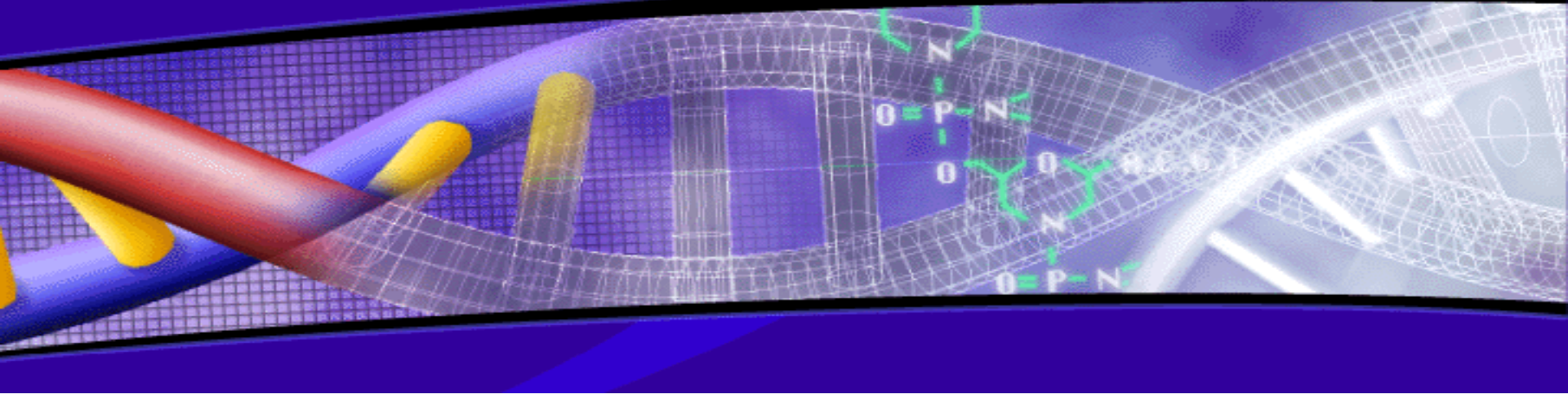


**Dr. Leslie Hudson**  
**President and CEO**  
**AVI BioPharma**

*UBS Investor Conference*  
*September 25, 2008*



# **Transitioning an Antisense Pioneer into a Leading RNA-based Drug Discovery and Development Company**

# ***New Investment Thesis***

- ◆ Focused R & D Programs On High Potential Therapeutic Targets
- ◆ Leveraging Newly Developed and Newly Acquired Applications and Technologies
- ◆ Gate-Keeper Intellectual Property Estate
- ◆ Re-started Active Partnering and Out-licensing
- ◆ New Management Team in Formation

# AVI Near Term Catalyst Opportunities

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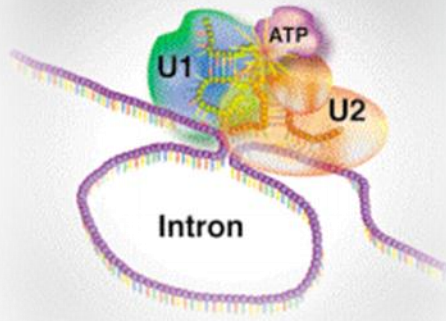
- ◆ Duchenne muscular dystrophy
  - Significant, near term BD opportunity for new franchise
- ◆ Cardiovascular restenosis
  - Partnered to Cook Medical for double digit royalty
- ◆ Ebola, Marburg and Dengue Viruses
  - IND-based contracts
  - BioDefense BD partnering
- ◆ Expand Viral Program
  - Opportunity to re-enter HCV with a strategic partner



