IMS-P14 Optimization of Therapeutic Phosphorothioate Oligonucletides by *P*-Chirality Control

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The introduction of internucleotide phosphorothioate (PS) linkages broadly improves the pharmaceutical properties of nucleic acid therapeutics. In the past, it was not possible to control the geometry of PS installation, such that conventional PS-containing therapeutics comprise mixtures of 2^n *P*-diastereoisomers, where *n* is the number of PS linkages. In small molecules, it is well-established that stereoisomers can exhibit radically different biological activities, thus rendering it inadvisable in that arena to administer stereochemical mixtures to patients. Recent advances at WaVe Life Sciences have enabled the practical synthesis of completely *P*-stereodefined PS oligonucleotides, which in turn has made it possible for the first time to assess the biological impact of *P*-stereochemical variation for this emerging class of next-generation drugs. Here we present the rational design and synthesis of *P*-stereopure therapeutic PS oligonucleotides and demonstrate a clear relationship between *P*-chirality and key pharmaceutical properties. These studies suggest that *P*-stereodefined PS-oligoncleotides will provide safer and more effective medicines.