# Kyowa Kirin R&D Meeting 2024

September 26th, 2024

Director of the Board, Senior Managing Executive officer and Chief Medical Officer
**Takeyoshi Yamashita, Ph.D.**

# Our Vision toward 2030

## Our Vision toward 2030

**Kyowa Kirin will realize the successful creation and delivery of life-changing value* that ultimately makes people smile, as a Japan-based Global Specialty Pharmaceutical company built on the diverse team of experts with shared passion for innovation.**

### Provide pharmaceuticals for unmet medical needs

We are focused on developing medicines for diseases where there is a clear patient need for new options. We make full use of multiple therapeutic modalities, including biotechnology such as antibody technology, and beyond, building on our Kyowa Kirin established strengths.

### Address patient-centric healthcare needs

We will meet the needs of patients and society by providing value across the entire patient care pathway, delivering cutting-edge science and technology, grounded in our in-depth pharmaceutical knowledge and expertise.

### Retain the trust of society

We pursue world-class product quality and operational excellence to grow our business in ways which build long-term trust with our stakeholders.

* Make patients smile through dramatic improvements in quality of life by identifying the unmet medical needs of people battling with medical conditions and by creating and supplying new drugs or services that help them overcome those challenges.

# Story for Vision 2030

## Strategies for creating and delivering life-changing value

### Disease Science

**Focus disease areas: bone & mineral, intractable hematological diseases/hemato oncology, and rare diseases**

- Explore UMN, causes and mechanisms of disease in depth
- Pursuit of molecular and cellular regulatory mechanisms for therapeutic realization

### Drug Discovery Technology

**Strengthening Innovative Modalities: Advanced Antibody Technologies, Hematopoietic stem cell gene therapy**

- Application of optimal modalities for therapeutic realization
- Evolution of drug discovery methods through AI and data science

### External Collaboration

- Open Innovation
- Partnering

**Life-changing Value Creation**

**Assets in focus disease areas**

**Strategic Partnering Assets ***

**Value delivery on our own**

Global deployment of products developed by taking full advantage of the company's strengths

**Collaborative value delivery**

Aim to maximize value by combining the strengths of the company and its partners

**Full-licensing**

Maximize the value of developed products and deliver them to patients faster by out-licensing to the most appropriate partners

***Assets outside of the disease areas of focus are designated as strategic partnering assets, and value maximization is achieved through collaboration with partners.**

# Research and Development Strategy Image Based on Story for Vision 2030

## Disease Science: Focus disease areas

- Bone & Mineral
- Intractable hematological diseases/hemato oncology
- Rare diseases

Explore UMN, causes and mechanisms of disease in depth
Pursuit of molecular and cellular regulatory mechanisms for therapeutic realization

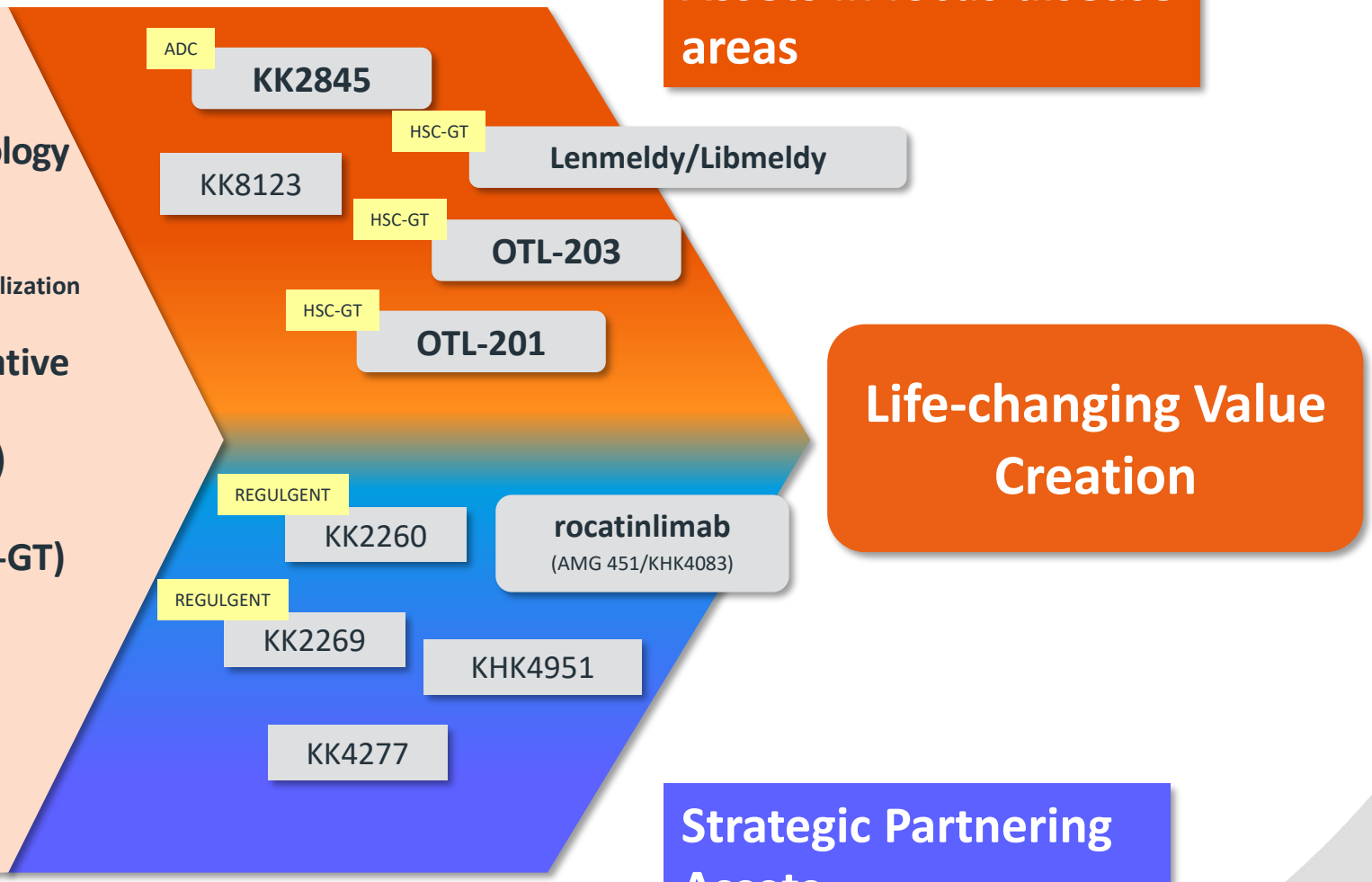
## Drug Discovery Technology: Strengthening Innovative Modalities

- Bispecific antibody technology(REGULGENT™)
- Antibody-drug conjugate（ADC）
- Hematopoietic Stem Cell – Gene Therapy(HSC-GT)

Application of optimal modalities for therapeutic realization
Evolution of drug discovery methods through AI and data science

## External Collaboration

- Open Innovation
- Partnering



# Today’s Agenda

- Rocatinlimab — ROCKET-Horizon Results and T-cell rebalance
- KK2845 — Kyowa Kirin’s First ADC Pipeline
- REGULGENT™ — Proprietary Bispecific Antibody Technology and Its Characteristics
- HST-GT Products — Latest Conference Presentation Data

# Rocatinlimab

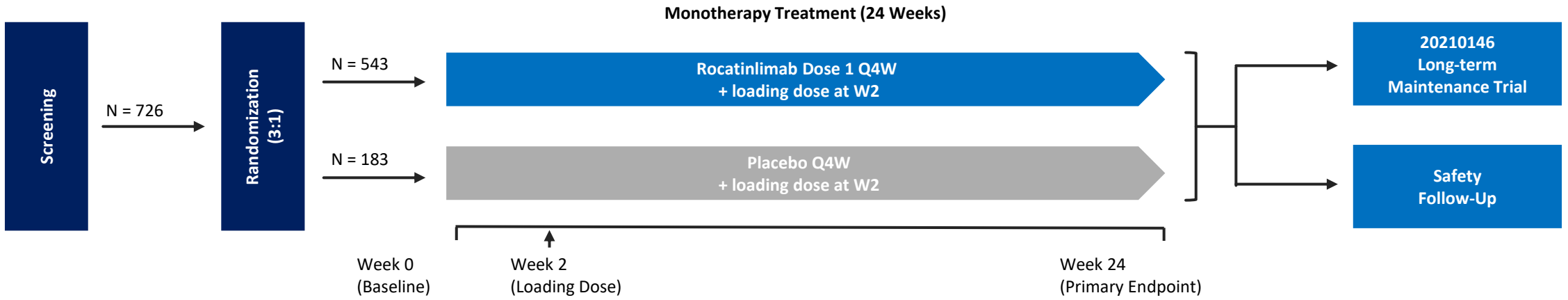
# Rocatinlimab - ongoing Clinical Trials

ROCKET
ROCatinlimab in Eczema Trials

| | | |
|---|---|---|
| Moderate to Severe ATOPIC DERMATITIS *Phase 3* | ***Adult*** | **HORIZON: placebo-controlled monotherapy rocatinlimab (N = 726)**<br>IGNITE: placebo-controlled monotherapy evaluating two rocatinlimab doses (N = 769)<br>SHUTTLE: placebo-controlled trial evaluating two rocatinlimab doses with topical therapy (N = 746)<br>VOYAGER: placebo-controlled trial assessing vaccine antibody response while on rocatinlimab (N = 221) |
| | ***Adolescent*** | ASTRO: 52-week trial evaluating two rocatinlimab doses (N = 500)<br>ORBIT: 52-week adolescent open-label trial (N = 187) |
| | ***Adult & Adolescent*** | ASCEND: maintenance trial with re-randomized withdrawal & extension cohorts (N = 2,200)<br>OUTPOST: 52-week open label trial of self-administered rocatinlimab (N = 100) |
| PRURIGO NODULARIS *Phase 3* | ***Adult & Adolescent*** | Phase 3 trial in prurigo nodularis |
| ASTHMA *Phase 2* | ***Adult & Adolescent*** | Phase 2 trial in moderate-to-severe asthma |

Clinical trials are also underway for nodular prurigo and asthma, in addition to the atopic dermatitis P3 ROCKET program.

# ROCKET HORIZON Study design




## KEY ELIGIBILITY CRITERIA

- ≥ 18 yo, M2S AD
- vIGA-AD 3 or 4
- EASI ≥ 16
- BSA ≥ 10%
- 7-day recall worst pruritus NRS ≥ 4
- Topical failure; bio experienced included

## KEY DESIGN CONSIDERATIONS

**Rescue therapy** was allowed, if deemed necessary

- Subjects who used rescue therapy were considered non responders
- Study treatment was to be discontinued if systemic rescue therapy for AD was used (except for corticosteroids used for ≤ 14 days)

**Stratification:**

- vIGA-AD 3 vs. vIGA-AD 4
- Japan vs. Non-Japan Asian countries vs. RoW

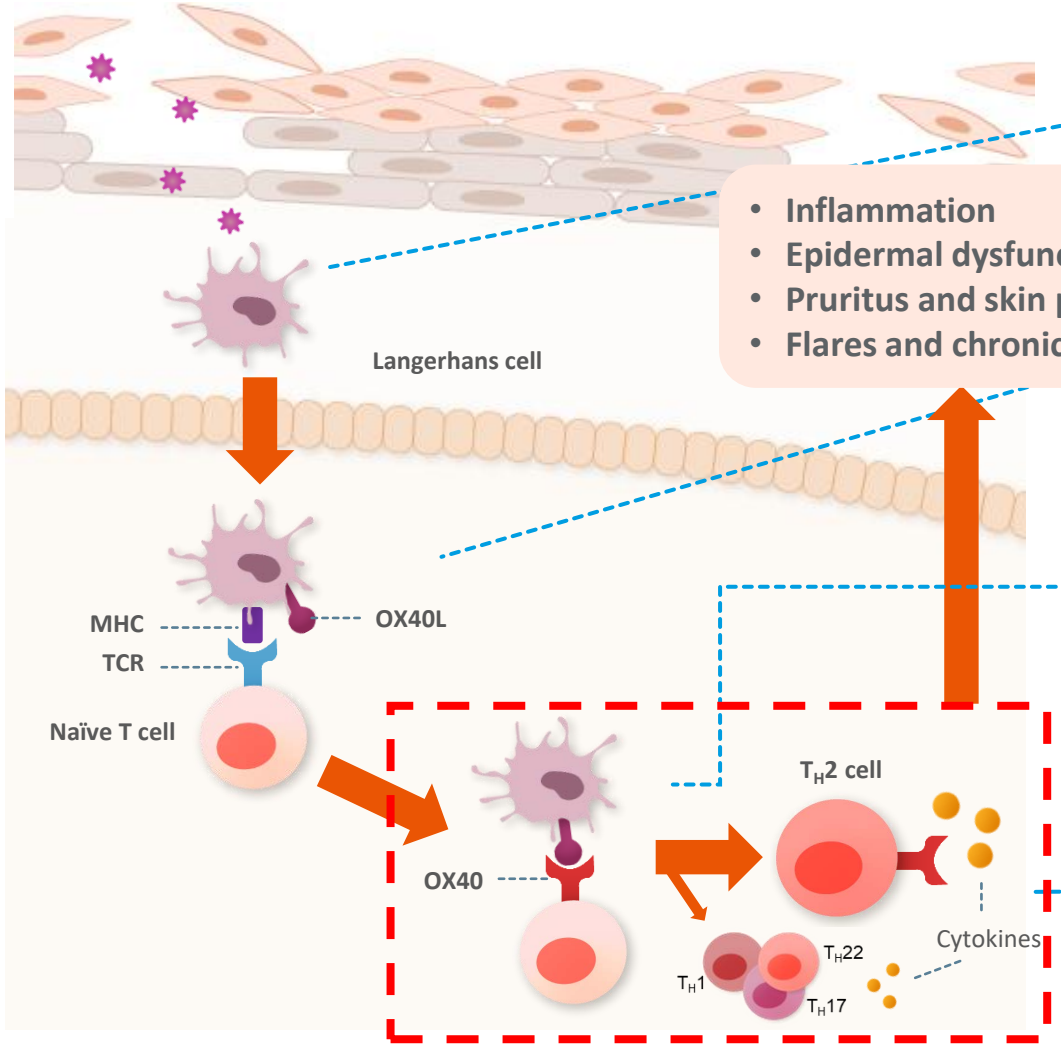
Q4W = every 4 weeks; W2 = week 2; vIGA-AD = Validated Investigator Global Assessment for Atopic Dermatitis;
EASI = Eczema Area and Severity Index; BSA = body surface area; NRS = numerical rating scale; RoW = rest of world.

