Cell and Gene Therapies
Transforming New Treatments Into Patient VALUE

Astellas Pharma Inc.
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Innovative Next-generation Treatments: The Potential of Cell and Gene Therapies

Aiming at a Paradigm Shift in Healthcare

In recent years, cell and gene therapies have started to become a reality, with innovative new treatments for diseases in development.

**Cell therapy** uses cells to restore impaired functions in the body or improve disease symptoms. It has the potential to treat diseases with currently limited treatment options, including cancer.

**Gene therapy** supplements or regulates genes in cells to recover from diseases. It can be applied to genetic and non-genetic diseases.

These modalities have the potential to resolve unmet medical needs and provide new **VALUE** to patients, their families and society.

<table>
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<tr>
<th>Characteristics of cell and gene therapies</th>
<th>VALUE that cell and gene therapy can deliver</th>
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| Potential to maintain efficacy with a single or a few treatments | **Patients**  
Transformative outcome or cure from life-threatening or serious diseases, resulting in increased daily activities |
|  | **Family**  
Reduced burden of care |
|  | **Healthcare/ Society**  
Transfer medical and human resources to others |

**History of medicine**

In the past, small molecules were the majority of generally used medicines. Since the 1990’s, biopharmaceuticals such as antibody drugs have brought new treatment options and dramatically changed the healthcare landscape. However, diseases remain that lack treatment options. Cell and gene therapies have emerged as innovative next-generation treatments.

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**Source:** R&D Meeting on December 13, 2018, Astellas Pharma Inc.

**Note:** The diagram shows the human body with different parts labeled: Organ: A body part with particular functions (e.g., liver, heart); Tissue: Gathering of similar cells with a function (e.g., skin, cartilage); Cell: Minimum constituent unit in the body, 0.01-0.03 mm in diameter; Gene: A blueprint in the cell to create human body.
Be on the forefront of healthcare change to turn innovative science into VALUE for patients. Under this VISION, Astellas strives to create new medicines and deliver them to patients, using novel methods such as cell and gene therapies.

With an aspiration of bringing life-changing treatments to patients suffering from diseases that lack treatment options, Astellas focuses on the potential of cell and gene therapies. These therapies may have the potential to transform patients’ lives and cure diseases in one or only a few treatments by addressing the root cause of the diseases rather than the symptoms.

Astellas has expertise and experiences as a pharmaceutical company in research, development, manufacturing and delivery of therapies to patients. Leveraging this capability, Astellas is working to develop new treatments by incorporating patient insights and collaborating with external partners.

### The VALUE that Astellas Creates and Delivers Through Cell and Gene Therapies

**Transforming Dreams into Reality**

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### Diseases Astellas is working on

**Cell therapy**

- Eye diseases
- Cancer
- Diseases with high unmet medical needs

**Gene therapy**

- Genetic neuromuscular diseases
- Other genetic diseases
- Non-genetic diseases with high unmet medical needs

Transform “Dream of Treatment” to “Reality”

What Astellas Can Do: Outline

**Cell Therapy**

1. **Create desired cells**
   - To apply cell therapy to various diseases
     - Develop cell therapy which allows preparation in advance
     - Establish methods to effectively produce approx. 20 types of cells

2. **Suppress immune rejection**
   - To ensure safety and efficacy
     - Universal Donor Cell technology creates cells which can avoid immune rejection
     - Expand applications of disease areas

3. **Mass production of high-quality cells**
   - To deliver the therapy to many patients
     - Expertise and experiences are cultivated at the frontier of cell therapy
     - Utilize state-of-the-art laboratories and facilities

**Gene Therapy**

1. **Directly work on the cause of diseases**
   - Targeting transformative treatment of diseases
     - Multiple types of technology to affect diseased genes
     - Apply to genetic diseases and other disease states

2. **Functional gene to work at the right place**
   - Cutting-edge technology to deliver a gene into the body
     - Utilize vehicles delivering genes into the body: Adeno-associated virus
     - Research ongoing in neuromuscular diseases

3. **Mass production of high-quality gene therapies**
   - To deliver the therapy to many patients
     - Advanced manufacturing technology
     - Designated manufacturing sites capable for mass production
1 Create Desired Cells
To apply cell therapy to various diseases

Astellas’ goal is to deliver cell therapy for allogeneic cell transplantation which allows preparation in advance to help as many patients as possible. Allogeneic cell transplantation uses pluripotent stem cells, undifferentiated cells which can change to various cells with a desired function.

