AdenoVerse™ Platform for Translational Development of Innovative Gene and Cell Therapies

Cell & Gene Therapy World
January 18, 2017

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Chief Scientific Officer
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Gene and Cell Therapies are Coming of Age

Ushering in an exciting new era of gene-based medicine
Biotechnology company leveraging its proprietary AdenoVerse™ platform to develop cutting-edge gene-based medicines

Developing a novel treatment for hemophilia A using the company’s innovative PEC delivery technology

Exploring opportunities in regenerative medicine, oncology, hematology, infectious diseases, and other cell and gene therapies

Validating partnerships demonstrating the power and value of GenVec technology and expertise for therapeutic approaches

- Novartis: Regenerative medicine gene therapy for hearing loss
- TheraBiologics: Neural stem cell therapy for oncology indications
- Merial: Vaccines for FMD (animal health)
<table>
<thead>
<tr>
<th>Program Area and Indication</th>
<th>Partner / Collaborator</th>
<th>Technology Highlights</th>
<th>Development Status</th>
<th>Notes</th>
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<tbody>
<tr>
<td><strong>GENE AND CELL THERAPIES</strong></td>
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<tr>
<td>Hearing Loss and Balance Disorders</td>
<td><a href="https://www.novartis.com">NOVARTIS</a></td>
<td>Regenerative medicine gene therapy</td>
<td>Preclinical</td>
<td>First gene therapy for hearing; Phase1/2 clinical trial ongoing</td>
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<tr>
<td>Oncology</td>
<td><a href="https://www.treatment.com">THERABILOGICS</a></td>
<td>Ex vivo engineered neural stem cells</td>
<td>Clinical</td>
<td>2nd generation product to enter the Phase 1 trial in 1H2017</td>
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<tr>
<td>Hemophilia A</td>
<td><a href="https://www.unc.edu">Washington University in St Louis</a></td>
<td>PEC delivery + gene editing</td>
<td>Notes</td>
<td>Proof of principle studies ongoing</td>
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<tr>
<td><strong>INFECTIOUS DISEASE VACCINES</strong></td>
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<tr>
<td>RSV</td>
<td>Available for partnering</td>
<td>Prophylactic vaccine</td>
<td>Notes</td>
<td>Proof of principle established in multiple animal models</td>
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<tr>
<td>HSV-2</td>
<td>Available for partnering</td>
<td>Prophylactic and therapeutic vaccine</td>
<td>Notes</td>
<td>Proof of principle established in multiple animal models</td>
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<tr>
<td>Malaria</td>
<td>NMRC / NIH-LMIV</td>
<td>Discovery of new Malaria vaccines</td>
<td>Notes</td>
<td>Proof of principle ongoing in multiple animal models</td>
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<tr>
<td>FMD</td>
<td><a href="https://www.merial.com">Merial</a></td>
<td>DIVA compatible vaccine</td>
<td>Notes</td>
<td>First U.S. conditionally approved FMD molecular vaccine</td>
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New Gene-Based Technologies and Approaches

- Vectors enabling delivery of new gene-based technology:
  - Product-focused vector design to deliver payloads to the desired cellular targets

- Translational expertise across a spectrum of diseases:
  - Manufacturing and clinical development

Novel Therapeutic Product Opportunities

Delivery Barriers
These powerful new genetic technologies have the potential to revolutionize medicine. The AdenoVerse platform enables the full potential of new gene-based technologies.

**AdenoVerse™ Platform**

Diverse Biological Properties and Broad Applications

A library of adenoviral vectors with diverse and unique biological properties

- Vectors for eliciting long-lasting adaptive immune responses
- Vectors for immunologically stealth gene delivery

**Immuno-therapies**
- Vaccines
  - Prophylactic & Therapeutic

**Oncolytics**

**Gene Editing**
- Cell Therapies
  - Ex: CAR-T & Stem Cells

**Nucleic Acid Therapeutics**

- Infectious Disease
- Oncology
- Otology
- Ophthalmology
- Cardiology
- Neurology
- Rheumatology
- Rare Diseases

- These powerful new genetic technologies have the potential to revolutionize medicine.
GenVec AdenoVerse™ Platform

**Adenovector Advantages**
- Efficient transduction in dividing cells and non-dividing cells
- Non-integrating transgene limits probability of disturbing vital cellular genes

**AdenoVerse Strengths**
- Vectors with no or very low seroprevalence
- Featuring Tunable Tropism option to allow cell-type specific gene delivery
- Large packaging capability (up to 12 kb) with multiple expression cassettes
- Improved safety with multiple deletions in vector genomes
- Administered to over 3,000 clinical study subjects
- Commercializable platform with efficient manufacturing process and attractive cost of goods
- Strong IP position
AdenoVerse™ Platform
Overcoming the Known Adenovector Limitations

**Standard Adenovector Known Limitations**
- Pre-existing immunity
- Innate immunity associated toxicity
- Vector liver sequestration

**GenVec’s AdenoVerse Adenovector Superiority**
- Proprietary adenovector backbones from rare human and non-human primate serotypes with low to no seroprevalence in the human population
- Adenovector deleted for E1, E3, and E4 regions, limiting the expression of viral proteins mainly responsible for innate immune responses
- Some of these adenovectors appear not to be sequestered in the liver and could be suitable for systemic delivery

The AdenoVerse platform is the next generation of adenovector technology and has unprecedented potential for new medical treatments
Combination of Technologies
For Durable Correction of Genetic Disorders

**Key technologies**
- PEC delivery
- Gene editing
- AdenoVerse™ vectors

Proprietary product design incorporating all the key technologies

**Advantages**
- Harnesses the lung for protein expression
- Therapeutic gene durable expression
- Systemic administration
GenVec is developing gene therapeutics leveraging the lung, the second largest organ in the body, as a site for *in vivo* protein production.