# RNA-based Therapeutics

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**Pre-mRNA**



**mRNA**

**Protein  
Expression**

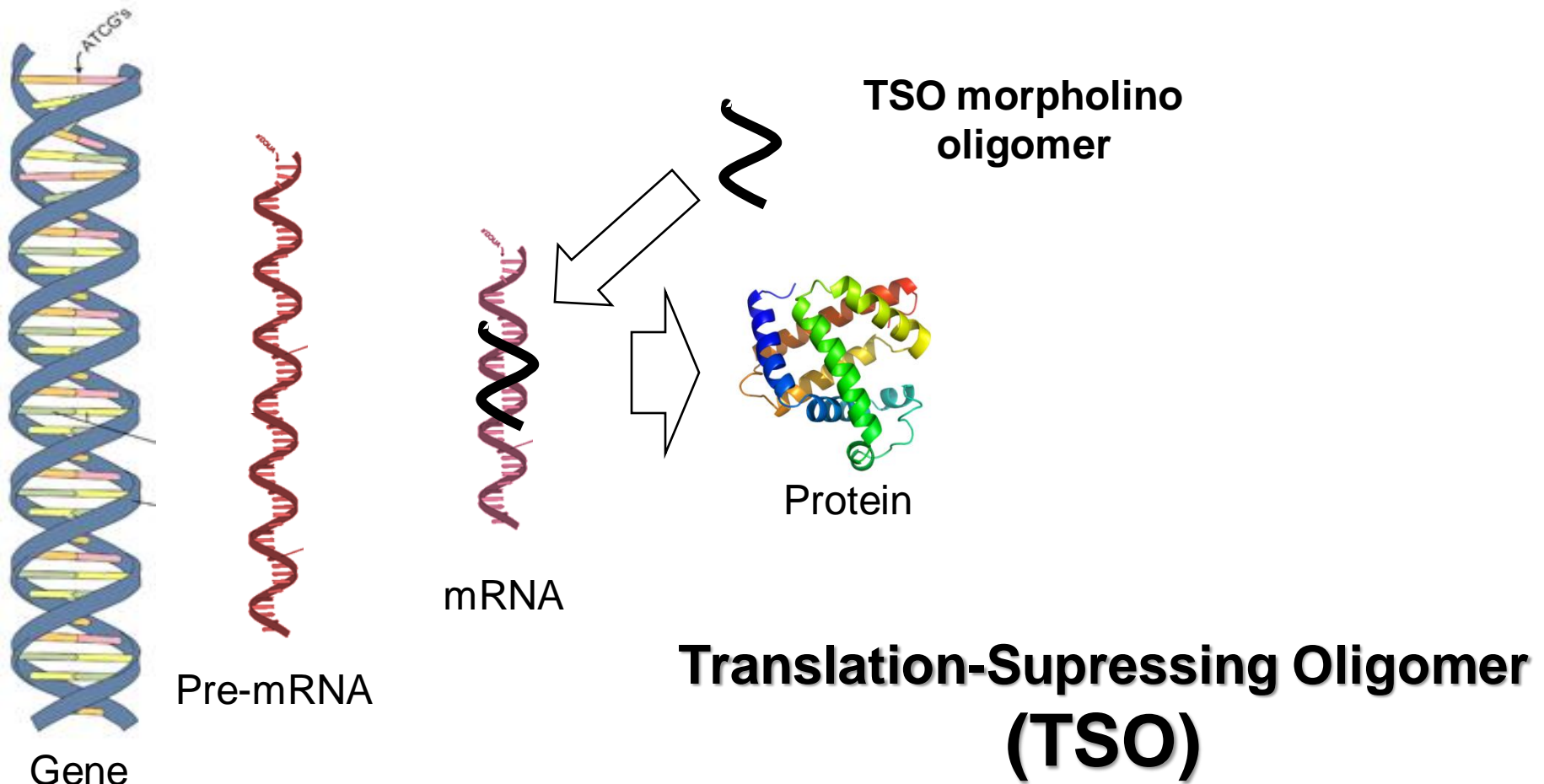
# RNA-based Therapeutics

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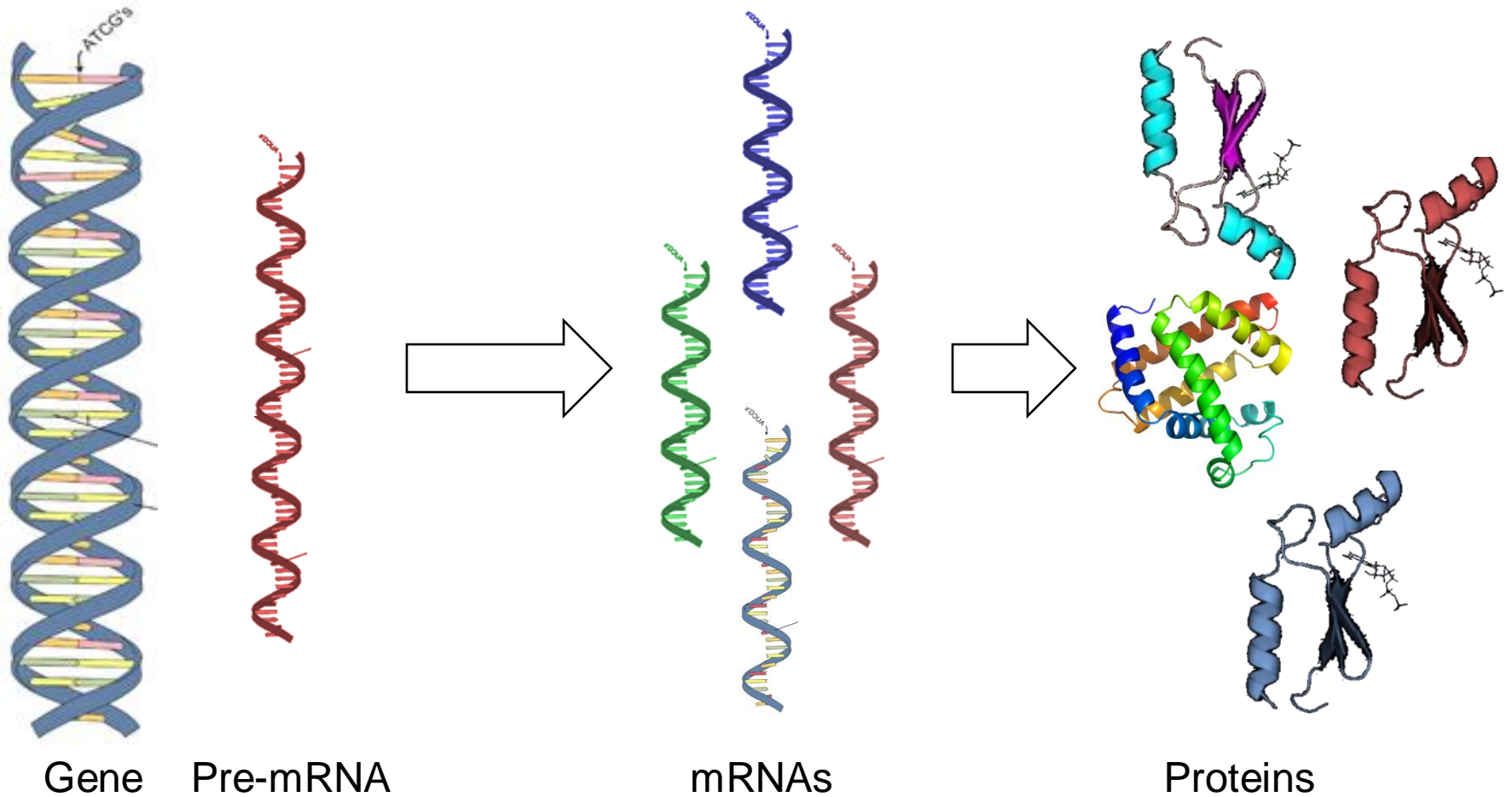
**Pre-mRNA**  
Splice-Switching Oligomer  
(SSO)

**mRNA**  
Translation-Suppressing Oligomer  
(TSO)

# RNA-based Therapeutics – RNA Blockade

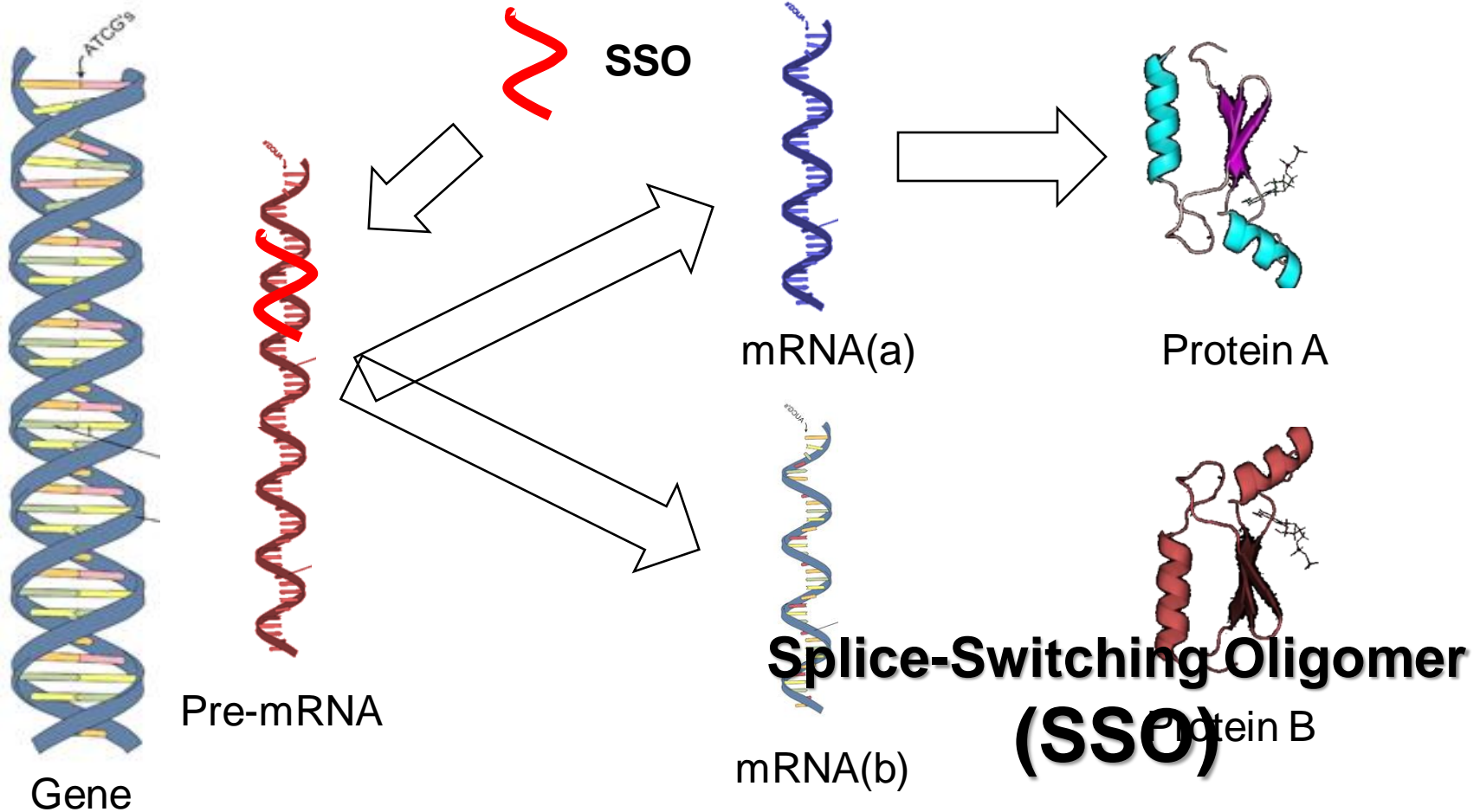


# One Gene - Several Proteins - Splicing





# RNA-based Therapeutics – Splice Switching



# RNA-based Therapeutics

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Can up- and down-regulate pre-mRNA and mRNA

