# INITIATIVES IN CELL THERAPY

## -TURNING INNOVATIVE SCIENCE INTO VALUE FOR PATIENTS-

R&D Meeting – December 13, 2018

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# CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING INFORMATION



In this material, statements made with respect to current plans, estimates, strategies and beliefs and other statements that are not historical facts are forward-looking statements about the future performance of Astellas Pharma. These statements are based on management's current assumptions and beliefs in light of the information currently available to it and involve known and unknown risks and uncertainties. A number of factors could cause actual results to differ materially from those discussed in the forward-looking statements. Such factors include, but are not limited to: (i) changes in general economic conditions and in laws and regulations, relating to pharmaceutical markets, (ii) currency exchange rate fluctuations, (iii) delays in new product launches, (iv) the inability of Astellas to market existing and new products effectively, (v) the inability of Astellas to continue to effectively research and develop products accepted by customers in highly competitive markets, and (vi) infringements of Astellas' intellectual property rights by third parties.

Information about pharmaceutical products (including products currently in development) which is included in this material is not intended to constitute an advertisement or medical advice.

# PROGRAM



I

## Cell Therapy

-A novel approach to treating disease-

II

## Leading with Science

-Investigating pluripotent stem cell therapies-

III

## ASP7317

-To offer the hope to regain lost sight-

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# CELL THERAPY

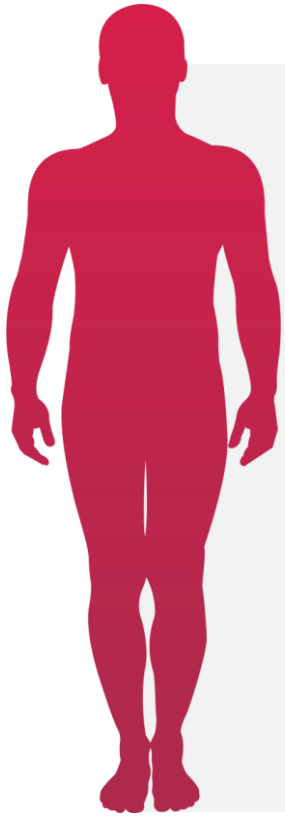
## A novel approach to treating disease

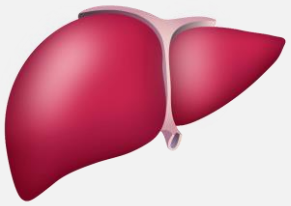
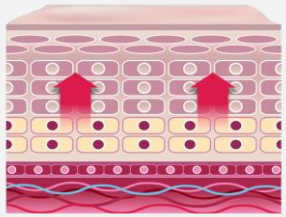


**Kenji Yasukawa, Ph.D**
**President and CEO**

# WHAT IS CELL THERAPY?

*Cell therapy is a medical treatment using viable cells to regenerate functions of tissues or organs impaired by disease or injury*



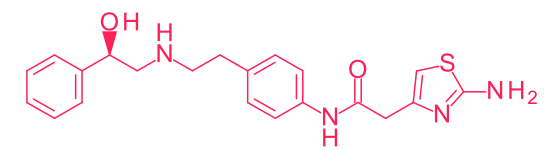
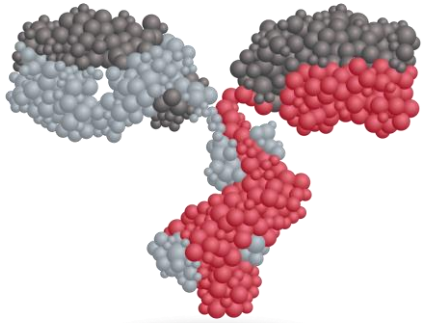
| ORGAN | ORGAN BUD | TISSUE | CELLS |
|---|---|---|---|
| A part that has particular functions in the body (e.g. liver, heart) | Minimum set of cells of an organ | Aggregation of similar cells with a function (e.g. skin, cartilage) | Minimum constituent unit in the human body (e.g. nerve cells, cardiomyocytes) |
|  |  |  |  |
| | | | Central player in cell therapy |

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# ADVANTAGES OF CELL THERAPY



*Multi-functional nature of cells offers high efficacy that existing therapies cannot deliver*

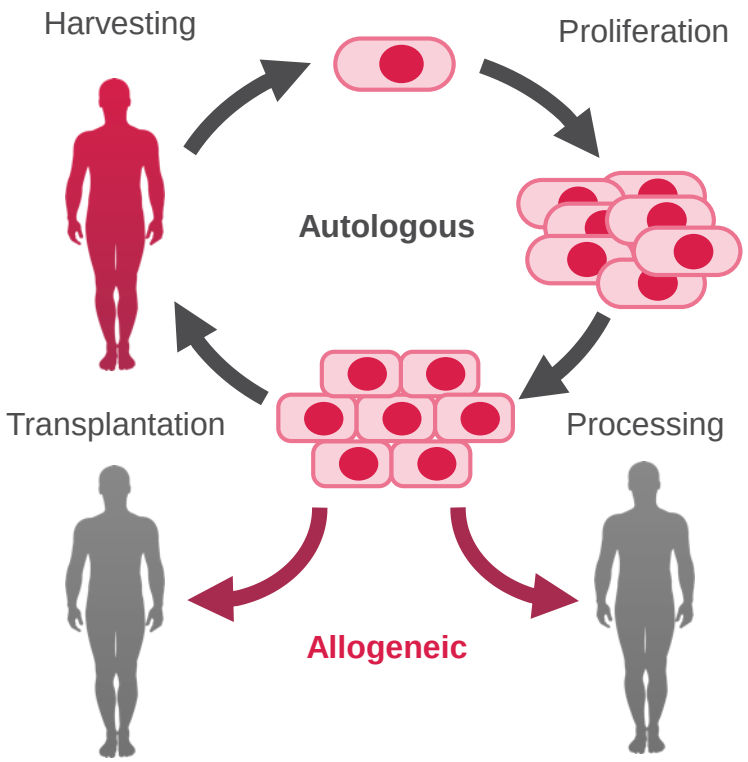
| | SYNTHETIC COMPOUNDS | BIOPHARMACEUTICALS | CELLS |
|---|---|---|---|
| |  |  |  |
| MW SIZE | **<500** | **10K～150K (a few nm)<br>(- Synthetic compounds x 3,000)** | **NA (10-30 μm）<br>(- Bopharmaceuticals x 10,000)** |
| FUNCTION | **Single**<br>*e.g. agonist, antagonist* | **Single**<br>*e.g. agonist, antagonist, ADCC etc.* | **Multiple**<br>*e.g. sensor, phagocytosis, secretion, antigen presentation, neurotransmission, metabolism* |

MW: Molecular weight, ADCC: Antibody-dependent cellular cytotoxicity

# TWO CATEGORIES OF THERAPEUTIC CELLS



*Allogeneic cells may greatly expand potential impact*




## AUTOLOGOUS CELLS

- Individualized
  - Avoids immunological rejection
  - Costly
  - Requires a long period from harvesting to transplantation

## ALLOGENEIC CELLS

- Commercialized cell therapy
  - Scalable
  - Requires countermeasure for immune rejection
  - Requires an established route for responsible cell acquisition

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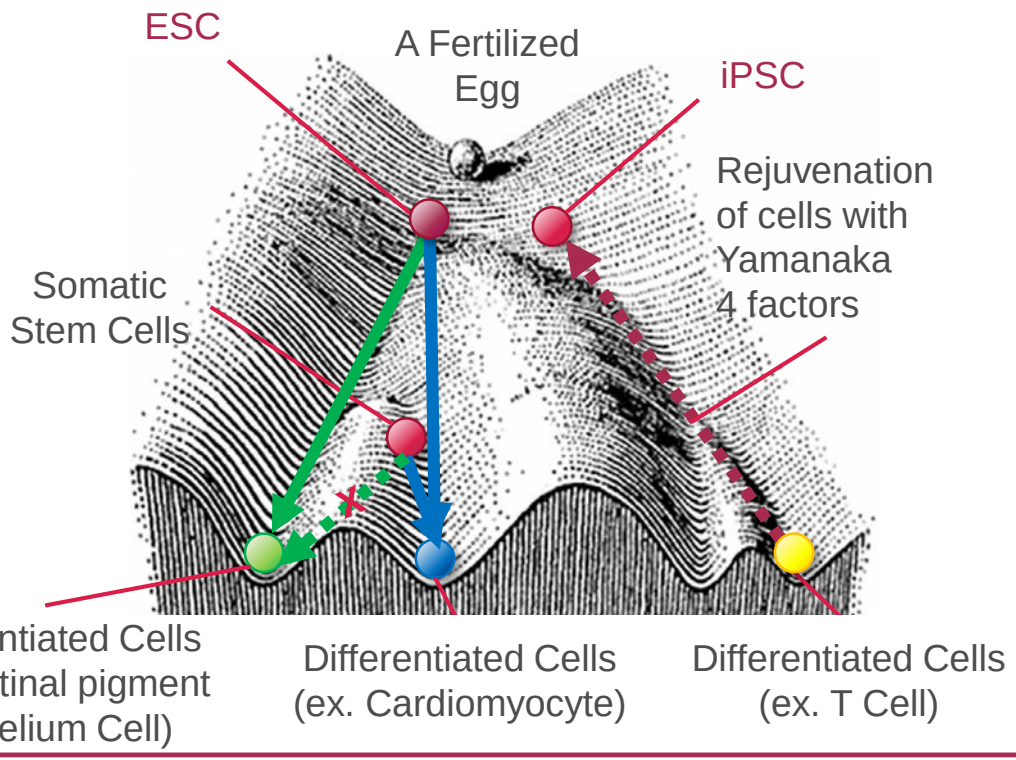
# CELLS TO BE USED IN CELL THERAPY



*Astellas will pursue commercialization of various cell therapy products using pluripotent stem cells (PSCs).*

*The key to this approach is establishment of efficient differentiation protocol*

## EPIGENETIC LANDSCAPE BY CONRAD WADDINGTON




## KINDS OF STEM CELLS

**PSC**

- Embryonic stem cell (ESC)
- induced pluripotent stem cell (iPSC)
  - Derived from embryo or made by rejuvenation of cell
  - Differentiate to almost all kind of cells.

**Somatic Stem Cell**

- Somatic stem cell
  - Exist in the normal body
  - Differentiate to limited organs

Source: The Epigenetics Revolution: How Modern Biology is Rewriting Our Understanding of Genetics, Disease and Inheritance (Written by Nessa Carey)

# ASTELLAS CELL THERAPY

*PSC-derived differentiated cells are most suitable for our business model*

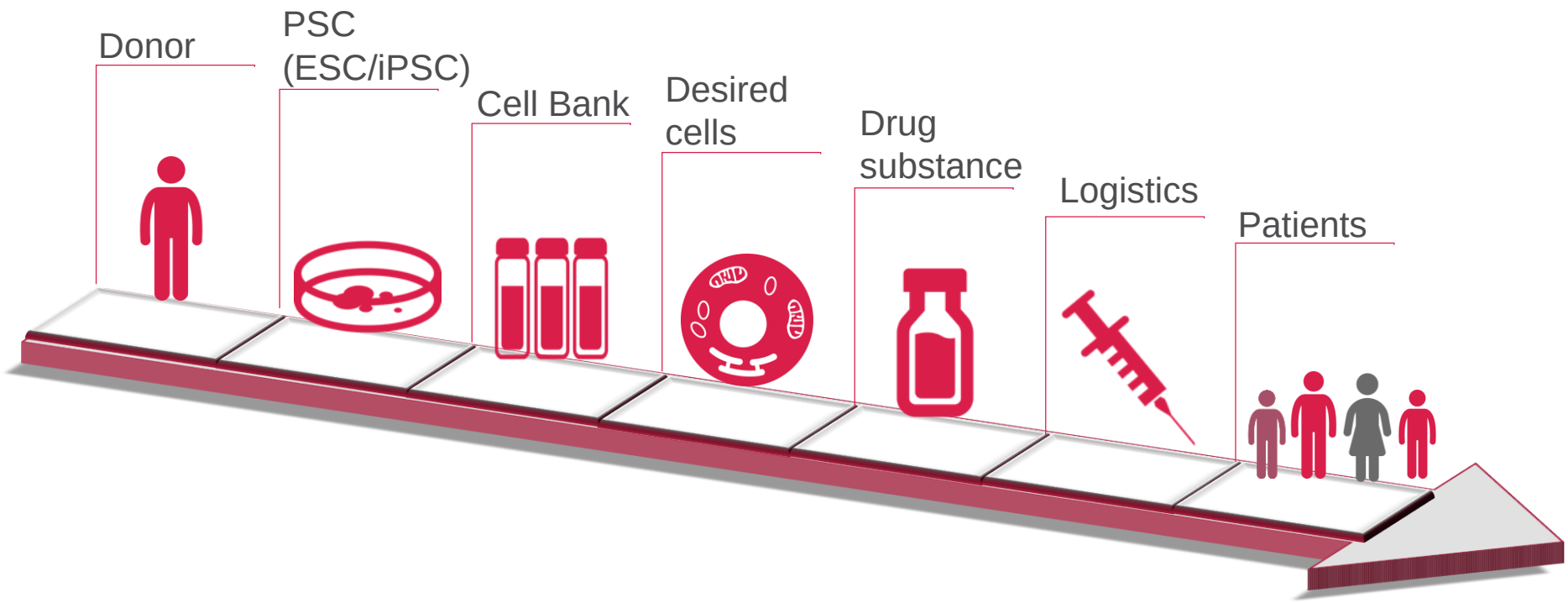
| | AUTOLOGOUS CELLS | ALLOGENEIC CELLS | |
|---|---|---|---|
| | | SOMATIC STEM CELLS-DERIVED DIFFERENTIATED CELL | PSC-DERIVED DIFFERENTIATED CELL |
| **Immunological rejection** | No | Yes | Yes |
| **Applicable tissue** | Limited*1 | Limited | **Non-limited** |
| **Inter-donor variability** | NA | Yes | **No** |
| **Scale (expandability)** | NA | Scalable but limited | **Scalable** |
| **Duration for preparation** | Long time*2 | Less time | **Less time** |
| **Manufacturing cost** | High | Middle | **Middle** |

*1：Considering the time for generating autologous iPS cells, applicable tissue might be limited.
*2：Contain the time for generating autologous iPS cells.