# ROCKET HORIZON: Summary of Results

- **Co-primary endpoints were achieved**
  - **vIGA-AD™ 0/1[1] with a ≥ 2-point reduction from baseline:** Ex-US
    **rocatinlimab 19.3% vs. Placebo 6.6%　(12.8% difference,　p<0.001)**
  - **EASI-75[2]：** Ex-US For US
    **rocatinlimab 32.8% vs. Placebo 13.7%　(19.1% difference, p<0.001)**
  - **rIGA 0/1[3]：** For US
    **rocatinlimab 16.4% vs. Placebo 4.9%　(11.5% difference, p<0.001)**
- **All key secondary endpoints[4] were also achieved**
- **Overall safety results were comparable to the Phase 2b trial**

1. validated Investigator Global Assessment for Atopic Dermatitis score of 0 (clear) or 1 (almost clear)
2. ≥ 75% reduction from baseline in Eczema Area and Severity Index score
3. A more stringent measure of efficacy than vIGA 0/1. Defined as achieving vIGA-AD 1 response with presence of only barely perceptible erythema or vIGA-AD 0 response and ≥ 2-point reduction from baseline
4. vIGA 0/1 and EASI-75 at week 16 and EASI-90 at week 24, the Pruritus Numeric Rating Scale, Atopic Dermatitis Skin Pain Scale, Dermatology Quality of Life Index, and severity scores of hand atopic dermatitis and facial atopic dermatitis

# Critical Role of OX40 Signaling in Orchestrating T-Cell Driven Inflammation and AD Pathogenesis




- **Inflammation**
- **Epidermal dysfunction**
- **Pruritus and skin pain**
- **Flares and chronicity**

Langerhans cells are activated upon encounter with antigens that penetrate skin and express OX40L[1-3]

Following TCR/MHC interaction, naïve T cells become activated and **express OX40**[1,4,5]

**OX40 signaling** leads to the activation of downstream pathways that **drive T-cell proliferation, survival, differentiation, and effector function**[3-6]

**Downstream of OX40 signaling**, $T_H2$ cells in AD skin secrete cytokines that drive inflammation and AD pathogenesis[1,7,8]

Other T-cell subsets (eg, $T_H1$ $T_H17$, $T_H22$) involved in AD pathogenesis undergo this same process[2,8-10]

**OX40 signaling in effector T cells also promotes development of memory T cells**, which contribute to the chronic nature of AD[1,3,11]

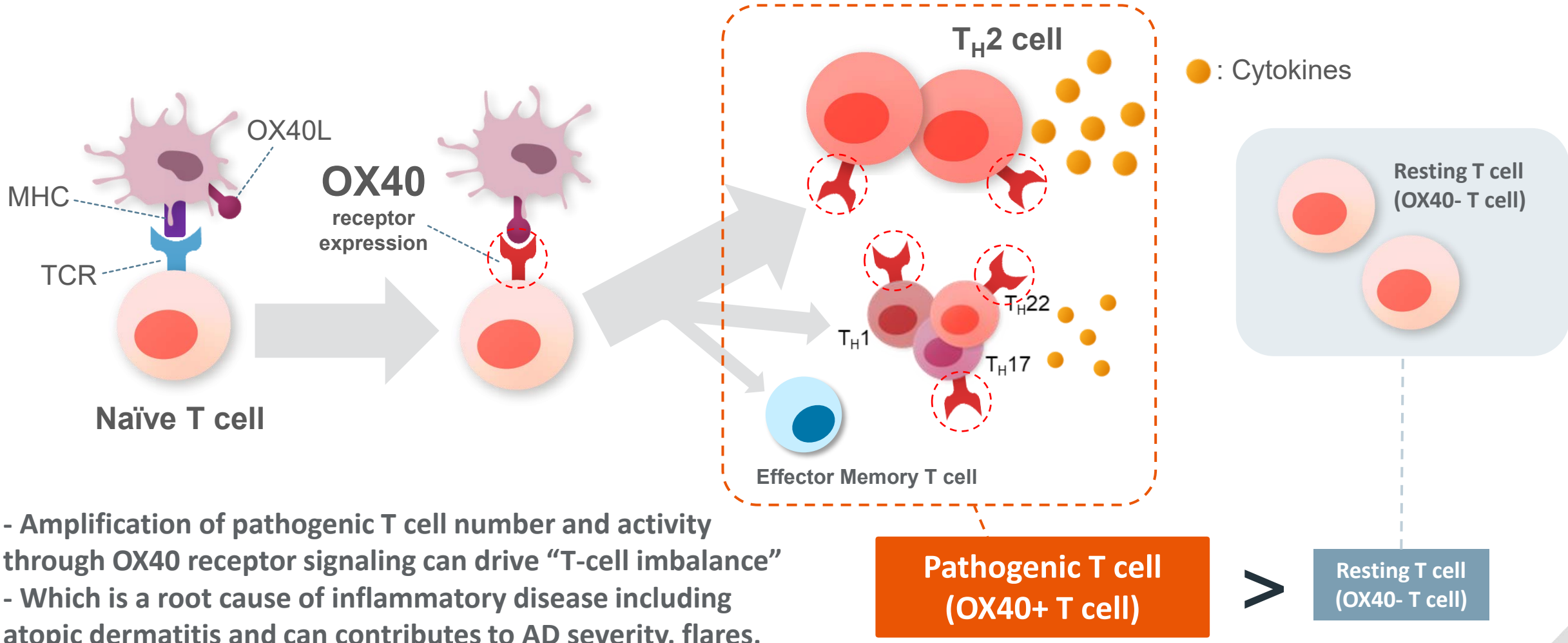
From 2023 AAD annual Meeting 2023
17-21 March 2023

AD=atopic dermatitis; MHC=major histocompatibility complex; OX40=OX40 receptor; OX40L=OX40 ligand; TCR=T-cell receptor; $T_H$=T helper cell.

**1.** Furue M, et al. *J Clin Med*. 2021;10:2578. **2.** Guttman-Yassky E, et al. *Semin Cutan Med Surg*. 2017;36:100-103. **3.** Croft M, et al. *Immunol Rev*. 2009;229:173-191. **4.** Magee CN, et al. *Am J Transplant*. 2012;12:2588-2600. **5.** Goronzy JJ, et al. *Arthritis Res Ther*. 2008;10(suppl 1):S3. **6.** Mascarelli DE, et al. *Front Cell Dev Biol*. 2021;9:692982. **7.** Krohn IK, et al. *Allergy*. 2022;77:827-842. **8.** De Bruyn Carlier T, et al. *J Autoimmun*. 2021;120:1026345. **9.** Kumar S, et al. *Int J Mol Sci*. 2019;20:2159. **10.** Fu Y, et al. *Acta Pharm Sin B*. 2020;10:414-433. **11.** Chen L, et al. *Cell Mol Immunol*. 2020;17:64-75.

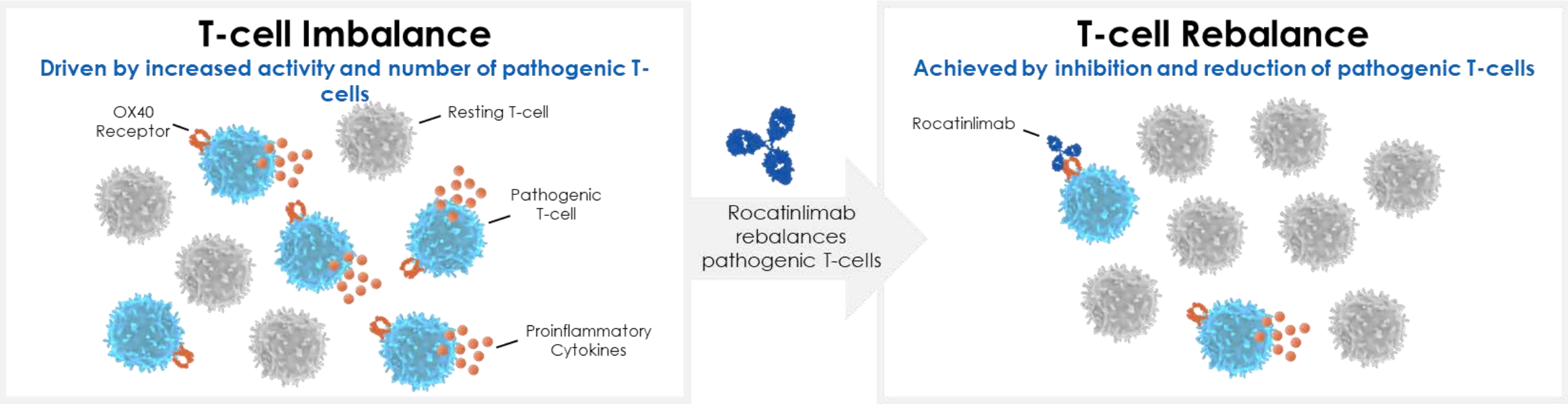
# OX40 Signaling induces T-cell imbalance

From 2023 AAD annual Meeting 2023
17-21 March 2023 (Modified)



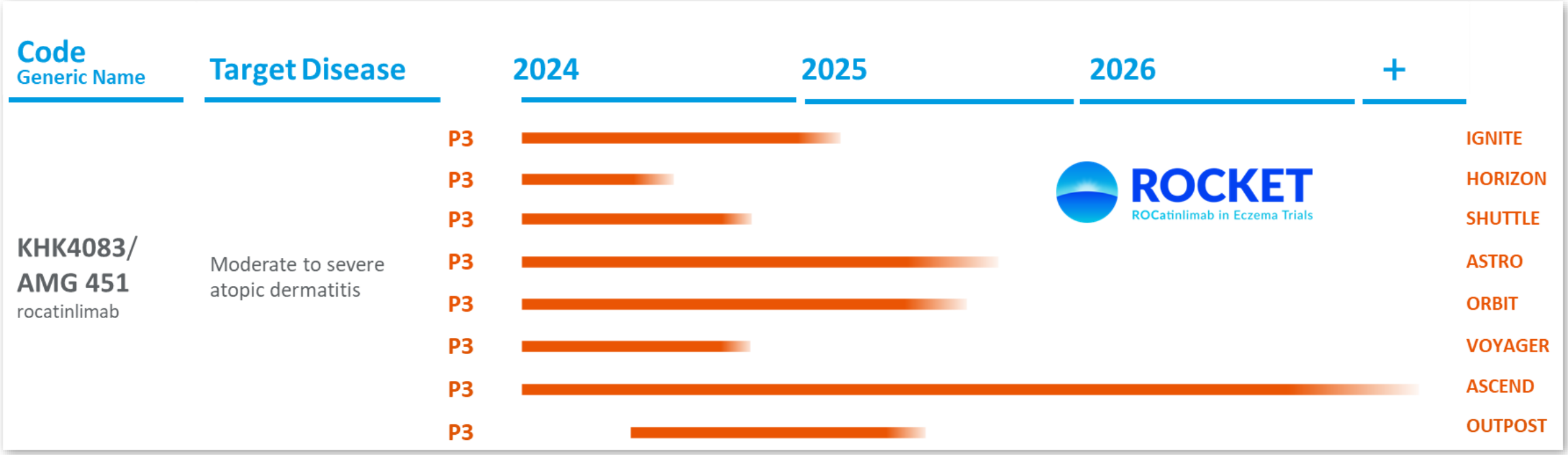

- Amplification of pathogenic T cell number and activity through OX40 receptor signaling can drive “T-cell imbalance”
- Which is a root cause of inflammatory disease including atopic dermatitis and can contributes to AD severity, flares, and disease persistence

# Rocatinlimab Rebalances T-cells by Targeting OX40 Receptor




- T-cell imbalance is a root cause of inflammatory disease
- Atopic dermatitis is driven in part by the proliferation of pathogenic T-cells
- Rocatinlimab has the potential to inhibit and reduce pathogenic T-cells across heterogeneous patient types by targeting OX40 inhibitor

# ROCKET program – Future Plans




**The results of the HORIZON trial introduced today are the first of eight pivotal study readouts in the ROCKET program**
**We will continue this program to further our understanding of the profile of rocatinlimab**

# KK2845

# Overview of Acute Myeloid Leukemia (AML) and ADC Development Status

## AML - Disease Overview

- Hematological malignancy characterized by the abnormal proliferation of immature blood cells (blasts) in the bone marrow, suppressing the production of normal blood cells.
- Challenges in Current Treatments: High relapse rates, with many cases recurring within five years post-treatment.
- It is believed that a small number of leukemic stem cells (LSCs) in the bone marrow, contributing to relapse and drug resistance after treatment.
- The number of patients with relapsed/refractory AML is estimated to remain be approximately 22,000 in Japan, the US, and Europe.