SSO and  
TSO

**Pre-mRNA**

Pre-mRNA

**mRNA**

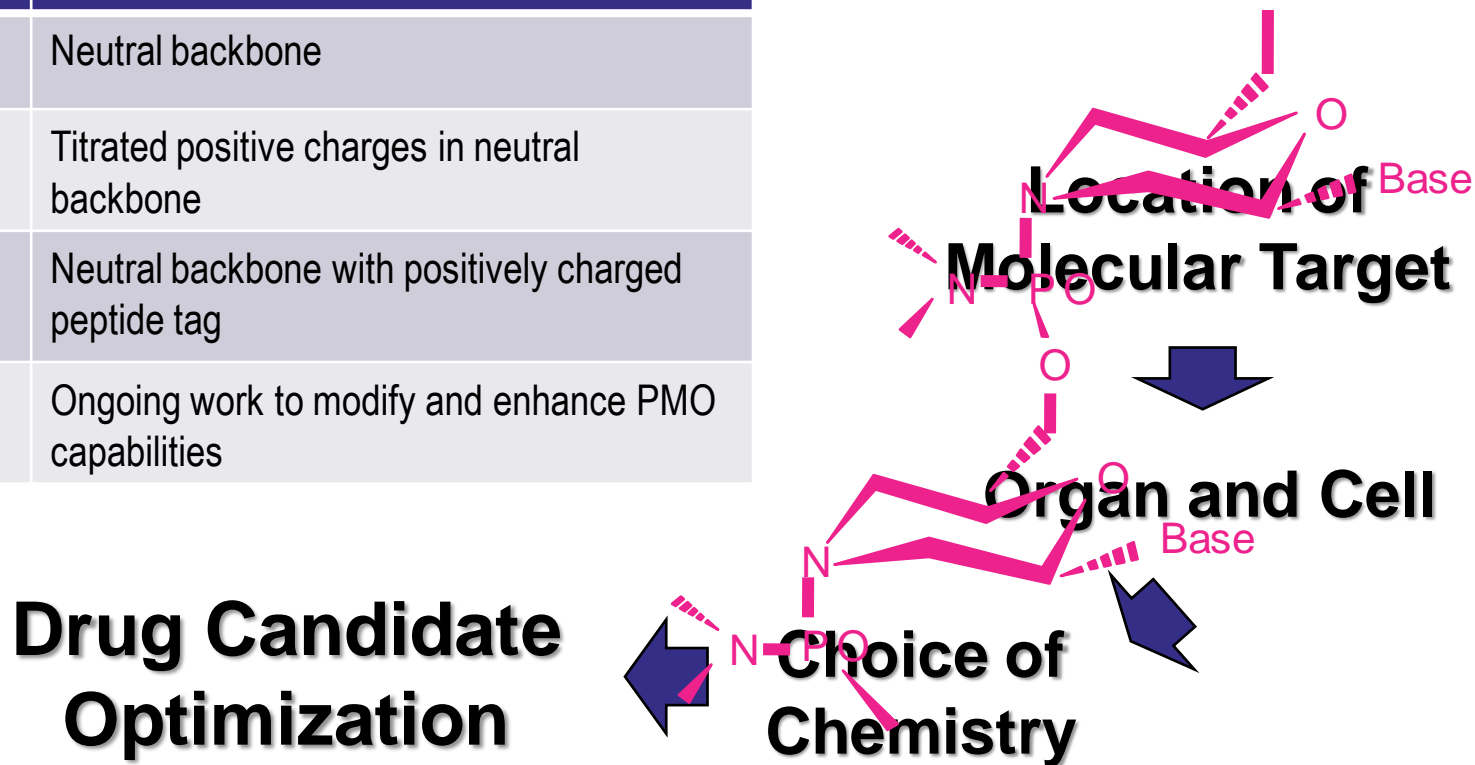
mRNA

siRNA down regulates mRNA only

mRNA

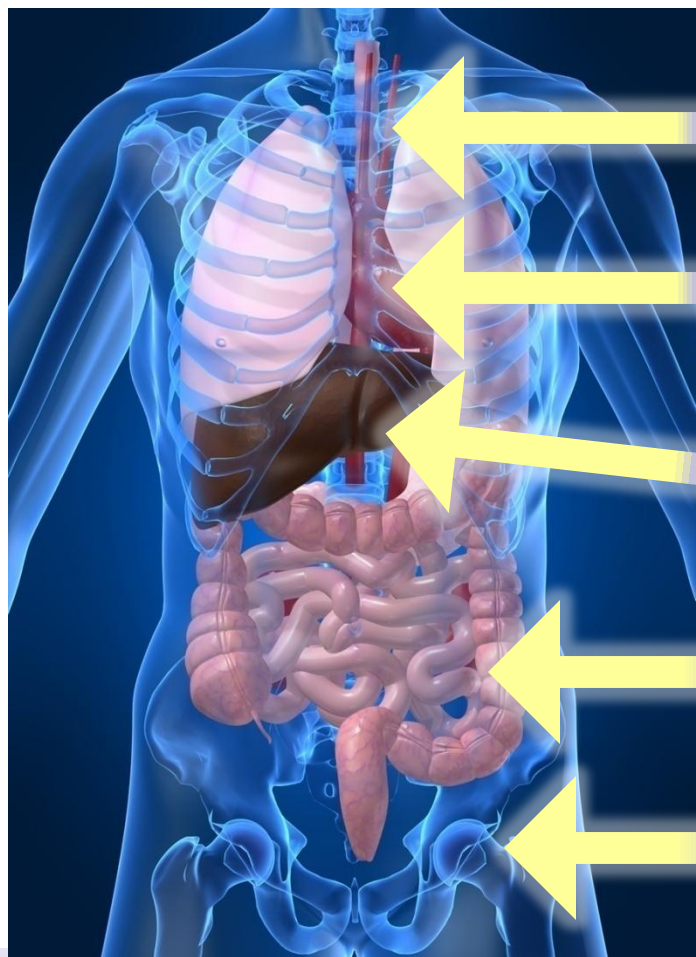
# Expanded Therapeutic Target Opportunities via Additions to Core Chemistry Portfolio and IP

Chemistry	Chemical Character
PMO	Neutral backbone
PMO+	Titrated positive charges in neutral backbone
PPMO	Neutral backbone with positively charged peptide tag
PMO-X	Ongoing work to modify and enhance PMO capabilities



# Organ Location of Therapeutic Target Dictates Choice of Chemistry

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**Lymphoid cells – PPMO – IL-10**

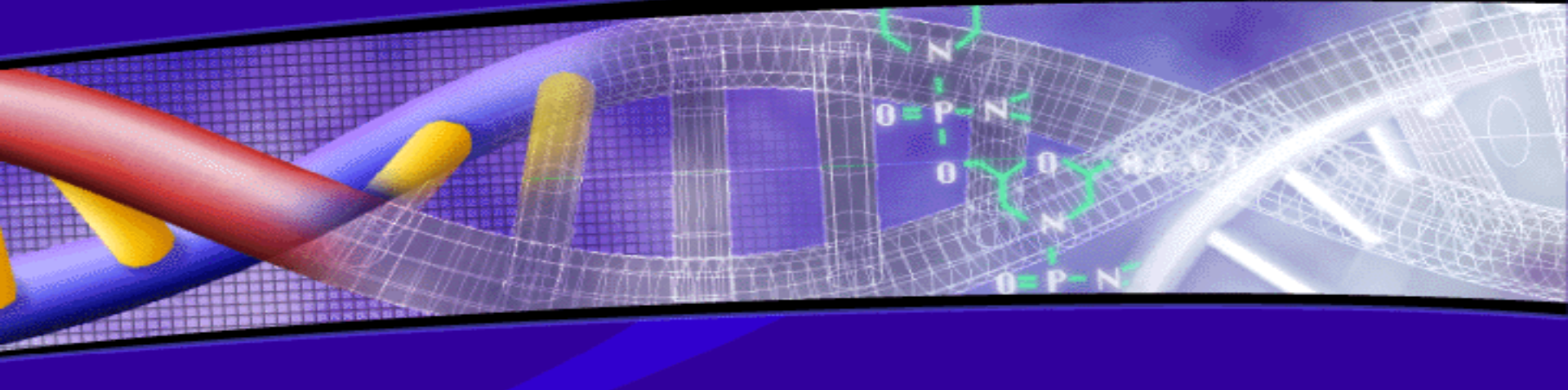
**Heart muscle & diaphragm – PMO  
& PPMO - DMD**