# JOURNEY OF CELLS: LABORATORY TO PATIENTS



*Living cells require a different pathway than conventional medicines*




PSC: Pluripotent stem cell, ESC: Embryonic stem cell, iPSC: induced pluripotent stem cell

# FUTURE OUTLOOK OF CELL THERAPY



*Many patients will receive the benefits from broader application of cell therapy*

| OUTLOOK IN 2030 |
| --- |
| Allogeneic PSC-derived products are widely used. |
| Next generation cell-derived products, such as combination with gene editing technology, are developed and launched. |
| Infrastructures critical for commercialization of cell therapy, such as manufacturing cost reduction, improvement of distribution system, facility expansion, etc., are improved. |
| A sustainable business model of cell therapy is established. |

# ESTIMATED FUTURE MARKET SIZE



*The regenerative medicine market is expected to be 38 trillion yen worldwide by 2050*

## 22 STEM-CELL-DERIVED PRODUCTS CURRENTLY ON THE MARKET (JUN. 2017)

Black: Autologous cells, Red: Allogeneic cells

**Japan**
- Temcell(GVHD), Heart sheet (Heart Failure )

**US**
- Osteocel Plus(Bone Repair), Grafix (Wound healing)
- Trinity Evolution (361HCT/P, Musculoskeletal defect)
- Trinity ELITE (361HCT/P, Musculoskeletal defect)
- BIO4 (361HCT/P, Bone Repair)

**EU**
- Holoclar (Corneal epithelial stem cell deficiency)
- Strimvelis (ADA-SCID)

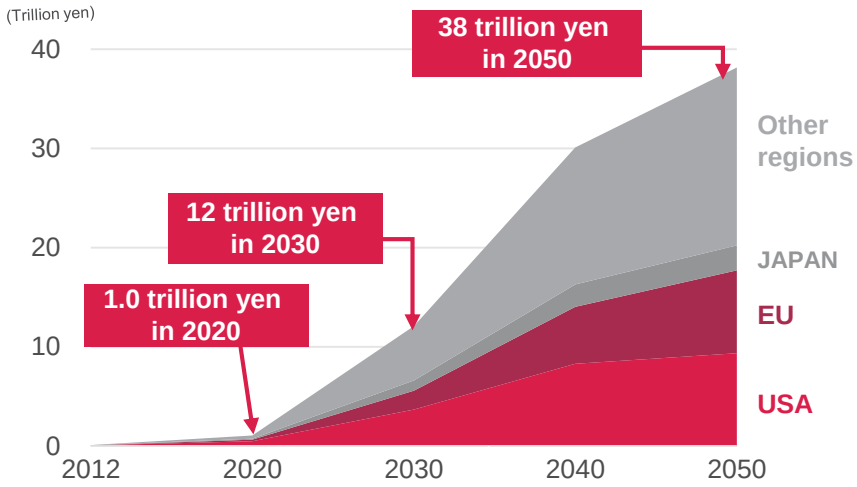
**KOREA**
- CARTISTEM (Osteoarthritis), Cupistem injection (Crohn's disease)
- Queencell (Subcutaneous fat tissue repair)
- NEURONATA-R inj (Near amyotrophic lateral sclerosis)
- Autostem (Subcutaneous fat tissue repair)
- Cellgram-AMI (Myocardial infarction), Ossron (Bone Repair)

**INDIA**
- Stempeucel (Limb ischemia), Ossron (Bone Repair)
- ReilNethra (Corneal epithelial stem cell deficiency)
- ReilNethra C (Composite conjunctival epithelial cell)
- CardioRel (Myocardial infarction)

**OTHERS**
- Prochymal (NZ&CA, GVHD)

Reprinted from the report by Japan Patent Office's

## ESTIMATED FUTURE MARKET




Reprinted from the report by Ministry of Economy, Trade and Industry

GVHD: graft versus host disease, ICRS: International Cartilage Research Society,
ADA-SCID: Adenosine deaminase (ADA) deficiency severe combined immunodeficiency

# NAVIGATING REGULATORY PATHWAYS



*Authorities are rapidly establishing cell therapy specific regulatory processes*

**KEY POINTS**

- **Issue of guidelines for the products categorized for cell therapy**
- **Issue of guidance for quality control and conducting non-clinical and clinical studies**
- **Quicker approval pathways**

| | PRODUCT CATEGORY | PRODUCT | REGULATION | ACCELERATION |
|---|---|---|---|---|
|  | Regenerative Medicine Product | Regenerative Medicine Product | ➢ Pharmaceutical Affairs Law<br>➢ Technical Guidance for the Quality of Regenerative Medical Products (Human Cell Processed Products), and Implementation of Non-Clinical and Clinical Studies | Conditional & Time-limited Approval for Regenerative Medicine Products |
|  | Biologics or Medical Device | 351HCT/Ps* | 21st Century Cures Act Part 1271 | Regenerative Medicine Advanced Therapy (RMAT) Designation |
|  | Pharmaceutical | Advanced Therapy Medicinal Products (ATMP) | Regulation (EC) No 1394/2007 | |

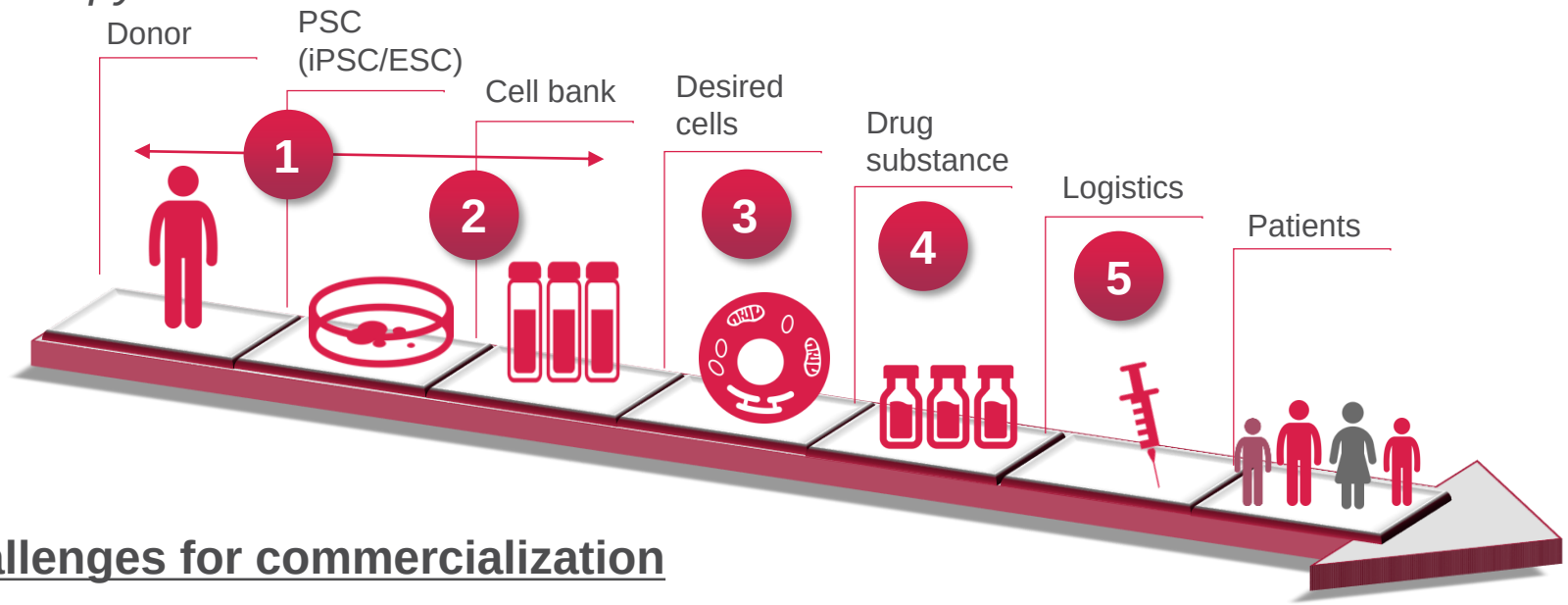
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*Human Cells and Tissues and Cellular and Tissue-based Products Regulated Under Section 351 of the Public Health Service Act

# KEY CAPABILITIES FOR CELL THERAPY



*Over the past several years, we have acquired capabilities to realize the promise of cell therapy*




## Challenges for commercialization

1. **Secure own PSC line / banks with safety and pluripotency**
2. **Avoid immune rejection**
3. **Develop efficient differentiation protocols for desired cell types**
4. **Establish expertise and infrastructure for GMP cell manufacturing**
5. **Establish efficient logistics system**

PSC: Pluripotent stem cell, iPSC: Induced pluripotent stem cell, ESC: Embryonic stem cells, GMP: Good manufacturing practice

# LEADING WITH SCIENCE

## Investigating pluripotent stem cell therapies



**Yoshitsugu Shitaka, Ph.D.**
**President**
**Astellas Institute for Regenerative Medicine**

# AGENDA



1 **Snapshot of Astellas Cell Therapy**

2 **Strategy of Astellas Cell Therapy**

3 **Challenges of PSC-based cell therapies**

4 **Measurement & accomplishment for challenges**

5 **Future challenge & perspective**

# 1. SNAPSHOT OF ASTELLAS CELL THERAPY ~CENTERS OF INNOVATION AND EXCELLENCE~



*180 employees are dedicated to cell therapy at 3 sites and expediting programs in collaboration with internal and external partners*




## Universal Cells Inc. (UCells)

- 2018 UCells acquisition
- CSO: Dr. D. Russell
- Hub of Astellas gene-editing
- AAV technology, UDC, etc.
- Internal programs
- Partnership programs
- Active participation and cooperation in industrial organization activities (ARM)

## AIRM

- 2016 Ocata acquisition
- CSO: Dr. R. Lanza
- Hub of Astellas regenerative medicine
- Stem cell science and technology for differentiated cells
- GMP manufacturing
- Clinical development for ophthalmology
- Internal programs
- Collaborations (academia, biotech)

## AIRM Satellite Office

- Collaboration with functions specialized in Drug Discovery
- Collaborations in Japan
- Active participation and cooperation in industrial organization activities (FIRM)

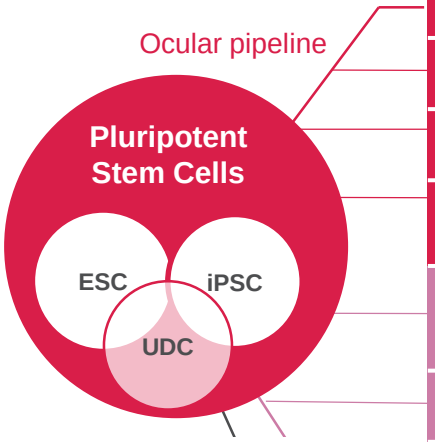
*Granted patents/pending applications: US(30/22, others(61/144)
CSO: Chief Scientific Officer, AAV: Adeno-associated virus, UDC: Universal donor cell, ARM: Alliance for regenerative medicine,
AIRM: Astellas institute for regenerative medicine, GMP: Good manufacturing practice, FIRM: Forum for innovative regenerative medicine

# PIPELINE



*Focus on diseases-cell types with high unmet needs*

- *4 programs in ophthalmology area (ASP7317 is in clinical stage)*
- *Enhanced pipeline by UCells acquisition and new external collaborations (especially peripheral diseases)*




| Cell/ Program | ES /iPS | UDC Application | Potential Disease | Development Progress: Pre-clinical | Clinical: P1 | Clinical: P2 |
|---|---|---|---|---|---|---|
| Retinal pigment epithelium (RPE) | ES | Applicable | • Dry AMD<br>• Other macular degeneration | ASP7317 | | |
| Photo-receptor progenitors (PhRPs) | ES /iPS | Applicable | • Retinitis pigmentosa<br>• Macular degeneration | | | |
| Retinal ganglion progenitors (RGPs) | ES /iPS | Applicable | • Glaucoma<br>• Optic neuropathies | | | |
| Corneal endothelium | ES /iPS | Applicable | • Corneal diseases<br>• Corneal injuries | | | |
| Hemangioblast-derived MSCs (HMCs) | ES /iPS | Applicable | • Autoimmune diseases: Lupus Nephritis, Crohn's Disease | IND planned in 2020 | | |
| Vascular progenitors | ES /iPS | High priority | • Critical limb ischemia<br>• Pulmonary hypertension | | | |
| Hematopoietic Stem Cells New | ES /iPS | High priority | • Leukemia/ Hematopoietic disorders | | | |
| Other various Cell Types New | ES /iPS | High priority | • Peripheral diseases | | | |
| NK New | ES /iPS | High priority | • Cancer | | | |
| Others (Partnering) New | ES /iPS | High priority | | | | |

New Added after the previous R&D meeting in December 2016.

