

INITIATIVES IN CELL THERAPY

-TURNING INNOVATIVE SCIENCE INTO VALUE FOR PATIENTS-

R&D Meeting – December 13, 2018



CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING INFORMATION

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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

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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-

CELL THERAPY

A stylized illustration of a cell with a blue outer membrane and a purple nucleus, set against a background of other similar cells. The cell in the foreground is larger and more detailed, showing a blue outer membrane and a purple nucleus. It is surrounded by several other cells, which are smaller and less detailed, creating a sense of depth. The background is a dark blue gradient.

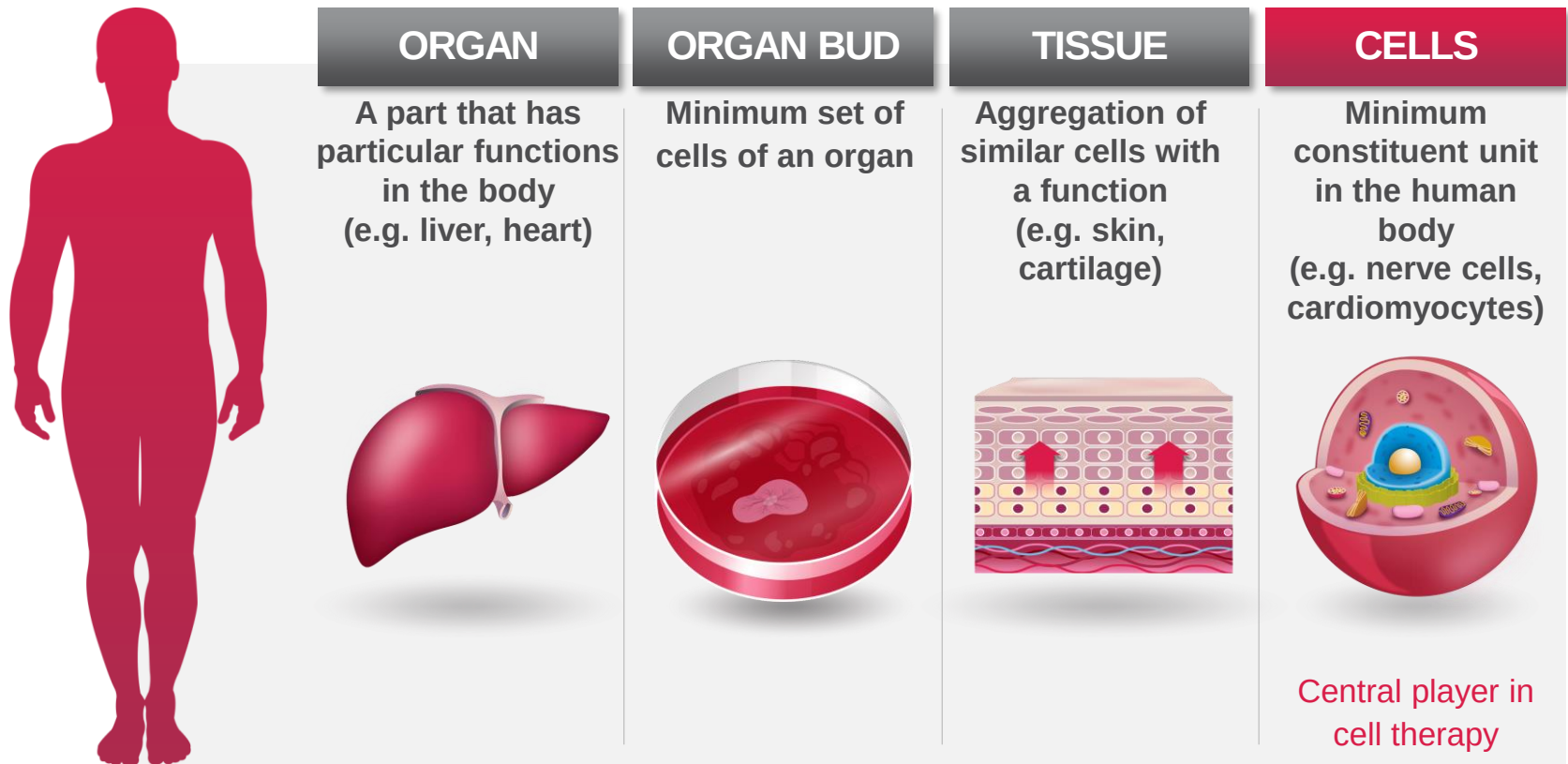
A novel approach to treating disease

Kenji Yasukawa, Ph.D
President and CEO

WHAT IS CELL THERAPY?

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

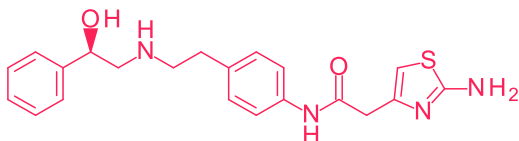


ADVANTAGES OF CELL THERAPY

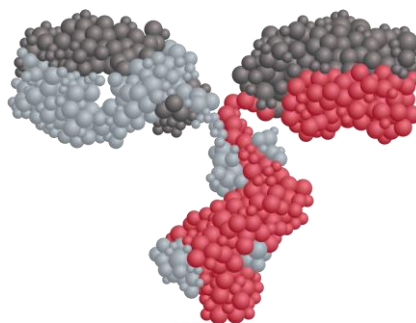
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Multi-functional nature of cells offers high efficacy that existing therapies cannot deliver

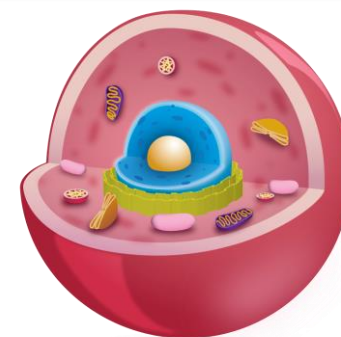
SYNTHETIC COMPOUNDS



BIOPHARMACEUTICALS



CELLS

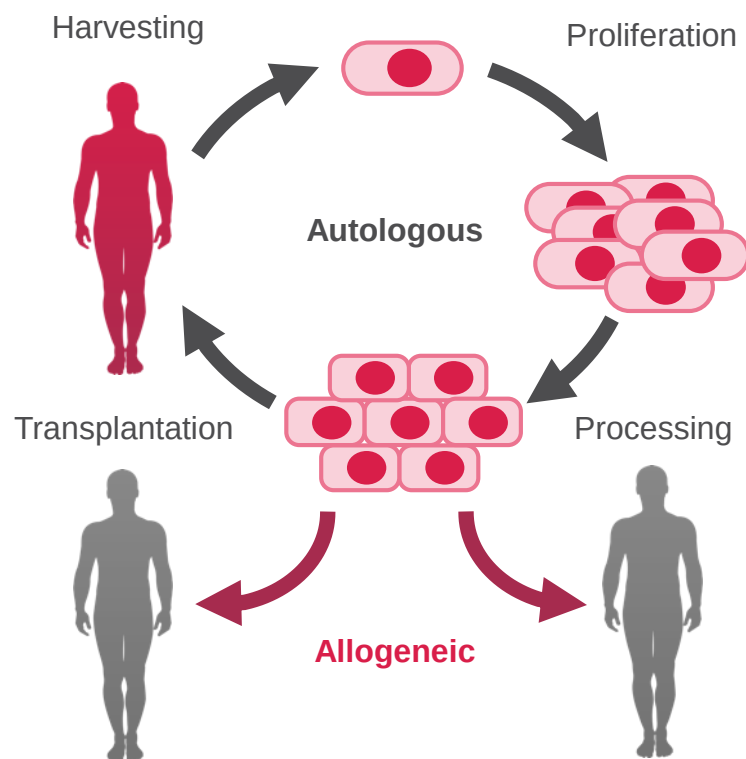


MW SIZE	<500	10K~150K (a few nm) (- Synthetic compounds x 3,000)	NA (10-30 μm) (- Biopharmaceuticals x 10,000)
FUNCTION	Single e.g. agonist, antagonist	Single e.g. agonist, antagonist, ADCC etc.	Multiple e.g. sensor, phagocytosis, secretion, antigen presentation, neurotransmission, metabolism

TWO CATEGORIES OF THERAPEUTIC CELLS

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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

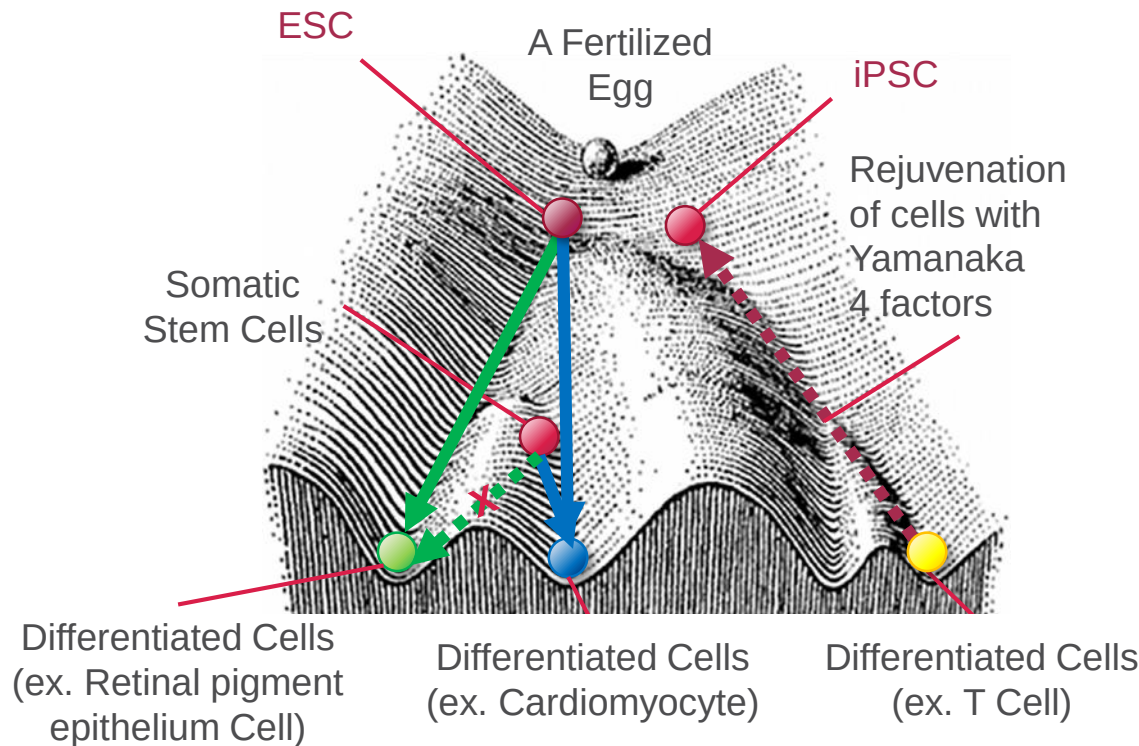
CELLS TO BE USED IN CELL THERAPY

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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



ASTELLAS CELL THERAPY

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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

