The development story of REGULGENT™

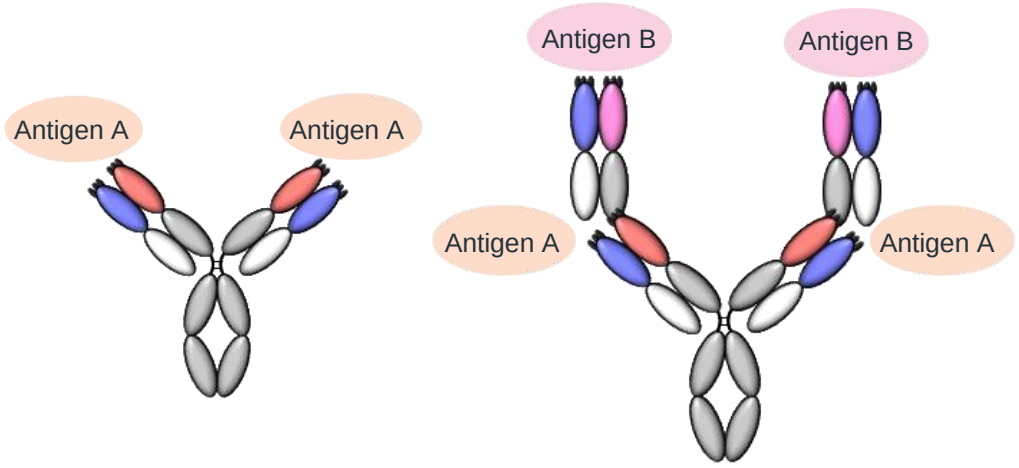
Antibody Biology Group, Core Research Laboratory

Hikaru Miyagi

Why Bi-Specific Antibodies?

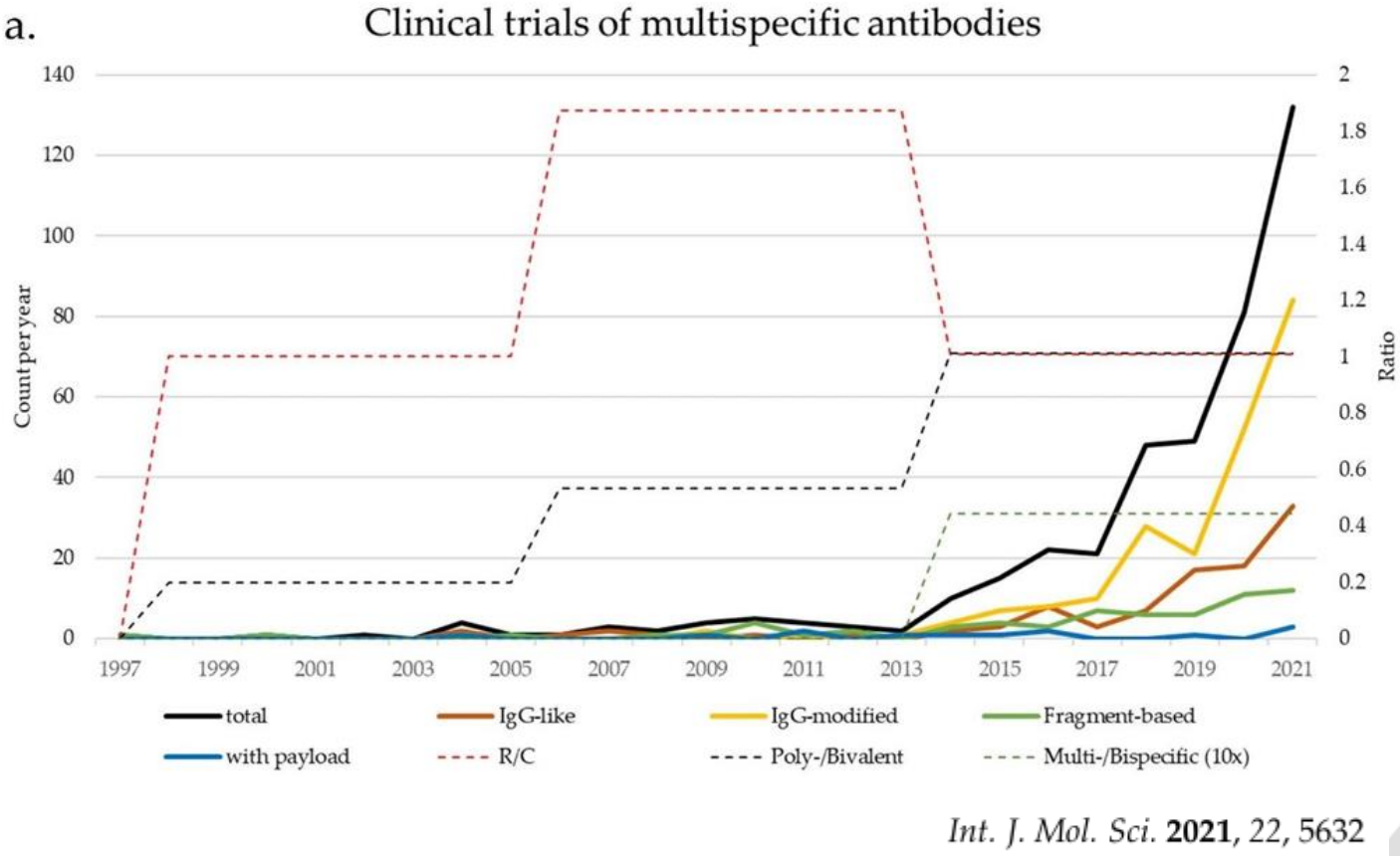
Limits of conventional monospecific antibodies