PEC (pulmonary endothelial cell) delivery enables this novel therapeutic approach.
PEC delivery technology allows for specific gene therapeutic delivery into the lung endothelium via AdenoVerse™ vectors.

The lung endothelium is turned into a surrogate long-term production factory for therapeutic proteins.

This novel approach can be used to address multiple unmet medical needs (hemophilia, passive immunotherapies, etc.).

PEC delivery combined with AdenoVerse™ vectors limits liver toxicities observed with systemic administration of more traditional gene therapeutics.
PEC Delivery Platform
Mechanism of Action

Step 1: Loading of granulocytes with adenovectors

Step 2: Hand-off of adenovectors to lung endothelial cells

Step 3: Endothelial cell transduction and gene integration

Step 4: Therapeutic protein production and secretion into blood stream
PEC specifically targets granulocytes.

The lung endothelium harbors the majority of the body’s granulocytes.

The targeted granulocytes upload adenovector particles without being transduced and then “hand-off” the particles to the lung endothelium, which constitutes the end target.

Granulocytes carry adenovectors to be handed-off to lung endothelial cells.
PEC technology enables specific delivery to lung endothelial cells.

Selective targeting of lung observed with systemic administration in mice.

Technology developed by Dr. David Curiel at Washington University in St. Louis.

Solution for lung targeting:

Upon systemic administration in mice, a preferred distribution in the lung was observed.
Gene Editing Technologies
Tools to Perform Genome Surgery

Delivery of the complete gene editing payload to targeted cells

Target cell genome DNA

Precise double-stranded break created

Integration of the therapeutic gene

Programmable endonucleases
- Zinc Finger Nuclease (ZFN)
- Meganuclease (MN)
- TALEN
- CRISPR/Cas 9

Therapeutic gene

Nuclease expression

**Durable expression via permanent addition of the therapeutic gene sequence**
GenVec’s AdenoVerse platform provides a unique set of solutions for the key gene editing field requirements:

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<tr>
<th>Gene Editing Requirements</th>
<th>AdenoVerse Platform Solutions</th>
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| “Hit and run” (limited off-target effects) | Non-integrating vector:  
  • Transient nuclease expression minimizing potential off-target cuts  
  • Reduced chromosomal positional effects and risk of insertional mutagenesis |
| Large Capacity | Delivery of large payload (up to 12Kb):  
  • All the components in a single vector  
  • Multiple expression cassettes |
| Low Immunogenicity | • AdenoVerse vectors can be designed to have low immunogenicity properties |
Systemic administration has been a long-standing challenge for gene therapeutics.

GenVec’s AdenoVerse platform has addressed this hurdle by developing new adenovector serotypes offering:

- No to low sensitivity to pre-existing neutralizing antibodies
- Reduction of liver sequestration, minimizing hepatotoxicities

**Solution for systemic administration:**
GenVec’s novel non-human primate serotypes are resistant to pre-existing neutralizing antibodies.
### PEC Technology Applications

#### Examples of Potential Indications

<table>
<thead>
<tr>
<th>Category</th>
<th>Indications</th>
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| **Bleeding disorders**          | • Hemophilia A (FVIII)  
• Hemophilia B (FIX)             |
| **Metabolic disorders**         | • Type-1 diabetes                                                           |
| **Respiratory diseases**        | • Alpha 1-antitrypsin deficiency  
• Chronic obstructive pulmonary disease |
| **Anemia**                      | • Erythropoietin deficiency                                                  |
| **Passive immunizations**       | • Anti-pathogen or anti-toxin agents                                        |
AdenoVerse™ Platform
Identifying Vectors for New Therapeutic Applications

GenVec’s Screening Methodology

• Identify vectors with preferred performance for any given application and unique need

Data from screenings to identify vectors that efficiently transduce cells of interest

AdenoVerse Vectors

Data shown from human primary T cell screening
Data from initial screenings to identify vectors that efficiently transduce NK cells

<table>
<thead>
<tr>
<th>Vector</th>
<th>Transduction Score</th>
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<tr>
<td>Uninfected</td>
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<tr>
<td>Ad5</td>
<td>-/+</td>
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<tr>
<td>A</td>
<td>+</td>
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<td>B</td>
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</table>

- Identify vectors with preferred performance for any given application and unique need

GenVec unpublished data
A novel therapy for hearing loss and imbalance disorders

- A multi-deleted Ad5 vector carrying the Atonal gene (Hath 1)
  - Induces supporting cells in the inner ear to differentiate into sensory cells
- Proven ability to deliver material to the cochlea and vestibular system
- Demonstrated efficacy in various models (explants and \textit{in vivo})
- Subject of an ongoing Phase 1/2 clinical study designed to evaluate safety and efficacy
Neural stem cells (NSCs) for directed enzyme prodrug therapy

- NSCs transduced by a proprietary GenVec vector express and secrete carboxylesterase (CE) for a second generation, commercializable product

NSCs penetrate the tumor microenvironment, and the secreted CE enzyme provides radius of action throughout the tumor

CE converts irinotecan to SN-38, which is 1,000x more toxic to tumor cells than irinotecan alone

Second generation NSC.CE product candidate expected to enter the Phase 1 trial 1H 2017
Collaboration Approach

AdenoVerse™ platform:
• Offers multiple opportunities for product development and licensing
• Supported by GenVec’s extensive translational expertise

Actively exploring opportunities to:
• Expand application of the platform
• Add complementary assets or technologies to the current portfolio

Open Innovation and Collaboration to Expand the Reach and Unlock the Potential of AdenoVerse Vector Technology for New Medical Treatments
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