**Liver – LNA – TNF Receptor in RA**

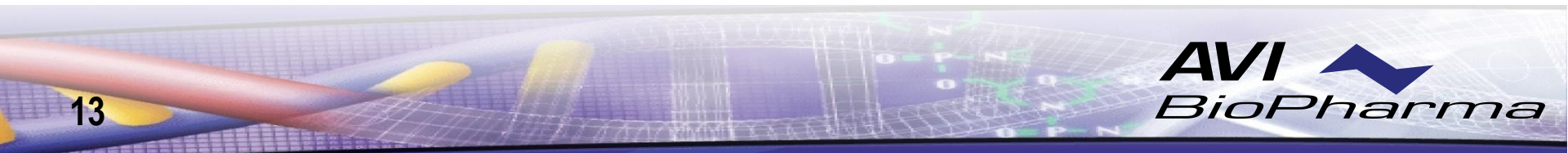
**Liver & kidney– PMO+ - viral  
infections**

**Skeletal muscle – PMO & PPMO -  
DMD**





# CURRENT DEVELOPMENT PORTFOLIO

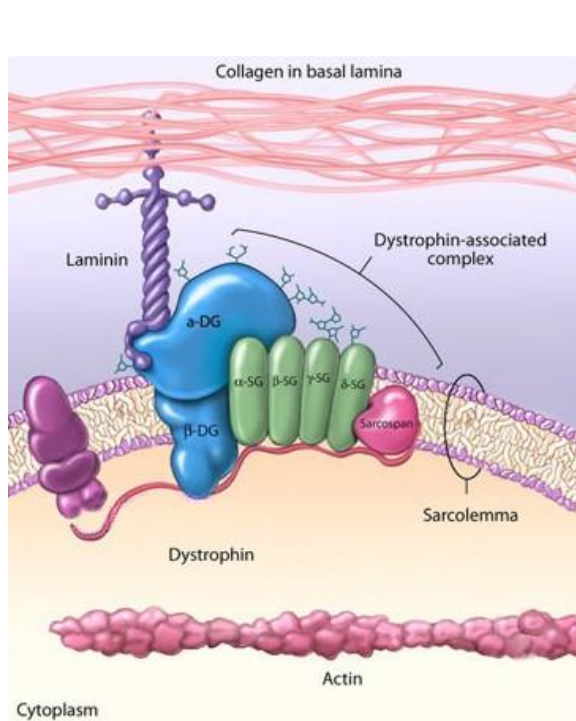


# Duchenne Muscular Dystrophy (DMD)

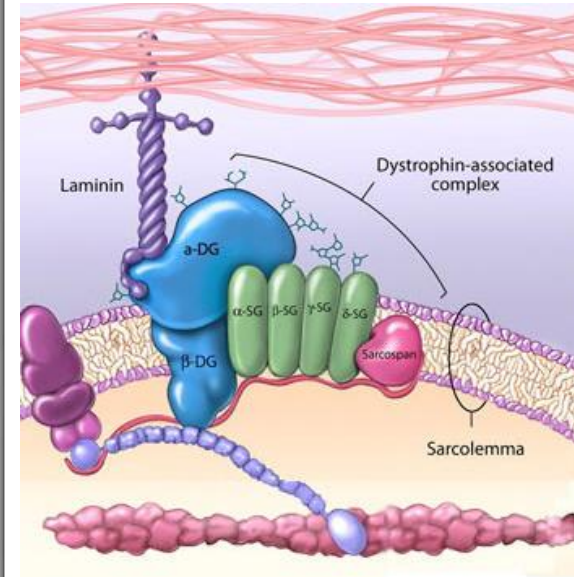
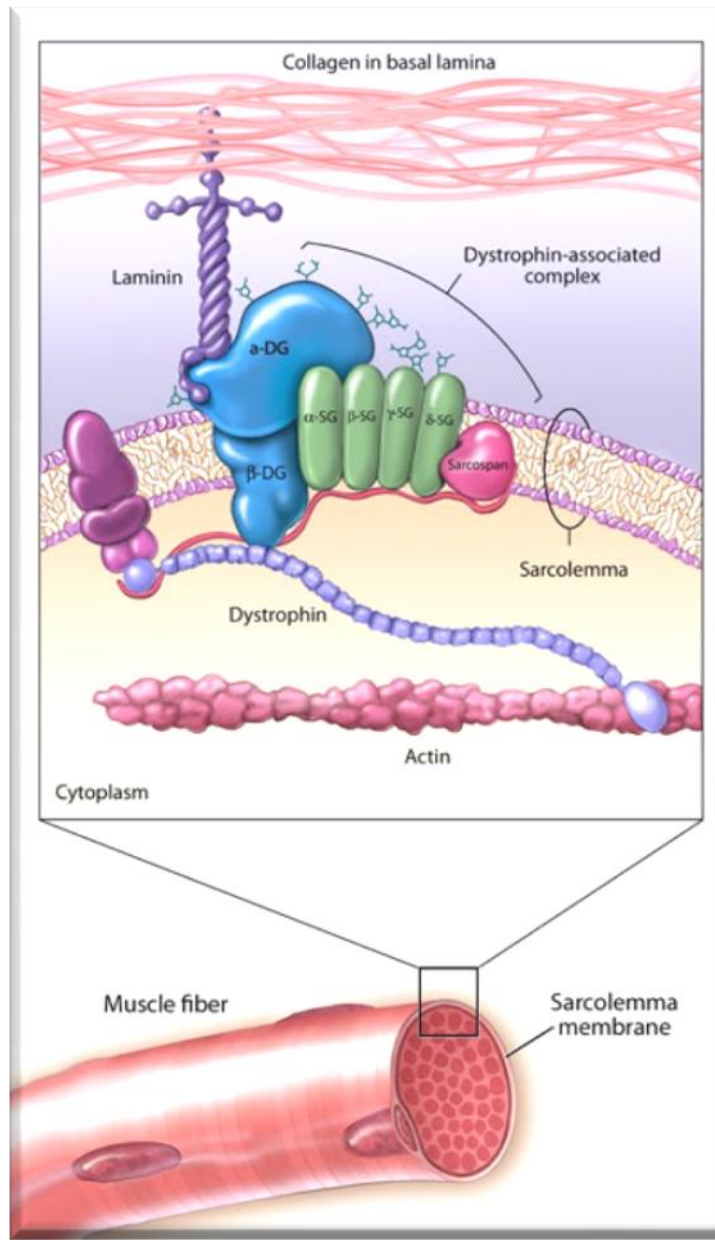
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- ◆ Defects in the dystrophin gene; no protein expression
  - X-linked recessive
  - Mutational hot spot: exons 45 and 55: *functionally silent* region
  - 1 in 3 cases arise by spontaneous mutation; limits control via genetic counseling
- ◆ Symptoms present at 3-5 years of age
  - Muscle degeneration overwhelms regenerative capacity
  - Patients restricted to wheelchair by age 12
  - Death from cardiac respiratory complications
- ◆ Effects 1 in 3,500 male births; High yearly cost of care

# Clinical Expectations for Exon Skipping



Duchenne muscular dystrophy



Becker muscular dystrophy

# AVI's DMD Exon Skipping Strategy

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- ◆ Clinical trials for exon 51 (17.5% of cases)
  - IM dose escalation on-going in EU
  - CTA for systemic trial approved by MHRA in EU
  - Preclinical pathway in US negotiated with the FDA
- ◆ PMO drug candidate: AVI-4658
- ◆ First generation: 6 single-exon drugs