AMD: Age-related macular degeneration. IND: Investigational new drug application

# 2. STRATEGY OF ASTELLAS CELL THERAPY ~STRATEGIC GOALS~



| *1st Wave* | *2nd Wave* | *3rd Wave* |
|---|---|---|
| Establish a solid foothold in ophthalmology and build cell therapy foundation throughout value chain | Enrich cell therapy pipeline including non-ocular area by leveraging UDC technology | Create next generation cell product by combining stem cell technology and gene-editing technologies |
| **Measures:**<br>• Intake of ASP7317 and stem cell technologies (incl. manufacturing) through Ocata acquisition<br>• More efficient R&D by centralization at AIRM | **Measures:**<br>• Intake of gene-editing technologies (incl. UDC) through UCells acquisition<br>• New collaborations in the US, EU and Japan | **Measures:**<br>• Enhancement of UCells capabilities<br>• Pursuit of synergy between AIRM and UCells and value maximization of our technologies |

**Strategic Goals**

UDC: Universal donor cell

# WHY OPHTHALMOLOGY?



*1st WAVE : Pursue ophthalmology as an initial focus area for Astellas cell therapy*

## GENERAL ISSUES FOR CELL THERAPY

**Difficulty in manufacturing large amount of cells** ✖ **Immune rejection** ✖ **Need invasive surgery**

## BENEFIT OF OPHTHALMOLOGY

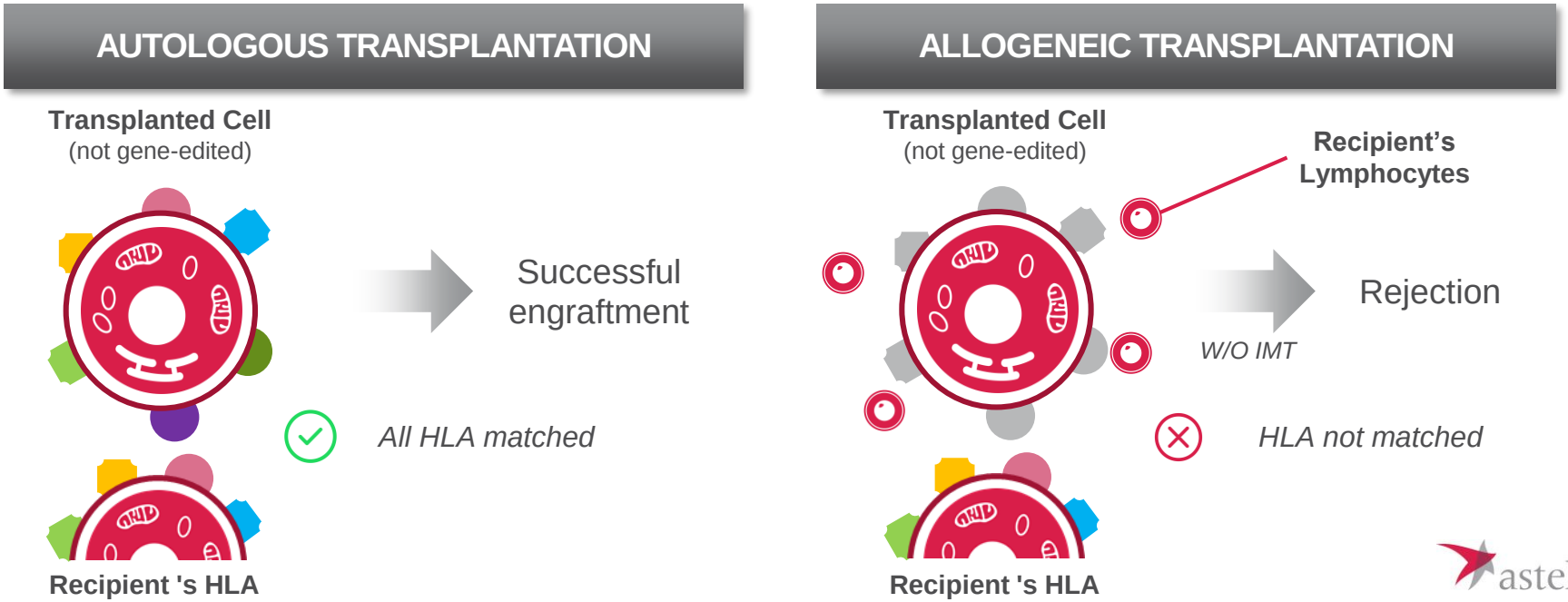
**Small amount of cells required for small organ** ✖ **Immuno-privileged** ✖ **Easy access organ**

# WHY UNIVERSAL DONOR CELLS (UDC)? (1/2)



## Mechanism of immune rejection

- The mechanism that distinguishes self from non-self, which is well-known in organ transplantation, is also equipped with cells.
- T cells, a type of leukocyte, recognize molecules called human leukocyte antigen (HLA) expressed on cell membrane, and exclude non-self cells if mismatched.
- Such a mechanism is indispensable for biological defense such as the elimination of bacteria, viruses and cancer cells, but on allogeneic cell transplantation, transplanted cells are subjected to immune rejection by lymphocytes. This could be a major barrier in cell therapy.

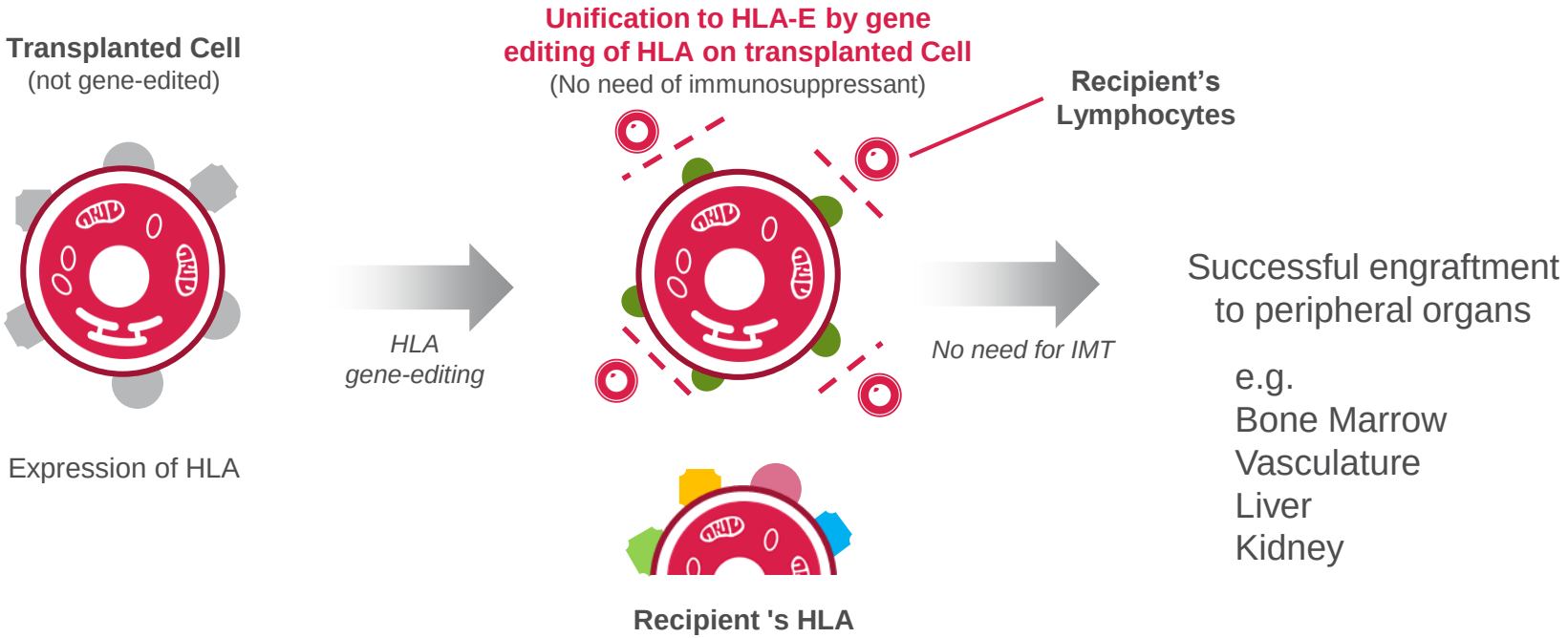



: human leukocyte antigen (HLA) , IMT: Immunosuppressant

# WHY UDC? (2/2)



*2nd WAVE: Expand to non-ophthalmology by leveraging UDC technology*



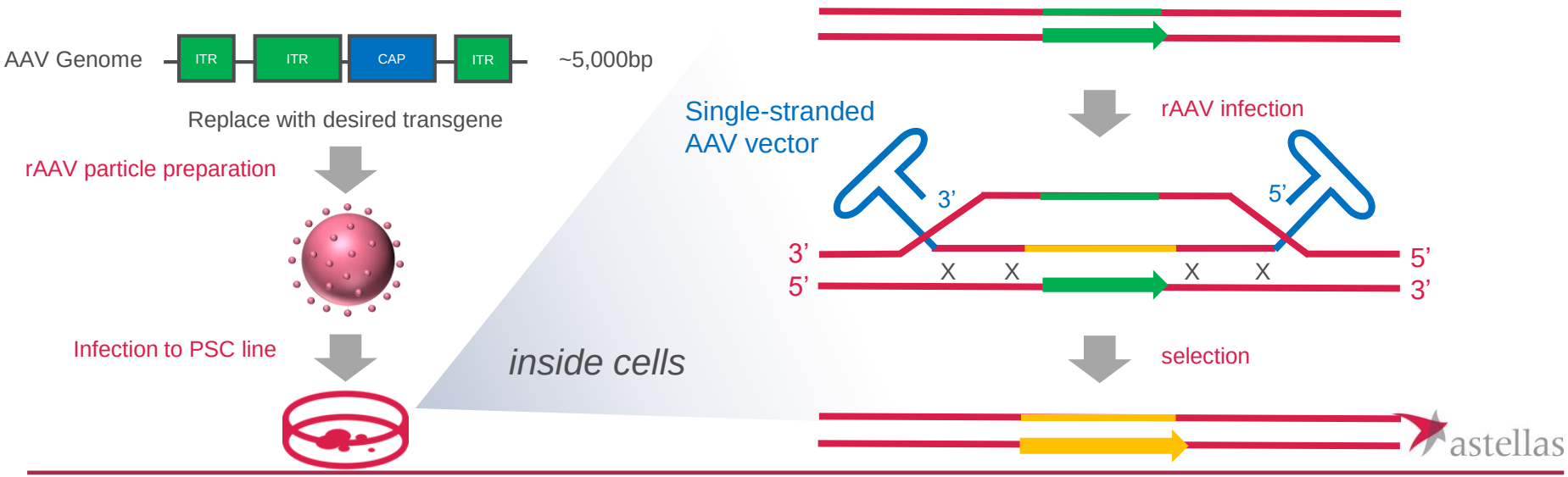

UDC: Universal donor cells, HLA: Human leucocyte antigen, IMT: Immunosuppressant

# NEXT GENERATION ENHANCED CELL (1/2)



## Advantages of AAV-based gene-editing technology by UCells

- Precise gene-editing by homologous recombination
- Low off-target mistakes
- No pathogenicity in wild-type AAV
- Applicable to both knock-in and knock-out→Broader applicability other than UDC
- Low integration frequency into host genome




AAV: Adeno-associated virus, rAAV: Recombinant adeno-associated virus

# NEXT GENERATION ENHANCED CELL (2/2)



*3rd WAVE : Create next generation enhanced cells combining cell therapy and gene-editing technologies*

## Application of gene-editing

**AIRM**

PSC technology

×

**UCells**

Gene-editing

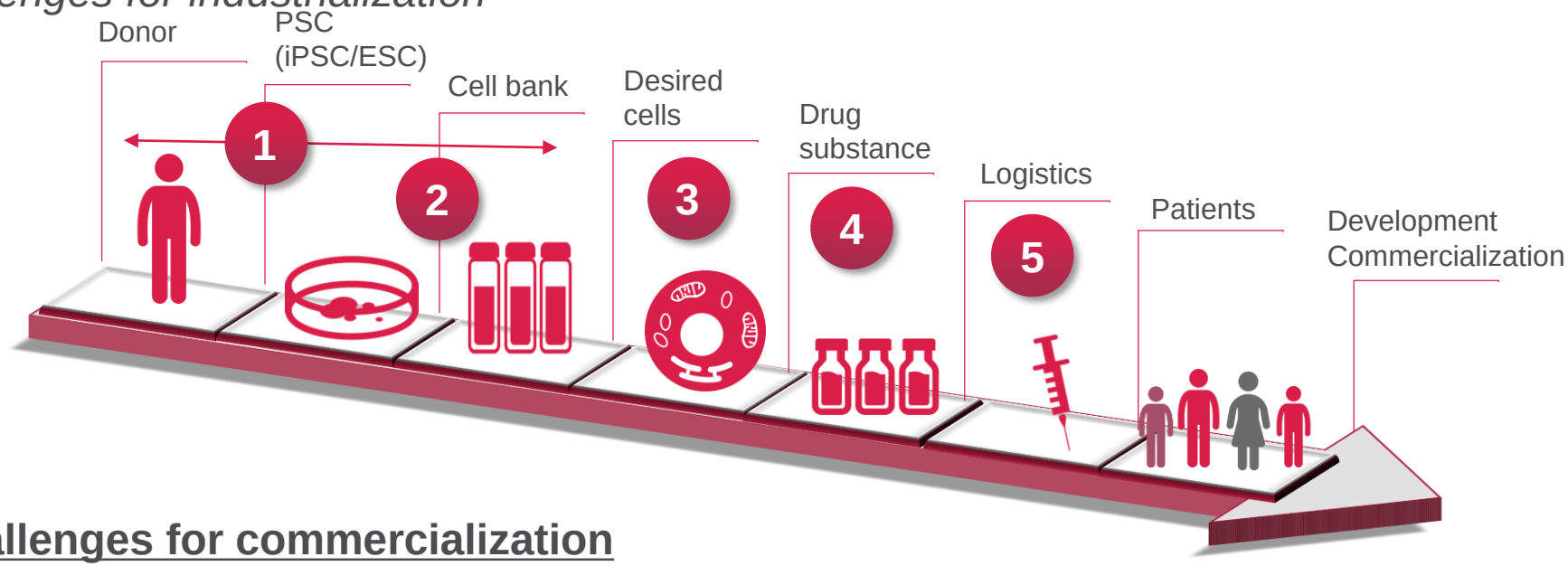
| | Next Generation enhanced cell product |
|---|---|
| Knock-out molecules responsible for immune rejection | Avoidance of Immune rejection (=UDC) |
| Gene-editing to secrete more beneficial factors | Enhance efficacy |
| Gene-editing to shorten differentiation period | Cost reduction |
| Gene-editing to enhance homing to affected legion | Reduction of cells |
| Install safety system for abnormal proliferation | Further safety |

