About the Lasker Foundation and the Lasker Awards

- About the Lasker Foundation
  - Established in 1942 by Albert and Mary Lasker
  - Through the internationally renowned Lasker Awards, educational initiatives, and public advocacy, the Foundation raises awareness of the power of biomedical science to save and improve human lives
  - Advocates support for biomedical research and aims to contribute to the prevention and treatment of diseases and disabilities

- About the Lasker Awards
  - Renowned as the most prestigious biomedical research award in the U.S.; since 1945, 360 laureates have received Lasker Medical Research Awards; 101 Lasker laureates have also received the Nobel Prize, including 28 in the last 20 years
  - Laureates are selected by an international jury chaired by Joseph L. Goldstein, laureate of the 1985 Lasker Award for Basic Medical Research and Nobel Prize in Physiology or Medicine

Important Notice

- This presentation may contain forward-looking statements regarding Chugai's business and outlook. These statements reflect Chugai's current analysis of existing information and various trends. Actual results may differ from current expectations due to risks and uncertainties affecting the business.

- This presentation may include information on prescription medicines and products in development. It is intended solely to provide information to the participants of this conference and is not intended for promotional or advertising purposes or as medical advice.

Agenda

1. Remarks from the Laureates
2. Creation of emicizumab (Hemlibra)
3. Q&A Session

A Challenge Born in Japan that Transformed Hemophilia A Treatment Worldwide

The Creation of Emicizumab (Hemlibra)
-A journey inspired by the desire to transform the lives of people with hemophilia A-

September 10, 2026

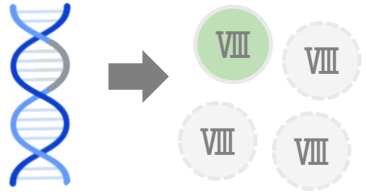
Chugai Pharmaceutical Co., Ltd.

Dr. Kunihiro Hattori, Dr. Takehisa Kitazawa, Dr. Tomoyuki Igawa

What Is Hemophilia A?

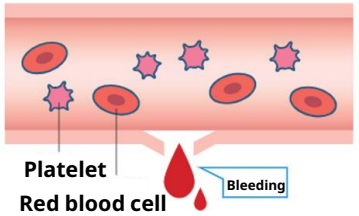
Hemophilia A is caused by a deficiency of coagulation Factor VIII, a protein essential for normal blood clotting

1. Cause: hereditary or autoimmune



A genetic alteration on the X chromosome results in a deficiency of coagulation Factor VIII, a protein needed for blood clotting

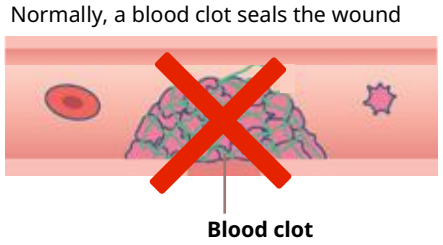
2. Blood-clotting function is weakened



-Blood clotting does not function sufficiently after injury
-Factor VIII activity relative to normal:

<1%: severe
1–5%: moderate
≥5% to <40%: mild

3. Bleeding is difficult to stop



A stable blood clot does not form properly, making wounds difficult to seal and bleeding difficult to stop

4. Bleeding continues longer

-Bleeding and internal bleeding, including into joints, occur more readily
-In severe cases, repeated bleeding may cause joint damage

Number of people with hemophilia A

- Worldwide: 224,353 reported (202,548 males; 8,223 females; 13,557 unspecified)[1]; the actual number is estimated to be higher
- Japan: 3,813 (3,685 males; 128 females)[2]

1. World Federation of Hemophilia (WFH), Annual Global Survey 2024 https://wfh.org/ja/research-and-data-collection/
2. Nationwide Survey of Patients with Coagulation Disorders 2025 (Japan) https://api-net.jfap.or.jp/image/data/blood/r07_research/r07_research.pdf (In Japanese only)

