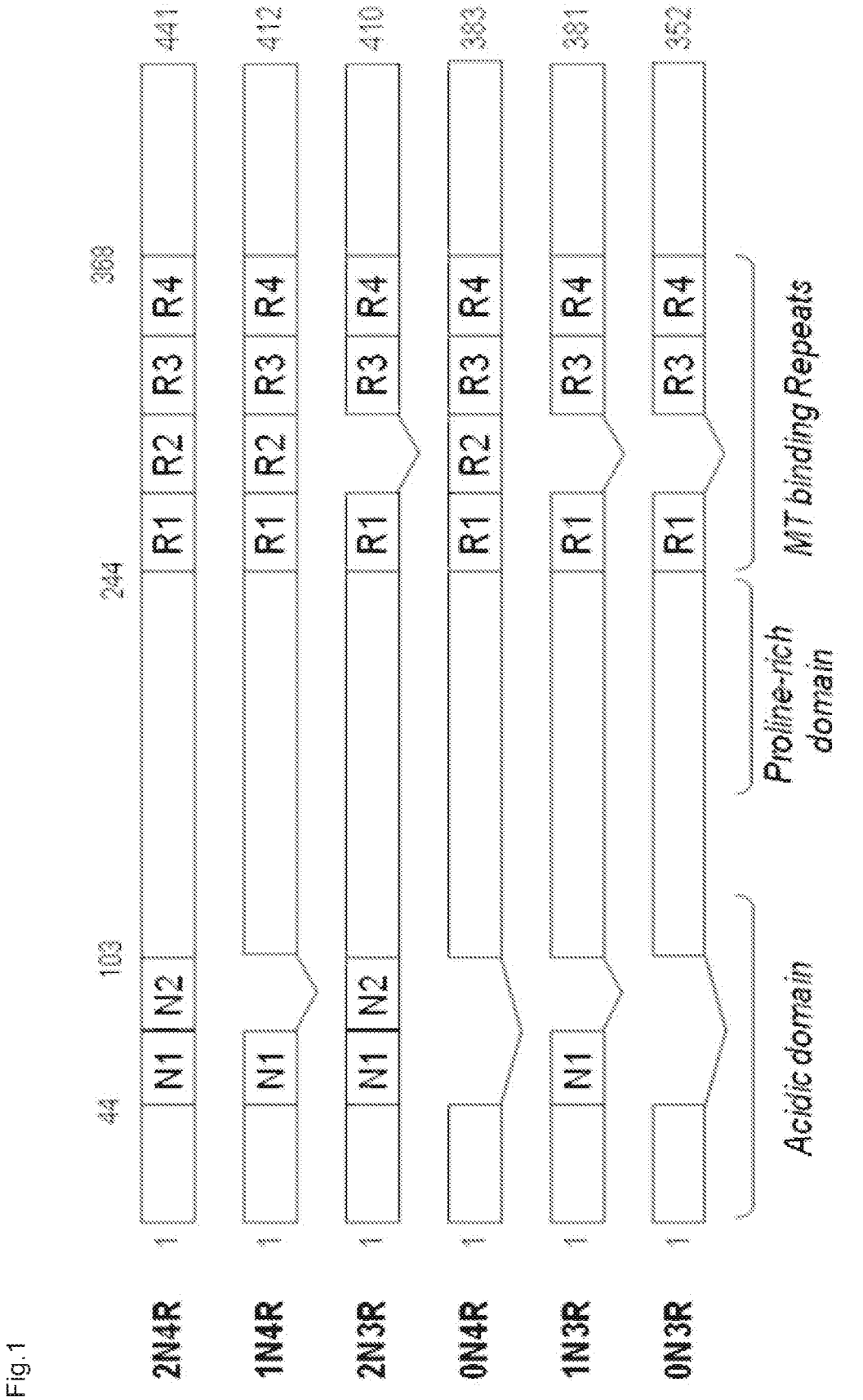
2N4R
1N4R
2N3R
0N4R
1N3R
0N3R
1
44
103
244
368
441
412
410
383
381
352
N1
N2
R1
R2
R3
R4
Acidic domain
Proline-rich domain
MT binding Repeats