PSC: Pluripotent stem cell, UDC: Universal donor cells

# 3. CHALLENGE OF PSC-DERIVED ALLOGENEIC CELLS



*PSC-derived allogeneic cells have a large potential opportunity but there are several challenges for industrialization*




## Challenges for commercialization

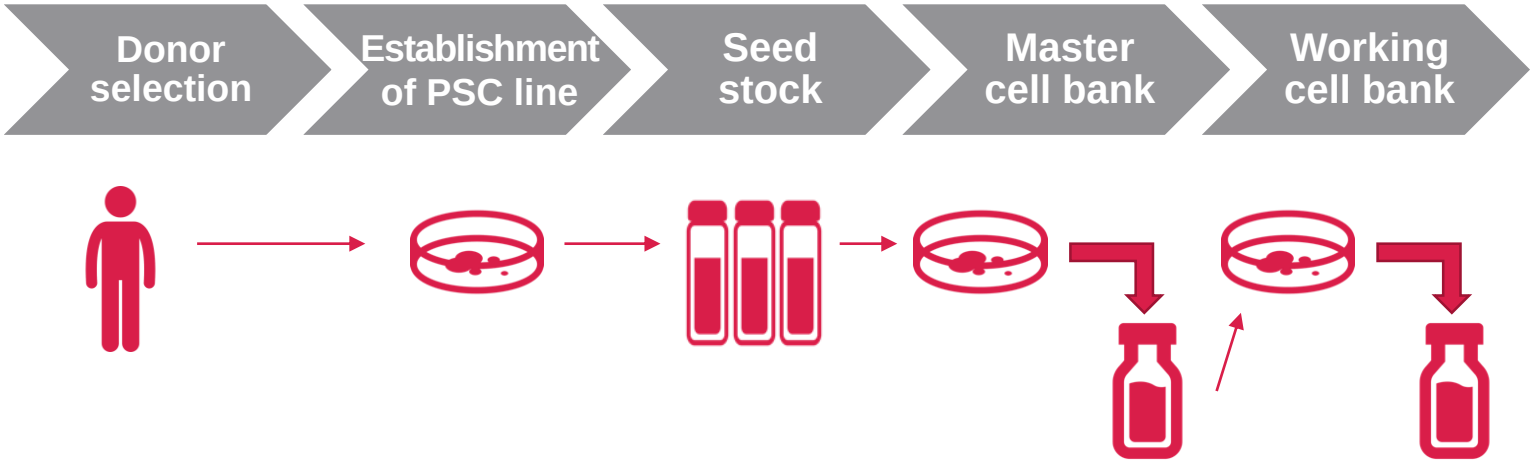
1. **Secure own PSC line / banks with safety and pluripotency**
2. **Avoid immune rejection**
3. **Develop efficient differentiation protocols for desired cell types**
4. **Establish expertise and infrastructure for GMP cell manufacturing**
5. **Establish efficient logistics system**

PSC: Pluripotent stem cell, iPSC: Induced pluripotent stem cell, ESC: Embryonic stem cells, GMP: Good manufacturing practice

# 4. MEASUREMENT & ACCOMPLISHMENT FOR CHALLENGES ~SECURE OWN PSC LINE/BANKS WITH SAFETY AND PLURIPOTENCY(1/2)~



| 1 CHALLENGE | EXAMPLE |
|---|---|
| **Secure own PSC line / banks with safety and pluripotency** | - **Compliance to donor eligibility (virus inspection, etc.) which varies in different regions**<br>- **Expansion culture maintaining and securing pluripotency and genome stability**<br>- **Management of cell line as an important product raw material with an eye to commercial use: A new cell line is handled as a different product** |




Donor eligibility (interview, virus inspection, Informed consent)

Creating cell bank after characterization of pluripotency and genome stability, etc.

Securing sufficient amount is important for consistent and sustainable product supply

Used for Drug Substance production

PSC: Pluripotent stem cell

# SECURE OWN PSC LINE/BANKS WITH SAFETY AND PLURIPOTENCY (2/2)





*Established multiple clinical and commercial grade PSC stocks that are compliant with the 3-region regulations. Securing high-quality and sufficient amount of seed stocks/commercial MCBs for future stable supply*

## Our capabilities and achievements

- In-house ability to establish clinical and commercial grade PSC strains from donor selection to cell banking, and have established multiple PSC strains compliant with the regulations of 3 regions
- Applying the experience over 15 years and expertise in ES cells to iPS cells. Possessing high-quality cell seed stocks with maintaining pluripotency and securing genome stability
- Manufacturing and managing commercial MCBs for each cell type from own PSC stock to secure future stable supply
- Continuously establishing new PSC stock (backup, next generation cell, etc.)

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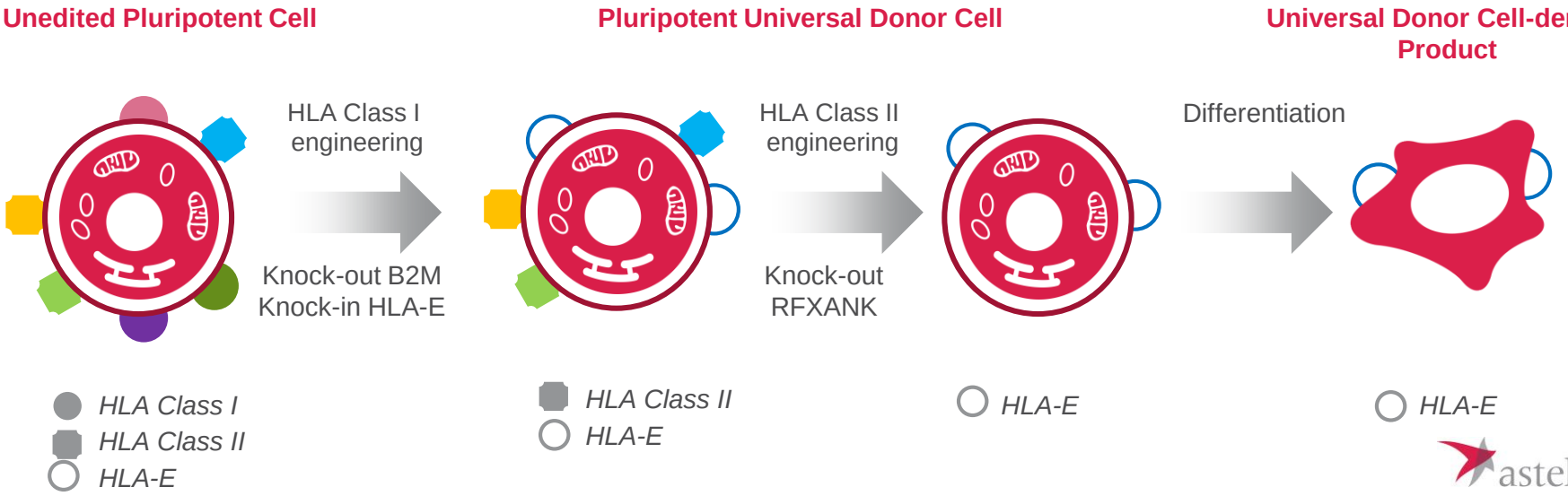
PSC: Pluripotent stem cell, MCB: Master cell bank

# AVOID IMMUNE REJECTION (1/2)



| 2 CHALLENGE | EXAMPLE |
|---|---|
| Avoid immune rejection | - **When targeting long-term engraftment in peripheral tissues, it is necessary to avoid immune rejection**<br>- **Depending on the immunogenicity of transplanted cells, it is difficult to administer cells multiple times**<br>- **Concerns of handling increased numbers of cell lines if using HLA matched cell lines** |

## Flow of UDC creation




UDC: Universal donor cells, HLA: Human leucocyte antigen, B2M: Beta-2 Microglobulin

# AVOID IMMUNOLOGICAL REJECTION (2/2)



*Acquired UDC technology to avoid immune rejection. Expect enhancement of drug efficacy and cost reduction*

## Our capabilities and achievements

- Acquired UDC technology to avoid immune rejection
- Can be administered to any patient without limitation of HLA compatibility with expected benefits in the table below
- Increased number of researchers for broader application after acquisition of UCells

Table. Potential benefits from UDC technology

| | Engraftment | IMT | Multiple dosing |
|---|---|---|---|
| UDC allogeneic cell | Available | Not necessary/lower dosage | Available |
| Non-UDC allogeneic cell | Difficult | Necessary | Difficult |

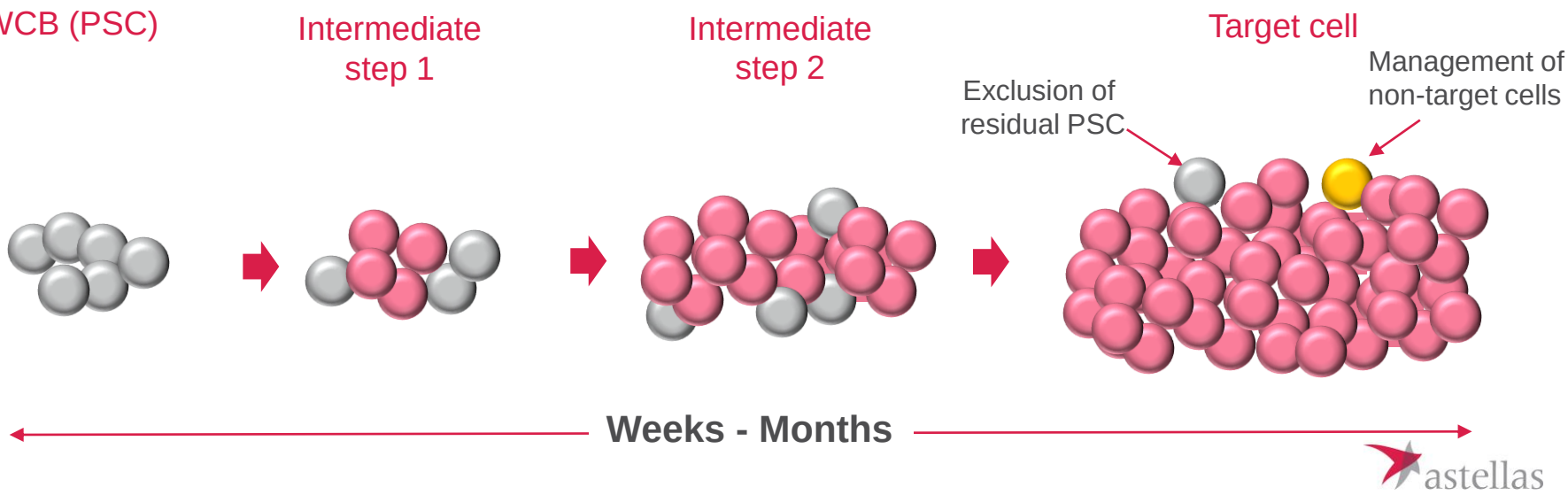
UDC: Universal donor cells, IMT: Immunosuppressant

# DEVELOP EFFICIENT DIFFERENTIATION PROTOCOLS FOR DESIRED CELL TYPES (1/4)



| 3 CHALLENGE | EXAMPLE |
|---|---|
| Develop efficient differentiation protocols for desired cell types | - Optimization / hardening of different processes for each cell type, securing of intellectual property<br>- Process control over weeks to months (function of desired cells, residual PSC strains, non-target cells)<br>- Requiring large amount of cells depending on cell type and indication (RPE-AMD: cell number of ~ $10^5$ order / patient*1 vs. MSC-GVHD: cell number of ~ $10^8$ or more / patient*2) |

## Flow from WCB to target cell (generalized)




*1:in-house clinical trial, *2: clinical trials conducted by other companies,
WCB: Working cell bank, PSC: Pluripotent stem cell, RPE-AMD: Retinal pigment epithelium cell-Dry aged related macular degeneration,
MSC-GVHD: Mesenchymal stem cells－Graft-versus-host disease

# DEVELOP EFFICIENT DIFFERENTIATION PROTOCOLS FOR DESIRED CELL TYPES (2/4)



*Established robust differentiation process for ASP7317 by utilizing in-house science base*
*Continue optimization for next programs to prepare for commercialization*
*Expanding types of peripheral cells through collaborative research*