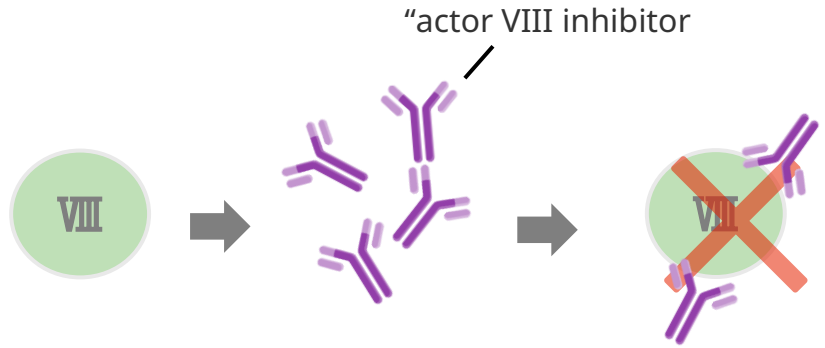
Medical Challenges in Hemophilia A

Because of challenges associated with home-based factor VIII (FVIII) replacement therapy and immune responses to FVIII, there has been a need for treatment options that would reduce the burden of treatment and could be used by more people with hemophilia A

Burden of intravenous infusions at home multiple times a week

Difficulty in obtaining venous access and infusion-related pain can be burdensome, particularly for children and for the caregivers who administer the infusions

Reduced or lost effectiveness due to an immune response to FVIII treatment

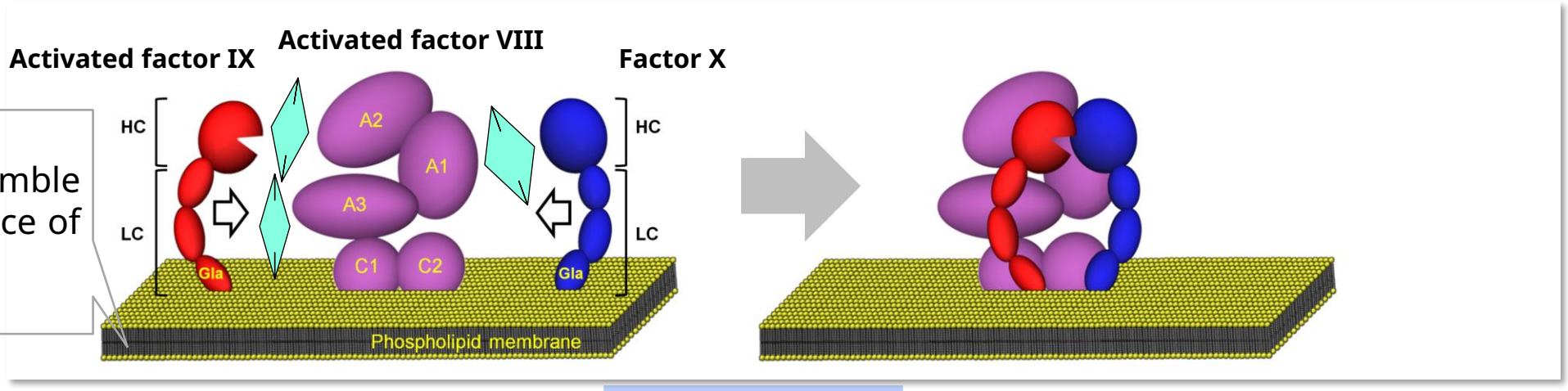


If the immune system recognizes infused factor VIII as foreign and develops inhibitors, FVIII replacement therapy becomes less effective

Unconventional concept:
Replacing factor VIII function with a bispecific antibody

Function of factor VIII: Promotes the reaction in which activated factor IX activates factor X

