

antibody or antigen-binding fragment thereof can penetrate the blood brain barrier to exert its action, and extend the half-life to maintain an efficacy for a long time.

Moreover, the anti- α -Syn/anti-IGF1R bispecific antibody of the present invention binds to IGF1R on the cell surface without affecting the binding of the ligand, and has properties of no effect on the signaling pathway through IGF1R. Because it does not inhibit the binding of IGF1R to its ligand and signaling through IGF1R, it can be used as a shuttle mean to penetrate the blood brain barrier.

Particularly, the anti-IGF1R antibody or antigen-binding fragment thereof of the present invention specifically recognizes IGF1R (Insulin-like Growth Factor 1 Receptor) and binds to IGF1R, particularly human IGF1R, mouse IGF1R, rat IGF1R, and monkey IGF1R. However, it does not interfere with the binding of IGF1R ligand such as IGF-1, IGF-2 and/or insulin to IGF1R and does not inhibit signal transduction through IGF1R, and can be used for transcytosis to pass through BBB. It does not have antibody-dependent cell-mediated cytotoxicity (ADCC), and thus does not decrease IGF1R levels in the brain even when administered to animals repeatedly, thereby having no toxicity.

In particular, the anti-IGF1R antibody of the present invention binds to IGF1R located on the surface of brain endothelial cells constituting BBB and internalizes into the inner part of the cell.

For example, the anti-IGF1R antibody may have a form of scFv, and may be combined to therapeutic antibody in various ways. For example, the scFv of an anti-IGF1R antibody can be prepared in a bispecific antibody, for example a bivalent form of a bispecific antibody in which two scFvs are bound to C-terminus of the therapeutic antibody, for example, α -syn antibody, or a

monovalent form of a bispecific antibody in which one scFv is bound to C-terminus of the therapeutic antibody. Both of these bispecific antibodies can internalize into the cells expressing IGF1R. The IGF1R antibody has a high binding affinity to the antigen on the cell surface, which enhances the internalization effect and lead to BBB-passing ability. If an antibody has the ability to pass BBB and interfering with the signaling of IGF1R, it can cause side effects. However, the antibody of present invention is characterized in both the binding capacity suitable for BBB shuttle and non-blocking property for the IGF1R signaling.

The anti-IGF1R antibody or antigen-binding fragment thereof has excellent property to be developed easily. In this aspect, the post-translational modification, such as deamidation, that occurs in the CDR region of the anti-IGF1R antibody and reduces the stability and efficacy of the antibody is to be removed.

Alternatively, at least one of the amino acids located on both sides of the deamidation site of the antibody may be substituted, and preferably, the amino acid immediately adjacent to the C-terminal side of the deamidation site of the antibody may be substituted. For example, by substituting with A for G located next to Asn located at the deamidation site of the antibody or substituting with V for S located next to Asn, it is possible to produce deamidated antibodies having a similar binding affinity to that of parental anti-IGF1R antibody, and at the same time has excellent stability and BBB penetrating ability.

Additionally, when linked to a bioactive substance acting in the brain, the anti-IGF1R antibody of the present invention can induce improved BBB-penetrating ability and efficacy compared to the bioactive substance alone.

The anti-IGF1R antibody according to one aspect of the present invention may be used

bivalent form of bispecific antibody, in which the scFv of anti-IGF1R antibody is linked to each Fc of two heavy chains of a complete immunoglobulin, for example at the ends of the heavy chain directly or via a linker and a monovalent form of bispecific antibody, in which a scFv of an anti-IGF1R antibody linked to only one end of the two heavy chains of a complete immunoglobulin directly or via a linker, but a monovalent double antibody is preferred.

Specifically, in one embodiment of the present invention, there is a case in which the monovalent form clone has an improved half-life than the bivalent form clone, and the structure of the monovalent form clone is form that domain antibody (scFv) against IGF1R is bound to only an end of one heavy chain in the intact immunoglobulin via a linker. Specifically, the antibody is a heterodimer applied by Knob-In-Hole method that includes two different heavy chains of the intact immunoglobulin in which one heavy chain has domain antibody (scFv) against IGF1R bound to C-terminus thereof, and the other heavy chain has not any at the C-terminus thereof.

In the bispecific antibody, the second antibody that is bound to an anti-IGF1R antibody or antigen-binding fragment thereof may be a human antibody, a humanized antibody, a chimeric antibody, or an isolated antibody specifically binding to IGF1R. The second antibody includes, but is not limited to, complete antibodies, bispecific antibodies, minibodies, domain antibodies, antibody mimetics (or synthetic antibodies), antibody fusions (or antibody conjugates), and fragments thereof. In the bispecific antibody, an example of the second antibody that is bound to the anti-IGF1R antibody or antigen-binding fragment thereof may be the anti-syn antibody or antigen-binding fragment thereof according to the present invention.