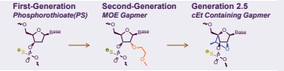
IScEt: Generation 2.5

ANTISENSE DRUGS

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



	First-Generation *Phosphorothioate(PS)*	Second-Generation *MOE Gapmer*	Generation 2.5 *cEt Containing Gapmer*
Chemistry Attributes	✓ Adds stability ✓ Improves distribution to tissues	✓ Increases potency ✓ Increases stability ✓ Reduces non-specific toxicities	✓ Improves potency & therapeutic index ✓ Expands range of targets & tissues
Potency	1,200 to 3,500 mg/week	~100 to 400 mg/week	<5 to 40 mg/week
Dose Frequency	Daily to 3x/week	Weekly to monthly	Weekly to monthly
Cost of Therapy	Between branded small molecules & antibodies	Competitive with upper end of small molecules	>3-fold less costly
Routes of Administration	IV, enema & intrathecal	SC, IV, inhalation, topical & intrathecal	Same + Oral

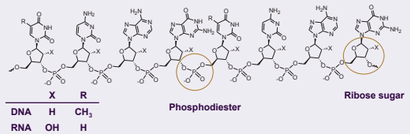
Antisense Offers All the Qualities to Create Better Drugs

- **High specificity for the target**
  - More selectivity a drug has for its target the better the drug
- **Broad applicability**
  - More potential targets opens up the possibilities for many diseases where there are no treatment options
- **Rational drug design**
  - Distribution & metabolism of antisense drugs are very similar drug-to-drug; predictable safety profiles
- **Efficiency of platform**
  - Saves time & lowers development expenses
- **Cost competitive manufacture**
  - Advances in process chemistry applicable across platform

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

- **Improve distribution to target tissues**
- **Increase stability of the drug in the body**
- **Improve potency**
  - Will decrease the necessary dose
  - Opens up oral as commercially feasible for antisense
- **Improve therapeutic index**

Natural Nucleic Acids Like DNA & RNA Make Poor Drugs

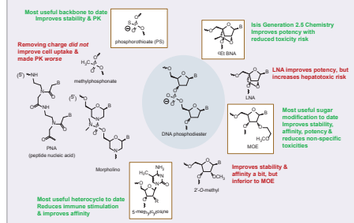


	X	R
DNA	H	CH_3
RNA	OH	H

- **Limitations of DNA & RNA as drug molecules**
  - Low binding affinity for target RNA
  - Clearance from the body is too quick
  - The pharmaceutical industry has addressed these issues with other 'natural products' using medicinal chemistry
- **Structural Limitations of DNA & RNA**

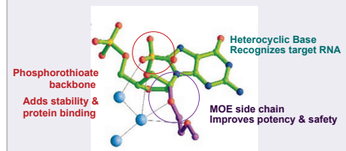
HISTORY OF ASO CHEMISTRIES

History of Antisense Oligonucleotide Medicinal Chemistry *The Most Useful Chemistries*



The Magic of MOE Confers Unique Qualities That Make Great Drugs

- **2'-Methoxyethyl (MOE) Oligonucleotide Crystal Structure**

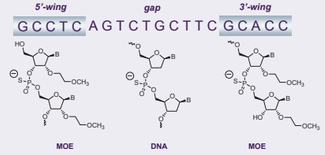


Teplova, M. et al. *Nat. Struct. Biol.* 1999, 6, 535-539.

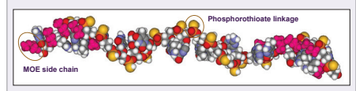
- **Structure of MOE**
  - Increases affinity
  - Increases stability in animals
  - Improves safety by reducing non-specific protein binding interactions

Structure of Mipomersen, A Representative Second-Generation Antisense Drug

- **'Gapmer' design**
  - MOE modification at ends
  - DNA in middle
  - Phosphorothioate throughout



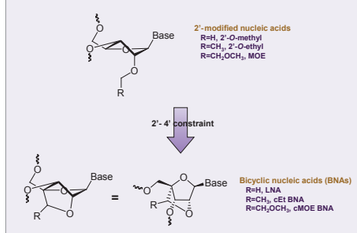
- **Molecular model of mipomersen**



GENERATION 2.5 ADVANTAGES - IScEt Chemistry

Isis' Chemistry Improves Second-Generation Drugs

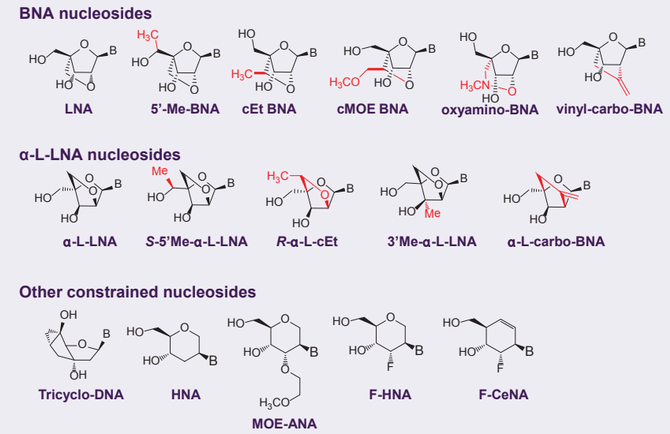
- **Chemistry improves binding affinity & potency**



What Generation 2.5 Means for Isis' Pipeline

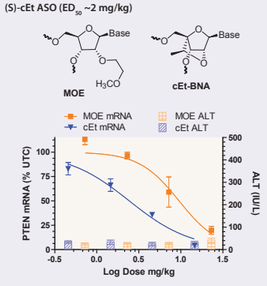
- **Second-generation drugs – Proven Potent & Safe**
  - Extensive clinical safety experience with first- & second-generation antisense drugs
    - >6,000 subjects dosed
  - Well tolerated in multiple patient populations
  - >20 drugs into the clinic
- **Generation 2.5 extends the application of antisense drug discovery**
  - Increased potency
  - Increased patient convenience
    - Lower dose
    - Potential for commercially feasible oral dosing
  - Expands the breath of target opportunities
    - Improved target reduction in tumor tissue
  - Extends Isis' antisense technology intellectual property position
- **Staged integration into Isis' pipeline**
  - First Generation 2.5 drug in cancer – ISIS-STAT3$_{Rx}$
  - As safety experience grows, expand into other diseases
    - Use for developing drugs for specific diseases where increase in potency offers unique value

More than 80 Nucleoside Structures Profiled For Improved Properties



Generation 2.5 Chemistry Safely Improves Potency of Antisense Drugs

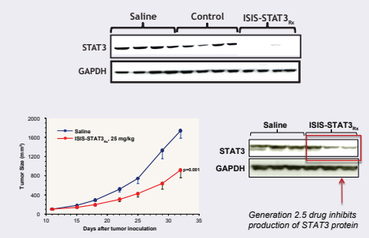
- **MOE ASO (ED_{50} ~10 mg/kg)**
- **(S)-cEt ASO (ED_{50} ~2 mg/kg)**



Seth et al. *J. Med. Chem.* **2009**, *52*, 10; Seth et al. *J. Org. Chem.* **2010**, *75*, 1569

First Demonstration of Generation 2.5 Potential *Potent Activity of STAT3 Inhibitor in Human Tumors*

- **25mg/kg, sc, 5x/week for 4 weeks**
- **No effect on BW or other toxicity end points**



Antitumor activity of ISIS-STAT3$_{Rx}$ in Human Breast Cancer Xenograft