**Unique translational clinical pharmacology challenges with novel, non-traditional drug molecules: the example of siRNA therapeutics**

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Drugs are traditionally low molecular weight chemicals (“small molecules”) or high molecular weight proteins (“large molecules”). But many other types of drug molecules are being developed and increasingly entering clinical use. Examples include RNA therapeutics (e.g., mRNA vaccines), cell-based therapies (e.g., CAR-T), various genomic editing technologies (e.g., CRISPR), and complex multi-specific drug conjugates (e.g., T-cell engagers). Most clinical development programs start with first-in-human (FIH) studies in healthy volunteers using single- and multiple ascending dose (SAD and MAD) designs, with pharmacokinetics, safety and tolerability the primary objectives. This translational step from nonclinical to clinical work is a major milestone in drug development, but poses unique clinical pharmacology challenges when developing novel, non-traditional drug molecules. This presentation covers some of these challenges using small interfering RNA (siRNA) therapeutics as examples. Key points include the following:

1. Relevance of nonclinical data for predicting target organs of toxicity and human safety
2. Selection of FIH clinical trial populations and starting doses
3. Accurate measurement of drugs in biological fluids for pharmacokinetic analyses
4. Data requirements for dose escalation decisions
5. Importance of pharmacokinetic-pharmacodynamic modelling to guide go/no-go decisions
6. Selection of recommended phase 2 dose(s)
7. Requirements for “special population” studies, including drug-drug interactions, QT-interval etc.
8. Evolving regulatory environments

Guidance with these challenges can be sort from similar past programs, where information is available, and by working with expert reviewers on HRECs, FIH trial clinicians with experience, sponsors with previous successes with a given type, and international regulators. Translational clinical pharmacology is an exciting field with unique challenges for novel, non-traditional drug molecules. Scientists and clinicians who enjoy turning principles into practice are urgently needed at the nonclinical-clinical interface to ensure new drug types enter human trials safely and efficiently.