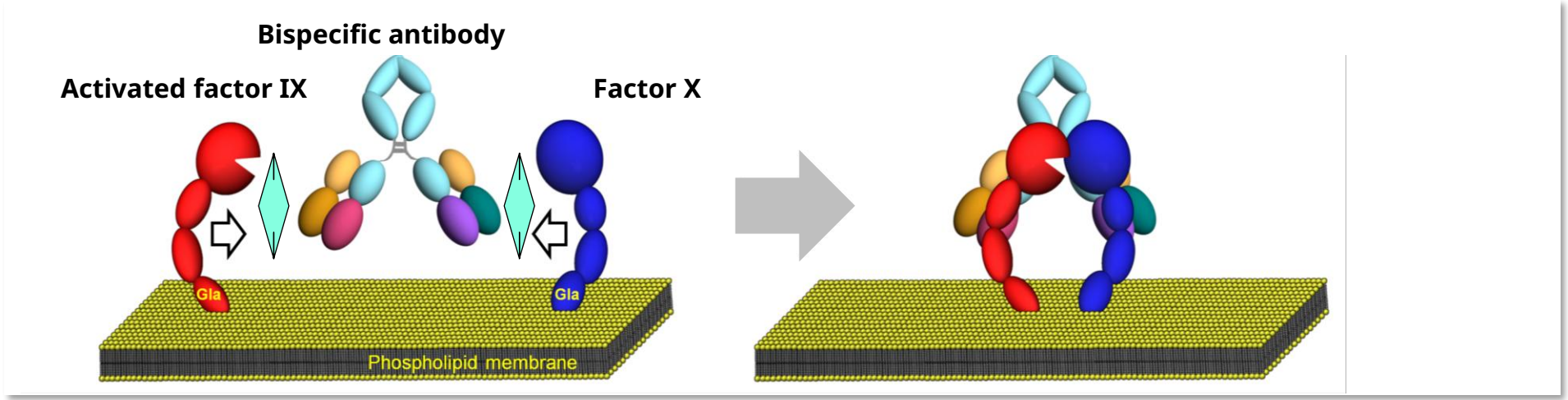
Coagulation factors assemble on the surface of activated platelets



