PROGRESS IN FOCUS AREA APPROACH

R&D Meeting - December 10, 2020

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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.

AGENDA

I

Introduction

Kenji Yasukawa, Ph.D., President and Chief Executive Officer

II

Primary Focus (PF) & PF Candidates

	(Primary Focus Lead)
☐ PF - Genetic Regulation	Ulf Tollemar
☐ PF - Blindness and Regeneration	Jotaro Suzuki, Ph.D.
☐ PF - Immuno-oncology	Peter Sandor, M.D.
☐ PF Candidate - Cancer Genomic Alteration	Peter Sandor, M.D.
☐ PF - Mitochondria Biology	Itsuro Nagase, Ph.D.
☐ PF Candidate - Immune Homeostasis	Shigetada Furukawa, Ph.D.

III

Innovative Technology Platforms for Drug Discovery & Research to Support Focus Area Approach

Kenji Yasukawa, Ph.D.

PRIMARY FOCUS
& PRIMARY FOCUS CANDIDATE

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Primary Focus: **Genetic Regulation**

Developing potentially curative gene therapy treatments to transform the lives of people with genetic diseases



Ulf Tollemar
Primary Focus Lead, Genetic Regulation

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SIGNIFICANTLY IMPROVING OUTCOMES FOR SERIOUS LIFE-LIMITING AND POTENTIALLY FATAL GENETIC DISEASES

*Our mission is to **identify**, **develop** and **deliver transformative gene-based therapies** for patients with genetic diseases*



~7,000 diseases

Often present from birth and affecting young children, nearly 7,000 human diseases are caused by mutations or deficiencies in genetic code [1]

- A single intervention could replace missing genes or regulate genes that are behaving abnormally, to significantly improve outcomes for serious, life-limiting diseases
- Alongside our world-renowned collaborators, we are building a Center of Excellence with competitive capabilities across the value chain for leadership in genetic regulation medicines
- We aim to develop life-changing medicines for diseases where no, or few, treatment options exist

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1: U.S. Department of Health & Human Services. Rare Diseases FAQ, Version 11/30/2017.

AUDENTES THERAPEUTICS



Audentes Therapeutics, which became an Astellas company in January 2020, is developing genetic medicines with the potential to deliver transformative value for patients.

Based on their innovative scientific approach and industry-leading internal manufacturing capability and expertise, the company has become an Astellas Center of Excellence. Audentes is exploring several AAV-based gene therapy technologies to regulate genes; gene replacement, exon skipping gene therapy and vectorized RNA knockdown, with plans to expand focus and geographic reach under Astellas.

AAV: Adeno-associated virus, RNA: Ribonucleic acid

STRATEGIC APPROACH
- BUILDING A NEW MULTIDISCIPLINARY FRANCHISE

Astellas is the global leader in Genetic Regulation medicines with Audentes as its Center of Excellence (CoE)

AAV Manufacturing

Continued global industry leadership in AAV manufacturing

Integrated R&D Pipeline

Pipeline of transformative therapies, starting with rare disease with aspirations toward more common diseases

Robust Research Capability

Focused on next-generation genetic regulation technologies

Strong CoE infrastructure for sustained growth

AAV: Adeno-associated virus, R&D: Research and development

AAV MANUFACTURING AT COE - A KEY STRATEGIC CAPABILITY ACROSS ASTELLAS

South San Francisco, California



- Internal AAV manufacturing capability provides self sufficiency from research to commercial
- Capabilities to expand to support future AAV manufacturing and supply chain needs

AAV Drug Substance Manufacturing

- Suspension bioreactor systems at 1,000 L (2x500 L) scale
- AAV production supports clinical-stage GMP material with preparations in place for AT132 commercial launch
- Over 4 years of production experience
- Adding new Pilot Plant (2021) to expand development and IND-enabling material generation capacity, support tech transfer and new technology / innovation initiatives



AAV Drug Product (DP) Manufacturing

- All AAV DP batches filled in-house (no CMO reliance)
- Current semi-automated process will be augmented by new state-of-the-art automated fill line (2021)
- Capacity to support all CoE programs in the future



Plasmid Manufacturing

- Added internal plasmid manufacturing capability to supply research grade through GMP grade plasmid
- Move CoE toward controlling the supply chain of this critical raw material



Sanford, North Carolina



- This fully approved capital project is currently under construction
  - Scheduled to be operational and GMP ready by mid 2022
- First phase provides 4,000 L of bioreactor capacity
- Two future phases can bring the total bioreactor capacity to 20,000 L
- Plant can supply all CoE late stage clinical and commercial demand well into the future
- The building and site are expandable to support additional future demand

CoE: Center of Excellence, AAV: Adeno-associated virus, L: Liter, GMP: Good Manufacturing Practice, IND: Investigationall New Drug application, CMO: Contract manufacturing organization

RESEARCH CAPABILITY AT COE - ACCESS TO AND USE OF TECHNOLOGIES

Our innovative use of technologies has the potential to transform outcomes for patients with rare, neuromuscular diseases

AGENT	DELIVERY	MECHANISM	DISEASE TARGETS
Gene → Protein 	 **AAV-based medicines** • Safe and efficient tissue transduction • Tailored biodistribution leading to durable specific expression	**Gene Replacement** Delivery of new functional gene copy to **replace** missing protein	**XLMTM** **Pompe disease**
snRNA 		**Gene Regulation (Exon Skipping)** *In situ* production of a snRNA to induce exon skipping to **correct** translation to a functional protein	**DMD** **Myotonic dystrophy**
miRNA 		**Gene Regulation (RNA Knockdown)** *In situ* production of a miRNA to **eliminate** an unwanted toxic RNA or protein	**Myotonic dystrophy**

Access to new novel technologies will expand our potential to transform outcomes for patients with rare as well as more common diseases

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CoE: Center of Excellence, RNA: Ribonucleic acids, snRNA: Small nuclear RNA, miRNA: Micro RNA, AAV: Adeno-associated virus, XLMTM: X-linked myotubular myopathy, DMD: Duchenne muscular dystrophy

R&D PIPELINE
- CURRENT FOCUS ON MUSCLE DISEASES

Compound	Mechanism	Target indication	Current phase	Origin/Partner
AT132	MTM1 gene replacement	X-linked myotubular myopathy	Phase 2 - Pivotal (Clinical hold due to serious adverse events)	AUDENTES*
AT845	GAA gene replacement	Pompe disease	Phase 1 (Enrolling patients)	AUDENTES*
AT753	Vectorized exon 53 skipping	Duchenne muscular dystrophy	Preclinical (To enter into clinical phase in FY2021)	AUDENTES*
AT702	Vectorized exon 2, 1-5 skipping	Duchenne muscular dystrophy	Discovery	AUDENTES*
AT751	Vectorized exon 51 skipping	Duchenne muscular dystrophy	Discovery	AUDENTES*
AT466	Vectorized exon skipping / vectorized RNA knockdown for DMPK	Myotonic dystrophy	Discovery	AUDENTES*
GT0001X	ADAR2 gene expression	Sporadic amyotrophic lateral sclerosis	Preclinical	Gene Therapy Research Institution**
MDL-201	(Not disclosed)	Muscle disease	Preclinical	MODALIS
MDL-202	(Not disclosed)	Muscle disease	Preclinical	MODALIS

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* Acquired (current programs classified as 'in house'), ** Option agreement
R&D: Research and development, MTM: Myotubularin, GAA: Acid alpha-glucosidase, RNA: Ribonucleic acid, DMPK: Myotonic dystrophy protein kinase, ADR2: Adenosine deaminase acting on RNA2

AT845:
DISEASE MODIFYING GENE REPLACEMENT THERAPY RESTORES THE KEY ENZYME IN POMPE DISEASE

DISEASE

- In Pompe disease, a deficient GAA enzyme causes glycogen build-up leading to tissue and organ damage predominantly in skeletal muscle, cardiac muscle and the nervous system
- Infantile-onset Pompe disease is a severe condition with a high and early fatality rate, while the late-onset form of Pompe disease has less severe symptoms and a slower rate of progression
- Current treatment is enzyme replacement therapy (ERT) which is limited by immunogenicity and its inability to penetrate key tissues affected by the disease

MODALITY

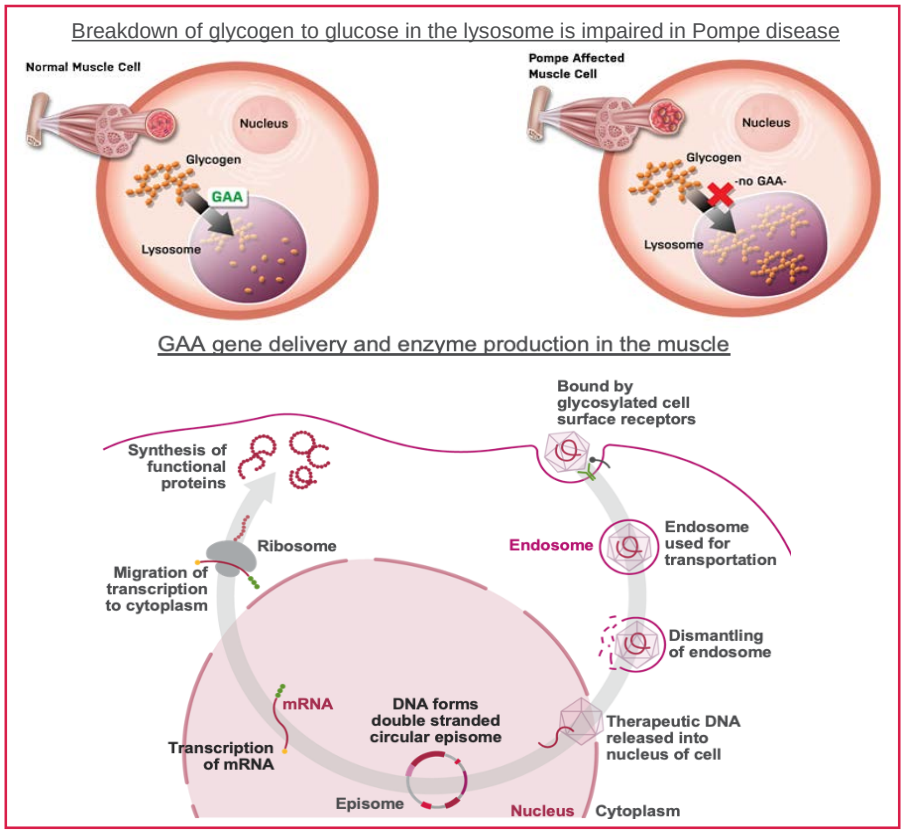
- AAV is a non-pathogenic virus that has been engineered to carry and deliver functional genes into the nucleus of target cells

BIOLOGY

- Gene replacement is achieved by AAV delivering a functional GAA gene to produce the missing GAA enzyme which breaks down glycogen into glucose in the lysosome
- AT845 has the potential to generate GAA directly in the muscle to restore function in affected organs and reduce the need for chronic ERT treatment

CURRENT STATUS AND NEXT STEPS

- Phase 1/2 open label, ascending dose “FORTIS” study in late-onset Pompe Disease is actively enrolling



GAA: Acid alpha-glucosidase, AAV: Adeno-associated virus, DNA: Deoxyribonucleic acid, mRNA: Messenger ribonucleic acid

DMD FRANCHISE (AT702, AT751, AT753):
VECTORIZED EXON SKIPPING, GENERATING FUNCTIONAL DYSTROPHIN TO TREAT DUCHENNE MUSCULAR DYSTROPHY (DMD)

DISEASE

- Dystrophin is one of the largest proteins in humans, consisting of 79 exons, and is needed for muscle strength
- In DMD, multiple genetic mutations on the dystrophin gene prevent functional dystrophin production causing deterioration and death of skeletal and cardiac muscle cells
- Over time DMD causes muscle weakness and heart problems leading to disability and early death
- There are limited treatments available, other than physical therapy. Many gene therapy studies are ongoing, mostly targeting the delivery of a truncated version of dystrophin

MODALITY

- AAV is a non-pathogenic virus that has been engineered to carry and deliver a gene generating snRNA with antisense sequences into the nucleus of target cells

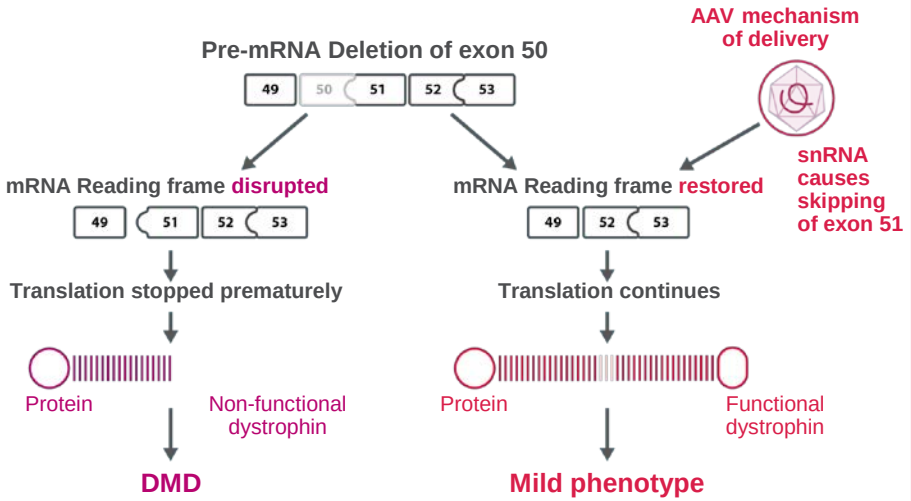
BIOLOGY

- snRNAs are capable of regulating gene expression through exon skipping, bypassing faults in the dystrophin gene to enable cells to generate functional dystrophin protein
- Increased functional dystrophin reduces deterioration of skeletal and cardiac muscle cells and may restore muscle strength and heart function
- Range of mutations covered by the three lead assets affect up to 25% of the DMD population

CURRENT STATUS AND NEXT STEPS

- Collaborative study with NCH ongoing, AT753 is on track to start a clinical study in FY2021
- An efficient ‘umbrella’ clinical study protocol is being planned

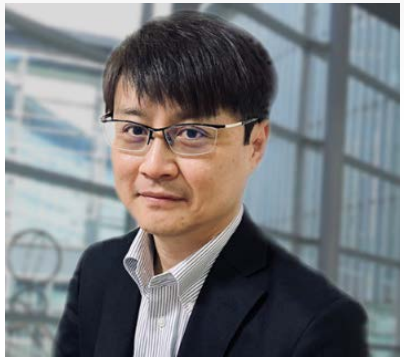
Exon skipping (AT751)



AAV: Adeno-associated virus, snRNA: Small nuclear ribonucleic acid, NCH: Nationwide Children’s Hospital

Primary Focus:
Blindness and Regeneration

Developing revolutionary therapies to free patients from the fear of deteriorating vision and regain lost sight



Jotaro Suzuki, Ph.D.
Primary Focus Lead, Blindness and Regeneration

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OFFERING POTENTIAL TO PROTECT AGAINST DECLINING VISION AND EVEN RESTORE LOST SIGHT IN PATIENTS WITH RETINAL DISEASES

*Our mission is to **identify**, **develop** and **deliver next generation treatments** to restore sight for patients with retinal diseases*



160+ million worldwide

Vision loss caused by diseases of the eye affects over 160 million people globally [1,2] and can have a devastating long-term impact on quality of life

- Many diseases causing vision loss have few, or no, effective treatment options
- Utilizing our in-house ophthalmology expertise and rapidly expanding regenerative medicine capabilities, we are targeting transformational changes in the management of multiple devastating eye diseases
- Through revolutionary cell and gene therapies, we aim to restore and preserve the critical vision-supporting cells in the eye

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1: Data from the WHO Blindness and Visual Impairment fact sheet. Version 8 Oct 2019.
2: Data from the Foundation Fighting Blindness 2019 Annual Report.

