R&D Meeting

February 24, 2023

ONO PHARMACEUTICAL CO.,LTD.

Cautionary Notes

Forecasts and other forward-looking statements included in this document are based on information currently available and certain assumptions that the Company deems reasonable.
Actual performance and other results may differ significantly due to various factors. Such factors include, but are not limited to:

- ***(i) failures in new product development***
- ***(ii) changes in general economic conditions due to reform of medical insurance system***
- ***(iii) failures in obtaining the expected results due to effects of competing products or generic drugs***
- ***(iv) infringements of the Company's intellectual property rights by third parties***
- ***(v) stagnation of product supply from the delay in production due to natural disasters, fires and so on***
- ***(vi) onset of new side effect of post-licensure medical product***
- ***and, (vii) currency exchange rate fluctuations and interest rate trend.***

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

Agenda

Research and Development Strategy of ONO

President, Representative Director, and Chief Executive Officer

Gyo Sagara

Drug Discovery Strategy & Alliance Updates

Senior Executive Officer, Executive Director of Discovery and Research

Toichi Takino

Itolizumab (Anti-CD6 antibody)

Executive Officer, Executive Director of Clinical Development

Kiyoaki Idemitsu

Q&A

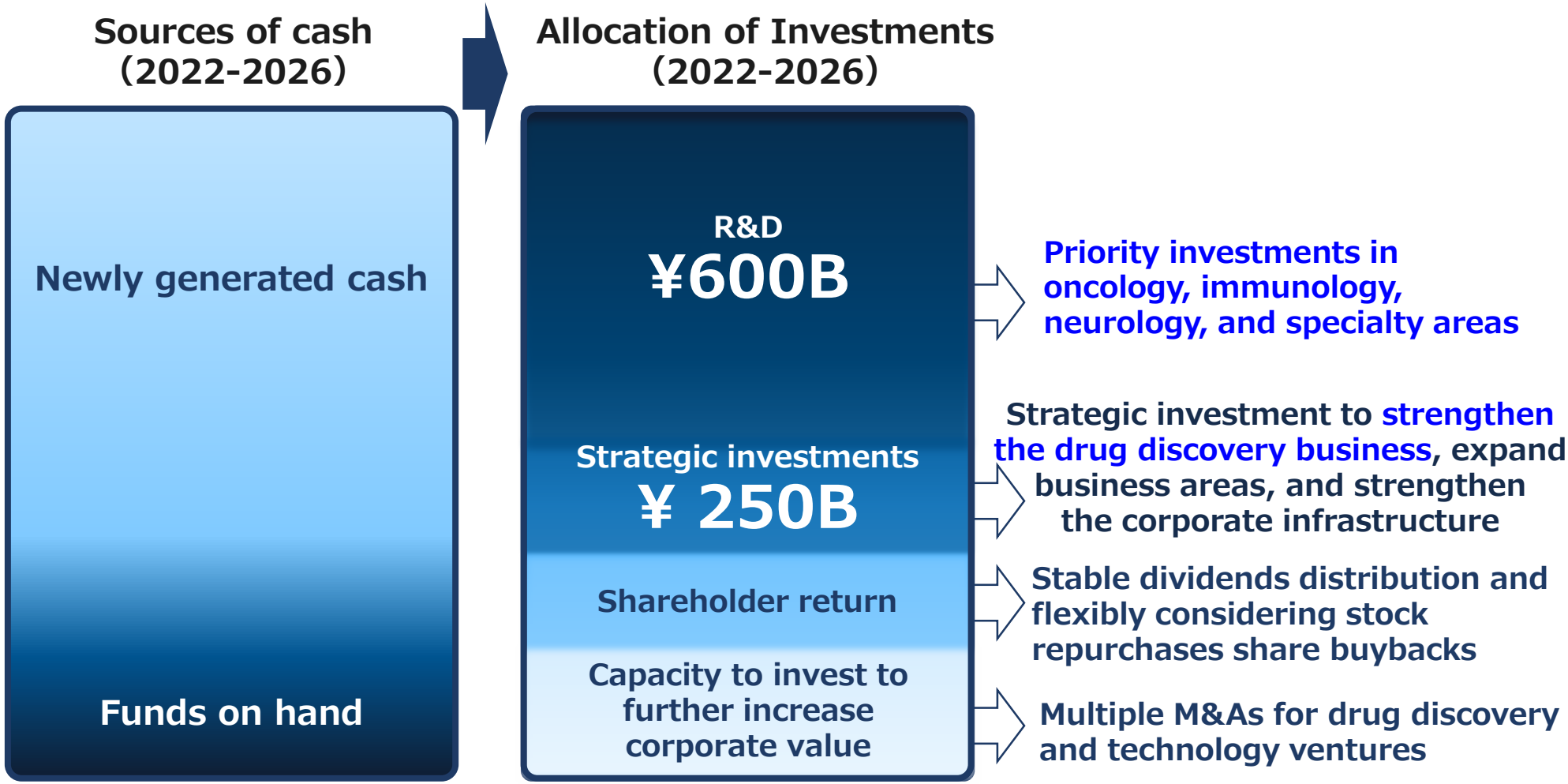
Research and Development Strategy of ONO

President, Representative Director, and Chief Executive Officer

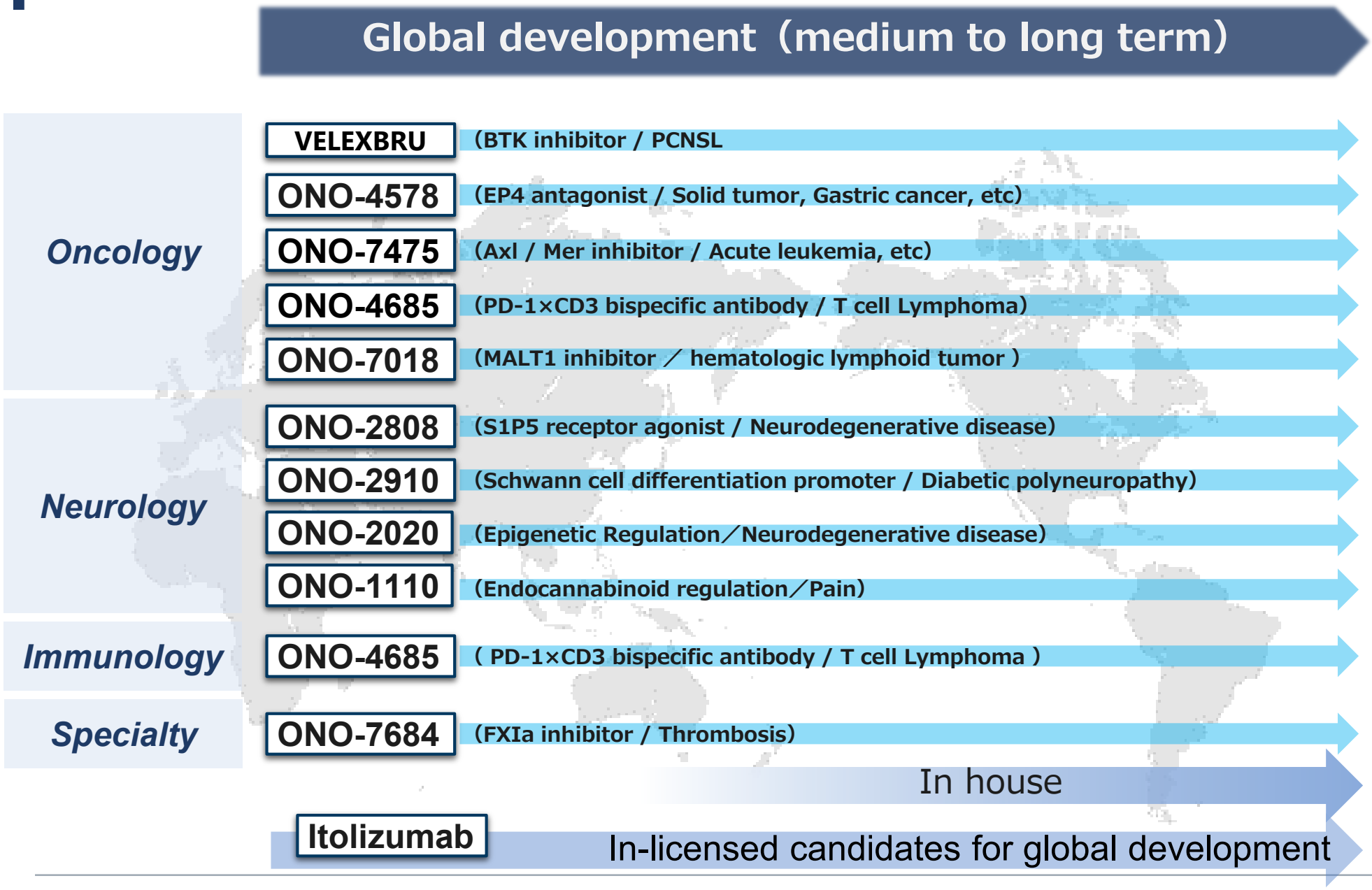
Gyo Sagara

Investment strategy over the next 5 years

Aggressive R&D investment　to overcome patent cliff and further growth



Global pipeline expansion



Drug Discovery Strategy & Alliance Updates

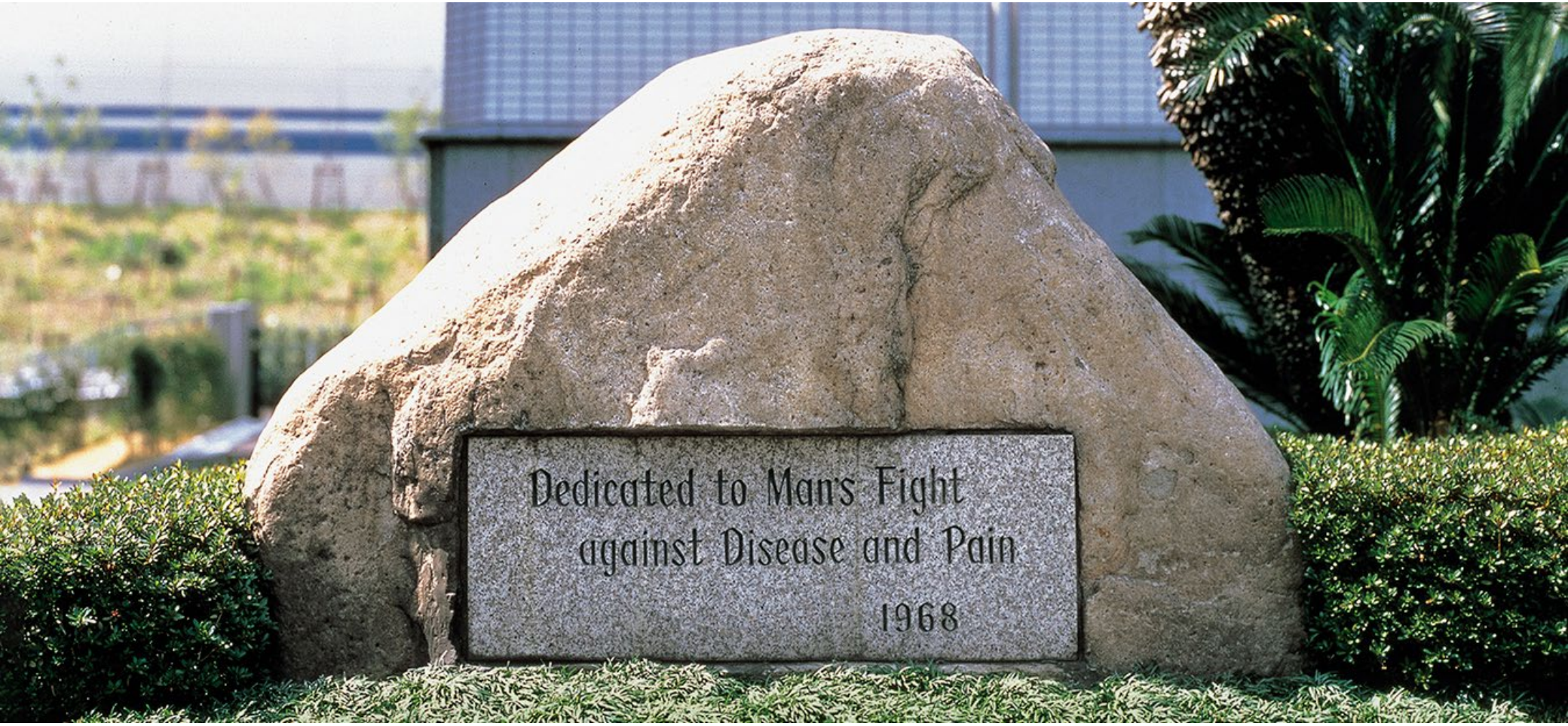
Senior Executive Officer/Executive Director

Discovery & Research

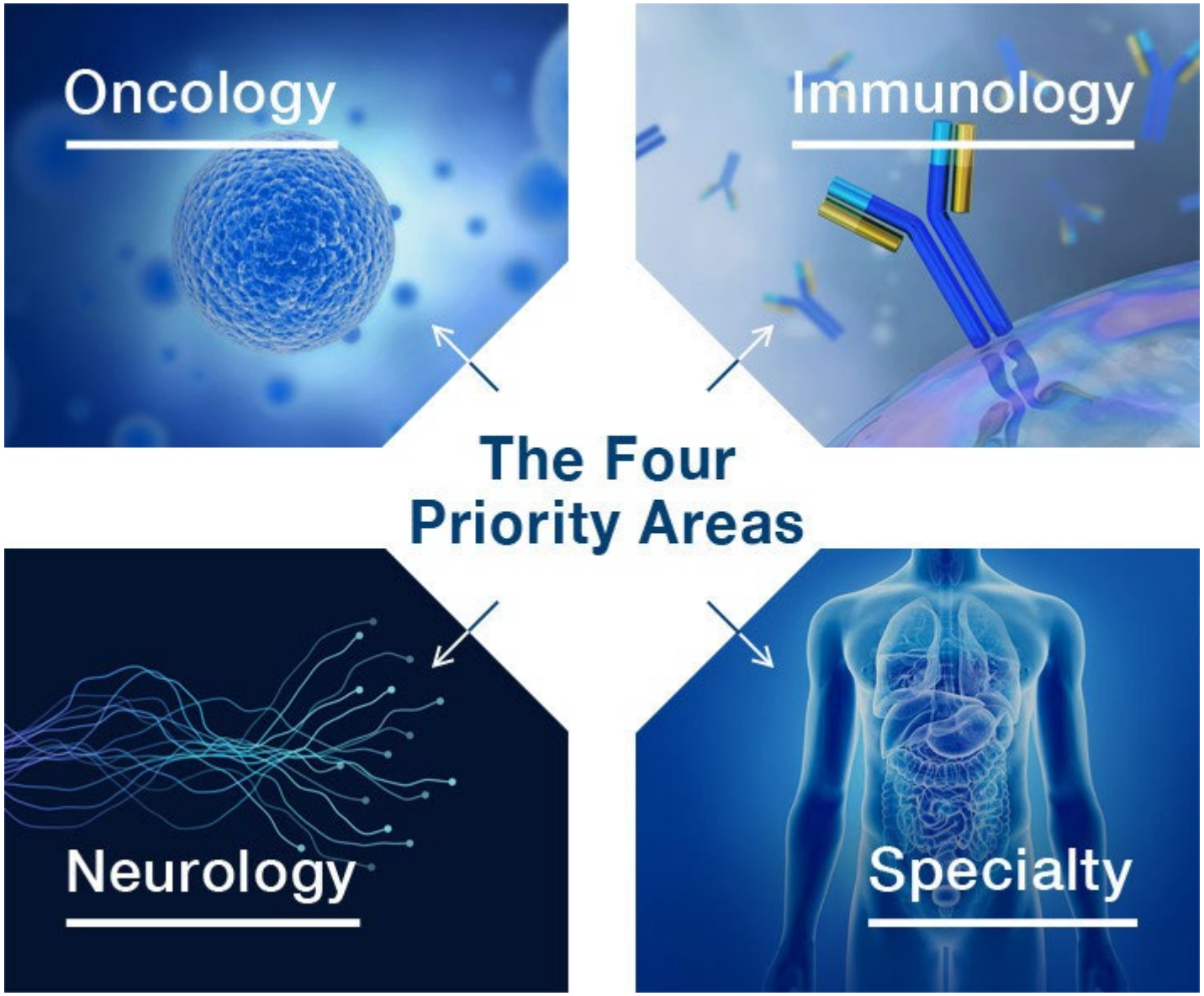
Toichi Takino

Corporate Philosophy

” Dedicated to the Fight against Disease and Pain”