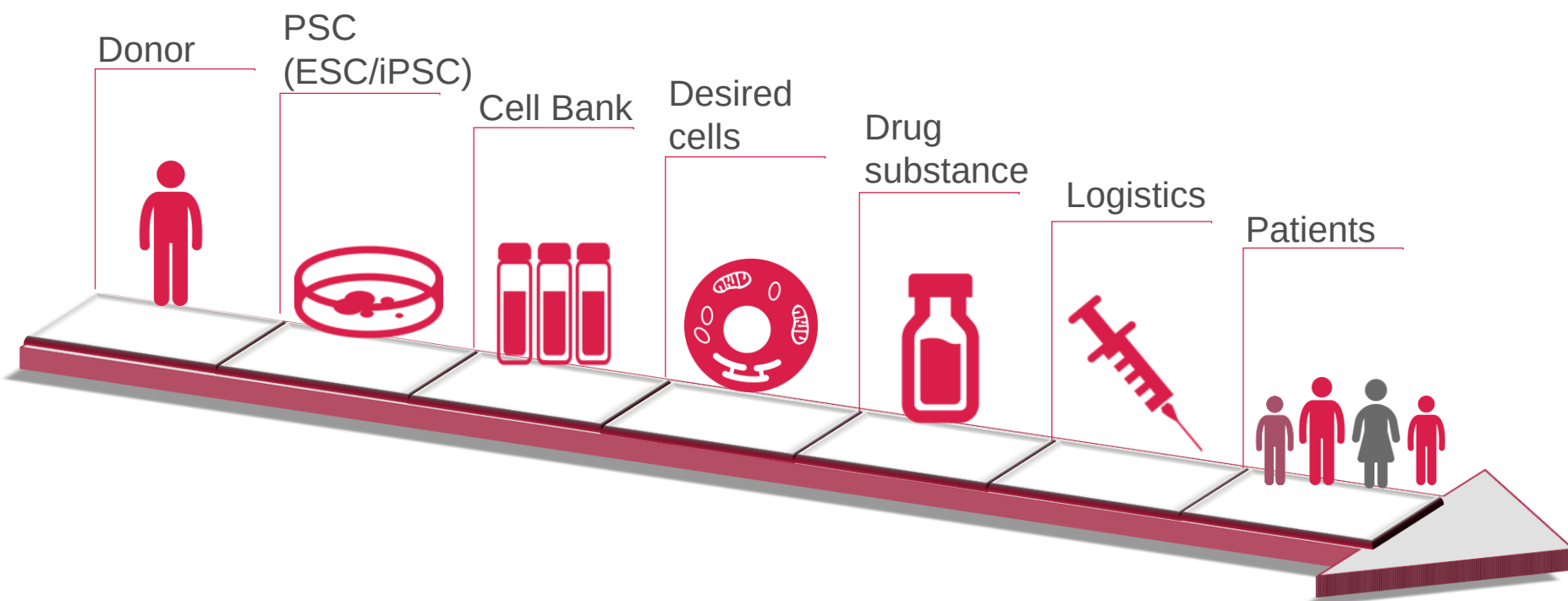
*1: Considering the time for generating autologous iPS cells, applicable tissue might be limited.

*2: Contain the time for generating autologous iPS cells.

JOURNEY OF CELLS: LABORATORY TO PATIENTS

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Living cells require a different pathway than conventional medicines



FUTURE OUTLOOK OF CELL THERAPY

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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

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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)

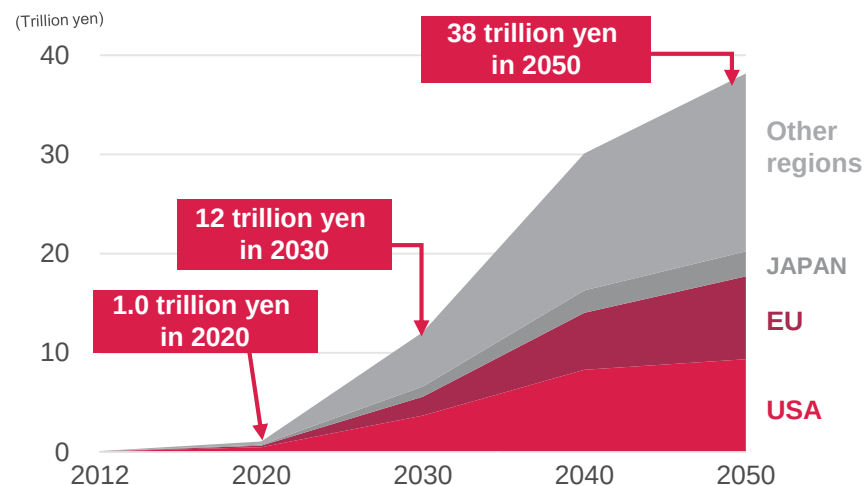
INDIA

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)

ESTIMATED FUTURE MARKET



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

Reprinted from the report by Japan Patent Office's



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

NAVIGATING REGULATORY PATHWAYS

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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 ➤ 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*	21 st Century Cures Act Part 1271	Regenerative Medicine Advanced Therapy (RMAT) Designation
	Pharmaceutical	Advanced Therapy Medicinal Products (ATMP)	Regulation (EC) No 1394/2007	

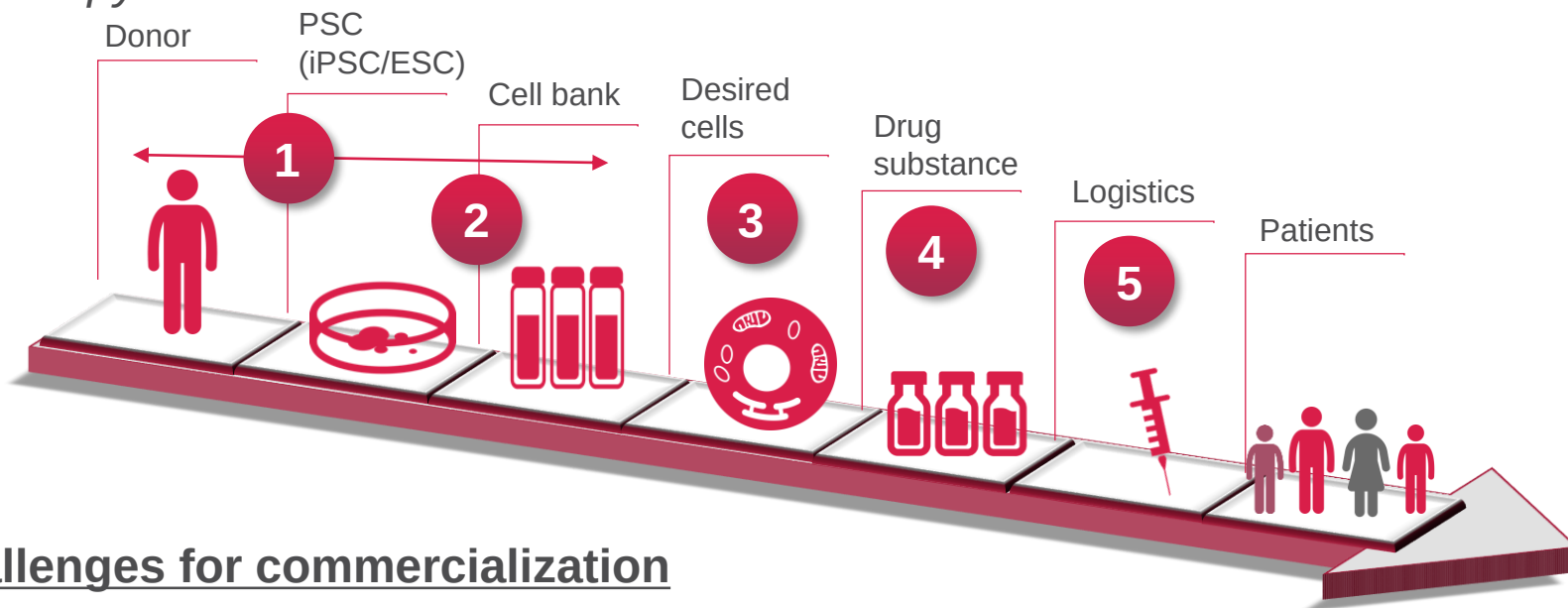


*Human Cells and Tissues and Cellular and Tissue-based Products Regulated Under Section 351 of the Public Health Service Act

KEY CAPABILITIES FOR CELL THERAPY

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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

A scientist wearing a white lab coat, blue gloves, a blue surgical cap, and a blue face mask is working in a laboratory. They are using a green pipette to transfer liquid into a small, clear, rectangular dish. In the background, there is a large, black, multi-well plate and a round-bottom flask containing a blue liquid. The scene is illuminated with a strong blue light, creating a high-tech, scientific atmosphere. The text "LEADING WITH SCIENCE" is overlaid in a red banner at the top left, and "Investigating pluripotent stem cell therapies" is overlaid in a white banner below it. At the bottom left, the name "Yoshitsugu Shitaka, Ph.D." and his title "President" are listed, followed by "Astellas Institute for Regenerative Medicine".

LEADING WITH SCIENCE

Investigating pluripotent stem cell therapies

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

AGENDA

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1

Snapshot of Astellas Cell Therapy

2

Strategy of Astellas Cell Therapy

3

Challenges of PSC-based cell therapies

4

Measurement & accomplishment for challenges

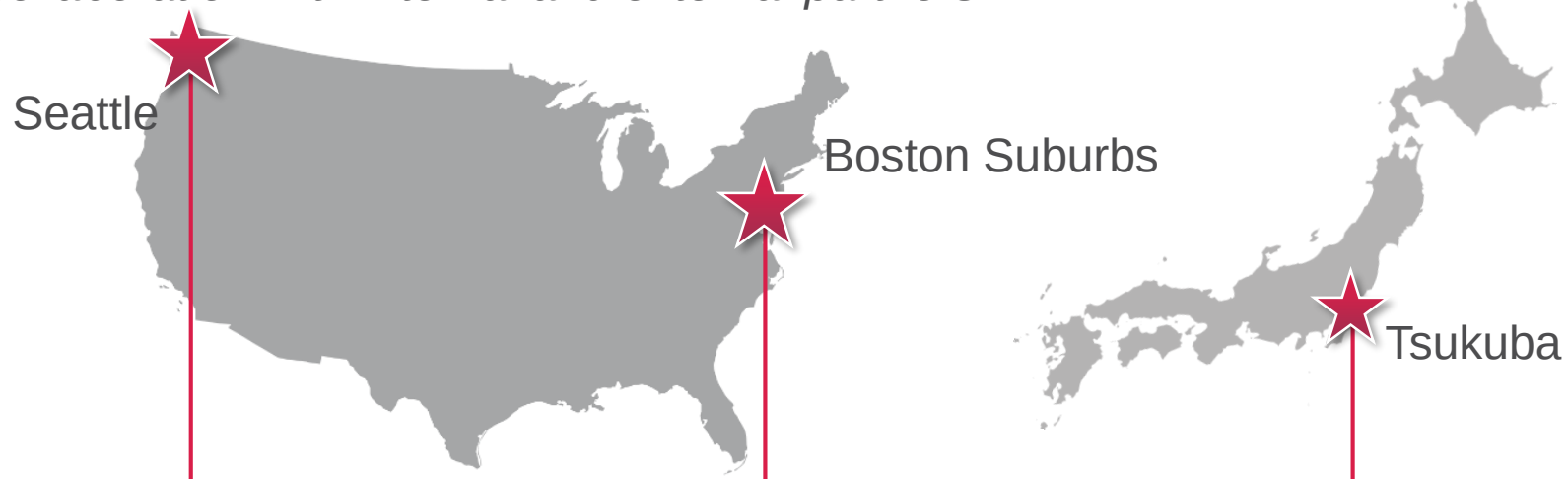
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Future challenge & perspective

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

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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

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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	P2
Ocular pipeline	Retinal pigment epithelium (RPE)	ES	Applicable	• Dry AMD • Other macular degeneration			ASP7317
	Photo-receptor progenitors (PhRPs)	ES /iPS	Applicable	• Retinitis pigmentosa • Macular degeneration			
	Retinal ganglion progenitors (RGPs)	ES /iPS	Applicable	• Glaucoma • Optic neuropathies			
	Corneal endothelium	ES /iPS	Applicable	• Corneal diseases • Corneal injuries			
Non-ocular Pipeline	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 • Pulmonary hypertension			
	Hematopoietic Stem Cells	ES /iPS	High priority	• Leukemia/ Hematopoietic disorders			
	Other various Cell Types	ES /iPS	High priority	• Peripheral diseases			
	NK	ES /iPS	High priority	• Cancer			
UCells origin pipeline	Others (Partnering)	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~

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1st Wave

Establish a solid foothold in ophthalmology and build cell therapy foundation throughout value chain

Measures:

- Intake of ASP7317 and stem cell technologies (incl. manufacturing) through Ocata acquisition
- More efficient R&D by centralization at AIRM

2nd Wave

Enrich cell therapy pipeline including non-ocular area by leveraging UDC technology

Measures:

- Intake of gene-editing technologies (incl. UDC) through UCells acquisition
- New collaborations in the US, EU and Japan

3rd Wave

Create next generation cell product by combining stem cell technology and gene-editing technologies

Measures:

- Enhancement of UCells capabilities
- Pursuit of synergy between AIRM and UCells and value maximization of our technologies

Strategic Goals

WHY OPHTHALMOLOGY?

