

the present disclosure comprises

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 8 or an amino acid sequence that differs from the amino acid sequence of SEQ ID NO: 8 by having amino acid substitution selected from H48R, H49R, H49D, H50R, H50S, H50F, H52R, H52Q, H72R, H73D, H73R, H73Y, H119R, H119F, H48S, H71Y, H72A, H72L, H72N, H72T, H72W, H75H, H75L, H75N, H75Q, H79H, H79K, H79Q, H79R, H83R, H117Q, H119E, H119H, H119K, H119N, H119Q, H119S, H119T, H120A, H120D, H120F, H120N, H120Q, H122F, H54T, H54N, H71R, H71H, and H71I, and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that differs from the amino acid sequence of SEQ ID NO: 9 by having amino acid substitution selected from L47R, L48E, L48R, L48S, L48K, L50D, L50R, L50F, L50Y, L73R, L111F, L111Y, L112E, L112R, L112D, L112F, L113D, L113R, L113F, L48H, L48Y, L50Q, L50W, L51Q, L69Y, L70F, L70H, L72D, L72E, L72R, L72Y, L73K, L73N, L73Y, L75Q, L87K, L87N, L111A, L111N, L111S, L112H, L112Q, L112T, L112Y, L113S, L114F, L114H, L114I, L114N, L114Y, L116H, L116Y, L51Y, L72F, L73Q, and L74H.

[0001]

In a further embodiment, the anti-hGDF15 antibody of the present disclosure comprises

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 8 or an amino acid sequence that differs from the amino acid sequence of SEQ ID NO: 8 by having amino acid substitution selected from H49R, H49D, H50R, H50S, H50F, H73D, H73R, H73Y, H48S, H71Y, H72A, H72L, H72N, H72T, H72W, H75H, H75L, H75N, H75Q, H79H, H79K, H79Q, H79R, H83R, H119N, H119S, H120F, H120Q, H54T, H54N, H71R, and H71H, and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that differs from the amino acid sequence of SEQ ID NO: 9 by having amino acid substitution selected from L47R, L48E,

the amino acid sequence of SEQ ID NO: 8 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 9.

5 [49] The antibody of any one of items 1 to 48, wherein the antibody comprises
a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 8 or an amino acid sequence that differs from the amino acid sequence of SEQ ID NO: 8 by
10 having amino acid substitution selected from H48R, H49R, H49D, H50R, H50S, H50F, H52R, H52Q, H72R, H73D, H73R, H73Y, H119R, H119F, H48S, H71Y, H72A, H72L, H72N, H72T, H72W, H75H, H75L, H75N, H75Q, H79H, H79K, H79Q, H79R, H83R, H117Q, H119E, H119H, H119K, H119N, H119Q, H119S, H119T, H120A, H120D, H120F, H120N,
15 H120Q, H122F, H54T, H54N, H71R, H71H, and H71I, and
a light chain variable region comprising the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that differs from the amino acid sequence of SEQ ID NO: 9 by having amino acid substitution selected from L47R, L48E, L48R,
20 L48S, L48K, L50D, L50R, L50F, L50Y, L73R, L111F, L111Y, L112E, L112R, L112D, L112F, L113D, L113R, L113F, L48H, L48Y, L50Q, L50W, L51Q, L69Y, L70F, L70H, L72D, L72E, L72R, L72Y, L73K, L73N, L73Y, L75Q, L87K, L87N, L111A, L111N, L111S, L112H, L112Q, L112T, L112Y, L113S, L114F, L114H, L114I, L114N, L114Y,
25 L116H, L116Y, L51Y, L72F, L73Q, and L74H.

[50] The antibody of any one of items 1 to 49, wherein the antibody comprises
a heavy chain variable region comprising the amino acid
30 sequence of SEQ ID NO: 8 or an amino acid sequence that differs from the amino acid sequence of SEQ ID NO: 8 by having amino acid substitution selected from H49R, H49D, H50R, H50S, H50F, H73D, H73R, H73Y, H48S, H71Y, H72A, H72L, H72N, H72T, H72W, H75H, H75L, H75N, H75Q, H79H, H79K, H79Q, H79R,
35 H83R, H119N, H119S, H120F, H120Q, H54T, H54N, H71R,

Table 24

Antibody name	Sequence name		Mutation site		Sequence	SEQ ID NO:
	H chain	L chain	Chain	Region		
H54T-L7	H54T	L7	H	CDR-H1	SDCYW T	149
H54N-L7	H54N	L7	H	CDR-H1	SDCYW N	150
H71R-L7	H71R	L7	H	CDR-H2	Y R YSGITYYNPSLAS	151
H71H-L7	H71H	L7	H	CDR-H2	Y H YSGITYYNPSLAS	152
H71 I -L7	H71 I	L7	H	CDR-H2	YT I YSGITYYNPSLAS	153
H3-L51Y	H3	L51Y	L	CDR-L1	RASQDIS Y YLN	154
H3-L72F	H3	L72F	L	CDR-L2	YT F TLHS	155
H3-L73Q	H3	L73Q	L	CDR-L2	YTS Q LHS	156
H3-L74H	H3	L74H	L	CDR-L2	YTST H HS	157

[0002]

5 Further, the H chain (H49R, H49D, H48S, H71Y, H83R, or H120F) and L chain (L48K, L112D, L72F, or L74H) (Table 25), which were from the HuMAB2 variants having high binding activity to hGDF15, were combined and the binding of the antibody thus obtained to hGDF15 was examined. The results
10 are shown in Fig. 11. A large number of antibodies showing a binding amount equal to or higher than that of HuMAB2 were obtained.