Supplementary material

Table S1. Correspondence between the IMGT unique numbering for C-DOMAIN, the IMGT exon numbering, the EU and Kabat numberings: Human IGHG [1,2] https://www.imgt.org/IMGTScientificChart/Numbering/Hu_IGHGnber.html.

Table S2. IMGT nomenclature (alphanumeric order) of engineered variants involved in effector properties (ADCC, ADCP, CDC), half-life and structure of therapeutical monoclonal antibodies.

Type	Species	IMGT engineered Fc variant name	IMGT engineered variant definition	IMGT amino acid changes on IGHG CH domain (Eu numbering between parentheses)	Amino acid changes with the Eu positions	Motif identifiable in gene and domain with positions according to the IMGT unique numbering and with Eu positions between parentheses	1. Property and function	2. Property and function	3. Property and function /3D
1	**Homsap**	**G1v1**	**CH2** **P1.4**	CH2 **E**1.4>**P** (233)	E233P	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > APPLLGGPS	**ADCC reduction**. Prevents FcγRI binding [3]		
1	**Homsap**	**G1v2**	**CH2** **V1.3**	CH2 **L**1.3>**V** (234)	L234V	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > APEVLGGPS	**ADCC reduction**. Decreases FcγRI binding [3]		
1	**Homsap**	**G1v3**	**CH2** **A1.2**	CH2 **L**1.2>**A** (235)	L235A	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > APELAGGPS	**ADCC reduction**. Prevents FcγRI binding [3]		
6	**Homsap**	**G1v4**	**CH2** **A114**	**CH2** **P**114>**A** (329)	P329A	IGHG1 CH2 FG 105-117 (322-332) KVSNKA..LPAPI > KVSNKA..LAAPI	**ADCC reduction**. Reduces FcγR binding [4]	**CDC reduction**. Reduces C1q binding [4]	
1, 4	**Homsap**	**G1v5**	**CH2** **W109**	**CH2** **K**109>**W** (326)	K326W	IGHG1 CH2 FG 105-117 (322-332) KVSNKA..LPAPI > KVSNWA..LPAPI	**ADCC reduction** [5]	**CDC enhancement**. Increases C1q binding [5]	
2	**Homsap**	**G1v6**	**CH2** **A85.4, A118, A119**	CH2 **S**85.4>**A** (298), **E**118>**A** (333), **K**119>**A** (334)	S298A, E333A, K334A	IGHG1 CH2 84.1-85.1 (294-301) EQYNSTYR > EQYNATYR FG 105-117,118,119 (322-334) KVSNKA..LPAPIEK > KVSNKA..LPAPIAA	**ADCC enhancement**. Increases FcγRIIIa binding [6]		

2	**Homsap**	**G1v7**	**CH2** **D3,** **E117**	CH2 S3>D (239), I117>E (332)	S239D, I332E DE	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > APELLGGPD FG 105-117 (322-332) KVSNKA..LPAPI > KVSNKA..LPAPE	**ADCC enhancement**. Increases FcγRIIIA binding [7].		
2, 5	**Homsap**	**G1v8**	**CH2** **D3,** **L115,** **E117**	CH2 S3>D (239), A115>L (330), I117>E (332)	S239D, A330L, I332E DLE, 3M	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > APELLGGPD FG 105-117 (322-332) KVSNKA..LPAPI > KVSNKA..LPLPE	**ADCC enhancement**. Increases FcRIIIA binding [7] Decreases FcγRIIB binding [7]	**CDC reduction**. Ablates CDC [7]	3D [8]
2	**Homsap**	**G1v9**	**CH2** **L7,** **P83,** **L85.2,** **I88.** **CH3** **L83**	CH2 F7>L (243), R83>P (292), Y85.2>L (300), V88>I (305). CH3 P83>L (396)	F243L, R292P, Y300L, V305I. P396L LPLIL	IGHG1 CH2 6-10 (242-246) LFPPK > LLPPK 83-88 (292-305) REEQYNSTYRVVSV > PEEQYNSTLRVVSI CH3 83-84.4 (396-401) PVLDSD > LVLDSD	**ADCC enhancement**. 100% increase. [9]		
2	**Homsap**	**G1v10**	**CH2** **Y1.3,** **Q1.2,** **W1.1,** **M3,** **D30,** **E34,** **A85.4**	CH2 L1.3>Y (234), L1.2>Q (235), G1.1>W (236), S3>M (239), H30>D (268), D34>E (270), S85.4>A (298)	L234Y, L235Q, G236W, S239M, H268D, D270E, S298A	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > APEYQWGPM 27-31,34 (265-270) DVSHED > DVSDEE 84.1-85.1 (294-301) EQYNSTYR > EQYNATYR	**ADCC enhancement**. Increases FcγIIIA binding [10] >2000-fold (F158), >1000-fold (V158) in the association of G1v10 and G1v11 [10]		

2	**Homsap**	**G1v11**	**CH2** **E34,** **D109,** **M115,** **E119**	CH2 **D**34>**E** (270), **K**109>**D** (326), **A**115>**M** (330) **K**119>**E** (334)	D270E, K326D, A330M, K334E	IGHG1 CH2 27-31,34 (265-270) DVSHE**D** > DVSHE**E** FG 105-117,118,119 (322-334) KVSN**K**A..LP**A**PIE**K** > KVSN**D**A..LP**M**PIE**E**	**ADCC enhancement**. Increases FcγIIIA binding [10] >2000-fold (F158), >1000-fold (V158) in the association of G1v10 and G1v11 [10]		
3	**Homsap**	**G1v12**	**CH2** **A1.1,** **D3,** **L115,** **E117**	CH2 **G**1.1>**A** (236), **S**3>**D** (239), **A**115>**L** (330), **I**117>**E** (332)	G236A, S239D, A330L, I332E GASDALIE	IGHG1 CH2 1.6-3 (231-239) APELLG**G**P**S** > APELL**A**GP**D** FG 105-117 (322-332) KVSNKA..LPA**P**I > KVSNKA..LP**L**P**E**	**ADCC enhancement.** Increases FcγRIIIA binding [11].	**ADCP enhancement**. NK cell activation. Increases FcγRIIA binding [11]	5d4q, 5d6d
3	**Homsap**	**G1v13**	**CH2** **A1.1,** **D3,** **E117**	CH2 **G**1.1>**A** (236), **S**3>**D** (239), **I**117>**E** (332)	G236A, S239D, I332E GASDIE, ADE	IGHG1 CH2 1.6-3 (231-239) APELLG**G**P**S** > APELL**A**GP**D** FG 105-117 (322-332) KVSNKA..LPAP**I** > KVSNKA..LPAP**E**	**ADCC enhancement**. Increases FcγIIIA binding [12].	**ADCP enhancement**. NK cell activation. Increases FcγRIIA binding (70>fold). Increases FcγRIIA/FcγRIIB binding ratio (15-fold) [12]	
6	**Homsap**	**G1v14**	**CH2** **A1.3,** **A1.2**	CH2 **L**1.3>**A** (234), **L**1.2>**A** (235)	L234A, L235A LALA	IGHG1 CH2 1.6-3 (231-239) APE**LL**GGPS > APE**AA**GGPS	**ADCC reduction**. Reduces FcγR binding [13,14].	**CDC reduction**. Reduces C1q binding [13,14]	
6	**Homsap**	**G1v14-1**	**CH2** **A1.3,** **A1.2,** **A1**	CH2 **L**1.3>**A** (234), **L**1.2>**A** (235), **G**1>**A** (237)	L234A, L235A, G237A	IGHG1 CH2 1.6-3 (231-239) APE**LL**G**G**PS > APE**AA**G**A**PS	**ADCC reduction**. Reduces FcγR binding.	**CDC reduction**. Reduces C1q binding.	Combines Homsap G1v14 and G1 CH2 A1.

6	**Homsap**	**G1v14-4**	**CH2** **A1.3,** **A1.2,** **A114**	CH2 L1.3>A (234), L1.2>A (235, P114>A (329)	L234A, L235A, P329A	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > APEAAGGPS FG 105-117 (322-332) KVSNKA..LPAPI > KVSNKA..LAAPI	**ADCC reduction**. Reduces FcγR binding.	**CDC reduction**. Reduces C1q binding.	Combines Homsap G1v14 and Gv4.(G1 CH2 A114).
6	**Homsap**	**G1v14-48**	**CH2** **A1.3,** **A1.2,** **R113**	CH2 L1.3>A (234), L1.2>A (235), L113>R (328)	L234A, L235A, L328R	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > APEAAGGPS FG 105-117 (322-332) KVSNKA..LPAPI > KVSNKA..RPAPI	**ADCC reduction**. Reduces FcγR binding.	**CDC reduction**. Reduces C1q binding.	Combines Homsap G1v14 and G1v48.(G1 CH2 R113).
6	**Homsap**	**G1v14-49**	**CH2** **A1.3,** **A1.2,** **G114**	CH2 L1.3>A (234), L1.2>A (235), P114>G (329)	L234A, L235A, P329G LALAPG	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > APEAAGGPS FG 105-117 (322-332) KVSNKA..LPAPI > KVSNKA..LGAPI	**ADCC reduction**. Reduces FcγR binding [15].	**CDC reduction**. Reduces C1q binding [15].	Combines Homsap G1v14 and G1v49 (G1 CH2 G114).
6	**Homsap**	**G1v14-67**	**CH2** **A1.3,** **A1.2,** **S27**	CH2 L1.3>A (234), L1.2>A (235), D27>S (265)	L234A, L235A, D265S	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > APEAAGGPS 23-31 (261-269) CVVVDVSHE > CVVVSVSHE	**ADCC reduction**. Reduces FcγR binding [15].	**CDC reduction**. Reduces C1q binding [15].	Combines Homsap G1v14 and G1v67 (G1 CH2 S27).
4	**Homsap**	**G1v15**	CH2 **S118**	CH2 E118>S (333)	E333S	IGHG1 CH2 FG 105-117,118 (322-333) KVSNKA..LPAPIE > KVSNKA..LPAPIS	**CDC enhancement**. Increases C1q binding [5].		

