Scoring a Therapeutic Bulls-Eye with Genetic Medicine Targeted to the CNS

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Vice President, Vector Delivery
Voyager Therapeutics, Cambridge, MA
Voyager Therapeutics
• public company (IPO: 11/16/2015)
• NASDAQ: VYGR
• based in Cambridge, MA
• ~50+ employees

Mission: build a leading gene therapy company using Adeno-Associated Virus (AAV) for CNS disorders:
  - neurodegenerative disease
  - genetic disorders

http://voyagertherapeutics.com/about.php
Product Engine Based on:

Vector Engineering
- Generate novel AAV vectors
- Understand AAV vector structure-activity relationship
- Rational capsid design for desired tropism

AAV Manufacturing
- Next-generation baculovirus / Sf9 system
- High yield at scale with good quality
- Strategic collaboration with MassBiologics for GMP manufacturing

Dosing & Delivery Techniques
- Optimized intrathecal and intracerebral delivery
- Novel delivery methods and dosing regimens
- Leverage image-guided neurosurgical methods
<table>
<thead>
<tr>
<th>Program</th>
<th>Indication</th>
<th>Target</th>
<th>Modality</th>
<th>PreClinical</th>
<th>Phase I</th>
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<tbody>
<tr>
<td>VY-AADC01</td>
<td>Advanced Parkinson’s Disease</td>
<td>AADC</td>
<td>Gene Replacement</td>
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<td>VY-SOD101</td>
<td>Monogenic Form of ALS</td>
<td>SOD1</td>
<td>Gene Knockdown</td>
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<td>VY-SMN101</td>
<td>Spinal Muscular Atrophy</td>
<td>SMN1</td>
<td>Gene Replacement</td>
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</table>

* Part of Genzyme Collaboration
### Viruses Vectorized for Gene Therapy

<table>
<thead>
<tr>
<th></th>
<th>Adenovirus</th>
<th>Adeno-Associated Virus (AAV)</th>
<th>Herpes Simplex Virus (HSV)</th>
<th>Lentivirus</th>
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<tr>
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<td>Yes</td>
<td>Yes</td>
<td>Unlikely</td>
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## Treating Severe CNS Diseases with AAV Gene Therapy

### Why AAV? (Adeno-Associated Virus)

- Ability to target a variety of tissue & cell types within the CNS
- >1,300 patients (>200 in CNS) treated, no AAV-related SAEs to date
- AAV does not readily integrate into the target cell genome, reducing potential for oncogenesis
- Ability to manufacture at commercial quality and scale

### Why CNS?

- Significant unmet medical need
- Genetically-validated targets
- Targeted delivery to regions of the brain & broader delivery to the spinal cord is achievable
- Durable transgene expression as CNS cells are terminally differentiated
- Immune-privileged site
Key Components of AAV Gene Therapy

**Vectorizing AAV:**
1) remove most viral DNA and replace with therapeutic DNA ⇒
2) replication-deficient (infect once & done)

**Capsid:** The outer viral protein shell houses therapeutic DNA – determines cell targeting (tropism)
   AAV-1, 2, 4, 5, 6, 9, rh10, DJ, DJ8, etc

**Promoter:** DNA leader sequence drives:
1) level of transgene expression (CBA, pgk)
2) cell specific expression (syn = neuron)

**Transgene:** The therapeutic DNA sequence being delivered & expressed in cell

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Gene Replacement
Therapeutic Gene

Gene Knockdown
miRNA Cassette
AAV Transduction of target cells
Targeting Disease with Gene Therapy

Graphical representation showing the concepts of Delivery ↔ Distribution, Capsid ↔ Tropism, Promoter ↔ Expression, and Transgene. The targets are labeled Gene Editing, Replacement, and Suppression.
The **Blood Brain Barrier** excludes most drugs from Brain and Spinal Cord . . .

. . . despite most dense vascular bed of any organ.