STRATEGIC APPROACH

We are combining truly innovative cell and gene modalities with a deep understanding of the biology of retinal diseases to establish a robust platform of regenerative medicine

FOCUS

- Delivery of novel therapeutic options for patients suffering from retinal diseases

ENRICH

- Leveraging cell and gene therapies with our ophthalmology R&D and manufacturing capabilities to target key cells central to the pathophysiology of retinal diseases
- Building a broad, differentiated pipeline of potentially transformative treatments

EXPAND

- Continually searching for next-generation cell/gene therapies and entirely new modalities, collaborating with our external partners to deliver value for patients

Our differentiated platform technologies include:



A strong foundation in pluripotent stem cell (PSC)-derived cell therapies in all aspects of the value chain, including development, manufacturing and access capabilities



Expertise in AAV-based gene delivery technology

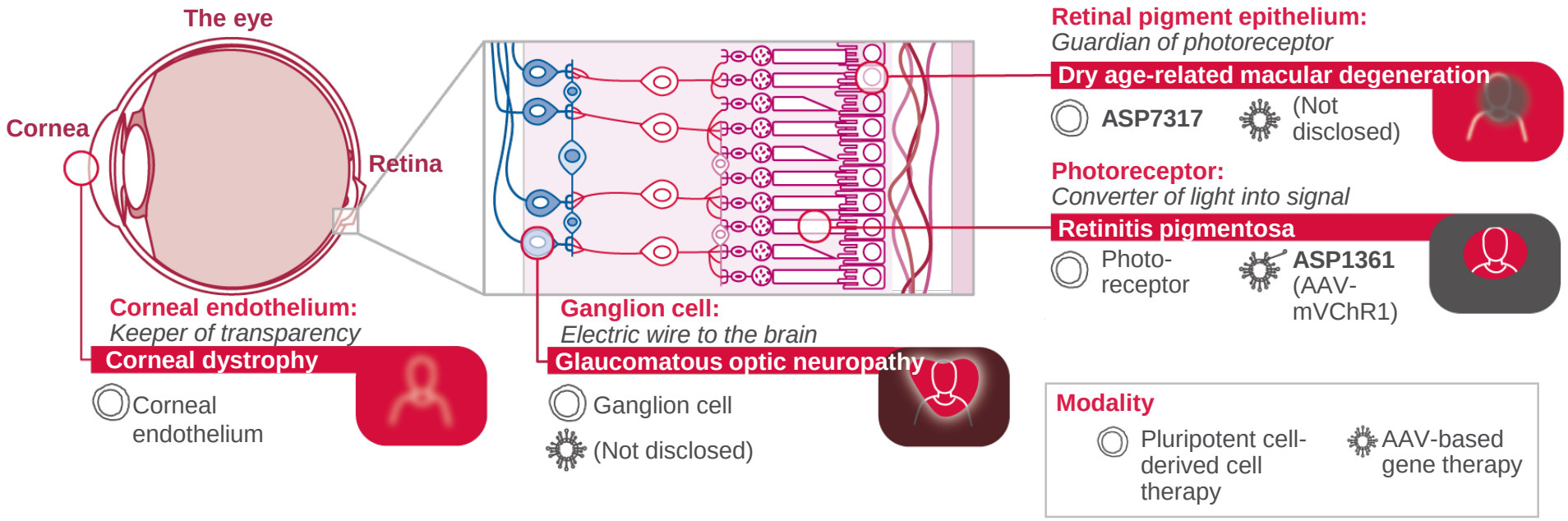


Ophthalmology research and development capability for a variety of modalities

R&D: Research & Development, AAV: Adeno-associated virus

PIPELINE (1/2)

We are exploring innovative modalities to protect and/or restore degenerating cells important to visual function



AAV: Adeno-associated virus, mVChR1: Modified Volvox channelrhodopsin-1

PIPELINE (2/2)

Compound	Modality/Mechanism	Indication	Current phase	Origin/Partner
ASP7317	RPE cell	Dry AMD, Other macular degeneration	Phase 1b/2 (Protocol to be amended to decouple PoC part)	ocata THERAPEUTICS * (AIRM)
ASP1361	Gene therapy (AAV-mVChR1)	Retinitis pigmentosa	Preclinical (IND planned in 2021)	Clinical Innovation CLINO CO.
(Not disclosed)	Gene therapy (AAV)	Glaucoma	Preclinical (IND planned in 2023)	Quethera *
(Not disclosed)	Photoreceptor rescue cell	Retinitis pigmentosa	Discovery	ocata THERAPEUTICS * (AIRM)
(Not disclosed)	Ganglion rescue cell	Glaucoma, Optic neuropathy	Discovery	ocata THERAPEUTICS * (AIRM)
(Not disclosed)	Corneal endothelial cell	Corneal dystrophy	Discovery	ocata THERAPEUTICS * (AIRM)
(Not disclosed)	Universal donor cell (UDC) RPE	Dry AMD, Other macular degeneration	Discovery	Universal Cells *
(Not disclosed)	Gene therapy (AAV)	Dry AMD, Other macular degeneration	Discovery	University of Pittsburgh

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* Acquired (current programs classified as 'in-house')
RPE: Retinal pigment epithelial, AIRM: Astellas Institute for Regenerative Medicine, AMD: Aged-related macular degeneration,
AAV: Adeno-associated virus, mVChR1: Modified Volvox channelrhodopsin-1, IND: Investigational New Drug application

ASP1361:
GENE THERAPY WITH THE POTENTIAL TO REVERSE VISION LOSS IN RETINITIS PIGMENTOSA

DISEASE

- Retinitis pigmentosa is a group of eye diseases caused by numerous gene mutations that cause photoreceptor cells in the retina to degenerate, leading to severe and permanent vision loss
- Significant unmet needs exist for effective treatment options in ultra-low vision patients with retinitis pigmentosa due to lack of standard-of-care

MODALITY

- AAV is a non-pathogenic virus that can be engineered to deliver functional genes to target cells
- A mutation-independent gene therapy is a desirable approach

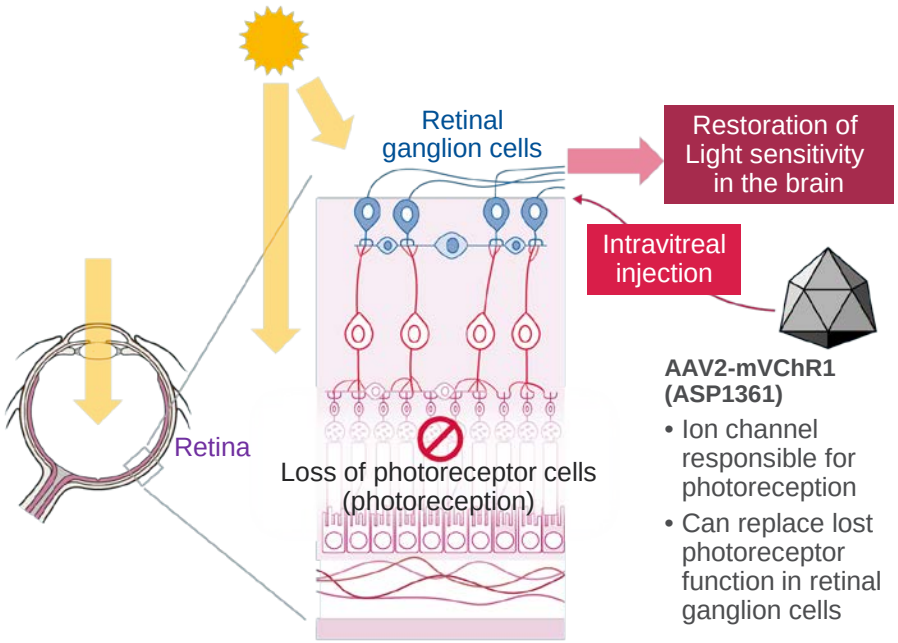
BIOLOGY

- AAV2-mVChR1 can introduce the channel rhodopsin-1 gene (mVChR1) to retinal ganglion cells, rather than to the retinal photoreceptors that have been damaged as a result of gene mutations
- This results in the expression of photosensitive ion channels in the retinal ganglion cells, restoring light sensitivity and visual function

CURRENT STATUS AND NEXT STEPS

- IND submission planned in 2021 to start a clinical study in patients

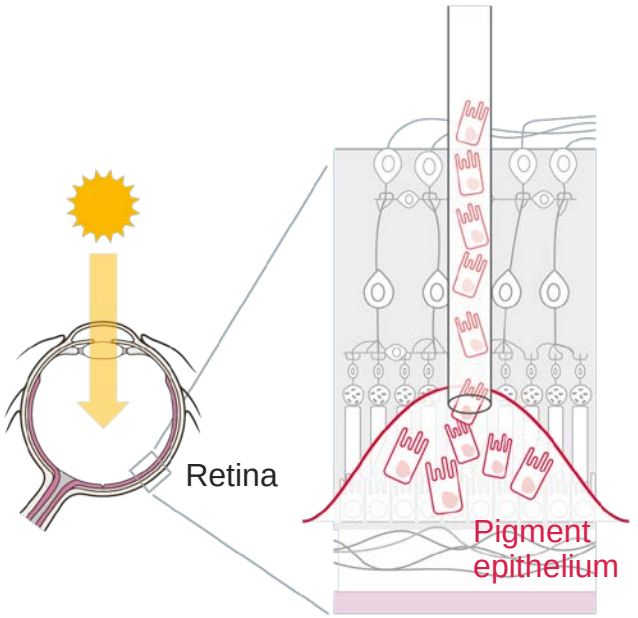
ASP1361 mechanism of action



AAV: Adeno-associated virus, mVChR1: Modified Volvox channelrhodopsin-1, IND: Investigational New Drug application

ASP7317:
PLURIPOTENT STEM CELL-DERIVED ALLOGENIC CELL THERAPY TO REPLACE RETINAL PIGMENT EPITHELIUM TO RESTORE LOST SIGHT

- Completion of 1st cohort in Phase 1b/2 study
- Phase 1b/2 study amendment aimed to optimize the overall development program has been submitted for FDA's review (announced at the Q2/FY2020 earnings)
- Agreement by PMDA that new DS raw materials are acceptable for use in future clinical studies in Japan
- Completion of GMP DS manufacturing to support the future PoC supply
- Established cell manufacturing process to cover early commercial supply
- BLA is planned after completion of PoC study



FDA: Food and Drug Administration, PMDA: Pharmaceuticals and Medical Devices Agency, DS: Drug substance, GMP：Good Manufacturing Practice, PoC: Proof of concept, BLA: Biologics License Application

EVOLUTION OF CELL THERAPY CAPABILITY

Enhancement of PSC lines and evolution of cell differentiation protocols

- Multiple clinical grade PSC lines with safety and quality assurance
- Develop the cells of interest by using the best PSC lines. Multiple INDs planned in 5 years from 2021
- Hundreds-fold increase of productivity of RPE cells

Achievement of rejection-free allogenic cell therapy

- Multiple UDC-based PSC lines and establishment of master cell bank
- UDC-RPE is the leading program and multiple follow-on programs
- Research collaboration with panCELLa for Immune-cloaking technology

Development of technology and infrastructure for GMP-level production

- Completion of the new facility with GMP-level production n US
- Selection of regulatory compliant raw materials for development in US / EU / JP
- Completion of GMP production of ASP7317 for PoC study

Efficient logistics system for cell therapy

- Development of original and new formulation technology has advanced
- Optimization for each product candidate

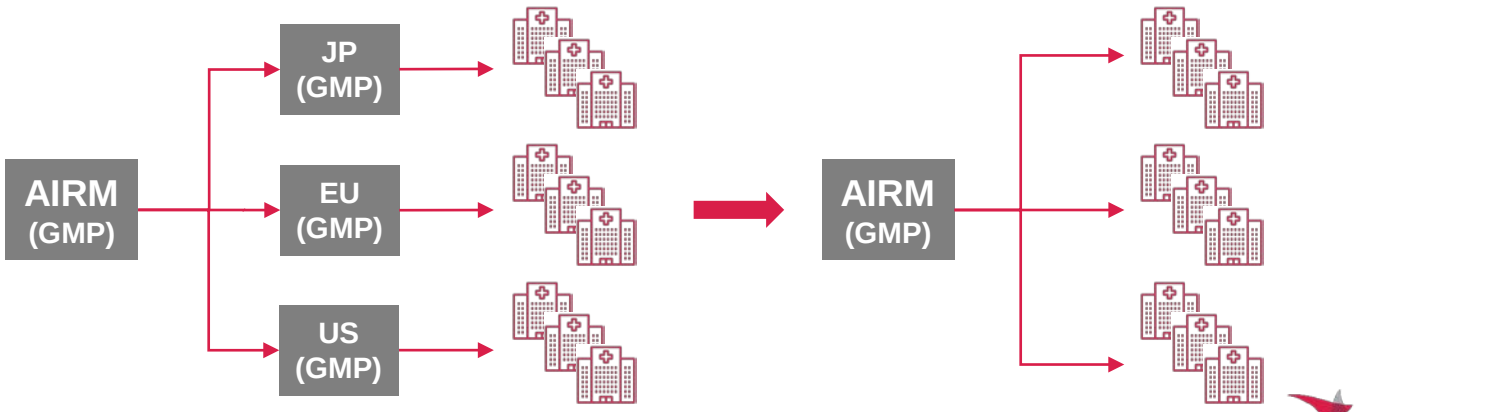
Steady progress since R&D meeting in 2018

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PSC: Pluripotent stem cell, IND: Investigational New Drug application, RPE: Retinal pigment epithelium, UDC: Universal donor cell, GMP: Good Manufacturing Practice, PoC: Proof of concept, R&D: Research and development

ESTABLISH EFFICIENT LOGISTICS SYSTEM

	Current drug product	New drug product
Feature	Cryopreservation of DS. Formulation into DP at GMP facilities for administration	Cryopreservation of DP. Reconstitution at the hospital just before administration
GMP DP production facility (or CMO)	Required for each region/country to manufacture final DP	Not required
Shelf-life of DP	Hours to days	Years
Timing of DP release	Just before the treatment (hours to days before the surgery). Risk of transportation problems	Flexible regardless of the surgery schedule
DP manufacturing scale	Frequent productions of only required number of units	Batch production (> hundreds of vials)
Quality control of DP	Conduct at each DP GMP site for an individual DP	Conducted centrally at AIRM. Performed on batch-basis