Fig.1

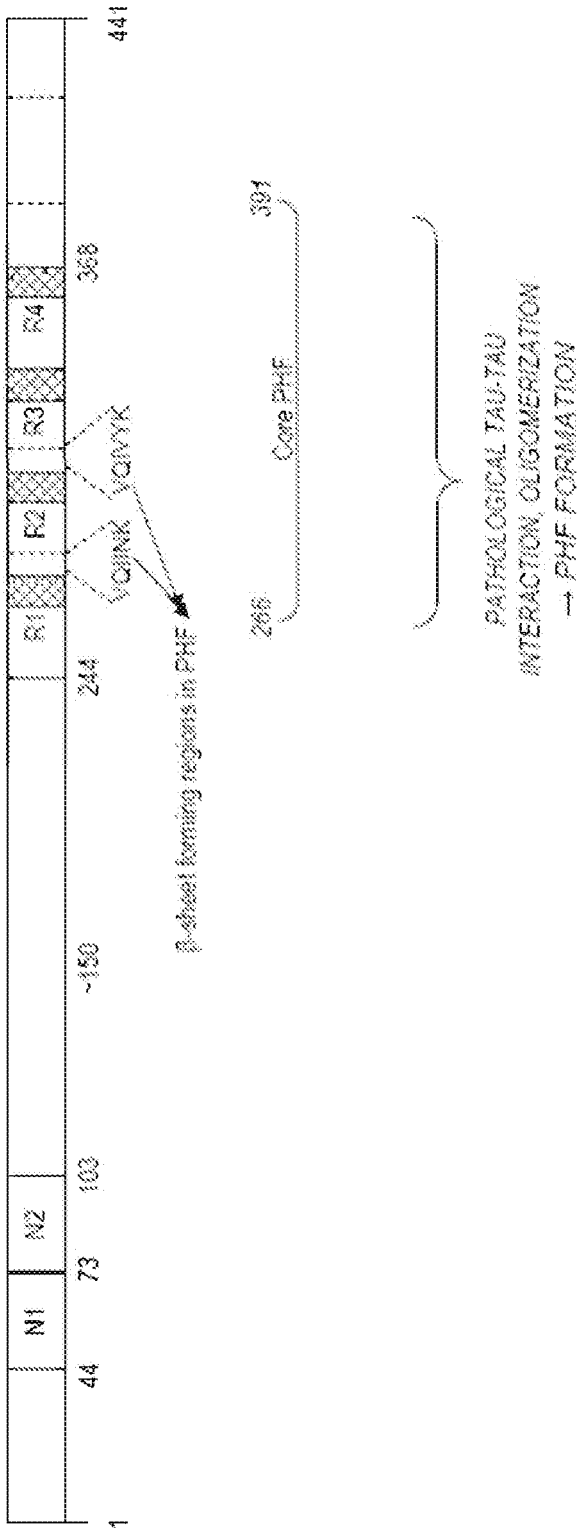
1
44
N1
73
N2
103
~150
244
R1
R2
R3
R4
368
441
VQIINK
VQIVYK
β-sheet forming regions in PHF
266
Core PHF
381
PATHOLOGICAL TAU-TAU
INTERACTION, OLIGOMERIZATION
→ PHF FORMATION