- Depletion of target antigens
- Limitations with a single antigen (efficacy, resistance, multiple factors)
- Target Selectivity and Toxicity



Monospecific antibody (IgG)

Bispecific antibody



Int. J. Mol. Sci. **2021**, *22*, 5632

Clinical trials of multispecific antibodies have surged over the past decade

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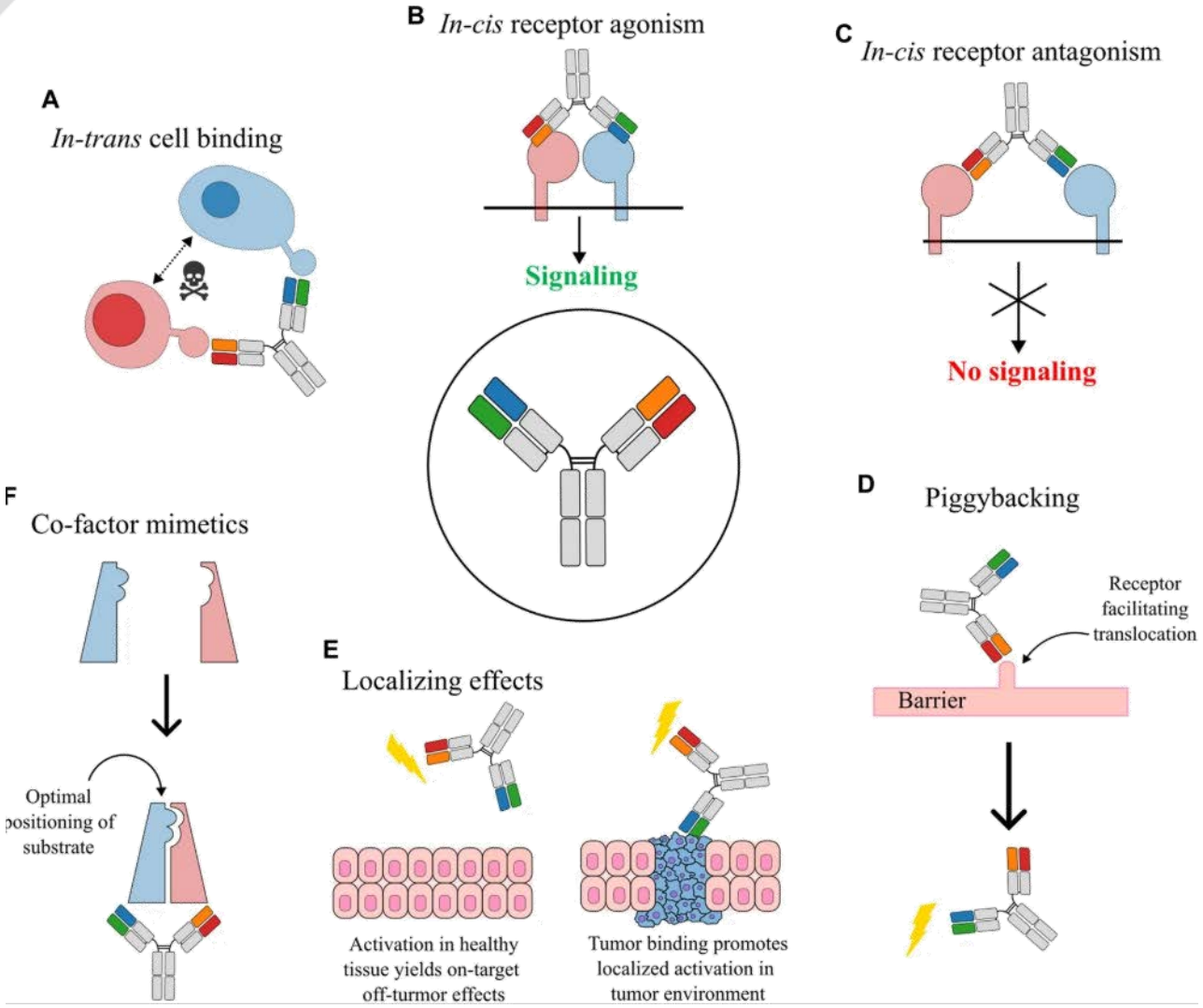
Mechanism of Bispe's Antibody



Front. Bioeng. Biotechnol., 25 January 2024
Sec. Bioprocess Engineering
Volume 12 - 2024 | https://doi.org/10.3389/fbioe.2024.1352014

Table created by the presenter based on Beacon

Analysis by Drug Status × Mechanism

Drug Status	Total number of items	Mechanism	Number of items	What can be read
Approved	22	T cell engager	12	CD3 engagers dominate marketed products
		Two ligand inactivation	6	dual blockade type is also established
		Two ligand recruitment	3	ligand bridging type also partially exists
		Other	1	Other Special Formats
Clinical	613	Two ligand recruitment	232	Immune modulation is the largest pipeline category
		T cell engager	210	TCE remains the central modality
		Two ligand inactivation	101	Checkpoint/ligand dual blockade expanding
		Other	70	trispecific, fusion, etc.

