Technology from Kyoto University

Novel Method for Producing Bispecific Antibodies

We are looking to out-license the technology for its commercialization.

High-purity bispecific antibodies can be obtained at a reduced cost using antigen-binding molecules that enable correct pairing of heavy and light chains.

◆Background

IgG-type bispecific antibodies (BsAbs), which have antibody variable domains that bind to two different epitopes of an antigen, are gaining attention as a new modality for the diagnostic and therapeutic pharmaceuticals development.

BsAbs are expected for their enhanced binding ability, as they form large complexes through intermolecular cross-linking with two BsAb molecules binding to two epitopes. However, special manufacturing strategies are required to correctly pair the heavy and light chain variable regions for each of the two binding sites.

To date, technologies such as knobs-into-holes and Duobody have been developed to form hetero-Fc dimers. However, four different light chain combinations can occur for each intended pairing of heavy chains, resulting in low yields and posing significant challenges in terms of separation and purification (Fig.1). For this, technological development that resolves this light chain issue is desired.

◆Description

The research team at Kyoto University has developed a new method to solve this light chain issue. Specifically, they identified a protein X as a molecule that is structurally similar to the CH1 and CL domains of IgG and does not interfere with pairing or cross-react with other parts. Furthermore, by applying appropriate modification processes to the protein X, they obtained the antigen-binding Fab-like molecule, with which BsAb can be produced in a single batch.

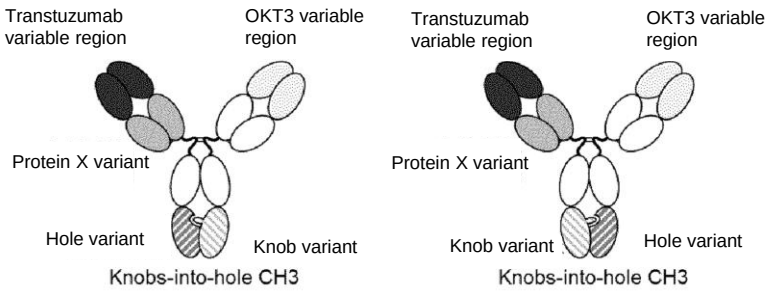

Fig. 1 An example of an IgG-type asymmetric BsAb obtained by the proposed method

One variable region is derived from Trastuzumab, which recognizes HER2, while the other is derived from OKT3, which recognizes CD3. The Fab derived from Trastuzumab incorporates an IgM-CH4 mutant. Additionally, for Fc heterodimerization, a Knobs-into-Hole mutation is used, allowing the design of two bispecific antibodies: one in which the heavy chain forming the Trastuzumab-derived variable region is a hole mutant (left) and another in which it is a knob mutant (right).

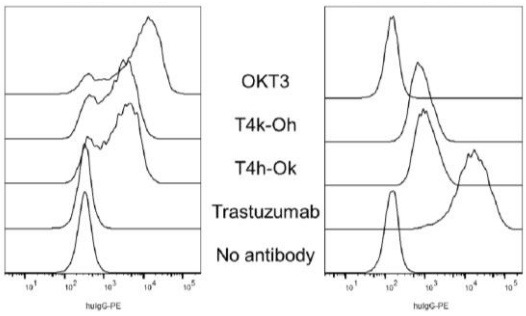

Fig. 2 Flow cytometric evaluation of the binding affinity to two antigens

The results of the R-PE fluorescence quantitative evaluation using HER2-expressing cells (SK-OV-3) and CD3-expressing cells (Jurkat) confirmed that the BsAb obtained in this invention binds to both HER2 and CD3.

◆Development Status

- Confirmed the production of correct pairing of heavy and light chains
- Isolation and purification of the model BsAb confirmed
- Binding affinity to two antigens confirmed (Fig.2)
- Ongoing evaluation of the frequency of mispairing
- Seeking strategies/partners for a more scalable purification method

◆Applications

- BsAb production

◆Offer

- Patent License
- Collaborative Research

◆Contact

TLO-KYOTO Co., Ltd.

licensing_ku@tlo-kyoto.co.jp
Phone: +81-75-753-9150

Level 5, International Science Innovation Bldg., Kyoto Univ., Yoshidahonmachi, Sakyo-ku, Kyoto 606-8501, Japan

https://www.tlo-kyoto.co.jp/en

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