# DMD – Therapeutic Exon Skipping

Exon to Skip	Therapeutic for Deletions (exons)	% in Leiden Database
51	45–50, 47–50, 48–50, 49–50, 50, 52, 52–63	17.5
45	12–44, 18–44, 44, 46–47, 46–48, 46–49, 46–51, 46–53, 46–55	11.2
44	14–43, 19–43, 30–43, 35–43, 36–43, 40–43, 42–43, 45, 45–54	7.8
53	10–52, 45–52, 46–52, 47–52, 48–52, 49–52, 50–52, 52	7.5
46	21–45, 45, 47–54, 47–56	5.6
50	51, 51–53, 51–55	<u>5.2</u>
	Total top six skipped exons	54.8%

Source: van Deutekom & Ommen, Nature Reviews Genetics **4**, 774, 2003

# AVI-4658 Pre-clinical Efficacy: Two Species

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- ◆ Single treatment in mdx mouse model of DMD leads to 10-100% dystrophin production; HE dose 2.5 to 8.3 mg/kg
- ◆ Results in sustained functional improvement
  - Reduced serum CK and improved muscle force measurements
- ◆ Serial injections have cumulative effect on expression and clinical benefit
- ◆ Serial IV administration of PMOs at 20 mg/kg (exons 5, 6 and 7) in canine DMD model leads to significant functional improvement

# Exon Skipping “Proof of Concept” Performed by Collaborators in Dystrophic Canine Model



Courtesy of Toshifumi Yokota, Shin'ichi Takeda, National Institute of Neuroscience, Tokyo, Japan and Eric Hoffman, Children's National Medical Center, Washington DC

# Equivalent clinical assessment scales

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# Near Term Milestones in DMD Program

		Event
2008	Q4	<ul style="list-style-type: none"><li>• Exon 51 IM AVI-4658 Study completed</li><li>• Exon 51 IV AVI-4658 First patient dosed</li><li>• Exon 23 AVI-4225 Mechanistic toxicology study in <i>mdx</i> mouse</li></ul>
	Q1	Note Filing of IND for exon 50 study in US will await completion of <i>mdx</i> mouse toxicology study
2009	Q2	<ul style="list-style-type: none"><li>• Exon 51 IV AVI-4658 Data on third cohort of patients</li><li>• Exon 23 AVI-4225 Mechanistic toxicology study in <i>mdx</i> mouse study completed</li></ul>

# DMD: *SuperNiche* Specialty Pharma

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- ◆ Incidence
  - 1 per 3,500 male births
  - 600 new cases each year in US
  - 700 new cases each year in EU
- ◆ Prevalence
  - 12,500 patients US
  - 14,000 patients EU
- ◆ 65% patients amenable to exon-skipping therapy
- ◆ Annual cost of care \$4-500,000 per non-ambulatory patient

# Precedent for Pricing to Value in Fatal / Debilitating Diseases

Drug	Company	Indication	Annual Price
Vectibix	Amgen	Colon cancer	\$100,000
Kuvan	BioMarin	Phenylketonuria	\$76,000
Cerezyme	Genzyme	Gaucher disease	\$200,000
Fabrazyme	Genzyme	Fabry disease	\$180,000
Myozyme	Genzyme	Pompe disease	\$250,000
Erbix	ImClone	Colon, head and neck cancers	\$120,000
Elaprase	Shire	Hunter syndrome	\$300,000

# DMD Market Opportunity

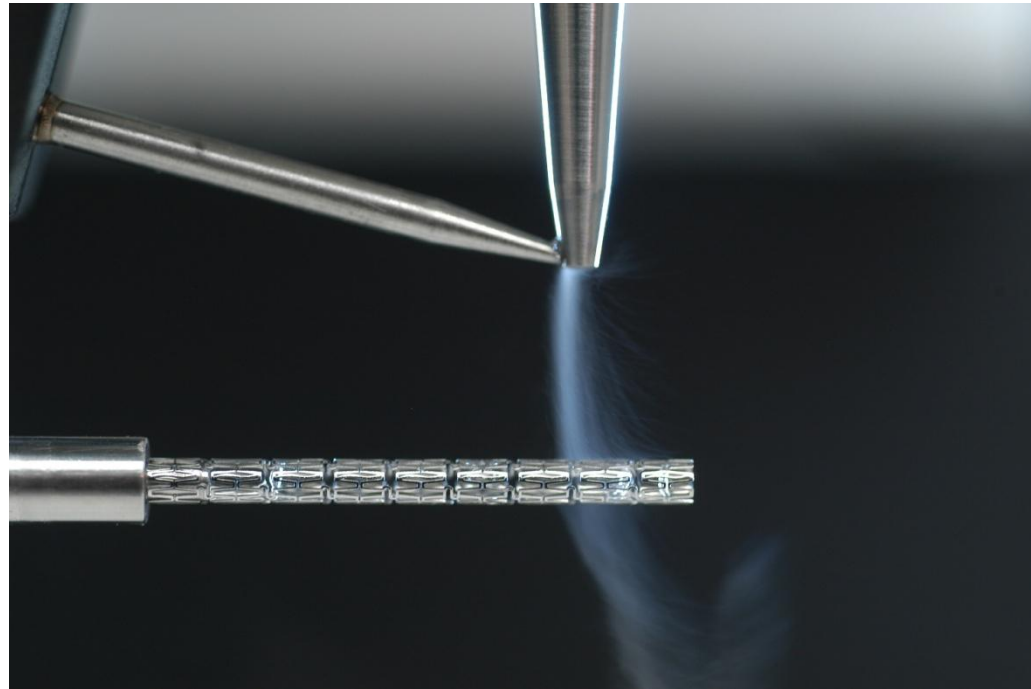
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- ◆ Sales Potential for Exon-Skipping Drugs:
  - Number of patients in US and EU: 26,500
  - % amenable to exon-skipping therapy: 65%
  - Potential range of revenue per year per eligible patient: \$100,000 - \$200,000
- ◆ US & EU potential market for exon-skipping DMD drugs is \$1.5 - 3.0 billion
- ◆ Key clinical criteria for market estimates have yet to be established - size of true amenable population, optimal time to begin treating, treatment duration, etc.



# Cardiovascular Restenosis Program

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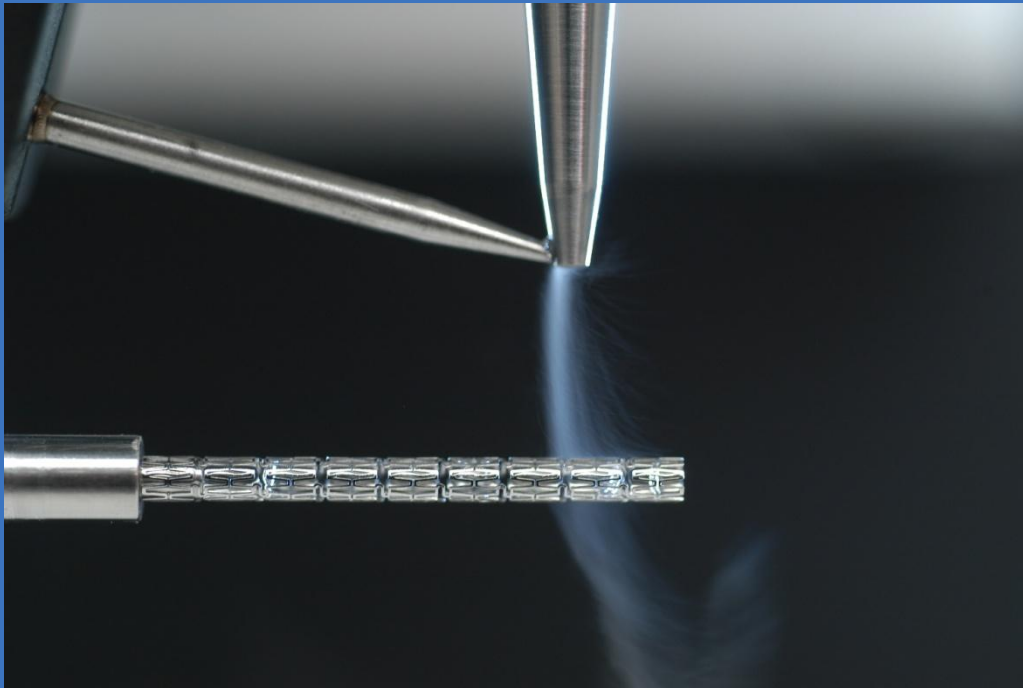


