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Translation

Novel Concept for Treatment of Hemophilia A Published in Nature Medicine

—*Bispecific antibody substitutes for the function of blood coagulation factor VIII*—

October 1, 2012 (Tokyo) - Chugai Pharmaceutical Co., Ltd. ("Chugai") [Main Office: Chuo-ku, Tokyo. Chairman & CEO: Osamu Nagayama] announced today that Chugai, jointly with Nara Medical University, published online in Nature Medicine October edition that a bispecific antibody[1)] mimicking the function of blood coagulation factor VIII effectively exerts its hemostatic action in an animal model of hemophilia A. This paper can be accessed since September 30 (BST) on the website of Nature Medicine. (http://dx.doi.org/10.1038/nm.2942). While a typical antibody, a Y-shaped protein, has two antigen binding sites at its upper ends, each of which commonly binds a single antigen, a bispecific antibody is an artificially engineered antibody having two different antigen binding sites which can respectively bind two different antigens.

Hemophilia A is an inherited disorder, presenting severe bleeding symptoms repeated from childhood. In this disease, the blood coagulation reaction does not normally proceed because of congenital deficiency of factor VIII. Factor VIII simultaneously binds factor IXa and factor X to promote factor IXa-mediated factor X activation and the consequent blood coagulation reaction[2)]. For the treatment of hemophilia A, the supplementary intravenous injection of a factor VIII agent is usually employed to stop on-going bleeds and to prevent bleeding. In recent years, its prophylactic routine supplementation, which requires multiple intravenous injections every week, has prevailed to constantly prevent bleeding. Occasionally, anti-factor VIII neutralizing antibodies (inhibitors) arise to eliminate the supplemented factor VIII agent as foreign substance because factor VIII is congenitally deficient in hemophilia A patients. In such a case, the factor VIII agent can no longer fully exert its hemostatic activity.

This paper reveals that the bispecific antibody simultaneously binds factor IXa and factor X, exerting factor VIII-mimetic function to promote the blood coagulation reaction under the factor VIII lacking condition regardless of the presence of inhibitors against factor VIII[3)]. Moreover, the bispecific antibody exerts a hemostatic action in the non-clinical animal model, and has a long-acting property and the feasibility to be injected subcutaneously. From these results, the bispecific antibody to mimic the factor VIII function is expected to show a prophylactic efficacy to prevent bleeding by once weekly subcutaneous injections, offering a novel concept for the treatment of hemophilia A.

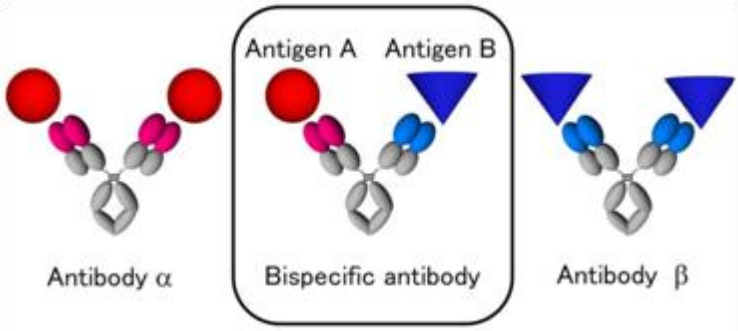
To date, no recombinant bispecific antibody has been approved as a therapeutic drug. This is because it is challenging for the conventional technologies to achieve commercial manufacturing of a recombinant bispecific therapeutic antibody due to the complexity of its molecular structure. Chugai has been engaged in developing innovative antibody engineering technologies, and has also established original technologies enabling to apply bispecific antibodies to therapeutic drugs. The bispecific antibody mimicking the factor VIII function described in this paper is one of the achievements from our continuous efforts.

Chugai has modified and improved the molecule described in this paper into a further superior bispecific antibody molecule (development code: ACE910), and is currently conducting a phase I clinical study in healthy adults and hemophilia A patients (both with inhibitors and without inhibitors) in Japan starting from August 2012.

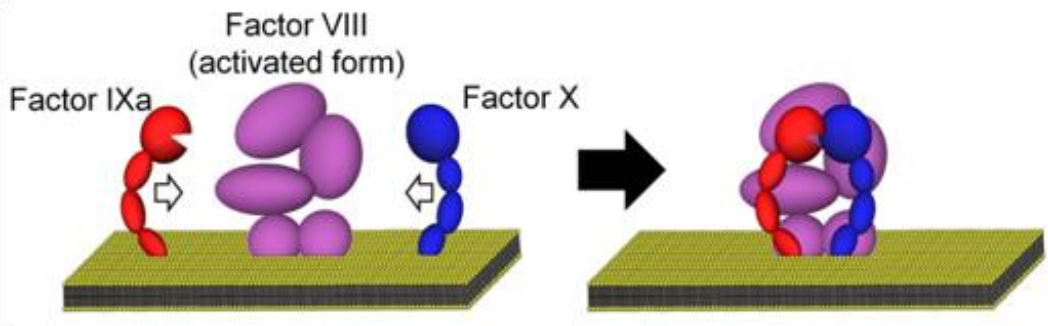
Chugai, as a leading company in the biotechnology field, will continue working to develop innovative technologies applicable to drug discovery, in order to contribute to the human health around the world.

Reference

1) Bispecific antibody

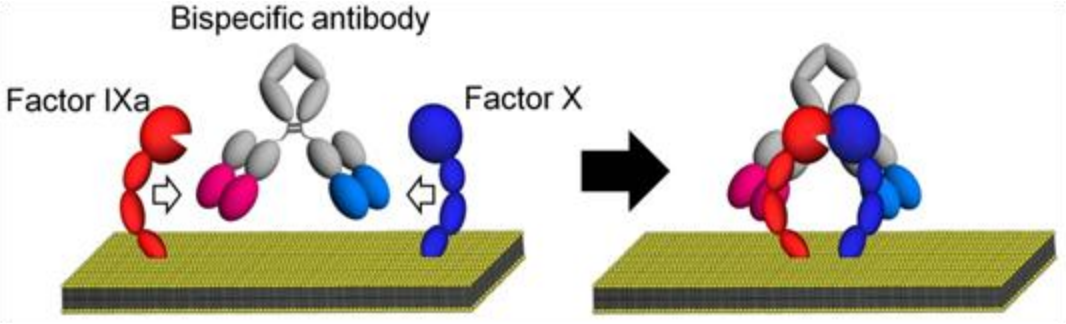


2) Mechanism of factor VIII to promote blood coagulation reaction



Factor VIII takes on cofactor activity when activated at the site of coagulation reaction. An activated form of factor VIII simultaneously binds factor IXa and factor X to promote factor IXa-mediated factor X activation and the consequent blood coagulation reaction.

3) Mechanism of the bispecific antibody to promote blood coagulation reaction in a status of hemophilia A



The bispecific antibody also simultaneously binds factor IXa and factor X, exerting factor VIII-mimetic function to promote the blood coagulation reaction under the factor VIII lacking condition.