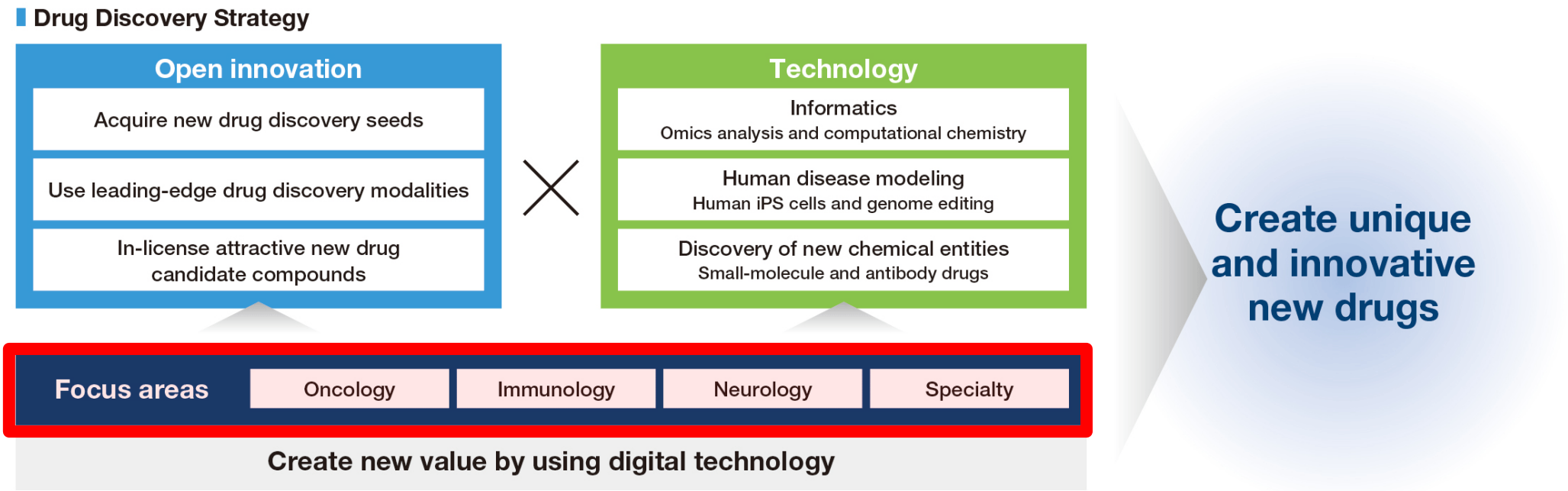


Focused Areas of Drug Discovery Research



Drug Discovery Strategy

「Open Innovation」×「Technology」
allows us create unique & innovative new drugs



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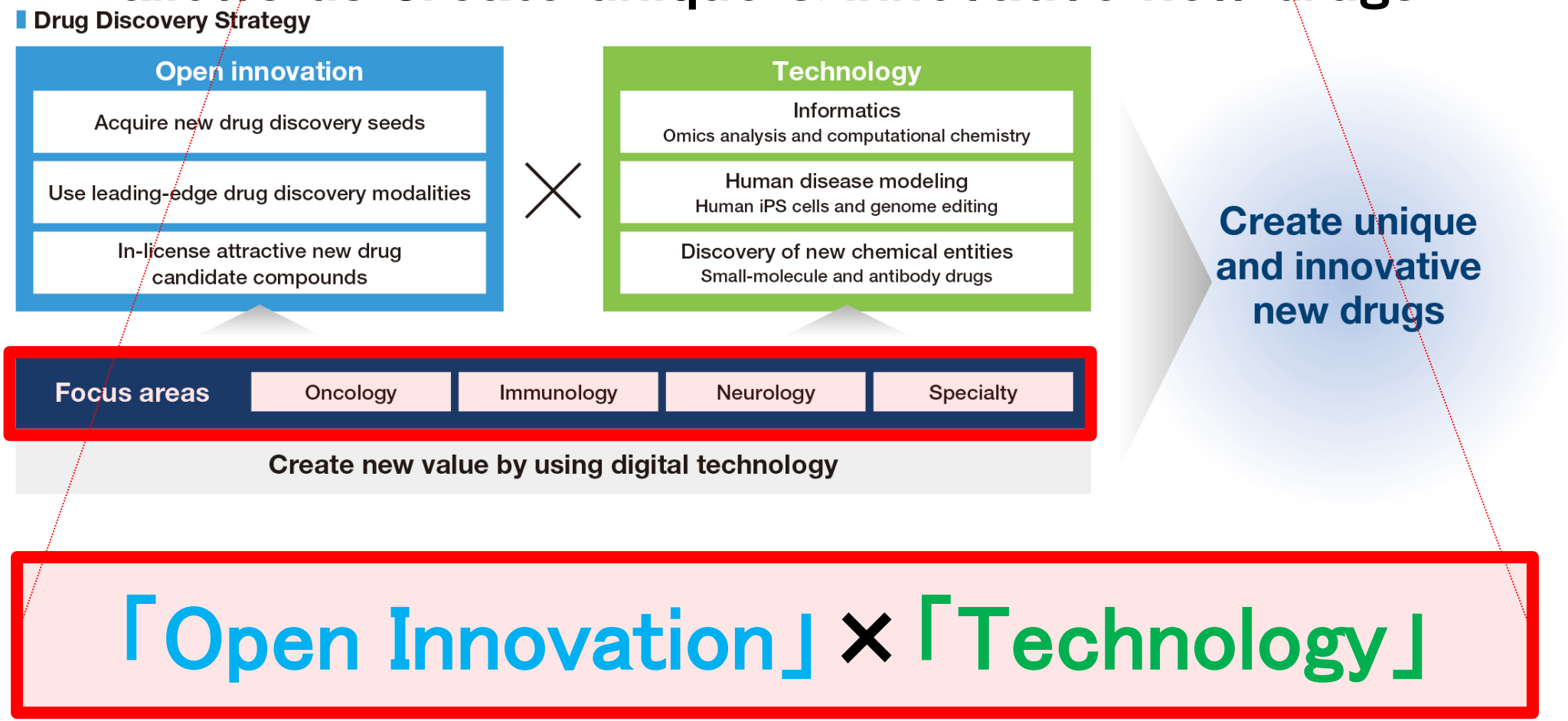

「Open Innovation」×「Technology」

Recent Updates of Discovery Alliances (2021～)

2021

月	提携先
Feb	Lab Central / MBC biolabs
Mar	PeptiDream
Mar	UCDDC UNIVERSITY OF CALIFORNIA DRUG DISCOVERY CONSORTIUM
Aug	healx
Aug	MiraBiologics
Dec	Varderbilt Univ.

2022年

月	提携先		
Jan	neurimmune		
Mar	IKTOS Artificial Intelligence for new drug design		
Apr	DOMAIN THERAPEUTICS Université de Montréal		
Jun	Fate THERAPEUTICS	CAR-T/CAR-NK	Cancer
Aug	knowledge palette	Large-scale Transcriptome Analysis	undisclosed
Nov	MEMO THERAPEUTICS AG	Antibody/Immuno-Oncology	Cancer
Nov	Captor Therapeutics®	Target Protein Degradation	CNS
Dec	precisionlife improving health | for everyone	Target Identification	CNS

2023年

月	提携先	概要	領域
Jan	MONASH University	Anti-GPCR Antibodies	Autoimmune Diseases
Jan	KSQ®	DNA Damage Response	Cancer
Feb	CUE BIOPHARMA	Modified Cytokine	Autoimmune Diseases

Our Focus on Drug Discovery Platform and Modalities

Technology Platform	Small Molecule	Peptide	Protein/Antibody	Cell Therapy
Oncology	2021 ribon therapeutics; 2023 KSQ; Chordia Therapeutics; REPARE THERAPEUTICS; CANCER RESEARCH UK		2022 MEMO THERAPEUTICS AG; NUMAB Drug Innovators; lifeArc	2022 Fate THERAPEUTICS
Immunology			NUMAB Drug Innovators	
Neurology	2022 precisionlife improving health | for everyone; expanded in 2021 Vanderbilt Univ.; Captor Therapeutics 2022; ARIA PHARMACEUTICALS		2022 neurimmune	Expanding Biologics
Specialty	2022 DOMAIN THERAPEUTICS; Université de Montréal		MONASH University 2023; CUE BIOPHARMA 2023	
Others	2021 Lab Central; MBC biolabs Enabling awesome 2021; UCDDC knowledge palette 2021 2022; 2021 healx; 2022 IKTOS Artificial Intelligence for new drug design; SCHRÖDINGER; Cyclenium pharma	2021 PeptiDream	2021 MiraBiologics; Ligand	

Drug Discovery Strategy

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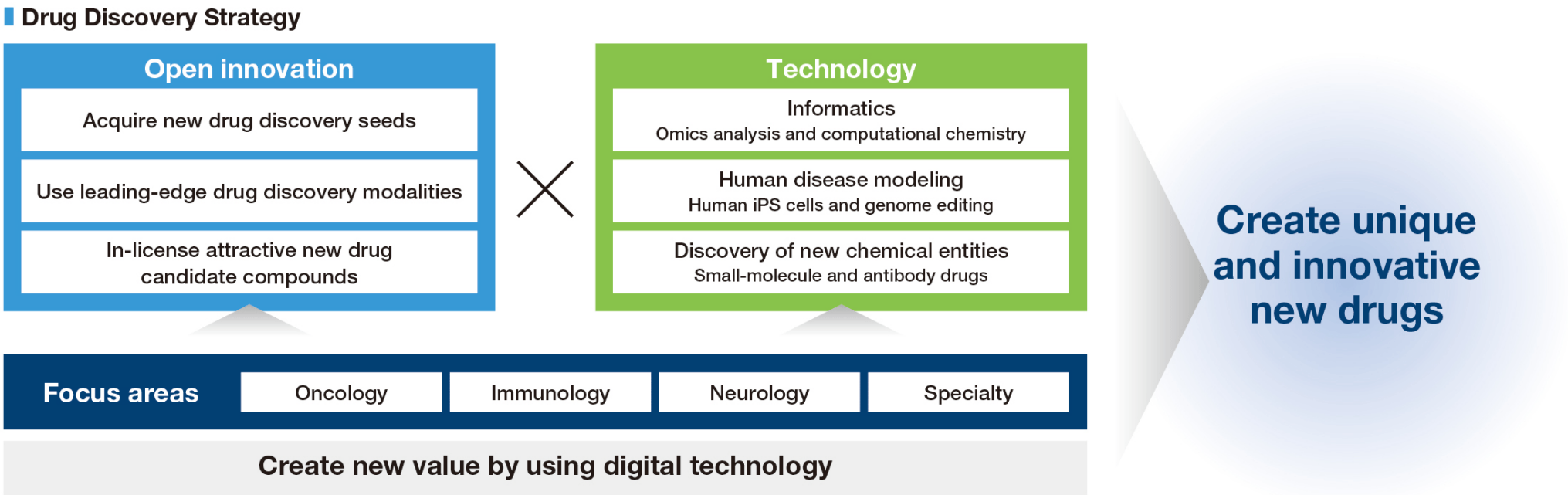

Drug Discovery Strategy

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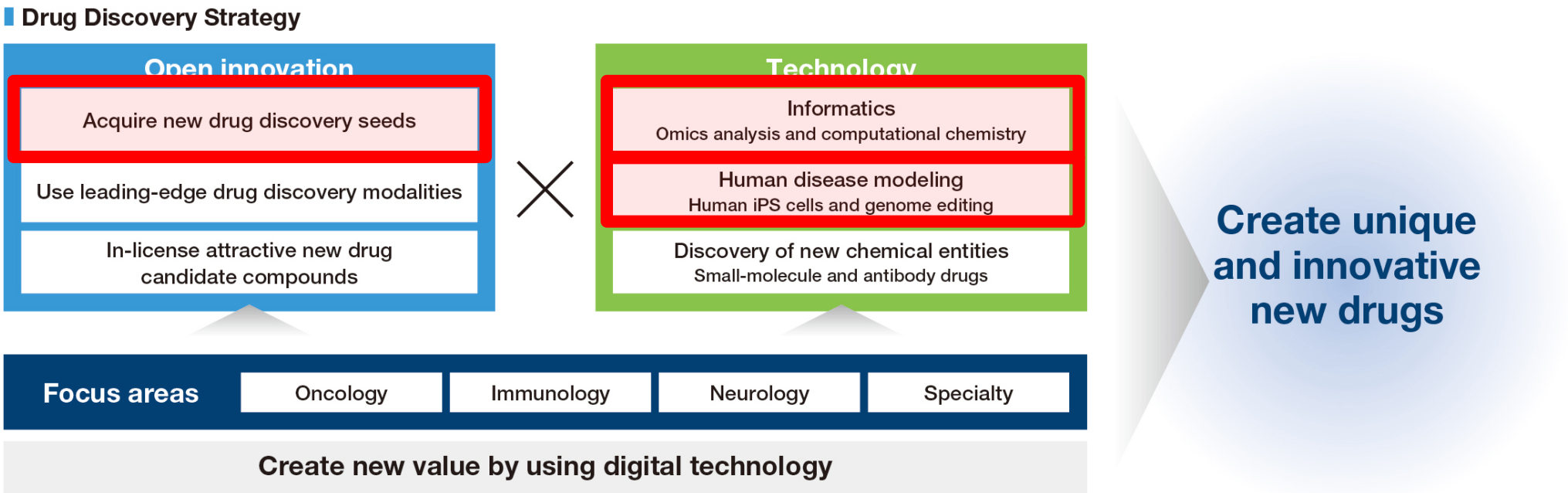


Exploratory of the original drug discovery seeds

Sponsorship Agreements with LabCentral and MBC BioLabs (2021.02.26)

"Investment to the start-up Biotech companies"