Globally, many MOAs* (relatively simple MOAs) have been developed

*TCE: T cell engager (molecule that bridges T cells with target cells) / MOA: Mechanism of Action

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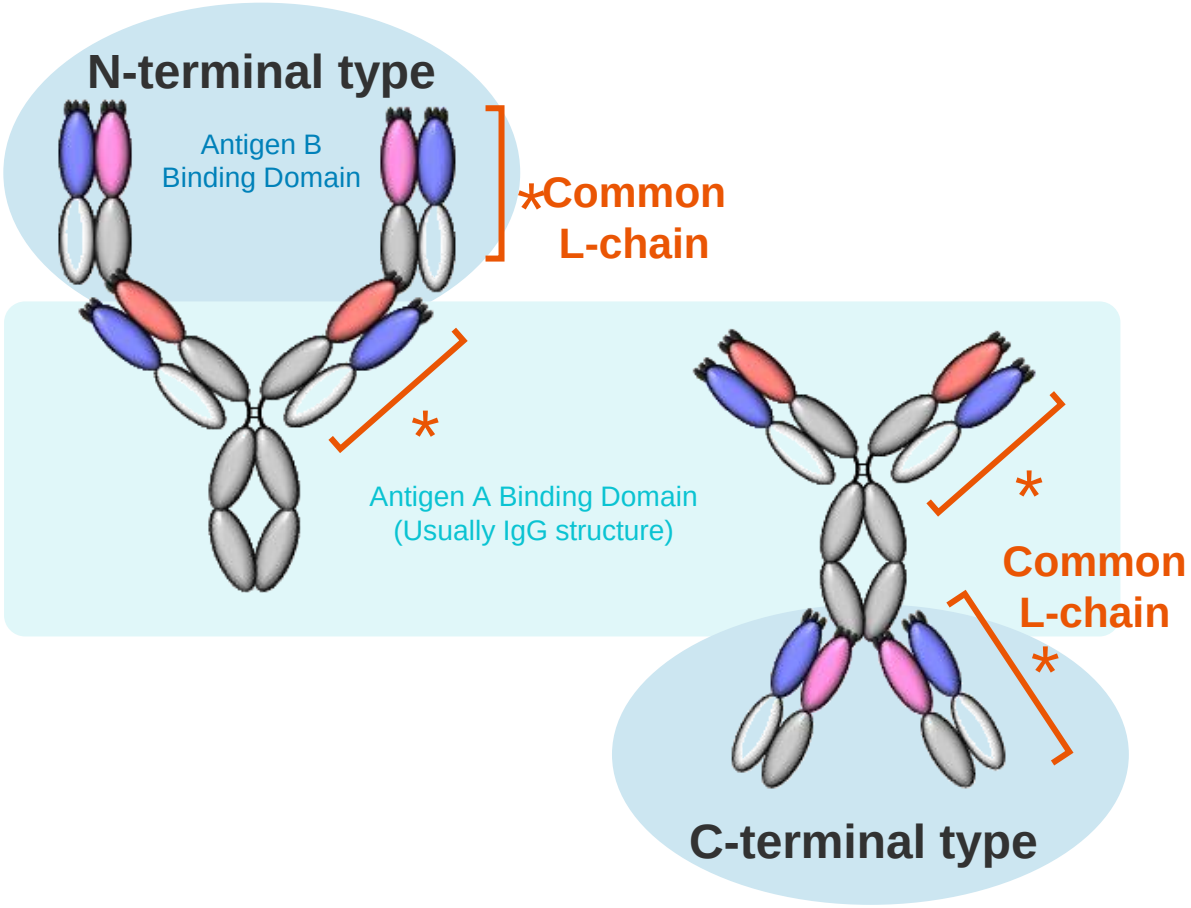
About REGULGENT™

Common light chains prevent light/heavy chain mispairing



Characteristics of REGULGENT™

Low-immunogenicity structure

- Common L-chain (*) + natural IgG sequences
- Uniform: no unwanted H/L pairings
- IgG-like properties and kinetics

N- and C-terminal bivalent forms

- Applicable to diverse mechanisms of action

Stable, easy-to-handle production

- IgG-equivalent productivity
- Uses conventional antibody processes

A unique bispecific technology built on our antibody research

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Manufacturing Challenges of Bispecific Antibodies

Molecular format	Chain variation	Molecules that might be produced
mAb	One H chain One L chain	Only one paring
Simple Bispe.	Two H chains Two L chains	Theoretically, 10 parings might be produced
Engineered Bispe.	Two H chains Two L chains	4 main parings, but other 6 parings might be produced
REGULGENT™	One H chain One L chain	Only one paring same as mAb !

Compatible with the same manufacturing method as monoclonal antibodies!

More chain types per molecule

Mispairing (impurities) occurs

Decline in production volume
Decline in purification efficiency

Cost increase
Increasing technical hurdles

Trispecifics* are emerging globally.
For complex molecules and CMC, fewer chain types are better!