## Our capabilities and achievements

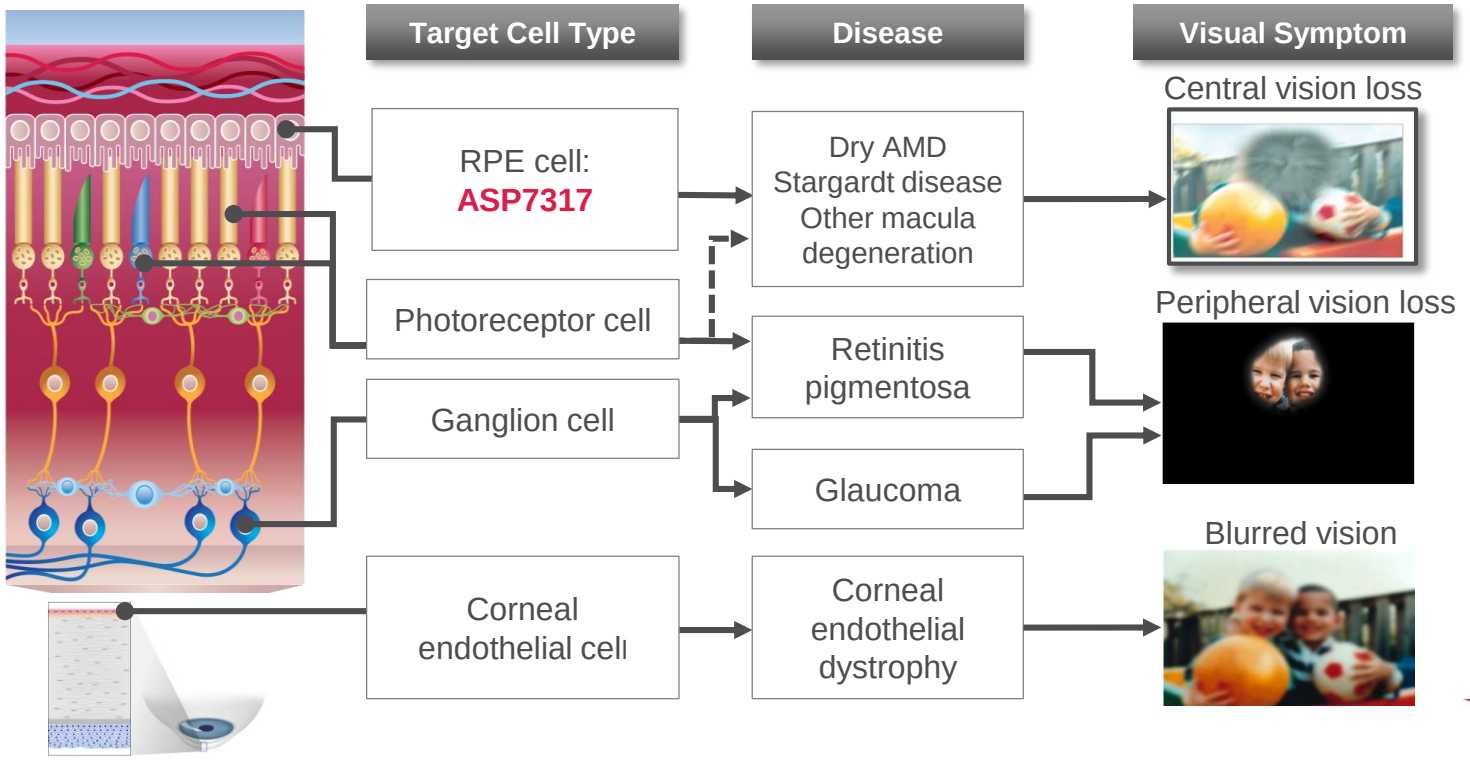
- Consolidated researchers with strong expertise in stem cell science/ development biology in AIRM and UCells. Established and optimized differentiation process in-house
- For ASP7317, established robust differentiation process. Succeeded in reproducing cells conforming to standards (drug function, purity, etc.) with good reproducibility by controlling complicated processes over several months
- For next programs, continue optimization to prepare for commercialization
- Utilizing network with Academia / Biotech to expand collaborative research on peripheral cell types
- Ongoing development of automation / mass production technology using bioimaging and bioreactor etc.

# DEVELOP EFFICIENT DIFFERENTIATION PROTOCOLS FOR DESIRED CELL TYPES (3/4)



## Ophthalmology program

*ASP7317 clinical trial is ongoing*
*Other 3 programs are preclinical and differentiation methods are optimized in-house*
*The 4 programs can cover broad range of ocular indications with unmet needs*



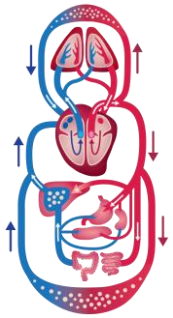

RPE: Retinal pigment epithelium cell, AMD: Age-related macular degeneration.

# DEVELOP EFFICIENT DIFFERENTIATION PROTOCOLS FOR DESIRED CELL TYPES (4/4)



## Non-ophthalmology program and UCells program

*Expanding peripheral programs by utilizing collaborative research*
*UCells internal programs are also being expanded*

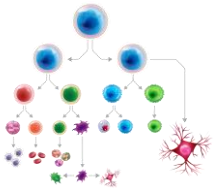


**Circulatory/Vascular Progenitor Cells**
- Brigham and Women's Hospital
- Stanford School of Medicine
- Brigham and Women's Hospital
- panCELLa
- Stanford School of Medicine
- Osaka University



**Hemangioblast-derived Mesenchymal Stem Cells**

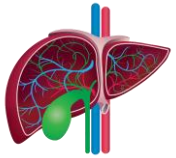
**PSC**



**Hemaopoietic Stem Cells**
- Angiocrine



**Renal Progenitor Cells**
- Brigham and Women's Hospital



**Liver Progenitor Cells**
- University of Edinburgh



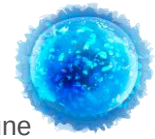
**Natural Killer Cells**

**Other Undisclosed Cells**

**RPE Cells**
- Healios



**T Cells**
- Adaptimmune



**In-house program**

**Collaborative program**

**UCells**

PSC: Pluripotent stem cell, RPE: Retinal pigment epithelium cell

# ESTABLISH EXPERTISE AND INFRASTRUCTURE FOR GMP CELL MANUFACTURING (1/3)



| 4 CHALLENGE | EXAMPLE |
|---|---|
| Establish expertise and infrastructure for GMP cell manufacturing | - Construction of GMP production system specialized for cells (quality assurance system, standards / quality inspection, etc.)<br>- Compliance to different standards (raw materials, manufacturing facilities) in each region<br>- Concern on outsourcing: time to transfer technology, inability to accumulate know-how in-house etc. |

## Capabilities needed for GMP cell manufacturing

- Worker training and certification system
- Quality assurance system
- Quality management system
- Raw material management
- Sterility guarantee system
- Supply chain management

GMP: Good manufacturing practice

# ESTABLISH EXPERTISE AND INFRASTRUCTURE FOR GMP CELL MANUFACTURING (2/3)



*Established a GMP cell manufacturing system compliant to each region's regulations to enable global cell supply. Completed to secure CTM cell of ASP7317*

## Our capabilities and achievements

- Established a GMP cell production regime through ASP7317 manufacturing (Table 1)
- Succeed in supplying CTM cell to US and UK. Discussing with PMDA in Japan
- Secured sufficient quality of CTM cell for ASP7317 in multiple lots
- Strengthening GMP manufacturing function by acquiring new facilities (next page)

Table 1. Status of establishment for GMP cell manufacture system

| Item | Establishment |
|---|---|
| Worker training and certification system | Completed |
| Quality Assurance System | Completed |
| Quality management system | Completed |
| Raw material management | Completed |
| Sterility guarantee system | Completed |
| Supply Chain Management | Completed |

GMP: Good manufacturing practice, CTM: Clinical trial material, PMDA: Pharmaceuticals and medical devices agency

# ESTABLISH EXPERTISE AND INFRASTRUCTURE FOR GMP CELL MANUFACTURING (3/3)



*The new facility enhances GMP manufacturing function and accelerates to POC*
*Early commercial production is available*

## Purpose of AIRM R&D- CMC complex (tentative name)

- To ensure smoother and more stable CTM supply
- Accelerate early clinical CMC work from late preclinical through early collaboration with R&D, UCells and future partners
- Response to initial commercial production



| | |
|---|---|
| **Location:** | **Massachusetts, USA** |
| **Total floor area:** | **approximately 24,000 m$^2$ (two stories above ground)** |
| **Specification (GMP part):** | **Seven clean rooms with independent air conditioning that can handle various cell manufacturing. Secure extended space** |
| **Total construction cost:** | **Approximately 14 billion yen** |
| **Schedule:** | **Construction started in September 2018, scheduled completion in January 2020** |

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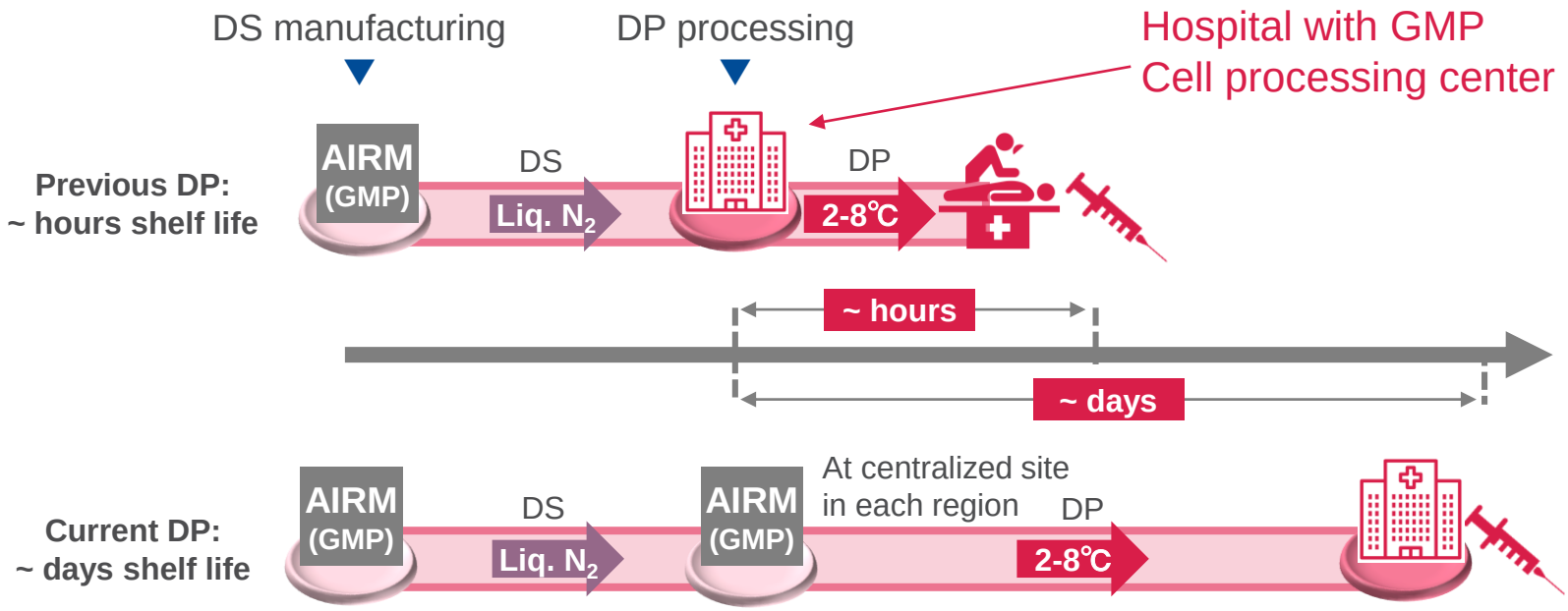
GMP: Good manufacturing practice, POC: Proof of concept, CMC: Chemistry, manufacturing and control, CTM: Clinical trial material

# ESTABLISH EFFICIENT LOGISTICS SYSTEM (1/2)



| 5 CHALLENGE | EXAMPLE |
|---|---|
| Establish efficient logistics system | - Determination of transport conditions according to the nature of the cell type, transport (compliance with quality)<br>- Depending on cell type indication, response to short quality retention period<br>- Construction of efficient logistics system realizing cost reduction and logistics increase |

## Flow from DP formulation to hospital (example of in-house upgrade)




DP: Drug Product, DS: Drug Substance, Liq. $N_2$: Liquid nitrogen

# ESTABLISH EFFICIENT LOGISTICS SYSTEM (2/2)



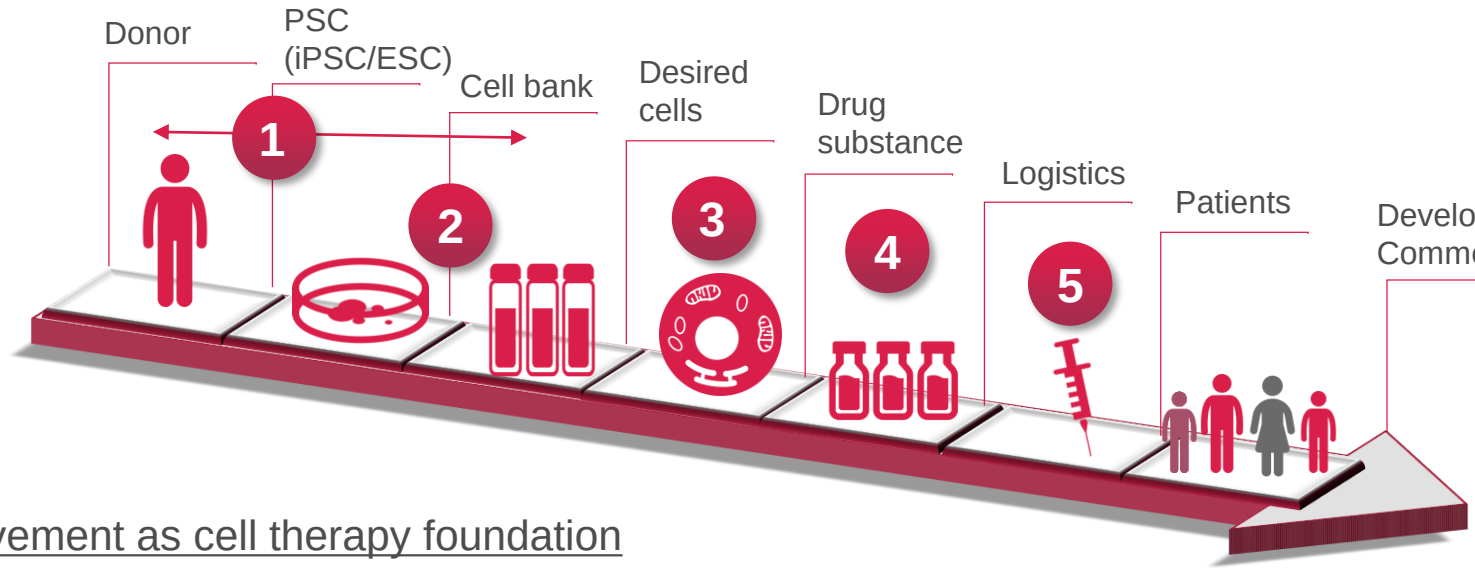
*The new DP formulation enables AIRM to make logistics efficient, ensure quality of DP, decrease costs and increase distribution*

