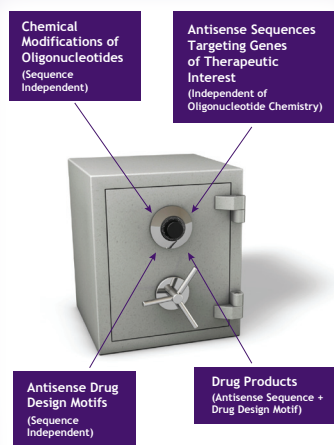


Intellectual Property: Capturing Value From Innovation

THE ISIS PATENT ESTATE

The Isis Patent Estate “Locks Up” Antisense Therapeutics



Isis Has Created & In-licensed Broad Patent Portfolios Covering Antisense Therapeutics



The Isis Patent Estate The Dominant Position in Antisense Therapeutics

- ▲ Isis has amassed an extensive patent estate by creating & in-licensing patent rights in the most important aspects of antisense therapeutics:
 - Antisense mechanisms of action
 - RNase H, RNAi, RNA splicing, microRNA & others
 - Fundamental oligonucleotide chemistry
 - Optimization of oligonucleotide chemical modifications
 - Antisense drug design motifs
 - Optimization of oligonucleotide design for a given antisense mechanism
 - Antisense sequence space
 - Metabolics, cardiovascular, CNS, oncology & others
 - Antisense drug compositions
 - Picture claims to our development compounds & primary methods
- ▲ The Isis Portfolios create
 - Strong protection for Isis' drug products; &
 - Protection against “me too” competition in the field of antisense therapeutics

Overview of the Isis Patent Estate

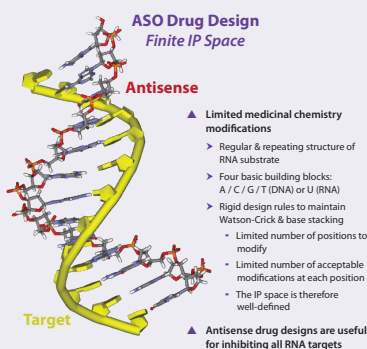
Pending Applications

288 Pending U.S.
35 Pending PCT
574 Pending foreign
897 Total

Issued Patents

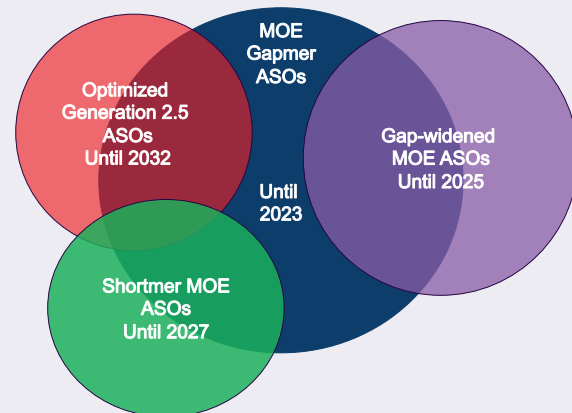
838 Issued U.S.
647 Issued foreign
1,485 Total

*Numbers include cases owned by or exclusively licensed to Isis, as of 04/12/2011



PATH TO GENERATION 2.5

We Continue to Extend Our MOE IP Estate to Cover Optimal MOE Drug Design Motifs



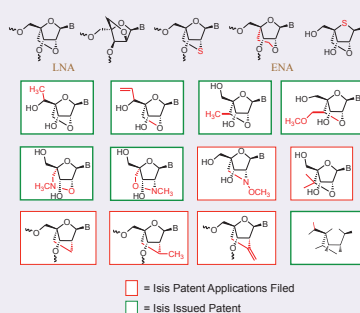
Path to Generation 2.5 Beyond 2'-MOE

- ▲ Isis has sought to further optimize 2'-MOE-containing drug designs & in doing so has created new drug design motifs that extend our control of MOE-containing antisense drugs
 - Gap-widened ASO therapeutic methods (US 7,919,472)
- 2-4 nts MOE 18 > DNA ≥ 12 MOE 2-4 nts
- The claims broadly cover the therapeutic use of these compounds for liver targets

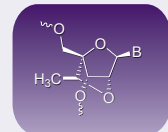
Path to Generation 2.5 Beyond 2'-MOE

- ▲ Isis has investigated new chemically modified nucleosides that will be incorporated into Isis' next generation of antisense compounds
 - We have evaluated numerous new nucleoside mimics or modifications
 - This effort has created IP covering more than 25 chemically distinct classes of novel nucleosides/oligonucleotides

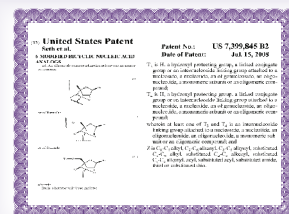
Isis' IP in the Bicyclic Nucleic Acid Space Path to Generation 2.5



Isis' Generation 2.5 Chemistry



First of Three Issued Patents Covering Generation 2.5 Protects Isis' Generation 2.5 Chemistry until 2027



- ▲ Protected broadly until 2022 by:
 - Issued U.S. Patent Nos. 7,399,845, 7,547,684 & 7,666,854
 - European Patent No. EP1984381
 - Pending patent applications in several other countries including China, Japan, India & S. Korea
- ▲ Preferred Generation 2.5 drug design motifs protected until at least 2027

INTELLECTUAL PROPERTY: CAPTURING VALUE FROM INNOVATION



- ▲ Partnership goals
 - Combine Isis' & Alnylam's intellectual property positions to enable Alnylam to develop dsRNAi therapeutics
 - Support Isis' strategy of exploiting multiple antisense mechanisms through partnerships with complementary expertise & technology
 - Enable Isis to participate fully in the success of RNAi
 - Continue Isis' leadership role in RNA-based drug discovery & development
- ▲ Results
 - \$54 million in up-front fees, sublicense revenue & R&D funding from Alnylam to date



Isis' Satellite Company Strategy Create Broad Consortium of Companies to Advance Drugs & Technology



The Isis Patent Estate “Locks Up” RNA-Based Therapeutics

Isis' portfolio creates strong protection for Isis' drugs & creates a competitive advantage in the field of RNA-based therapeutics



The breadth of the Isis patent estate in the field of RNA-based therapeutics has helped to create value through out-licensing transactions in areas outside of Isis' antisense focus

Isis' Antisense Technology Platform Extending Isis' Patent Protection of Chemistry & Drug Designs into the 2030s

