

**New Discoveries within Phosphorothioate ASOs**

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Drug discovery based on ASOs and siRNAs has during the last decade proven itself as a reliable and successful technology within the field of RNA therapeutics. In this talk, several highlights from the efforts of building and improving the ASO technology will be presented.

The talk will focus on using stereodefined phosphorothioate (PS) oligonucleotide chemistry in drug discovery and highlight some of the biological consequences of applying this in terms of e.g. *in vivo* compound efficacy and specific tissue uptake. Combining these platform developments with the established liver targeting Gal-NAC technology it is possible to reduce the required *in vivo* dose with a factor of 20 as compared to the naked parent oligonucleotide. In addition, the talk will show recent data around the stabilization of oligonucleotides using phosphorodithioates (PS<sub>2</sub>). Here the *in vitro* and *in vivo* read-outs with and without stereodefined linkages are presented together with the *in vivo* metabolite profile as well as the observed duration of action.