2021～

San Francisco

MBC biolabs
Enabling awesome

2021～

Boston

Lab | Central

ONO Golden Ticket 2022 Winner

Weatherwax Biotechnologies

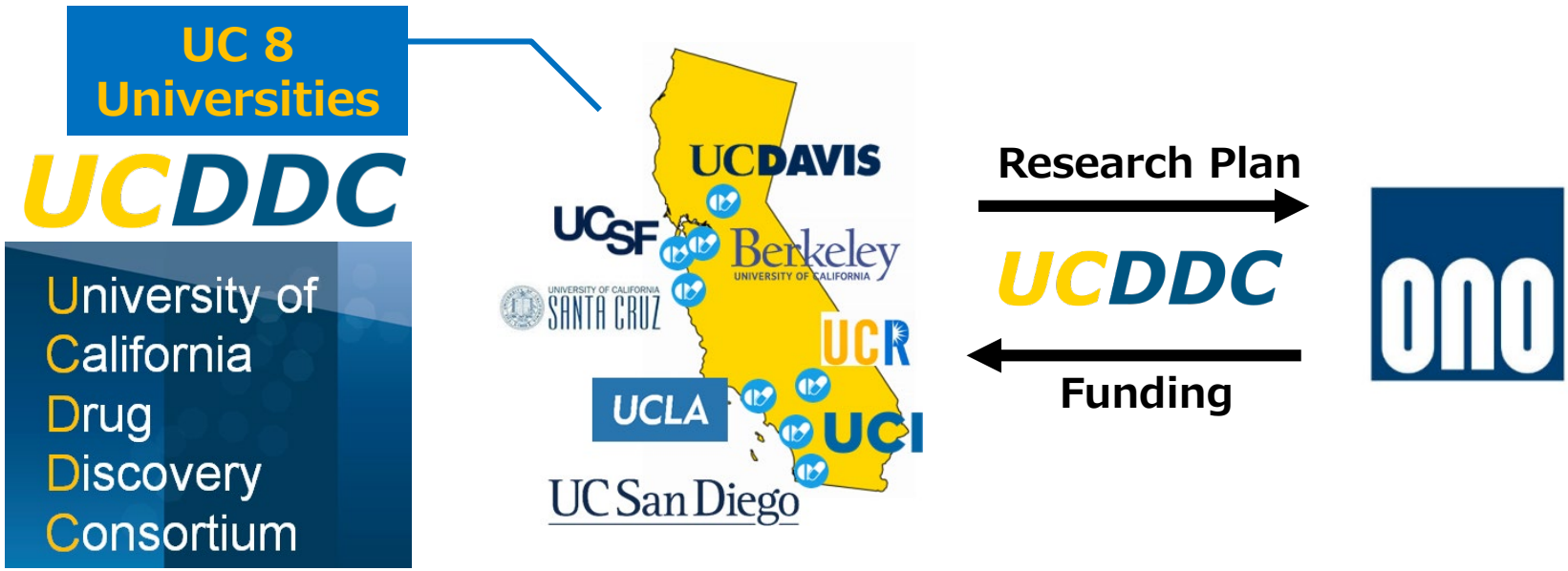
https://mbcbiolabs.com/ono-golden-ticket/ono-golden-ticket-2022-winner/

Access to the latest information and exploration of future collaborators

https://labcentral.org/news-events/press-releases/ono-entered-sponsorship-agreements-with-labcentral-and-mbc-biolabs

Joins the University of California Drug Discovery Consortium
(2021.03.16)

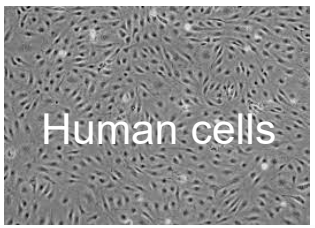
- Access to undiscovered top scientists
- Explore collaboration opportunities based on unverified and unpublished ideas
- Bridging academia's drug discovery seeds to pharma



Collaborative research with knowledge palette to build a data-driven new drug discovery platform using large-scale transcriptome analysis technology (2022.08.10)

knowledge palette

Treatment with many different compounds
Perturbations such as inhibition of gene function



Large-scale transcriptome analysis

Mapping Database

Artificial intelligence (AI)
Large-scale scientific computation

Elucidation of new target molecules and mechanisms

Cells | Gene Expression Profiling | Big Data of Cells

Quartz-Seq2
: Technology that enables comprehensive gene expression profiles with high precision (Mereu, et al. Nature Biotecnology, 2020)
https://www.knowledge-palette.com/technology.php

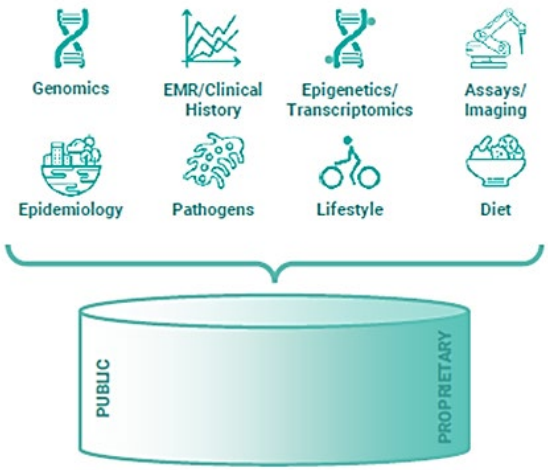
Elucidation of new target molecules and mechanisms in a data-driven manner by making large-scale database on the effects of existing drugs, gene knochout, etc. on human cells

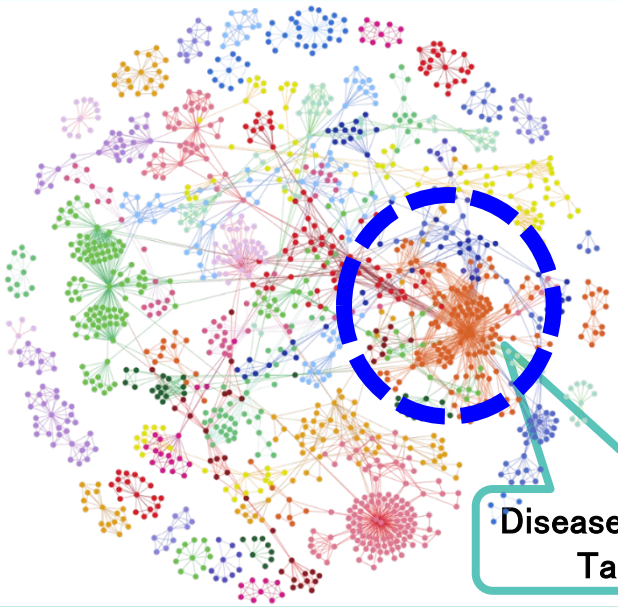
Multi Target R&D Collaboration Agreement with PrecisionLife to identify novel therapeutic targets in CNS disorders

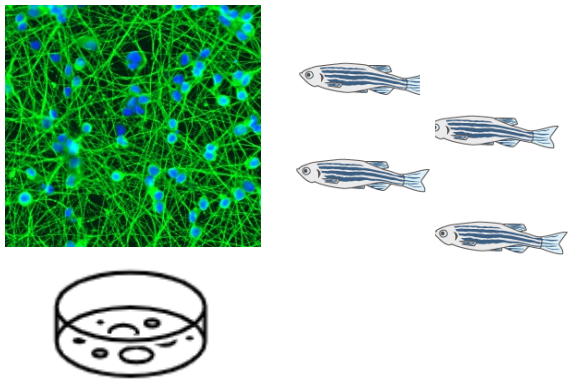
(2022.12.14)

precisionlife
improving health | for everyone

Target Patient → **Bioinformatics Analysis** → **Identification of Therapeutic Targets and Biomarkers**







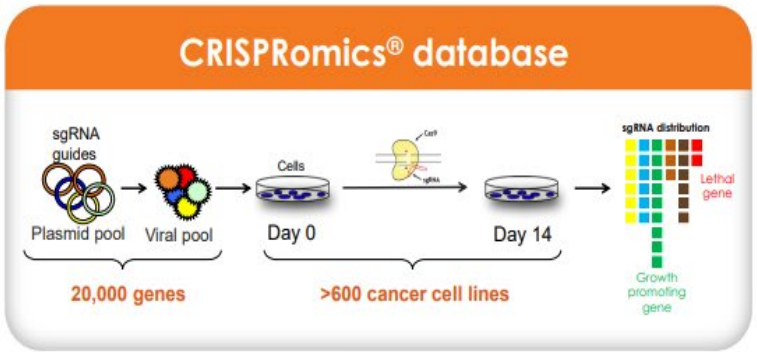
Patient Dataset

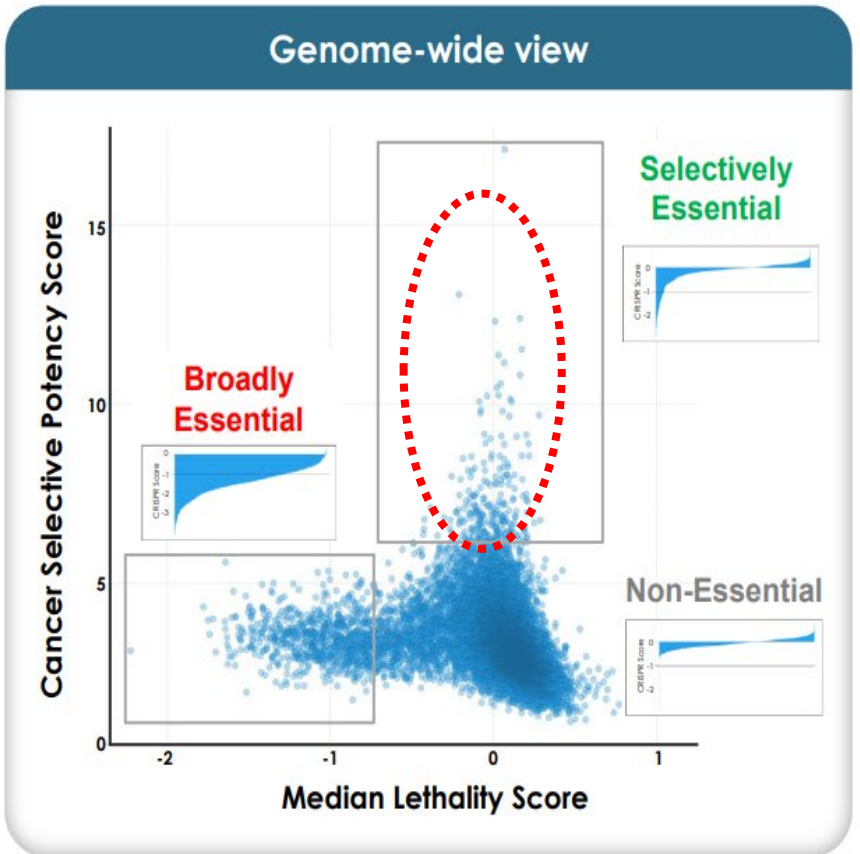
Unique Combinatorial Analytics Platform

Validation Study

Identification of Novel Therapeutic Targets and Patient Stratification Biomarkers through Unique Combinatorial Analytics Platform to Datasets of Treatment-resistant Patients

Acquisition of Multiple Research-Stage Oncology Programs from KSQ Therapeutics (2023.01.25)





Acquisition of multiple research-stage DNA damage response programs identified by KSQ's CRISPRomics® platform technology

Drug Discovery Strategy

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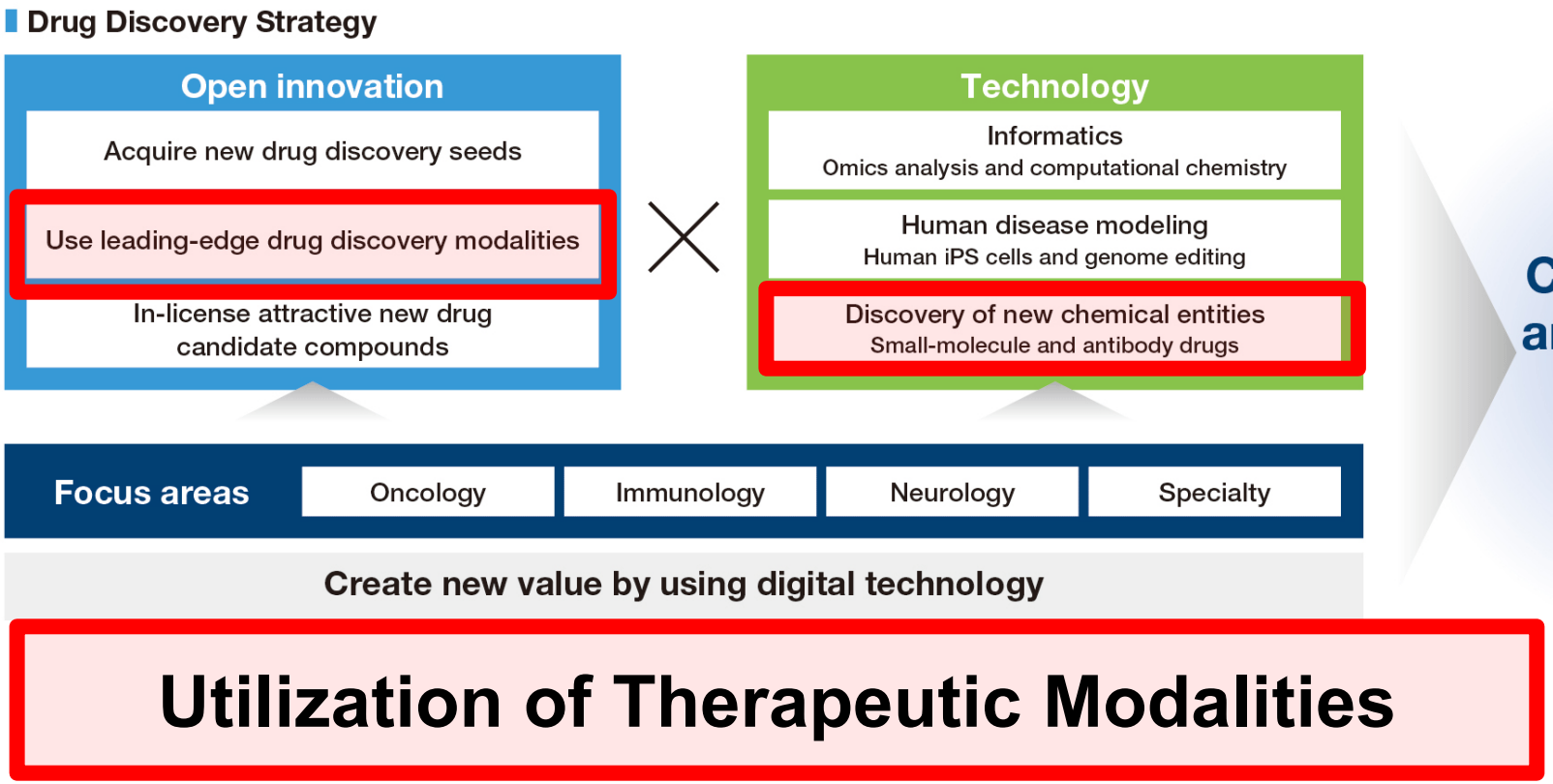
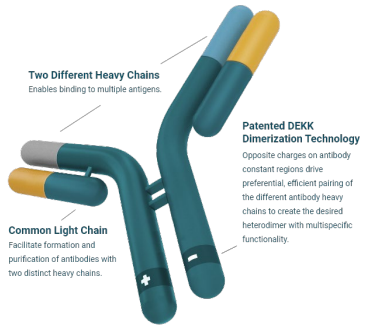