4	**Homsap**	**G1v16**	CH2 **W109,** **S118**	CH2 **K**109>**W** (326), **E**118>**S** (333)	K326W, E333S	IGHG1 CH2 FG 105-117,118 (322-333) KVSN**K**A..LPAPI**E** > KVSN**W**A..LPAPI**S**	**CDC enhancement**. Increases C1q binding [5].		
4	**Homsap**	**G1v17**	CH2 **E29,** **F30,** **T107**	CH2 **S**29>**E** (267), **H**30>**F** (268), **S**107>**T** (324)	S267E, H268F, S324T EFT	IGHG1 CH2 27-31 (265-269) DV**S**H**E** > DV**E**F**E** FG 105-117 (322-332) KV**S**NKA..LPAPI > KV**T**NKA..LPAPI	**CDC enhancement** Increases C1q binding [16].		
4	**Homsap**	**G1v18**	CH3 **R1,** **G109,** **Y120**	CH3 **E**1>**R** (345), **E**109>**G** (430), **S**120>**Y** (440)	E345R, E430G, S440Y	IGHG1 CH3 1.4-2 (341-346) GQPR**E**P > GQPR**R**P 105-110 (426-431) SVMH**E**A > SVMH**G**A 118-125 (438-445) QK**S**LSLSP > QK**Y**LSLSP	**CDC enhancement**. Increases C1q binding [17]. The triple mutant IgG1-005-RGY (IGHG1v18) form IgG1 hexamers [17].	Favors IgG1 hexamerization.	
5	**Homsap**	**G1v19**	CH2 **A34**	CH2 **D**34>**A** (270)	D270A	IGHG1 CH2 34-41 (270-277) **D**PEVKFN**W** > **A**PEVKFN**W**	**CDC reduction**. Reduces C1q binding [4]		
5	**Homsap**	**G1v20**	**CH2** **A105**	CH2 **K**105>**A** (322)	K322A	IGHG1 CH2 FG 105-117 (322-332) **K**VSNKA..LPAPI > **A**V**S**NKA..LPAPI	**CDC reduction**. Reduces C1q binding [4,14].		
9	**Homsap**	**G1v21**	**CH2** **Y15.1,** **T16,** **E18**	CH2 **M**15.1>**Y** (252), **S**16>**T** (254), **T**18>**E** (256)	M252Y, S254T, T256E YTE	IGHG1 CH2 13-18 (249-256) DTL**M**I**S**R**T** > DTL**Y**I**T**R**E**	**Half-life increase** Enhances FCGRT binding at pH 6.0 [18,19] (1).		
9	**Homsap**	**G1v22**	**CH2**	CH2		IGHG1 CH2	**Half-life increase**		

			Y15.1, T16, E18. **CH3** K113, F114, H116	M15.1>Y (252) S16>T (254) T18>E (256). CH3 H113>K (433) N114>F (434) Y116>H (436)	M252Y S254T T256E H433K N434F Y436H	13-18 (249-256) DTLMISRT > DTLYITRE CH3 FG 105-117 (426-437) SVMHEA.LHNHYT > SVMHEA.LKFHHT	Enhances FCGRT binding at pH 6.0 [19]		
6	**Homsap**	**G1v23**	**CH2** E1.2	CH2 L1.2>E (235)	L235E	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > APELEGGPS	**ADCC reduction**. Reduces FcγR binding [20]	**CDC reduction**. Reduces C1q binding [20]	
9	**Homsap**	**G1v24**	**CH3** L107, S114	CH3 M107>L (428), N114>S (434)	M428L, N434S	GHG1 CH3 FG 105-117 (426-437) SVMHEA.LHNHYT > SVLHEA.LHSHYT	**Half-life increase** Enhances FCGRT binding at pH 6.0 (11-fold increase in affinity) [21] (2).		
7	**Homsap**	**G1v25**	CH2 E29, F113	CH2 S29>E (267), L113>F (328)	S267E, L328F	IGHG1 CH2 27-31 (265-269) DVSHE > DVEHE FG 105-117 (322-332) KVSNKA..LPAPI > KVSNKA..FPAPI	Increases FcγRIIB binding (400-fold) [22] Inhibits by downstream ITIM signaling in B cells [23]		
14	**Homsap**	**G1v26**	**CH3** Y22	CH3 T22>Y (366)	T366Y	IGHG1 CH3 20-26 (364-370) SLTCLVK > SLYCLVK	**Knob** of knobs-into-holes G1v26 knob/G1v31 hole interactions between the CH3 of the two different gamma1 chains [24]		
16	**Homsap**	**G1v27**	**CH2** C3	CH2 S3>C (329)	S239C	IGHG1 CH2 1.6-4 (231-240) APELLGGPSV > APELLGGPCV	Site-specific drug attachment engineered cysteine		
16	**Homsap**	**G1v28**	**CH2** C(3^4)	CH2 (3^4)C(239^240)	**C**(239^240)	IGHG1 CH2 1.6-4 (231-240) APELLGGPSV > APELLGGPSCV	Site-specific drug attachment engineered cysteine		
8	**Homsap**	**G1v29**	**CH2** A84.4	CH2 N84.4>A (297)	N297A	IGHG1 CH2 83-86 REEQYNSTYRVV > REEQYASTYRVV	**ADCC reduction**. Reduces FcγR binding [25].	Owing to the absence of N-glycosylation at CH2 84.4 (297).	

8	**Homsap**	**G1v30**	**CH2** **G84.4**	CH2 N84.4>G (297)	N297G	IGHG1 CH2 83-86 REEQYNSTYRVV > REEQYGSTYRVV	**ADCC reduction**. Reduces FcγR binding [25].	Owing to the absence of N-glycosylation at CH2 84.4 (297).	
14	**Homsap**	**G1v31**	**CH3** **T86**	CH3 Y86>T (407)	Y407T	IGHG1 CH3 85.4-89 (404-410) GSFFLYSKL > GSFFLTSKL	**Hole** of knobs-into-holes G1v26 knob/G1v31 hole interactions between the CH3 of the two different gamma1 chains [24] (G1v26 knob/G1v31 hole).		
14	**Homsap**	**G1v32**	**CH3** **W22**	CH3 T22>W (366)	T366W	IGHG1 CH3 20-26 (364-370) SLTCLVK > SLWCLVK	**Knob** of knobs-into-holes G1v32 knob/G1v33 hole interactions between the CH3 of the two different gamma1 chains.		
14	**Homsap**	**G1v33**	**CH3** **S22,** **A24,** **V86**	CH3 T22>S (366), L24>A (368), Y86>V (407)	T366S, L368A, Y407V	IGHG1 CH3 20-26 (364-370) SLTCLVK > SLSCAVK 85.4-89 (404-410) GSFFLYSKL > GSFFLVSKL	**Hole** of knobs-into-holes G1v32 knob/G1v33 hole interactions between the CH3 of the two different gamma1 chains.		
13	**Homsap**	**G1v34**	CH3 **G109**	CH3 E109>G (430)	E430G	IGHG1 CH3 FG 105-117 (426-437) SVMHEA.LHNHYT > SVMHGA.LHNHYT	Favors IgG1 hexamerisation by increased intermolecular Fc-Fc interactions after antigen binding on the cell surface.		
4	**Homsap**	**G1v35**	**CH2** **E29**	CH2 S29>E (267)	S267E SE	IGHG1 CH2 27-31 (265-269) DVSHE > DVEHE	**CDC enhancement**. Increases C1q binding [16]	Binds to FCGRT and FcγRIIB, but not to other FcγR in a mouse model [26]	
8	**Homsap**	**G1v36**	**CH2** **Q84.4**	CH2 N84.4>Q (297)	N297Q	IGHG1 CH2 83-86 REEQYNSTYRVV > REEQYQSTYRVV	**ADCC reduction**. Reduces FcγR binding	Owing to the absence of N-glycosylation at CH2 84.4 (297).	
15	**Homsap**	**G1v37**	**h** **S5**	h C5>S (220)	C220S	IGHG1 h 1-15 (216-230) EPKSCDKTHTCPPCP > EPKSSDKTHTCPPCP	No disulfide bridge inter H-L		