DS: Drug substance, DP: Drug product, GMP: Good Manufacturing Practice, AIRM: Astellas Institute for Regenerative Medicine

CENTER OF CELL THERAPY MANUFACTURING
ASTELLAS INSTITUTE OF REGENERATIVE MEDICINE (AIRM)

Overview of New Facility

- A complex of research, CMC/manufacturing, and clinical development, optimized for the promotion of cell therapy
- CMC/GMP manufacturing occupy half of 24,000 m^2
- Central role in the manufacture of MCBs, investigational drugs and early commercial products
- 7 GMP clean rooms complied with US/EU/JP regulations. Expandable for future demands
- Independent air controlling system for clean rooms, enabling production of different cell types in parallel
- Seamless and fast GMP manufacturing by integration of Research and CMC

April 2020 in operation (Westborough, MA)



Cell Drug Substance Manufacturing

- 10 years' experiences of PSC-derived cell therapy and GMP manufacturing cultivated as a pioneer
- Accumulated regulatory know-how accumulated through interactions with regulatory authorities
- Now promoting GMP manufacturing with protocols optimized for each cell type
- Established large-scale culture using bioreactors for non-ophthalmic cell therapy

Cell Drug Product Manufacturing

- Experience in supplying CTM to US and UK (total of over 40 doses)
- Plans to expand our capabilities as a center of future supply chain (DP shipping)

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CMC: Chemistry, manufacturing and control, GMP: Good Manufacturing Practice, MCB: Master cell bank, PSC: Pluripotent stem cell, CTM: Clinical trial material, DP: Drug product

SNAPSHOT OF ASTELLAS CELL THERAPY - CENTERS OF INNOVATION AND EXCELLENCE

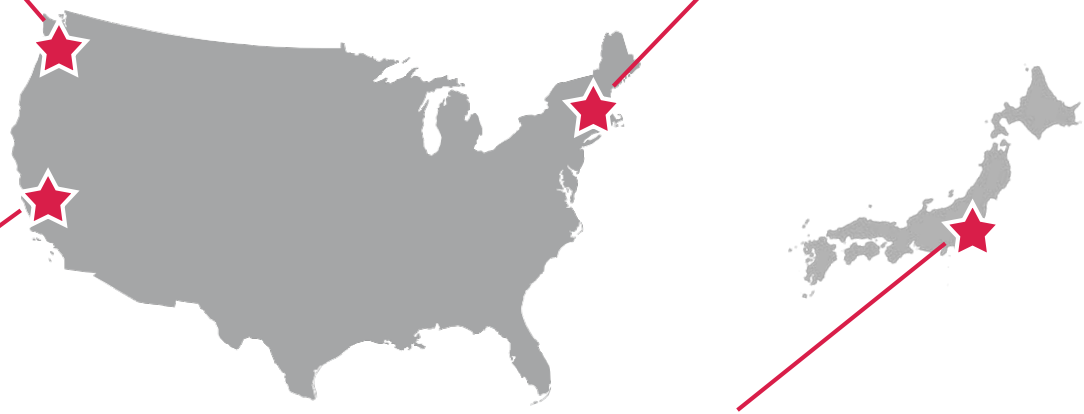
Dedicated members at four sites in US and JP for our cell therapy

Universal Cells

- 2018 Universal Cells acquisition
- CSO: Dr. D. Russell
- Center of Astellas gene-editing
- Universal donor cell technology
- Contribution to industrial organization activities (ARM)

AIRM

- 2016 Ocata acquisition
- CSO: Dr. R. Lanza
- Center of Astellas regenerative medicine
- Stem cell science and technology
- GMP manufacturing
- Clinical development for ophthalmology



Xyphos Biosciences

- 2020 Xyphos acquisition
- CSO: Dr. D. Martin
- Center of next-generation cancer immunotherapy
- Unique ACCEL™ technology

AIRM Satellite Office

- Collaboration with internal function
- Collaboration with academia in Japan
- Contribution to industrial organization activities (FIRM)

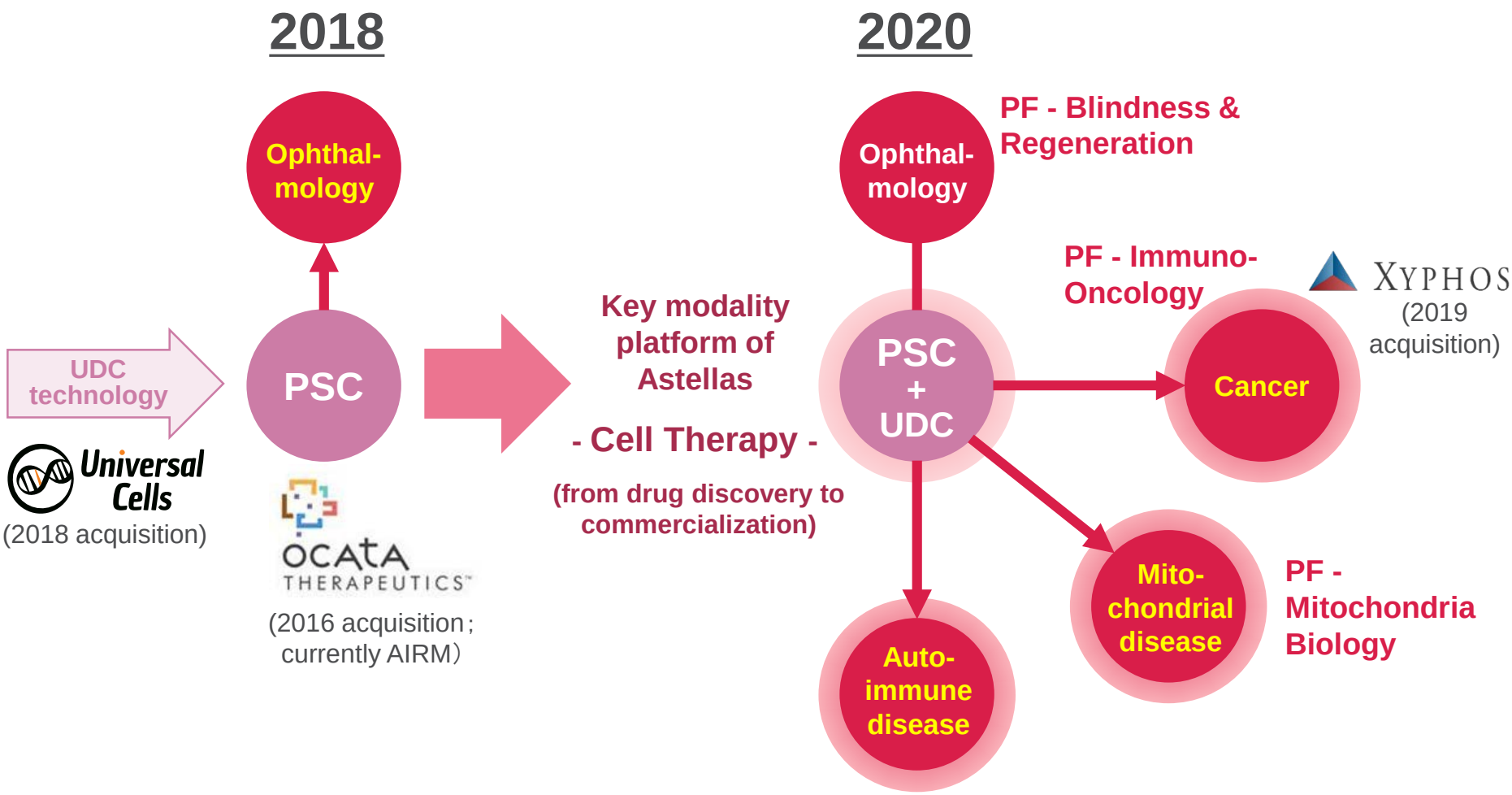
TBRC

- CTM manufacturing for use in early stage clinical trial

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CSO: Chief Scientific Officer, ARM: Alliance for Regenerative Medicine, GMP: Good Manufacturing Practice,
FIRM: Forum for Innovative Regenerative Medicine, TBRC: Tsukuba Biotechnology Research Center, CTM: Clinical trial material

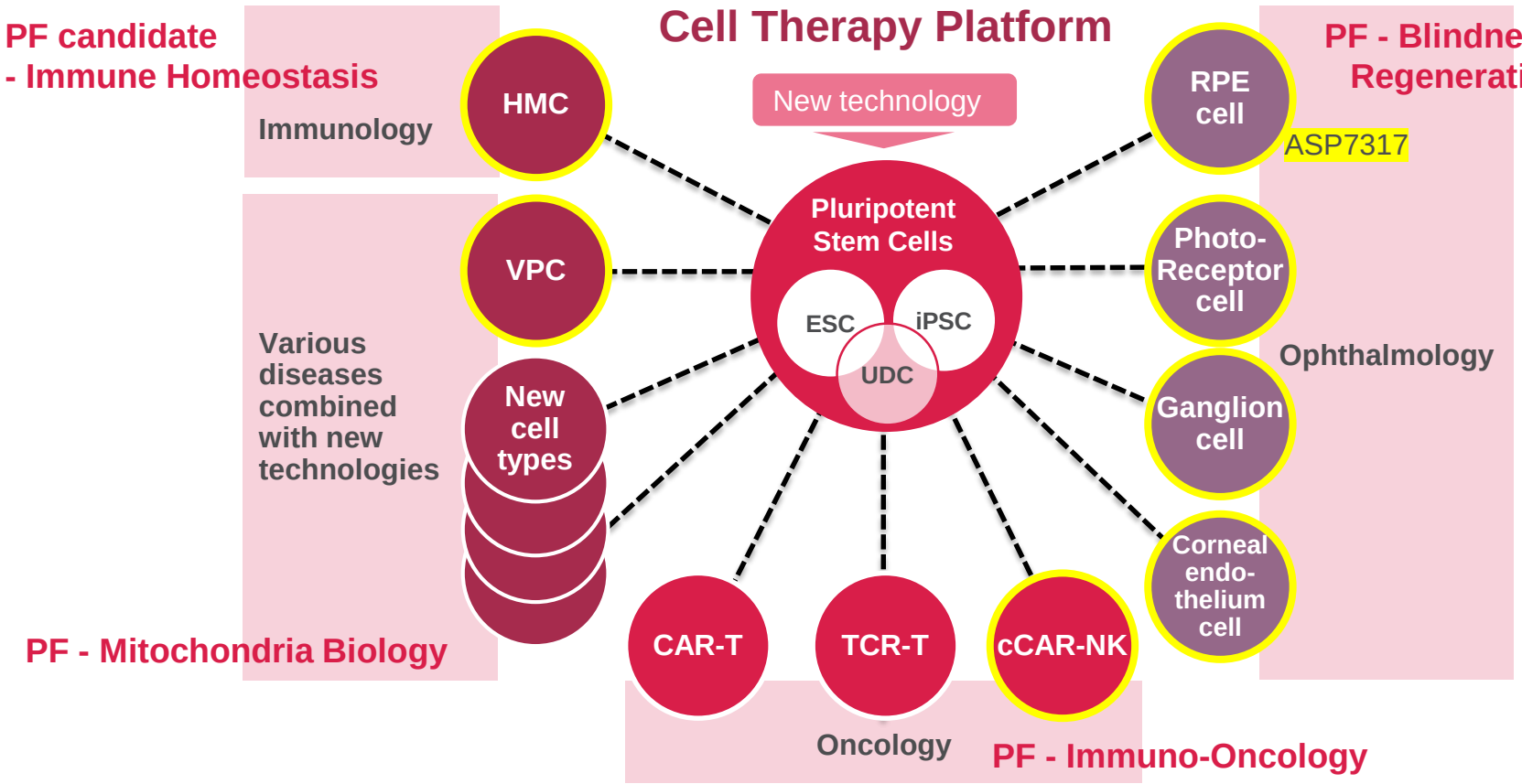
ORGANIC APPLICATION OF CELL THERAPY PLATFORM TO REALIZE MULTIPLE PF STRATEGY (1/2)



PF: Primary Focus, AIRM: Astellas institute for regenerative medicine, UDC: Universal donor cell, PSC: Pluripotent stem cell

ORGANIC APPLICATION OF CELL THERAPY PLATFORM TO REALIZE MULTIPLE PF STRATEGY (2/2)

Established cell differentiation protocols in multiple projects



Yellow-highlighted: Cell differentiation protocols established

PF: Primary Focus, ESC: Embryonic stem cell, iPSC: Induced pluripotent stem cell, UDC: Universal donor cell, RPE: Retinal pigment epithelium, HMC: Hemangioblast-derived mesenchymal stem cell, VPC: Vascular progenitor cell, CAR: Chimeric antigen receptor, TCR: T-cell receptor, cCAR: *convertible*CAR, NK: Natural killer

Primary Focus: **Immuno-oncology**

Dedicating our collective strengths to find new ways to cure cancer globally



Peter Sandor, M.D.
Primary Focus Lead - Immuno-oncology

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OUR GOAL IS TO DELIVER CURATIVE TREATMENT OPTIONS FOR PATIENTS WITH CANCER



Currently only approximately 20% of cancers respond to existing immuno-oncology treatments[1]

WE ARE PASSIONATE ABOUT TURNING

20% into **100%**

EXPERTISE and EXPERIENCE in cancer biology and cancer drug development

ADVANCED TECHNOLOGY capabilities to develop and improve novel modality platforms

PARTNERING with the best minds in immuno-oncology research and industry to create new ways to treat cancer

INNOVATIVE PIPELINE to **reinvigorate** the immune system's ability to **discover**, **disarm** and **destroy** more cancers in more patients

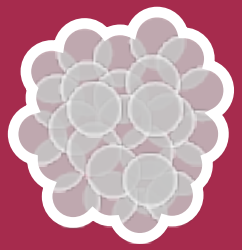
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1. Ventola CL,. Cancer Immunotherapy, Part 3: Challenges and Future Trends. P&T. 2017;42(8):514-521.