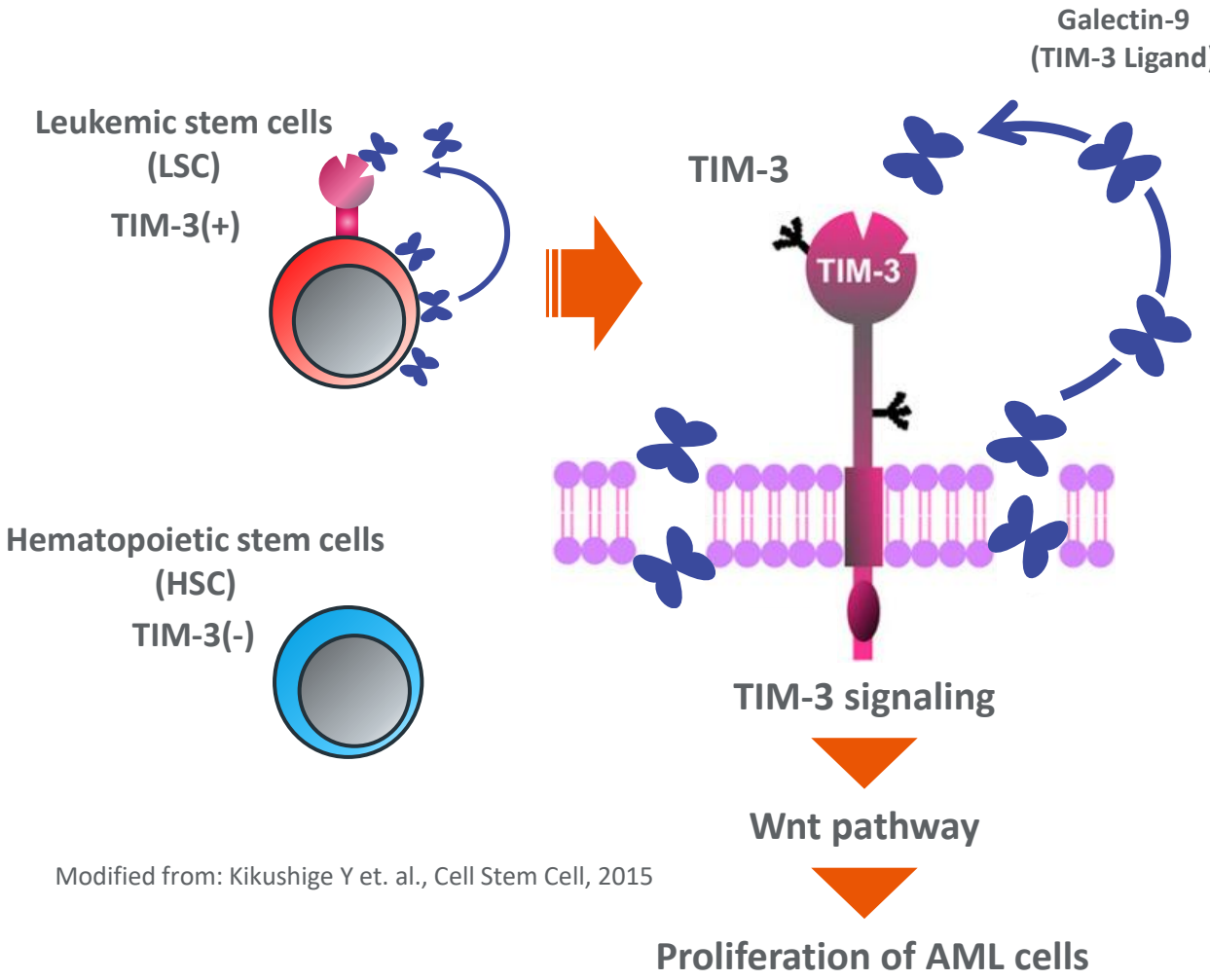
## Overview of ADC Development

- Although CD33-ADC has been developed, the expression of CD33 in normal stem cells has led to significant bone marrow suppression as a major issue.
- As a result, the development of new drugs for AML has been limited in its success.
  (J. Adv. Pract. Oncol. 2019;10(1):68–82.; Blood. 2018;132(11):1125-1133.; Leukemia. 2019 Jan;33(1):64-74.; Trends in Pharmacological Sciences, 2024;45(5):430-448.)

# KK2845 – Development History of ADC for r/r AML

- Conducted screening for novel therapeutic target molecules in collaboration with Kyushu University and identified TIM-3.
- TIM-3 is expressed on AML LSCs and blast cells but not on normal hematopoietic stem cells, demonstrating high expression selectivity. (Kikushige Y et. al., Cell Stem Cell, 2010)
- TIM-3 contributes to AML onset, LSCs self-renewal and propagation, and progression from MDS* to AML. (Kikushige Y et. al., Cell Stem Cell, 2015)

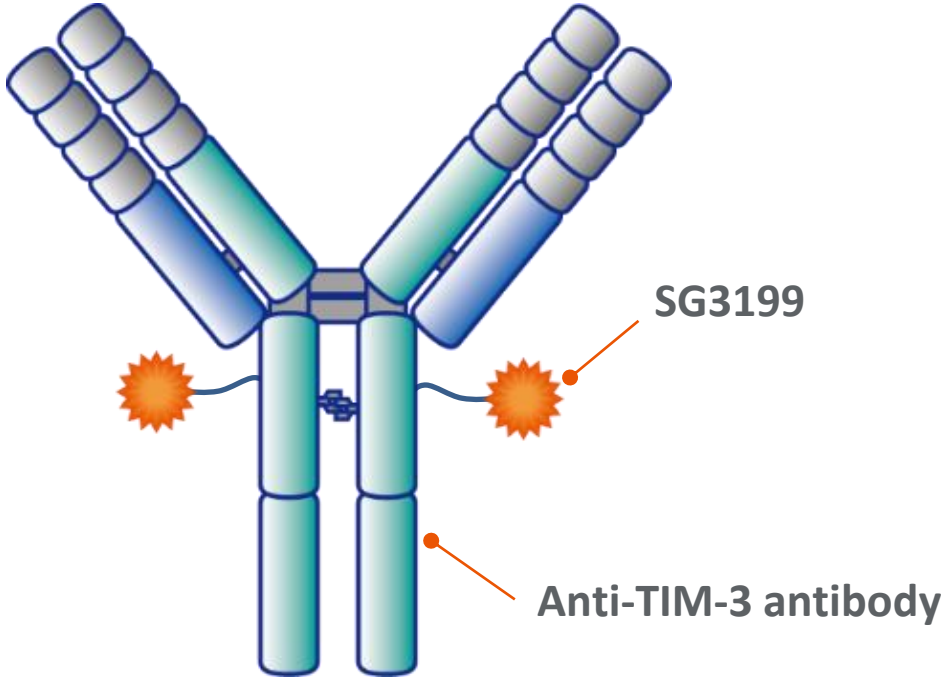
* myelodysplastic syndromes




Modified from: Kikushige Y et. al., Cell Stem Cell, 2015

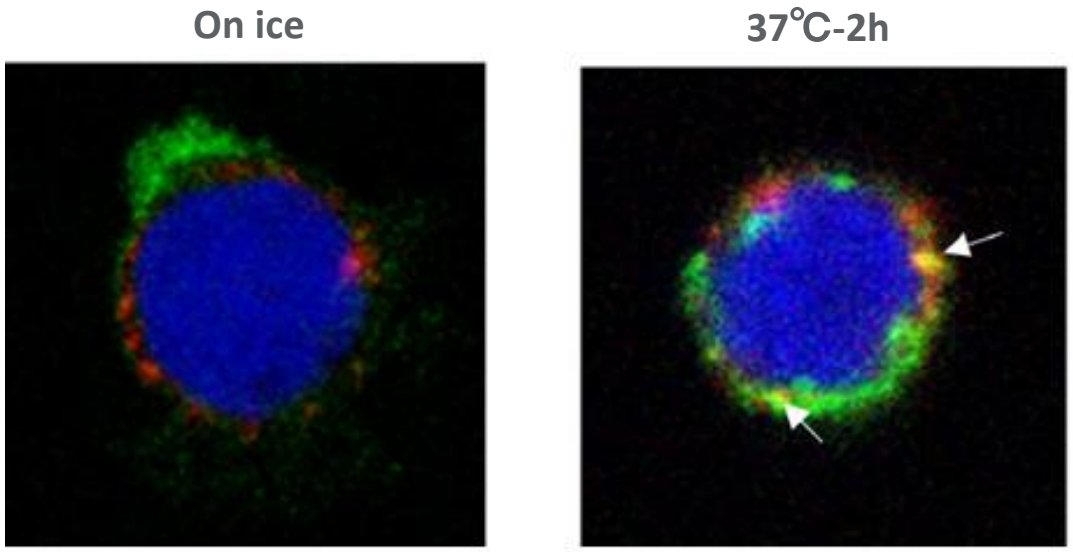
**Initiated development of TIM-3-targeted ADCs aiming to the balance of AML relapse prevention and safety, key challenges in AML treatment**

# KK2845 - Overview




**Internalization into cells**

Green : KK2845-Alexa488
Red : Lysosome
Blue : Nuclear

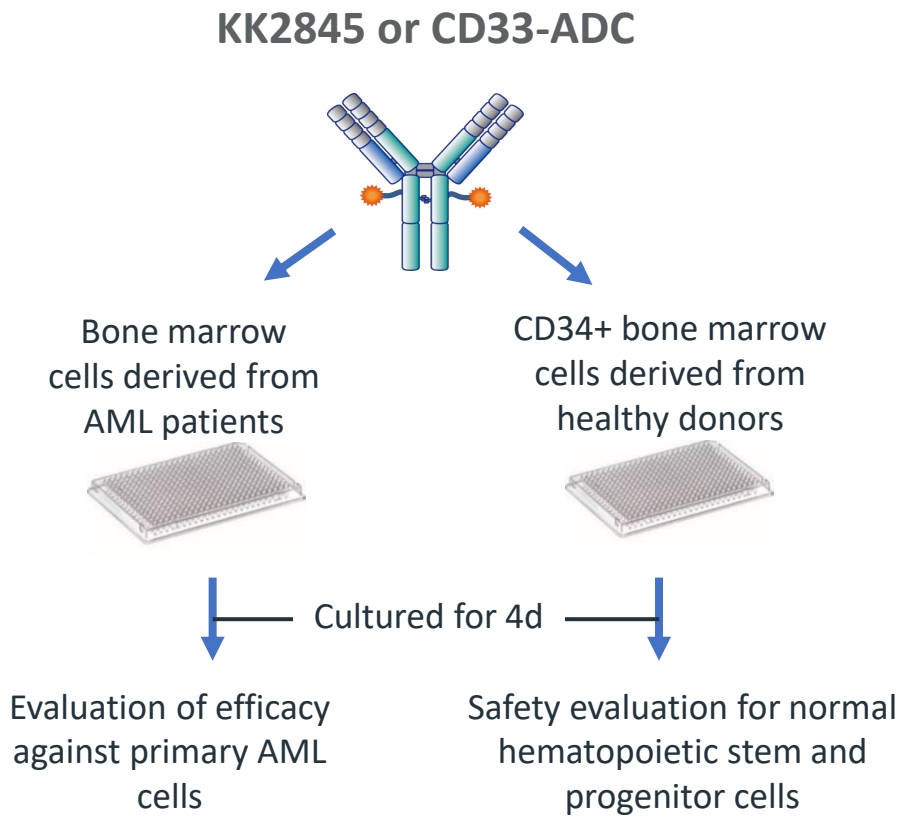


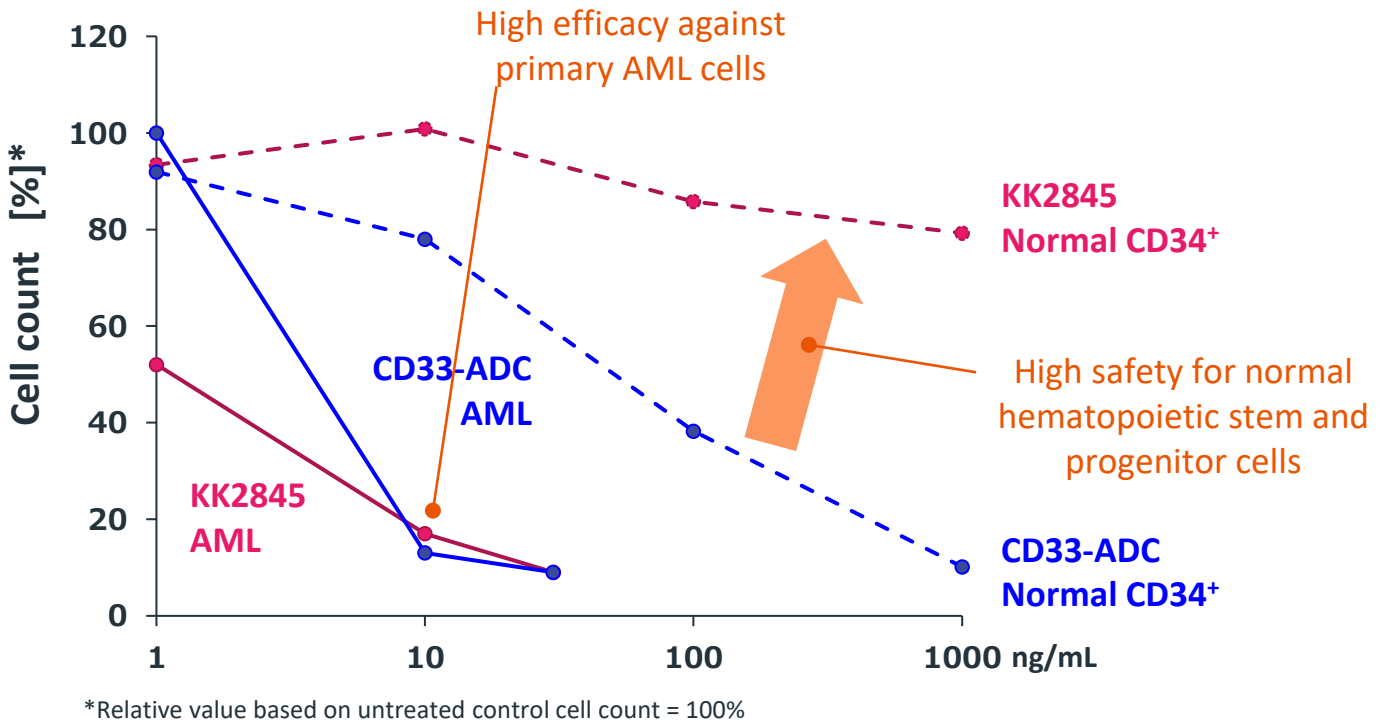

**Note: The arrows indicate where KK2845 merges with lysosomes**

- **Target Molecule : TIM-3** - Aiming to avoid myelosuppression
- **Payload : SG3199** - the PBD molecule also used in marketed drugs, with high expected efficacy