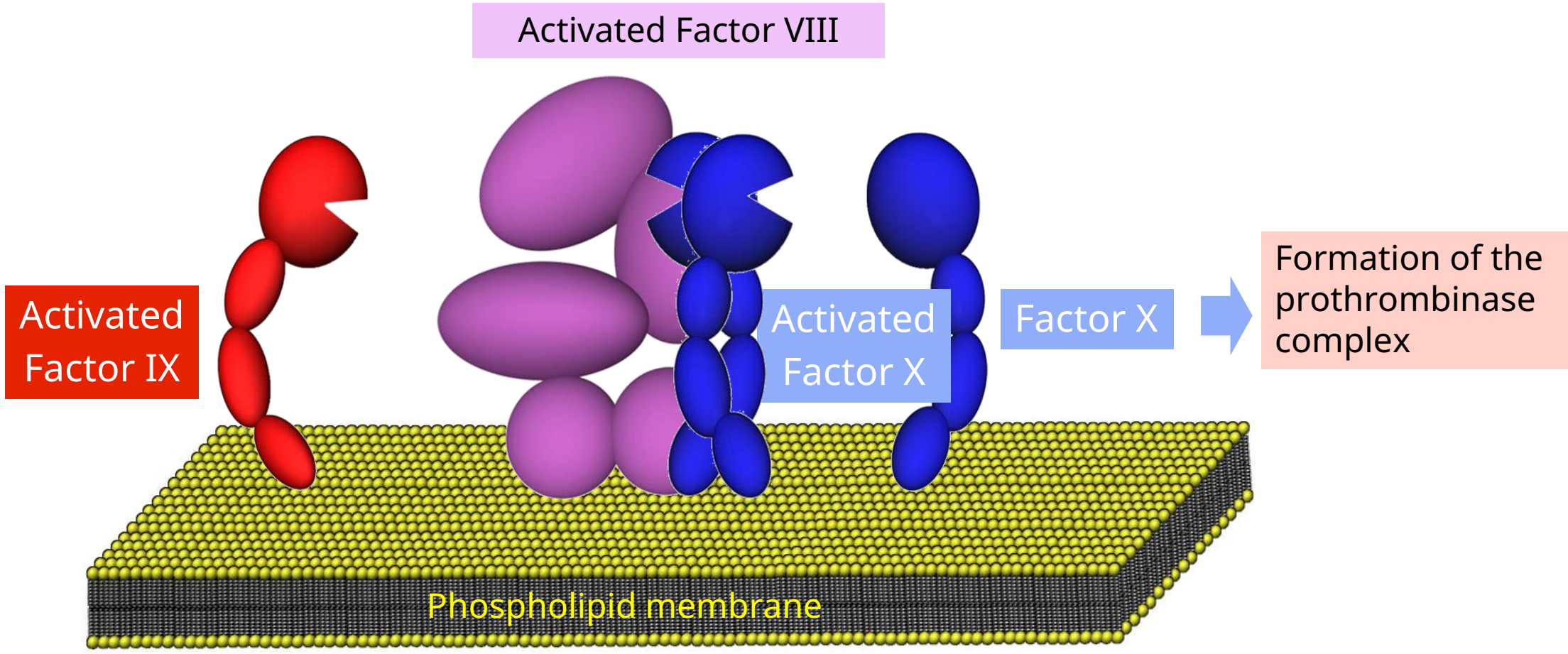
Kitazawa, Igawa. ⋯, Hattori. ***Nat Med.*** 18(10) 1570 (2012)