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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.

AUTOLOGOUS TRANSPLANTATION

Transplanted Cell
(not gene-edited)



All HLA matched

Successful
engraftment



Recipient's HLA

ALLOGENEIC TRANSPLANTATION

Transplanted Cell
(not gene-edited)



HLA not matched

Recipient's
Lymphocytes

Rejection

W/O IMT

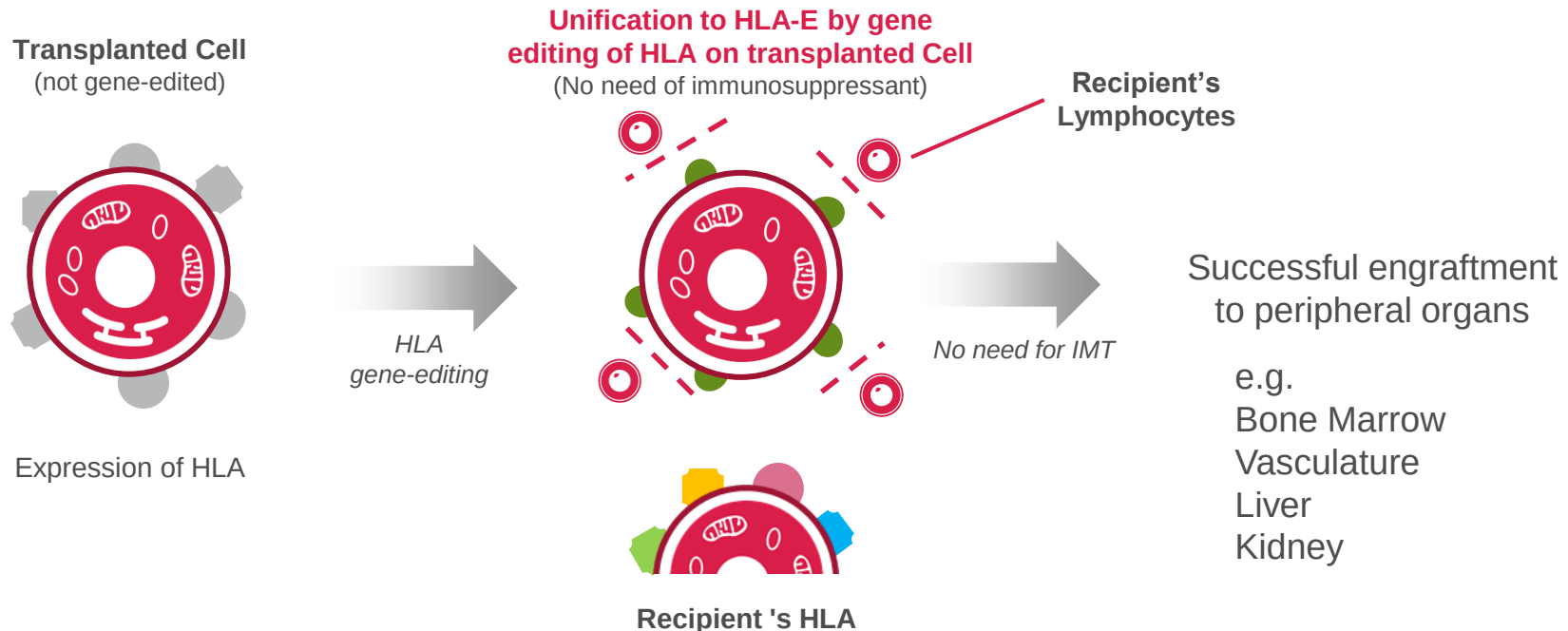


Recipient's HLA

WHY UDC? (2/2)

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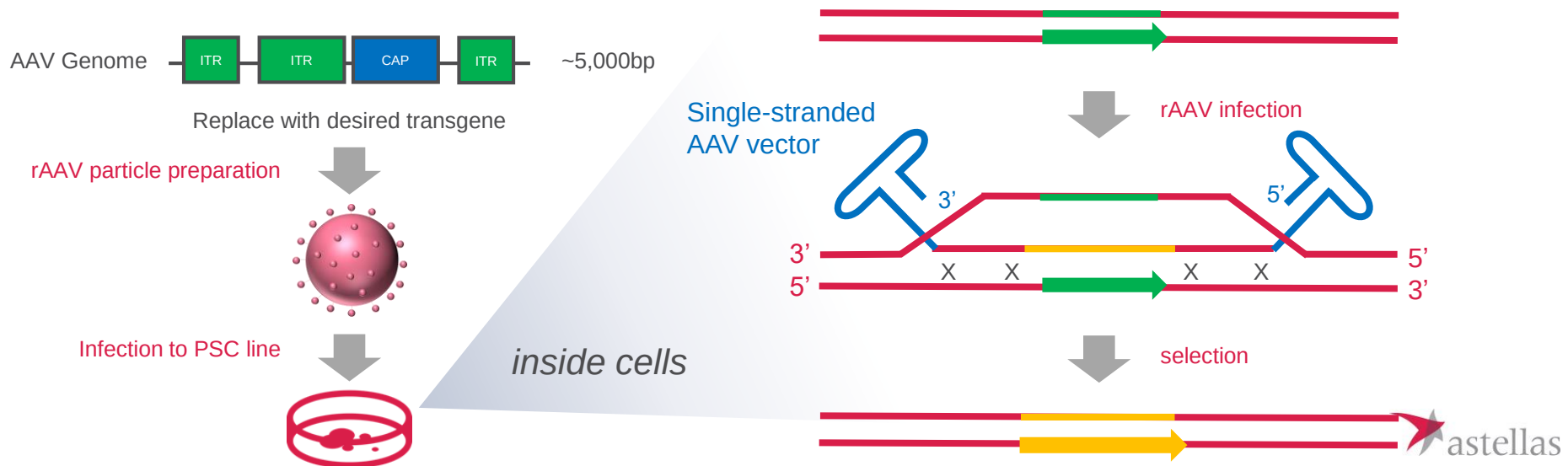
2nd WAVE: Expand to non-ophthalmology by leveraging UDC technology



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

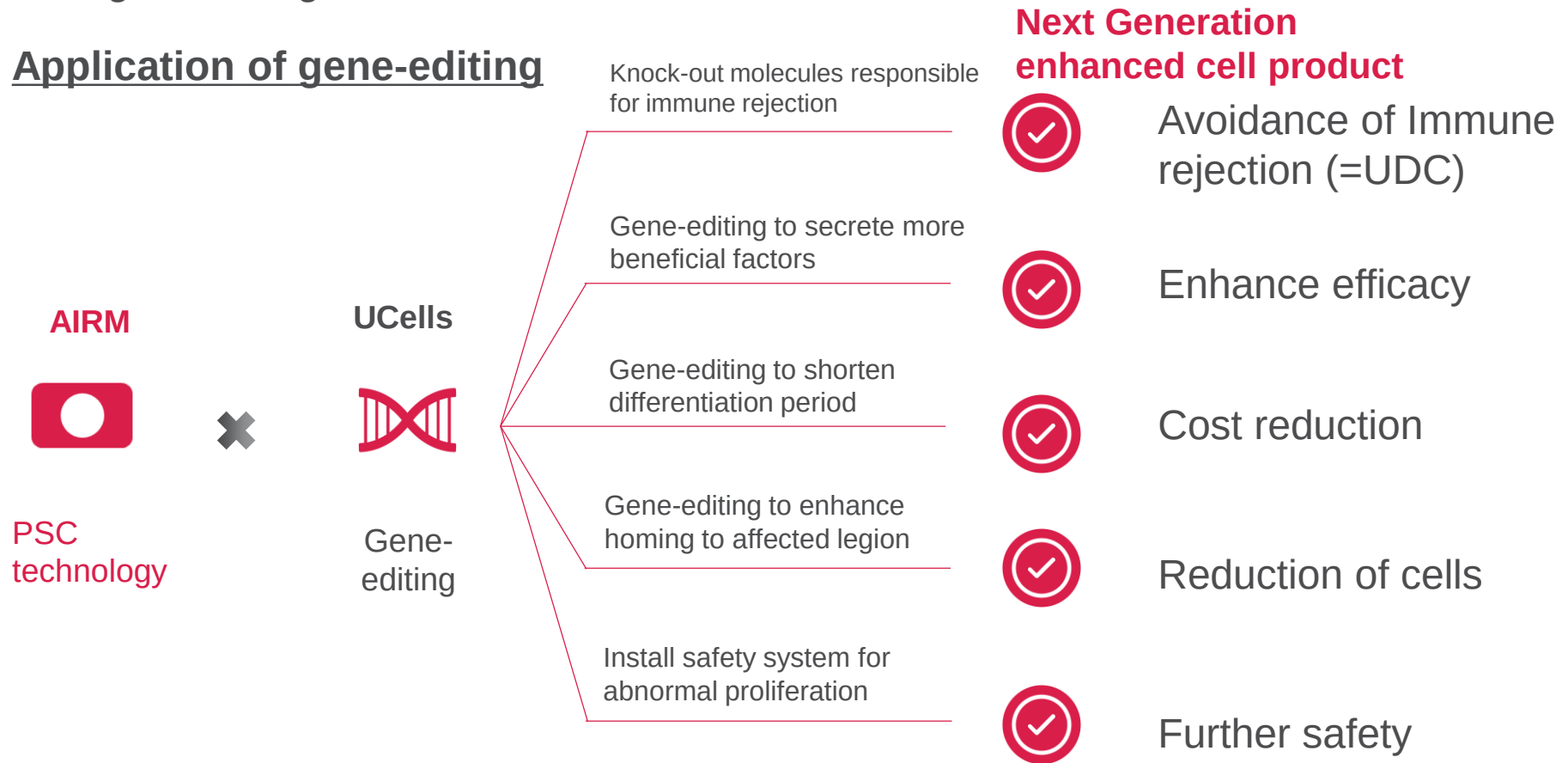


NEXT GENERATION ENHANCED CELL (2/2)