6	**Homsap**	**G1v38**	**CH2** **S108,** **F113**	CH2 N108>S (325), L113>F (328)	N325S, L328F	IGHG1 CH2 FG 105-117 (322-332) KVSNKA..LPAPI > KVSSKA..FPAPI	**ADCC reduction**. Abrogates FcγRIII binding, increases FcγRII binding, retains FcγRI high affinity binding [27]	**CDC reduction**. Abrogates C1q binding.	
6	**Homsap**	**G1v39**	**CH2** **F1.3,** **E1.2,** **S116**	CH2 L1.3>F (234), L1.2>E (235), P116>S (331)	L234F, L235E, P331S FES, TM	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > APEFEGGPS FG 105-117 (322-332) KVSNKA..LPAPI > KVSNKA..LPASI	**ADCC reduction**. Reduces FcγR effector properties [28]	**CDC reduction**. Reduces C1q binding [20]	3D 3c2s
6	**Homsap**	**G1v40**	**CH2** **A1.3,** **A1.2,** **S116**	CH2 L1.3>A (234), L1.2>A (235), P116>S (331)	L234A, L235A, P331S	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > APEAAGGPS FG 105-117 (322-332) KVSNKA..LPAPI > KVSNKA..LPASI	**ADCC reduction**. Reduces FcγR binding.	**CDC reduction**. Reduces C1q binding.	
6	**Homsap**	**G1v41**	**CH2** **F1.3,** **E1.2**	CH2 L1.3>F (234), L1.2>E (235) FE	L234F, L235E	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > APEFEGGPS	**ADCC reduction**. Reduces FcγR binding [28]	**CDC reduction**. Reduces C1q binding [20]	
9	**Homsap**	**G1v42**	**CH2** **Q14,** **CH3** **L107**	CH2 T14>Q (250) CH3 M107>L (428)	T250Q M428L	IGHG1 CH2 13-18 (249-256) DTLMISRT > DQLMISRT CH3 FG 105-117 (426-437) SVMHEA.LHNHYT > SVLHEA.LHNHYT >	**Half-life increase** Enhances FCGRT binding at pH 6.0 [19]		
6	**Homsap**	**G1v43**	**CH2** **A1.3,** **E1.2,** **A1**	CH2 L1.3>A (234), L1.2>E (235), G1>A (237)	L234A, L235E, G237A	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > APEAEGAPS	**ADCC reduction**. Reduces FcγR binding.	**CDC reduction**. Reduces C1q binding.	
16	**Homsap**	**G1v44**	**CH3** **C122**	CH3 S122>C (442)	S442C	IGHG1 CH3 118-125 (438-445)	Conjugation site-specific engineered cysteine		

						QKSLSLSP > QKSLCLSP			
3	Homsap	G1v45	CH2 A1.1, L115, E117	CH2 G1.1>A (236), A115>L (330), I117>E (332)	G236A, A330L, I332E GAALIE	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > APELLAGPS FG 105-117 (322-332) KVSNKA..LPAPI > KVSNKA..LPLPE	**ADCC enhancement**. Increases FcγIIIA binding.	**ADCP enhancement**. NK cell activation.	
9	Homsap	G1v46	CH3 K113, F114	CH3 H113>K (433), N114>F (434)	H433K, N434F	IGHG1 CH3 FG 105-117 (426-437) SVMHEA.LHNHYT > SVMHEA.LKFHYT	**Half-life increase** Enhances FCGRT binding at pH 6.0.		
1	Homsap	G1v47	CH2 delG1.1	CH2 G1.1>del (236)	G236del	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > APELL - GPS	**ADCC reduction**. Eliminates binding to FcγRI, FcγRIIA, FcγRIIIA [29].		
6	Homsap	G1v48	CH2 R113	CH2 L113>R (328)	L328R	IGHG1 CH2 FG 105-117 (322-332) KVSNKA..LPAPI > KVSNKA..RPAPI	**ADCC reduction**. Reduces FcγR binding.	**CDC reduction**. Reduces C1q binding.	
6	Homsap	G1v49	CH2 G114	CH2 P114>G (329)	P329G	IGHG1 CH2 FG 105-117 (322-332) KVSNKA..LPAPI > KVSNKA..LGAPI	**ADCC reduction**. Reduces FcγR binding [15].	**CDC reduction**. Reduces C1q binding [15].	
1	Homsap	G1v50	CH2 P1.4, V1.3, A1.2, delG1.1	CH2 E1.4>P (233), L1.3>V (234), L1.2>A (235), G1.1>del (236)	E233P, L234V, L235A, G236del	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > APPVA-GPS	**ADCC reduction**. Decreases FcgammaR binding (G2-like motif combines Homsap G1v1, v2, v3 and v47].		
6	Homsap	G1v51	CH2 K29	CH2 S29>K (267)	S267K	IGHG1 CH2 27-31 (265-269) DVSHE > DVKHE	**ADCC reduction**. Reduces FcγR binding.	**CDC reduction**. Reduces C1q binding.	

1	**Homsap**	**G1v52**	**CH2** **R1.1,** **R113**	G1.1>R (236) L113>R (328)	G236R, L328R GRLR	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > APELLRGPS IGHG1 CH2 FG 105-117 (322-332) KVSNKA..LPAPI > KVSNKA..RPAPI	**ADCC reduction**. Abrogates FcgammaR binding.		
6	**Homsap**	**G1v53**	**CH2** **F1.3,** **Q1.2,** **Q105**	CH2 L1.3>F (234) L1.2>Q (235) K105> Q (322)	L234F, L235Q, K322Q, FQQ	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > APEFQGGPS FG 105-117 (322-332) KVSNKA..LPAPI > QVSNKA..LPAPI	**ADCC reduction**. Reduces FcγR binding.	**CDC reduction**. Reduces C1q binding.	
11	**Homsap**	**G1v54**	**CH2** **C83,** **C85**	CH2 R83>C (292), V85>C (302)	R292C, V302C	IGHG1 CH2 83-86 REEQYNSTYRVV > CEEQYASTYRCV (v29) CEEQYGSTYRCV (v30) CEEQYQSTYRCV (v36)	Stabilizes CH2 in the absence of N84.4 (297) glycosylation (e.g. with G1v29, G1v30 or G1v36).		
11, 8	**Homsap**	**G1v54-29**	**CH2** **C83,** **A84.4,** **C85**	CH2 R83>C (292), N84.4>A(297) V85>C (302)	R292C, N297A V302C	IGHG1 CH2 83-86 (292-303) REEQYNSTYRVV > CEEQYASTYRCV	Stabilizes CH2 in the absence of N84.4 (297) glycosylation (Gv1-54).	**ADCC reduction**. Reduces FcγR binding [25] (G1v29).	Combines Homsap G1v54 and G1v29.
11, 8	**Homsap**	**G1v54-30**	**CH2** **C83,** **G84.4,** **C85**	CH2 R83>C (292), N84.4>G (297) V85>C (302)	R292C, N297G V302C	IGHG1 CH2 83-86 (292-303) REEQYNSTYRVV > CEEQYGSTYRCV	Stabilizes CH2 in the absence of N84.4 (297) glycosylation (G1v54)	**ADCC reduction**. Reduces FcγR binding [25] (Gv1-30).	Combines Homsap G1v54 and G1v30.
11, 8	**Homsap**	**G1v54-36**	**CH2** **C83,** **Q84.4,** **C85**	CH2 R83>C (292), N84.4>Q (297) V85>C (302)	R292C, N297Q V302C	IGHG1 CH2 83-86 (292-303) REEQYNSTYRVV > CEEQYQSTYRCV	Stabilizes CH2 in the absence of N84.4 (297) glycosylation (G1v54).	**ADCC reduction**. Reduces FcγR binding [25] (Gv1-36).	Combines Homsap G1v54 and G1v36.
16	**Homsap**	**G1v55**	**CH3** **C123**	CH3 L123>C (443)	L443C	IGHG1 CH3 118-125 (438-445) QKSLSLSP > QKSLSCSP	Conjugation site-specific engineered cysteine		
16	**Homsap**	**G1v56**	**CH2** **F85.2** **CH3** **F85.2**	CH2 Y85.2>F (pAMF) CH3 F85.2>F (pAMF)	Y300F F404F	IGHG1 CH2 84.1-85.1 (294-301) EQYNSTYR > EQYNSTFR CH3 84.1-85.1 (398-405)	Modified phenylalanine for conjugation (produced in *Escherichia coli*, non glycosylated)		