From European Hematology Association (EHA) 13-16 June 2024

# Evaluation of anti-cellular activity against primary AML cells and normal bone marrow cells



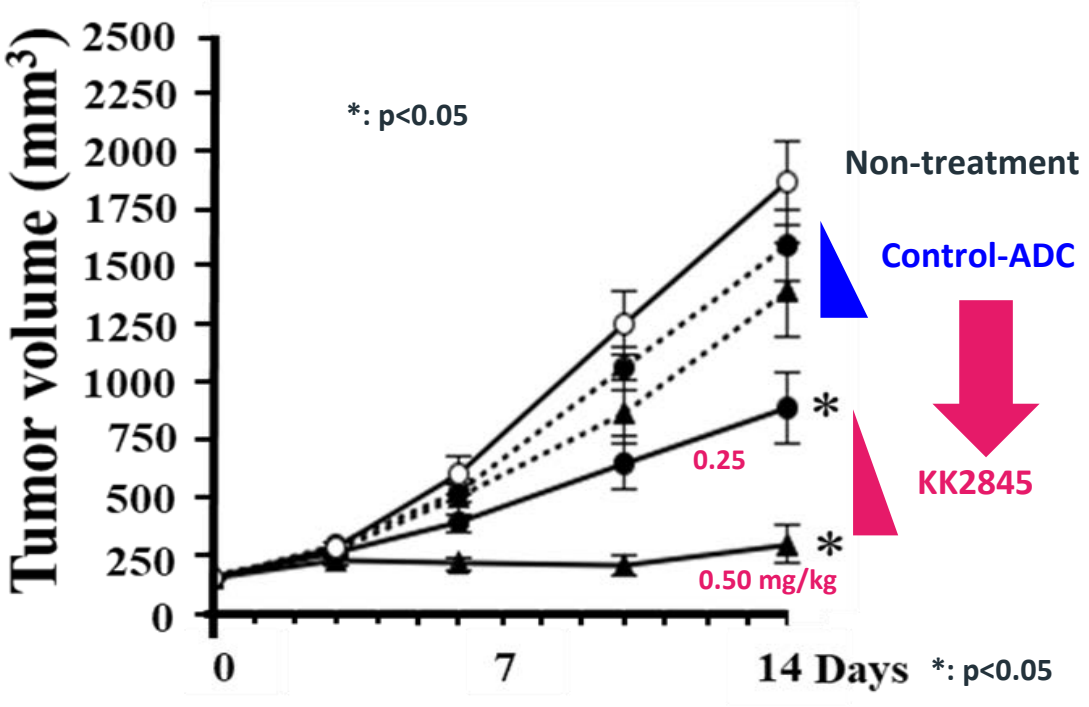

*Relative value based on untreated control cell count = 100%

**KK2845 demonstrated similar efficacy and higher safety compared to CD33-ADC**

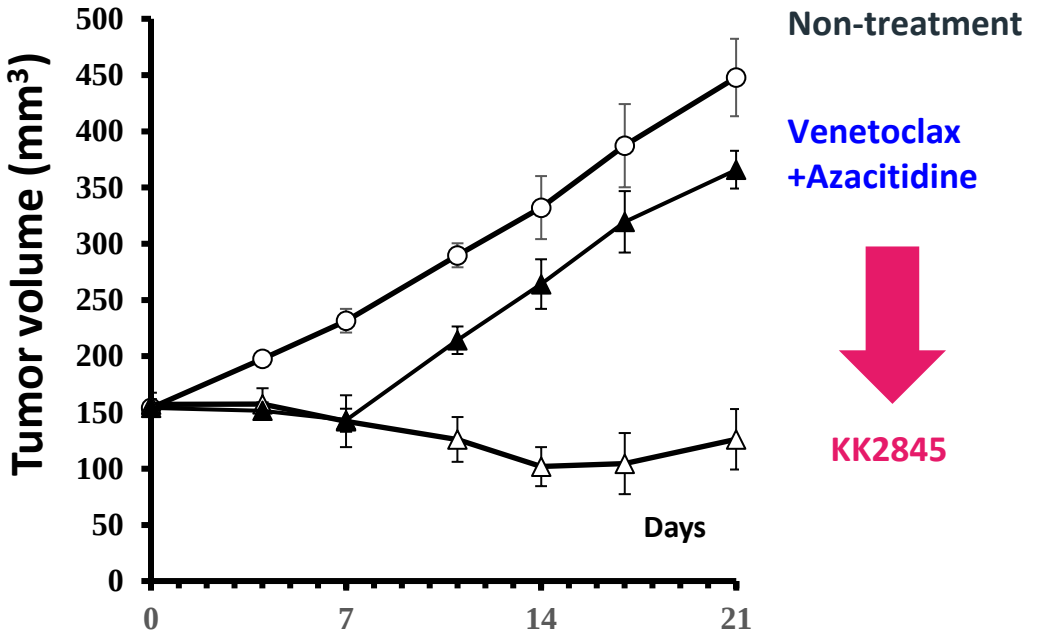
From European Hematology Association (EHA) 13-16 June 2024

# In vivo Anti-tumor Activity Evaluation

AML Cell Line CMK11-5 (TIM-3 positive) Mouse Model




AML Cell Line Kasumi-3 (TIM-3 positive) Mouse Model

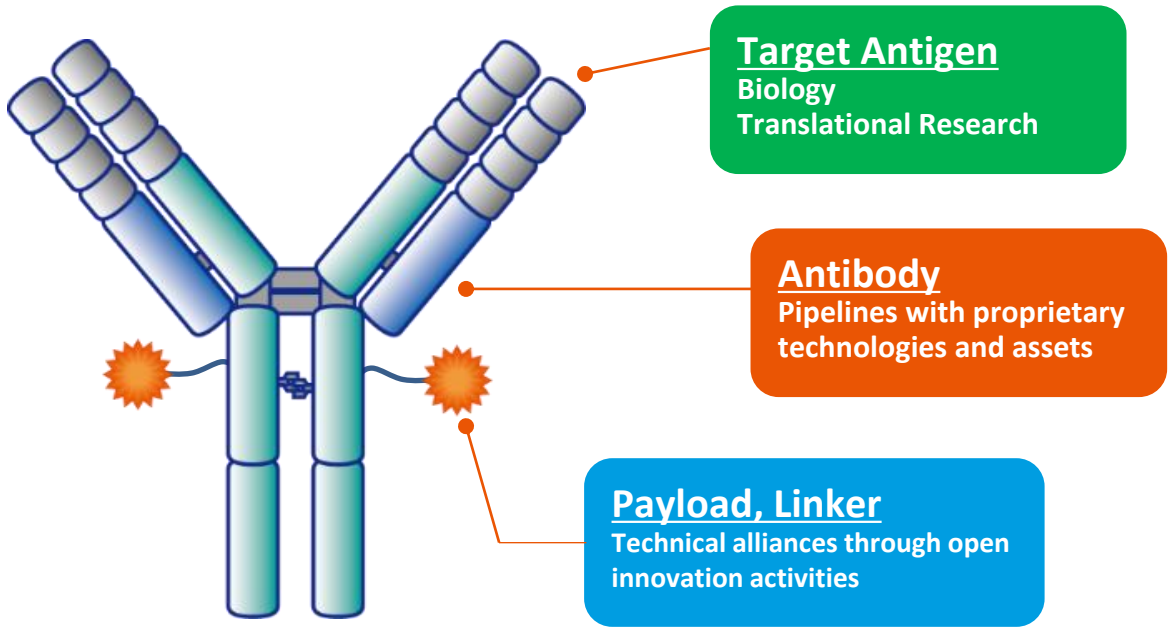



- TIM-3-dependent anti-tumor activity of KK2845 was observed
- KK2845 showed strong anti-tumor activity even in model resistant to Venetoclax/Azacitidine, the standard treatment for AML

From European Hematology Association (EHA) 13-16 June 2024

# ADC Research and Development Strategy

**Creation of new drugs in Intractable hematological diseases/hemato oncology through Kyowa Kirin's antibody technologies combined with ADC technologies**




| # | Current status & Plan |
|---|---|
| KK2845 | 2024 Q3 P1 Initiation |
| ADC-2 | Non-clinical/CMC stage; Phase 1 initiation planned for 2025 Q4 |
| ADC-3 | Non-clinical/CMC stage |
| ADC-4 | Research stage |

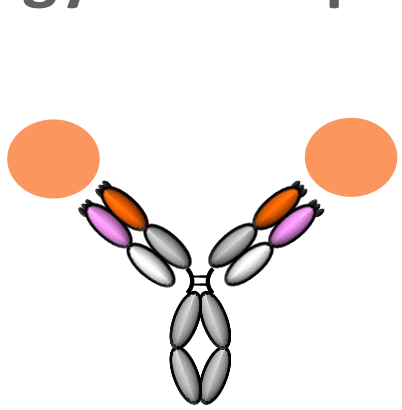
- Collaborative research maximizing antibody technologies of academia and Kyowa Kirin
- Partnering with entities possessing competitive payload technologies for hematological malignancies and refractory diseases
- Collaborating with CDMOs and technology partners to ensure the manufacture of high-quality ADCs

# REGULGENT™

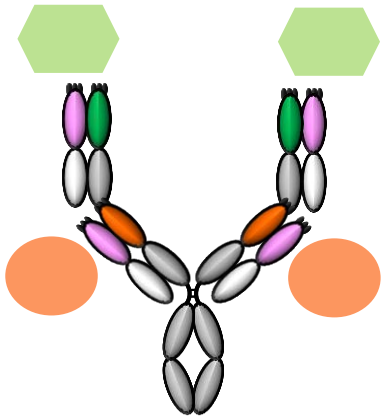
# Significance of Bispecific Antibody Technology Development

**Limitations of conventional monoclonal antibodies have been noted**

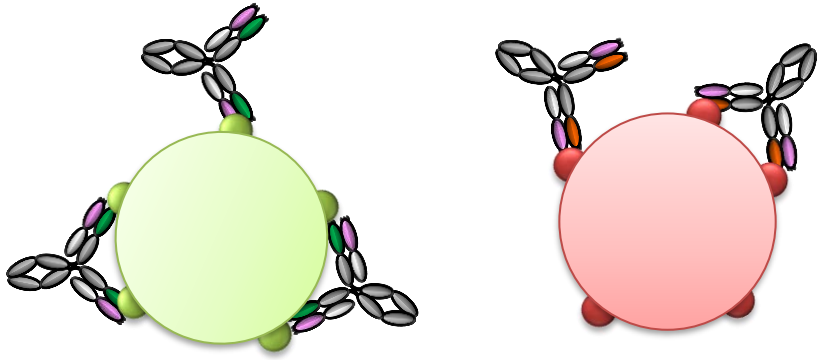
- Depletion of target antigens
- Exposure of limitations in efficacy and resistance
- Difficulty in acting on multiple factors
- Limitations in target selectivity and avoidance of side effects



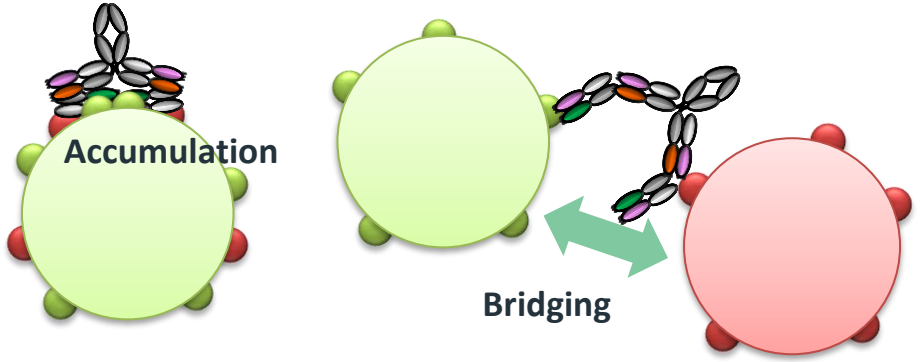
Monoclonal antibody (IgG)



Bispecific Antibody (Example)



Monoclonal antibody (IgG)




Bispecific Antibody (Example)
Achieves more diverse binding modes

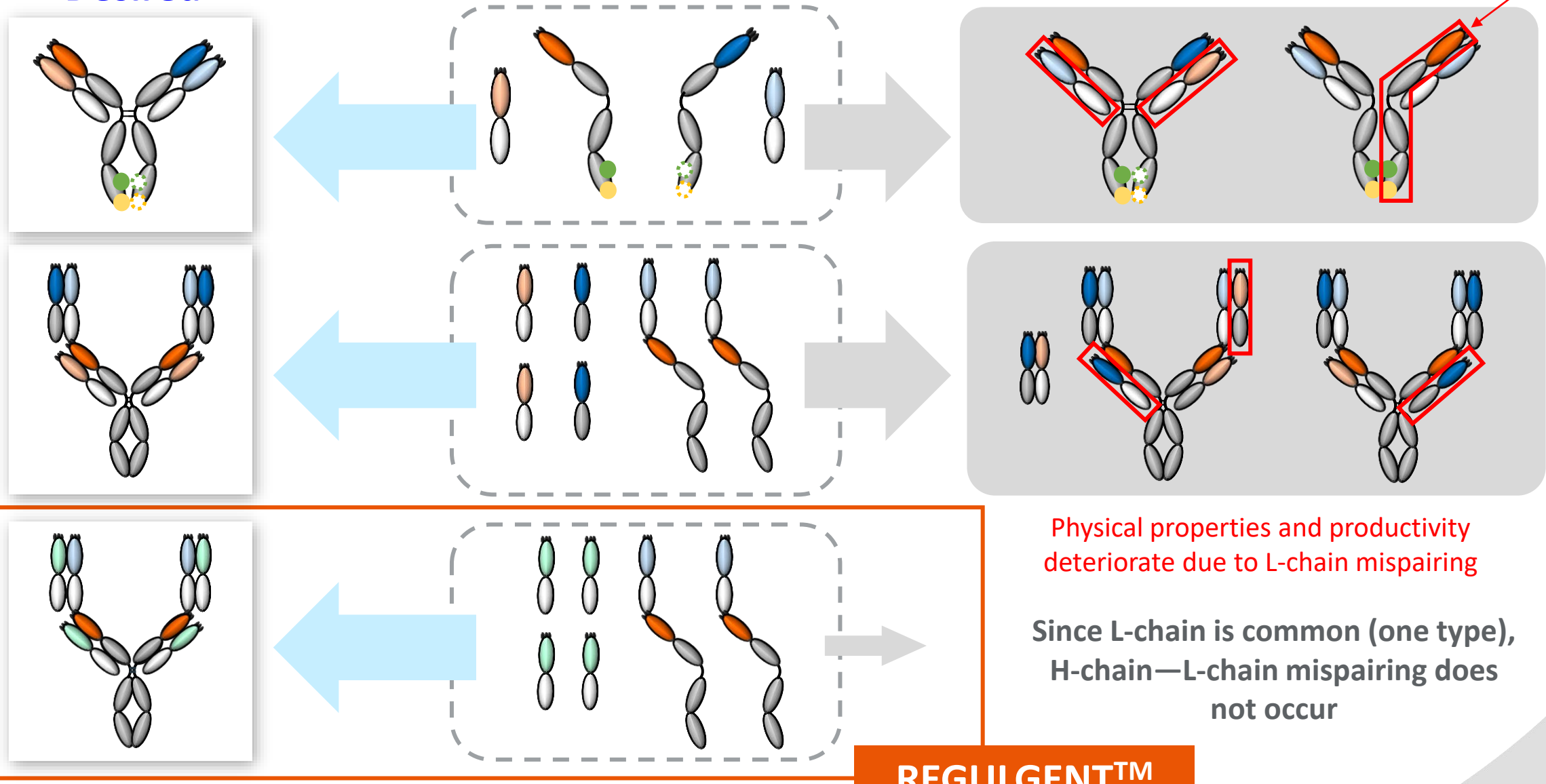
**Bispecific antibodies are developed as a technology to overcome the limitations of monoclonal antibodies**