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

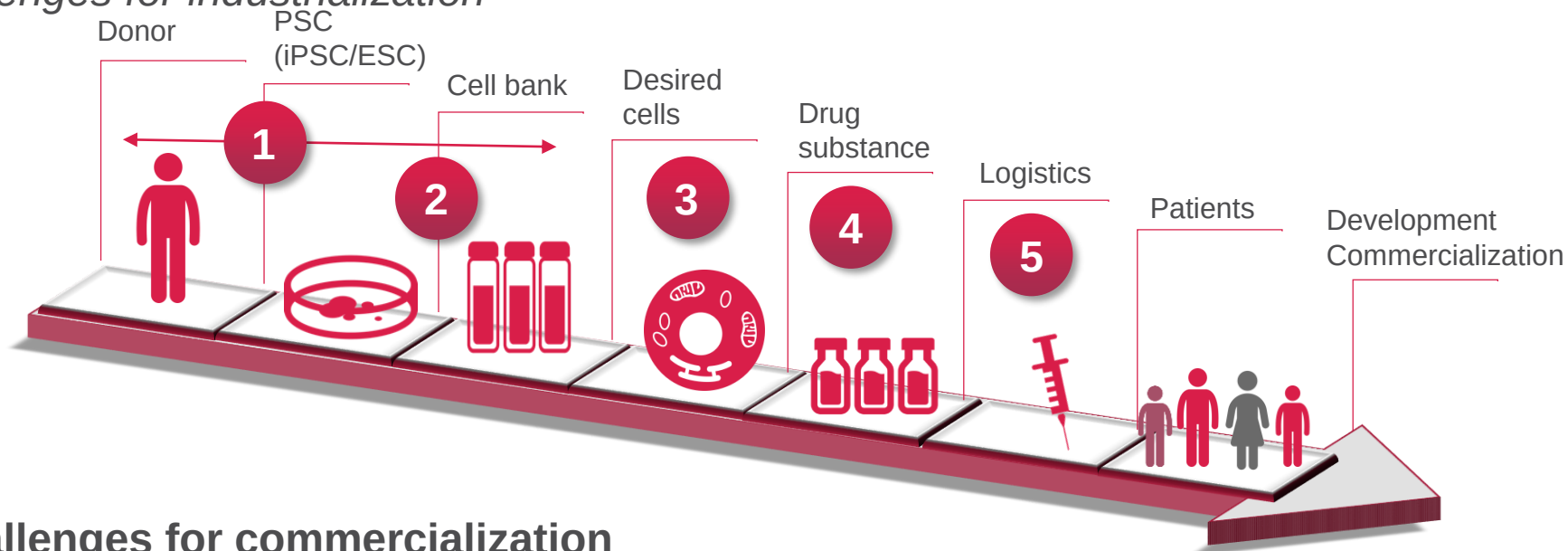
Application of gene-editing



3. CHALLENGE OF PSC-DERIVED ALLOGENEIC CELLS

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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

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



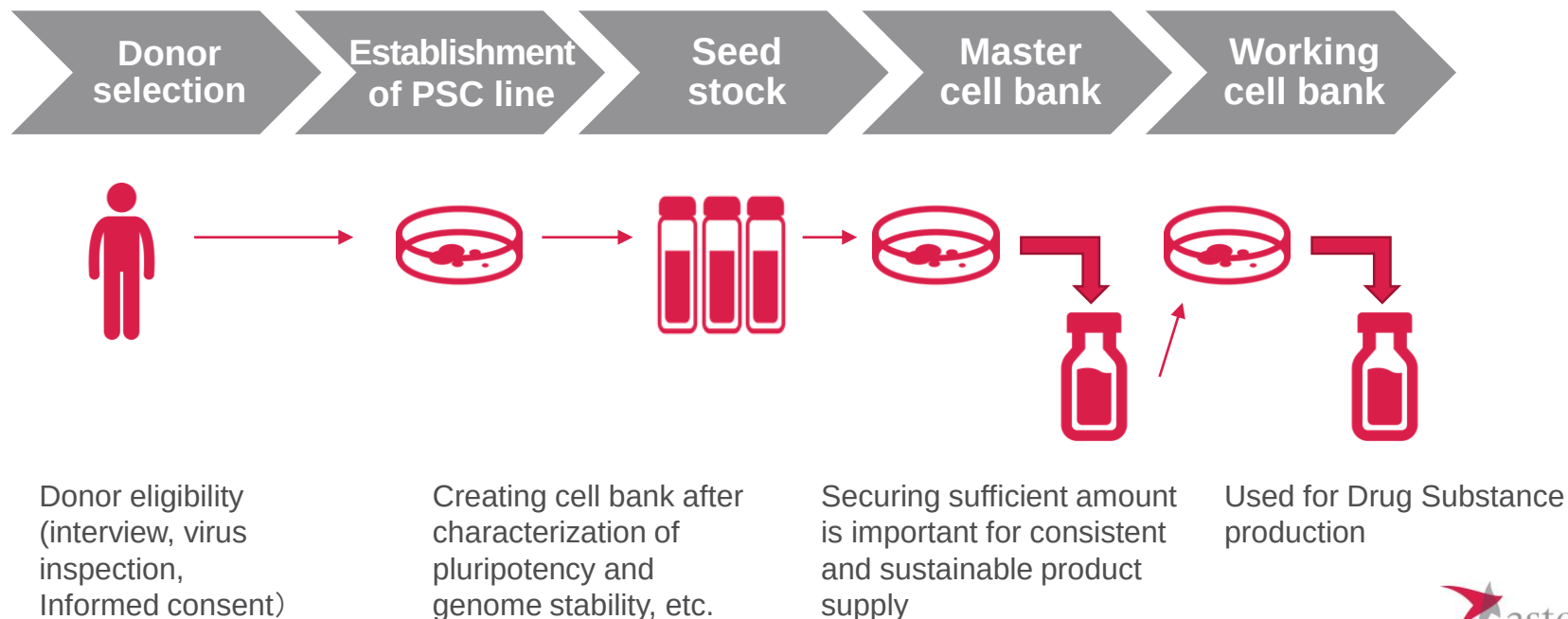
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1 CHALLENGE

Secure own PSC line / banks with safety and pluripotency

EXAMPLE

- Compliance to donor eligibility (virus inspection, etc.) which varies in different regions
- Expansion culture maintaining and securing pluripotency and genome stability
- 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



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



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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.)

AVOID IMMUNE REJECTION (1/2)



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2 CHALLENGE

EXAMPLE

Avoid immune rejection

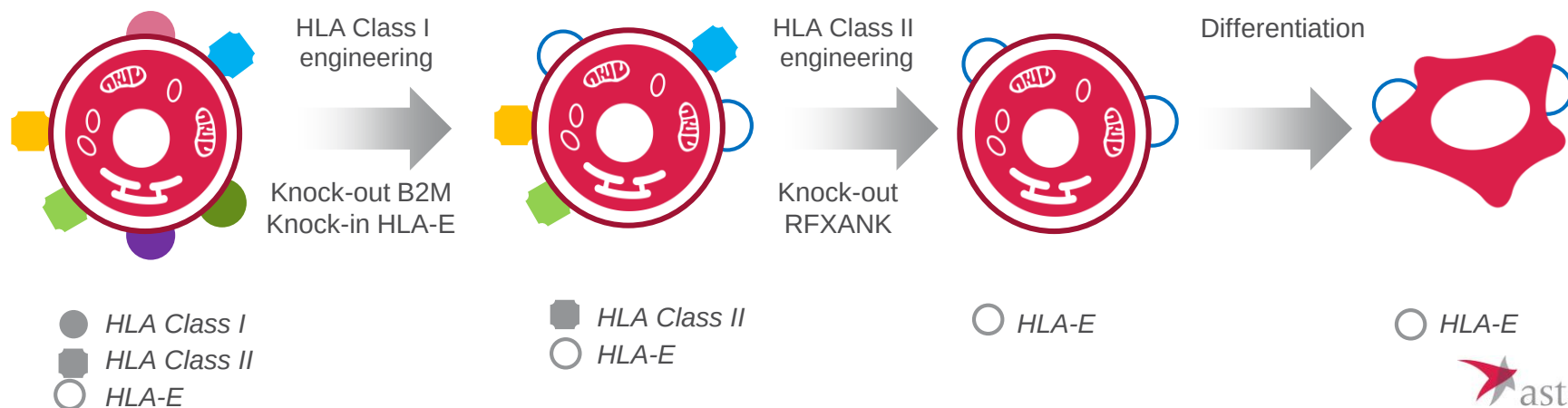
- When targeting long-term engraftment in peripheral tissues, it is necessary to avoid immune rejection
- Depending on the immunogenicity of transplanted cells, it is difficult to administer cells multiple times
- Concerns of handling increased numbers of cell lines if using HLA matched cell lines

Flow of UDC creation

Unedited Pluripotent Cell

Pluripotent Universal Donor Cell

Universal Donor Cell-derived Product



AVOID IMMUNOLOGICAL REJECTION (2/2)



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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

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



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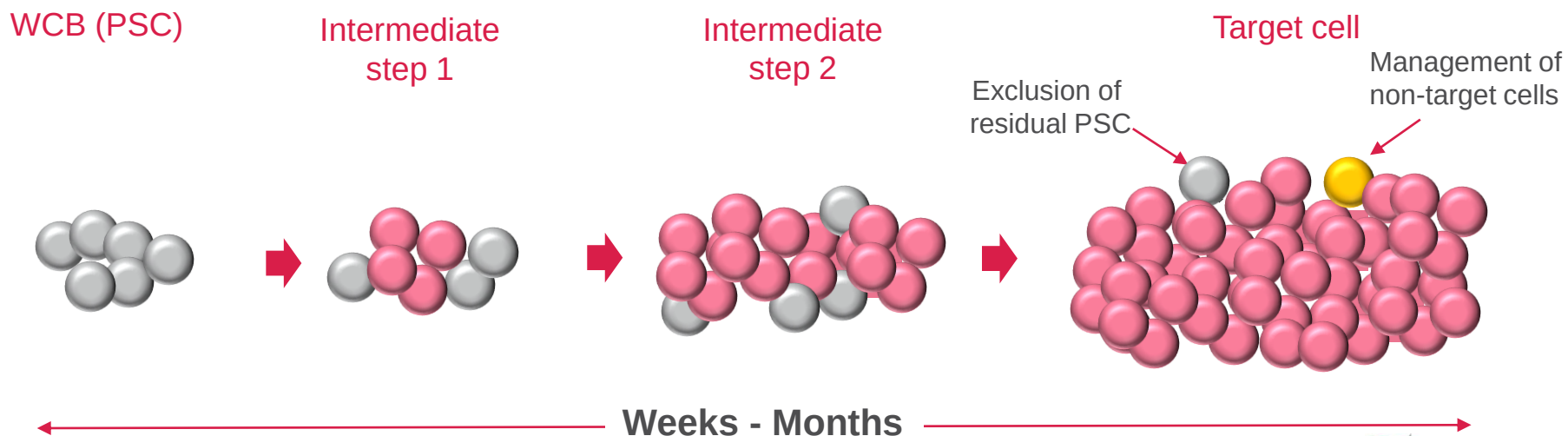
3 CHALLENGE

Develop efficient differentiation protocols for desired cell types

EXAMPLE

- Optimization / hardening of different processes for each cell type, securing of intellectual property
- Process control over weeks to months (function of desired cells, residual PSC strains, non-target cells)
- Requiring large amount of cells depending on cell type and indication (RPE-AMD: cell number of $\sim 10^5$ order / patient*¹ vs. MSC-GVHD: cell number of $\sim 10^8$ 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)



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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)