It is not easy to change pluripotent stem cells to the desired cells. It requires multiple complex steps such as identifying the necessary conditions, managing the process over weeks or even months, and removing cells that do not work.

Astellas has established the methods to effectively produce approximately twenty types of cells with various functions. We will continue to fully explore the cell therapy potential to expand the target diseases we can treat by increasing the number of cells that we can produce.

 Cells that Astellas can efficiently create

**Cells in eye**
- Retinal pigment epithelium
- Photoreceptor rescue cell
- Ganglion rescue cell
- Corneal endothelial cell

**Cells to be used in immuno-oncology**
- cCAR-NK
- TCR-T

**Others**
- Hemangioblast derived mesenchymal stem cell
- Immuno-regulatory cell
- Mitochondrial transfer
- Vascular progenitor cell

More diseases may be accessible with increased types of cells

CAR: Chimeric antigen receptor, cCAR: convertibleCAR, NK: Natural killer TCR: T-cell receptor

Lean more: General information

**Allogeneic cell transplantation**
Cell therapy to be delivered to many patients using cells from outside the body, instead of your own body

**Autologous transplantation requiring multiple complex processes:**
Two procedures are needed to collect and transplant cells, a time-consuming process for modifying cells, but no concerns of immune rejection.

**Allogeneic cell transplantation with a simple process:**
Using cells prepared in advance, this is applicable to many patients with just one procedure and a more simple process. There are potential risks of immune rejection due to using cells from other people (See next page.)

**Pluripotent stem cells**
Cells that can change to anything

A single cell that repeats cellular division to have various functions

CAR: Chimeric antigen receptor, cCAR: convertibleCAR, NK: Natural killer TCR: T-cell receptor
Cell Therapy: What Astellas Can Do

2 Suppress Immune Rejection
To ensure safety and efficacy

It is important to suppress immune rejection in allogeneic cell transplantation which uses cells from other people instead of the patients’ own cells.

Using our proprietary Universal Donor Cell technology, we can create cells that may not cause immune rejection, which may allow us to expand the target therapeutic areas of cell therapy.

Astellas’ Universal Donor Cell Technology

Astellas’ technology regulates the genes of the cells to remove marker on the cell surface that distinguishes others’ cells from own cells. This allows transplanted cells to escape from being recognized as foreign substances.

Astellas’ technology:
Transplanted cells are not recognized as others without the marker on the surface → No immune rejection

Cells used in the treatment

Key to success: Suppressing immune rejection

The immune system in the body eliminates infections from viruses or bacteria when they come into the body. This is also applicable to cells.

Cells have markers on the surface, and our immune system can recognize these foreign cells. When they enter the body, the immune system attacks the incoming cells, causing the rejection.

Cells used to treat diseases must be accepted in the body so that cell therapy can be effective.

Cells that come into the body have markers → Immune rejection
Cell Therapy: What Astellas Can Do

3 Mass Production of High-quality Cells
To deliver the therapy to many patients

Astellas has the experience and technology cultivated at the frontier of cell therapy and a state-of-the-art facility that boasts one of the largest cell libraries in the world. Astellas can produce high-quality cells in large quantities and deliver them to many patients.

Manufacturing facility in Astellas

Astellas Institute for Regenerative Medicine
Westborough, Massachusetts
- Footprint: Approx. 24,000m² (Size of three football fields)
- Total construction cost: Approx. 14 billion yen

“Bench to bedside” with manufacturing, research and development members collaborating in one site, allowing for the seamless exchange of insights and making the whole process faster

Seven clean rooms with expandable space, enabling production of multiple high-quality products at the same time. The supply of cells from research to commercial applications, is fully compliant with the global regulations

Manufacturing technology in Astellas

We established the technology to freeze the final cell products, allowing central manufacturing for worldwide distribution to be conveniently transported and used in hospitals.

In-house stock of various pluripotent stem cells lines, use the latest gene-editing technology to create desired cells

Technology for large scale expansion of targeted cells with high purity and consistency, with strict controls on temperature and pressure etc.