Could we create an antibody that performs the function of factor VIII?

Reproducing this function with a bispecific antibody that binds activated factor IX with one arm and factor X with the other



Unconventional Concept:
A Bispecific Antibody Substitutes for Factor VIII Function



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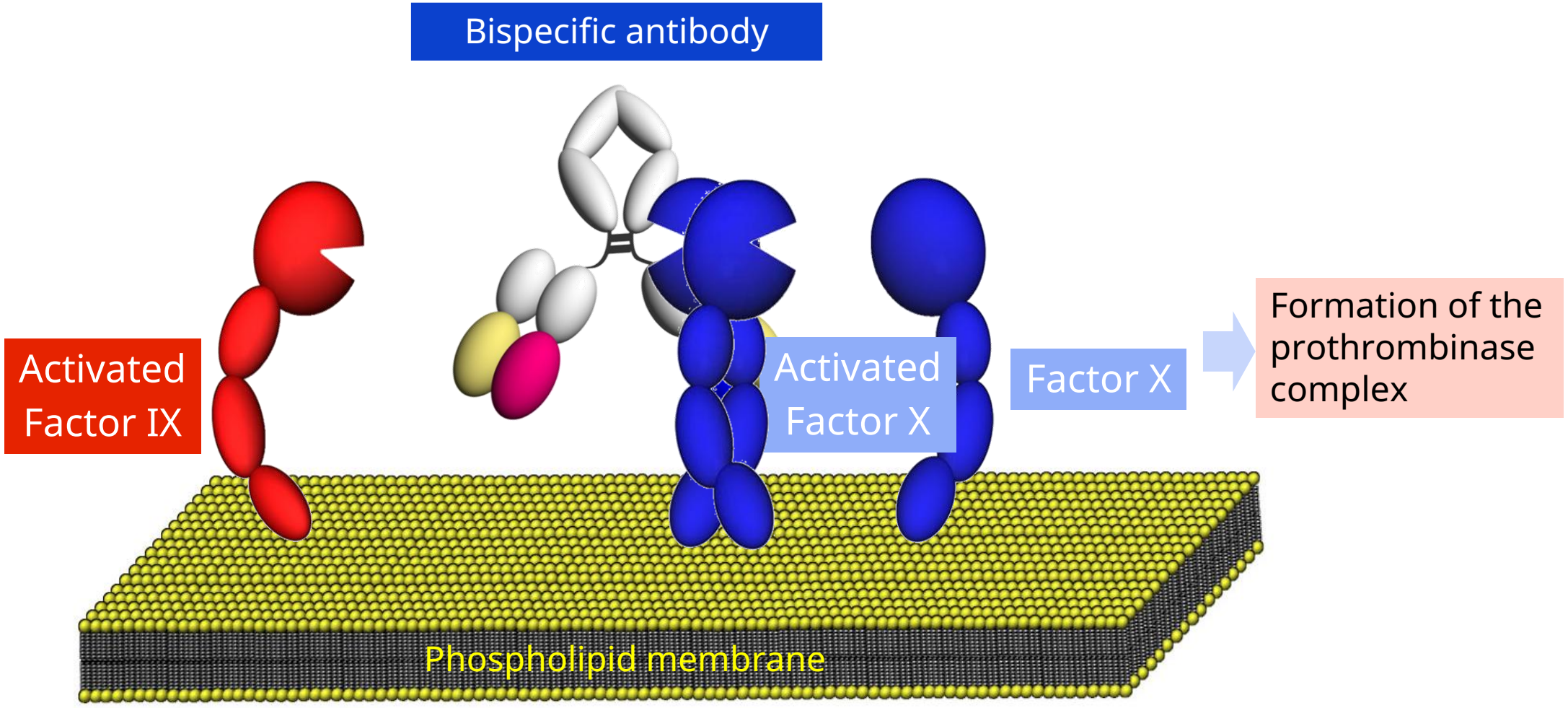
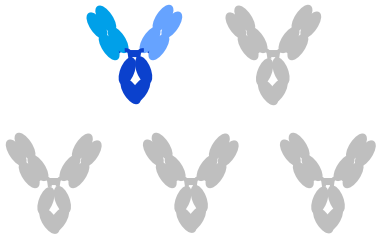
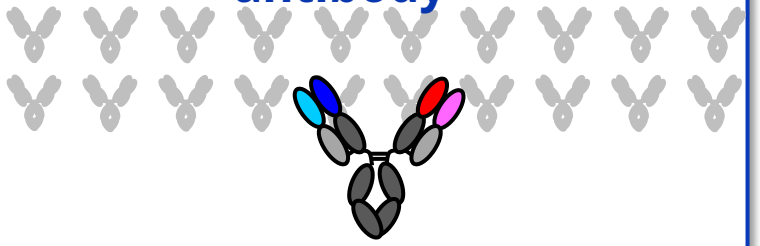


Kitazawa, Igawa, ···. Hattori.
Nature Medicine 18(10) 1570 (2012)