AVI-5126 is a PPMO against *c-myc*; partnered to Cook Global Therapeutics for use on a new drug-eluting stent

# The Drug Eluting Stent Market

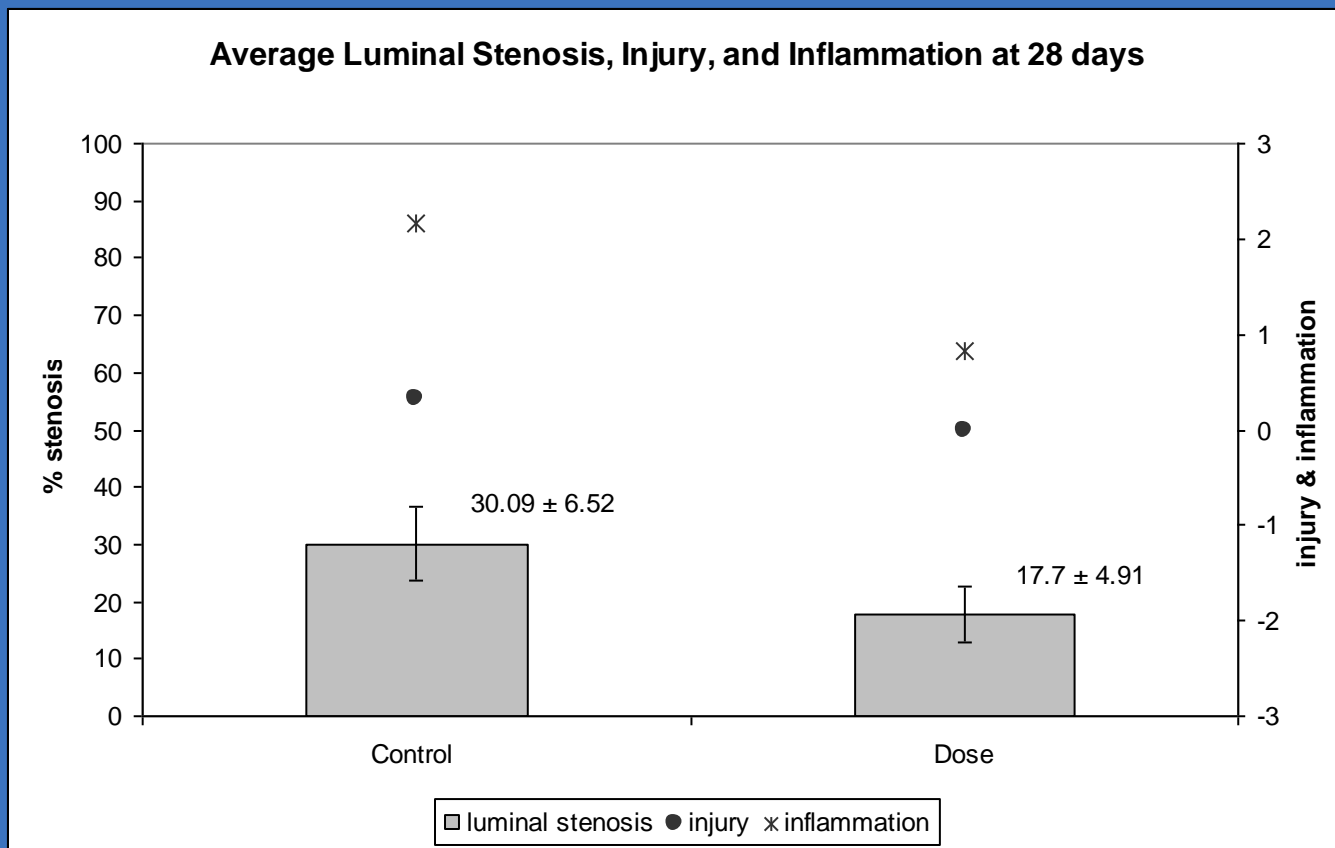
- Current market at \$5B
- US DES market ~\$4B
  - 6 DES products on market by 2009 (Cypher, Taxus, Endeavor, Zomaxx, Promus, Liberte)
- OUS market has more than 20 DES

# Global Therapeutics Silencer™ System



- Rapid release of drug
- Equivalent to bare metal stent after 2 hours once implanted

# Preclinical Results



Unpublished, Global Therapeutics, LLC



# Clinical Plans

- SMART I Study
  - 50 patients
  - Discrete, de novo lesions
  - 6 month QCA and IVUS follow-up
  - Multi-centered
  - Q4 2008

# Ebola and Marburg Viruses

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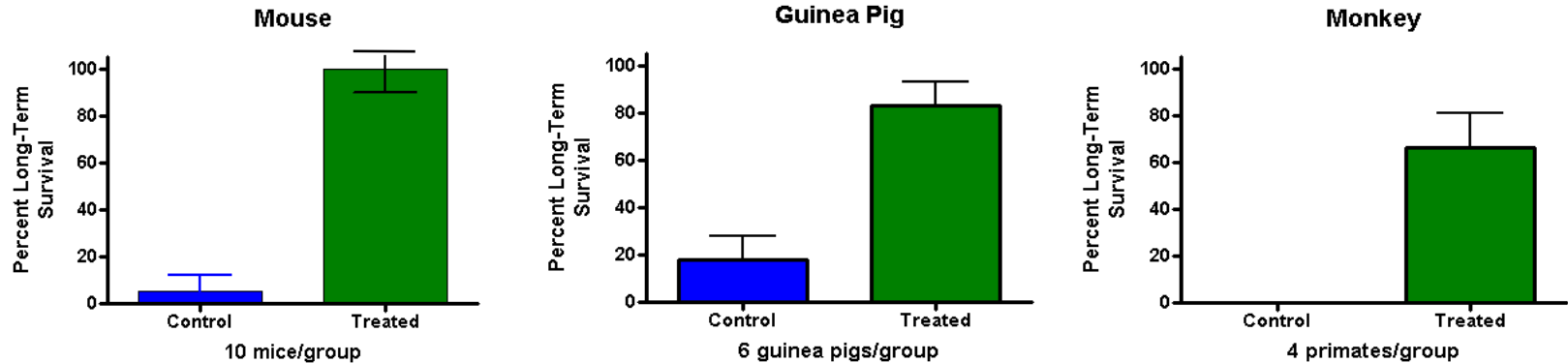
## Human infections:

- ◆ ~85% cases are lethal
- ◆ To date no therapeutic agents
- ◆ Major priority for Bioshield
- ◆ Ebola and Marburg are single-stranded(-) sense RNA viruses