*Trispecific: an antibody that binds three targets simultaneously

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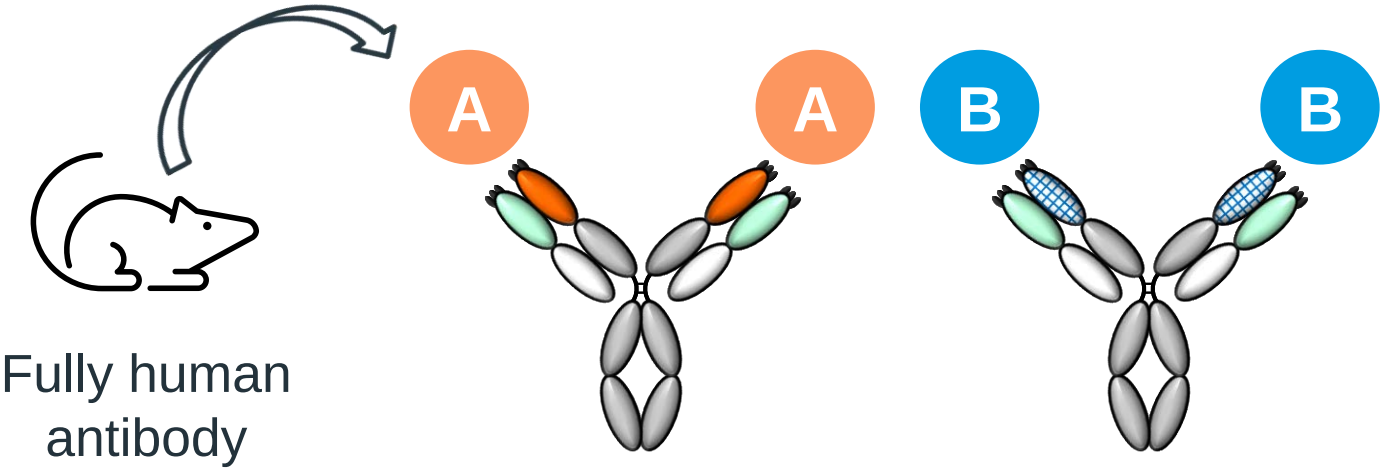
REGULGENT™ was inspired by Kyowa Kirin's original technology

Kyowa Kirin was ahead of the curve in developing fully human antibody-producing mice

- Developed HAC* technology that introduces human antibody genes into mice
- By producing antibodies similar to those in humans, it is expected that immunogenicity can be reduced.
- The potential for antibody drugs has greatly expanded, such as the ability to provide antibodies that can be continuously administered

*Human Artificial Chromosome



Fully human antibody Animals

Antibodies recognizing different targets happened to share the same light chain

Could we deliberately obtain antibodies sharing the same light chain?

Built on Kyowa Kirin's R&D expertise

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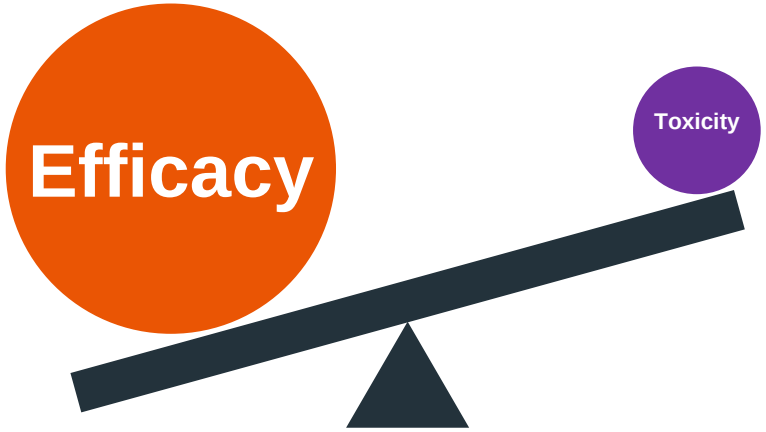
The value REGULGENT™ offers

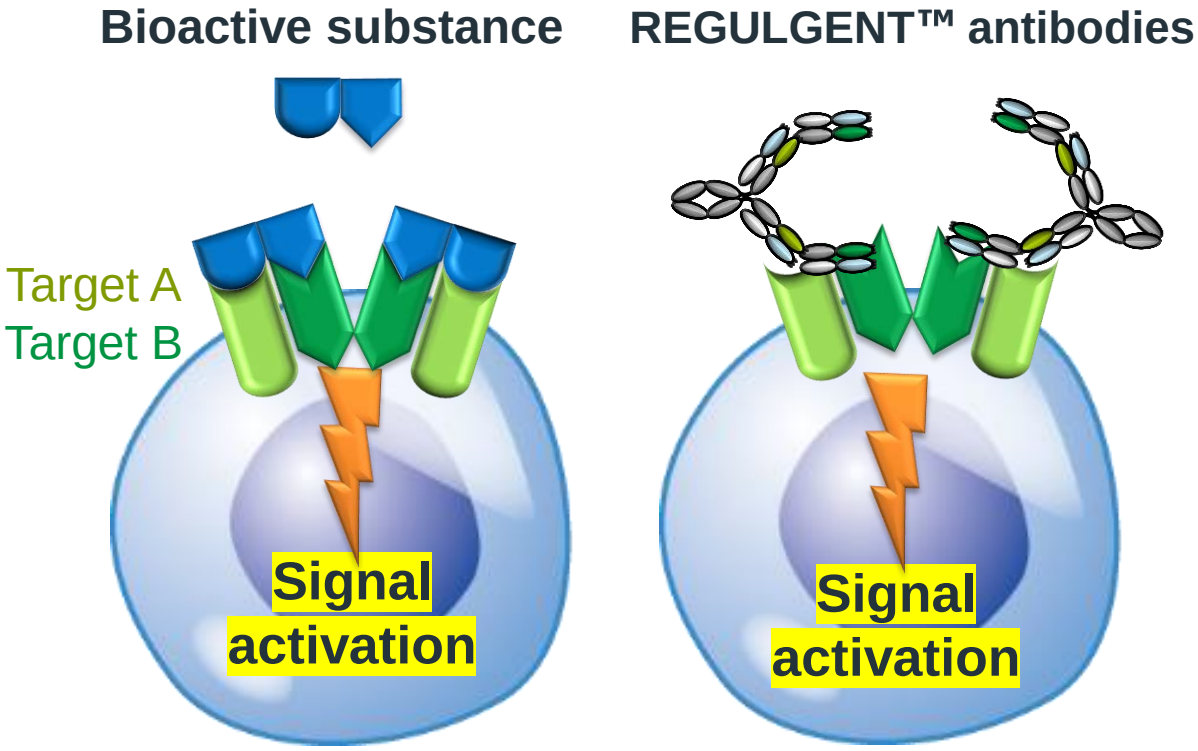
Previously undruggable toxic targets

Standard antibody

REGULGENT™ antibody



Mimicking complex-forming ligands



Previously impossible drug concepts become possible!
No CMC concerns, so medicines reach patients faster