Identifying a Lead Antibody through Extensive Trial and Error

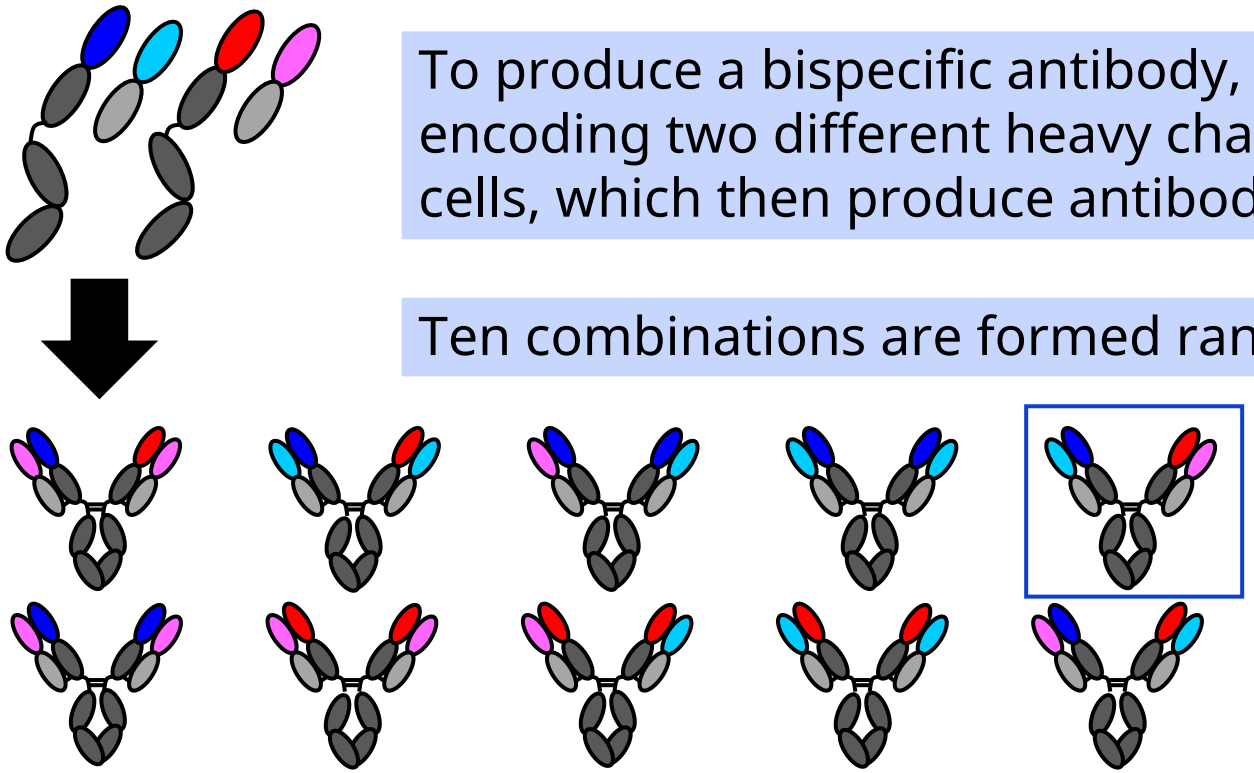
After screening 460, then 4,000, and ultimately 40,000 antibodies, the team overcame a temporary discontinuation and identified a lead antibody

STEP 1 (from 2002) 460 antibodies	STEP 2 (2006) 4,000 antibodies	STEP 3 (through 2008) 40,000 antibodies
Identified antibodies with activity  **A bispecific antibody can potentially substitute for Factor VIII function**	**Program discontinued due to efficacy and safety concerns**  **Insufficient hemostatic activity and induction of bleeding** **Program temporarily discontinued**	**Identified lead antibody**  **Just before the 18-month deadline, identified a lead antibody that became the basis of emicizumab**
Proof of concept	**Clarified requirements for success**	**Potential as a drug emerges**

Screening: the process of selecting promising drug candidates from a vast number of compounds

Challenges in Commercial Manufacturing of Bispecific Antibodies

Challenges remained for practical use and large-scale manufacturing



To produce a bispecific antibody, it is necessary to introduce the genes encoding two different heavy chains and two different light chains into cells, which then produce antibody proteins through cell culture

Ten combinations are formed randomly (nine are impurities)

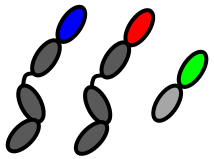
Correct pairing

Only a small amount of the correctly paired antibody is produced and most products are impurities
-Low production efficiency and difficult separation from impurities
-Stable, large-scale manufacturing as a drug is not feasible

Development of ART-Ig Technology to Overcome Manufacturing Challenges

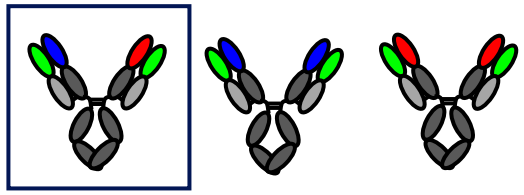
Chugai's proprietary ART-Ig technology enabled high-purity manufacturing and commercial-scale production