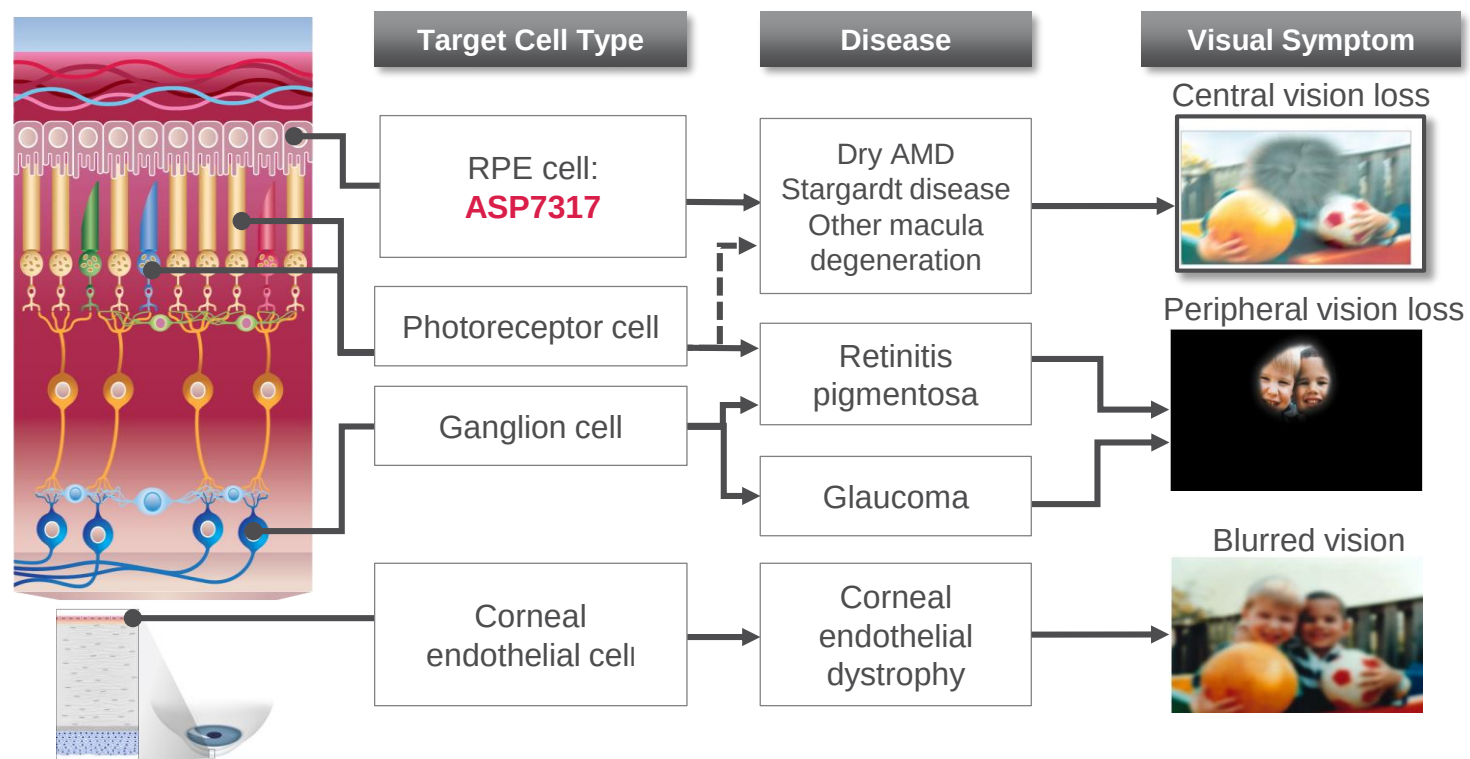
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Ophthalmology program

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



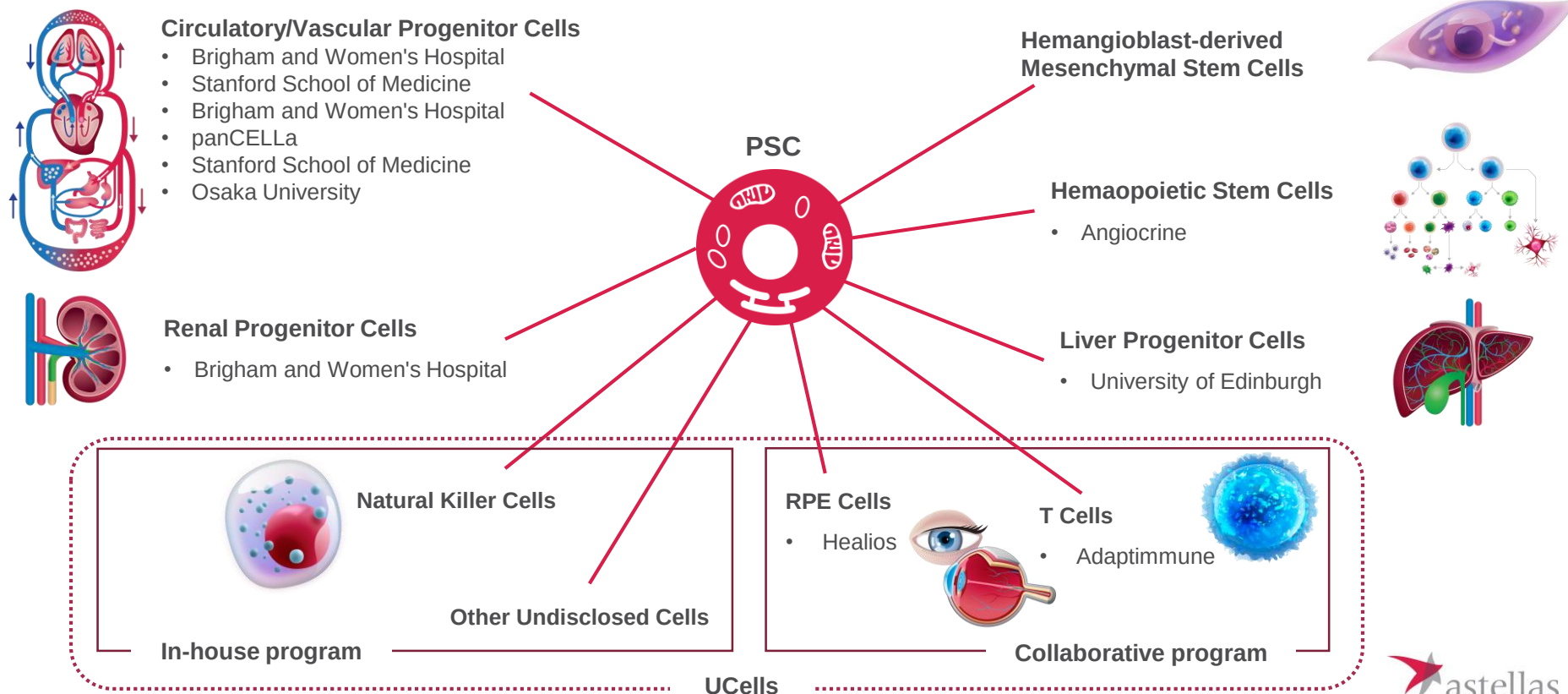
DEVELOP EFFICIENT DIFFERENTIATION PROTOCOLS FOR DESIRED CELL TYPES (4/4)



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Non-ophthalmology program and UCells program

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



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



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4 CHALLENGE

Establish expertise and infrastructure for GMP cell manufacturing

EXAMPLE

- Construction of GMP production system specialized for cells (quality assurance system, standards / quality inspection, etc.)
- Compliance to different standards (raw materials, manufacturing facilities) in each region
- 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

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

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



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*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





ESTABLISH EFFICIENT LOGISTICS SYSTEM (1/2)

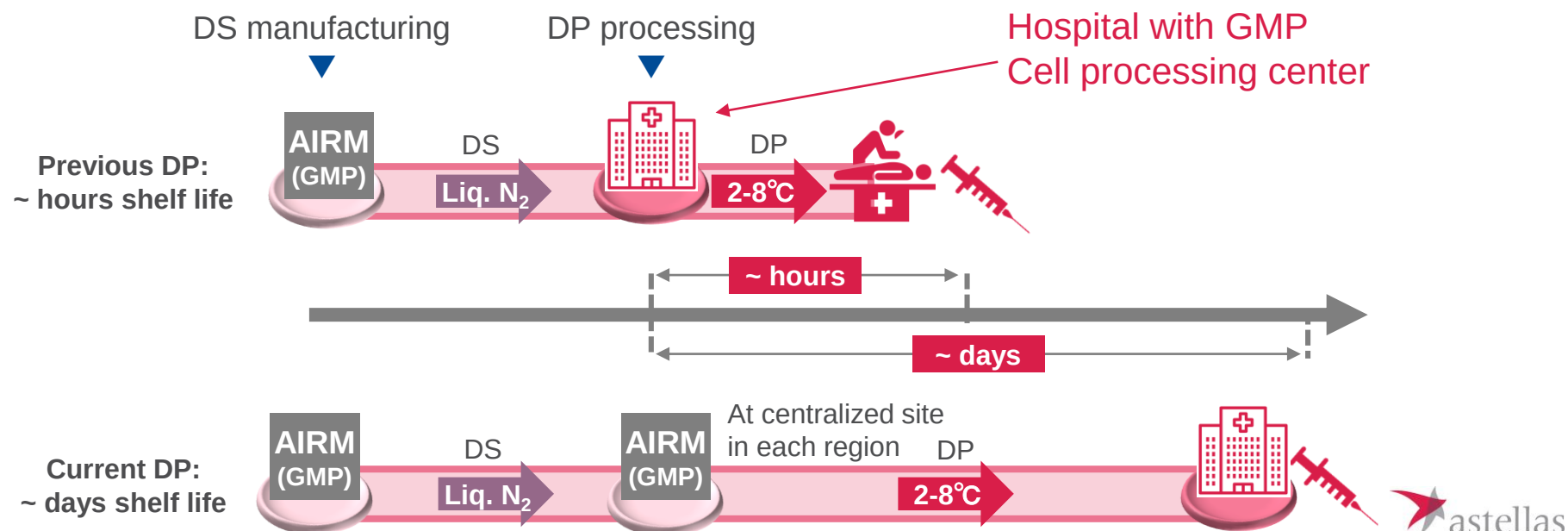
5 CHALLENGE

Establish efficient logistics system

EXAMPLE

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

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





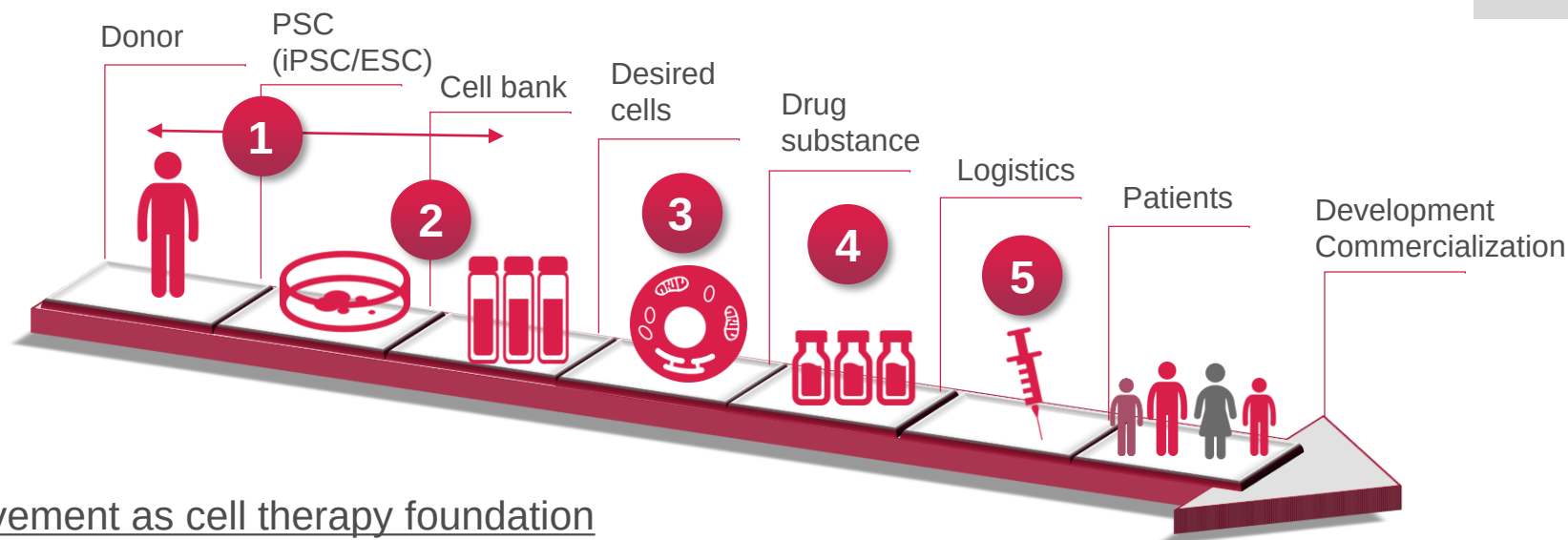
ESTABLISH EFFICIENT LOGISTICS SYSTEM (2/2)

