**IScEt: Generation 2.5**

**Antisense Drugs**

**Advances in Medicinal Chemistry Have Driven the Evolution of Isis Antisense Drugs**

- High specificity for the target
- Non-interacting oligonucleotides
- Broad applicability
- Non-polymeric synthetic oligonucleotides
- Reduced drug-drug interactions
- Stable oligonucleotides
- Optimized structure to eliminate toxicity

**Isis’ Medicinal Chemistry Improves on Antisense Qualities & Makes Even Better Drugs**

- Improved distribution to target tissues
- Increased stability of the drug in the body
- Improved potency
- Less stress on the necessary dose
- Low-dose equivalent to small molecule
- Improved therapeutic index

**Natural Nucleic Acids Like DNA & RNA Make Poor Drugs**

- Limited options for drug molecules
- Limited stability with regard to impurities
- Cleavage from the body too quick
- Non-therapeutic oligonucleotides
- Other issues with other small molecules

**HISTORY OF ASO CHEMISTRIES**

**History of Antisense Oligonucleotide Medicinal Chemistry: The Most Useful Chemicals**

- Improvement in effectiveness
- Potency & safety
- Improved stability & affinity

**Structure of Mipomersen, A Representative Second-Generation Antisense Drug**

- Target optimization
- Oligonucleotide synthesis
- Improved stability & affinity

**Generation 2.5 Advantages - IScEt Chemistry**

**Isis’ Chemistry Improves Second-Generation Drugs**

- Chemistry improves binding affinity & potency
- Improves safety by reducing non-specific protein binding interactions
- Improves stability, affinity, potency & specificity

**What Generation 2.5 Means for Isis’ Pipeline**

- Second-generation drug: Proven, Potent & Safe
- Extends clinical safety experience with first- & second-generation antisense drugs
- cEt ASO approved for use
- Well-tolerated in multiple patient populations
- Stable on oral dosing in the clinic
- Generation 2.5 extends the application of antisense & ag discovery
- Increased potency
- Increased patient convenience
- Lower doses
- Potential for commercially feasible oral dosing
- Improved target selection & knockdown
- Extends Isis’ therapeutic outreach to include property
- Targeted integration into ipi for pipeline
- First generation 2.5 drug in the clinic - ISIS-STAT3Rx
- 6,000 subjects dosed
- Efficient, potent, broad applicability

**More than 80 Nucleoside Structures Profiled For Improved Properties**

- BNA nucleosides
- ¥-Me-BNA
- cEt BNA
- MOE BNA
- oxynucleoside-BNA
- vinyl-carbo-BNA
- ¥-L-LNA nucleosides
- ¥-L-LNA
- ¥-Me¥-L-LNA
- ¥-Me¥-L-E
- ¥-L-LNA-carbo-BNA
- Other constrained nucleosides
- Tricyclo-BNA
- HNA
- MOE-ANA
- F-HNA
- F-CuNA

**First Demonstration of Generation 2.5 Potential**

**Potent Activity of STAT3 Inhibitor in Human Tumors**

- 80% inhibition of tumor growth
- No effect on BW or other toxicity endpoints
- First demonstration for specific disease where increase in efficacy for particular setting