Learn more: General information

- Much more difficult procedures and handling processes than conventional medicines
  - A process that may take months
  - Ensuring quality
  - Stability in storage
  - Securing the necessary amount

- Process to create targeted cells
  - Pluripotent stem cells
  - Expansion
  - Change to targeted cells
  - Expansion of targeted cells

*Source: Information from clinical trials of Astellas and other companies

Weeks - Months

Removal of remaining unchanged cells
Control of irregular cells

*Source: Information from clinical trials of Astellas and other companies
Gene therapy: What Astellas Can Do

1 Directly Work on the Cause of Diseases
Targeting transformative treatment of diseases

Gene therapy directly works on the genes that cause a disease to potentially provide a transformative treatment for that disease. Astellas has multiple technologies to improve functions of genes.

Technology to work on the cause of diseases with genes

Gene therapy and diseases caused by genetic deficiencies

Genes have a role in designing the body and producing proteins based on the blueprint they describe. Protein is one of the major constituents of the body and is involved in various biological activities. Gene therapy modifies the synthesis of protein in the body to treat diseases.

Learn more: General information

- 1. Disease and genetic deficiencies
- 2. Procedure for protein synthesis
- 3. Gene therapy and non-genetic diseases

These technologies allow Astellas to target a wide variety of genetic diseases and expand the potential of gene therapy to treat non-genetic diseases as well.
Gene therapy: What Astellas Can Do

Functional Gene to Work at the Right Place
Cutting-edge technology to deliver a gene into the body

Astellas develops gene therapies which administer a functional gene to the body. It is essential to deliver the gene so that it can work in the targeted cells in the body.

Astellas uses adeno-associated viruses to deliver functional genes to the targeted location. Among various types of adeno-associated virus, Astellas works with sero-type 8 (AAV8) that can deliver genes to muscles in whole body. Our initial focus is the treatment of life-threatening neuromuscular diseases with high unmet need. We are also working on other disease areas.

Astellas is among the front-runners for research and development using AAV8 and has the technology that may efficiently produce AAV8.

Learn more: General information

Adeno-associated virus

Vehicles delivering genes into the body
An adeno-associated virus is a natural virus that does not have a pathogenicity and is commonly used as a “vehicle” to deliver the gene without causing adverse reactions.

Various types of adeno-associated viruses are reported and they have unique characteristics.*

Gene Therapy: What Astellas Can Do

3 Mass Production of High-quality Gene Therapies
To deliver the therapy to many patients

Gene therapies are manufactured through a complex process in which living cells insert a functional gene into a virus. The process requires advanced technology and capable facilities to produce a large amount of high-quality gene therapy. Astellas has unique technology and state-of-the-art equipment to efficiently manufacture gene therapies so that they can be delivered to many patients.

Manufacturing facilities in Astellas: Astellas Gene Therapies

South San Francisco, California
- Research and manufacturing
- Equipped with bioreactor systems at 1,000L

Sanford, North Carolina (Under construction)
- Footprint: Approx. 13,000m² (Size of two football fields)
- Total construction cost: Approx. 11 billion yen

Manufacturing technology in Astellas

- Cover all the stages from research and development to commercialization
- World-leading size of bioreactors, capable for demand growth in the future
- Four times bigger bioreactor than the current equipment, to be expanded to 20 times. Capable for supply in muscle diseases.

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Challenges in gene therapy production using adeno-associated virus

- Appropriate gene design
  - Designed to be safe and productive
  - Genes should have adequate length and composition to be inserted into viruses.

- Ensure quality
  - Homogeneous, clinically proven quality
  - Quality can affect efficacy and safety if genes are not correctly inserted in viruses.

- Efficient production
  - Cost reduction required to secure access as a large amount of genes required
  - Approximately 100 billion genes are administered for eye diseases and 1,000 trillion genes are required to treat muscle diseases.*

Bioreactor

- An equipment which uses cells to produce gene therapy drugs
- Researchers use 2L bioreactors in their experiments

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*Source: https://www.nature.com/articles/s41423-018-00307-6
Astellas is working to develop new treatments by incorporating the voices of patients and collaborating with various internal and external partners globally. Our operations are centered in laboratories and manufacturing facilities in the United States and Japan.
Transform the “Dream of Treatment” to “Reality”

Age-related macular degeneration
Retinitis pigmentosa
Glaucoma
Cancer

X-linked myotubular myopathy
Pompe disease
Duchenne muscular dystrophy
Myotonic dystrophy

Note) Target diseases of drug candidates at Astellas

Astellas is making efforts in research and development of treatments for various diseases by utilizing cell and gene therapies. Some of these programs have already progressed to the clinical stage and are under evaluation for their efficacy and safety in patients.

Be on the forefront of healthcare change to turn innovative science into VALUE for patients

This states why Astellas keeps moving forward.