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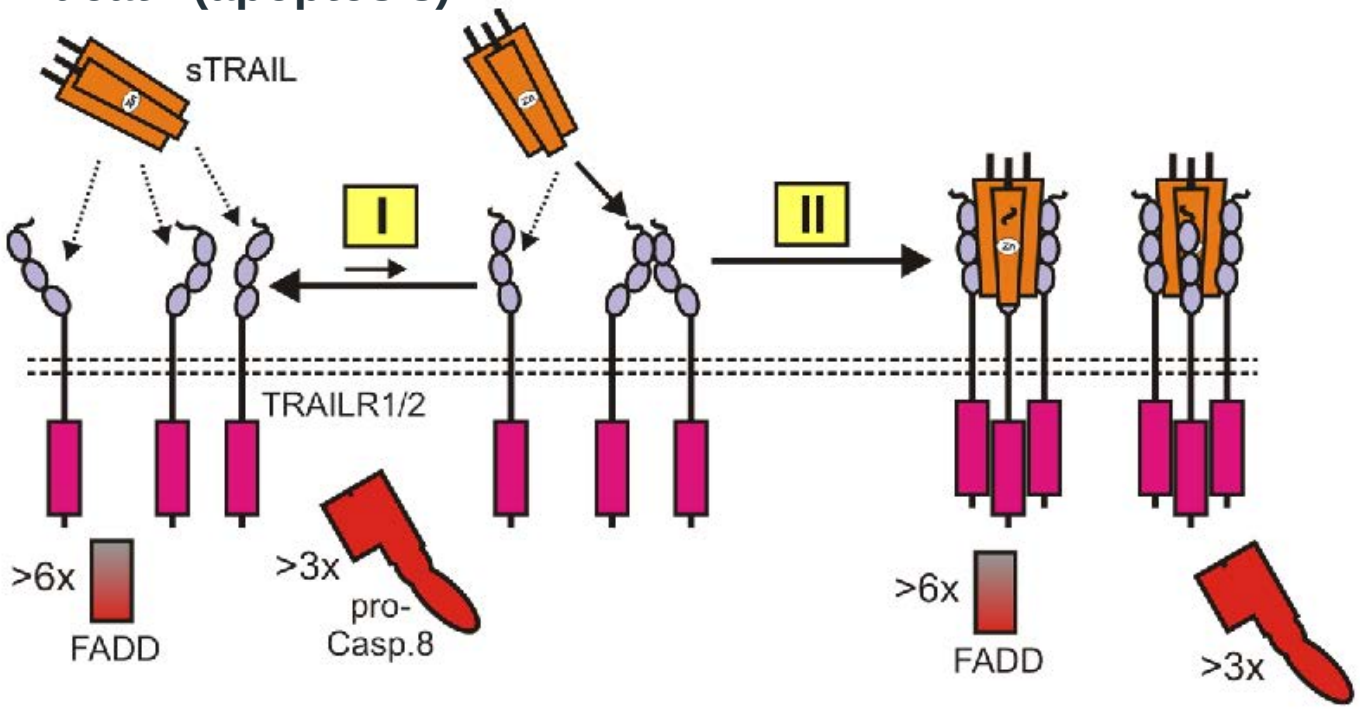
Application Example of REGULGENT™: TRAIL-R2 Bispecific

TRAIL-R2 (aka: DR5, Death Receptor 5, TNFRSF10B) is
A cell surface receptor that binds to the apoptosis-inducing ligand (TRAIL) to induce cell death (apoptosis)



(modified）Wajant Cancers 2019 Jul 7; 11(7):954. Licensed under CC-BY 4.0

- Belonging to the TNF receptor family
- Forming a trimer to induce the death signal
- It is widely expressed in both normal cells and solid tumors, but cancer cells are more susceptible
- Expected as a target for antibody drugs
- Several TRAIL-R2 drugs have entered clinical trials but have been **discontinued due to insufficient efficacy or liver toxicity**

Needed: a strong death signal only in cancer cells

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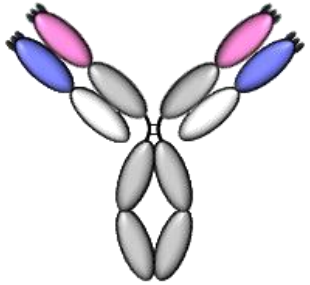
Cancer Target Antigen x TRAIL-R2 Bispecific Antibody