# Challenges of Bispecific Antibodies: Physical properties and productivity

Kyowa KIRIN

**Desired**

**Undesired**




Physical properties and productivity deteriorate due to L-chain mispairing

**Since L-chain is common (one type), H-chain—L-chain mispairing does not occur**

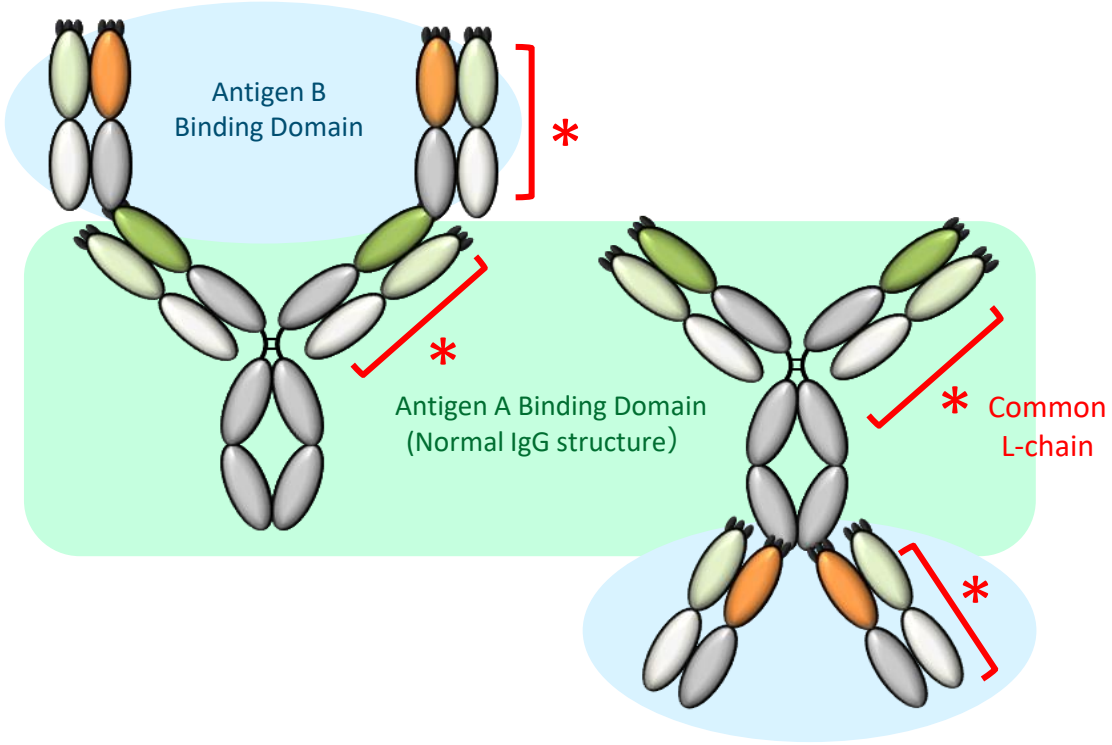
**REGULGENT™**

# About REGULGENT™

General characteristics of bispecific antibodies

- Able to perform actions that IgG cannot by acting on two types of antigens*
- Composed of a combination of non-common L-chain antibodies or by utilizing antibody-like molecules

* e.g., cross-linking of two types of cells or molecules




N-terminal type C-terminal type

## Characteristics of REGULGENT™

### Simple structure, minimized immunogenicity

- Use of common L-chain (*), only natural IgG sequence
- Uniformity with no combination of different molecules
- Physical properties and pharmacokinetics equivalent to IgG

### Bivalent-bivalent binding, N&C-terminal type

- Can be expanded to a variety of mechanisms of action

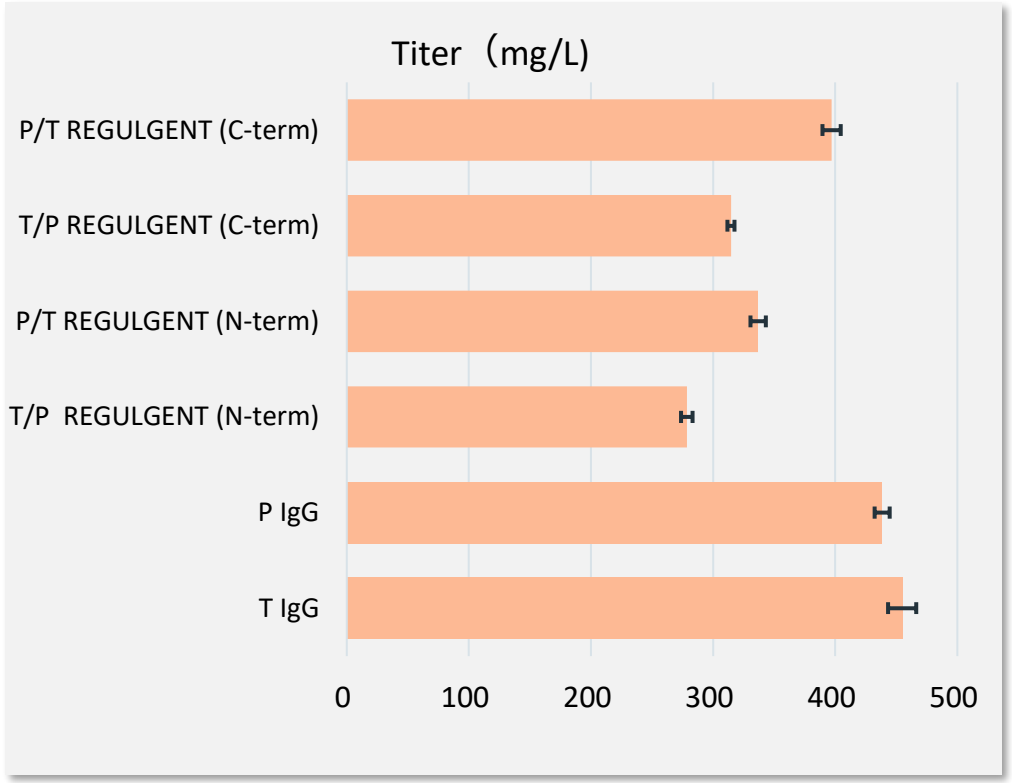
### Stable production process, easy handling

- High productivity equivalent to IgG
- Can be adapted to the conventional antibody manufacturing process

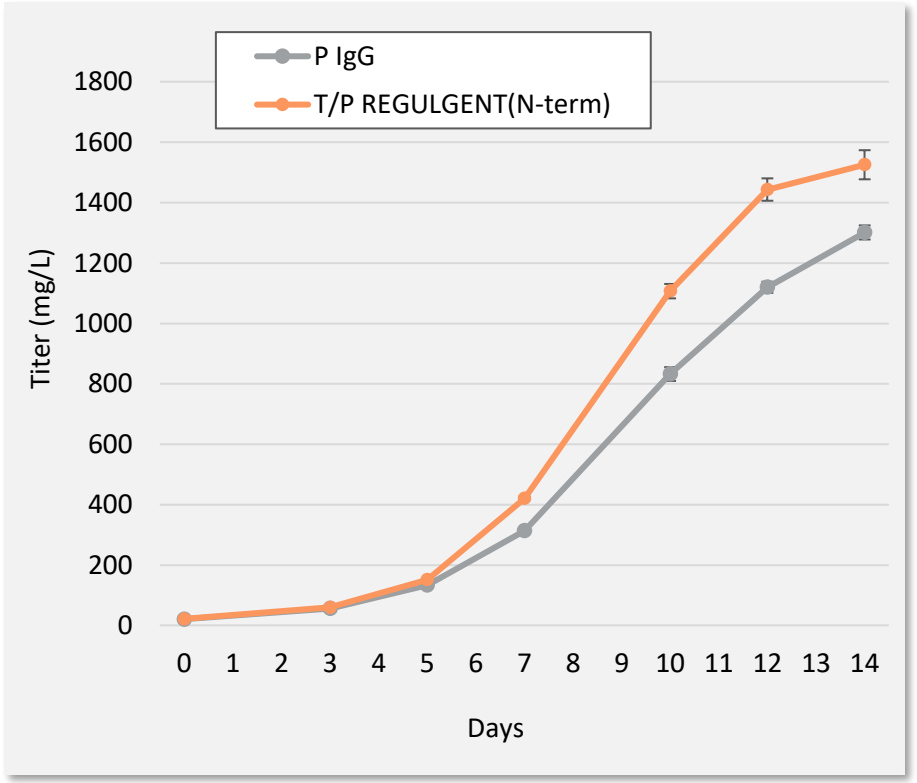
**Proprietary bispecific antibody technology created from our antibody R&D experience**

# Productivity of REGULGENT™

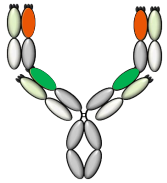
Transient expression using ExpiCHO-S™ cells
(day 8 post-transfection)

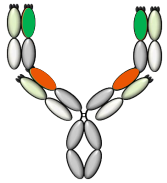


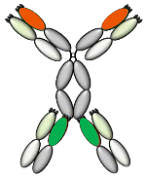

Stable expression using CHO cells

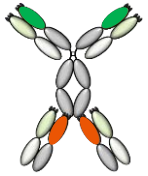



T : TRAIL-R2
P : PSMA


T/P REGULGENT (N-term)


P/T REGULGENT (N-term)


T/P REGULGENT (C-term)


P/T REGULGENT (C-term)

## All demonstrated high productivity comparable to IgG levels

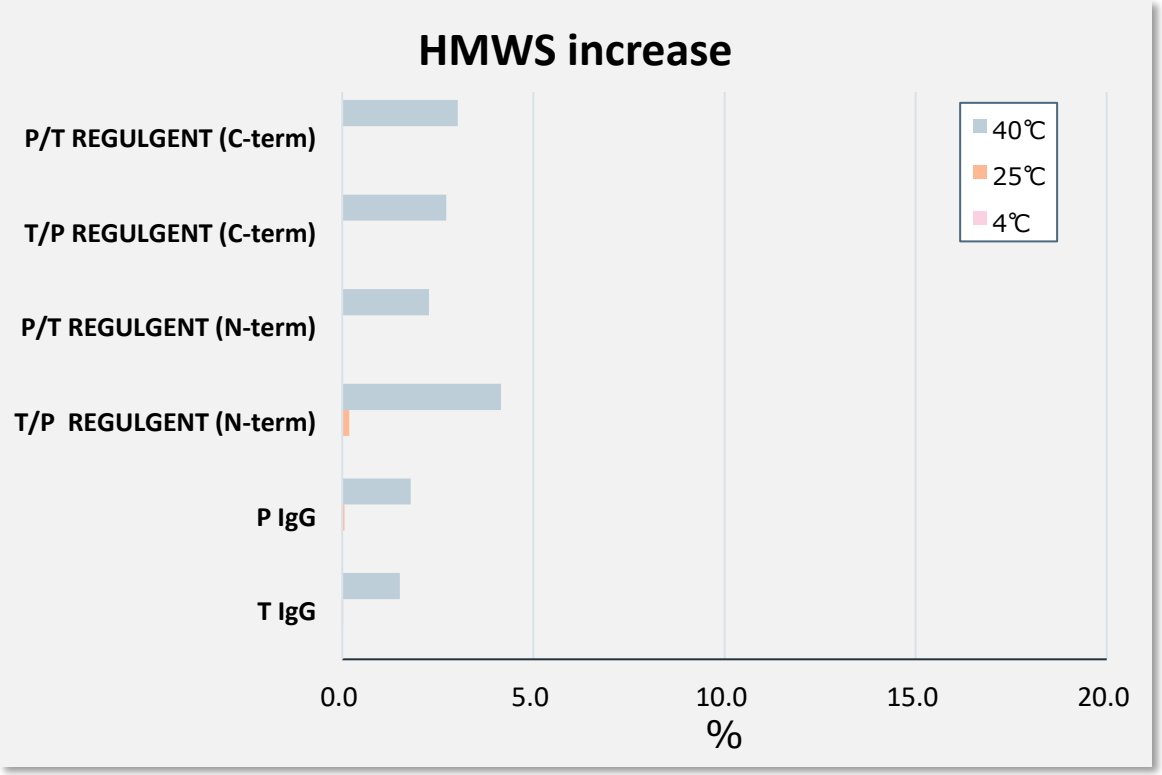


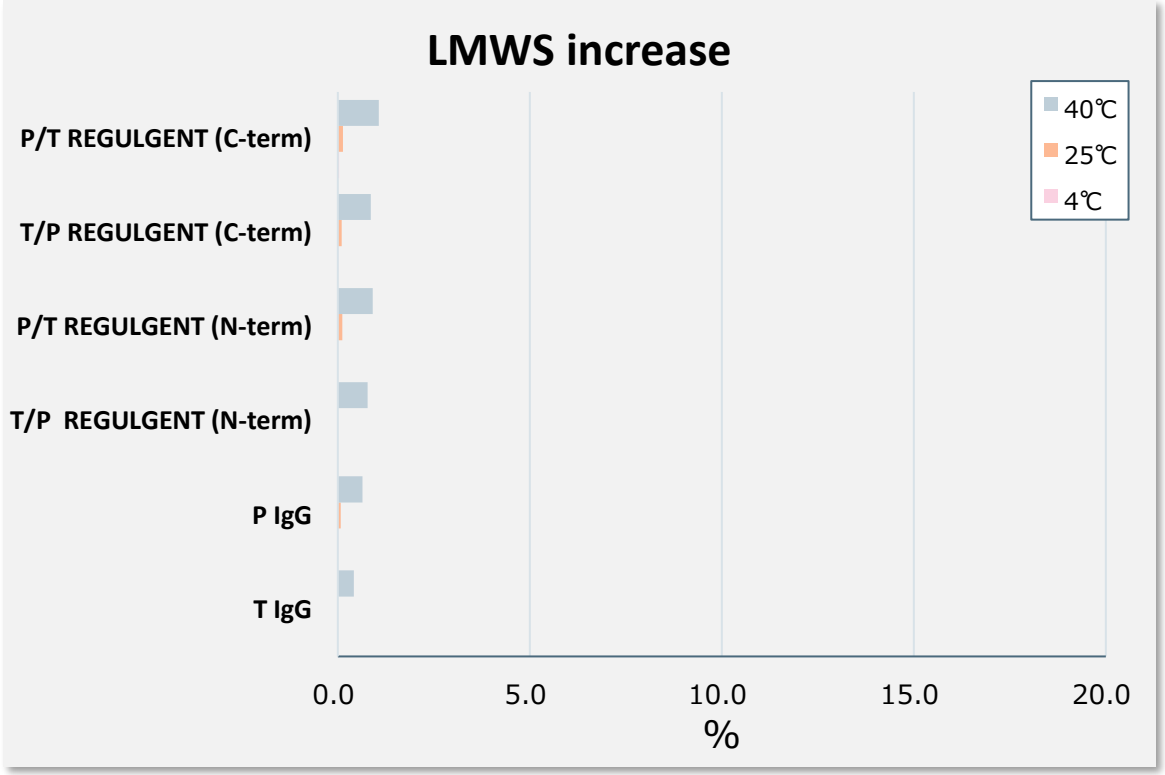

Protein Science. 2024;33:e5121.