Fig.2

Fig.3

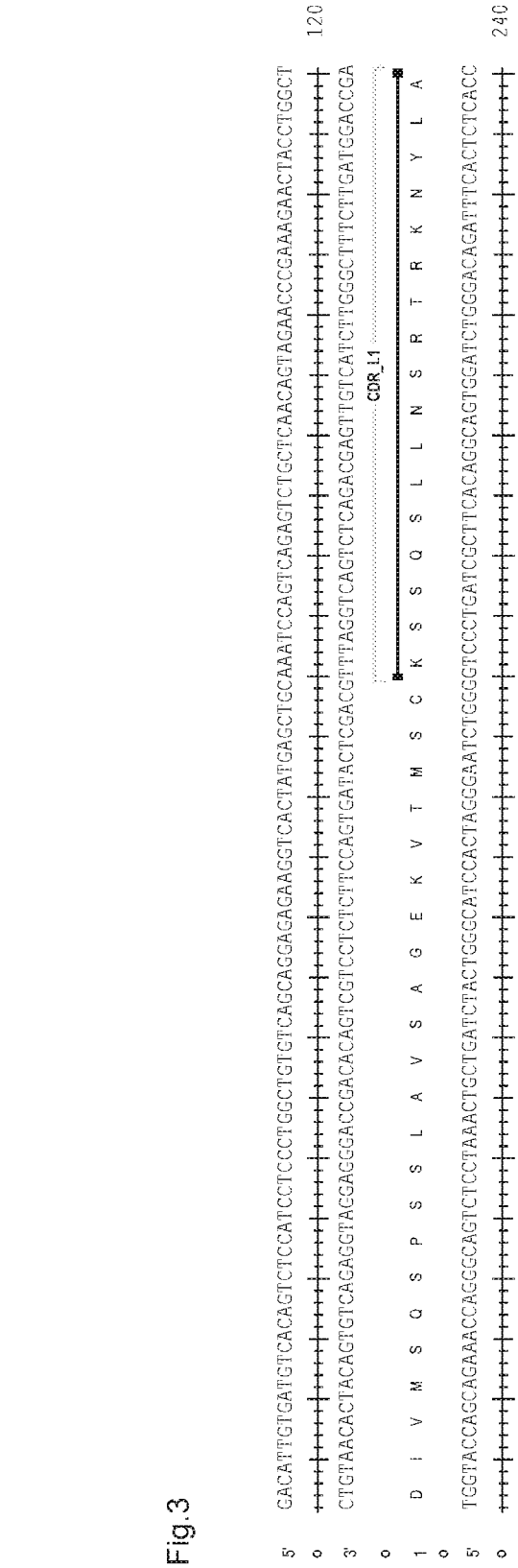
5' GACATTGTGATGTCACAGTCTCCATCCTCCCTGGCTGTGTCAGCAGGAGAAGGTCACTATGAGCTGCAAATCCAGTCAGAGTCTGCTCAACACTAGAACCCGAAAGAACTACCTGGCT 120
3' CTGTAACACTACAGTGTCAGAGGTACGAGGGACCGACACAGTCGTCCTCTCTTCCAGTGATACTCGACGTTTAGGTCAGTCTCAGACGAGTTGTCATCTTGGGCTTTCTTGATGGACCGA
CDR_L1
1 D I V M S Q S P S S L A V S A G E K V T M S C K S S Q S L L N S R T R K N Y L A
TGGTACCAGCAGAAACCAGGGCAGTCTCCTAAACTGCTGATCTACTGGGCATCCACTAGGGAATCTGGGGTCCCTGATCGCTTCACAGGCAGTGGATCTGGGACAGATTTCACTCTCACC 240
ACCATGGTCGTCTTTGGTCCCGTCAGGATTTGACGACTAGATGACCCGTAGGTGATCCCTTAGACCCCAGGGACTAGCGAACTGTCCGTCACCTAGACCCTGTCTCTAAAGTGAGAGTGG
CDR_L2
1 W Y Q Q K P G Q S P K L L I Y W A S T R E S G V P D R F T G S G S G T D F T L T
ATCAGCAGTGTGCAGGCTGAAGACCTGGCAGTTTATTACTGCAAGCAATCTTTTTATCTTCGGACGTTCGGTGGAGGCACCAAGCTGGACATCAAA
TAGTCGTCACACGTCCGACTTCTGGACCGTCAAATAATGACGTTCGTTAGAAAAATAGAAGCCTGCAAGCCACCTCCGTGGTTCGACCTGTAGTTT
CDR_L3
1 I S S V Q A E D L A V Y Y C K Q S F Y L R T F G G G T K L D I K

