Are in vitro DDI Studies Needed for Oligonucleotide Therapeutics?

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It is a truth universally acknowledged, that *in vitro* drug interaction studies may be unnecessary for oligonucleotide therapeutics. Furthermore, there have been multiple discussions that ONT development can be viewed as a 'platform' technology, and certain studies may not be needed based on historical data.

In fact, per US FDA June 2024 Guidance for Industry "Clinical Pharmacology Considerations for the Development of Oligonucleotide Therapeutics".

'*Based on current experience, oligonucleotide therapeutics either do not modulate or minimally modulate the major CYP enzymes and drug transporters. However, an overall recommendation for specific types of oligonucleotide therapeutics (e.g., based on chemistry or delivery strategies) cannot be provided at this time. The sponsor should provide justification if in vitro assessments of the potential of oligonucleotide therapeutics to affect CYP enzymes or transporters are not conducted.*

Other possible mechanisms for interactions between oligonucleotide therapeutics and CYP enzymes or transporters or their modulators (e.g., by interfering with the synthesis or degradation of heme or cytokines) should be considered based on the pharmacology of the oligonucleotide therapeutic.

If studies indicate that the oligonucleotide therapeutic could modulate CYP enzymes or transporters, the sponsor should consider clinical studies to evaluate in vivo drug interactions.'

In the past 15+ years, QPS have worked on 100+ *in vitro* DDI studies of different ONT (aptamer, single strand, double strand, GalNAc conjugate, lipid conjugate, peptide conjugate, proteins conjugate, antibody conjugate, and LNP encapsulated). The data is quite surprising – approximately 16% of ONT are CYP450 reversible inhibitors but almost not time-dependent inhibitors, 33% are SLC inhibitors but not efflux inhibitors, and 35% are CYP450 inducers for at least one CYP isoform. Unsurprisingly, none showed ONT being Efflux substrates nor SLC substrates nor CYP450 substrates.

In view of these historical data, are *in vitro* DDI studies really unnecessary for ONT? This presentation explore the concept that it may be more informative to view potential DDI

from the viewpoint of ONT concentrations within the specific cellular components with respect to relevant clinical concentrations.