## Our capabilities and achievements

- For ASP7317, DP composition was changed after Ocata acquisition. Quality retention period was changed to several days solving multiple problems on logistics (guarantee of quality through centralization of preparation site, reduction of burden on hospital side etc.)
- Completed verification test of packing method, container, temperature change, vibration, atmospheric pressure, etc. in the transfer process. Completed training for taking cell package at the clinical sites
- Expect to increase capacity in future by reduction of burden on hospital side

DP: Drug Product

# SUMMARY OF ACHIEVEMENTS




## Achievement as cell therapy foundation

| | Research | | | | | Manufacturing | | | Supply chain | | Development | | | Commercial | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ❶ PSC sourcing | UDC | ❷ Gene-editing | ❷ Differentiation | ❸ Standardization | ❹ QA | ❹ Facility | ❹ Freeze-thaw tech. | Formulation | ❺ Operation | RA | IMT regimen | Specialized platform | Business model |
| Post-Ocata Acquisition | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Post-UCells Acquisition | | ● | ● | | | | | | | | | | | |
| Current AIRM | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |

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●: Established, ●: Underway, ●: Not Established / To be considered,
PSC: Pluripotent stem cell, iPS: Induced pluripotent stem cell, ES: Embryonic stem cells,
UDC: Universal donor cell, QA: Quality assurance , RA: Regulatory affairs, IMT: Immunosuppressant

# 5. FUTURE CHALLENGES AND PERSPECTIVE



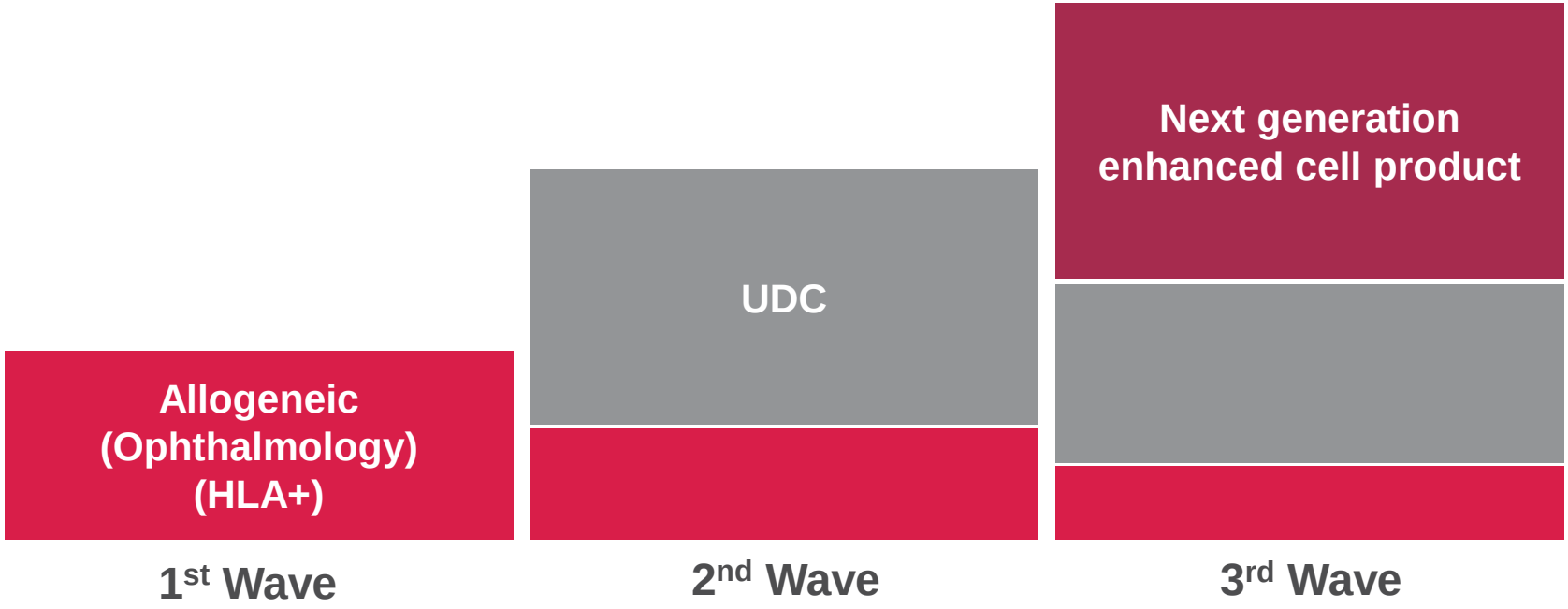
- Expedite ASP7317 development using accelerated regulatory pathways (e.g. RMAT designation) in each region
- Promote next programs and explore new collaborations by leveraging established capabilities
- Maximize and further reinforce current technologies
- Establish more efficient logistics
- Develop ecosystem for downstream commercialization
- Establish sustainable business model

RMAT: Regenerative medicine advanced therapy

# FUTURE PIPELINE (ILLUSTRATIVE)



*Develop market through allogeneic cell (ophthalmology) and UDC and further expand the market through next generation enhanced cells to establish sustainable business*




UDC: Universal donor cell

# SUMMARY



- Three bases in US and Japan collaborating with internal/external stakeholders for cell therapy. Expanding pipeline led by ASP7317 in ophthalmology (P1b/2)

- Astellas' cell therapy strategy:
  Establish a solid foothold in ophthalmology and build cell therapy medicine foundation throughout value chain
  →Enrich cell therapy pipeline including non-ocular area by leveraging UDC technology
  →Create next generation cell product by combining stem cell technology and gene-editing technologies

- Overcame multiple technological challenges for industrialization by leveraging acquisitions effectively

- Future challenges are implementation of current strategy, establishment of ecosystem for commercialization and development of sustainable business model

UDC: Universal donor cell

# ASP7317

**To offer the hope to regain lost sight**



**Eddy Anglade, MD**
**Ophthalmology Therapeutic Area Head, Development**

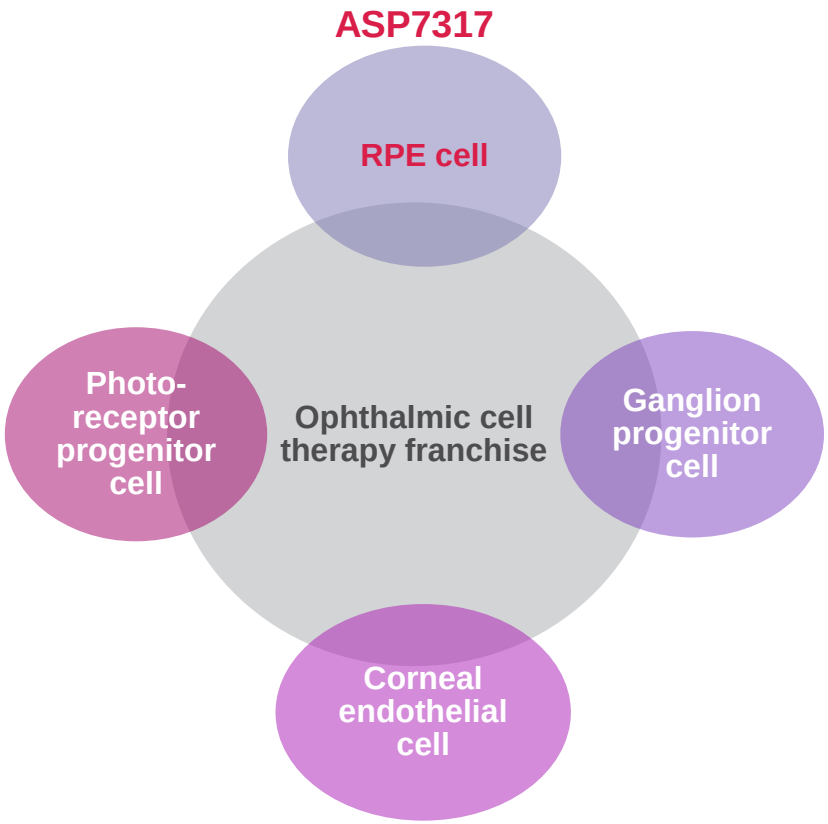
# OUR FOCUS IN OPHTHALMOLOGY: VISION THREATENING EYE DISEASE



*To free patients from the fear of vision loss and offer the hope to regain lost sight*



An estimated **1.3 billion people** worldwide live with some form of vision impairment*




*World Health Organization. Blindness and vision impairment – Key Facts. 10-11-2018.
RPE: Retinal Pigment Epithelium

# AGE-RELATED MACULAR DEGENERATION (AMD)

*AMD is a leading cause of visual disability in individuals over 55 years old in advanced countries*



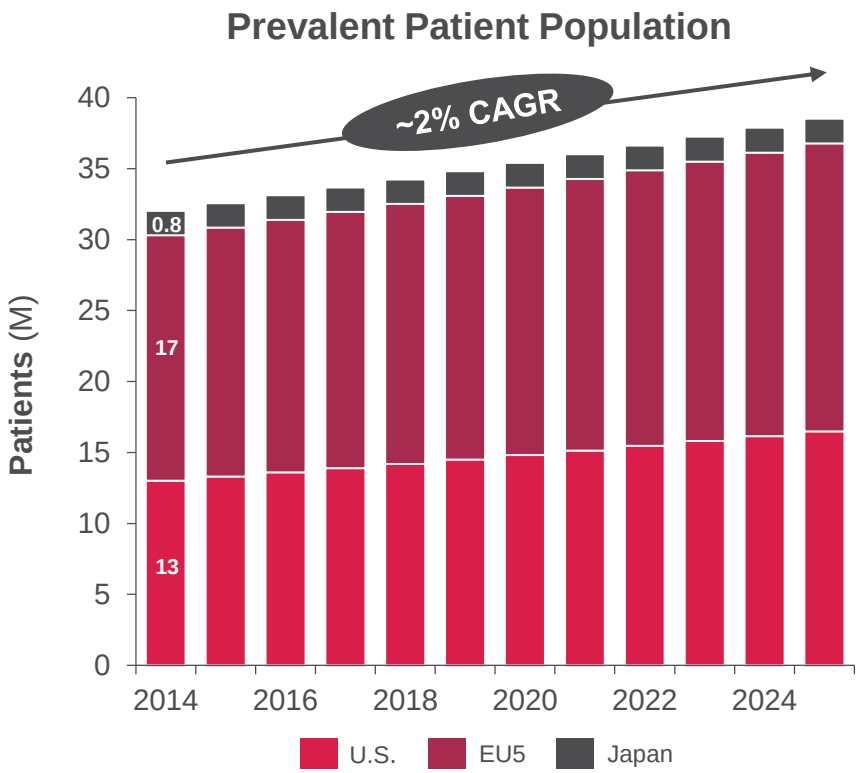

- AMD is a progressive degenerative disease affecting the central portion of the retina (i.e., RPE and photoreceptors in the macula) that results in loss of central vision.
- Symptoms of AMD:
  - Straight lines start to appear distorted, or the center of vision becomes distorted
  - Increased difficulty adapting to low light levels, such as in a theater or dimly lit restaurant
  - Reduced central vision in one or both eyes
  - Decreased intensity or brightness of colors

Photos: National Eye Institute, National Institutes of Health

# DRY AMD: PREVALENT PATIENT POPULATION



*Approximately 37 million people in advanced countries have Dry AMD, prevalence is expected to increase due to aging populations*




- Age is a risk factor, and the aging population will expand the Dry AMD population
- Prevalence of late stage Dry AMD varies from ~0.05% in 40 – 49 year olds to ~12% in individuals ≥80 years of age

## High unmet medical needs:

- Disease progression results in irreversible damage to the photoreceptors of the retina
- The ability to restore vision would have a significant impact on patients' quality of life.
- There are no safe and effective treatments available to stop or slow the progression of Dry AMD.