PF IMMUNO-ONCOLOGY: STRATEGIC APPROACH

We are allocating significant, sustained investment in understanding cancer biology and deploy this knowledge to establish multi-functional modality platforms and generate a broad, novel pipeline

Biology

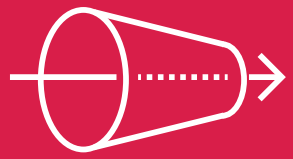


Deep understanding of immune compromised cancer

Multi-functional Modality Platforms

- Bispecific immune cell engager
- Oncolytic virus
- Artificial adjuvant vector cell (aAVC)
- Allogenic cell therapy

Diseases

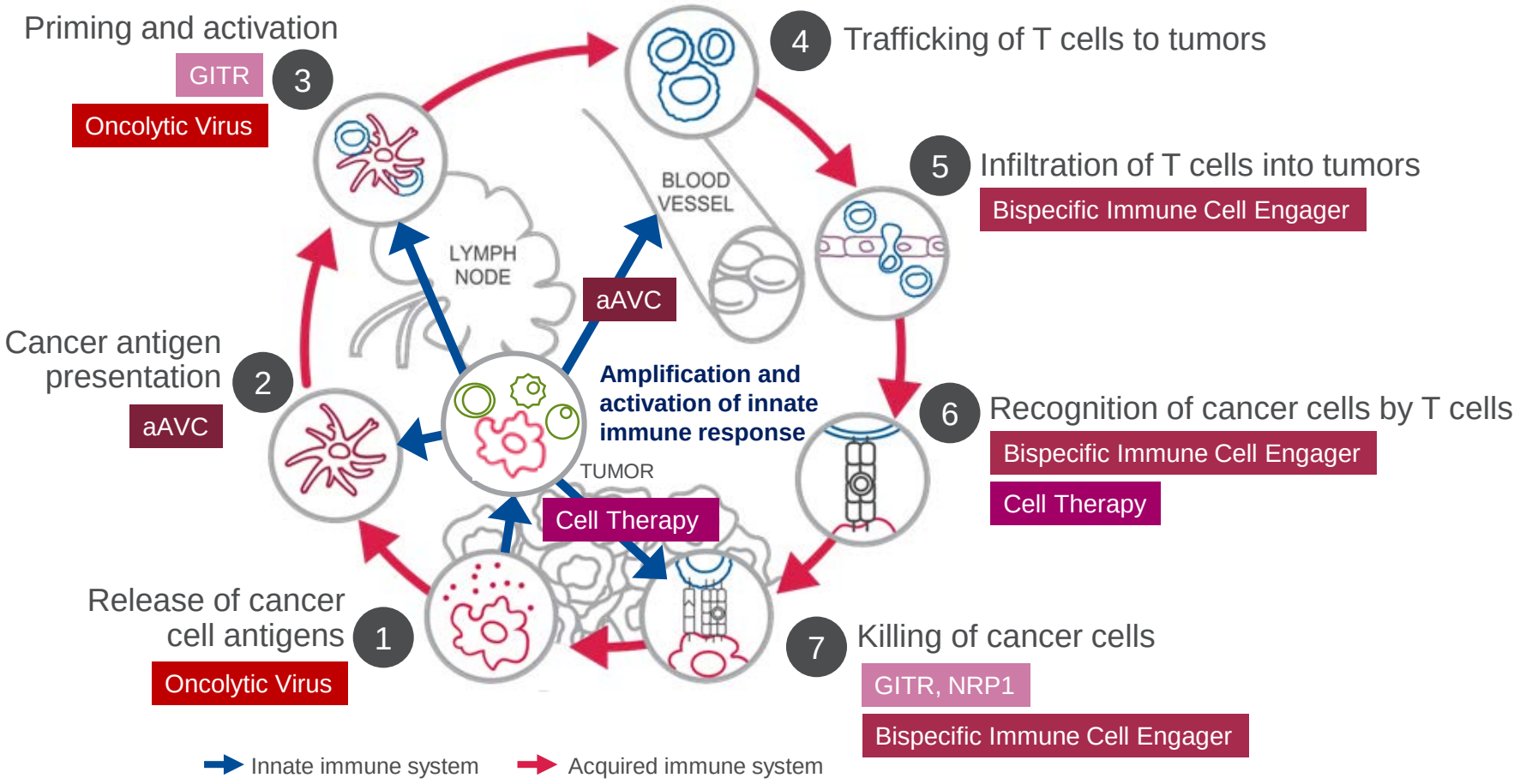


Deliver a sustainable pipeline of novel, differentiated candidates in multiple cancers with high unmet needs

PF: Primary Focus

TRANSLATING BIOLOGY INTO A MODALITY TOOLBOX

Our early-stage platforms are built to trigger anti-tumor immune response by stimulating multiple immune functions at the same time



Source for Cancer Immunity Cycle: Chen DS & Mellman I. Immunity. 2013;39(1):1-10 and Demalia O. et al. Nature. 2019;574(7776):45-56.
aAVC: Artificial adjuvant vector cell, GITR：Glucocorticoid-induced TNFR-related protein、NRP1：Neuropilin-1

STRONG PROGRESS WITH THE IO PIPELINE SINCE Q3 FY19

MODALITY	COMPOUND	MECHANISM	DISCOVERY	PRE-CLIN	PHASE 1	PARTNER
Checkpoint	ASP1948	NRP1				
	ASP1951	GITR agonist				
Oncolytic virus (OV)	ASP9801	OV IL-7, IL-12				Tottori University
	VET2-L2	Systemic OV Leptin-IL2 fusion				KALIVIR IMMUNOTHERAPEUTICS
aAVC	ASP7517	WT1				RIKEN
	ASP0739	NY-ESO-1				
Bispecific immune cell engager	(Not disclosed)	Bispecific antibody				xencor
	(Not disclosed)	Probody® T cell engagers				CYTOMX
	(Not disclosed)	Bispecific immune cell engager				
Cell therapy	(Not disclosed)	CD20 *convertible*CAR-T				
	(Not disclosed)	Mesothelin HiT TCR-T				Adaptimmune
	(Not disclosed)	*convertible*CAR-NK				

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IO: Immuno-oncology, NRP1: Neuropilin-1, GITR: Glucocorticoid-induced TNFR-related protein, IL: Interleukin, aAVC: Artificial adjuvant vector cell, CAR: Chimeric antigen receptor, TCR: T-cell receptor, HiT: HLA (human leukocyte antigen)-independent TCR, NK: Natural killer

IMMUNE CELL ENGAGERS:
REDIRECTING IMMUNE CELLS TO KILL TUMOR CELLS

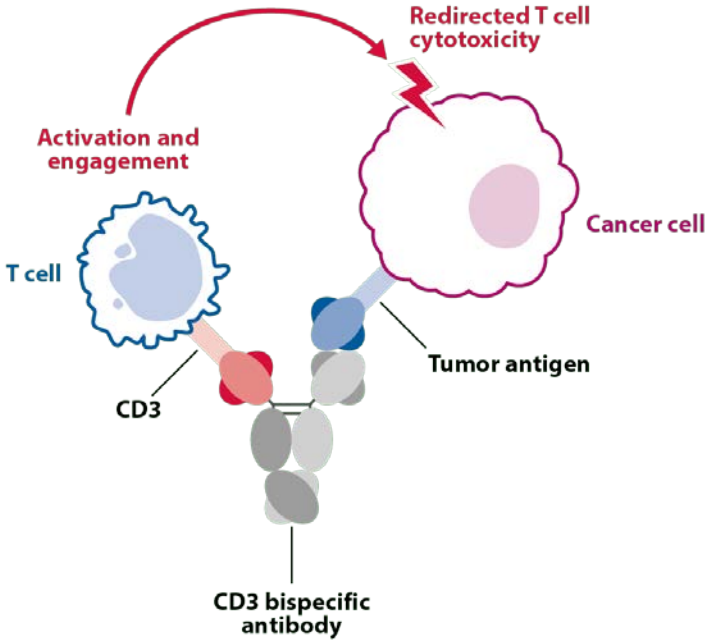
Strong progress building a differentiated bispecific immune cell engager pipeline targeting solid tumors

Internal platform and pipeline development

2019 | 2020 | 2021 | 1st IND

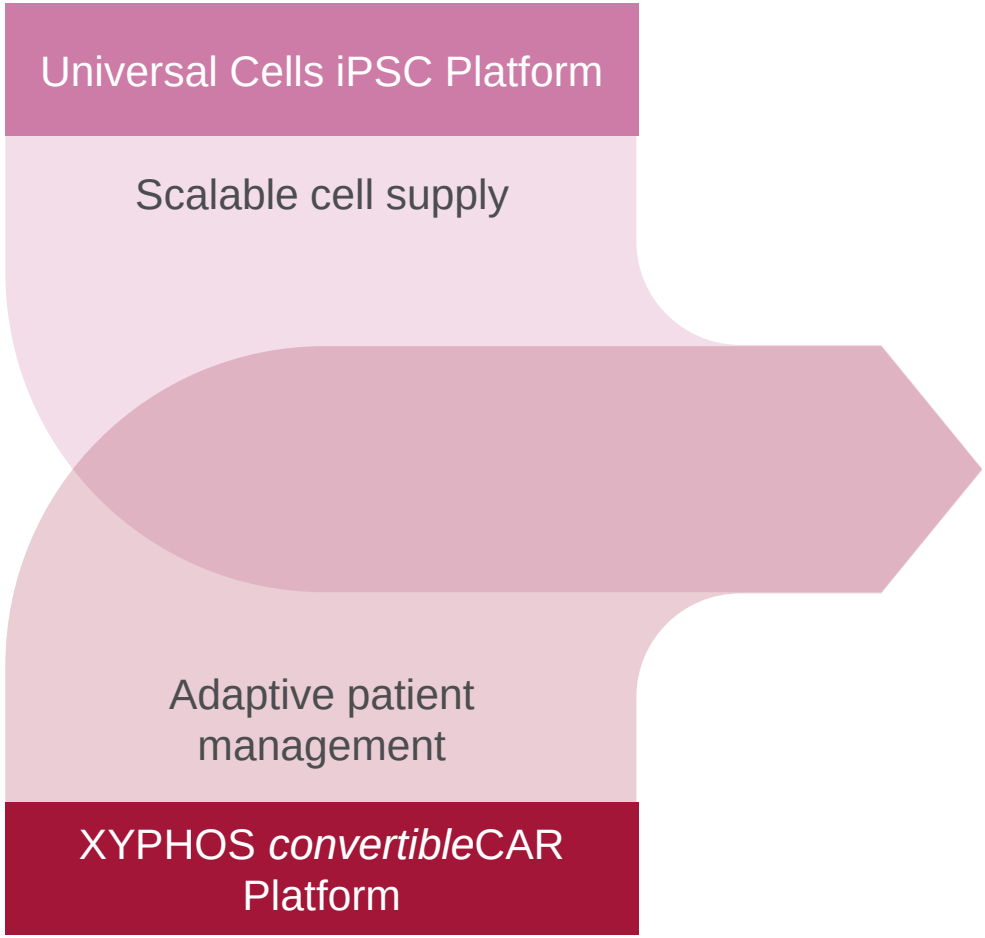
Xencor partnership leveraging bispecific antibody technology XmAb
(April 2019)

CytomX partnership leveraging Probody® T-cell engaging bispecific antibody platform
(Mar 2020)



IND: Investigational New Drug application

COMBINING UNIVERSAL CELLS' AND XYPHOS' TECHNOLOGIES CREATES A DIFFERENTIATED CELL THERAPY PRODUCT CONCEPT



PATIENT ACCESS

Potential to treat all eligible patients

Truly off the shelf

ECONOMY

Efficient and scalable manufacturing

Lower cost processes

FLEXIBILITY

Dynamically modulate cells without additional engineering

Directly address tumor heterogeneity within a patient and between patients

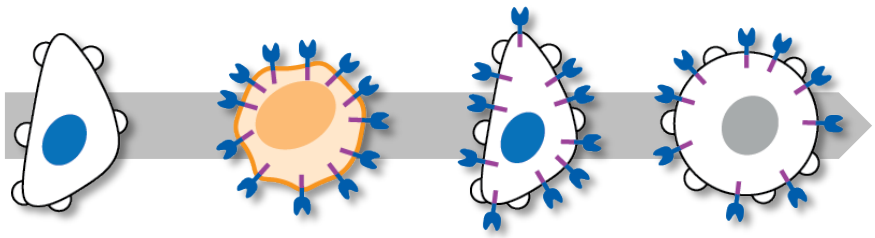
RELIABILITY

Standard product without variability

Single cell source

iPSC: Induced pluripotent stem cells

GENERATION OF FUNCTIONAL NK CELLS FROM UNIVERSAL DONOR CELL AND OPTIMIZATION OF *convertible*CAR FOR NK CELLS



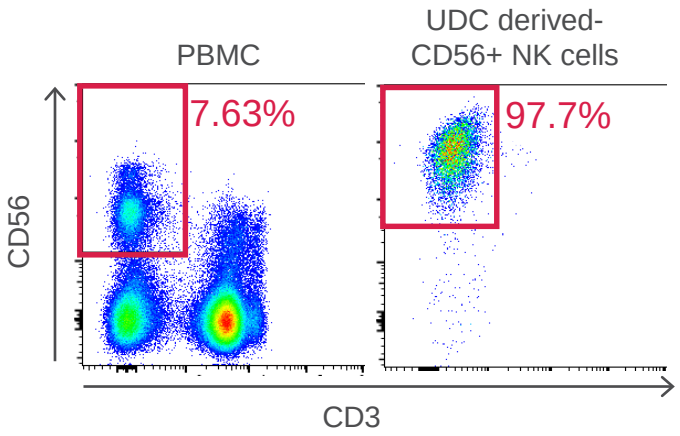
Universal Donor Cell (**UDC**)

Optimized *convertible*CAR (NK signaling)

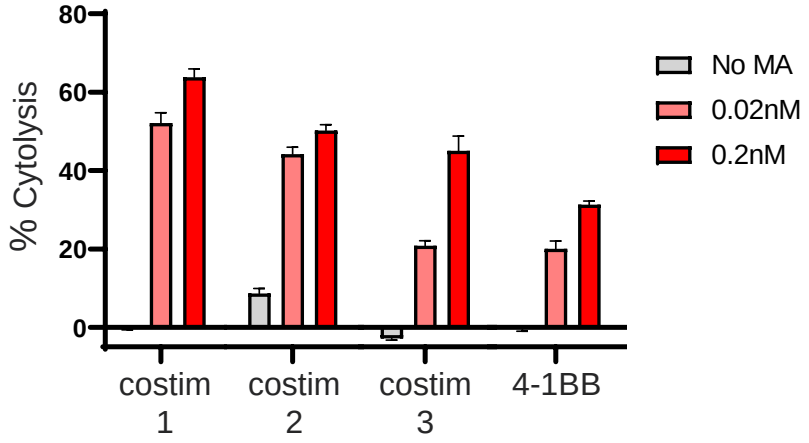
*convertible*CAR in UDC

Differentiated **universal CAR** on **UDC**

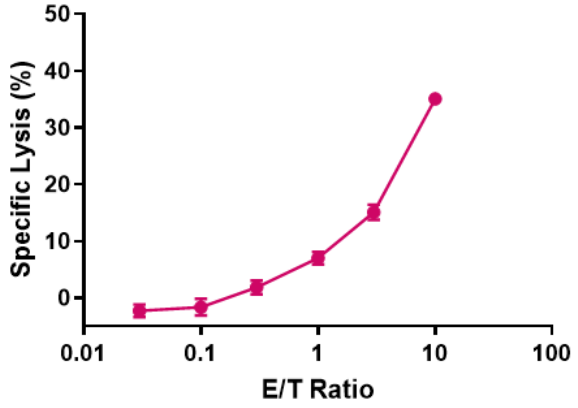
Generation of functional CD56+ NK cells from UDC



Optimization of CAR costimulatory domain with enhanced cytotoxicity in a NK cell line