						LDSDGSFF LDSDGSFF			
17	**Homsap**	**G1v57**	**CH1** **E26,** **E119**	CH1 K26>E (147), K119>E (213)	K147E, K213E	IGHG1 CH1 23-26 (144-147) CLVK >CLVE 118-121 (212-215) DKKV >DEKV	Enhances, with KCv57, the hetero pairing H-L of bispecific antibodies		
17	**Homsap**	**KCv57**	**IGKC** **R12,** **K13**	IGKC E12>R, Q13>K	E123R, Q124K	IGKC 10-15 (121-126) SDEQLK >SDRKLK	Enhances, with G1v57, the hetero pairing H-L of bispecific antibodies		
17	**Homsap**	**G1v58**	**CH1** **C5,** **h** **V5**	CH1 F5>C (126), h C5>V (220)	F126C, C220V	IGHG1 CH1 1.4-15 (118-136) ASTKGPSVFPLAPSSKSTS >ASTKGPSVCPLAPSSKSTS IGHG1 h 1-15 (216-230) EPKSCDKTHTCPPCP >EPKSVDKTHTCPPCP	Alternative interchain cysteine mutations to enhance, with LC2v58, the heteropairing H-L of bispecific antibodies		
17	**Homsap**	**LC2v58**	**LC2** **C10,** **V126**	IGLC S10>C (121), C126>V (214)	S121C, C214V	IGLC2 1.5-15 (107A-126) GQPKAAPSVTLFPPSSEELQ >GQPKAAPSVTLFPPCSEELQ IGLC2 118-127 (206-215) EKTVAPTECS >EKTVAPTEVS	Alternative interchain cysteine mutations to enhance, with G1v58, the heteropairing H-L of bispecific antibodies		
6	**Homsap**	**G1v59**	**CH2** **S1.3** **T1.2** **R1.1**	CH2 L1.3>S (234) L1.2>T (235) G1.1>R (236)	L234S L235T G236R	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > APESTRGPS	**ADCC undetectable.** Abrogates FcγR binding [30].	**CDC undetectable.** Abrogates C1q binding [30].	
6	**Homsap**	**G1v60**	CH2 **S115,** **S116**	CH2 A115>S (330) P116>S (331)	A330S P331S	FG 105-117 (322-332) KVSNKA..LPAPI >QVSNKA..LPSSI	**ADCC reduction**. Reduces FcγR binding	**CDC reduction**. Reduces C1q binding.	

15	**Homsap**	**G1v61**	**h** **S11**	h C11>S (226)	C226S	IGHG1 h 1-15 (216-230) EPKSCDKTHTCPPCP > EPKSCDKTHTSPPCP	No disulfide bridge inter H-H h 11.		.
15	**Homsap**	**G1v62**	**h** **S14**	h C14>S (229)	C229S	IGHG1 h 1-15 (216-230) EPKSCDKTHTCPPCP > EPKSCDKTHTCPPSP	No disulfide bridge inter H-H h 14.		
6	**Homsap**	**G1v63**	**CH2** **S2**	CH2 P2>S	P238S	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > APELLGGSS	**ADCC reduction**. Reduces FcγR binding.	**CDC reduction**. Reduces C1q binding.	
16	**Homsap**	**G1v64**	**CH2** **C36**	CH2 E36>C	E272C	IGHG1 CH2 34-41 (270-277) DPEVKFNW > DPCVKFNW	Conjugation site-specific engineered cysteine		
6	**Homsap**	**G1v65**	**CH2** **delE1.4,** **delL1.3,** **delL1.2**	CH2 E1.4>**del**, L1.3>del, L1.2>del	E233del, L234del, L235del	IGHG1 CH2 1.6-3 (231-239) APELLGGPS > AP- - - GGPS	**ADCC reduction**. Reduces FcγR binding.	**CDC reduction**. Reduces C1q binding.	
1	**Homsap**	**G1v66**	**CH2** **A27**	CH2 D27>A	D265A	IGHG1 CH2 23-31 (261-269) CVVVDVSHE > CVVVAVSHE	**ADCC reduction**. Reduces FcγR binding.		
1	**Homsap**	**G1v67**	**CH2** **S27**	CH2 D27>S	D265S	IGHG1 CH2 23-31 (261-269) CVVVDVSHE > CVVVSVSHE	**ADCC reduction**. Reduces FcγR binding.		
14	**Homsap**	**G1v68**	**CH3** **V6,** **L22,** **L79,** **W81**	CH3 T6>V (350) T22>L (366) K79>L (392) T81>W (394)	T350V T366L K392L T394W	IGHG1 CH3 3-9 (347-353) QVYTLPP > QVYVLPP 20-26 (364-370) SLTCLVK > SLLCLVK 77-83 (390-396) NYKTTPP > NYLTWPP	Enhances, with G1v69, the heteropairing H-H of bispecific antibodies		

14	**Homsap**	**G1v69**	**CH3** **V6,** **Y7,** **A85.1,** **V86**	CH3 **T**6>**V** (350) **L**7>**Y** (351) **F**85.1>**A** (405) **Y**86>**V** (407)	T350V L351Y F405A Y407V	IGHG1 CH3 3-9 (347-353) QVY**T**LPP > QVY**V**YPP IGHG1 CH3 85.4-89 (404-410) GSF**F**LYSKL > GSF**A**LVSKL	Enhances, with G1v68, the heteropairing H-H of bispecific antibodies		
6	**Homsap**	**G1v70**	**h** **S5,** **S11,** **S14,** **CH2** **S2**	h **C**5>**S** (220), **C**11>**S** (226) **C**14>**S** (229) CH2 **P**2>**S**	C220S C226S C229S P238S	IGHG1 h 1-15 (216-230) EPKS**C**DKTHT**C**PP**C**P > EPKS**S**DKTHT**S**PP**S**P IGHG1 CH2 1.6-3 (231-239) APELLGG**P**S > APELLGG**S**S	**ADCC reduction**. Reduces FcγR binding.	**CDC reduction.** Reduces C1q binding.	Combines G1v63 with G1v37 (no H-L), G1v61 (no H-H h11) and G1v62 (no H-H h14).
6, 9	**Homsap**	**G1v53,** **G1v21**	**CH2** **F1.3,** **Q1.2,** **Q105** **Y15.1,** **T16,** **E18**	CH2 **L**1.3>**F** (234), **L**1.2>**Q** (235), **K**105> **Q** (322) **M**15.1>**Y** (252), **S**16>**T** (254), **T**18>**E** (256)	L234F, L235Q, K322Q, M252Y, S254T, T256E FQQ-YTE	IGHG1 CH2 1.6-3 (231-239) APE**L**L**G**GPS > APE**F**Q**G**GPS 15-18 (251-256) L**M**I.**S**R**T** > L**Y**I**T**R**E** FG 105-117 (322-332) **K**VSNKA..LPAPI > **Q**VSNKA..LPAPI	**ADCC reduction**. Reduces FcγR binding [31] (G1v53).	**CDC reduction**. Reduces C1q binding [31] (G1v53).	**Half-life increase** Enhances FCGRT binding at pH 6.0 [32] [19] (G1v21)..
4	**Homsap**	**G1G3v1**	CH2 **Q**38, **K**40, **F**85.2	CH2 **K**38>**Q** (274), **N**40>**K** (276), **Y**85.2>**F** (300)	K274Q, N276K, Y300F chimere G1-G3 (1)	IGHG1 CH2 34-41 (270-277) DPEV**K**F**N**W > DPEV**Q**F**K**W 84.1-85.1 (294-301) EQYNST**Y**R > EQYNST**F**R	**CDC enhancement**. Increases C1q binding [33].		
2	**Homsap**	**G2v1**	**CH2** **L1.3,** **L1.2,** **G1.1**	CH2 **V**1.2>**LL** (234,235) **A**1.1>**G** (236)	V235LL, A236G	IGHG2 CH2 1.6-3 (231-239) AP.P**V**A**G**PS > APP**LLG**GPS	**ADCC enhancement**. Confers FcγRI binding (WT does not show any binding capacity) [3]		