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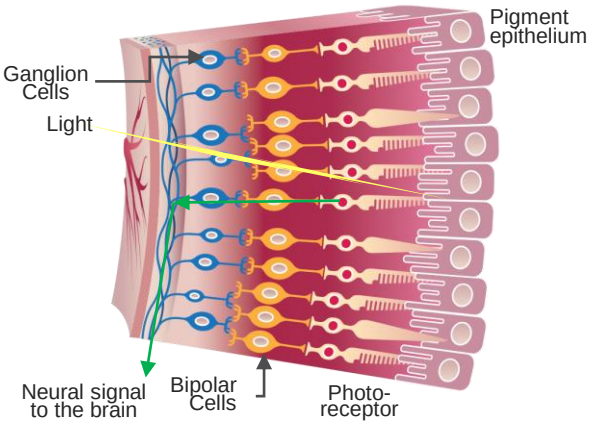
Friedman. *Arch Ophthal.* 2004;122:564; Physician Interviews; ClearView Analysis.
EU5: UK, France, Germany, Italy, Spain, CAGR: Compound annual growth rate, M: million

# THESIS OF CELL THERAPY APPROACH TO RPE TRANSPLANTATION

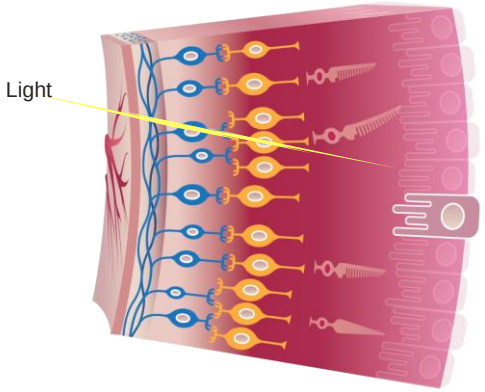
*Replacement of RPE to potentially restore visual function*

## PATHOGENESIS OF DRY AMD

**Normal**

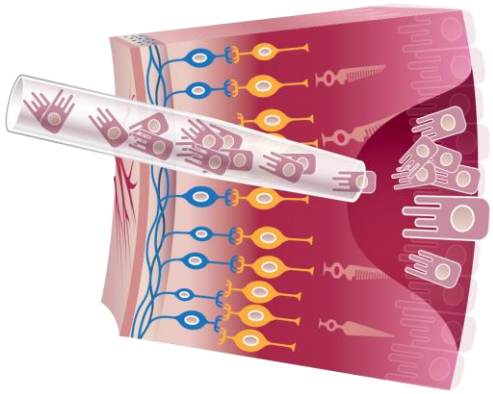



**Macular Degeneration**

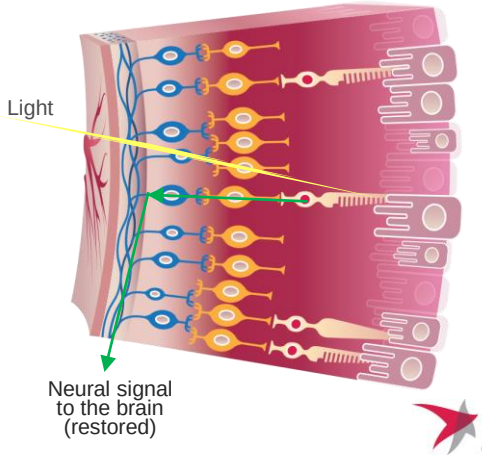



## RESTORE RPE CELL FUNCTION BY CELL THERAPY

**RPE transplantation**



**Neural signal restored**



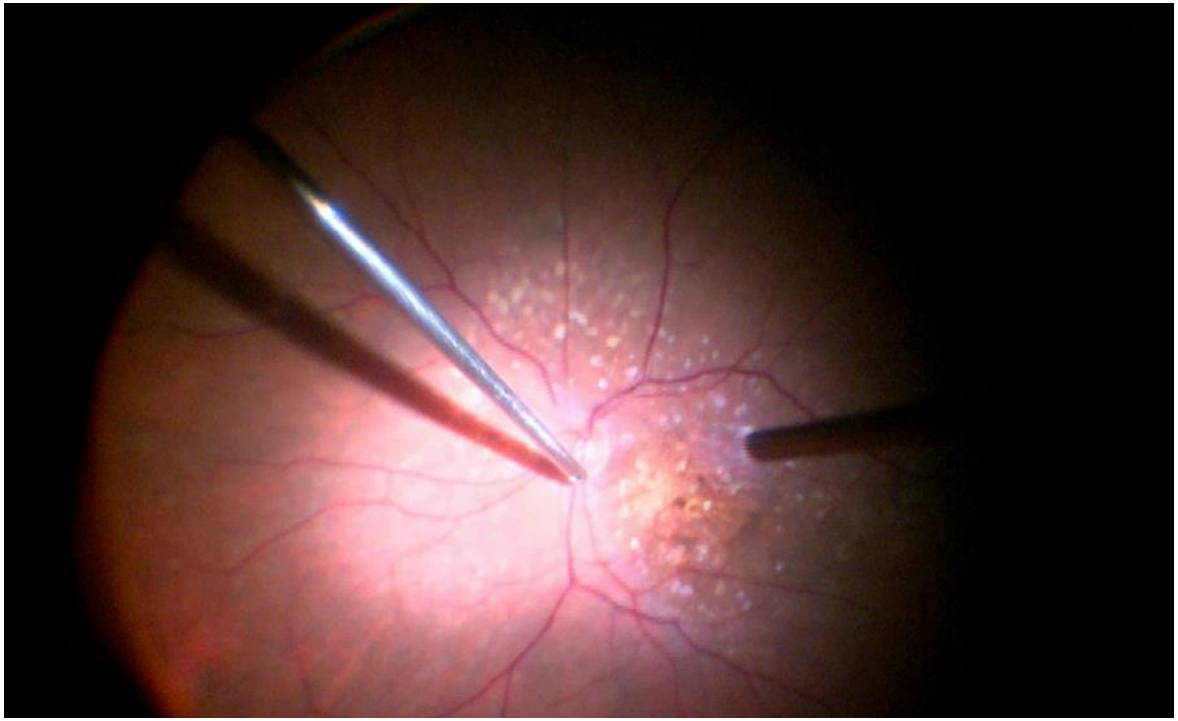

RPE: Retinal pigment epithelium

# RPE CELL TRANSPLANTATION: SUBRETINAL INJECTION



*Surgical technique used commonly by posterior segment surgeons*

1. 23-27 gauge pars plana vitrectomy
2. Posterior vitreous detachment induction
3. Sub-retinal hESC-RPE injection
4. Bleb confirmation
5. Optional air-fluid exchange



hESC: human embyonic stem cell, RPE: Retinal pigment epithelium

# RPE PROGRAM OVERVIEW



*38 patients have been successfully transplanted with hESC-derived RPE, and the clinical trial is ongoing with new cell line*

## Previous cell line: MA09-hRPE

- Three Phase 1/2 clinical trials for Dry AMD and Stargardt disease (STGD)
  - US: 13 patients treated (Dry AMD)
  - 13 patients treated (STGD)
  - UK: 12 patients treated (STGD)

THE LANCET

- First-ever report of the safety of hESC-RPE in human with any disease[1]
- Follow-up data 12 months post-transplantation[2]

ARVO

The Association for Research in Vision and Ophthalmology

- Follow-up data 36 months post-transplantation[3]

## Established new cell line: ASP7317

- Phase-Ib/II dose-ranging and POC trial for dry AMD is ongoing with a new cell line and formulation

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1: Schwartz SD. *et. al.*, Lancet 2012; 379: 713-20, 2: Schwartz SD. *et. al.*, Lancet 2015; 385: 509-16, 3: Schwartz SD. *et. al.*, ARVO 2018
POC: Proof of Concept

# PHASE 1/2 STUDY (MA09-hRPE): STUDY DESIGN



*Efficacy and safety have been investigated up to 36 months*

**P1/2 study**
NCT01344993
NCT01345006

**Long term follow up study**
NCT0246334
NCT02445612

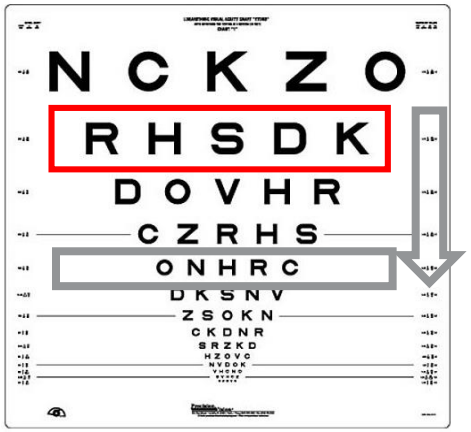
**Safety surveillance study***
NCT03167203

Transplantation — 12M — 36M — 60M

| Phase 1/2 study | |
|---|---|
| **Design** | Open-label, sequential dose-escalating studies |
| **Patient population** | **Low vision group:**<br>ETDRS Best corrected visual acuity (BCVA) ≤ 20/400<br>Four cohorts (50,000, 100,000, 150,000, 200,000 cells)<br>**Better vision group:**<br>ETDRS Best corrected visual acuity (BCVA) ≤ 20/100<br>a single 100,000 cells cohort |
| **Enrollment** | 13 pts (AMD), 13 pts (STGD) |
| **Primary endpoints** | **Safety:**<br>• Incidence of grade 2 or greater TEAEs<br>• Evidence of graft failure or rejection and engraftment |
| **Secondary endpoints** | **Exploratory Efficacy:**<br>• BCVA<br>• Area of atrophy on autofluorescence and color fundus photographs<br>• 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25)<br>• Reading speed (AMD study only) |

*: A safety surveillance study has implemented in accordance with regulatory obligations
US: 15-year follow-up from the date of transplant for enrolled US subjects

Best corrected visual acuity (BCVA)




- A measure of the spatial resolution of the vision whilst using corrective lenses to maximize the visualization ability
- 3 Lines improvement in BCVA is considered clinically meaningful by FDA

Image : National Eye Institute, National Institutes of Health
ETDRS: Early treatment diabetic retinopathy study, AMD: Age-related macular degeneration, STGD: Stargardt disease ,
TEAEs: Treatment-emergent adverse events

# PHASE 1/2 STUDIES (MA09-hRPE): SAFETY



*Subretinally transplanted hESC-derived RPE cells were well tolerated at all dose up to 3 years post -transplantation*

- The proportion of subjects with ocular treatment-emergent adverse events (TEAEs) in the treated eye was similar in the AMD (36.4%) and in the STGD (38.5%) cohorts over the follow-up period.
- No evidence of graft failure or rejection.
- There were two serious infectious TEAEs (appendicitis and urinary tract infection), one serious neurologic TEAE (syncope), two events of squamous cell cancer, and one event of basal cancer.
- Hyperpigmented areas of varying sizes, which increased in size and in apparent pigmentation for the first 6–12 months and persisted for up to 3 years, were observed in 21 of 26 subjects (81%).
  - Size of the area of hyperpigmentation did not correlate with cell dose or visual acuity outcomes.
  - Optical coherence tomography shows that the hyperpigmentation is at the level of the RPE.

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Schwartz SD. *et. al.*, ARVO 2018, TEAEs: Treatment-emergent adverse events, AMD: Age-related macular degeneration, STGD: Stargardt disease, hESC: human embyonic stem cell, RPE: Retinal pigment epithelium

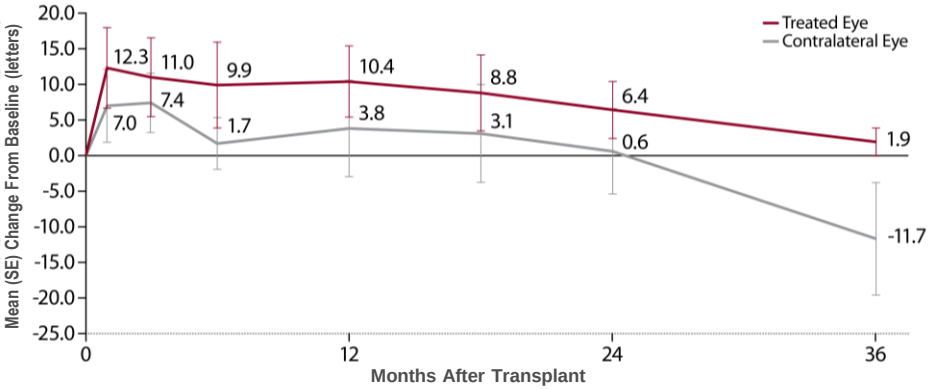
# PHASE 1/2 STUDY (MA09-hRPE): EFFICACY IN DRY AMD



*Initial gains in vision followed by gradual loss in patients with late stage AMD*

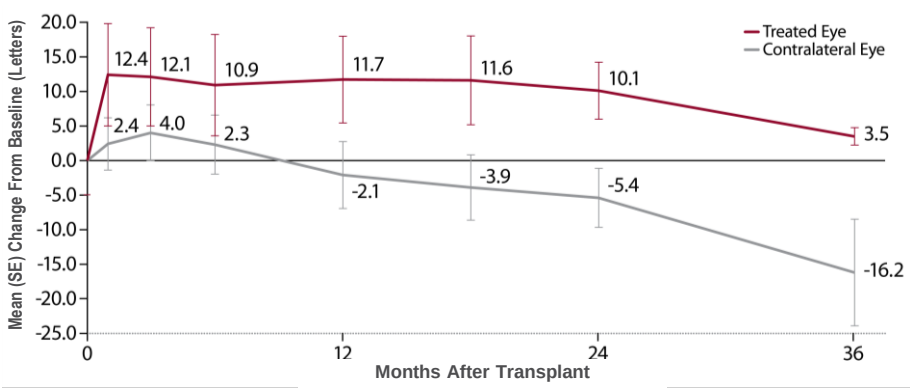
**Mean Change in ETDRS BCVA in the 36 Months Post-Transplantation in the Low Vision Group (AMD)**

**All Subjects with AMD**




Note: Months 1 to 24, n=9; Month 36, n=7. One of the 10 subjects with advanced AMD did not enter the long-term follow-up study.

**Subjects with AMD Excluding Two Subjects With Significant Cataracts or Posterior Capsule Opacification**




Note: Months 1 to 24, n=7; Month 36, n=6.