1 Method for reducing incorrect pairings



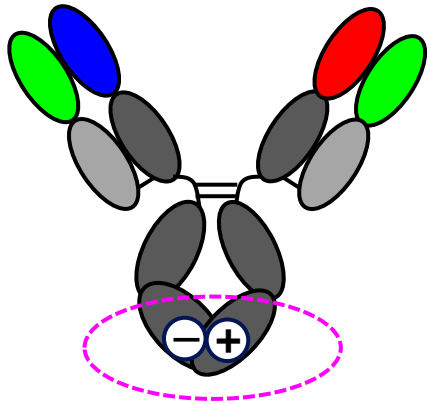
Identifies common light chain that functions in both arms

Reduces the number of combinations to three (two are impurities)



Correct pairing

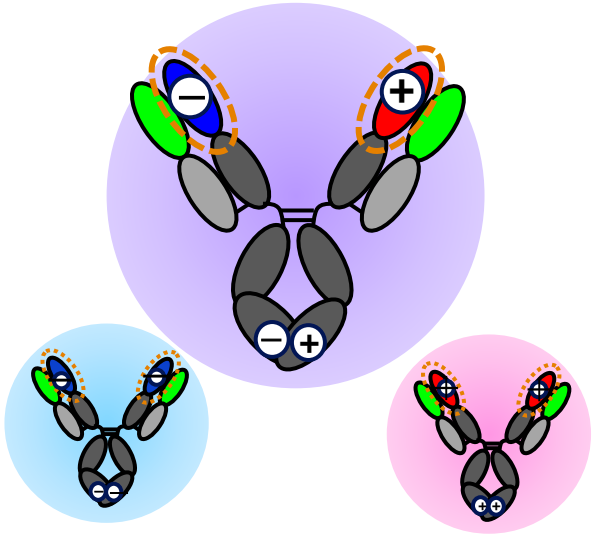
2 Method for promoting correct pairings



Uses electrostatic interactions (attraction and repulsion) to promote pairing of different heavy chains and formation of the target antibody

3 Method for removing residual impurities

Uses charge properties to differentiate molecular characteristics and enable separation



Sampei *et al.* ***PLoS One*** 8(2) e57479 (2013)
Shiraiwa *et al.* ***Methods*** 154:10 (2019)

Multidimensional Optimization led to the Molecule that Became Emicizumab

- **Repeated design and evaluation led to the creation of a molecule balancing efficacy and safety and suitable for development**
- **A clinical candidate antibody, later named emicizumab, was created**

Lead antibody

Humanization

ART-Ig technology

Approximately 2,400 engineered antibodies prepared and evaluated

Increase activity substituting for Factor VIII function

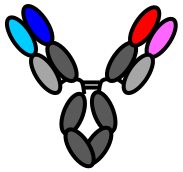
Facilitate purification

Improve absorption after subcutaneous administration

Improve solubility for manufacturing and high-concentration formulation

Maintain stability during storage and in the body

Reduce the likelihood of immune responses



Clinical development antibody (later named emicizumab)

In 2012, clinical studies began in healthy volunteers and people with hemophilia A

Iterative trial and error enabled optimization across efficacy, safety, and manufacturability

Sampei *et al.* ***PLoS One*** 8(2) e57479 (2013)

Bleed Prevention with Emicizumab Demonstrated in Clinical Studies

Clinical studies in people with hemophilia A demonstrated the bleed-prevention efficacy and tolerability of emicizumab regardless of Factor VIII inhibitor status, disease severity, or age