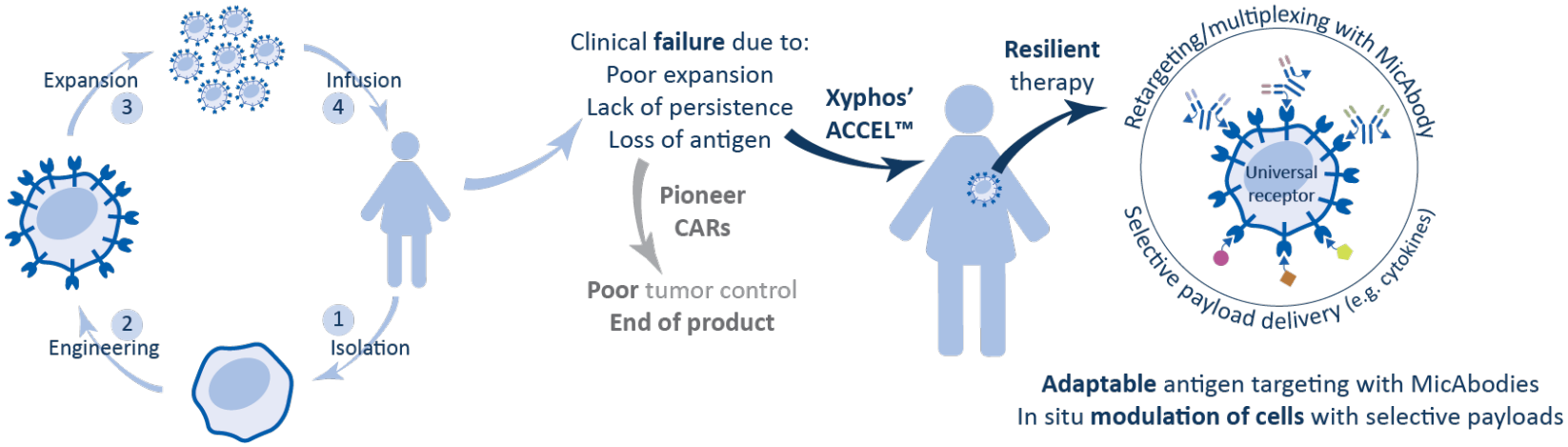


Natural Cytotoxicity (K562 cells)



NK: Natural killer, PBMC: Peripheral blood mononuclear cells

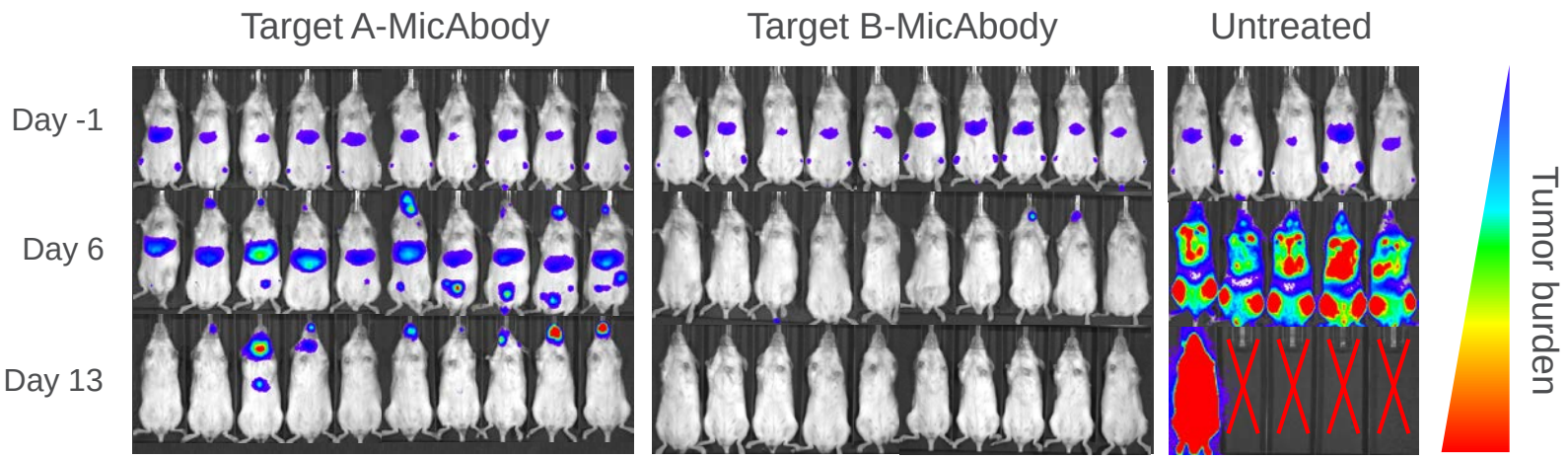
*convertible*CAR RESILIENCE ENHANCES TUMOR TARGETING



- Provides a **solution to directly address** tumor heterogeneity within a patient and between patients
- **Creates opportunities to dynamically modulate** cells without additional engineering to affect expansion, persistence, and tumor access

CAR: Chimeric antigen receptor

TARGETING DIFFERENT ANTIGENS WITH THE SAME *convertible*CAR CELLS



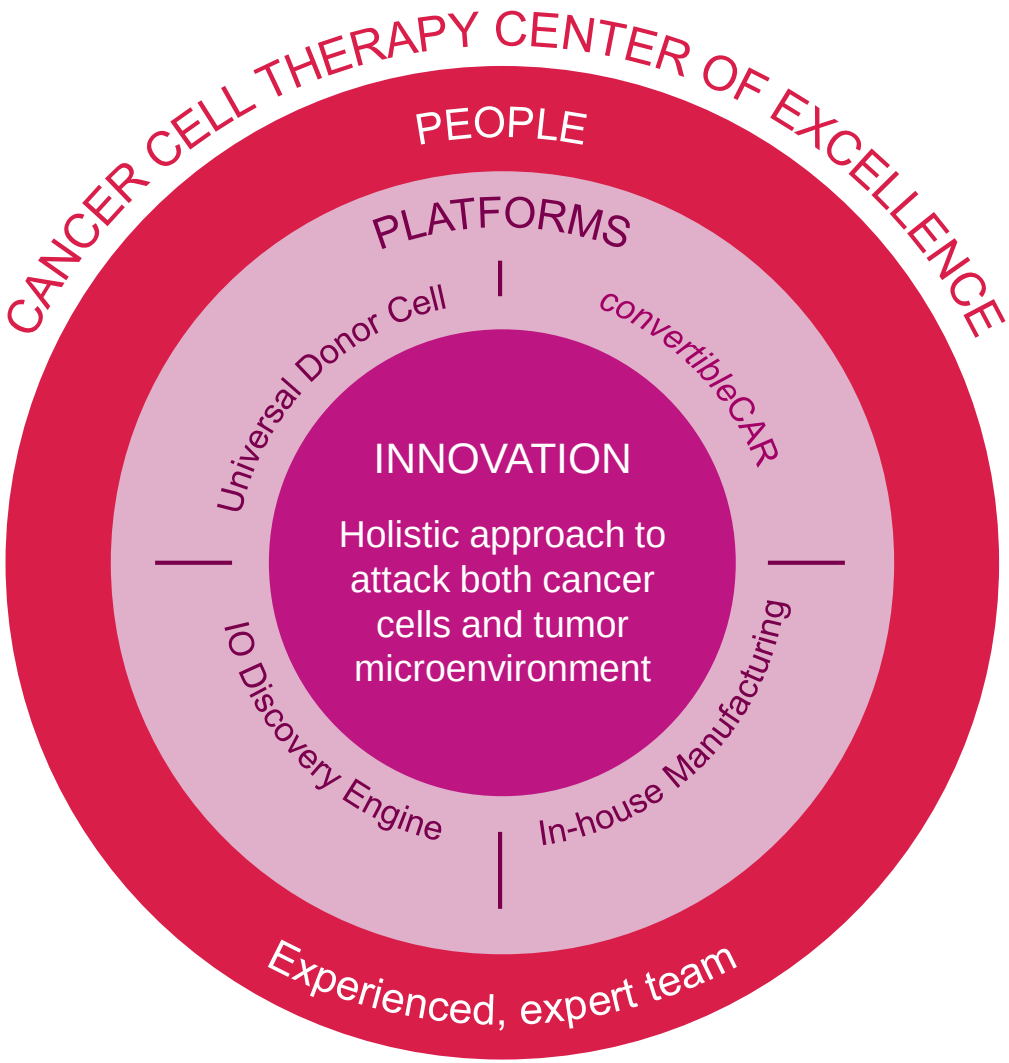
Disseminated Raji B cell leukemia; *convertible*CAR treatment initiated after 3 days; Q2Dx5 MicAbody dosing

Side-by-side demonstration of differential antigen targeting function with the **same** *convertible*CAR-T cells to treat Non-Hodgkin's Lymphoma

- Sets the stage for multiplex targeting to reduce relapse due to antigen loss in patients

CANCER CELL THERAPY: ADDITIONAL FOCUS THROUGH NEW CENTER OF EXCELLENCE

Center of Excellence will lead a holistic approach to developing novel allogeneic cancer cell therapy



Adaptimmune PARTNERS PARKER INSTITUTE for CANCER IMMUNOTHERAPY

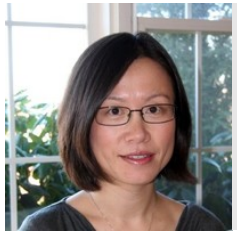
EXPERIENCED TEAM TO DRIVE CELL THERAPY R&D AND MANUFACTURING WITH DIVERSE ACADEMIC AND INDUSTRY BACKGROUND