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

SUMMARY OF ACHIEVEMENTS

Achievement as cell therapy foundation

	Research					Manufacturing			Supply chain	Development		Commercial		
	1 PSC sourcing	2 UDC	2 Gene-editing	2 Differentiation	3 Standardization	4 QA	4 Facility	4 Freeze-thaw tech.	5 Formulation	5 Operation	RA	IMT regimen	Specialized platform	Business model
Post-Ocata Acquisition	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Post-UCells Acquisition		●	●											
Current AIRM	●	●	●	●	●	●	●	●	●	●	●	●	●	●

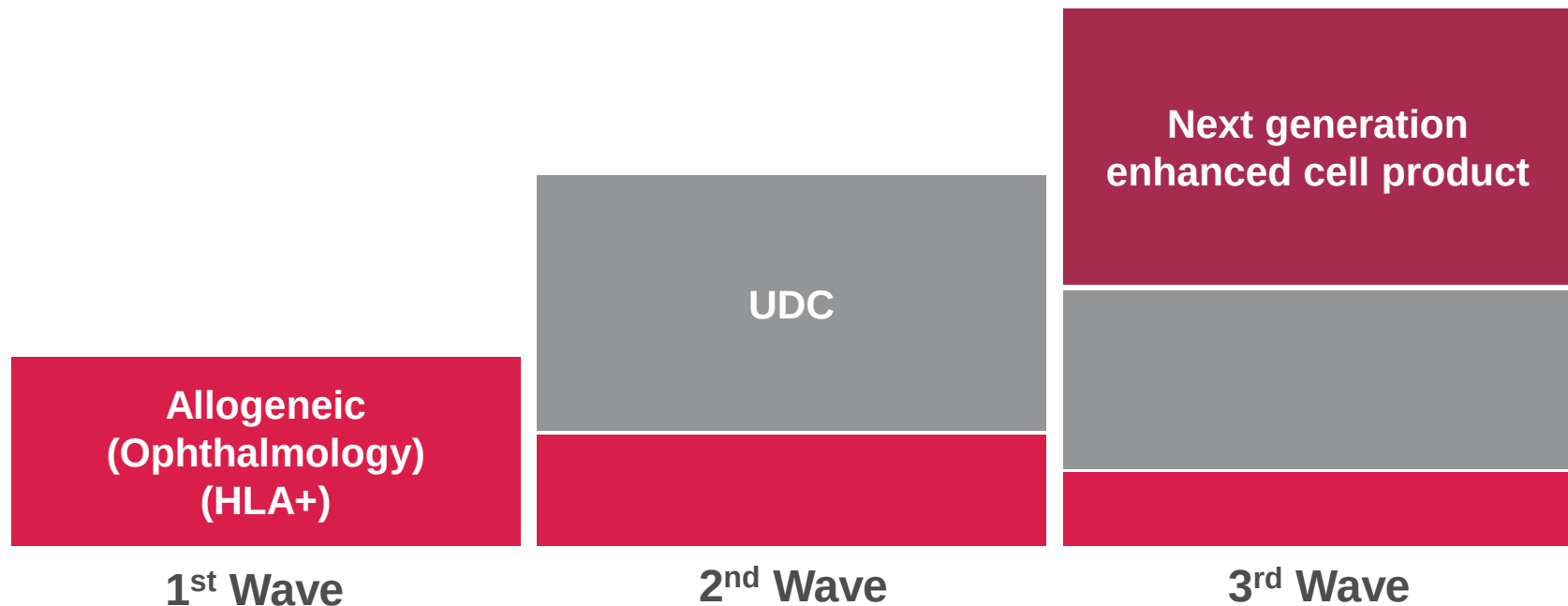
5. FUTURE CHALLENGES AND PERSPECTIVE

40

- 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

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



- 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

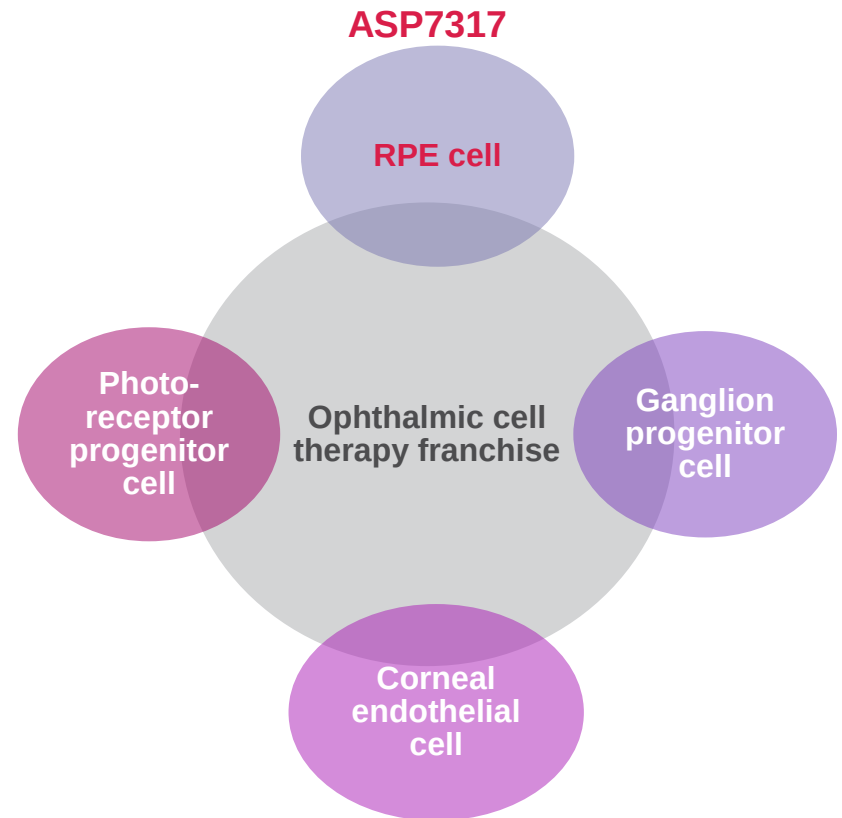
ASP7317

To offer the hope to regain lost sight

Eddy Anglade, MD
Ophthalmology Therapeutic Area Head,
Development



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



AGE-RELATED MACULAR DEGENERATION (AMD)

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

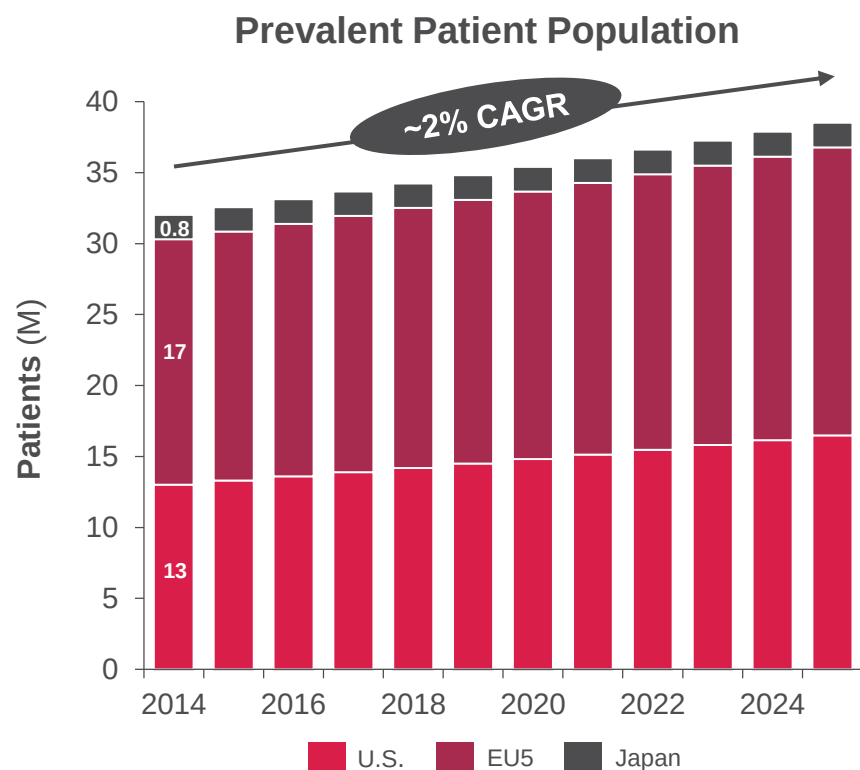


- AMD is a progressive degenerative disease affecting the central portion of the retina (i.e., RPE and photoreceptors in the macula) that results in loss of central vision.
- Symptoms of AMD:
 - Straight lines start to appear distorted, or the center of vision becomes distorted
 - Increased difficulty 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

DRY AMD: PREVALENT PATIENT POPULATION

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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.