6	**Homsap**	**G2v2**	**CH2** **Q30,** **L92,** **S115,** **S116**	CH2 **H**30>**Q** (268), **V**92>**L** (309), **A**115>**S** (330), **P**116>**S** (331)	H268Q, V309L, A330S, P331S IgG2m4	IGHG2 CH2 27-38 (265-274) DVS**H**EDPEVQ > DVS**Q**EDPEVQ 89-96 (306-313) LTV**V**HQDW > LTV**L**HQDW FG 105-117 (322-332) KVSNKG..LP**A**PI > KVSNKA..LP**S**S**I**	**ADCC reduction**. Reduces FcγR binding [34]	**CDC reduction**. Reduces C1q binding [34]	
6	**Homsap**	**G2v3**	**CH2** **A1.2,** **A1,** **S2,** **A30,** **L92,** **S115,** **S116**	CH2 **V**1.2>**A** (235), **G**1>**A** (237), **P**2>**S** (238), **H**30>**A** (268), **V**92>**L** (309), **A**115>**S** (330), **P**116>**S** (331)	V235A, G237A, P238S, H268A, V309L, A330S, P331S G2sigma	IGHG2 CH2 1.6-3 (231-239) AP.P**V**A**GP**S > AP.P**A**A**AS**S 27-38 (265-274) DVS**H**EDPEVQ > DVS**A**EDPEVQ 89-96 (306-313) LTV**V**HQDW > LTV**L**HQDW FG 105-117 (322-332) KVSNKG..LP**A**PI > KVSNKA..LP**S**SI	**ADCC reduction**. Reduces FcγR binding [28]. Undetectable ADCC andV1 ADCP [28]	**CDC reduction**. Reduces C1q binding [28]. Undetectable CDC [28]	
9	**Homsap**	**G2v4**	**CH2** **Q14**	CH2 **T**14>**Q** (250)	T250Q	IGHG2 CH2 13-18 (249-256) D**T**LMISRT > D**Q**LMISRT	**Half-life increase** Enhances FCGRT binding at pH 6.0 [35]		
9	**Homsap**	**G2v5**	**CH3** **L107**	CH3 **M**107>**L** (428)	M428L	IGHG2 CH3 FG 105-117 (426-437) SV**M**HEA.LHNHYT > SV**L**HEA.LHNHYT	**Half-life increase** Enhances FCGRT binding at pH 6.0 [35]		
9	**Homsap**	**G2v6**	**CH2** **Q14,** **CH3** **L107**	CH2 **T**14>**Q** (250) CH3 **M**107>**L** (428)	T250Q M428L	IGHG2 CH2 13-18 (249-256) D**T**LMISRT > D**Q**LMISRT CH3 FG 105-117 (426-437) SV**M**HEA.LHNHYT > SV**L**HEA.LHNHYT	**Half-life increase** Enhances FCGRT binding at pH 6.0 [35]		

19, 6	**Homsap**	**G2v7**	**CH2** **Y85.2,** **L92,** **A339**	CH2 **F**85.2>**Y** (300) **V**92>**L** (309) **T**339>**A** (339)	F300Y V309L T339A	IGHG2 CH2 85.4- 92 (300-309) STFRVVSVLTVV > STYRVVSVLTVL 118-125 (333-340) EKTISKTK > EKTISKAK	Reduces acid-induced aggregation [36]	**Low ADCC** Low FcγR binding [36]	**Low CDC** Low C1q binding [36]
9	**Homsap**	**G2v8-1**	**CH2** **A93**	CH2 **H**93>**A** (310)	H310A	IGHG2 CH2 89-96 (306-313) LTVVHQDW > LTVVAQDW	**Abrogates FCGRT binding** at pH 6.0 (G2v8 for any amino acid replacement of H93 except cystein) [37]. Number 1 of G2v8-1 is for A.		
6	**Homsap**	**G2G4v1 (1)**	**CH2** **E1.4>del** **P1.3,** **V1.2,** **A1.1**	CH2 **E**1.4>**del** (233), **F**1.3>**P** (234), **L**1.2>**V** (235), **G**1.1>**A** (236)	E233del, F234P, L235V, G236A	IGHG4 CH2 1.6-3 (231-239) APEFLGGPS > AP.PVAGPS	**ADCC reduction**. Reduces FcγR binding [38]	**CDC reduction**. Reduces C1q binding [38]	
9	**Homsap**	**G3v1**	**CH3** **H115**	CH3 **R**115>**H** (435)	R435H	IGHG3 CH3 FG 105-117 (426-437) SVMHEA.LHNRFT > SVMHEA.LHNHFT	**Half-life increase** Extends half-life [39]		
2	**Homsap**	**G4v1**	**CH2** **L1.3**	CH2 **F**1.3>**L** (234)	F234L	IGHG4 CH2 1.6-3 (231-239) APEFLGGPS > APELLGGPS	**ADCC enhancement**. Increases FcγRI affinity [3].		
4	**Homsap**	**G4v2**	CH2 **P**116	CH2 **S**116>**P** (331)	S331P	IGHG4 CH2 FG 105-117 (322-332) KVSNKG..LPSSI > KVSNKG..LPSPI	**CDC enhancement** [40] (G1-, G2-, G3-like).		
6	**Homsap**	**G4v3**	**CH2** **E1.2**	CH2 **L**1.2>**E** (235)	L235E LE	IGHG4 CH2 1.6-3 (231-239) APEFLGGPS > APEFEGGPS	**ADCC reduction**. Reduces FcγR binding [20]	**CDC reduction**. Reduces C1q binding [20]	

6	**Homsap**	**G4v3-49**	**CH2** **E1.2** **G114**	CH2 **L**1.2>**E** (235) **P**114>**G** (329)	L235E P329G LEPG	IGHG4 CH2 1.6-3 (231-239) APEF**L**GGPS > APEF**E**GGPS FG 105-117 (322-332) KVSNKG..L**P**SSI > KVSNKG..L**G**SSI	**ADCC reduction**. Reduces FcγR binding [15].	**CDC reduction**. Reduces C1q binding [15].	Combines G4v3 (G4 CH2 E1.2) and G4v49.(G4 CH2 G114).
6	**Homsap**	**G4v4**	**CH2** **A1.3,** **A1.2**	CH2 **F**1.3>**A** (234), **L**1.2>**A** (235)	F234A L235A FALA	IGHG4 CH2 1.6-3 (231-239) APE**FL**GGPS > APE**AA**GGPS	**ADCC reduction**. Reduces FcγR binding [13]	**CDC reduction**. Reduces C1q binding [13]	
12	**Homsap**	**G4v5**	**h** **P10**	h **S**10>**P** (228)	S228P	IGHG4 h 1-12 (216-230) ESKYGPPCP**S**CP > ESKYGPPCP**P**CP (G1-like)	Prevents *in vivo* and *in vitro* IgG4 half-IG exchange [41]		
12	**Homsap**	**G4v6**	**CH3** **K88**	**CH3** **R**88>**K**	R409K	IGHG1 CH3 85.4-89 (404-410) GSFFLYS**R**L > GSFFLYS**K**L	Reduces IgG4 half-IG exchange [42]. IGHG4 CH3 K88 is an allelic polymorphism present in Homsap IGHG4*03 (CH3 codon 69) [43].		
6	**Homsap**	**G4v7**	**CH2** **delE1.4** **P1.3,** **V1.2,** **A1.1, -**	CH2 **E**1.4>del (233) **F**1.3>**P** (234), **L**1.2>**V** (235), **G**1.1>**A** (236),	E233del, F234P, L235V, G236A	IGHG4 CH2 1.6-3 (231-239) AP**EFLG**GPS> AP-**PVA**GPS (G2-like)	**ADCC reduction**. Reduces FcγR binding.	**CDC reduction**. Reduces C1q binding.	
10	**Homsap**	**G4v8**	**CH3** **R115,** **F116,** **P125**	CH3 **H**115>**R** (435), **Y**116>**F** (436), **L**125>**P** (445)	H435R, Y436F, L445P	IGHG4 CH3- FG 105-117 (426-437) SVMHEA.LHN**HY**T > SVMHEA.LHN**RF**T 118-125 (438-445) QKSLSLS**L** > QKSLSLS**P**	Abrogates binding to Protein A		
18	**Homsap**	**G4v10**	**CH3** **L85.1,** **K88**	CH3 **F**85.1>**L** (405), **R**88>**K** (409)	F405L, R409K	IGHG1 CH3 85.4-92 (402-413) GSF**F**LYS**R**LTVD > GSF**L**LYS**K**LTVD	Control of half-IG exchange of bispecific IgG4		
9	**Homsap**	**G4v21**	**CH2** **Y15.1,** **T16,**	CH2 **M**15.1>**Y** (252), **S**16>**T** (254),	M252Y, S254T,	IGHG4 CH2 13-18 (249-256) DTL**M**I**S**R**T** >	**Half-life increase** Enhances FCGRT binding at pH 6.0 [19].		