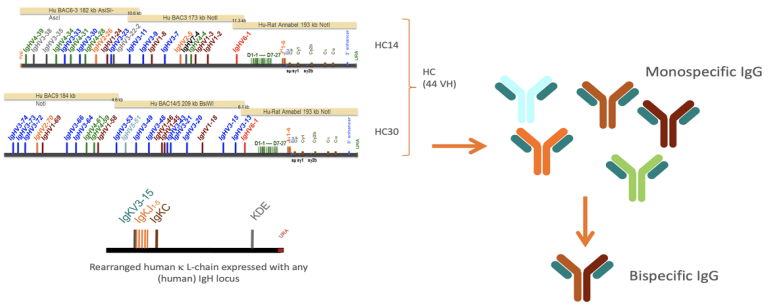
Alliances on Multispecific Antibodies



Biclonics® technology platform

Merus

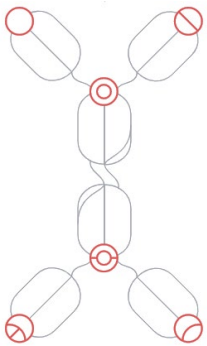
Holland
2014～



OmniRat®, OmniMouse® and OmniFlic®

Ligand

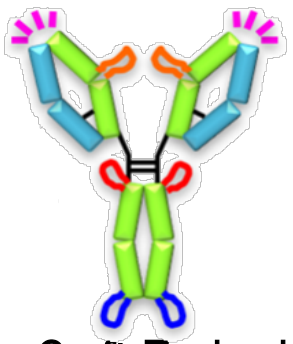
The US
2016～



Highly flexible multispecific format, MATCH

NUMAB Drug Innovators

Switzerland
2017～



LassoGraft Technology®

MiraBiologics

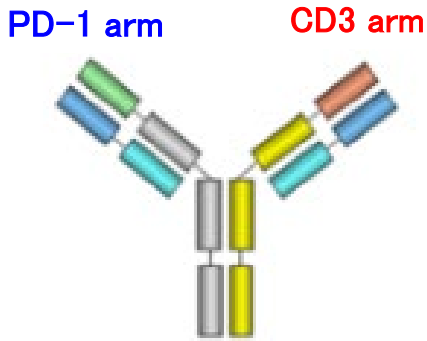
Japan
2021～

ONO-4685：PD-1 × CD3 Bispecific Antibody

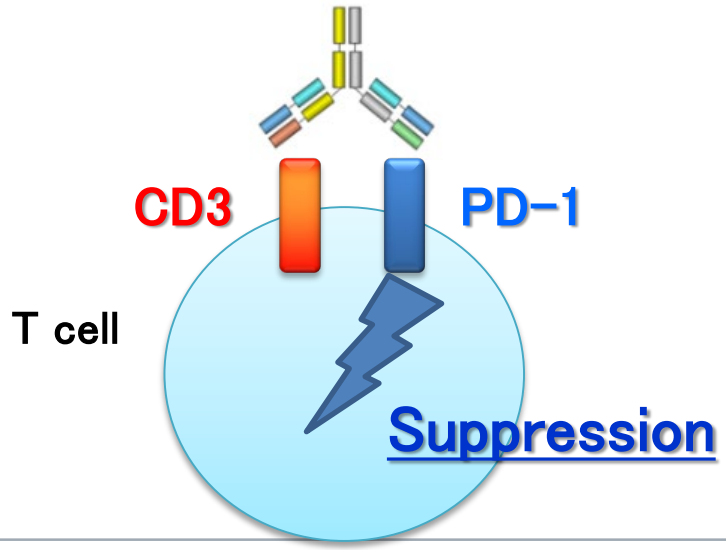
Merus

- PD-1 × CD3 Bispecific Antibody generated by Biclonics® Discovery Platform

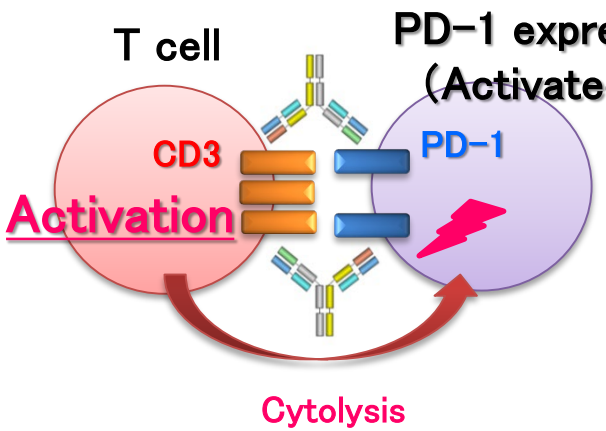
T cell lymphoma （USA, Phase 1）
Autoimmune Diseases（Japan・EU, Phase1）



Suppression of activated T cell

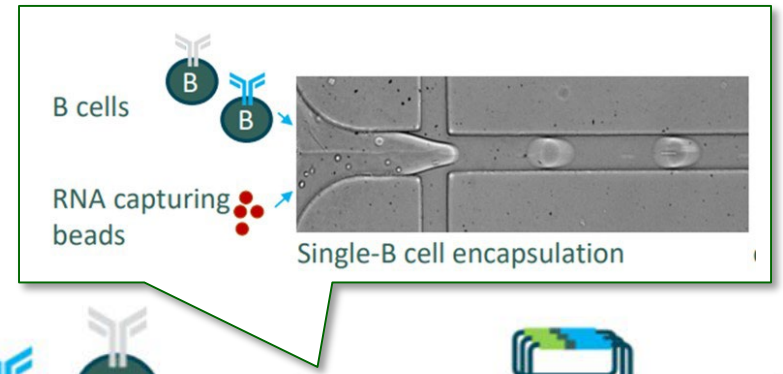


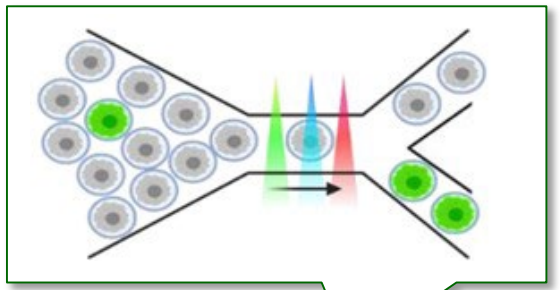
Cytotoxicity on activated T cells

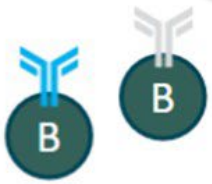


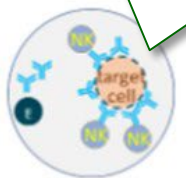
Antibody Discovering Partnership for Immuno-oncology with MEMO Therapeutics (2022.11.01)

MEMO THERAPEUTICS AG









B cells (Entire repertoire) → Entire repertoire library → Repertoire copied in HEK → High throughput Functional Screening

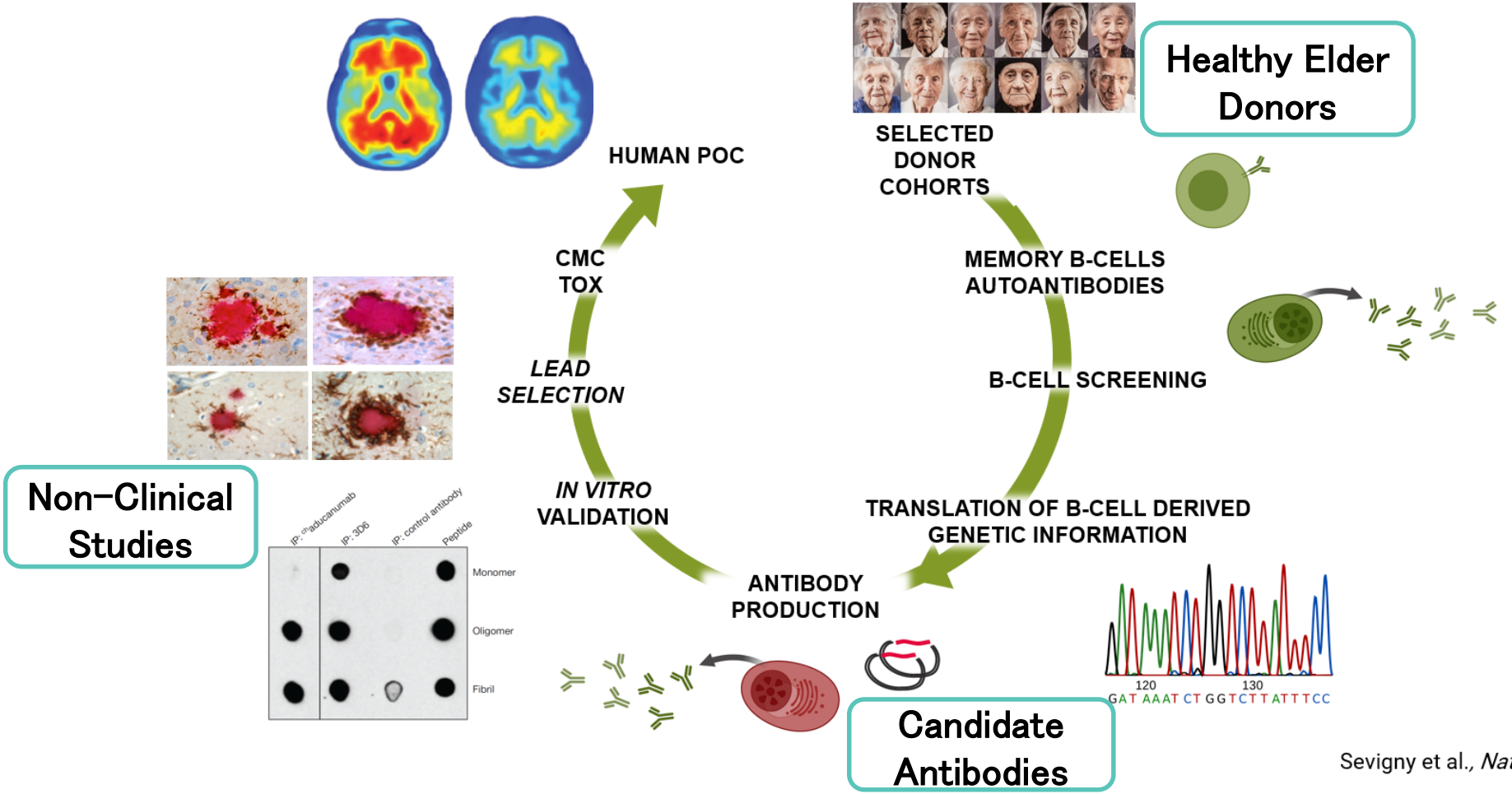
Maximizing antibody repertoire against target antigens

Therapeutic Antibody for Immuno-oncology

Antibody discovery by microfluidic single-cell molecular cloning and screening technologies (Dropzylla®) at unprecedented speed, efficiency, and sensitivity.

Antibody Drug Discovery Collaboration with Neurimmune AG in the Field of Neurodegenerative Diseases (2022.01.17)

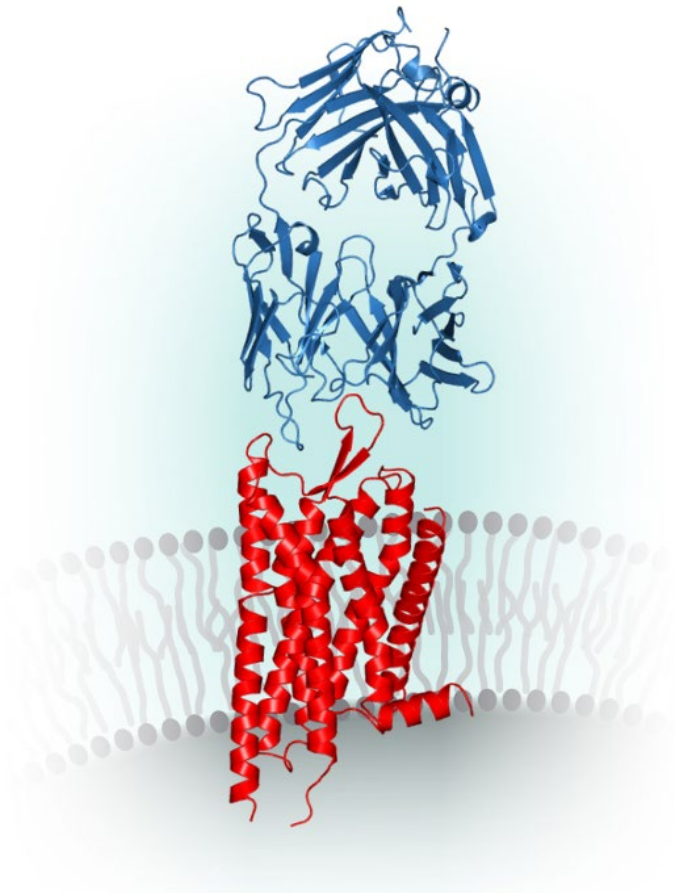
neurimmune



Sevigny et al., *Nature* 2016

Creating Selective High Affinity Antibodies Using the Reverse Translational Medicine™ Technology Platform Based on Immune Responses to Disease-related Proteins in Healthy Elderly

Research Collaboration with Monash University in the Autoimmune and Inflammatory Diseases (2023.01.13)



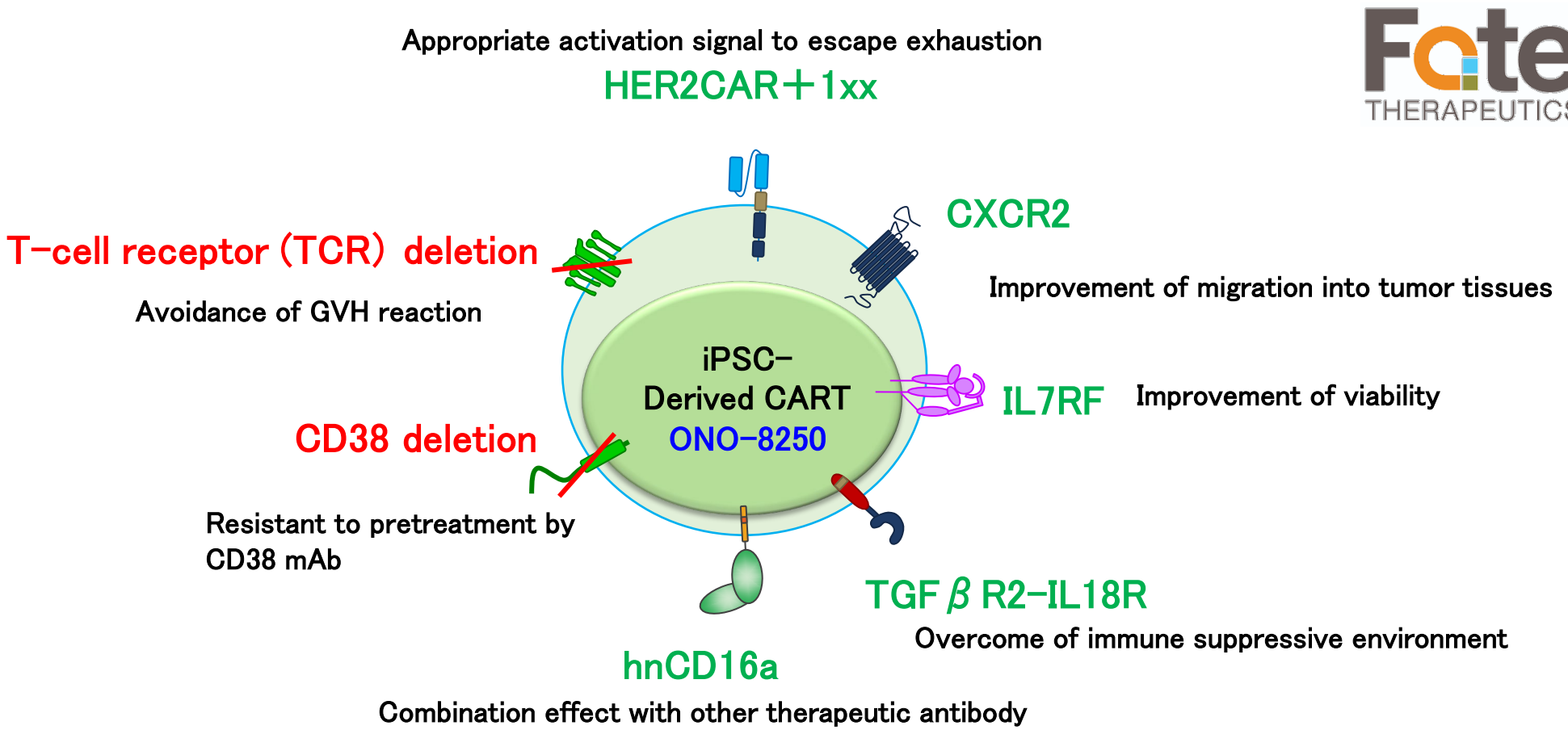
Biochem Pharmacol. 2013 Jan 15; 85 (2): 147–52

- Monash University's sophisticated technologies for antibody discovery which enables the creation of therapeutic antibodies using monoclonal antibodies against two GPCRs traditionally hard to target.