DAVID MARTIN MD

CSO of Cell Therapy CoE

UCSF-HHMI, Genentech, Du-Pont Merck, Chiron, Xyphos



QUNLI XU PhD

Head Translational Science

Roche, Eisai, Verastem, Takeda, Forma



DAVID RUSSEL MD PhD

CSO Universal Cell

University of Washington



ANDREW KRIVOSHIK MD PhD

SVP Head of Oncology TA

Mayo Clinic, Duke Univ, AbbVie



KEITH BAHJAT PhD

Lead Scientist CoE

Providence Cancer Center, Medarex, BMS, Pfizer



CARLOS YURASZECK

Executive Director, GMP Operations, Astellas Institute of Regenerative Medicine

Celgene, Pfizer, Pharmacia, and Merck



TAKU YOSHIDA PhD

Head of IO Research

Eisai, Dana Farber Cancer Institute



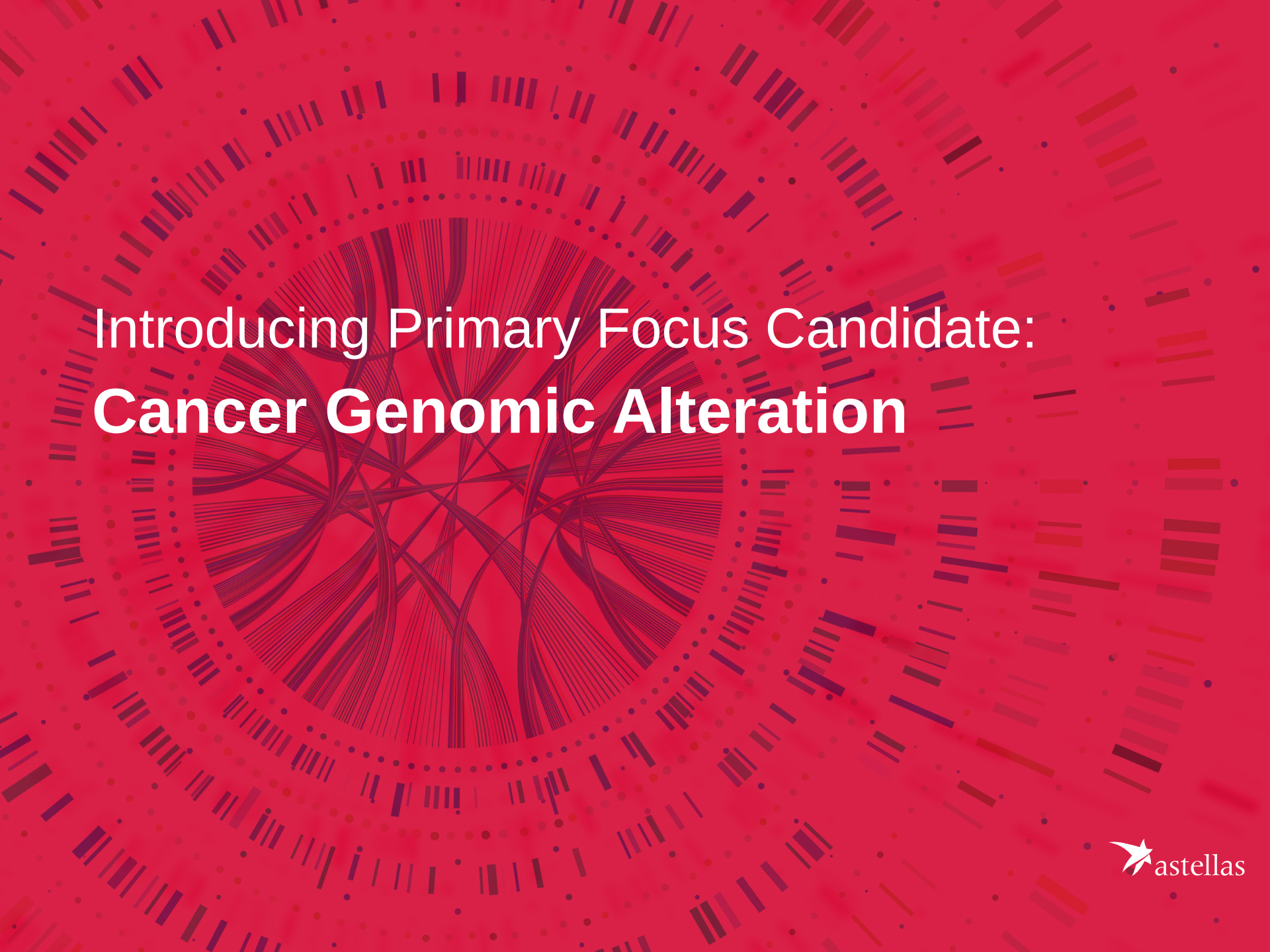
ALISON HAYLES

VP Regulatory Affairs, Oncology

Abbott Laboratories, Takeda

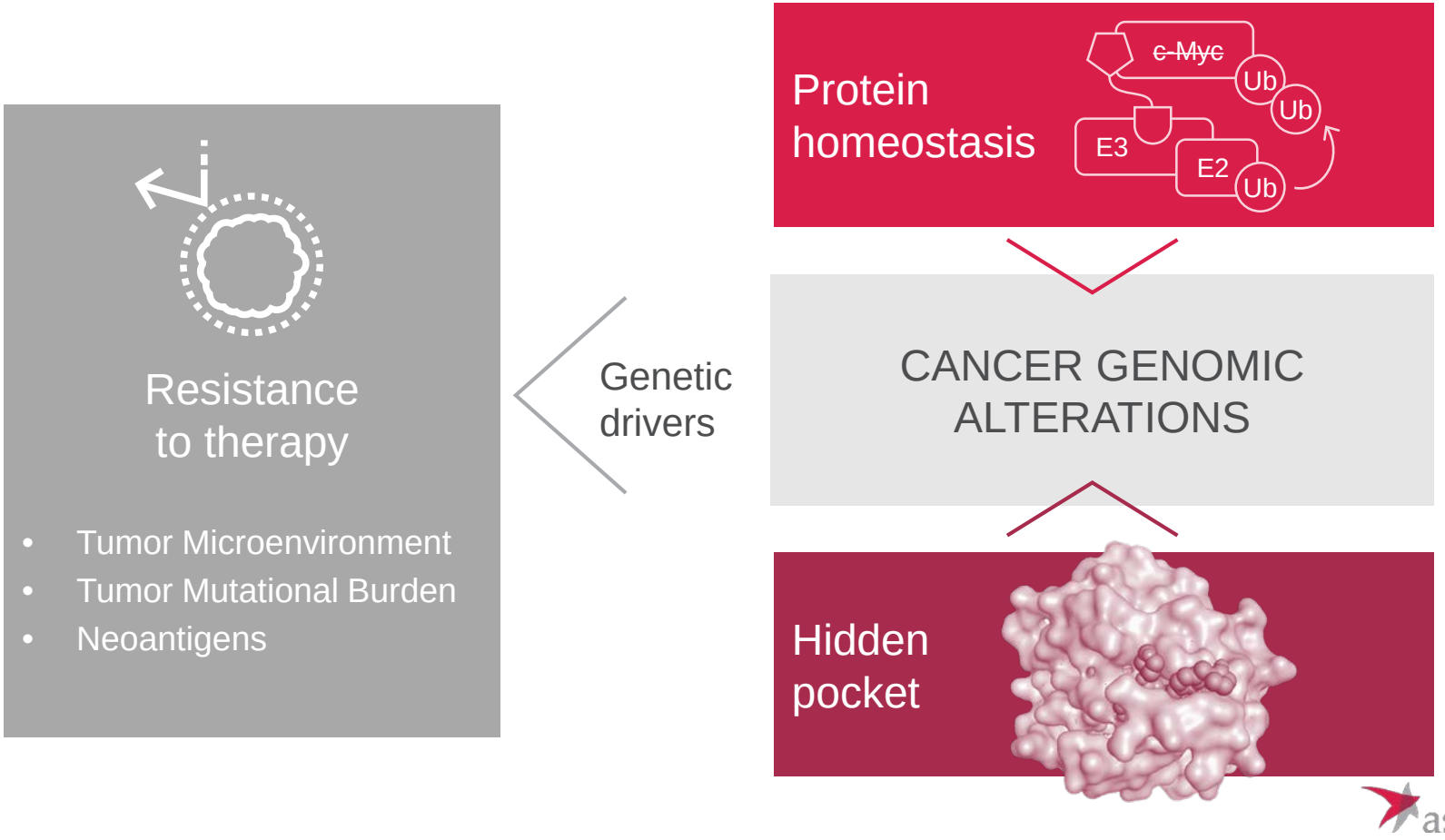
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CSO: Chief Scientific Officer, CoE: Center of Excellence, IO: Immuno-oncology, TA: Therapeutic area, GMP: Good Manufacturing Practice, (S)VP: (Senior) Vice President


Introducing Primary Focus Candidate:
Cancer Genomic Alteration
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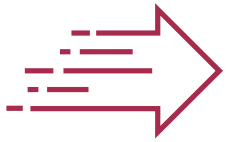
PRIMARY FOCUS CANDIDATE: EXTENDING RESEARCH TO CANCER GENOMIC ALTERATIONS

Established a Primary Focus Candidate to develop novel pipeline targeting Genomic Alterations to overcome resistance to standard cancer therapies



Ub: Ubiquinone, E2: Ubiquitin-conjugating enzyme, E3: Ubiquitin ligase

WHAT'S NEXT? KEY PF IO MILESTONES IN FY2021



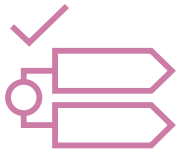
Pipeline

Continue to progress our key modality platforms and pipeline programs



Data Updates

Clinical data updates on ongoing Phase 1 studies



Clinical Initiation

Phase 1 study initiation

- ASP7517 and ASP0739 in advanced solid tumours

PF: Primary Focus, IO: Immuno-oncology

Primary Focus: **Mitochondria Biology**

Targeting mitochondrial function as an innovative new way of addressing diseases with high unmet needs



Itsuro Nagase, Ph.D.
Primary Focus Lead, Mitochondria Biology

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OFFERING POTENTIAL TO CREATE AN ENTIRELY NEW WAY OF TREATING DISEASES WITH HIGH UNMET MEDICAL NEEDS BY TARGETING MITOCHONDRIA

*Our mission is to become **the global leader** in **discovering**, **developing** and **bringing to market mitochondrial biology-based medicine** that provides clear value for patients, clinicians and healthcare systems*



Mitochondria are specialized structures in cells that have their own maternally inherited DNA (mtDNA)

- Mitochondria are present in **almost all human cell types** and play essential roles in energy production and in processes such as metabolism and cell signalling
- Mitochondrial dysfunction is associated with diseases of the kidneys, liver, muscles, central nervous system, eyes and ears [1]
- Many of these diseases have **significant unmet medical needs** and **few treatment options**

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1: Suomalainen A. & Battersby B.J. Nature Reviews Molecular Cell Biology. 2018:19;77-92.
DNA: Deoxyribonucleic acid

STRATEGIC APPROACH

Allocating significant, sustained investment to mitochondria biology-based therapy development

FOCUS

- Mitochondrial biology, our unique and top-notch capability
- Diseases impacted by mitochondrial dysfunction

ENRICH

- Disease identification through deep understanding of the link between mitochondrial biology and disease pathophysiology
- New leads and innovative target molecules identified through phenotypic screening platform
- Faster understanding of molecules' potential through selection of scientifically relevant indications for PoC/PoP

EXPAND :

- Expansion into commercially viable indications after PoC
- Addition of mitochondrial cell therapy to modality approaches

Our early stage assets include candidates for:



Mitochondrial stress response
Mitochondrial stress signals are a key factor in cell damage and inflammation



NAD+ enhancement and increased mitochondrial membrane potential
Many clinical manifestations of mitochondrial diseases stem from the central role of bioenergetics in the cell



Gene regulation & mitochondrial biogenesis
Genetic regulatory factors are essential for mitochondrial biogenesis and function, playing a key role in cellular energy metabolism



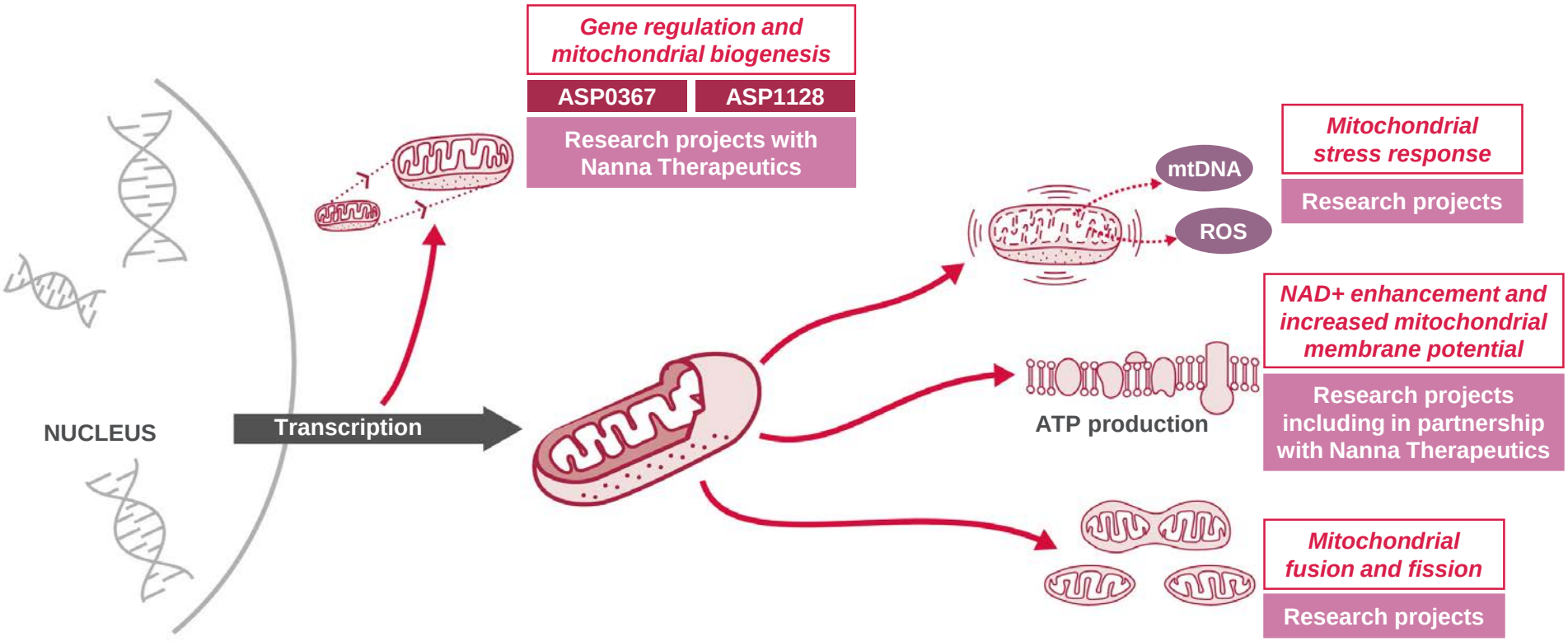
Mitochondrial fusion and fission
Fusion and fission play a critical role in maintaining normal mitochondrial function

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PoC: Proof of concept, PoP: Proof of principle, NAD+: Nicotinamide adenine dinucleotide

PIPELINE (1/2)

Build Primary Focus - Mitochondria Biology portfolio with various scientific approaches for multiple mitochondrial functions



mtDNA: Mitochondrial deoxyribonucleic acid, ROS: Reactive oxygen species, ATP: Adenosine triphosphate, NAD+: Nicotinamide adenine dinucleotide

PIPELINE (2/2)

Steady progress toward obtaining PoC / entering into the pivotal phase in PPARδ modulator programs

Compound	Modality	Mechanism	Target indication	Current phase	Origin
ASP1128	Small molecule (i.v. form)	PPARδ modulator	Cardiac surgery associated acute kidney injury	Phase 2 (Phase 2a PoC study FSFT in Nov 2019)	mitobridge*
ASP0367	Small molecule (oral form)	PPARδ modulator	Primary mitochondrial myopathy	Phase 2 (To start Phase 2/3 study in 1Q 2021)	mitobridge*
			Duchenne muscular dystrophy	Phase 1 (To start Phase 1b study in patients in early 2021)	
(Not disclosed)	Small molecule	(Not disclosed)	(Not disclosed)	Discovery	mitobridge*
(Not disclosed)	Small molecule	(Not disclosed)	(Not disclosed)	Discovery	NANNA THERAPEUTICS*

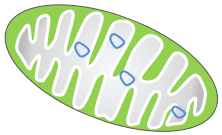
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* Acquired (current programs classified as 'in-house')
i.v.: Intravenous, PPARδ: Peroxisome proliferator-activated receptor delta, PoC: Proof of concept, FSFT: First subject first treatment

NANNA THERAPEUTICS

New approach to identify lead compounds / innovative target molecules that are directly associated with mitochondrial dysfunction



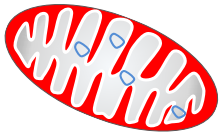


Focused Cambridge, UK-Based Team

Heart of European Biotech

- Unique medicinal chemistry for targeting mitochondrial biology
- Disease-relevant 'phenotypic' screens (patient-derived)
- World-leading mitochondrial scientists & medicine hunters
- Extensive world-class research & clinical network
- Connected to all major mitochondria patient advocacy groups





Access to -

All Primary Mitochondrial Myopathies
- Pediatric
- Adult

Secondary Mitochondrial Diseases
- Spinal muscular atrophy
- Duchene muscular dystrophy
- Charcot-Marie-Tooth disease
- Amyotrophic lateral sclerosis
- Friedreich's ataxia

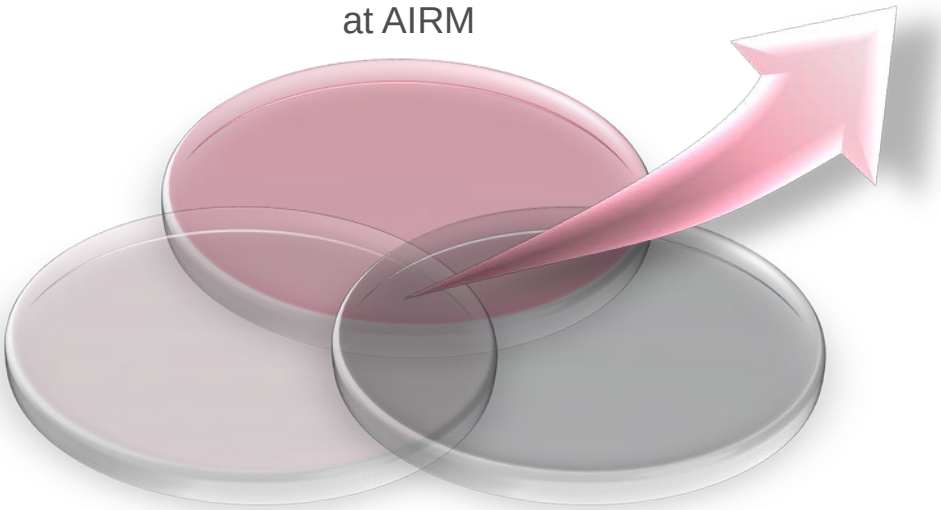
Rare Disease (Other)
- Life threatening viruses
- Co-treatments in oncology

Major Disease Areas
- Parkinson's disease
- Oncology

MITOCHONDRIAL CELL THERAPY APPROACH

Combining Astellas' unique capabilities and applying them to creating revolutionary mitochondrial cell therapy

Cell therapy platform at AIRM



Universal-donor cell technology at Universal Cells

Scientific knowledge on mitochondrial biology at mitobridge NANNA THERAPEUTICS

New cell therapy approach focusing on mitochondrial transfer

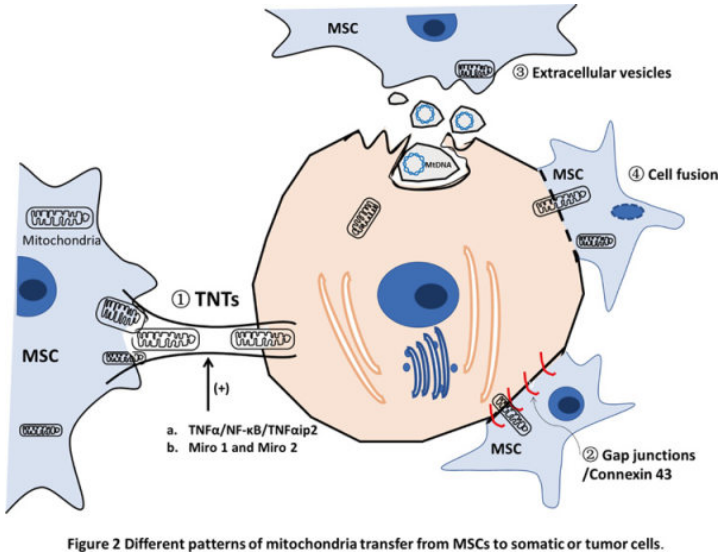


Figure 2 Different patterns of mitochondria transfer from MSCs to somatic or tumor cells.