# Physical Properties and Stability of REGULGENT™

Stored for one month at 4, 25, and 40°C, and the increase in HMWS (aggregates) and LMWS (degradation products) was evaluated by size exclusion chromatography

| | |
|---|---|
| HMWS | High-molecular-weight species |
| LMWS | Low-molecular-weight species |



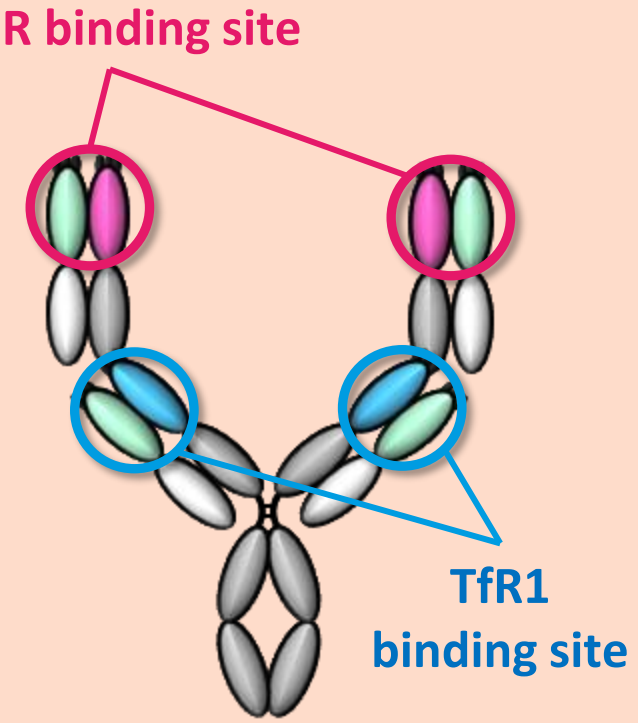




**REGULGENT™ demonstrated favorable physical properties and high stability comparable to IgG levels**

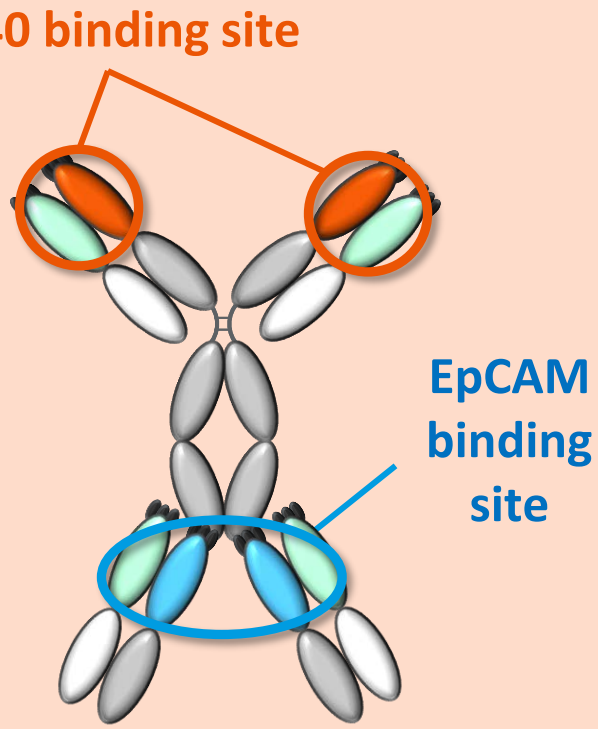



Protein Science. 2024;33:e5121.

# REGULGENT™ Technology Pipelines




**KK2260**
N-terminal type




**KK2269**
C-terminal type

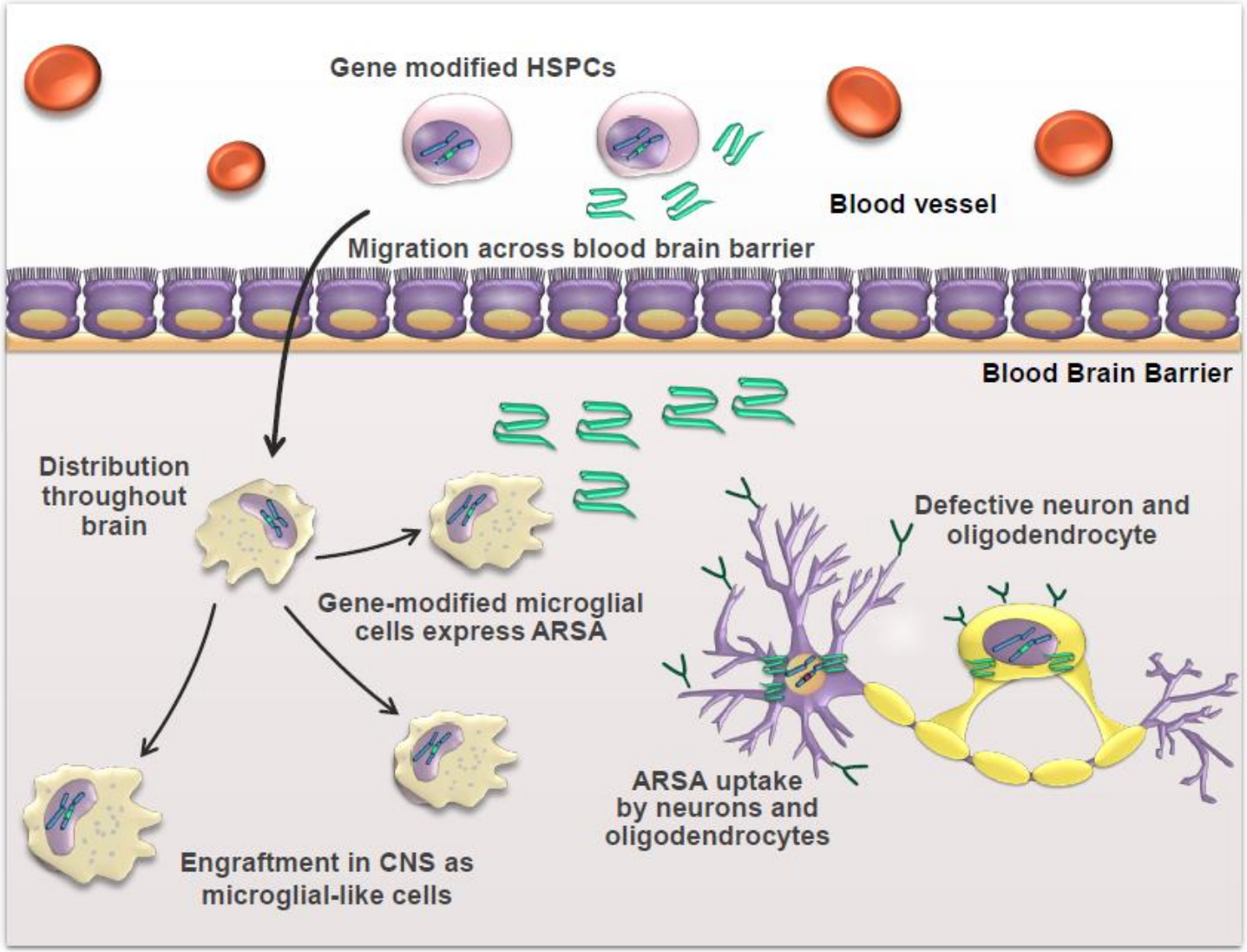
- **Disease under development**
  Advanced or metastatic solid tumors
- **Development status**
  Phase 1

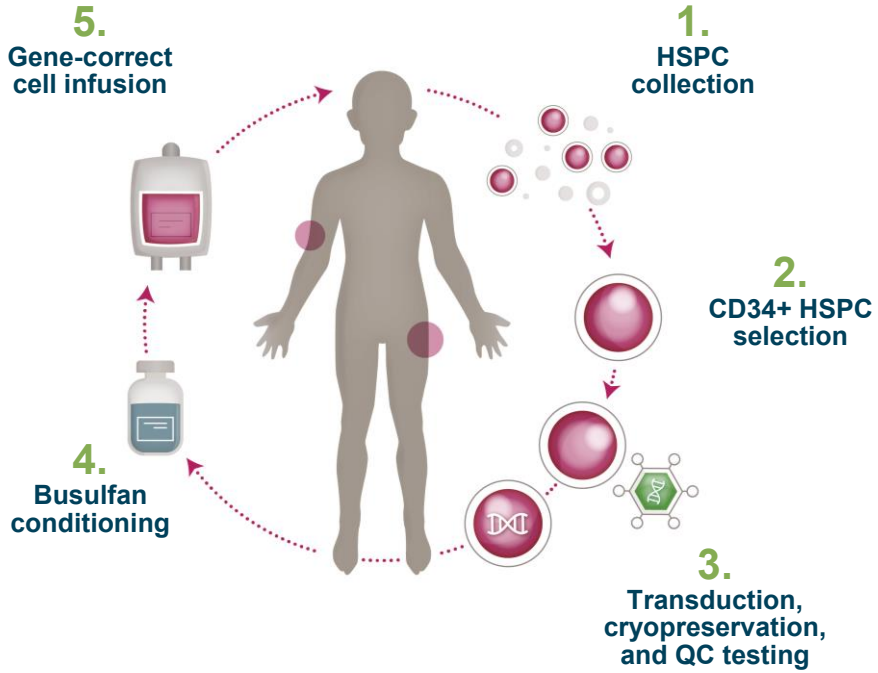
**We will continue to create new pipelines that leverage the characteristics of this technology in the future**

# HSC-GT

- HSC-GT MoA
- Lenmeldy/Libmeldy
- OTL-203 (Registrational study)
- OTL-201 (PoC study)

# HSC-GT: Enabling localized delivery of therapeutic proteins and enzymes to the CNS to treat multi-system neurometabolic diseases

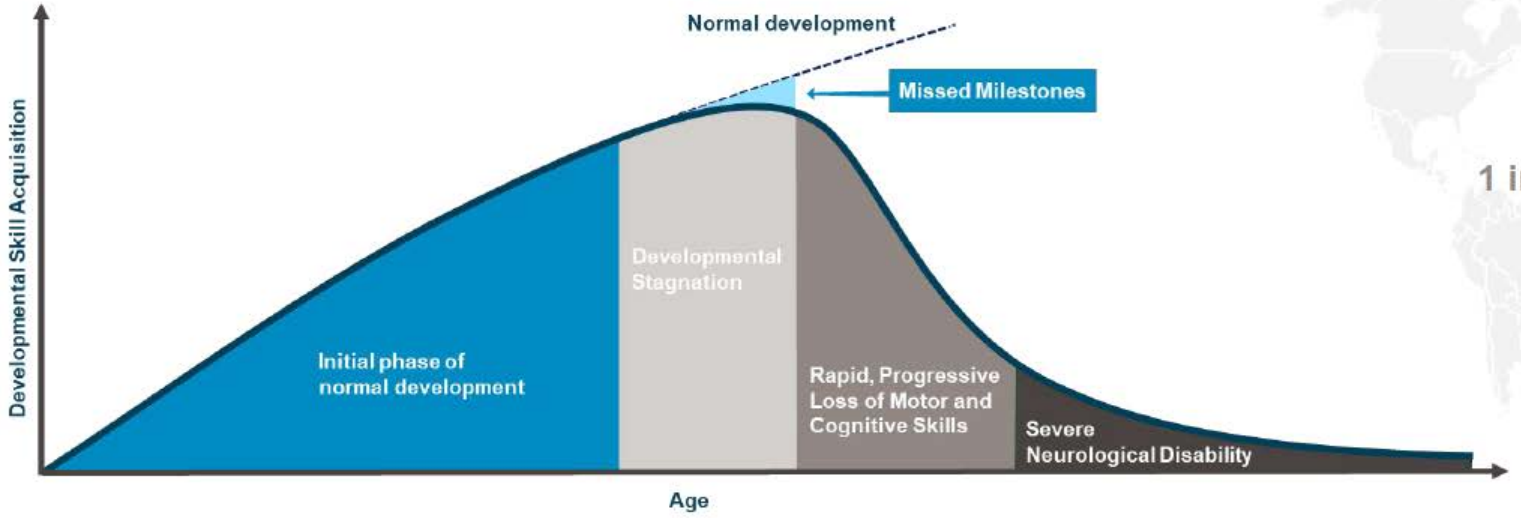


# Metachromatic Leukodystrophy (MLD): A devastating genetic disease

***Demyelinating lysosomal storage disorder caused by arylsulfatase A (ARSA) deficiency and subsequent accumulation of sulfatides in the CNS and PNS***

## Clinical Course of Early-Onset MLD




## MLD Global incidence:

Estimated

1 in 100,000 live births[1,2]