Fig.4

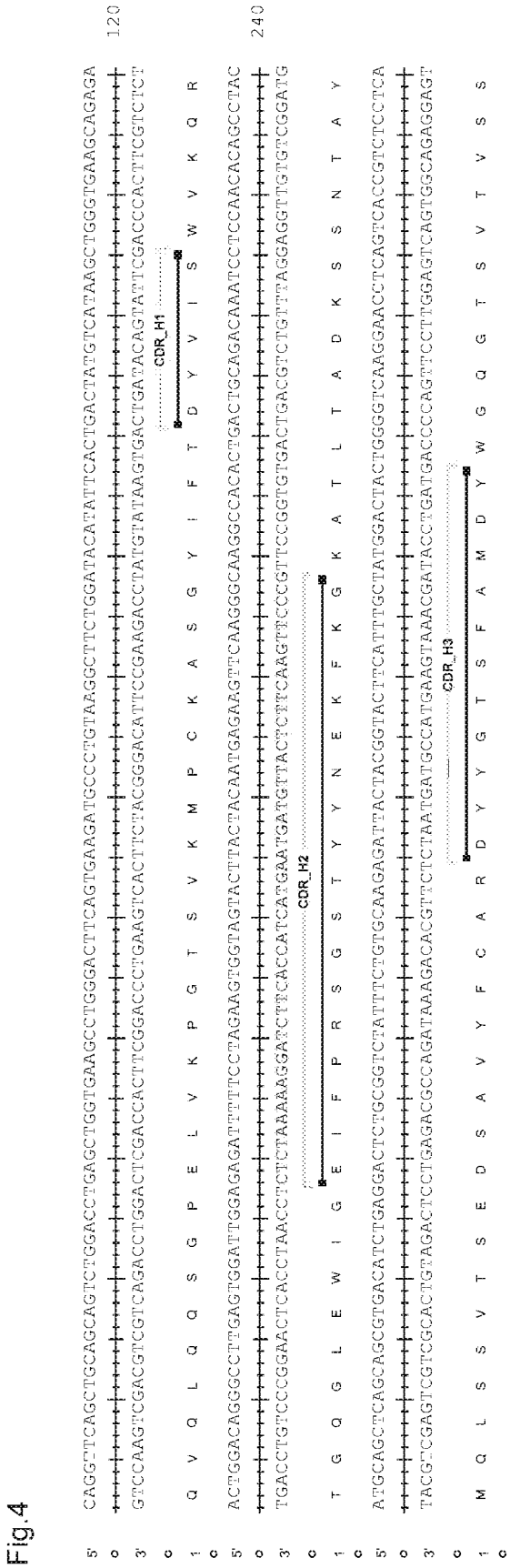

Fig.5

DC8E8_VK

Closest V-REGIONs (evaluated from the V-REGION first nucleotide to the 2nd-Cys codon plus 15 nt of the CDR3-IMGT)

	Score	Identity
Y15982 Musmus IGKV8-21*01 F	1453	98.99% (294/297 nt)
L17135 Musmus IGKV8-28*02 F	1264	91.92% (273/297 nt)
Y15980 Musmus IGKV8-19*01 F	1255	91.58% (272/297 nt)
AJ235948 Musmus IGKV8-30*01 F	1255	91.25% (271/297 nt)
AJ235947 Musmus IGKV8-28*01 F	1228	90.57% (269/297 nt)

```
                10        20        30        40        50        60        70        80        90        100
                ----------+---------+---------+---------+---------+---------+---------+---------+---------+-
Y15982.seq      DIVMSQSPSSLAVSAGEKVTMSCkssqsllnsrtrknylaWYQQKPGQSPKLLIYwastresGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCkqsynlp
DC8E8_VKc       ..............................................................................................fy.r
```