- We expect to increase the efficiency of finding new drug candidates that fulfil unmet medical needs in autoimmune and inflammatory diseases.

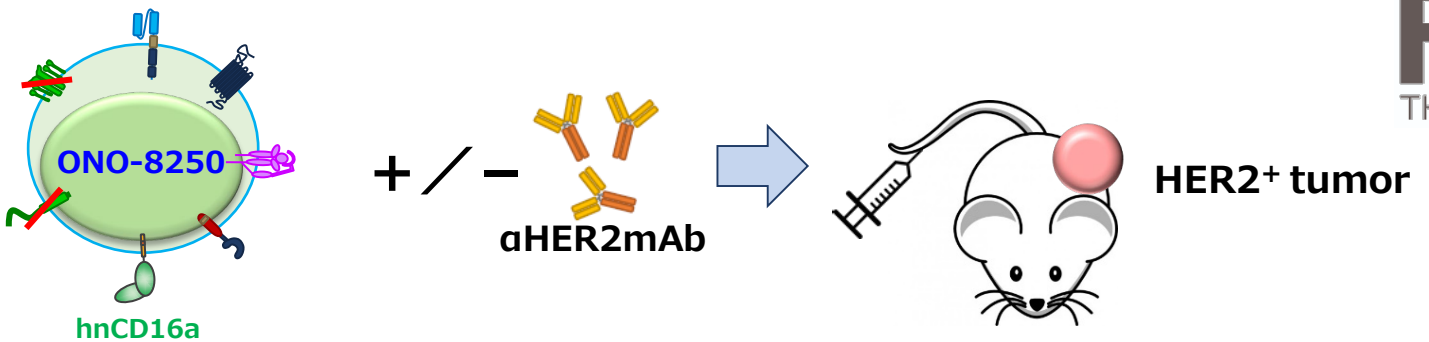
Strategic Collaboration with Fate Therapeutics to Develop iPSC-derived CAR-T (2018.09.18)

Exercise Option to HER2-targeted CAR T-Cell Product Candidate for Solid Tumors (2022.11.07)

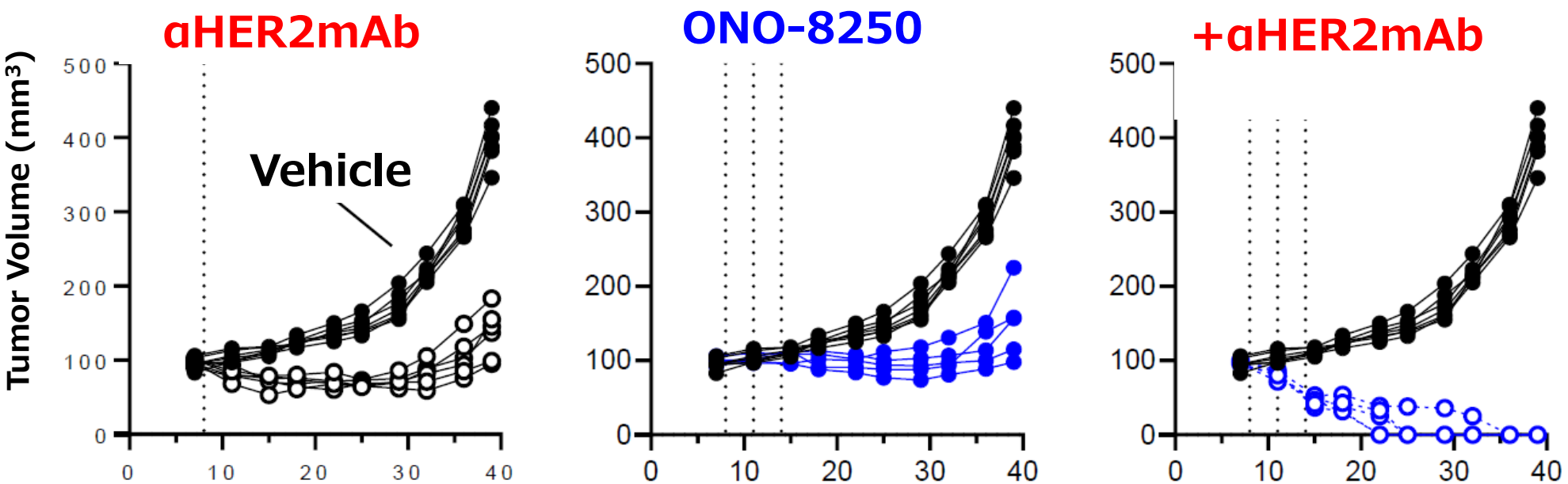


"Off the Shelf" iPSC-derived HER2-CAR-T armed with seven Functional Edits

ONO-8250：Anti-tumor effect on HER2+ tumor bearing model



Combination effect with other therapeutic antibody

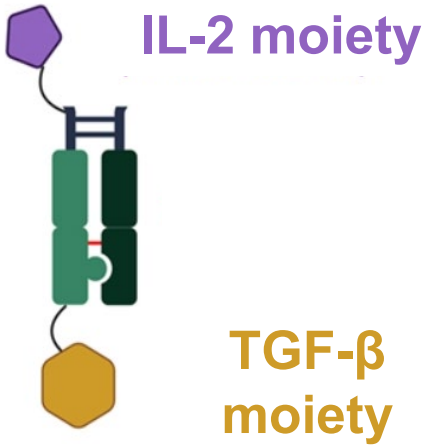


ONO-8250 showed anti-tumor effect in HER2+ tumor bearing model.
Combo with anti HER2mAb enhanced anti-tumor effect by hnCD16a activation

Hosking M, et al. SITC 2022 #304

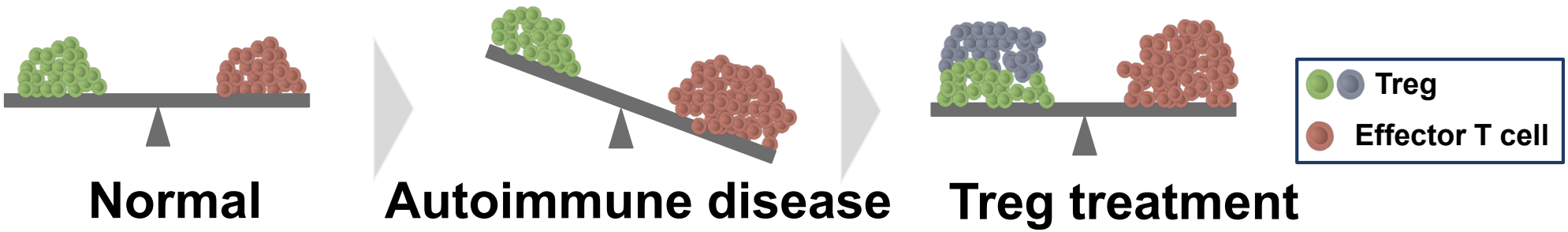
Collaboration and Option Agreement with Cue Biopharma for CUE-401, a Bispecific Protein (2023.02.22)

CUE-401



Tregs induced by CUE-401

- Diversity：Generated from vastly diverse T cells
- Phenotype：Regulatory phenotype can be achieved and sustained
- Disease impact：Conversion of pathogenic T cells into Tregs is an attractive strategy for immune re-set
- Application：Broad applications in numerous autoimmune diseases

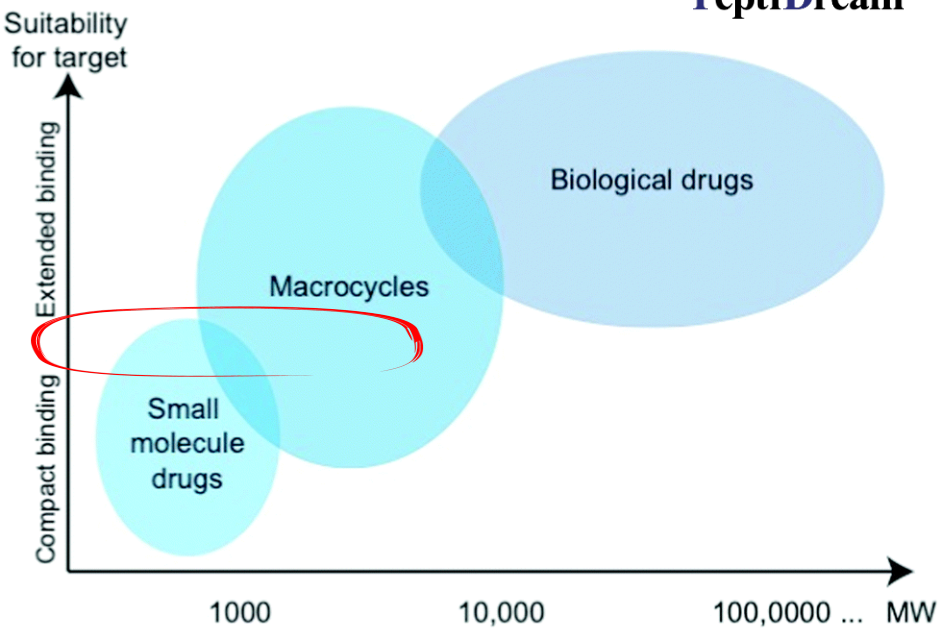


Efficient induction of Tregs from diverse repertoire is expected to restore the balance of immune cells to help patients suffering from autoimmune and inflammatory diseases.

https://cuebiopharma.gcs-web.com/node/8111/html revised

License agreement with PeptiDream Inc. on automated Peptide Discovery Platform System (2021.03.01)

Characteristics of Specialty Cyclicpeptide Drug Discovery			
	Small molecule	Specialty Cyclic peptide (Middle molecule)	Antibody (Large molecule)
MW	<500	500 – 2000	150000
Specificity	Low	High	High
Oral administration	Available	Available	Not available
Intracellular targets	Available	Available	Difficult
Off-target toxicity	Low – mid	Low	Low
Cost of goods	Low	Low	High



RSC Chem. Biol., 2022, 3, 7-17

Expansion of modality options suitable for tough targets by utilizing the original Peptide Discovery Platform System (PDPS)

Drug Discovery Collaboration with Captor Therapeutics to Develop Protein Degraders for Treatment of Neurodegenerative Diseases (2022.11.14)

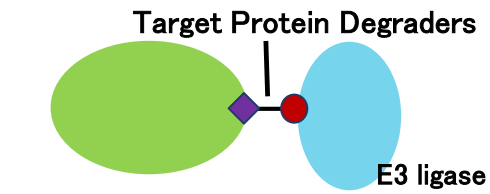
Captor Therapeutics®

Druggable Proteins
⇨ **Functional Inhibition**

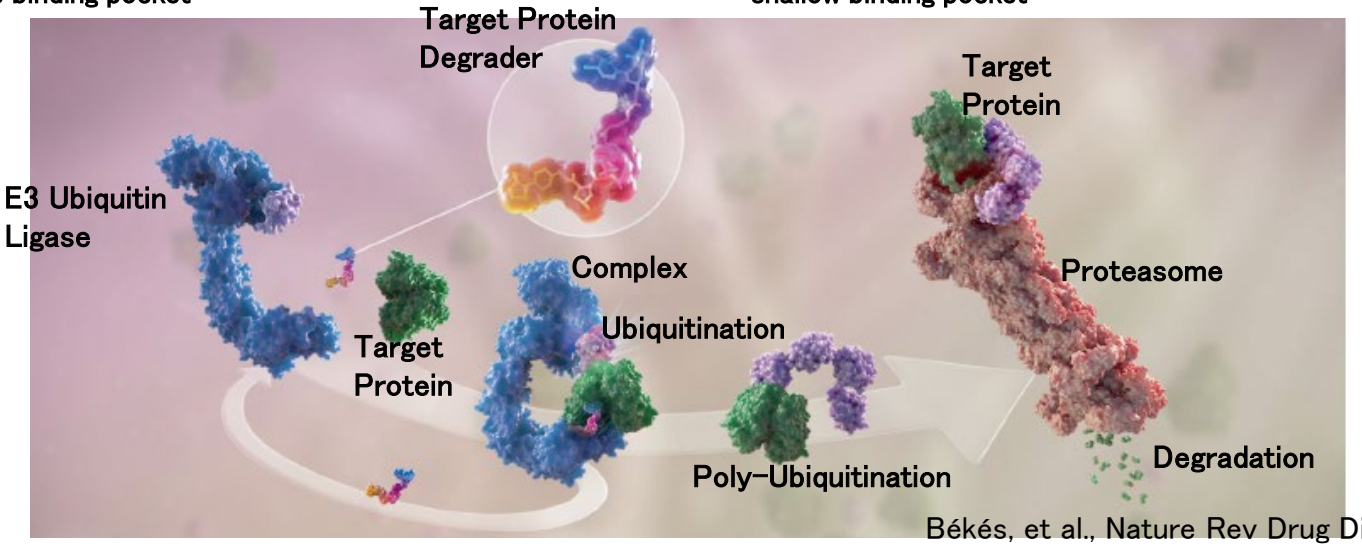
Target Proteins with deep binding pocket

Undruggable Proteins*
⇨ **Degradation**

*70–80% of all proteins



Target Proteins with shallow binding pocket



Békés, et al., Nature Rev Drug Dis, 2022, modified

Creating Degrader Drug Candidates using Unique Optigrade™ TPD Platform in Neurodegenerative diseases