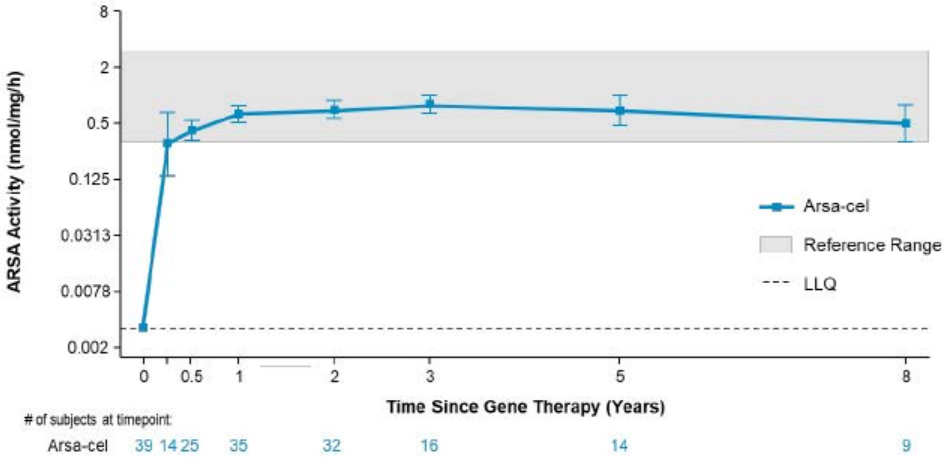
## MLD Classification

| | Early Onset (<7 yrs) | | Late Onset (≥7 yrs) | |
|---|---|---|---|---|
| | Late-infantile (LI) | Early Juvenile (EJ) | Late Juvenile (LJ) | Adult Onset |
| Age of onset | ≤ 30 mo | > 30 mo to < 7yrs | 7 to < 17 yrs | ≥ 17 yrs |
| Genotype | Typically 0/0 | Typically 0/R | Typically R/R | |
| ARSA Activity | Estimated residual ARSA enzyme activity *in vivo* | | | |

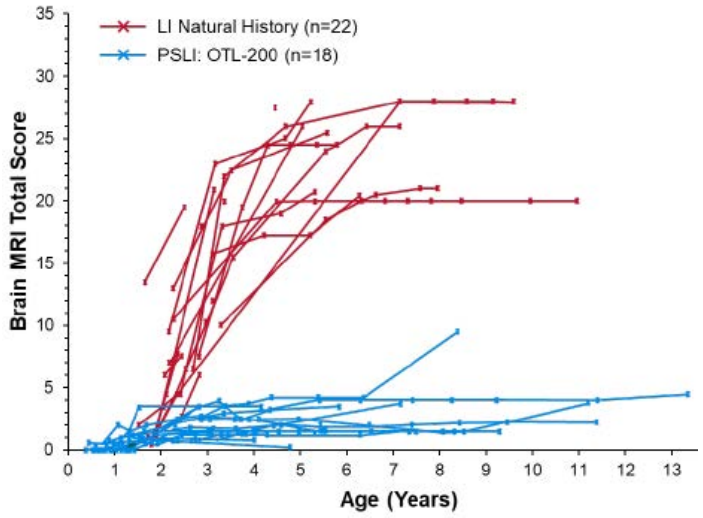
1. Gieselmann V, Krageloh-Mann I. *Neuropediatrics*. 2010;41(1):1-6. 2. Bonkowsky JL, et al. *JAMA Netw Open*. 2018;1(7):e185031.

# Results in Pre-Symptomatic Late Infantile (PSLI) patients

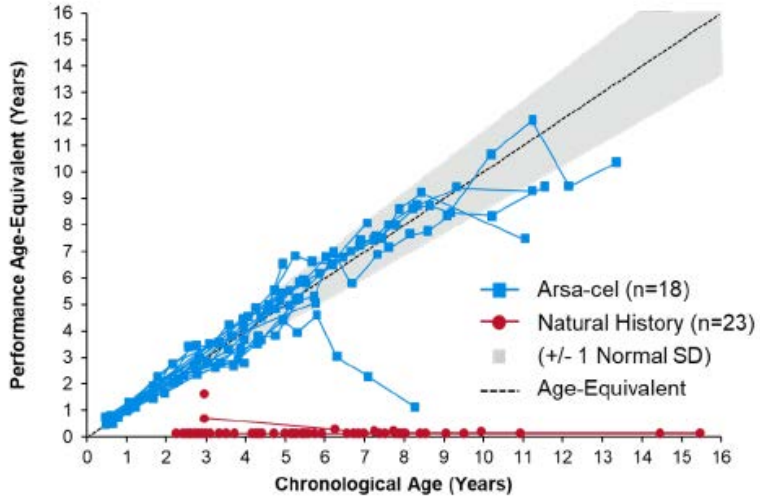
## ARSA Activity in CSF




## Brain MRI Total Score



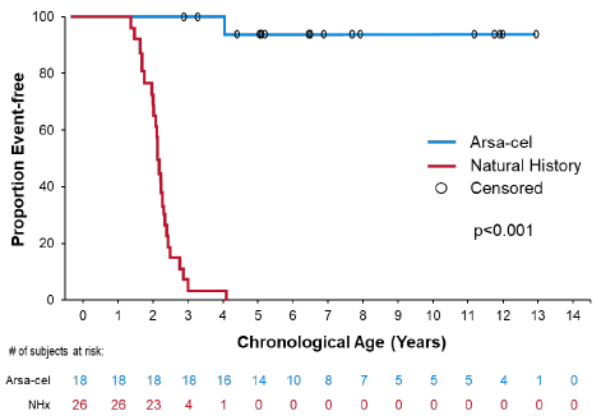

## Cognitive Performance Age Equivalent




## Motor and survival outcomes

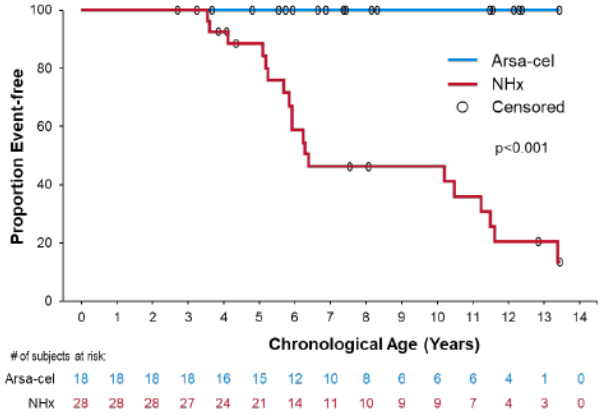
### Motor Impairment Free Survival (MFS)

Interval from birth to first occurrence of GMFC-MLD ≥ 3* (unable to walk with or without support) or death




### Overall Survival (OS)

Interval from birth to death from any cause



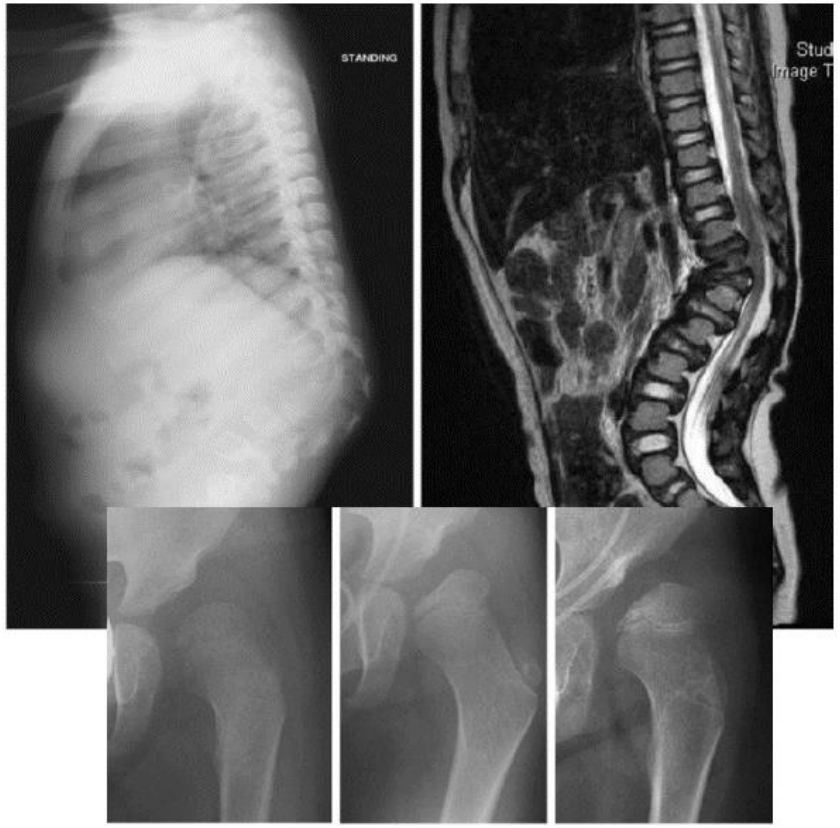

With extended follow-up (median 6.66 yrs, **max 12.19 yrs**) Lenmeldy/Libmeldy treatment:

- Preserves cognitive function and motor development in PSLI patients compared to disease natural history
- Continues to show a favorable benefit-risk profile and long-term durability of treatment effect

# OTL-203 – MPS-IH (Hurler Syndrome) disease background

## MPS-IH - Disease snapshot

- Multisystemic neurometabolic condition affecting cognition, growth and skeletal function
- Diagnosed during first 2 years of life; life-expectancy up to 10 yrs.
- Current standard of care: Allogeneic HSCT and~~/or~~ ERT, both of which have significant limitations
- ~1:100,000 live births; NBS established in some geographies, including U.S.



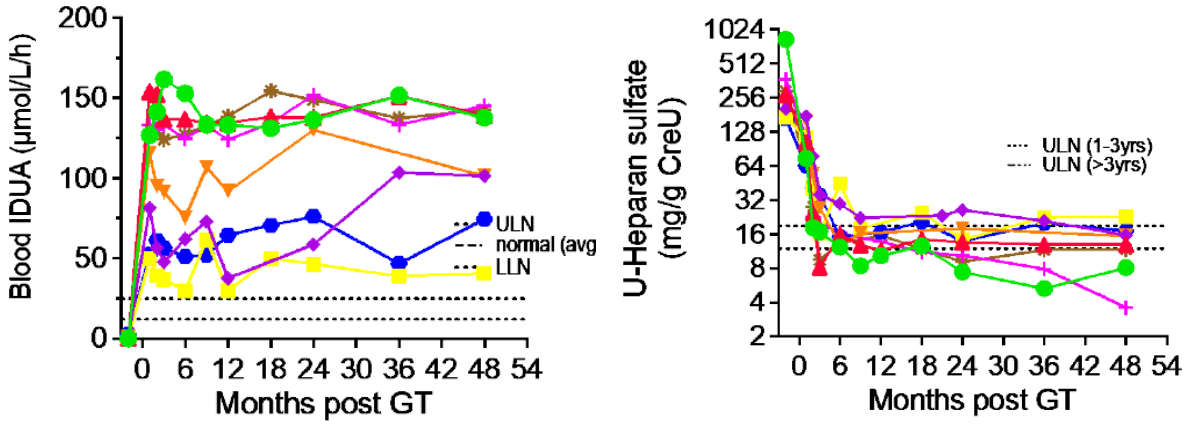

## Summary of the proof-of-concept (PoC) study

- Target group: Patients with MPS-IH, without access to a suitable allogeneic donor, preserved neurocognitive function (DQ/IQ ≥70), fit for transplant (N=8)
- Endpoints: IDUA in blood at 1Y, GROWTH VELOCITY at 1, 3 and 5Y, motorfunction, spine MR score at 1, 3 and 5Y.