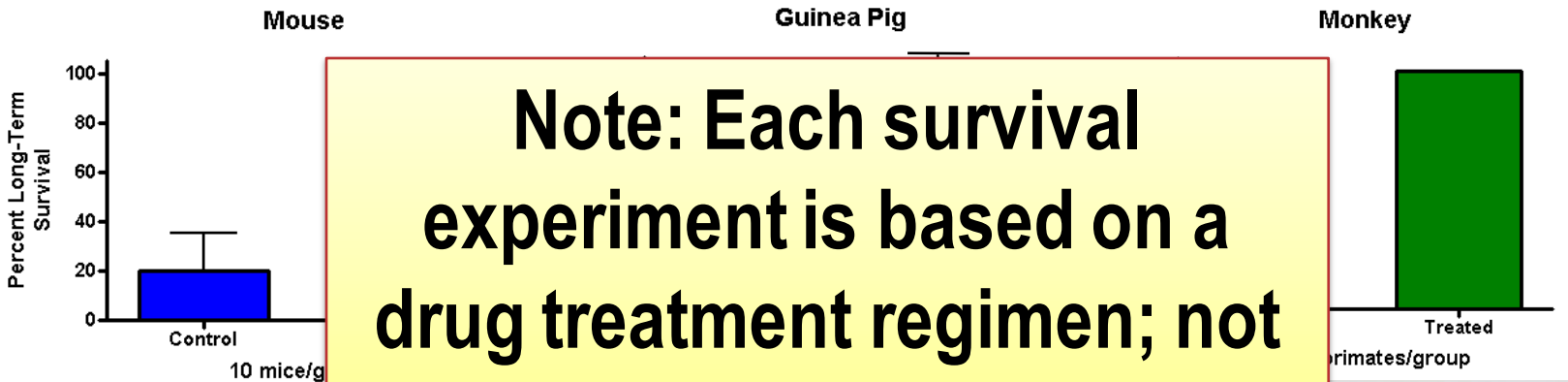


# Unparalleled Survival Data for Two Viruses in Three Preclinical Models

## AVI-6002 Ebola Survival Observations



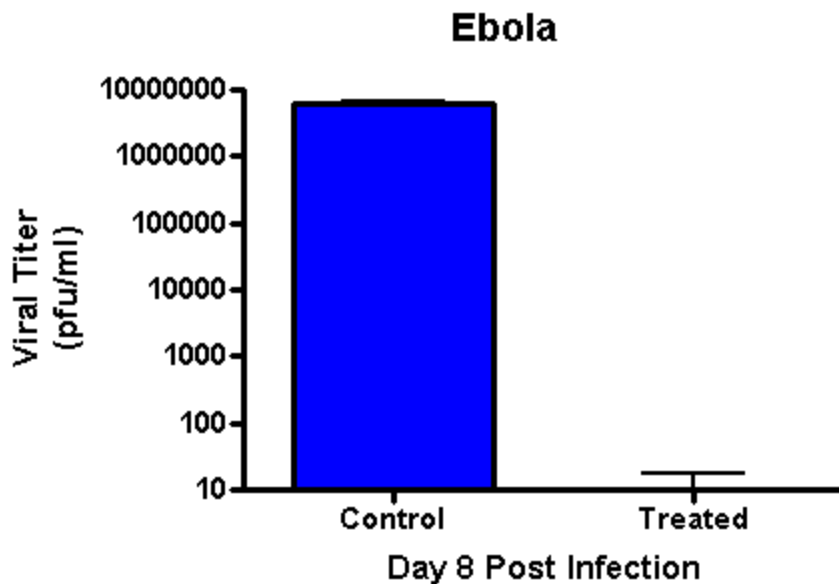
## AVI-6003 Marburg Survival Observations



**Note: Each survival experiment is based on a drug treatment regimen; not prophylaxis**

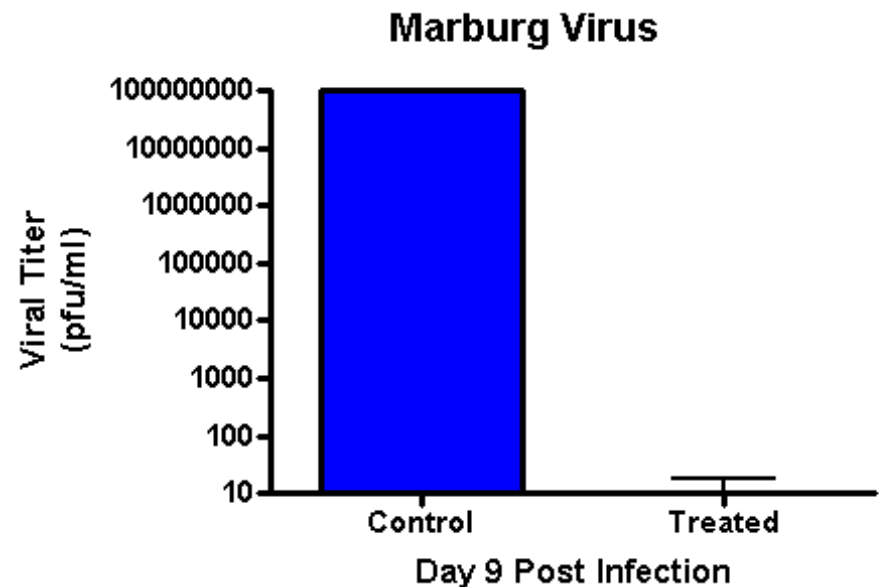
# Impressive Reduction in Viremia in Monkey Models of Ebola and Marburg

Greater than 5-log reduction in Ebola viremia



Virus no longer detected beyond day 10

Greater than 7-log reduction in Marburg viremia



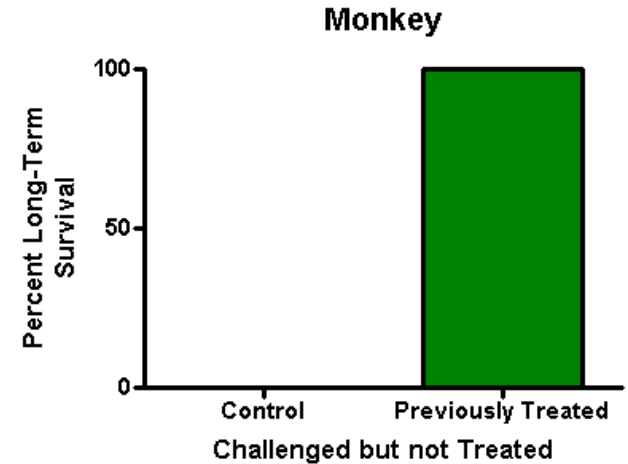
Virus no longer detected beyond day 14



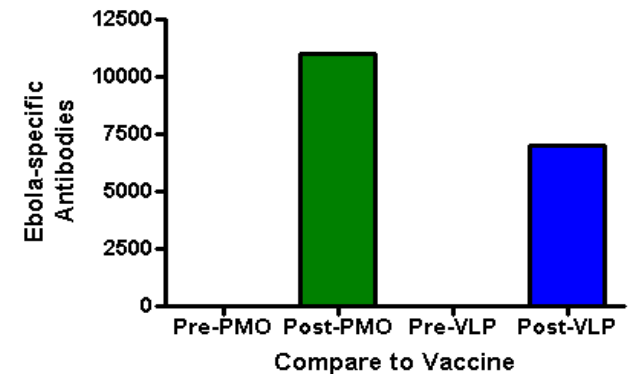
# Ebola Re-Challenge Studies

- ◆ Monkey re-challenge
  - Monkeys challenged **and** treated then re-challenged **but not** re-treated
  - 100% long term survival
- ◆ Mouse re-challenge
  - 100 percent survival
  - Enhanced antibody response
  - Cell mediated immune response increased 20 fold