Drug Discovery Strategy

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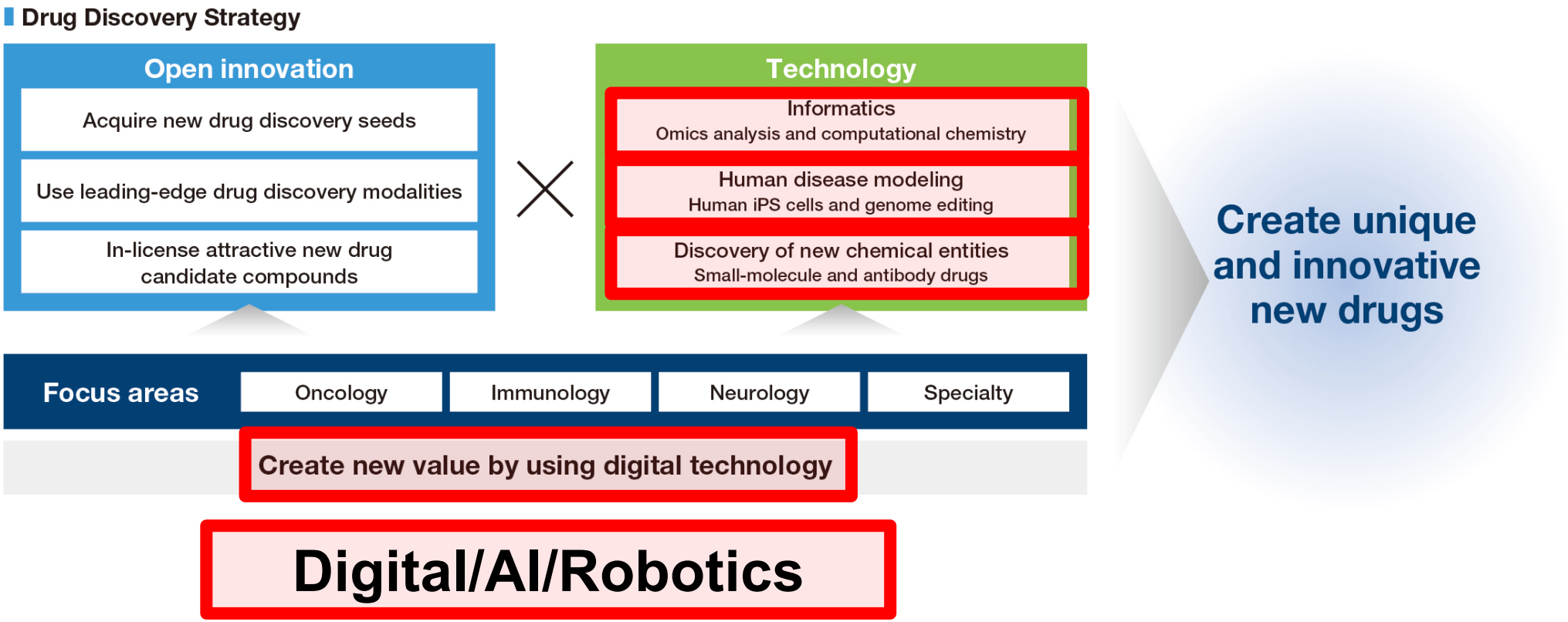
allows us create unique & innovative new drugs

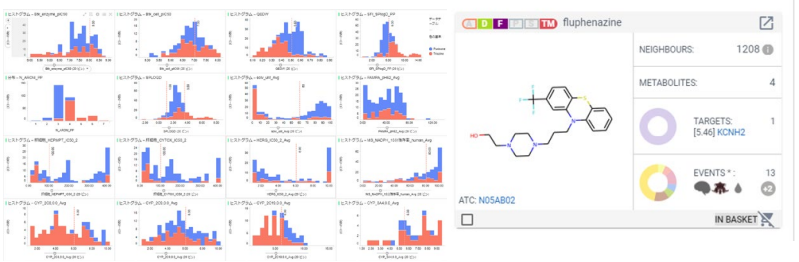


Collaboration agreement with Iktos to discover and develop a novel small molecule using AI technology.(2022.03.30)

SCHRÖDINGER. (2017.12.19～)

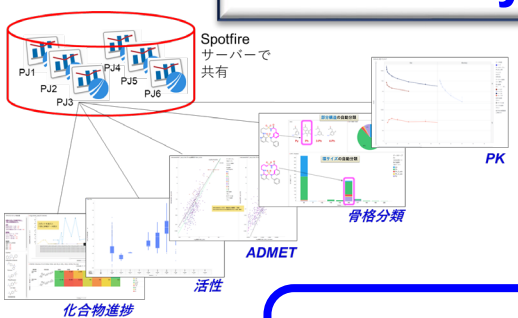
IKTOS

AI design・MPO



Auto-synthesis

Auto-analysis



Auto-testing

AI design・automation enables major productivity gains in upstream pharmaceutical research

Collaboration agreement with Curreio to access to structual analysis technology using Cryo EM.(2022.05.23)

Curreio

「Visualization of interaction mode between target protein and compound」

X-ray analysis soluble proteins

Kinase/protease
2005～

Array Biopharma

Evotec A.G.

X-ray analysis Membren proteins

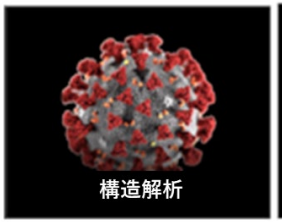
GPCR
2011～

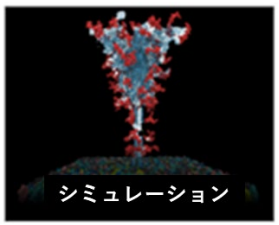
Receptos

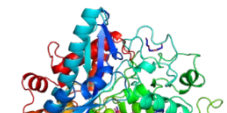
CryoEM

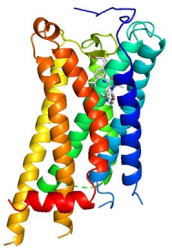
Target X
2022～

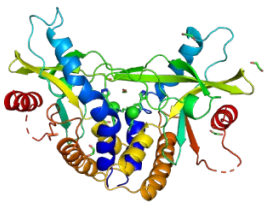
Curreio

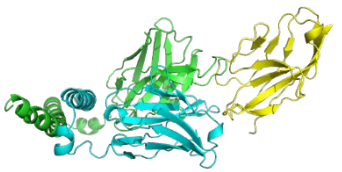


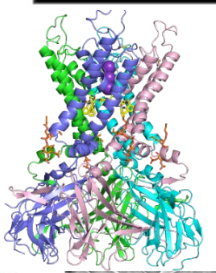


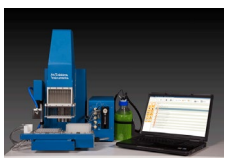












Acccessing super computing system
for using cutting-edge AI technology

Making full use of Human disease modeling

RBI Epistra Nikon

iPS cell technology

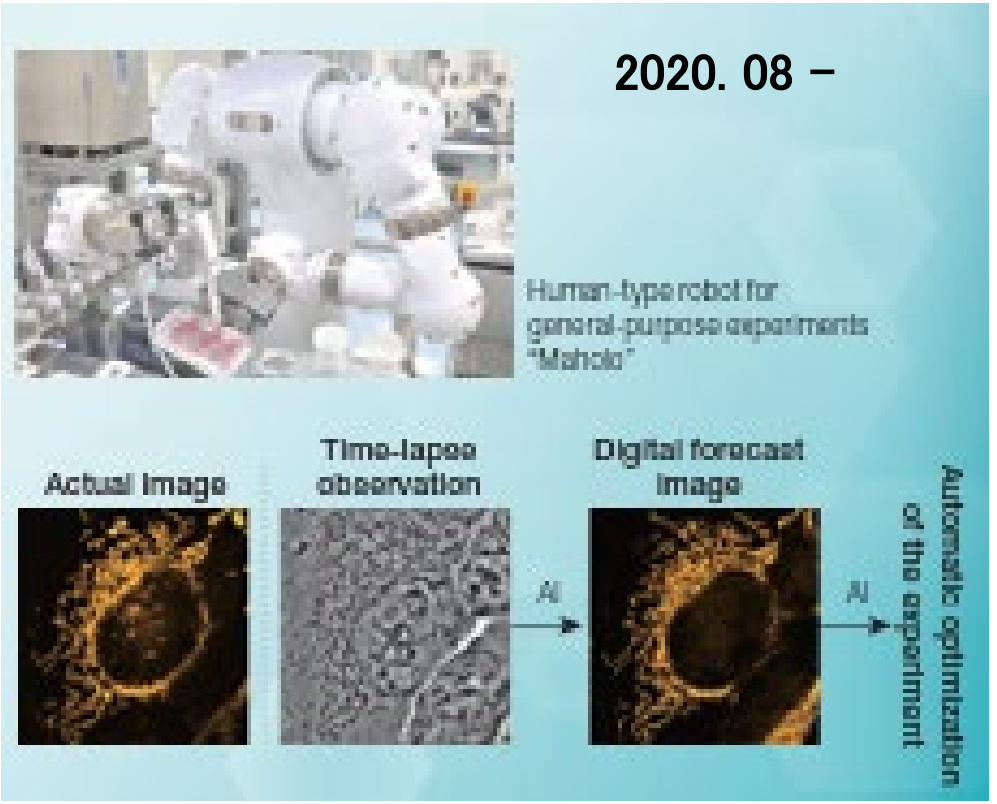
Joint research
(Academia)
Japan6・Overseas10

Alliance
(Biotech venture/CRO)
Japan and Overseas8

(2023.03)

×

Humanoid robot × Digital technology

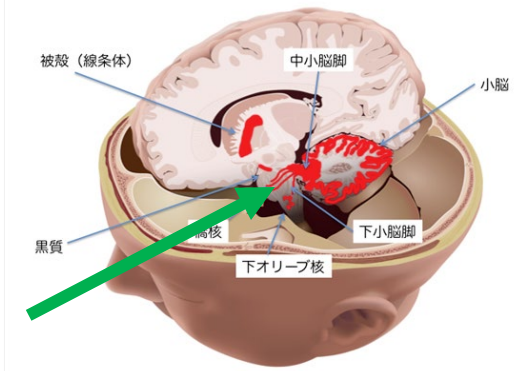


Drug discovery research based on human disease biology through active utilization of human disease iPS cell technology

Creation of PET for Bioimaging of Abnormal Protein "α-synuclein" in the Neurodegenerative Disease (2022.08.31)

α-synuclein accumulation (Multiple System Atrophy)

Ref.： Tokyo Medical Research Institute Neuropathology Database

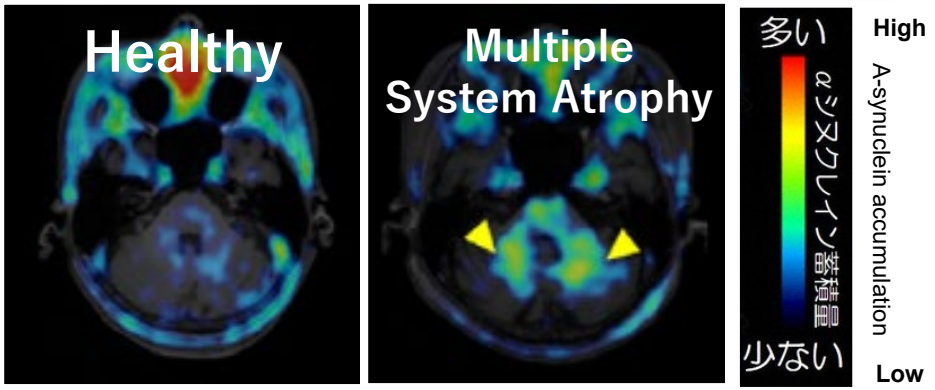


Inject radioactive drug

Captures α-synuclein accumulation Co-Development of Radiopharmaceuticals

調和ある多様性の創造 国立研究開発法人
QST 量子科学技術研究開発機構
National Institutes for Quantum Science and Technology

Eisai　ono　Takeda



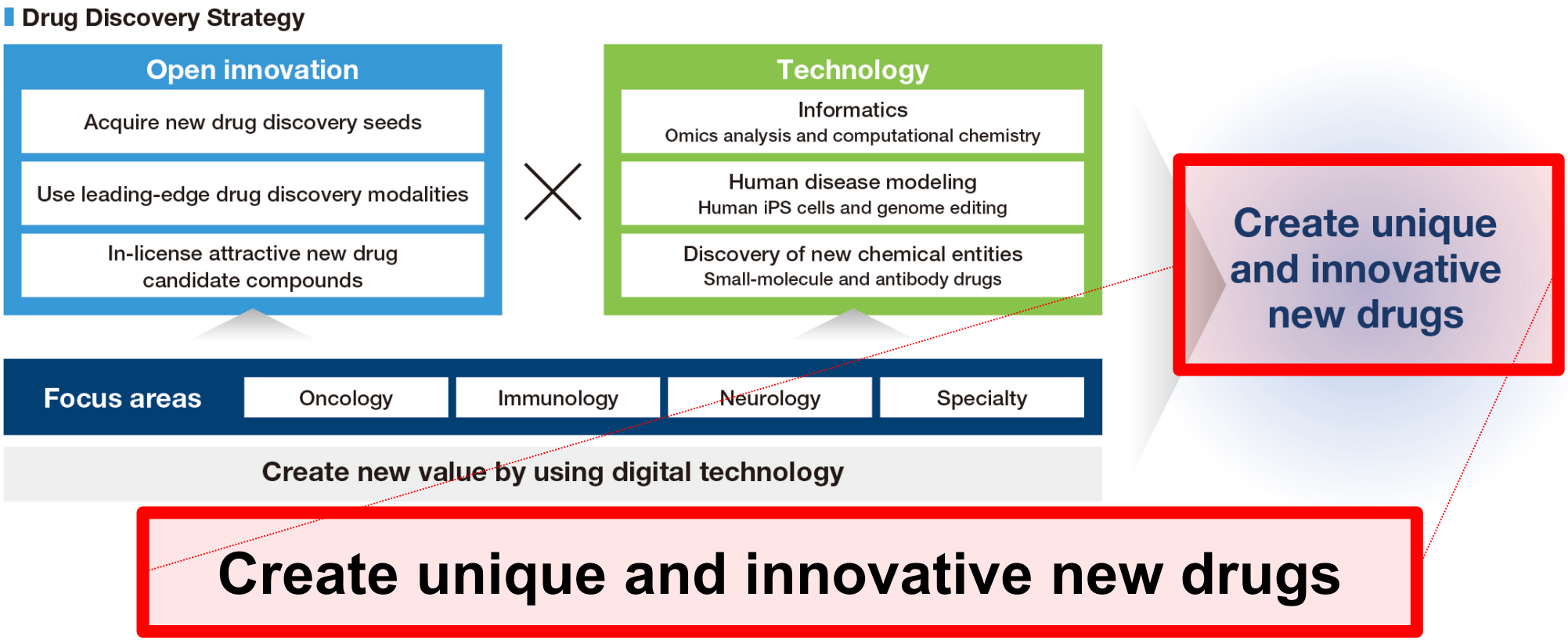
Ref.：Movement Disorder. 2022. 37:2159-2161.

PET（positron emission tomography）Successful Imaging of Brain α-Synuclein

Application of the PET to clinical development for neurodegenerative diseases is expected.