			E18	**T**18>**E** (256)	T256E YTE	DTL**Y**I**T**R**E**			
9	**Homsap**	**G4v22**	**CH2** **T16,** **P91,** **CH3** **A114**	CH2 **S**16>**T** (254), **V**91>**P** (308) CH3 **N**114>**A** (434)	S254T V308P N434A	IGHG4 CH2 13-18 (249-256) DTLMI**S**RT > DTLMI**T**RT 89-96 (306-313) LT**V**LHQDW > LT**P**LHQDW CH3 FG 105-117 (426-437) SVMHEA.LH**N**HYT > SVMHEA.LH**A**HYT	**Half-life increase** Enhances FCGRT binding at pH 6.0 [44]		
9	**Homsap**	**G4v24**	**CH3** **L107** **S114**	CH3 **M**107>**L** (428) **N**114>**S** (434)	M428L, N434S	CH3 FG 105-117 (426-437) SV**M**HEA.LH**N**HYT > SV**L**HEA.LH**S**HYT	**Half-life increase** Enhances FCGRT binding at pH 6.0.		
8	**Homsap**	**G4v36**	**CH2** **Q84.4**	CH2 **N**84.4>**Q** (297)	N297Q	IGHG4 CH2 83-86 REEQF**N**STYRVV > REEQF**Q**STYRVV	**ADCC reduction**. Reduces FcγR binding	Owing to the absence of N-glycosylation at CH2 84.4 (297).	
6	**Homsap**	**G4v49**	**CH2** **G114**	CH2 **P**114>**G** (329)	P329G	IGHG4 CH2 FG 105-117 (322-332) KVSNKG..L**P**SSI > KVSNKG..L**G**SSI	**ADCC reduction**. Reduces FcγR binding [15].	**CDC reduction**. Reduces C1q binding [15].	
6, **12**	**Homsap**	**G4v3** **G4v5**	**h** **P10,** **CH2** **E1.2**	h **S**10>**P** (228) CH2 **L**1.2>**E** (235)	S228P, L235E SPLE	IGHG4 h 1-12 (216-230) ESKYGPPCP**S**CP ESKYGPPCP**P**CP CH2 1.6-3 (231-239) APEF**L**GGPS > APEF**E**GGPS	**ADCC reduction**. Reduces FcγR binding [20] (G4v3).	**CDC reduction**. Reduces C1q binding [20] (G4v3).	Prevents *in vivo* and *in vitro* IgG4 half-IG exchange [41] (G4v5).
6, **12**	**Homsap**	**G4v3-49** **G4v5**	**h** **P10,** **CH2** **E1.2** **G114**	h **S**10>**P** (228) CH2 **L**1.2>**E** (235) **P**114>**G** (329)	S228P, L235E P329G SPLEPG	IGHG4 h 1-12 (216-230) ESKYGPPCP**S**CP ESKYGPPCP**P**CP CH2 1.6-3 (231-239) APEF**L**GGPS >	**ADCC reduction**. Reduces FcγR binding [15] (G4v3-49).	**CDC reduction**. Reduces C1q binding [15] (G4v3-49).	Prevents *in vivo* and *in vitro* IgG4 half-IG exchange [41] (G4v5).

						APEFEGGPS FG 105-117 (322-332) KVSNKG..LPSSI > KVSNKA..LGSSI			
6, 12	**Homsap**	**G4v4** **G4v5**	**h** **P10,** **CH2** **A1.3,** **A1.2**	h S10>P (228) CH2 F1.3>A (234) L1.2>A (235)	S228P, F234A, L235A IgG4 ProA-laAla	IGHG4 h 1-12 (216-230) ESKYGPPCPSCP ESKYGPPCPPCP CH2 1.6-3 (231-239) APEFLGGPS > APEAAGGPS	**ADCC reduction**. Reduces FcγR binding [28] (G4v4).	**CDC reduction**. Reduces C1q binding [13] (G4v4)	Prevents *in vivo* and *in vitro* IgG4 half-IG exchange [41] (G4v5).
6	**Canlupfam**	**G2v1**	**CH2** **A1.3,** **A1.2,** **A1**	CH2 M1.3>A (234), L1.2>A (235), G1>A (237).	M234A L235A G237A	IGHG2 CH2 1.6-3 (231-239) APEMLGGPS > APEAAGAPS	**ADCC reduction**. Reduces FcγR binding	**CDC reduction**. Reduces C1q binding	
6	**Canlupfam**	**G2v2**	**CH2** **A1.3,** **A1.2,** **G114**	CH2 M1.3>A (234), L1.2>A (235) P114>G (329)	M234A L235A P329G	IGHG2 CH2 1.6-3 (231-239) APEMLGGPS > APEAAGGPS IGHG1 CH2 FG 105-117 (322-332) KVNNKA..LPSPI > KVNNKA..LGSPI	**ADCC reduction**. Reduces FcγR binding	**CDC reduction**. Reduces C1q binding	
8	**Canlupfam**	**G2v29**	**CH2** **A84.4**	CH2 N84.4>A (297)	N297A	IGHG1 CH2 83-86 REEQFNGTYRVV > REEQFAGTYRVV	**ADCC reduction**. Reduces FcγR binding		
2	**Musmus**	**G2Bv1**	**CH2** **L1.2**	CH2 E1.2>L (235)	E235L	IGHG2B CH2 1.6-3 (231-239) APNLEGGPS > APNLLGGPS	**ADCC enhancement**. Increases FcγRI affinity [45]		
5	**Musmus**	**G2Bv2**	CH2 **A101**	CH2 E101>A (318)	E318A	IGHG2B CH2 317-327 KEFKCKVNNKD > KAFKCKVNNKD	**CDC reduction**. Reduces C1q binding [46].		

5	**Musmus**	**G2Bv3**	CH2 **A103**	CH2 **K**103>**A** (320)	K320A	IGHG2B CH2 317-327 KEFKCKVNNKD > KEFACKVNNKD	**CDC reduction**. Reduces C1q binding [46]		
5	**Musmus**	**G2Bv4**	CH2 **A105**	CH2 **K**105>**A** (322)	K322A	IGHG2B CH2 317-327 KEFKCKVNNKD > KEFKCAVNNKD	**CDC reduction**. Reduces C1q binding [46]		

Engineered amino acid changes are in bold in the IMGT variants (red before the change, green after the change. The motif is in yellow and shown before and after the AA change(s). Amino acids of the motifs at additional positions in the IMGT unique numbering for C-domain [47] (by comparison to the V-domain IMGT unique numbering [48]) are underlined. Alias variant names found in the literature are written in blue in column 4 'Amino Acid Changes with the Eu Positions'. The background color indicates a reduction (pink color) or an enhancement (green color) of the involved effector 'Property and Function'. For other 'Property and Function', background colors refer to structure (yellow), half-life (pale blue color) or protein A (pale orange).

IMGT nomenclature, Eu positions and IMGT motif of engineered Fc variants involved in:
The property and function type is indicated by a number from 1 to 19 with references to the separate tables per type of the manuscript.
1. antibody-dependent cellular cytotoxicity (ADCC) reductio (Table 5).
2. antibody-dependent cellular cytotoxicity (ADCC) enhancement (Table 6).
3. antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) enhancement (Table 7).
4. complement-dependent cytotoxicity (CDC) enhancement (Table 8).
5. complement-dependent cytotoxicity (CDC) reduction (Table 9).
6. antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) reduction (Table 10).
7. B cell inhibition by coengagement of antigen and FcγR on same cell (Table 11).
8. knock out CH2 84.4 glycosylation (Table 12).
9. half-life increase or decrease (Table 13).
10. abrogation of binding to Protein A (Table 14).
11. formation of additional bridge stabilizing CH2 in the absence of N84.4 (Eu 297) glycosylation (Table 15).
12. prevention of IgG4 half-IG exchange (Table 16).
13. hexamerisation (Table 17).
14. knobs-into-holes and enhancement of heteropairing H-H of bispecific antibodies (Table 18).
15. suppression of inter H-L and/or inter H-H disulfide bridges (Table 19).
16. site-specific drug attachment (Table 20).
17. enhancement of hetero pairing (Table 21).
18. control of half-IG exchange of bispecific IgG4.(Table 22).
19. reducing acid-induced aggregation (Table 23).

Amino acids: Amino acids are shown in the one-letter abbreviation [49]. Underlined amino acids in the 'Motif' column correspond to additional positions in the IMGT unique numbering for C-domain [47,50–52]

Species:
Homsap: Homo sapiens
Canlupfam: Canis lupus familiaris
Musmus: Mus musculus

IMGT engineered Fc variant name

G1v1: immunoglobulin gamma 1 heavy chain constant region engineered variant 1
Homsap
G2v1: immunoglobulin gamma 2 heavy chain constant region engineered variant 1
G3v1: : immunoglobulin gamma 3 heavy chain constant region engineered variant 1
G4v1: : immunoglobulin gamma 4 heavy chain constant region engineered variant 1
KCv: immunoglobulin kappa light chain constant region engineered variant
LCv: immunoglobulin lambda light chain constant region engineered variant