Bioscience Reports (2019) **39** BSR20182417

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Primary Focus Candidate: **Immune Homeostasis**

Developing potentially curative therapies for patients with immune-related diseases



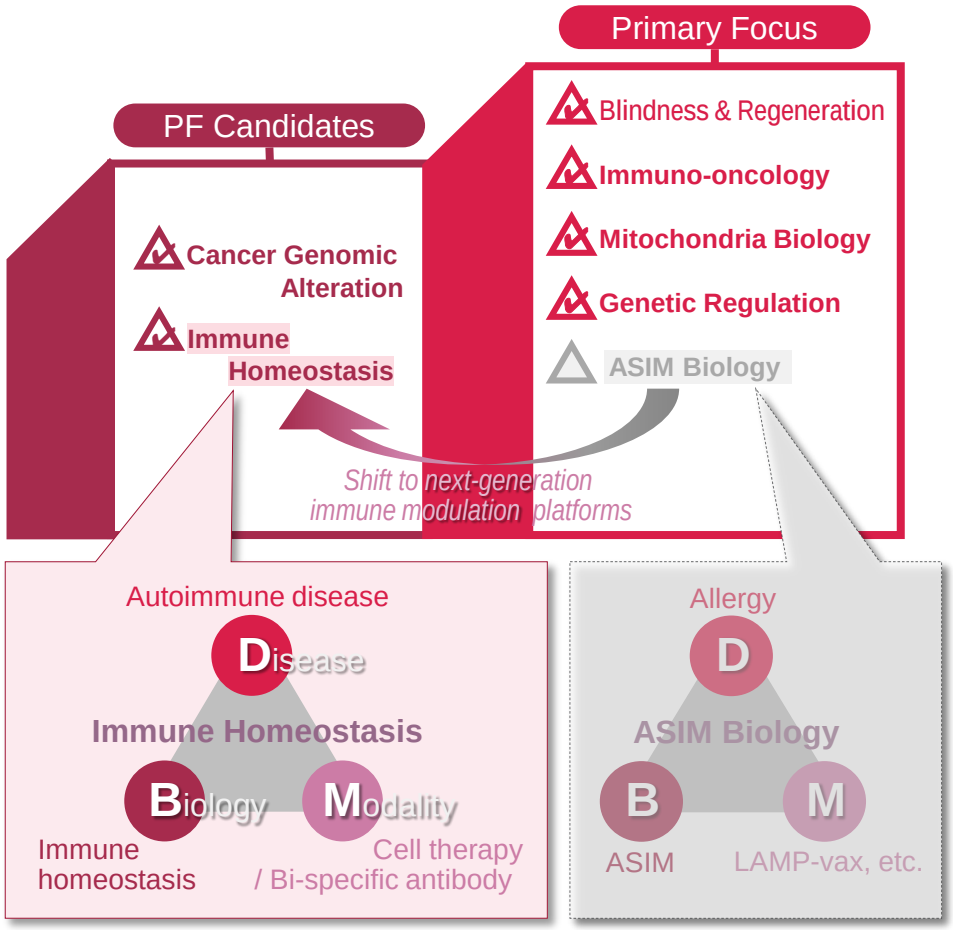
Shigetada Furukawa, Ph.D.
Primary Focus Lead, Immune Homeostasis

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COMPLETED PRIMARY FOCUS “ASIM BIOLOGY” AND SHIFT TO NEXT-GENERATION RESEARCH

- LAMP-vax, the key ASIM platform, has reached a stage of clinical validation, after completion of discovery research
  - ✓ ASP0892 for peanut allergy: Phase 1
  - ✓ ASP2390 for house dust mite-induced allergic rhinitis: Phase 1
- Exploration of next-generation immune modulation technologies led to identification of platforms with modalities distinct from ASIM
- To deliver innovative therapeutics, new in-house research (cell therapy) and research collaboration (Pandion Therapeutics) have been started

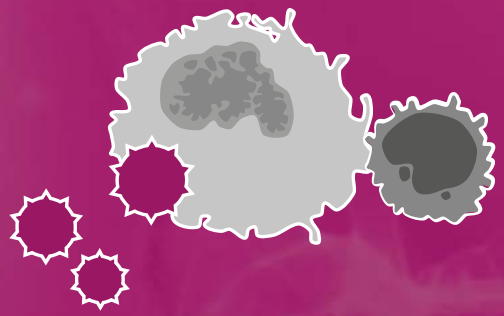
The next generation research has been designated as a PF Candidate “***Immune Homeostasis***”



ASIM: Antigen-specific immune modulation, PF: Primary Focus

SPECIFICALLY SUPPRESSING DISEASE-RELATED IMMUNE RESPONSE WITHOUT IMPACTING THE BODY'S OVERALL IMMUNE SYSTEM

*Our mission is to **deliver safe and potentially curative therapies** for patients suffering from immune-related diseases*



Current treatments for autoimmune diseases include general immunosuppressants and do not specifically target autoreactive immune cells

- Broad immune suppression can lead to debilitating and sometimes life-threatening side effects and increase susceptibility to infection
- Immune homeostasis is the regulatory mechanism maintaining the balance between immunogenicity to pathogens and immune tolerance to self
- Our aim is to develop innovative therapeutics to restore immune system equilibrium in patients whose immune system has become dysregulated due to autoimmune disease

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STRATEGIC APPROACH

We are establishing competitive and innovative modalities that can restore immune homeostasis by leveraging our Immunology R&D experience and cell therapy capabilities

FOCUS Focusing on the development of human hemangioblast-derived mesenchymal stem cells which have the potential to be recruited to the site of inflammation and stop the autoreactive inflammatory cascade

ENRICH Leveraging our regenerative medicine and gene-editing expertise at AIRM and Universal Cells to develop novel immunoregulatory cell therapies

EXPAND Engaging continually with the scientific community to expand our pipeline through partnering, collaboration and acquisition (e.g. collaboration with Pandion)

Our versatile platform technologies include:



Pluripotent stem cell derived immunoregulatory cell therapy for autoimmune diseases



Gene editing technology to enhance the immunomodulatory activity and increase disease specificity



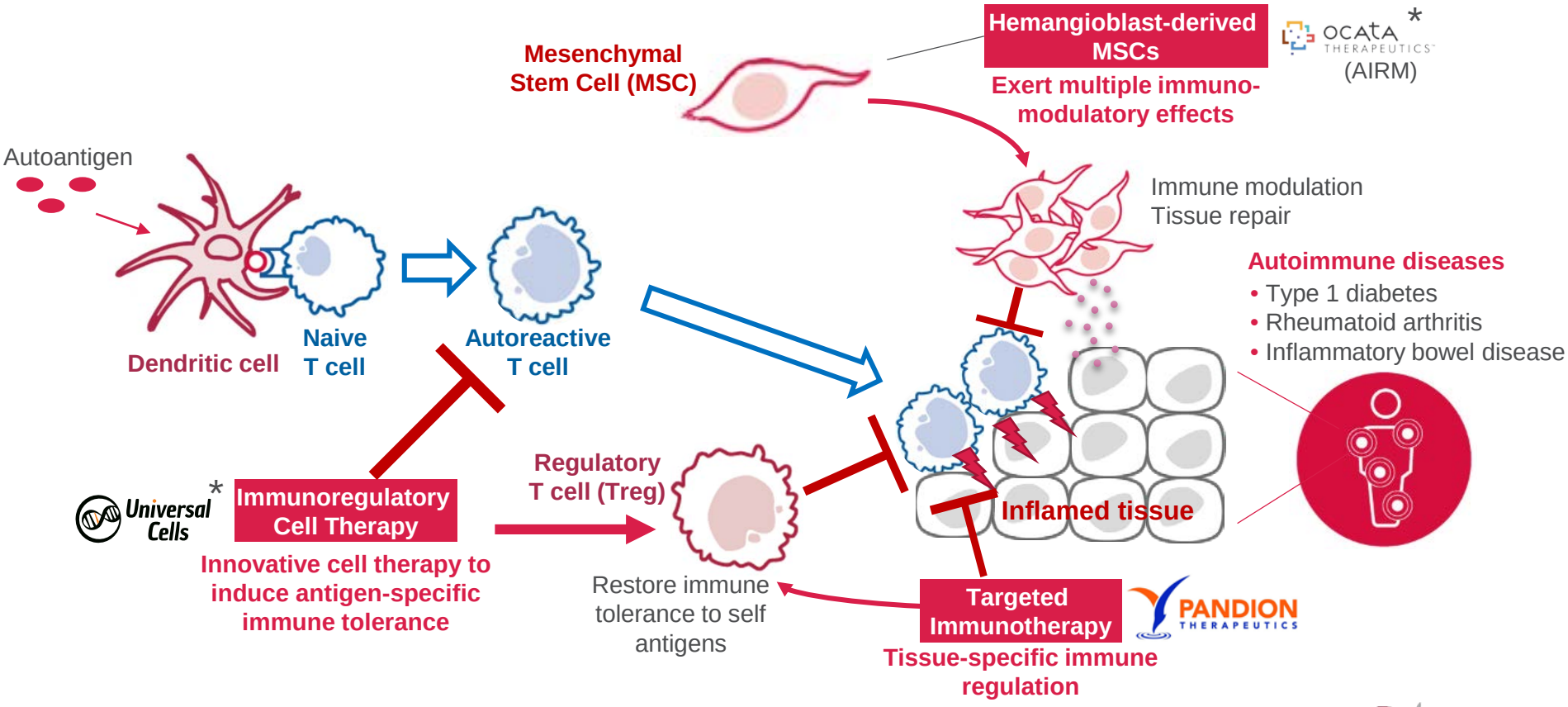
Innovative technology that can induce endogenous immunoregulatory cells, e.g. tissue-specific immune regulation by targeted immunotherapy

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R&D: Research & Development, AIRM: Astellas Institute for Regenerative Medicine

MODALITY AND MECHANISM OF ACTION OF CURRENT PROGRAMS

We are exploring innovative technologies and modalities that can eliminate disease-specific immune response and induce immune tolerance



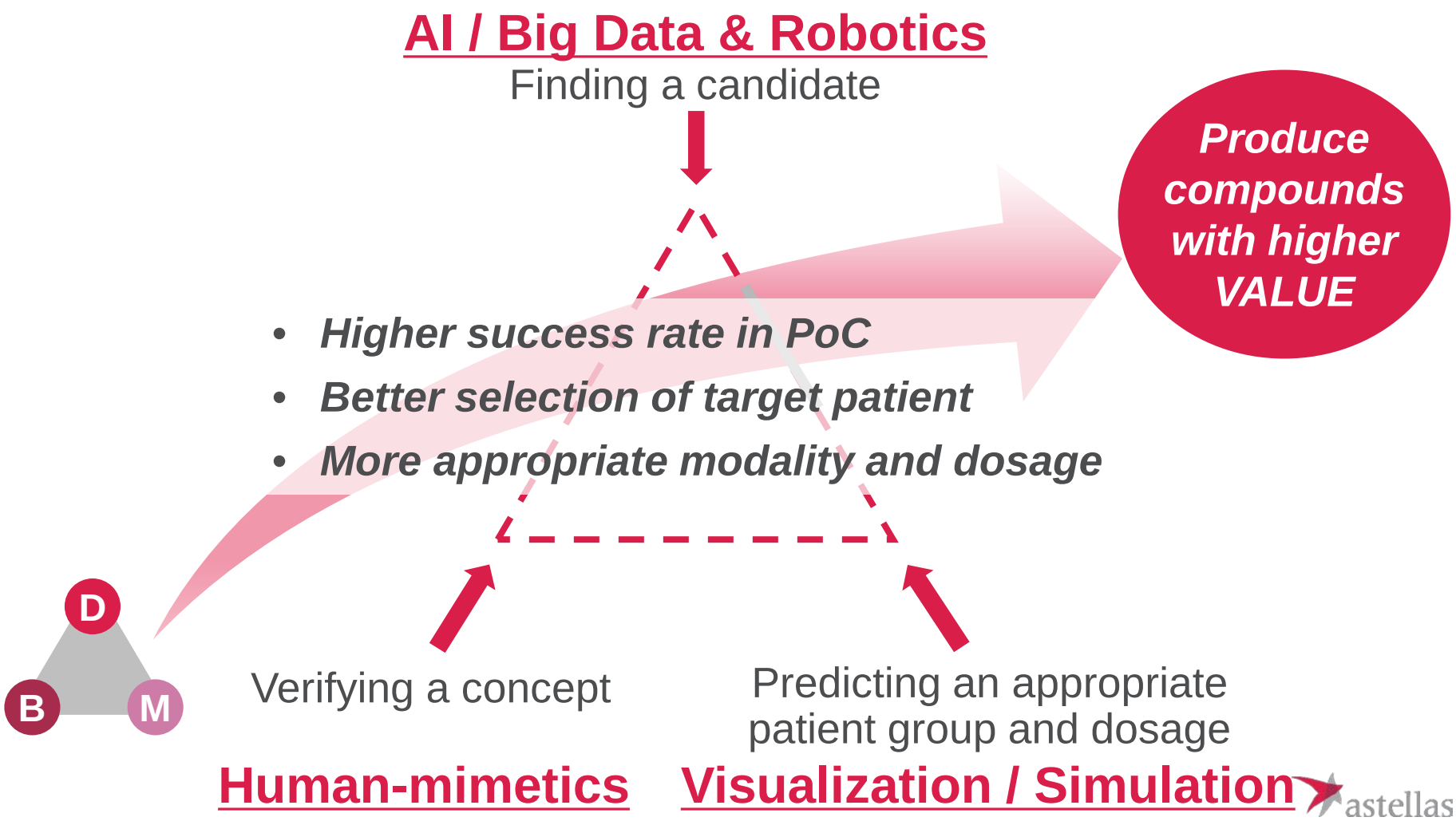
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* Acquired (current programs classified as 'in-house')
AIRM: Astellas Institute for Regenerative Medicine