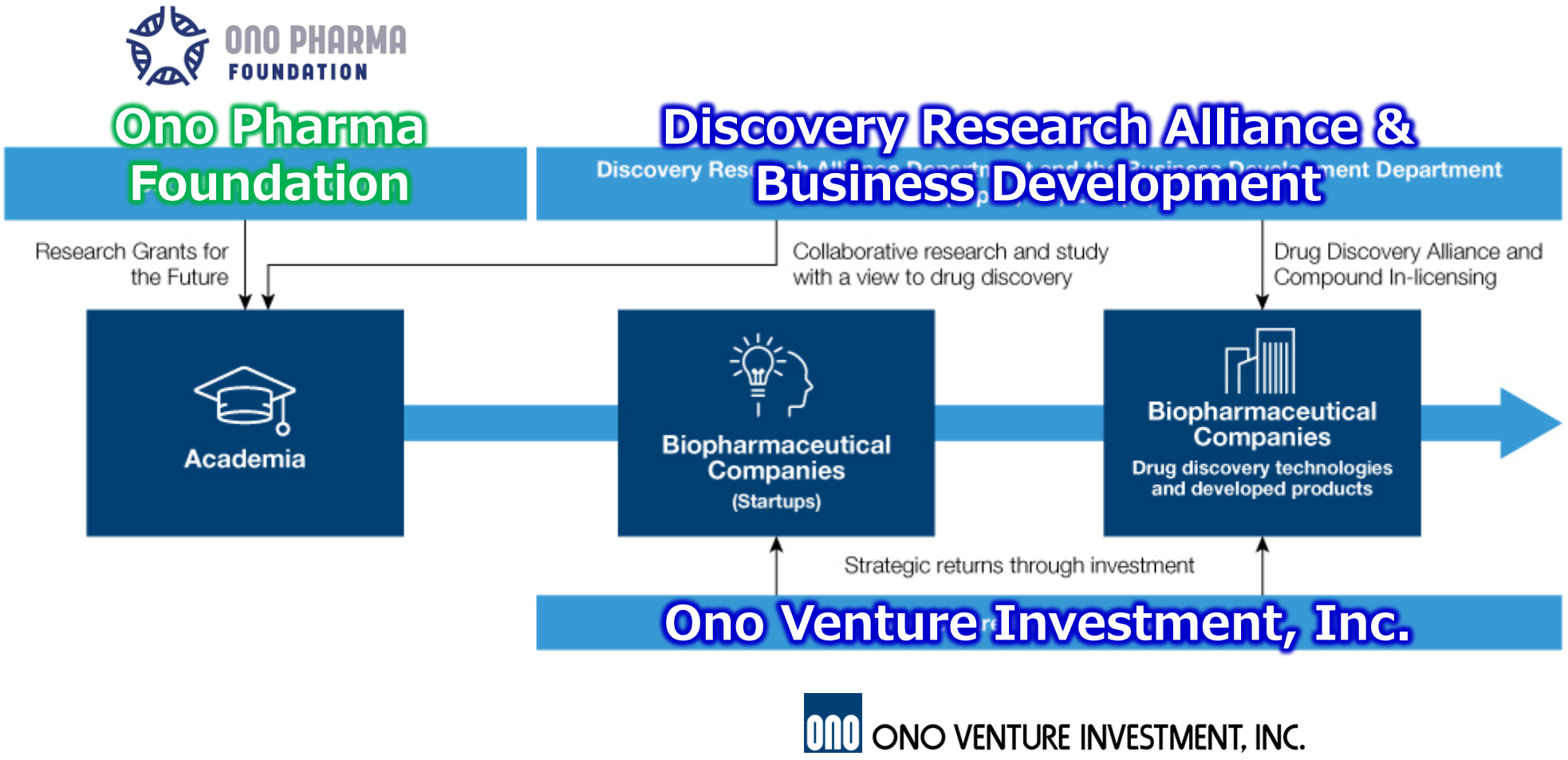
Drug Discovery Strategy

「Open Innovation」×「Technology」
allows us create unique & innovative new drugs



Create unique and innovative new drugs

Promotion System to Support Open Innovation Driven Drug Discovery



Investment to the start-up Bio-Venture

ONO VENTURE INVESTMENT, INC.

Start-up		Outline
Mediar Therapeutics	Cambridge, MA, USA	• Bio-Venture for development of new drugs for the treatment of fibrosis
Curreio	Tokyo, Japan	• Bio-venture for drug discovery based on detailed protein structure information by cryo-electron microscopy
Immunitas THERAPEUTICS	Waltham, MA, USA	• Bio-Venture Committed to the Creation and Development of Novel Therapies for Cancer Patients
arbor	Cambridge, MA, USA	• Bio-Venture for New Gene Editing Therapy with a Unique DNA/RNA Degrading Enzyme • Established based on the achievements of the Broad Institute and Harvard University
casma therapeutics™	Cambridge, MA, USA	• Bio-Venture for Development of New Therapeutic Drugs through Targeted Degradation by Autophagy

https://www.onoventure.com/news

Research Grant Activities by the Ono Pharma Foundation in the United States

Ono Pharma Breakthrough Science Initiative Awards Program：

is the embodiment of the Foundation's commitment to focus on and accelerate researcher-driven open innovation by supporting high-risk and high-reward science research projects which have potential to lead to science discoveries/solutions and, possibly, based on further research, to breakthrough treatments for patients.

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https://www.onofound.org/about/

Prof. Carolyn R. Bertozzi
Stanford University
2022 Nobel Prize Winner
in Chemistry

Itolizumab(Anti-CD6 antibody)

Executive Officer/Executive Director

Clinical Development

Kiyoaki Idemitsu

Itolizumab

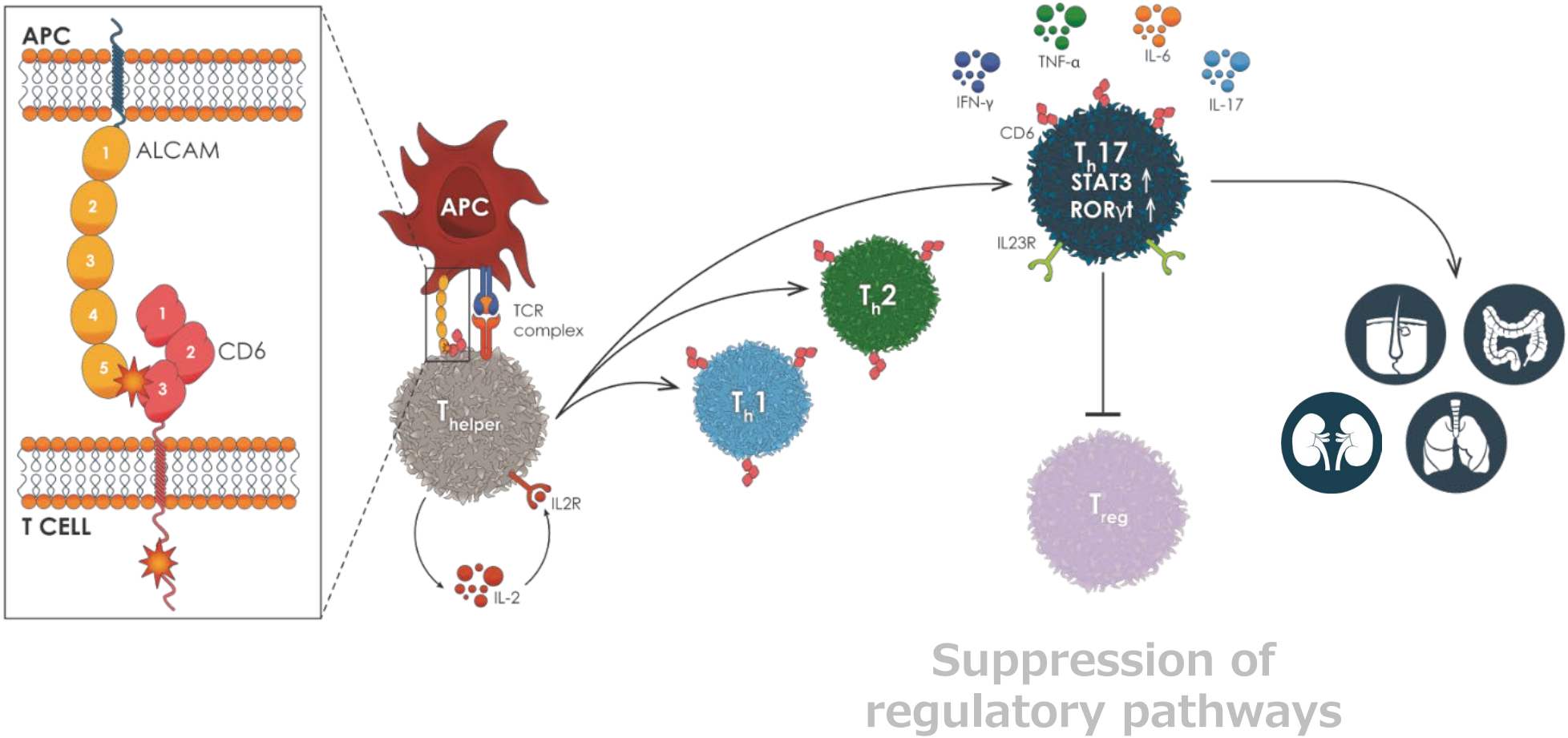
Ono and Equillium Announce Exclusive Option and Asset Purchase Agreement for the Development and Commercialization of Itolizumab（5 Dec, 2022）

Partner	Equillium, Inc（CA, USA）
Compound Name	Itolizumab
Mechanism	Anti-CD6 antibody
Characteristics	Highly safe FIC drug that change T-cell status to treat autoimmune diseases
Indications and stages	Acute graft-versus-host disease*（aGvHD）: Phase 3 Lupus nephritis : P1b study
Formulation	i.v.(aGvHD) ／ s.c.(Lupus nephritis)
Rights acquisition region	US/Canada/Australia/New Zealand, (Biocon／CIM** reserve rights in all other Region)

- aGvHD : Complications after hematopoietic stem cell transplantation, a treatment for hematologic cancer
- CIM : Centro de Inmunologia Molecular

CD6 Drives Pathogenic T Cell Activity & Trafficking

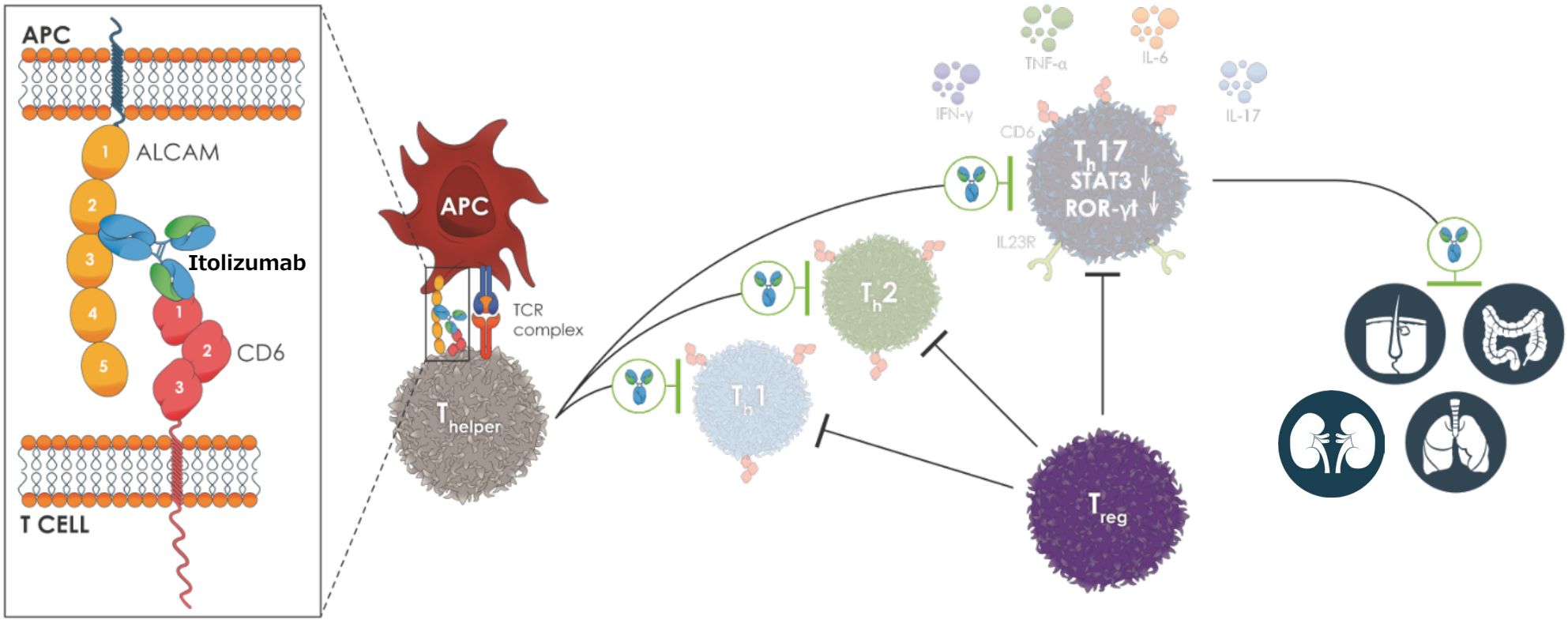
Co-stimulation ↑ = Activation ↑ Proliferation ↑ Differentiation/Survival ↑ Trafficking ↑



Suppression of regulatory pathways

Itolizumab inhibits pathogenic T Cell Activity & Trafficking

Co-stimulation ↓ = Activation ↓ Proliferation ↓ Differentiation/Survival ↓ Trafficking ↓



Restoration of regulatory pathways

aGvHD treatment guideline in the US

aGvHD : Complications After Hematopoietic Stem Cell Transplantation, a Treatment for Hematologic Cancer

aGvHD
Approx.4,500
patients in the US

【Abbreviations】
ATG： Antithymocyte globulin, CSP： Cyclosporine, MMF： Mycophenolate mofetil,
mPSL： Methylprednisolone, MTX： Methotrexate, TAC： Tacrolimus

Conditioning regimen
High-dose chemotherapy

Allogeneic hematopoietic stem cell transplantation
Donar to Patient

≤ 100 days after transplantation

GVHD予防

CSP／MTX／TAC
＋MMF
Abatacept*

aGvHD
Approx.50%

Skin disorder
Liver disorder
Gastrointestinal disorder

Grade I
Grade II
Grade III
Grade IV

1st line

Follow up

Steroids
mPSL→PSL
＋
Itolizumab

2nd line

Ruxolitinib

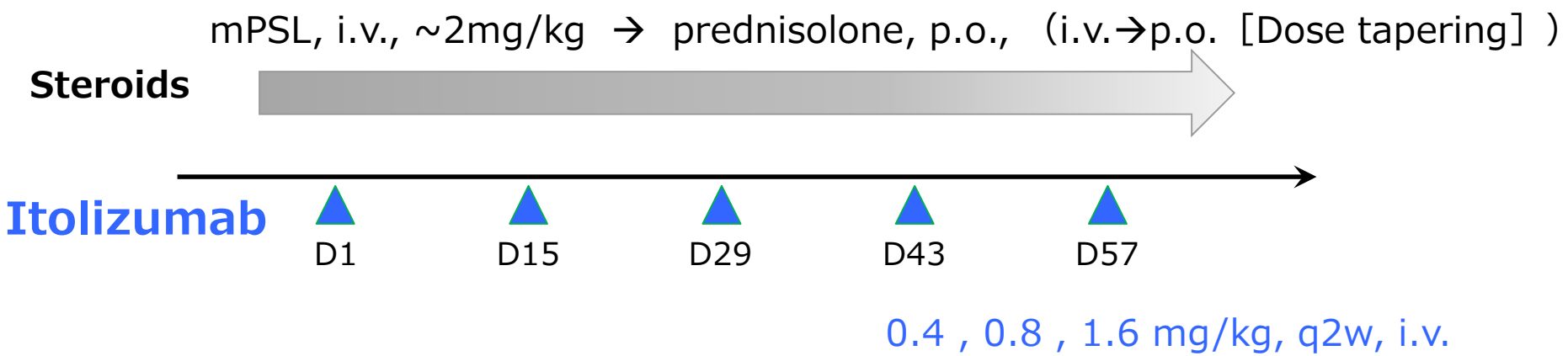
JAK inhibitor

anti-TNF agents, daclizumab（anti CD25 antibody）etc.