Survival

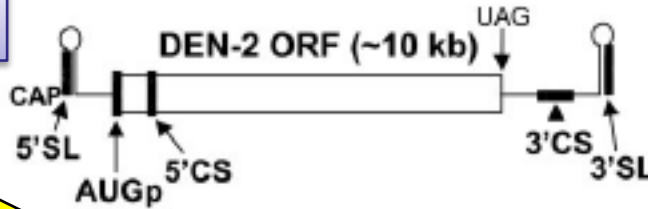


Antibody Response

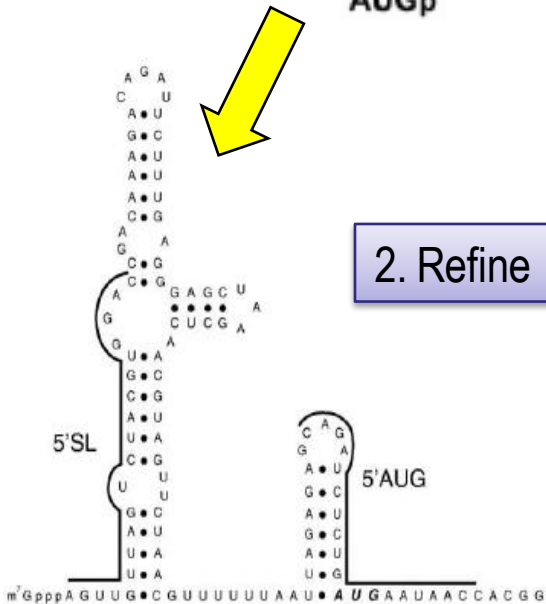


# Dengue Virus

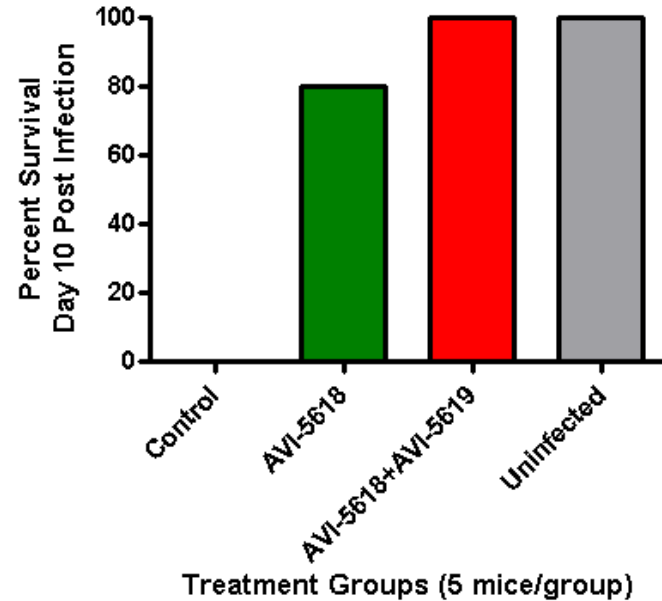
1. Screen



2. Refine



3. Explore Combinations



# Priority Review Voucher

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H. R. 3580

- ◆ Signed into law on September 27, 2007  
“mere tweak to the existing rules”

- ◆ Sen. Brownback incorporated into the:

*Neglected Disease amendment of the  
FDA Revitalization Act*

co-sponsors: Sens. S. Brown and J. Lieberman

One Hundred Tenth Congress  
of the  
United States of America

AT THE FIRST SESSION

*Began and held at the City of Washington on Thursday,  
the fourth day of January, two thousand and seven*

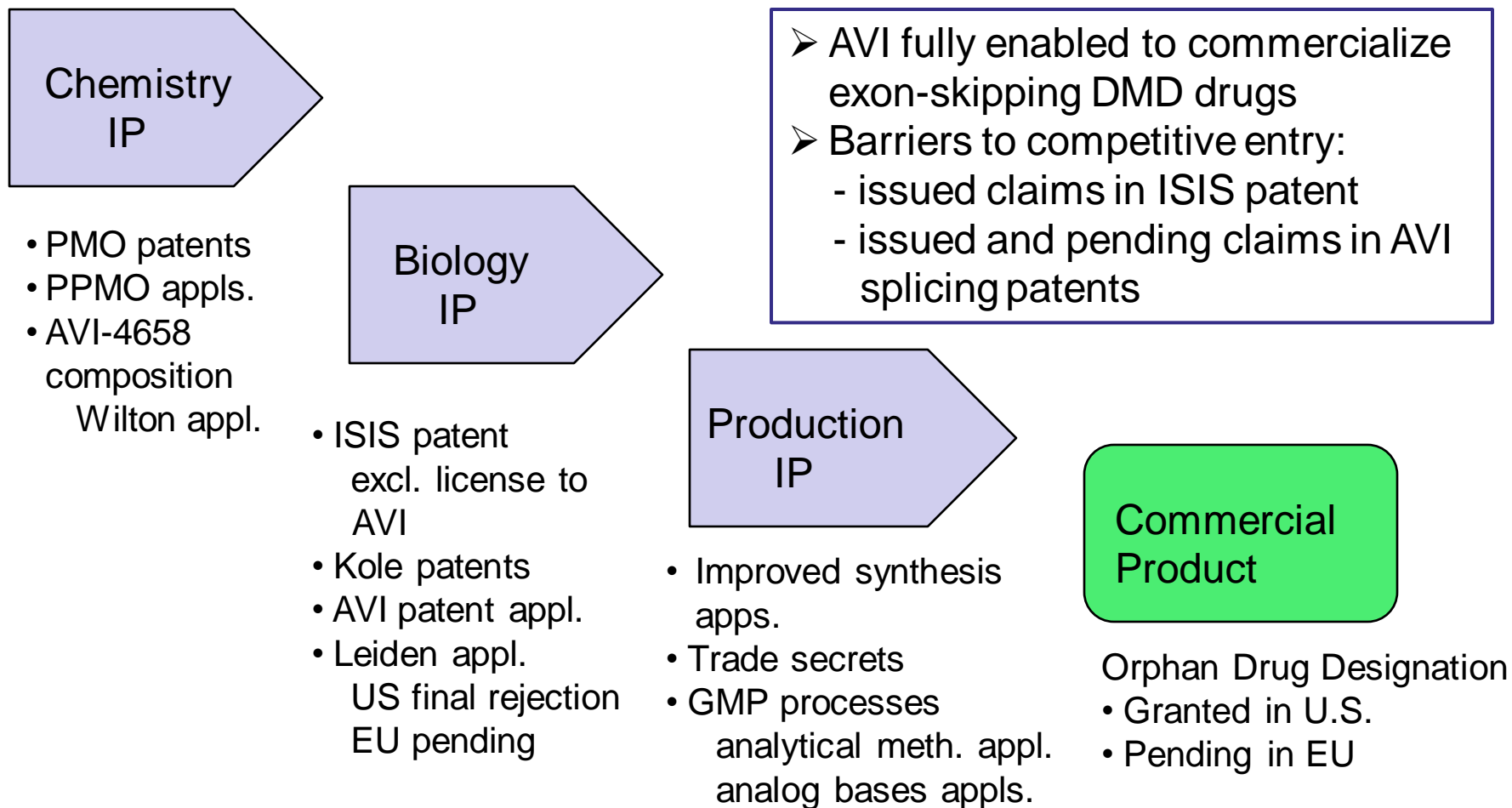
1. Approval of qualifying drug - neglected diseases, e.g., Dengue (named in act), Ebola, Marburg (within scope of the act)
2. FDA grants voucher
3. Voucher can be sold, traded or used
4. Reduce time to market by up to 6-12 months
5. Could be worth approximately \$300 million by speeding development and commercialization of another major drug

# Development Milestones in 2008

		Event
2008	Q1	<ul style="list-style-type: none"> <li>• AVI-6003 (Marburg Musoke) – pre-IND filed</li> <li>• AVI-4658 IV (DMD) – CTA filed for a systemic study</li> <li>• AVI-6002 (Ebola Zaire) – pre-IND filed</li> </ul>
	Q2	<ul style="list-style-type: none"> <li>• AVI-4658 (DMD) European Orphan Drug request filed</li> <li>• PMO-based exon 50 product (DMD) – pre-IND filed</li> </ul>
	Q3	<ul style="list-style-type: none"> <li>• Response to FDA pre-IND comments for:               <ul style="list-style-type: none"> <li>– PMO-based exon 51 product in USA</li> <li>– Ebola and Marburg</li> </ul> </li> </ul>
	Q4	<ul style="list-style-type: none"> <li>• Exon 51 IM AVI-4658 Study completed</li> <li>• Exon 51 IV AVI-4658 First patient dosed</li> <li>• Exon 23 AVI-4225 Mechanistic toxicology study in <i>mdx</i> mouse</li> <li>• Start of restenosis clinical trial in EU by Cook Global Therapeutics</li> <li>• AVI-6003 (Marburg Musoke) – IND to be filed</li> <li>• AVI-6002 (Ebola Zaire) – IND to be filed</li> </ul>



# Intellectual Property Overview



# Value Spectrum