References

1. Edelman, G.M.; Cunningham, B.A.; Gall, W.E.; Gottlieb, P.D.; Rutishauser, U.; Waxdal, M.J. The covalent structure of an entire gammaG immunoglobulin molecule. *Proc. Natl. Acad. Sci. USA* **1969**, *63*, 78–85. https://doi.org/10.1073/pnas.63.1.78.
2. Kabat, E.A.; Wu, T.T.; Reid-Miller, M.; Perry, H.M.; Gottesman, K.S. *Sequences of Proteins of Immunological Interest*, 5th ed.; NIH publication n° 91-3242; US Department of Health and Human Services: Washington, DC, USA, 1991; pp. 662, 680, 689.
3. Chappel, M.S.; Isenman, D.E.; Everett, M.; Xu, Y.Y.; Dorrington, K.J.; Klein, M.H. Identification of the Fc gamma receptor class I binding site in human IgG through the use of recombinant IgG1/IgG2 hybrid and point-mutated antibodies. *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 9036–9040. https://doi.org/10.1073/pnas.88.20.9036.
4. Idusogie, E.E.; Presta, L.G.; Gazzano-Santoro, H.; Totpal, K.; Wong, P.Y.; Ultsch, M.; Meng, Y.G.; Mulkerrin, M.G. Mapping of the C1q binding site on rituxan, a chimeric antibody with a human IgG1 Fc. *J. Immunol.* **2000**, *164*, 4178–4184. https://doi.org/10.4049/jimmunol.164.8.4178.
5. Idusogie, E.E.; Wong, P.Y.; Presta, L.G.; Gazzano-Santoro, H.; Totpal, K.; Ultsch, M.; Mulkerrin, M.G. Engineered antibodies with increased activity to recruit complement. *J. Immunol.* **2001**, *166*, 2571–2575. https://doi.org/10.4049/jimmunol.166.4.2571.
6. Shields, R.L.; Namenuk, A.K.; Hong, K.; Meng, Y.G.; Rae, J.; Briggs, J.; Xie, D.; Lai, J.; Stadlen, A.; Li, B.; et al. High resolution mapping of the binding site on human IgG1 for Fc gamma RI, Fc gamma RII, Fc gamma RIII, and FcRn and design of IgG1 variants with improved binding to the Fc gamma R. *J. Biol. Chem.* **2001**, *276*, 6591–6604. https://doi.org/10.1074/jbc.M009483200.
7. Lazar, G.A.; Dang, W.; Karki, S.; Vafa, O.; Peng, J.S.; Hyun, L.; Chan, C.; Chung, H.S.; Eivazi, A.; Yoder, S.C.; et al. Engineered antibody Fc variants with enhanced effector function. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 4005–4010. https://doi.org/10.1073/pnas.0508123103.
8. Oganesyan, V.; Damschroder, M.M.; Leach, W.; Wu, H.; Dall'Acqua, W.F. Structural characterization of a mutated, ADCC-enhanced human Fc fragment. *Mol. Immunol*. **2008**, *45*, 1872–1882. https://doi.org/10.1016/j.molimm.2007.10.042.
9. Stavenhagen, J.B.; Gorlatov, S.; Tuaillon, N.; Rankin, C.T.; Li, H.; Burke, S.; Huang, L.; Vijh, S.; Johnson, S.; Bonvini, E.; et al. Fc optimization of therapeutic antibodies enhances their ability to kill tumor cells in vitro and controls tumor expansion in vivo via low-affinity activating Fcgamma receptors. *Cancer Res.* **2007**, *67*, 8882–8890. https://doi.org/10.1158/0008-5472.CAN-07-0696.
10. Mimoto, F.; Igawa, T.; Kuramochi, T.; Katada, H.; Kadono, S.; Kamikawa, T.; Shida-Kawazoe, M.; Hattori, K. Novel asymmetrically engineered antibody Fc variant with superior FcγR binding affinity and specificity compared with afucosylated Fc variant. *mAbs* **2013**, *5*, 229–236. https://doi.org/10.4161/mabs.23452.

11. Ahmed, A.A.; Keremane, S.R.; Vielmetter, J.; Bjorkman, P.J. Structural characterization of GASDALIE Fc bound to the activating Fc receptor FcγRIIIa. *J. Struct. Biol*. **2016**, *1*, 78–89. https://doi.org/10.1016/j.jsb.2016.02.001.
12. Richards, J.O.; Karki, S.; Lazar, G.A.; Chen, H.; Dang, W.; Desjarlais, J.R. Optimization of antibody binding to FcgammaRIIa enhances macrophage phagocytosis of tumor cells. *Mol. Cancer Ther*. **2008**, *7*, 2517–2527. https://doi.org/10.1158/1535-7163.MCT-08-0201.
13. Xu, D.; Alegre, M.L.; Varga, S.S.; Rothermel, A.L.; Collins, A.M.; Pulito, V.L.; Hanna, L.S.; Dolan, K.P.; Parren, P.W.; Bluestone, J.A.; et al. In vitro characterization of five humanized OKT3 effector function variant antibodies. *Cell Immunol.* **2000**, *200*, 16–26. https://doi.org/10.1006/cimm.2000.1617.
14. Hezareh, M.; Hessell, A.J.; Jensen, R.C.; van de Winkel, J.G.; Parren, P.W. Effector function activities of a panel of mutants of a broadly neutralizing antibody against human immunodeficiency virus type 1. *J. Virol*. **2001**, *75*, 12161–12168. https://doi.org/10.1128/JVI.75.24.12161-12168.2001.
15. Schlothauer, T.; Herter, S.; Koller, C.F.; Grau-Richards, S.; Steinhart, V.; Spick, C.; Kubbies, M.; Klein, C.; Umaña, P.; Mössner, E. Novel human IgG1 and IgG4 Fc-engineered antibodies with completely abolished immune effector functions. *Protein Eng. Des. Sel.* 2016, *29*, 457–466. https://doi.org/10.1093/protein/gzw040.
16. Moore, G.L.; Chen, H.; Karki, S.; Lazar, G.A. Engineered Fc variant antibodies with enhanced ability to recruit complement and mediate effector functions. *mAbs* **2010**, *2*, 181–189. https://doi.org/10.4161/mabs.2.2.11158.
17. Diebolder, C.A.; Beurskens, F.J.; de Jong, R.N.; Koning, R.I.; Strumane, K.; Lindorfer, M.A.; Voorhorst, M.; Ugurlar, D.; Rosati, S.; Heck, A.J.; et al. Complement is activated by IgG hexamers assembled at the cell surface. *Science* **2014**, *343*,1260–1263. https://doi.org/10.1126/science.1248943.
18. Robbie, G.J.; Criste, R.; Dall'acqua, W.F.; Jensen, K.; Patel, N.K.; Losonsky, G.A.; Griffin, M.P. A novel investigational Fc-modified humanized monoclonal antibody, motavizumab-YTE, has an extended half-life in healthy adults. *Antimicrob. Agents Chemother*. **2013**, *57*, 6147–6153. https://doi.org/10.1128/AAC.01285-13.
19. Dall'Acqua, W.F.; Woods, R.M.; Ward, E.S.; Palaszynski, S.R.; Patel, N.K.; Brewah, Y.A.; Wu, H.; Kiener, P.A.; Langermann, S. Increasing the affinity of a human IgG1 for the neonatal Fc receptor: Biological consequences. *J. Immunol.* **2002**, *169*, 5171–5180. https://doi.org/10.4049/jimmunol.169.9.5171.
20. Alegre, M.L.; Collins, A.M.; Pulito, V.L.; Brosius, R.A.; Olson, W.C.; Zivin, R.A.; Knowles, R.; Thistlethwaite, J.R.; Jolliffe, L.K.; Bluestone, J.A. Effect of a single amino acid mutation on the activating and immunosuppressive properties of a "humanized" OKT3 monoclonal antibody. *J. Immunol*. **1992**, 148, 3461–3468.
21. Zalevsky, J.; Chamberlain, A.K.; Horton, H.M.; Karki, S.; Leung, I.W.; Sproule, T.J.; Lazar, G.A.; Roopenian, D.C.; Desjarlais, J.R. Enhanced antibody half-life improves in vivo activity. *Nat. Biotechnol*. **2010**, *28*, 157–159. https://doi.org/10.1038/nbt.1601
22. Chu, S.Y.; Vostiar, I.; Karki, S.; Moore, G.L.; Lazar, G.A.; Pong, E.; Joyce, P.F.; Szymkowski, D.E.; Desjarlais, J.R. Inhibition of B cell receptor-mediated activation of primary human B cells by coengagement of CD19 and FcgammaRIIb with Fc-engineered antibodies. *Mol. Immunol.* **2008**, *45*, 3926–3933. https://doi.org/10.1016/j.molimm.2008.06.027.
23. Szili, D.; Cserhalmi, M.; Bankó, Z.; Nagy, G.; Szymkowski, D.E.; Sármay, G. Suppression of innate and adaptive B cell activation pathways by antibody coengagement of FcγRIIb and CD19. *mAbs* **2014**, *6*, 991–999. https://doi.org/10.4161/mabs.28841.
24. Ridgway, J.B.; Presta, L.G.; Carter, P. 'Knobs-into-holes' engineering of antibody CH3 domains for heavy chain heterodimerization. *Protein Eng*. **1996**, *9*, 617–621. https://doi.org/10.1093/protein/9.7.617.
25. Leabman, M.K.; Meng, Y.G.; Kelley, R.F.; DeForge, L.E.; Cowan, K.J.; Iyer, S. Effects of altered FcγR binding on antibody pharmacokinetics in cynomolgus monkeys. *mAbs* 2013, *5*, 896–903. https://doi.org/10.4161/mabs.26436.
26. Smith, P.; DiLillo, D.J.; Bournazos, S.; Li, F.; Ravetch, J.V. Mouse model recapitulating human Fcγ receptor structural and functional diversity. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 6181–6186. https://doi.org/10.1073/pnas.1203954109.
27. Shang, L.; Daubeuf, B.; Triantafilou, M.; Olden, R.; Dépis, F.; Raby, AC.; Herren, S.; Dos Santos, A.; Malinge, P.; Dunn-Siegrist, I.; et al. Selective antibody intervention of Toll-like receptor 4 activation through Fc γ receptor tethering. *J. Biol. Chem*. **2014**, *289*, 15309–15318. https://doi.org/10.1074/jbc.M113.537936.
28. Vafa, O.; Gilliland, G.L.; Brezski, R.J.; Strake, B.; Wilkinson, T.; Lacy, E.R.; Scallon, B.; Teplyakov, A.; Malia, T.J.; Strohl, W.R.; An engineered Fc variant of an IgG eliminates all immune effector functions via structural perturbations. *Methods* **2014**, *65*, 114–126. https://doi.org/10.1016/j.ymeth.2013.06.035.
29. Brinkhaus, M.; Douwes, R.G.J.; Bentlage, A.E.H.; Temming, A.R.; de Taeye, S.W.; Tammes Buirs, M.; Gerritsen, J.; Mok, J.Y.; Brasser, G.; Ligthart, P.C.; et al**.** Glycine 236 in the lower hinge region of human IgG1 differentiates FcγR from Complement effector function. *J. Immunol*. **2020**, *205*, 3456–3467. https://doi.org/10.4049/jimmunol.2000961.
30. Wilkinson, I.; Anderson, S.; Fry, J.; Julien, L.A.; Neville, D.; Qureshi, O.; Watts, G.; Hale, G. Fc-engineered antibodies with immune effector functions completely abolished. *PLoS ONE* 2021, *16*, e0260954. https://doi.org/10.1371/journal.pone.0260954.