＊ Abatacept（Orencia）has been approved for prophylaxis of acute GVHD in the US in Dec. 2021

Phase 1b study - EQUATE study

Evaluate the clinical activity and safety of Itolizumab on top of steroids, as 1st line treatment for aGvHD

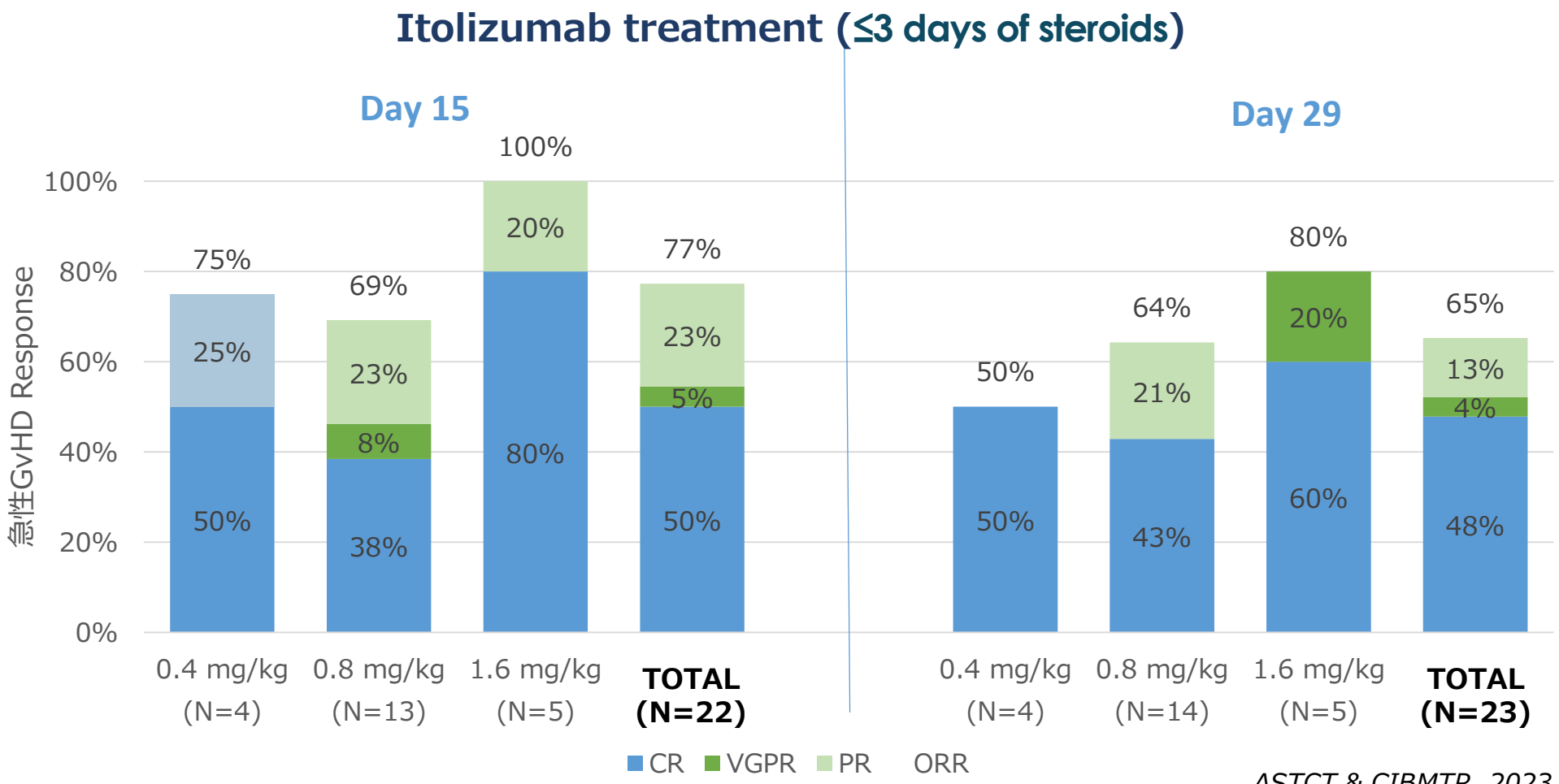


- **Scoring of skin, liver, and gastrointestinal symptoms were evaluated**

at D15 and D29.

- **<u>CR (Complete Response)</u> : Disappearance of all symptoms.**

High Response Rates to Itolizumab + Steroids

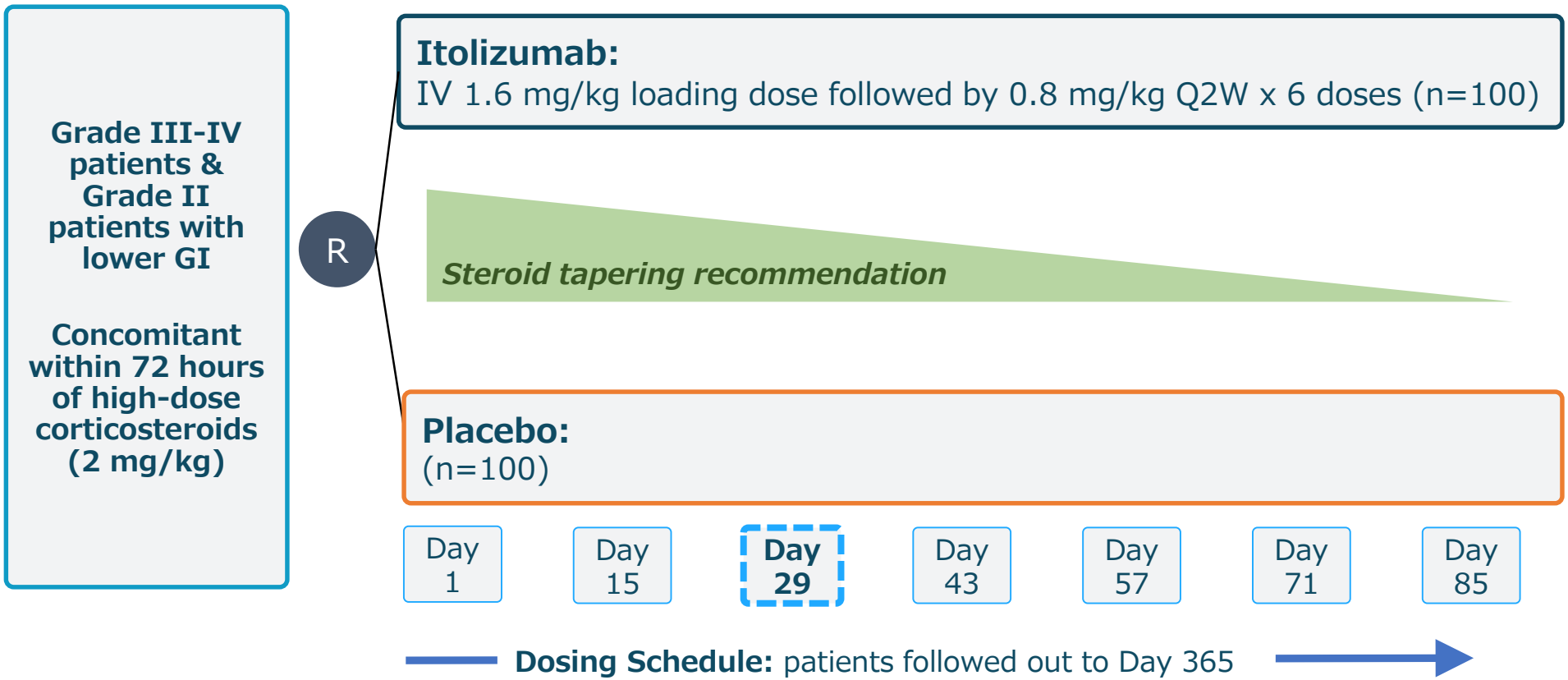


ASTCT & CIBMTR, 2023

CR, complete response
ORR, overall response rate (PR+VGPR+CR)
PR, partial response
VGPR, very good partial response

[per Martin 2009 Consensus criteria]

Phase 3 Study for aGvHD（EQUATOR study）



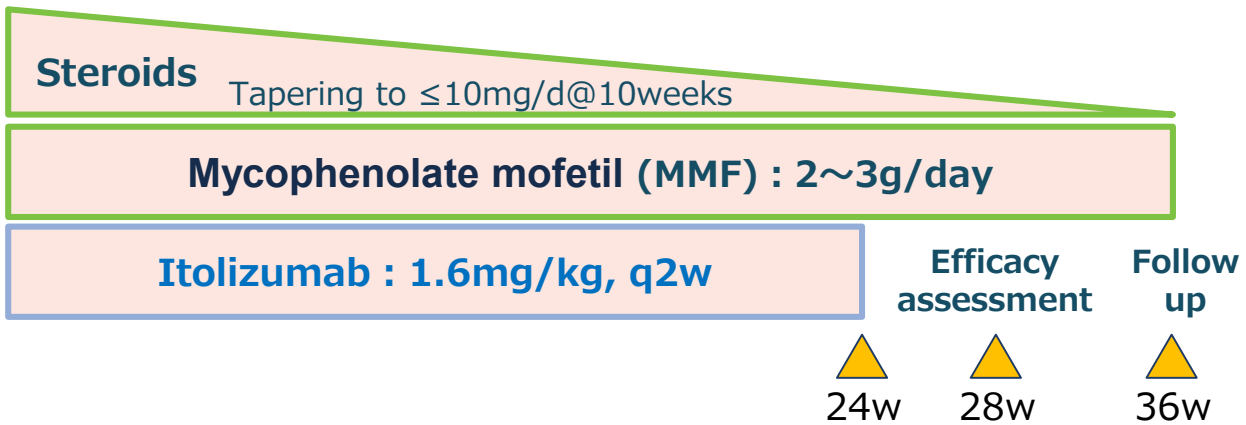
- Primary Outcome : Complete Response Rate at Day 29
- Secondary Outcome : Durability of Complete Response Rate from Day 29 through Day 99

(Interim DSMC Review @ 100 patients)

P1b Study for Lupus Nephritis （EQUALISE study）

Evaluate the efficacy and safety of Itolizumab as an add-on to Steroids + Mycophenolate mofetil

Target
- Class III/IV (with V) on renal biopsy
- UPCR > 1 g/g

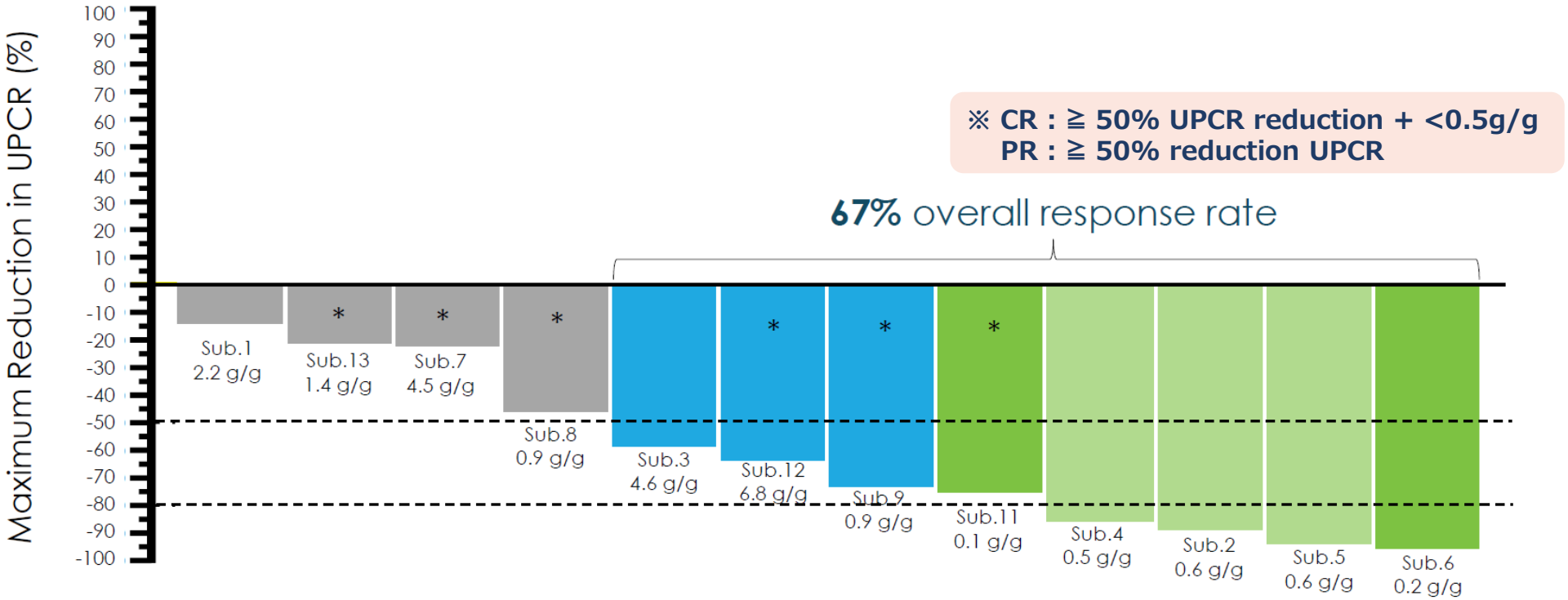


Complete Renal Response
- **UPCR : ≤0.5 g/g**
  (urine protein/creatinine ratio)
- **eGFR : Not less than 20% below baseline**
  (estimated glomerular filtration rate)

P1b Study for Lupus Nephritis

Change in UPCR and Best Clinical Response by Subject

Cut off : 2022/09/02



UPCR reduction in all cases

(Urine protein／Creatinine ratio)

CR ≧ 50% UPCR reduction + <0.5g/g
CR ≧ 50% UPCR reduction + 0.5-0.7g/g
PR ≧ 50% reduction UPCR
No Response < 50% reduction or worsening UPCR

N = 12 (subjects with > 1 dose and at least 1 post-baseline assessment)
* Subjects still actively dosing
Subject number with lowest UPCR achieved to date through study completion (week 36)

ONO PHARMACEUTICAL CO.,LTD.

Dedicated to the Fight against Disease and Pain