Schwartz SD. *et. al.*, ARVO 2018

AMD: Age-related macular degeneration, ETDRS: Early treatment diabetic retinopathy study, BCVA: Best corrected visual acuity

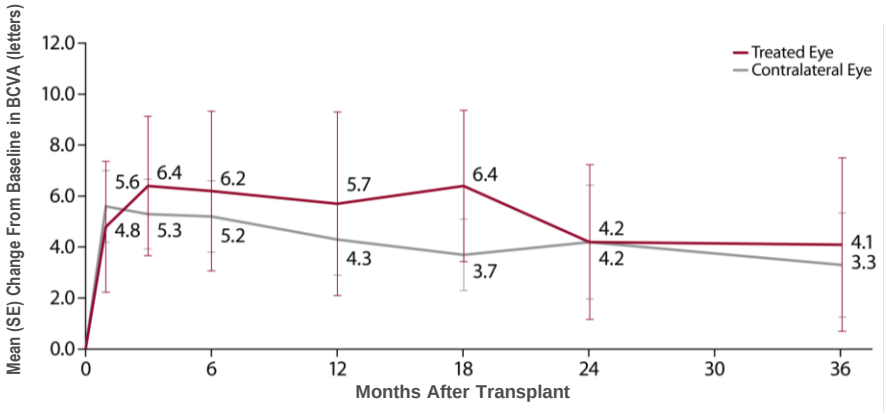
# PHASE 1/2 STUDY (MA09-hRPE): EFFICACY IN STARGARDT DISEASE



*Initial Gains in Vision followed by Gradual Loss in Patients with Late Stage STGD*

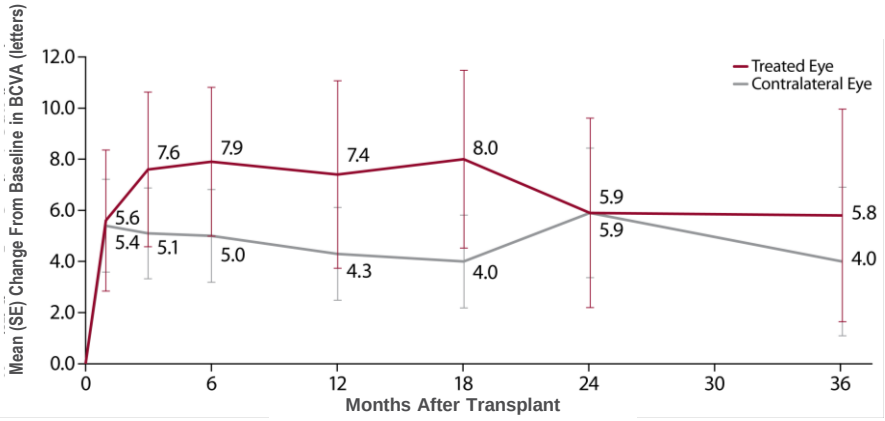
**Mean Change in ETDRS BCVA in the 36 Months Post-Transplantation in the Low Vision Group (STGD)**

**All Subjects with STGD**




Note: Months 1 to 24, n=9; Month 36, n=7. One of the 10 subjects with advanced STGD did not have ETDRS BCVA data for the first 9 months of the study.

**Subjects with STGD Excluding Two Subjects With Significant Cataracts or Posterior Capsule Opacification**




Note: Months 1 to 24, n=7; Month 36, n=5.

Schwartz SD. *et. al.*, ARVO 2018

STGD: Stargardt disease, BCVA: Best corrected visual acuity, ETDRS: Early treatment diabetic retinopathy study.

# NEW CELL LINE

ASP7317

# ASP7317: CELL LINE AND FORMULATION CHANGE FOR FURTHER DEVELOPMENT AND COMMERCIALIZATION



*A new cell line (ASP7317) and an enhanced formulation were developed, providing higher quality cells in anticipation of successful commercialization*

**Advantages of new cell line and formulation**

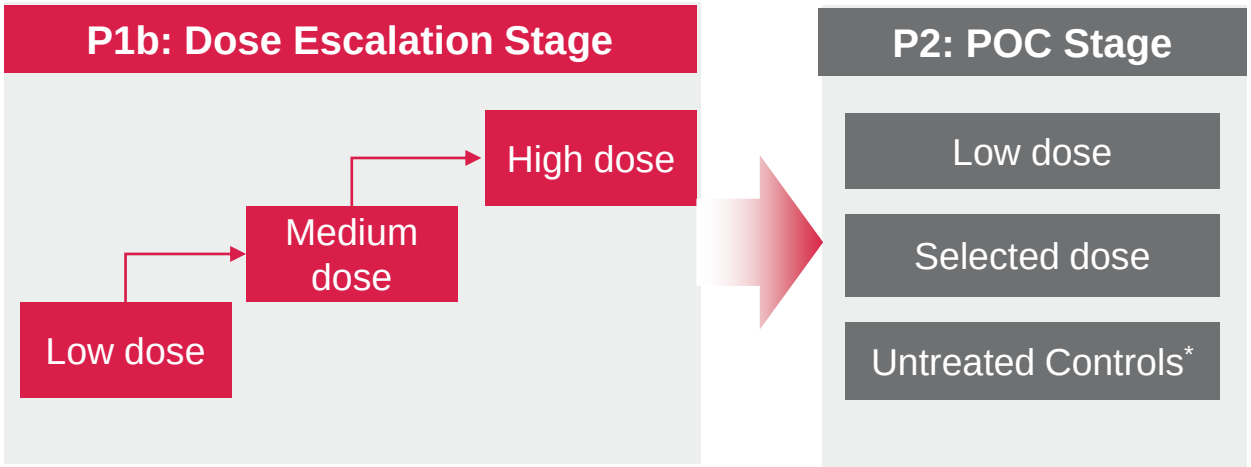
- Compliant with the regulations/guidance in each region (i.e. FDA tissue donor compliance regulations）
- Larger cell bank ensures a stable supply for clinical trial and commercialization
- Longer shelf-life
  - Enables centralized drug product (DP) preparation for clinical trial materials and products
  - Extended shelf-life could provide the flexibility of time management at clinical sites
- Non-xenogeneic product eliminates xenogeneic required blood sampling and archiving
- Protective effect on cells which reduce cell loss during extrusion and debris at injection site

**To evaluate the efficacy and safety of the new cell line, a new Phase 1b/2 study has been initiated**

# ASP7317: PHASE 1b/2 STUDY DESIGN



*Initiated clinical trial for Dry AMD in July 2018*




*If POC is demonstrated, eligible patients in untreated cohorts of POC part enroll to extension part of P1b/2 study

| | Dose escalation | POC |
|---|---|---|
| **Indication** | Severe Dry AMD with Geographic Atrophy | |
| **Enrollment number** | 9 (3 pts/cohort) | 141 (47 pts/cohort) |
| **Study period** | • 2 months screening prior to single administration of ASP7317<br>• 26 weeks (primary study period)<br>• Up to 60 months for safety and evaluation of graft failure/rejection (ASP7317 treated subjects only) | |
| **Endpoint** | Safety | Primary: Change from baseline in BCVA score at Week 26 |
| | | Secondary: Multiple efficacy and safety endpoints |

AMD: Age-related macular degeneration, POC: Proof of Concept, BCVA: Best corrected visual acuity

# ASP7317: DEVELOPMENT STRATEGY



*Accelerate the development of ASP7317 by seeking expedited regulatory pathway*

**Phase 1b/2 study**

- Determine optimal safe dose in P1b Dose Escalation Stage with potential to observe an early efficacy signal
- Confirmation of efficacy and safety in POC stage

**Regulatory Strategy**

- If the results of P1b/2 study are positive, seek expedited regulatory pathway in regenerative medicine (e.g. RMAT designation) for accelerated/conditional approval in each region to deliver ASP7317 to patients sooner

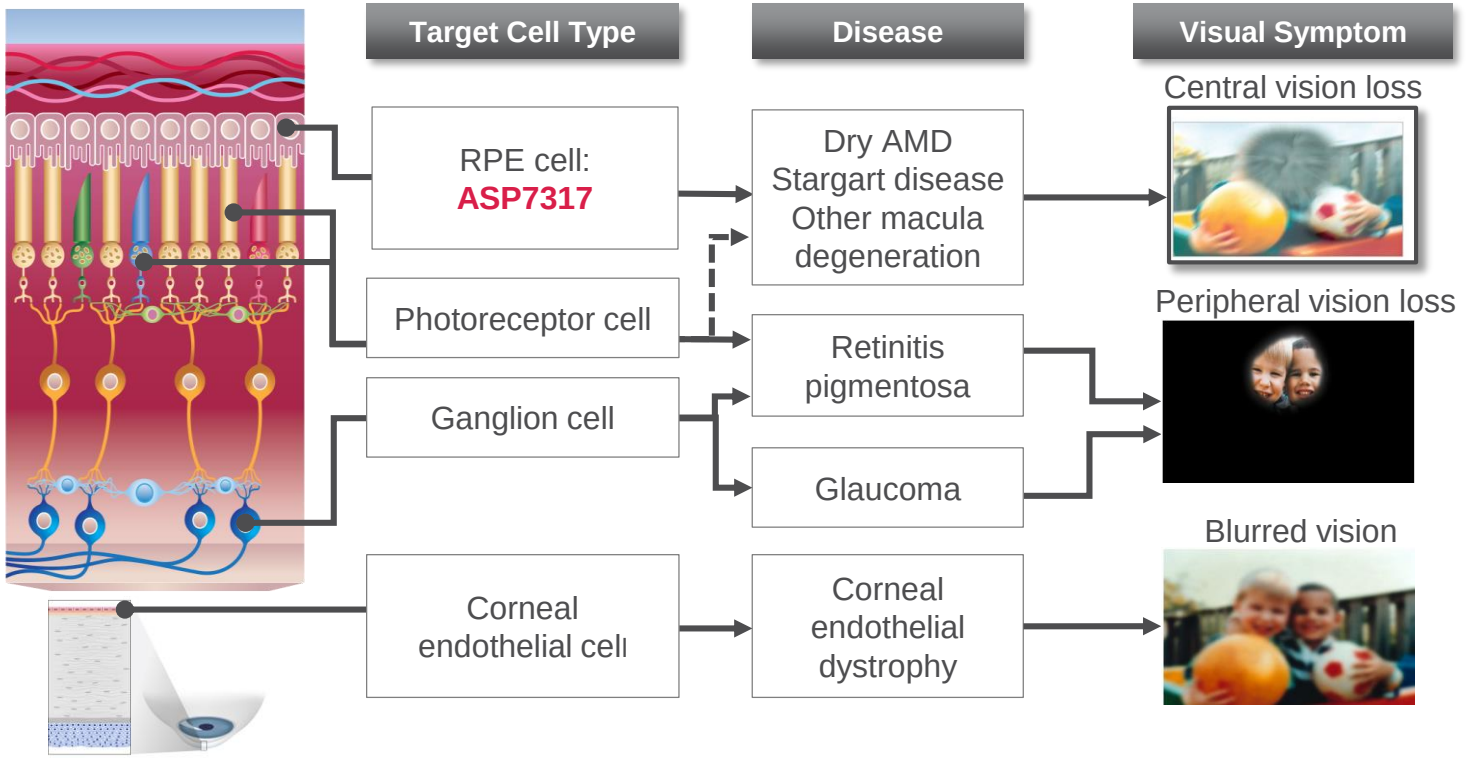
**Expansion to Other forms of Macular Degeneration**

- Broaden clinical development program to include less severely affected patients with Dry AMD and other forms of macular degeneration (e.g. Stargardt disease)

AMD: Age-related macular degeneration, POC: Proof of Concept, RMAT: Regenerative medicine advanced therapy

# ASP7317 AND BEYOND

*Experience and knowledge gained with ASP7317 can advance and expand R&D capabilities in cell therapy development*




- Building on a foundation of innovative science and technology
- Strengthen understanding, enhanced study operations in cell therapy and development speed
- Establish a robust ophthalmic disease cell therapy franchise

Photos：National Eye Institute, National Institutes of Health
RPE: Retinal pigment epithelium, AMD: Age-related macular degeneration

# CONTINUED EFFORTS TO DELIVER VALUE FOR PATIENTS WITH VISION IMPAIRMENT



*The ASP7317 program is the first of multiple cell therapy programs intended by Astellas to address major unmet clinical needs in ophthalmology*

## ASP7317

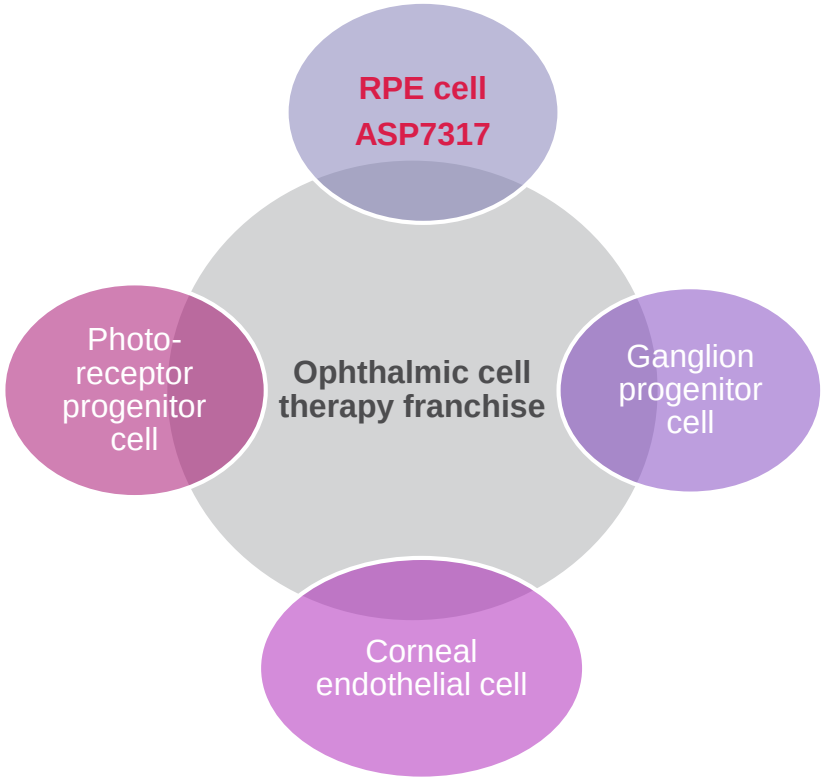
Broaden clinical development program to moderate AMD and other forms of macular degeneration

POC for severe Dry AMD

Initiated a Phase 1b/2 program in Dry AMD

Long-term safety data from the prior cell line remains encouraging

## BEYOND ASP7317




AMD: Age-related Macular Degeneration, POC: Proof of Concept

Turning innovative science
into value for patients by

**maximizing the potential of cell therapy**