Radioactively labeled tracer drug given intravenously

. . . But drugs keep getting bigger

- Gabapentin, small molecule (0.2kD)
- Prialt, peptide (3kD)
- siRNA (13kD)
- Protein – antibody (150kD)
- AAV – 4,500kD (not to scale)
Mission Define infusion principles that govern vector distribution in the CNS and optimize dosing regimen to meet the desired therapeutic profile for each program in development.

Basic Conditions/Challenges for AAV Delivery to the CNS:
• Distribution to majority of target cells
• Homogenous distribution (avoid ‘hot/cold spots’ of transduction)
• Limit peripheral organ exposure
• One-time single administration
• Low total molar dose of vector (1.0e13 = ~100µg)

• Safe and well-tolerated procedure
• Reproducible/Consistent
• Reliable
• Predictive
Intracranial Drug Administration

Intracerebroventricular (ICV) & Intrathecal (IT)
- Friedreich’s Ataxia (FA)
- Amyotrophic Lateral Sclerosis (ALS)
- Spinal Muscular Atrophy (SMA)

Intraparenchymal (IPa)
- Parkinson’s Disease (PD)
- Huntington’s Disease (HD)
Convection Enhanced Delivery: use of sustained pressure (or convection) to push a drug solution through brain tissue. Drug infused at a rate higher than it can diffuse away from injection site (≥1.0µl/min).
Convection Enhanced Delivery: AAV2-GDNF into NHP Thalamus

I/O MRI of AAV Infusion

GDNF Expression

Su et al, Molecular Ther. 18:2010
Axonal Transport Properties of AAV

Retrograde (to cell body)

Uptake of virus by synaptic terminals and transport back to neuron cell body

Anterograde (away from cell body)

Transneuronal Transduction: virus transported and released from synaptic terminals
Widespread AAV Distribution by Targeting Thalamic Circuitry

Salegio et al, Gene Ther. 20:2013
Intrathecal AAV Delivery yields Robust Transduction of Sensory and Motor Neurons

Motor Neurons / VH spinal cord

Sensory Neurons / dorsal root ganglion
Can a dosing regimen be identified that achieves desired AAV distribution across spinal cord/brain?

**Catheter Location**
- cervical vs lumbar
- one vs multi-site delivery

**Dosing Regimen**
- continuous vs bolus
- dose = rate x volume x duration

**Formulation**
- baricity, temperature, etc.

**Spinal Anatomy & Pathology**
- e.g. scoliosis in FA

**Spatial Orientation of Subject**
- e.g. horizontal vs vertical
New AAV Variants Capable of Crossing the Blood Brain Barrier

IV Injection in Adults Mice:

AAV9 - GFP

AAV-PHP.B - GFP

Deverman et al, Nature Biotechnology Feb 2016
## Systemic vs Targeted Delivery

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<thead>
<tr>
<th></th>
<th>IV (Systemic)</th>
<th>Intrathecal</th>
<th>Intra-parenchymal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>$10^{15} - 10^{16}$ (100 to 1,000x)</td>
<td>$10^{14}$ (10x)</td>
<td>$10^{13}$ (1x)</td>
</tr>
<tr>
<td><strong>AAV Distribution</strong></td>
<td>Whole Body</td>
<td>Widespread CNS</td>
<td>Regional CNS</td>
</tr>
<tr>
<td><strong>Peripheral Organ Exposure</strong></td>
<td>Very High</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Immune Response</strong></td>
<td>Very High</td>
<td>High</td>
<td>Low-Moderate (localized)</td>
</tr>
</tbody>
</table>

* estimate based on dosing adult patient (70kg)
If you could cross the BBB, would you really want to?

- Global

- Lysosomal Storage Disease
  - Alzheimer’s
  - Huntington’s

- Parkinson’s
- ALS
- Pain
- Stroke
- Dystonia
- Epilepsy
- Spinal Cord Injury
- Trauma
- Stroke

- Drug Development
  - Biological Specificity
  - Biological Activity
  - Potency
  - Off Target Toxicity
  - Size/Complexity