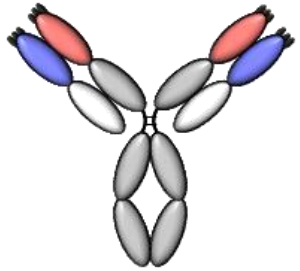
Anti-TRAIL-R2 antibody



TRAIL-R2

Induce cell death target antigen

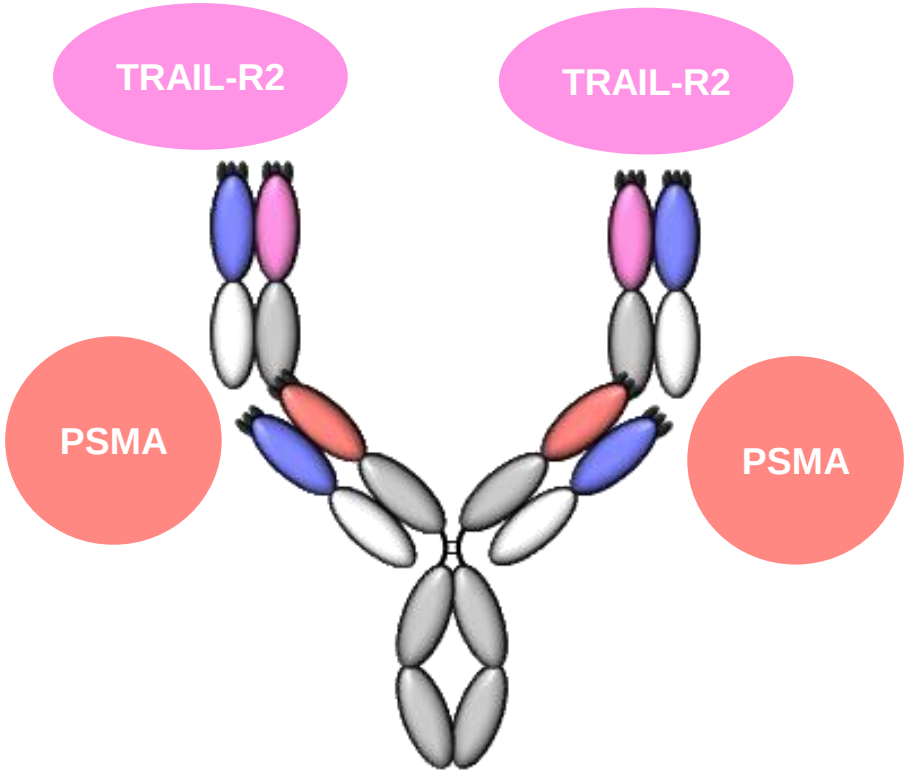
Anti-PSMA* antibodies



PSMA

Prostate cancer, etc. target antigen

Anti-PSMA/TRAIL-R2 antibody



PSMA arm targets cancer cells; TRAIL-R2 arm triggers cell death

PSMA: Prostate specific membrane antigen

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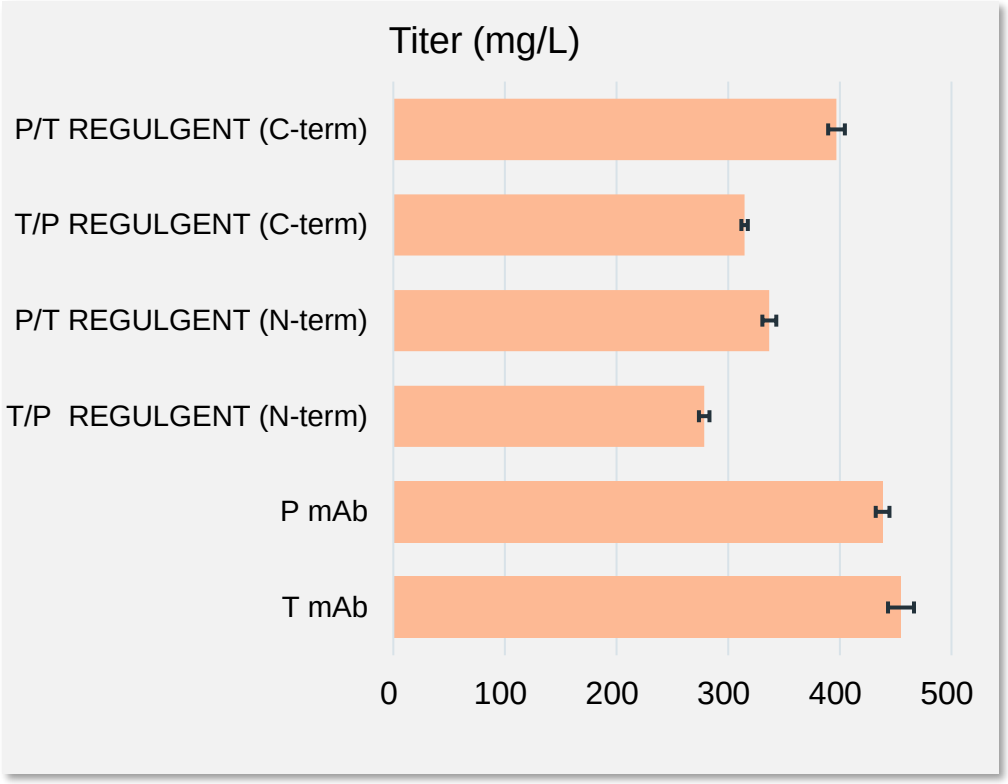
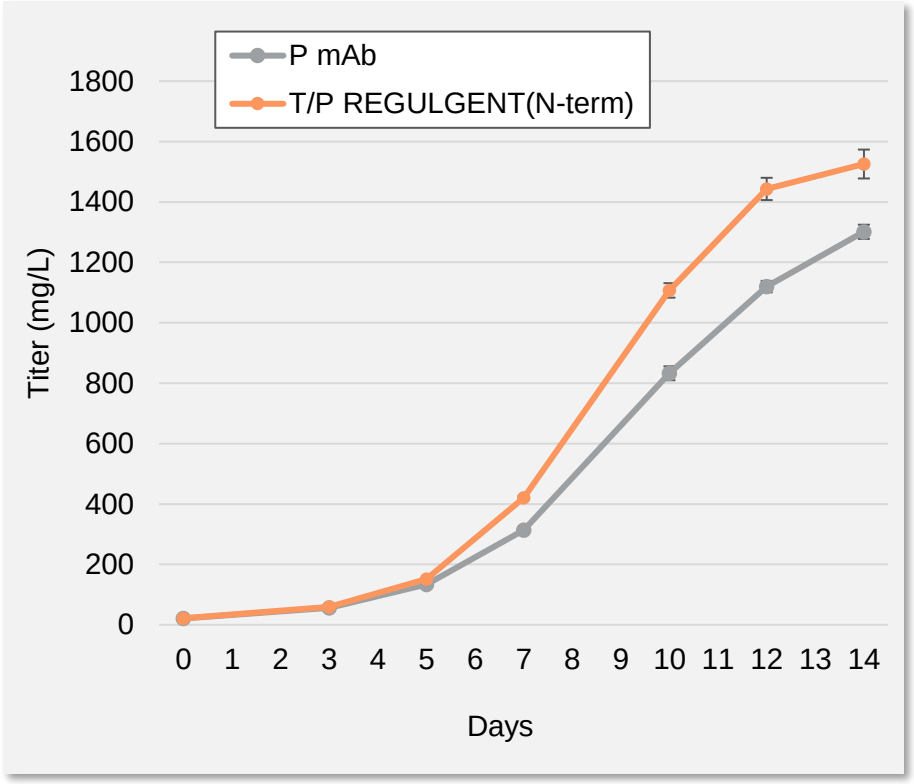
REGULGENT™ Productivity