THESIS OF CELL THERAPY APPROACH TO RPE TRANSPLANTATION

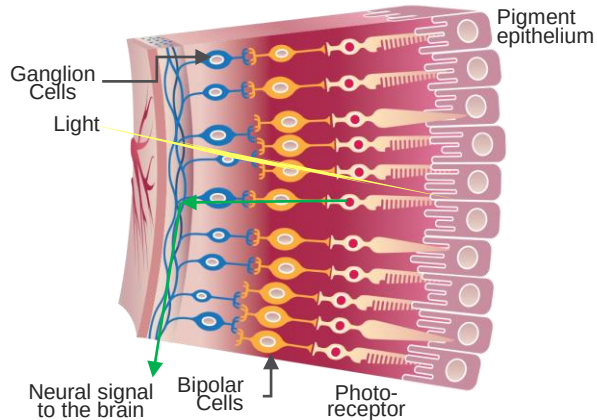
47

Replacement of RPE to potentially restore visual function

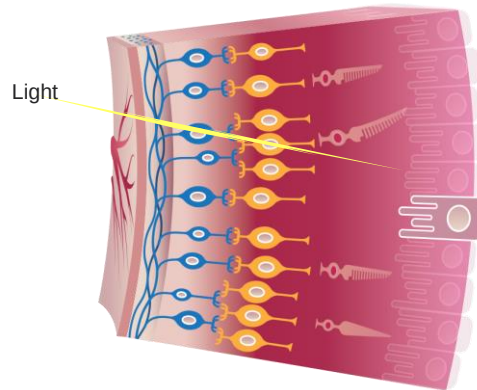
PATHOGENESIS OF DRY AMD

RESTORE RPE CELL FUNCTION BY CELL THERAPY

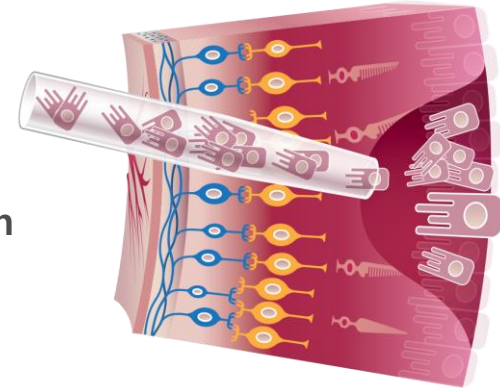
Normal



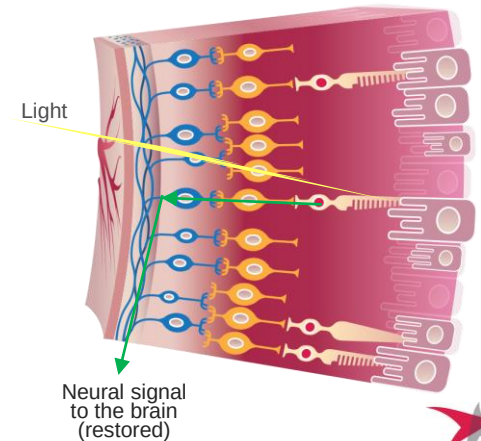
Macular Degeneration



RPE transplantation



Neural signal restored

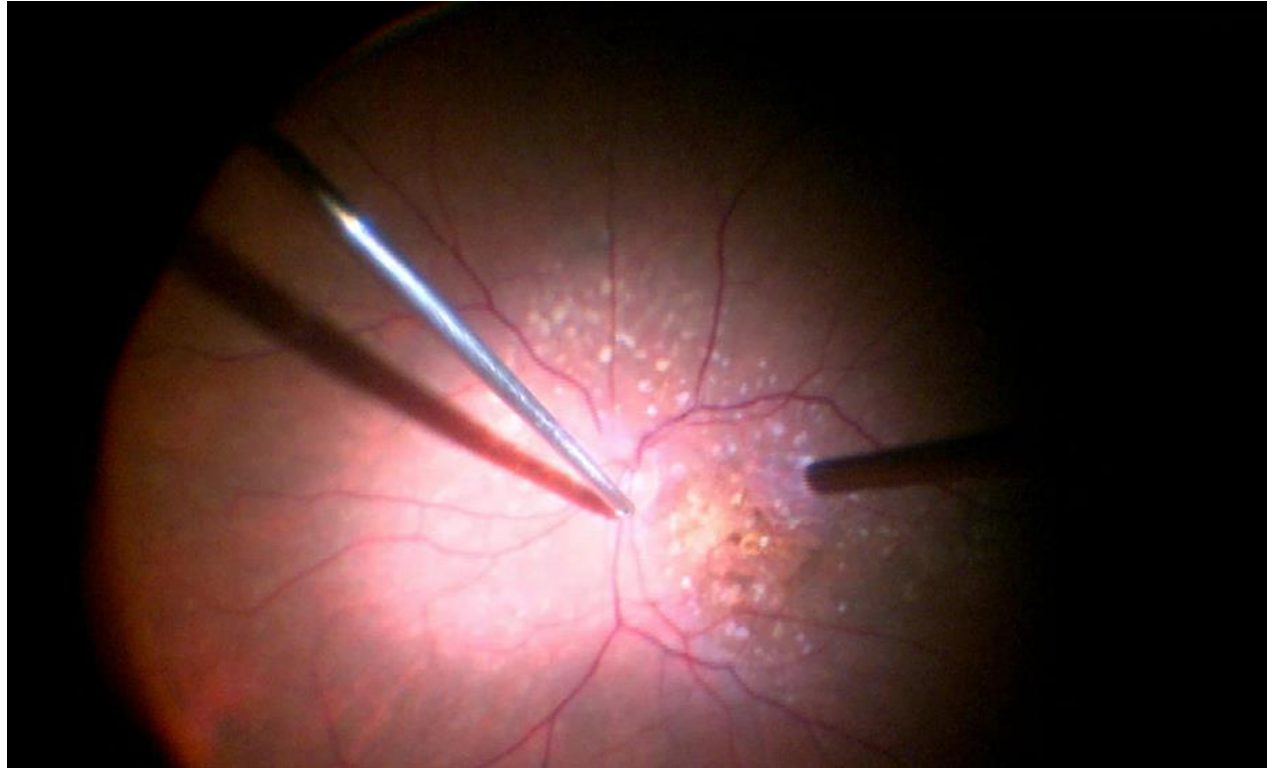


RPE CELL TRANSPLANTATION: SUBRETINAL INJECTION

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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



RPE PROGRAM OVERVIEW

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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 disease¹
- Follow-up data 12 months post-transplantation²



The Association for Research in Vision and Ophthalmology

- Follow-up data 36 months post-transplantation³

Established new cell line: ASP7317

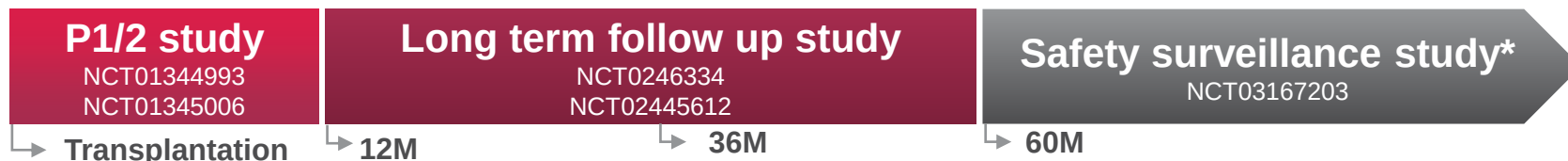
- ◆ Phase-1b/2 dose-ranging and POC trial for dry AMD is ongoing with a new cell line and formulation



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

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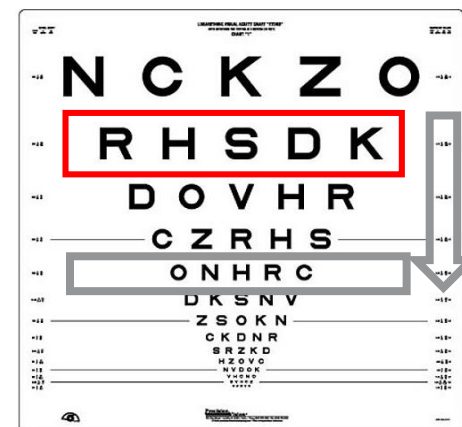
Efficacy and safety have been investigated up to 36 months



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

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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.



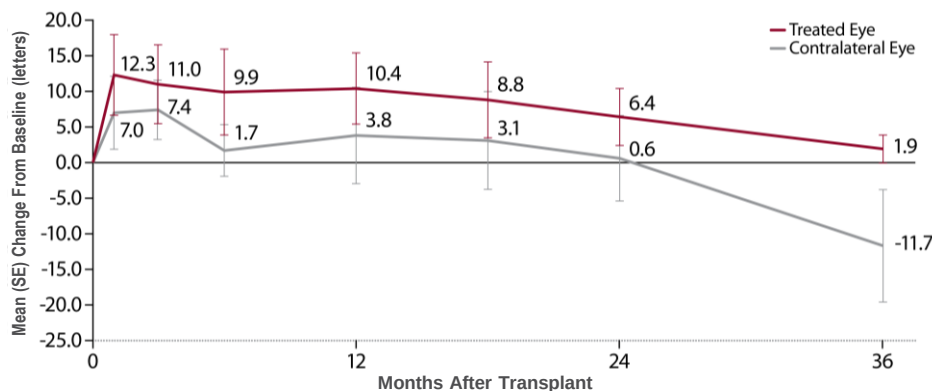
PHASE 1/2 STUDY (MA09-hRPE): EFFICACY IN DRY AMD

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

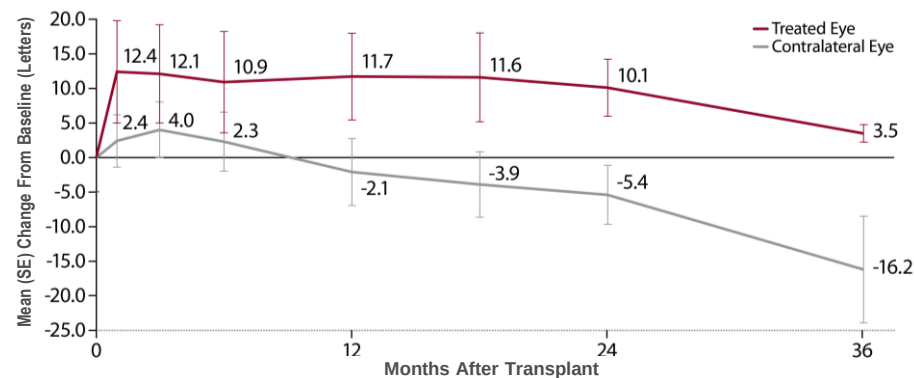
Mean Change in ETDRS BCVA in the 36 Months Post-Transplantation in the Low Vision Group (AMD)

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.



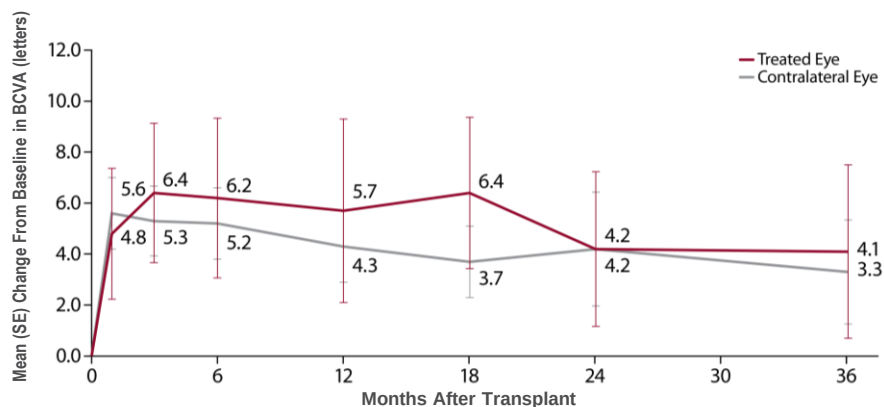
PHASE 1/2 STUDY (MA09-hRPE): EFFICACY IN STARGARDT DISEASE

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

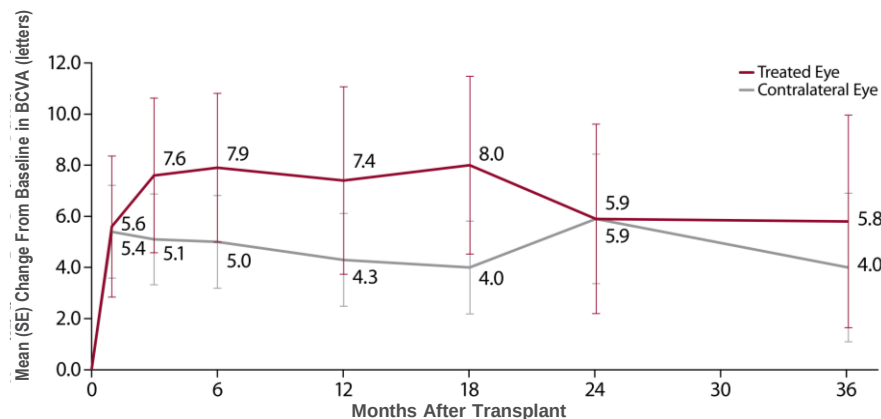
Mean Change in ETDRS BCVA in the 36 Months Post-Transplantation in the Low Vision Group (STGD)

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.