INNOVATIVE TECHNOLOGY PLATFORMS FOR DRUG DISCOVERY & RESEARCH TO SUPPORT FOCUS AREA APPROACH

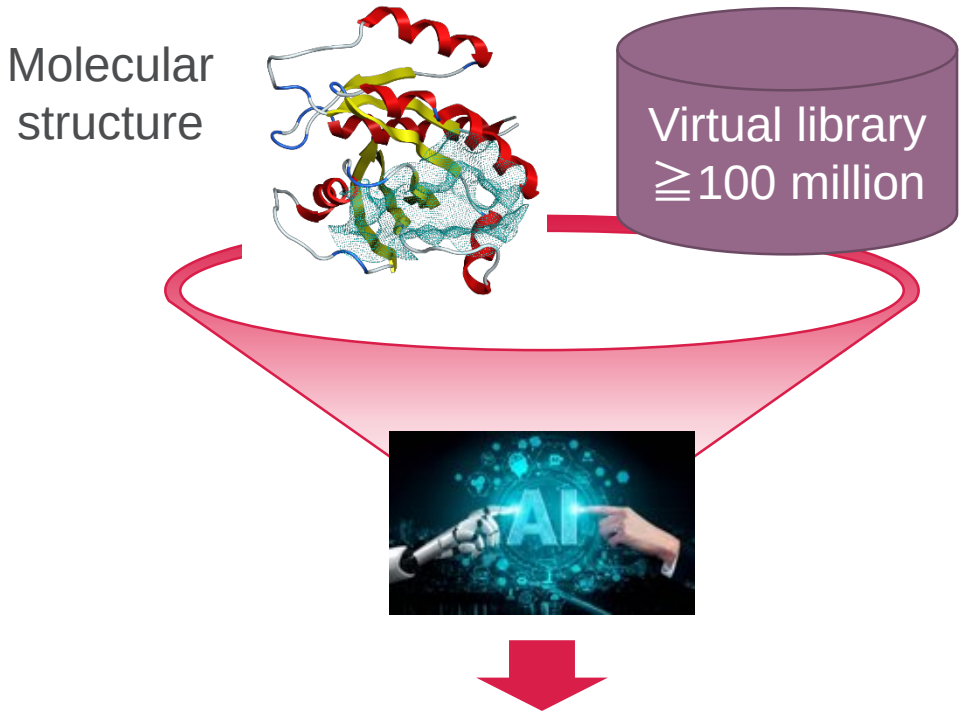
Kenji Yasukawa, Ph.D.
President and Chief Executive Officer

CREATING BREAKTHROUGHS IN DRUG DISCOVERY THROUGH SYNERGISTIC USE OF KEY METHODOLOGIES AND TECHNOLOGIES



AI: Artificial intelligence, PoC: Proof of concept

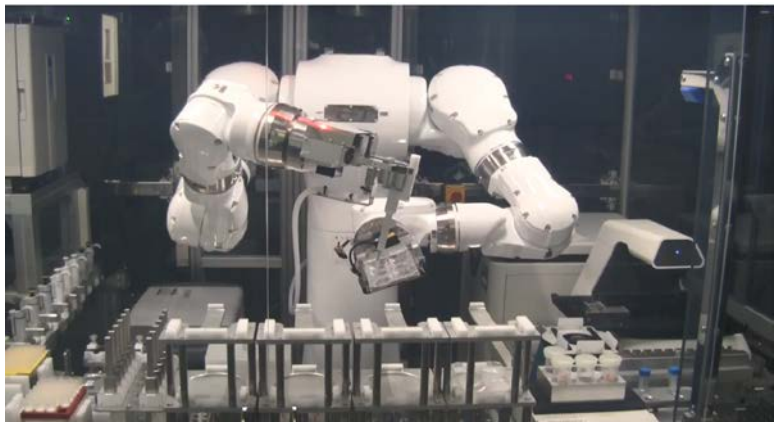
IN SILICO SCREENING WITH AI AND MACHINE LEARNING



Hit identification from vast virtual library

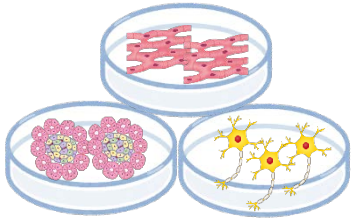
Conventional method: 300k chemical library that has not cover various chemical spaces

PHYSIOLOGICALLY RELEVANT ASSAY WITH ROBOTICS



Maholo

Perform complicated /long-term processes exactly the same every time



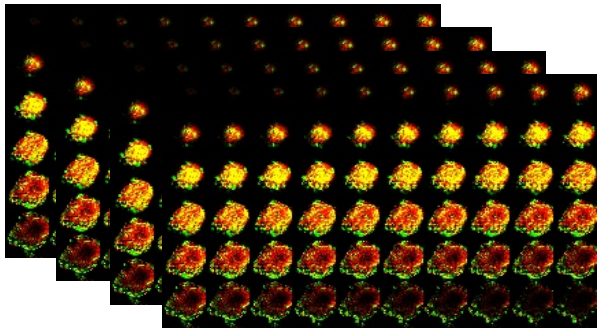
Complex system reflecting patho-physiology



Screening station

Obtain huge image data from vast amounts of samples

Conventional method:
Simple model that cannot evaluate complex cellular processes



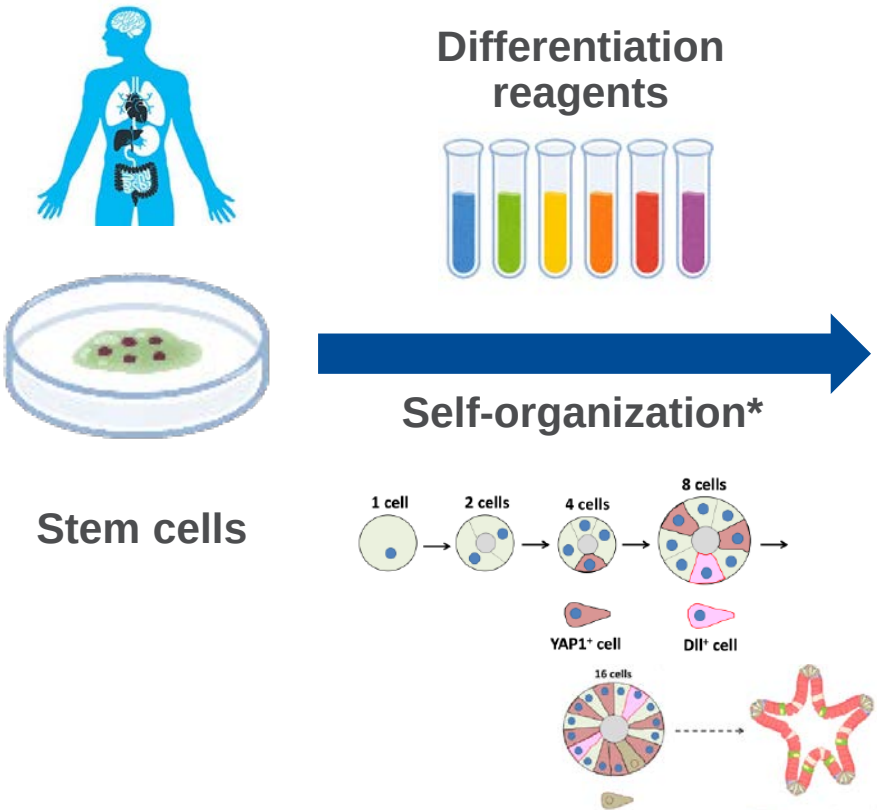
Images from more time points

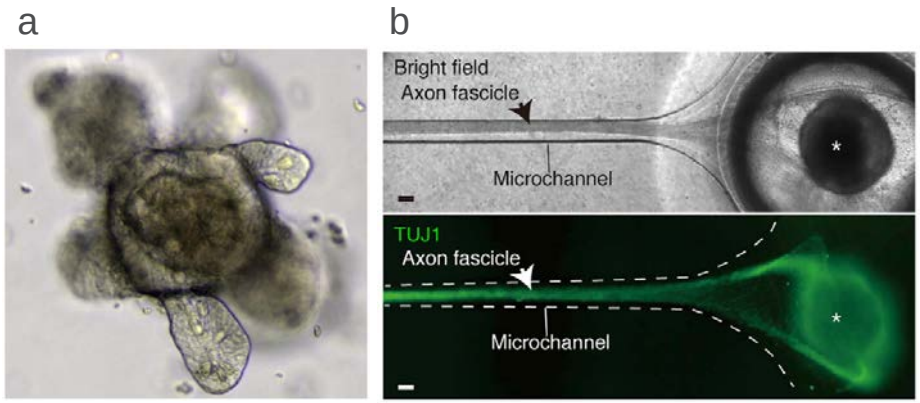
Hit identification considering complex mechanism

AI: Artificial intelligence

ORGANOID ALLOWS TO DETECT BIOLOGICAL INTERACTION BETWEEN HUMAN AND MEDICINES

Three dimensional organ-like structures derived from stem cells





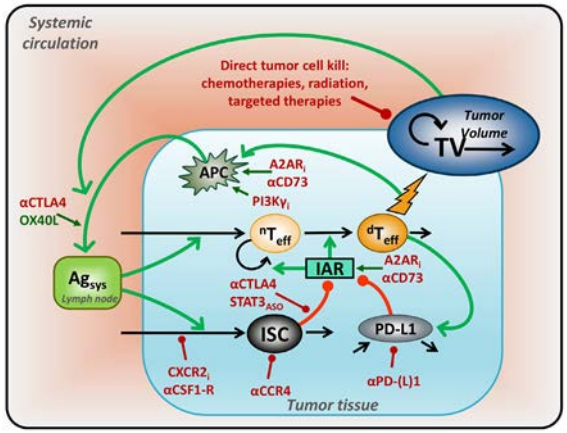
Organoids
(digestive tract, nerve)

a : PLoS Biol. 2015 6;13(5):e1002149. b : Stem Cell Reports 2017 14;9(5):1441-1449.
* Modified from Int. J. Mol. Sci. 2020, 21, 2032

QSP MODEL ENABLES US TO PREDICT VARIOUS CLINICAL OUTCOMES

QSP (Quantitative Systems Pharmacology)

Mathematical model describing interaction between biological system and drug(s)



CPT Pharmacometrics Syst. Pharmacol. (2019) 8, 380–395

- Can incorporate various mechanism of actions (MoA)
- Can describe biological inter individual differences in healthy/disease states

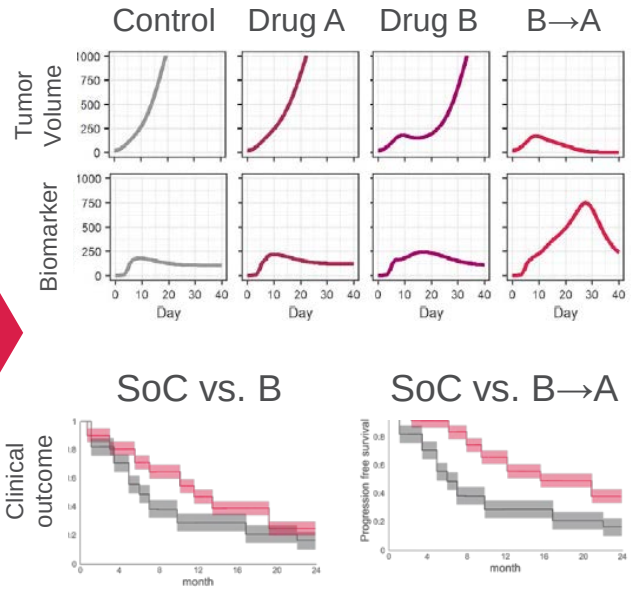
Virtual clinical trial (Computer simulation)

Generating virtual patients with various background



Simulating of various combination therapies / different regimens

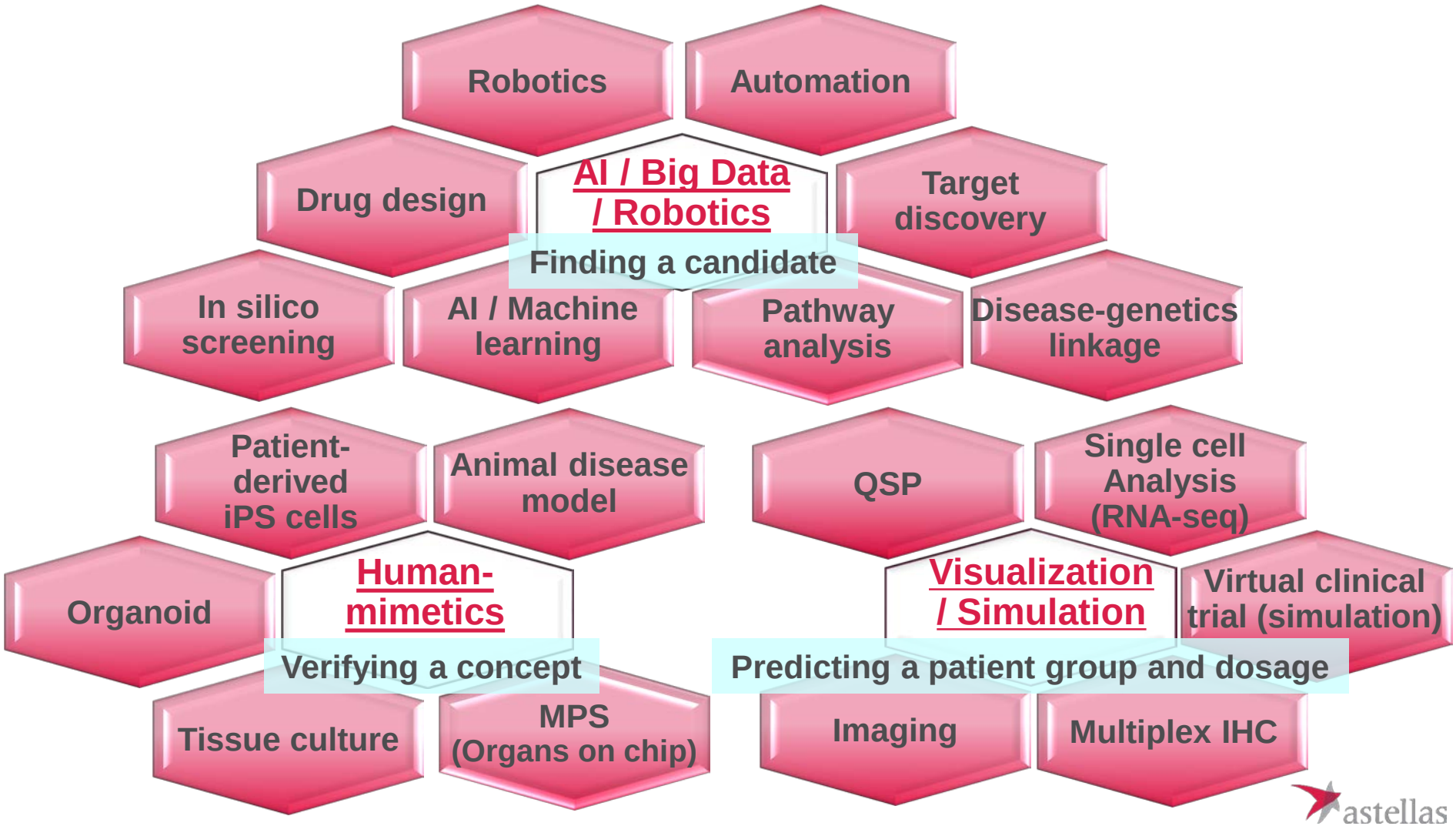
Prediction of biological response and clinical outcome



Can predict outcomes in various patient subpopulations and combination effect of drugs with different MoA

SoC: Standard of care

CREATING BREAKTHROUGHS IN DRUG DISCOVERY THROUGH SYNERGISTIC USE OF KEY METHODOLOGIES AND TECHNOLOGIES



AI: Artificial intelligence, iPS: Induced pluripotent stem, QSP: Quantitative systems pharmacology, RNA: Ribonucleic acid, MPS: Micro physiological system, IHC: Immunohistochemistry


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