Integrated Analysis of the HAVEN 1–4 Studies

Objective	To evaluate the long-term safety, efficacy, and pharmacokinetics of Hemlibra in people with hemophilia A through an integrated analysis of the HAVEN 1–4 studies
Subjects	HAVEN 1[1]: 113 people aged ≥12 years with inhibitors HAVEN 2[2]: 88 children aged <12 years with inhibitors HAVEN 3[3]: 152 people aged ≥12 years with severe hemophilia A without inhibitors HAVEN 4[4]: 48 people aged ≥12 years with or without inhibitors
Analysis population	Enrolled: 401 Efficacy analysis population (ITT): 400 Safety analysis population: 399
Results	[Efficacy] The primary endpoint, annualized bleeding rate (ABR) for treated bleeds over 24-week intervals throughout the study, was 1.4 events/year. For the secondary endpoint, 70.8% (277/391) had zero treated bleeds during Weeks 1–24, increasing to 82.4% (140/170) during Weeks 121–144. [Safety] No new safety signals were identified. The most common adverse event was injection-site reactions (27.8%).

1.Oldenburg J, et al: N Engl J Med. 377(9): 809-18, 2017
2.Young G, et al: Blood. 134(24): 2127-38, 2019
3.Mahlangu J, et al: N Engl J Med. 379(9): 811-22, 2018
4.Pipe SW, et al: Lancet Haematol. 6(6): e295-e305, 2019

How Emicizumab Changed Hemophilia A Treatment

- **Approved and launched under the product name Hemlibra**
- **Approved in the United States in 2017 and in Japan and Europe in 2018; now approved in more than 120 countries and regions, used by more than 30,000 people with hemophilia A**
- **A treatment that reduces bleeding frequency and treatment burden, expanding possibilities in daily life**

1 Reduced burden of home treatment

- Convenient at-home administration with a subcutaneous formulation
- Choice of dosing interval: once weekly, every 2 weeks, or every 4 weeks
- Psychological and time-related benefits for children and their families

2 Treatment option for people with Factor VIII inhibitors

- Bleed-prevention efficacy comparable to that in people without inhibitors
- Suggested effect on quality of life

3 Bleeding prevention and effects on joint health

- Demonstrated reductions in treated bleeds and bleeding frates
- Beyond bleeding control, a suggested benefit for joint health

Sato et al. The Japanese Journal of Pediatric Hematology/Oncology. 59(1) 19 (2022)
Fletcher et al. Health Expect. . 25(1) 443 (2022)
Shima et al. Haemophilia. 25(6)979 (2019)
Shima et al. Haemophilia. 27(1)81 (2021)
Shimozawa et al. J. Nihon Univ. Med. Ass. 82(1) 23 (2023)
Callaghan et al. Blood. 137(16) 2231 (2021)
Oldenburg et al. Haemophilia. 25(1) 33 (2019)
Mancuso et al. Haemophilia. 26(6) 1009 (2020)
Mahlangu et al. N Engl J Med. 379(9) 811 (2018)
Shima et al. Res Pract Thromb Haemost. 9(8)103228 (2025)
Astermark et al. Haemophilia. 31(6) 1271 (2025)

Our Commitment for the Future

- **We will continue working to address unmet medical needs**

Enabling a future where people can live fuller lives

- Develop better treatment approaches
  - Pursue “zero bleeds” regardless of lifestyle
  - Further reduce treatment burden

Reaching more people

- Continue efforts to expand access to treatment worldwide
  - Move forward together with the hemophilia community
- Generate further scientific evidence and provide reliable treatment based on that evidence

Acknowledgments

To the people with hemophilia A and their families who participated in clinical studies

Your courageous participation helped make this treatment possible

To healthcare professionals, including those at Nara Medical University

Your clinical insights, guidance, and dedicated collaboration supported this work

To our colleagues at Roche and Genentech

Your partnership in global development and supply, helping deliver the treatment to people with hemophilia A worldwide

To the Albert and Mary Lasker Foundation

We are deeply grateful for this honor. Inspired by this recognition, we will continue taking on new challenges

Our sincere gratitude to everyone who contributed to the research and development of emicizumab

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INNOVATION BEYOND IMAGINATION

CHUGAI PHARMACEUTICAL

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