31. Borrok, M.J.; Mody, N.; Lu, X.; Kuhn, M.L.; Wu, H.; Dall'Acqua, W.F.; Tsui, P. An "Fc-Silenced" IgG1 format with extended half-life designed for improved stability. *J. Pharm. Sci*. **2017**, 106, 1008–1017. https://doi.org/10.1016/j.xphs.2016.12.023.
32. Lefranc, M.-P. WHO-IUIS Nomenclature Subcommittee for Immunoglobulins and T cell receptors report. *Immunogenetics* **2007**, *59*, 899–902.
33. Natsume, A.; In, M.; Takamura, H.; Nakagawa, T.; Shiz, Y.; Kitajima, K.; Wakitani, M.; Ohta, S.; Satoh, M.; Shitara, K.; et al. Engineered antibodies of IgG1/IgG3 mixed isotype with enhanced cytotoxic activities. *Cancer Res.* **2008**, *68*, 3863–3872. https://doi.org/10.1158/0008-5472.CAN-07-6297.
34. An, Z.; Forrest, G.; Moore, R.; Cukan, M.; Haytko, P.; Huang, L.; Vitelli, S.; Zhao, J.Z.; Lu, P.; Hua, J.; et al. IgG2m4, an engineered antibody isotype with reduced Fc function. *mAbs* **2009**, *1*, 572–579. https://doi.org/10.4161/mabs.1.6.10185.
35. Hinton, P.R.; Johlfs, M.G.; Xiong, J.M.; Hanestad, K.; Ong, K.C.; Bullock, C.; Keller, S.; Tang, M.T.; Tso, J.Y.; Vásquez, M.; et al. Engineered human IgG antibodies with longer serum half-lives in primates. *J. Biol. Chem*. **2004**, *279*, 6213–6216. https://doi.org/10.1074/jbc.C300470200.
36. Saito, S.; Namisaki, H.; Hiraishi, K.; Takahashi, N.; Iida, S. Engineering a human IgG2 antibody stable at low pH. *Protein Sci*. **2020**, *29*, 1186–1195. https://doi.org/10.1002/pro.3852.
37. Oganesyan, V.; Damschroder, M.M.; Cook, K.E.; Li, Q.; Gao, C.; Wu, H.; Dall'Acqua, W.F. Structural insights into neonatal Fc receptor-based recycling mechanisms. *J. Biol. Chem.* **2014**, *289*, 7812–7824. https://doi.org/10.1074/jbc.M113.537563.
38. Rother, R.P.; Rollins, S.A.; Mojcik, C.F.; Brodsky, R.A.; Bell, L. Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria. *Nat. Biotechnol*. **2007**, *25*, 1256–1264. https://doi.org/10.1038/nbt1344.
39. Stapleton, N.M.; Andersen, J.T.; Stemerding, A.M.; Bjarnarson, S.P.; Verheul, R.C.; Gerritsen, J.; Zhao, Y.; Kleijer, M.; Sandlie, I.; de Haas, M.; et al. Competition for FcRn-mediated transport gives rise to short half-life of human IgG3 and offers therapeutic potential. *Nat. Commun.* **2011**, 2, 599. https://doi.org/10.1038/ncomms1608.
40. Tao, M.H.; Smith, R.I.; Morrison, S.L. Structural features of human immunoglobulin G that determine isotype-specific differences in complement activation. *J. Exp. Med*. **1993**, *178*, 661–667. https://doi.org/10.1084/jem.178.2.661.
41. Labrijn, A.F.; Buijsse, A.O.; van den Bremer, E.T.; Verwilligen, A.Y.; Bleeker, W.K.; Thorpe, S.J.; Killestein, J.; Polman, C.H.; Aalberse, R.C.; Schuurman, J.; et al. Therapeutic IgG4 antibodies engage in Fab-arm exchange with endogenous human IgG4 in vivo. *Nat. Biotechnol*. **2009**, *27*, 767–771. https://doi.org/10.1038/nbt.1553.
42. Labrijn, A.F.; Rispens, T.; Meesters, J.; Rose, R.J.; den Bleker, T.H.; Loverix, S.; van den Bremer, E.T.; Neijssen, J.; Vink, T.; Lasters, I.; et al. Species-specific determinants in the IgG CH3 domain enable Fab-arm exchange by affecting the noncovalent CH3-CH3 interaction strength. *J. Immunol*. **2011**, *187*, 3238–3246. https://doi.org/10.4049/jimmunol.1003336.
43. Lefranc, M.-P.; Lefranc, G. *The Immunoglobulin FactsBook*; Academic Press: London, UK, 2001; pp. 1–457.
44. Zhang, J.; Huang, Y.; Xi, G.; Zhang, F. HX008: A humanized PD-1 blocking antibody with potent antitumor activity and superior pharmacologic properties. *mAbs* **2020**, *12*, 1724751. https://doi.org/10.1080/19420862.2020.1724751.
45. Duncan, A.R.; Woof, J.M.; Partridge, L.J.; Burton, D.R.; Winter, G. Localization of the binding site for the human high-affinity Fc receptor on IgG. *Nature* **1988**, *332*, 563–564. https://doi.org/10.1038/332563a0.
46. Duncan, A.R.; Winter, G. The binding site for C1q on IgG. *Nature* **1988**, *332*, 738–740. https://doi.org/10.1038/332738a0.
47. Lefranc, M.-P.; Pommié, C.; Kaas, Q.; Duprat, E.; Bosc, N.; Guiraudou, D.; Jean, C.; Ruiz, M.; Da Piedade, I.; Rouard, M.; et al. IMGT unique numbering for immunoglobulin and T cell receptor constant domains and Ig superfamily C-like domains. *Dev. Comp. Immunol.* **2005**, *29*, 185–203.
48. Lefranc, M.-P.; Pommié, C.; Ruiz, M.; Giudicelli, V.; Foulquier, E.; Truong, L.; Thouvenin-Contet, V.; Lefranc, G. IMGT unique numbering for immunoglobulin and T cell receptor variable domains and Ig superfamily V-like domains. *Dev. Comp. Immunol.* **2003**, *27*, 55–77.
49. Pommié, C.; Levadoux, S.; Sabatier, R.; Lefranc, G.; Lefranc, M.-P. IMGT standardized criteria for statistical analysis of immunoglobulin V-REGION amino acid properties. *J. Mol. Recognit.* **2004**, *17*, 17–32.
50. Lefranc, M.-P. IMGT unique numbering for the Variable (V), Constant (C), and Groove (G) domains of IG, TR, MH, IgSF, and MhSF. *Cold Spring Harb. Protoc.* **2011**, *6*, 633–642. https://doi.org/10.1101/pdb.ip85.
51. Lefranc, M.-P. IMGT unique numbering. In *Encyclopedia of Systems Biology*; Dubitzky, W., Wolkenhauer, O., Cho, K.-H., Yokota, H., Eds.; Springer: New York, NY, USA, 2013; pp. 952–959. https://doi.org/10.1007/978-1-4419-9863-7_127.
52. Lefranc, M-P. Immunoinformatics of the V, C, and G domains: IMGT® definitive system for IG, TR and IgSF, MH, and MhSF. In *Immunoinformatics: From Biology to Informatics*, 2nd ed.; De, R.K., Tomar, N., Eds.; Methods in Molecular Biology' Humana Press: New Yor, NY, USA, 2014; Volume 1184, pp. 59–107. https://doi.org/10.1007/978-1-4939-1115-8_4.