivery vehicles for RNAi transport via a variety of routes. Preliminary results in liver cirrhosis are very promising and demonstrate efficient systemic delivery to target tissues. The company has strengthened its IP within the arena and plans to enter clinical development late 2010/early 2011. The development of companion diagnostics could add another string to the company's bow and provide additional revenues for R&D reinvestment. Additional investment from collaborators is likely as the company progresses candidates within the clinic and accumulates proof-of-concept data for its delivery technology in vivo.

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[i] http://www.nitto.com/dpage/11.html

[ii] http://www.nitto.com/company/release/08_04_03/index.html

[iii] http://www.ndtcorp.com/img_publication/nbt1396.pdf