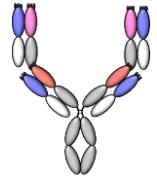
Transient expression, ExpiCHO-S™ cells (Day 8)



Stable expression using CHO cells

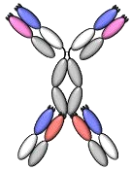


T: TRAIL-R2
P: PSMA

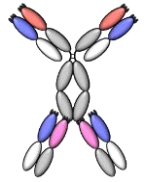


T/P REGULGENT (N-term)

P/T REGULGENT (N-term)



T/P REGULGENT (C-term)



P/T REGULGENT (C-term)

Kyowa Kirin R&D Briefing September 26, 2024: Presenter Alters Materials

Productivity comparable to IgG

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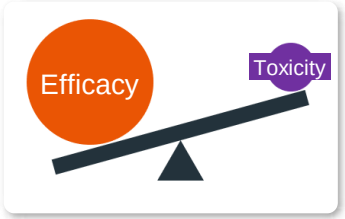
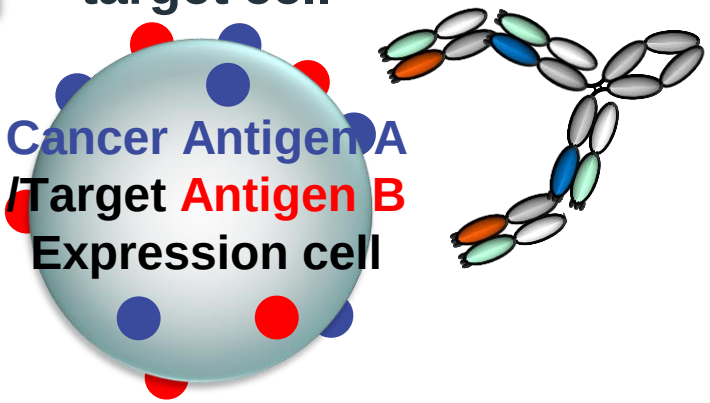
Leveraging REGULGENT™ in multiple layers



KK2260

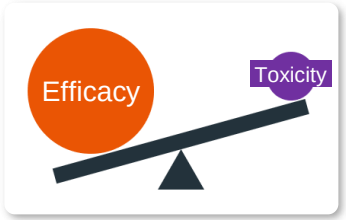
target cell



Only when binding to cancer antigens

Blocks cellular iron uptake

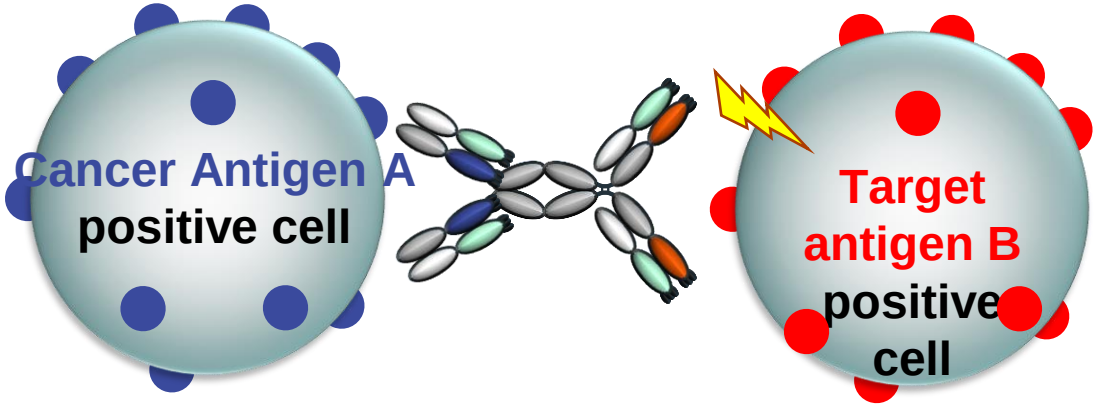
Patient-derived tumors in mice regress



KK2269

target cells

immune cell



Only when binding to cancer antigens

Activates anti-tumor immune cells

Anti-tumor immunity makes implanted tumors regress

Broadly deployable technology, now in clinical trials

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Our drug discovery approach, via REGULGENT™

1 Start with Patients

Start with unmet medical needs and design medicines that deliver meaningful efficacy and safety.