NEW CELL LINE

ASP7317

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

55

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

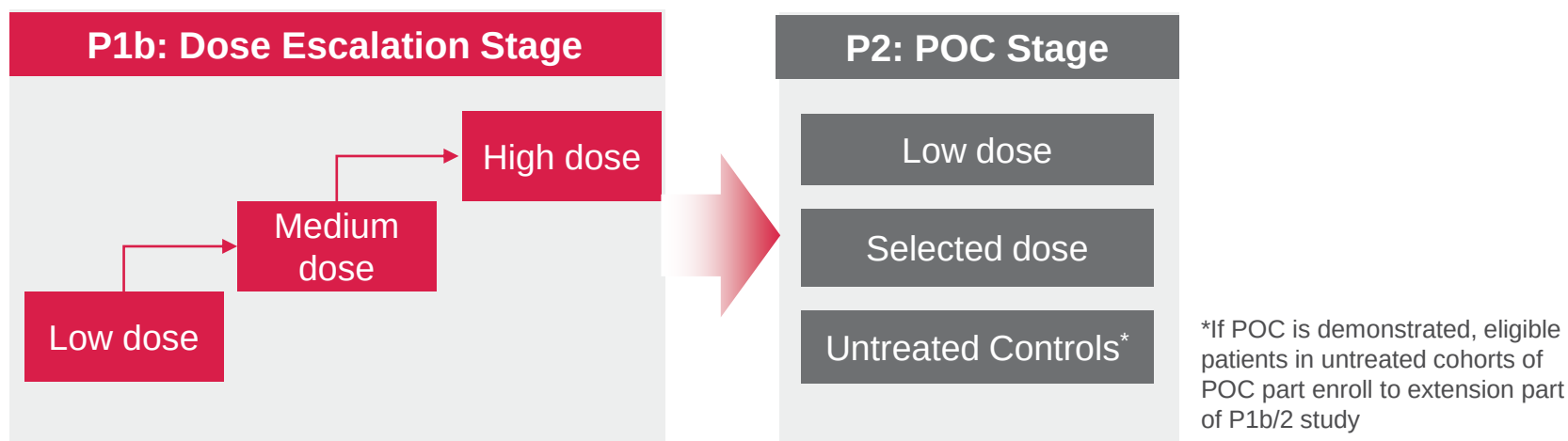


To evaluate the efficacy and safety of the new cell line, a new Phase 1b/2 study has been initiated

ASP7317: PHASE 1b/2 STUDY DESIGN

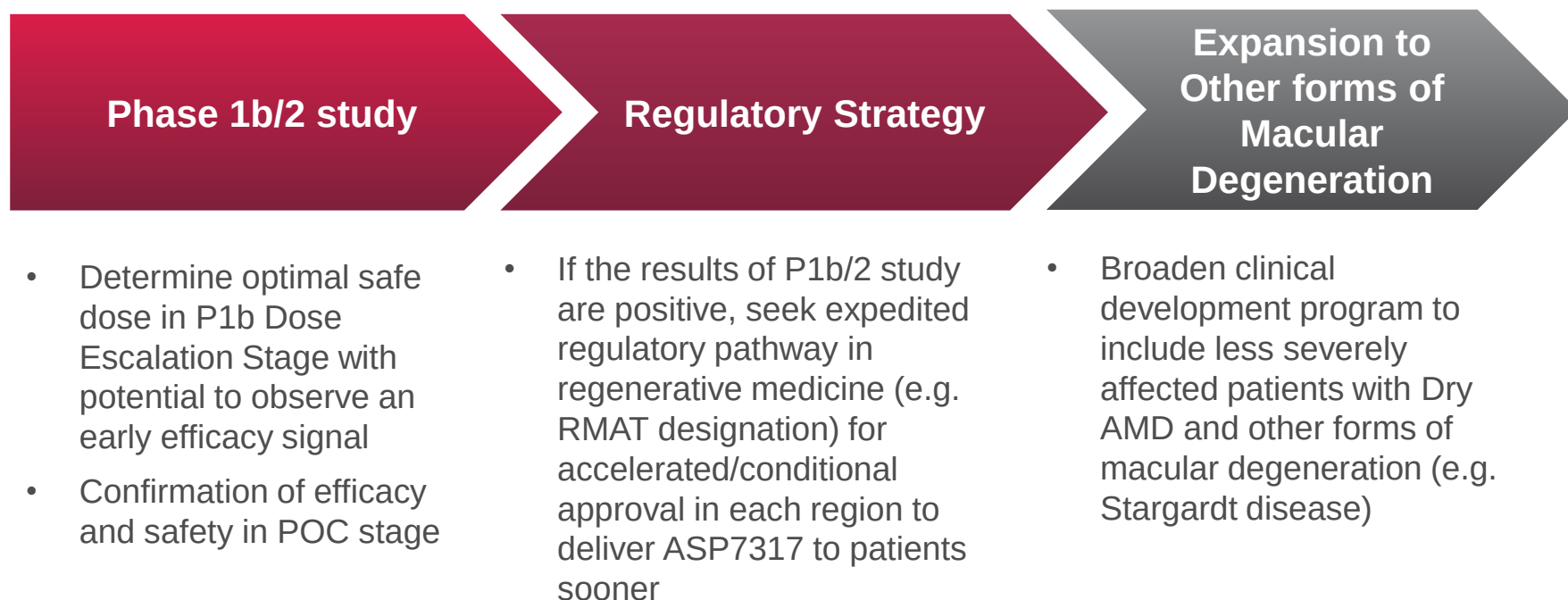
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Initiated clinical trial for Dry AMD in July 2018



	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 26 weeks (primary study period) - 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

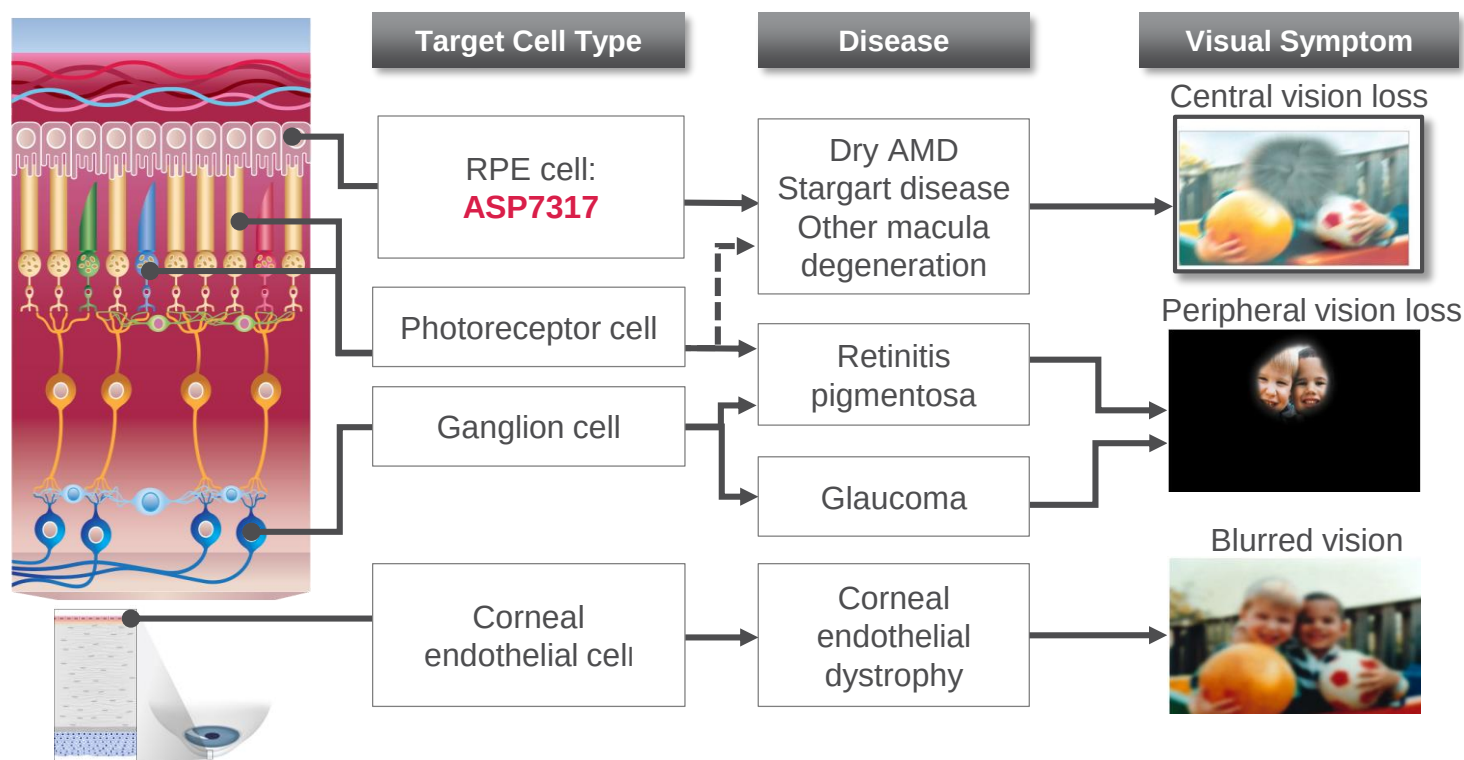
Accelerate the development of ASP7317 by seeking expedited regulatory pathway



ASP7317 AND BEYOND

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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



CONTINUED EFFORTS TO DELIVER VALUE FOR PATIENTS WITH VISION IMPAIRMENT

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

ASP7317

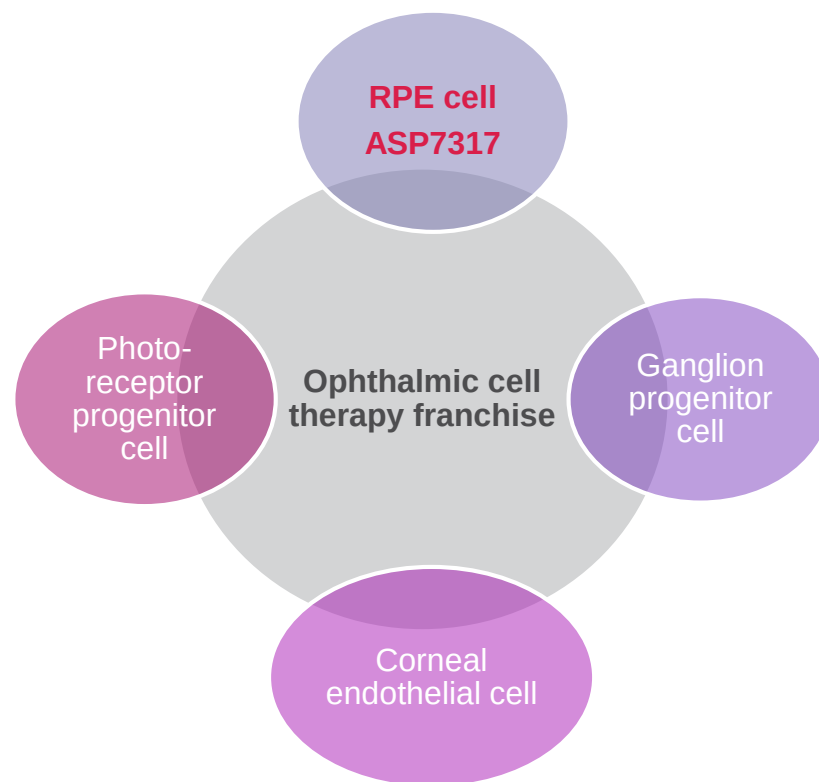
Broaden clinical development program to moderate AMD and other forms of macular degeneration

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



Turning innovative science
into value for patients by
**maximizing the potential of
cell therapy**