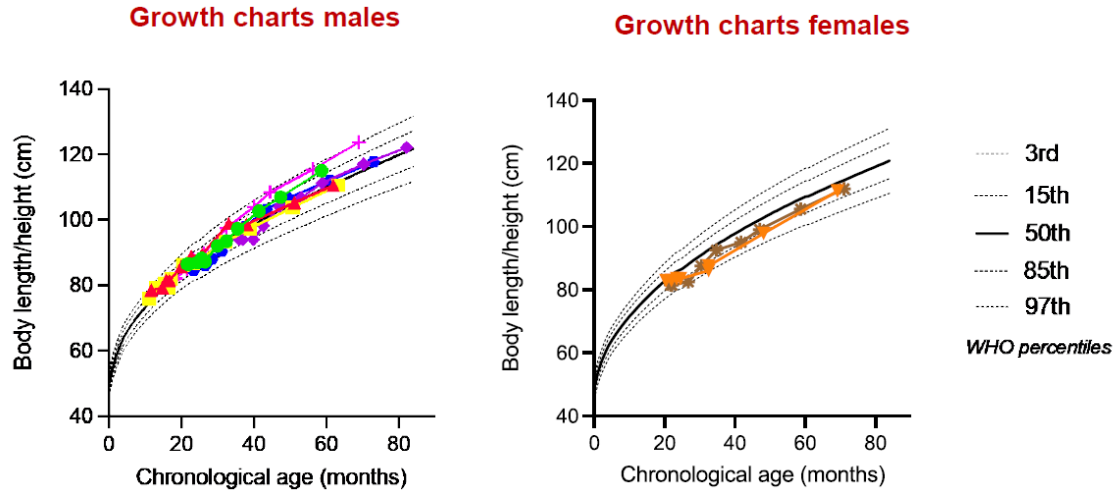
Gentner, … & Bernardo. N Engl J Med2021

# PoC study results: Biochemical and early skeletal outcomes

## Biochemical outcome after GT

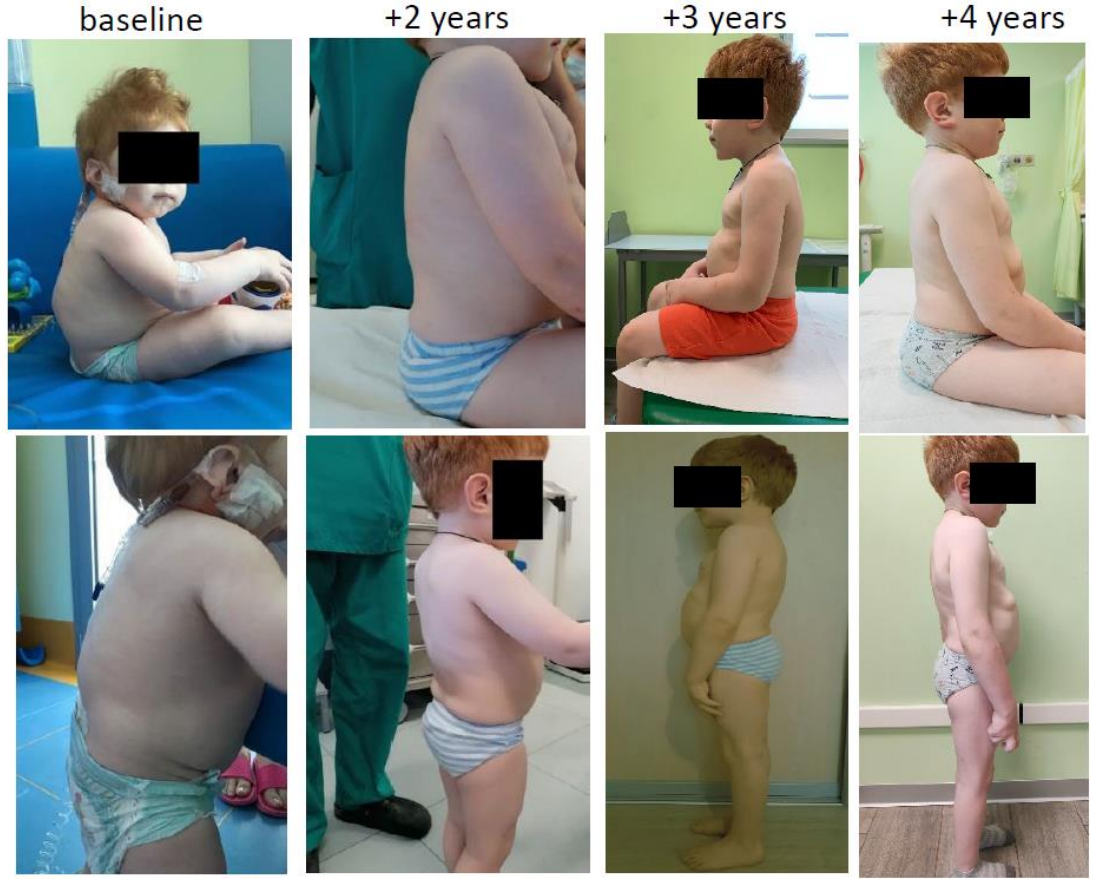



## Auxological parameters after GT




[Short stature defined as height -2 SDS]

## Standing & sitting kyphosis after GT



# OTL-201 – MPS-IIIA (Sanfilippo syndrome type A)

## Disease snapshot

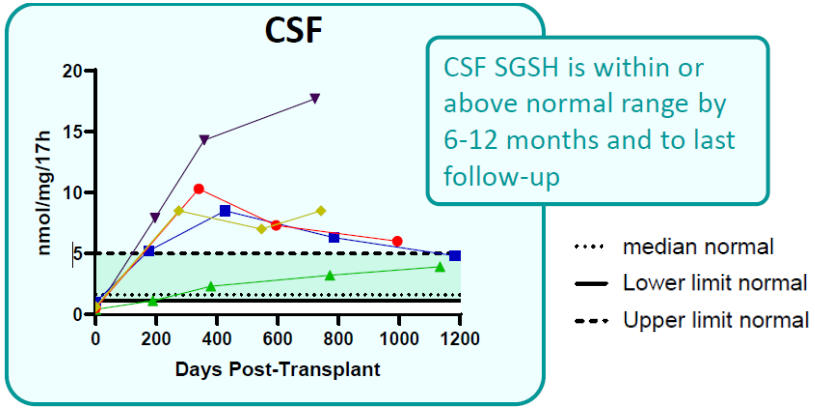
- Sanfilippo syndrome type A; pathogenic variants in *SGSH* gene
- Accumulation of substrate heparan sulfate leading to severe CNS degeneration w/ some somatic manifestations
- Severe phenotype development slows from 3 years of age, followed by cognitive decline, behavioural disturbances, loss of skills and eventual death
- No successful treatment options
- Incidence: ~1 in 100,000 live births

## Summary of ongoing PoC study

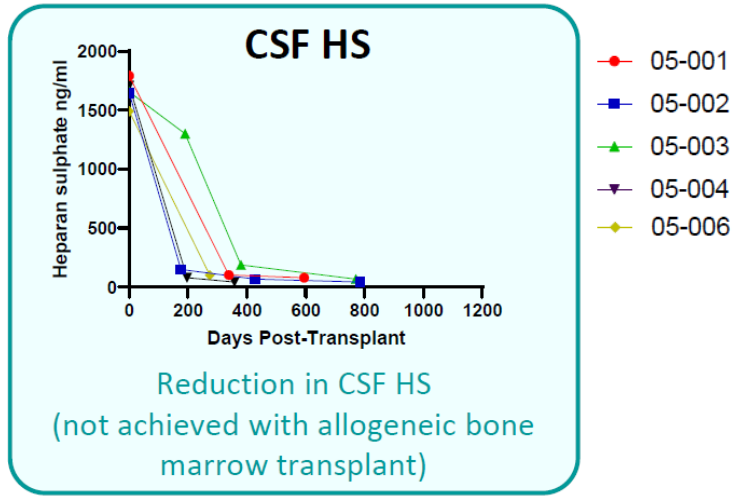
- Recruited 5 patients with severe rapidly progressive MPS-IIIA; study fully enrolled
- No untreated/placebo/comparator patients -findings will be compared with historical cohorts
- Primary Endpoints: Safety and tolerability, biological efficacy via activity in leukocytes
- Secondary and Exploratory Endpoints: OS, HS in CSF/plasma/urine, SGSH in CSF/plasma/PBMC and subpopulations, Efficacy on cognitive function, Impact on behaviour, adaptive function, QoL and family

# Summary of early biochemical and clinical outcomes

## SGSH activity




## Heparan sulphate

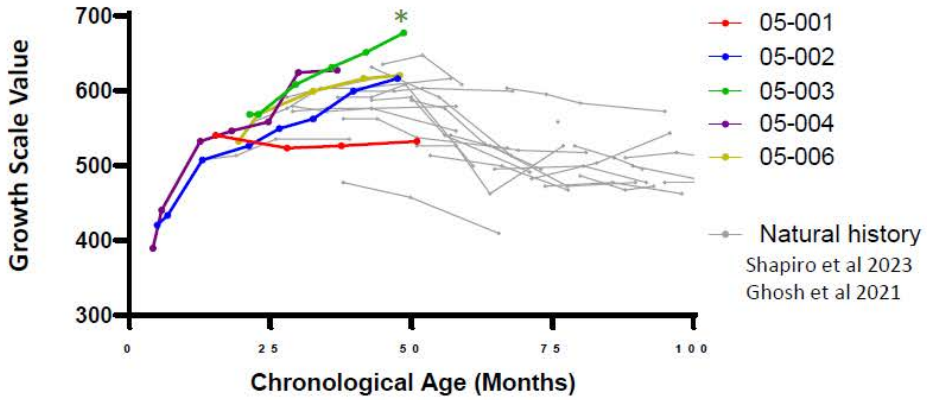



**Early follow up in trial patients**

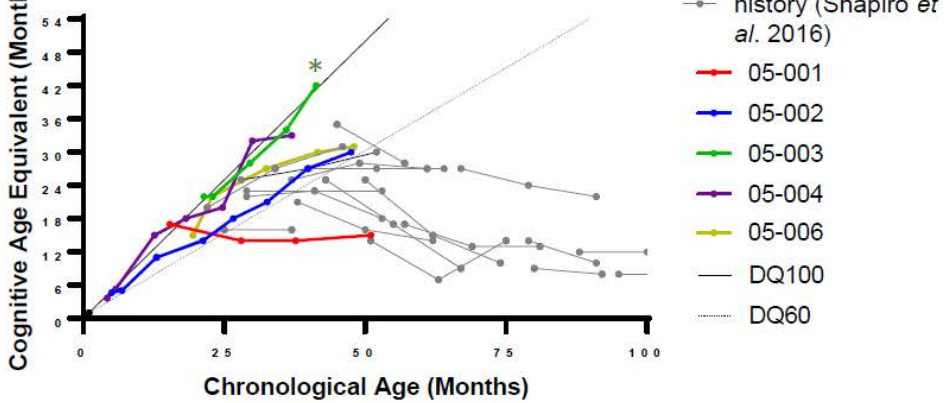
- **Gain of skills after investigational medicinal product delivery in 4 out of 5 patients**
- **Developmental gains not seen in untreated MPS-IIIA, *e.g.*, acquisition of speech (although some delays), continence and complex play**

## Neurocognitive outcomes

### Bayley's Growth Scale Value




### Bayley's Age Equivalent



# Summary

# Research and Development Strategy Image Based on Story for Vision 2030

## Disease Science: Focus disease areas

- Bone & Mineral
- Intractable hematological diseases/hemato oncology
- Rare diseases

Explore UMN, causes and mechanisms of disease in depth
Pursuit of molecular and cellular regulatory mechanisms for therapeutic realization

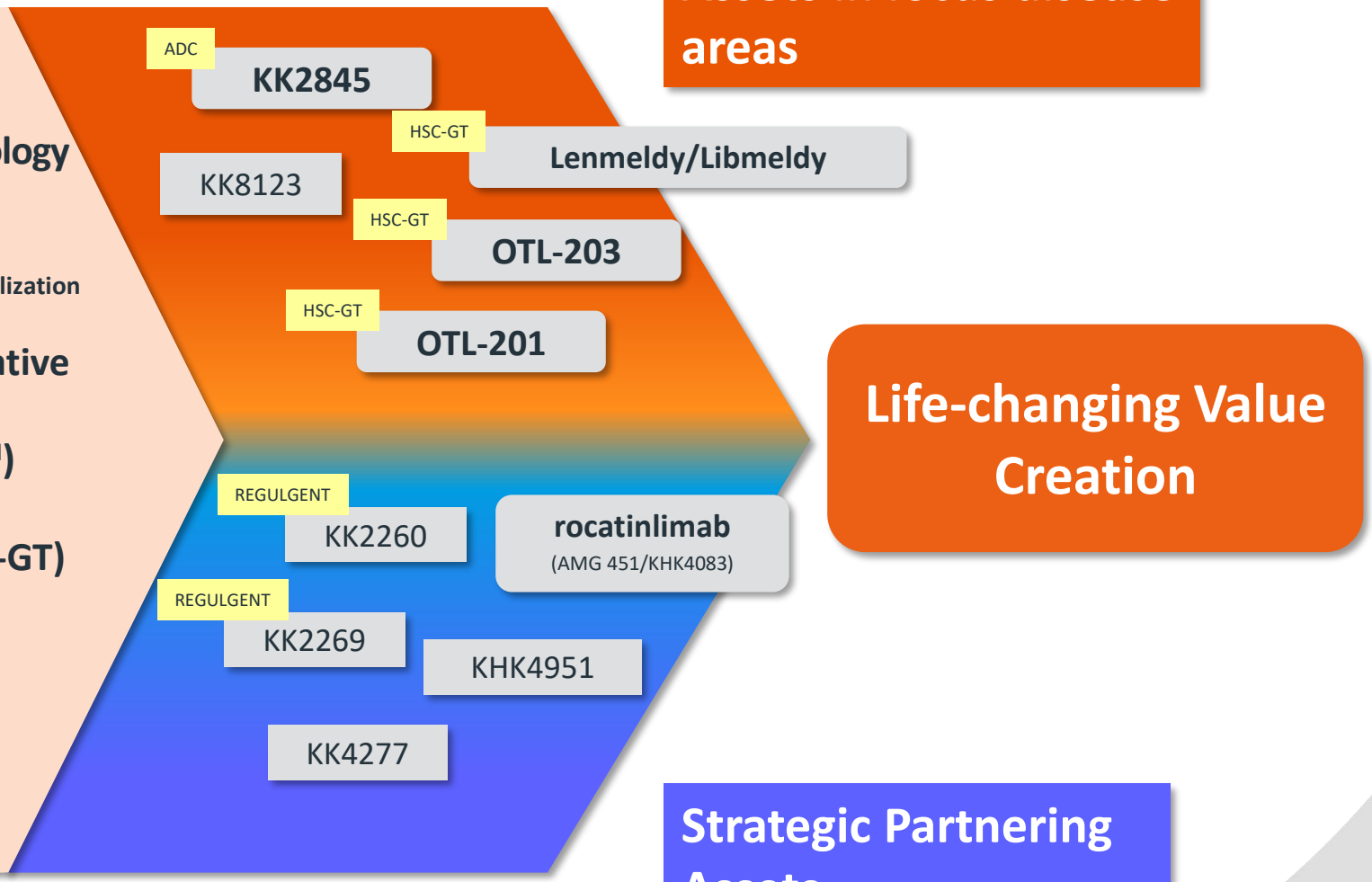
## Drug Discovery Technology: Strengthening Innovative Modalities

- Bispecific antibody technology (REGULGENT™)
- Antibody-drug conjugate（ADC）
- Hematopoietic Stem Cell – Gene Therapy(HSC-GT)

Application of optimal modalities for therapeutic realization
Evolution of drug discovery methods through AI and data science

## External Collaboration

- Open Innovation
- Partnering



# Story for Vision 2030

## Strategies for creating and delivering life-changing value

### Disease Science

**Focus disease areas: bone & mineral, intractable hematological diseases/hemato oncology, and rare diseases**

- Explore UMN, causes and mechanisms of disease in depth
- Pursuit of molecular and cellular regulatory mechanisms for therapeutic realization

### Drug Discovery Technology

**Strengthening Innovative Modalities: Advanced Antibody Technologies, Hematopoietic stem cell gene therapy**

- Application of optimal modalities for therapeutic realization
- Evolution of drug discovery methods through AI and data science

### External Collaboration

- Open Innovation
- Partnering

**Life-changing Value Creation**

**Assets in focus disease areas**

**Strategic Partnering Assets ***

**Value delivery on our own**

Global deployment of products developed by taking full advantage of the company's strengths

**Collaborative value delivery**

Aim to maximize value by combining the strengths of the company and its partners

**Full-licensing**

Maximize the value of developed products and deliver them to patients faster by out-licensing to the most appropriate partners

***Assets outside of the disease areas of focus are designated as strategic partnering assets, and value maximization is achieved through collaboration with partners.**


Kyowa KIRIN