2 Focus on Value, Not Technology

Use data and technology to create real value for patients, rather than pursuing technology for its own sake.

3 Design Medicines for Real-World Delivery

Consider efficacy, safety, quality, manufacturability, and productivity from the start to develop medicines that can reach patients.

4 Learn, Adapt, and Grow

Learn from both successes and failures, and turn knowledge, technology, and data into future drug discoveries.

5 Build a Sustainable Drug Discovery Platform

Build shared knowledge and capabilities to continuously discover and develop new medicines.

6 What Defines Kyowa Kirin

Our strength lies in scientific curiosity and research integrity, transforming technology into life-changing value for patients.

*Generated AI-generated images

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APPENDIX

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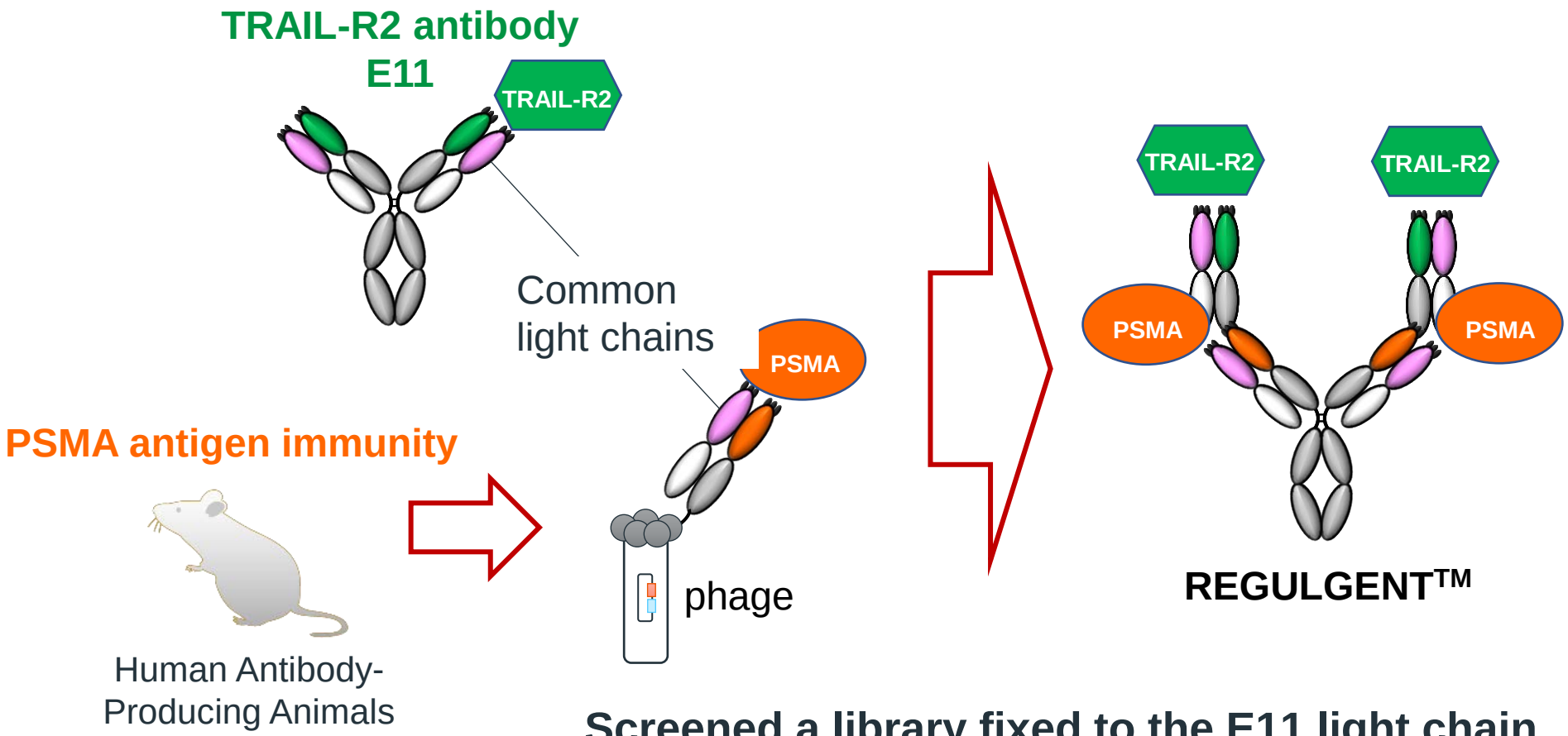
Acquisition of light chain common antibody

Acquisition of PSMA antibodies with the same light chain as E11 using phage display



Screened a library fixed to the E11 light chain
Obtained antibodies sharing a fully human light chain

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