Fig.6

DC8E8_VH

Closest V-REGIONs (evaluated from the V-REGION first nucleotide to the 2nd-Cys codon)

	Score	Identity
AC160990 Musmus IGHV1-81*01 F	1237	92.36% (266/288 nt)
AC160473 Musmus IGHV1-77*01 F	1219	91.67% (264/288 nt)
AC160990 Musmus IGHV1-83*01 P	1210	91.32% (263/288 nt)
AC160473 Musmus IGHV1-75*01 F	1192	90.62% (261/288 nt)
X02064 Musmus IGHV1-54*02 F	1174	89.93% (259/288 nt)

```
                10        20        30        40        50        60        70        80        90
                ----------+---------+---------+---------+---------+---------+---------+---------+---------
AC160990.seq QVQLQQSGAELARPGASVKLSCKASGYTFTsygisWVKQRTGQGLEWIGeiyprsgntyynekfkgKATLTADKSSSTAYMELRSLTSEDSAVYFCAR
DC8E8_VHc    ........P..VK..T...MP......I..d.v.................f....s..................N....Q.S.V............
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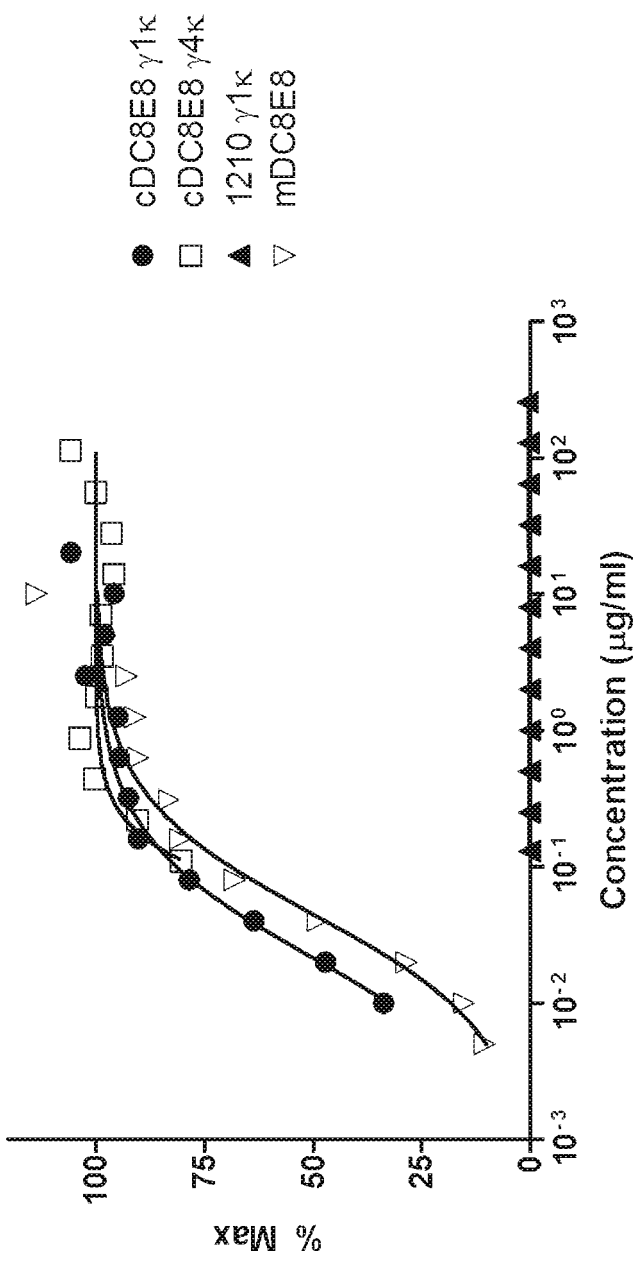


EC50 (µg/ml)			
cDC8E8 γ1κ	cDC8E8 γ4κ	mDC8E8	1210 γ1κ
0.02144	0.05074	0.04480	*NA*

Fig.7

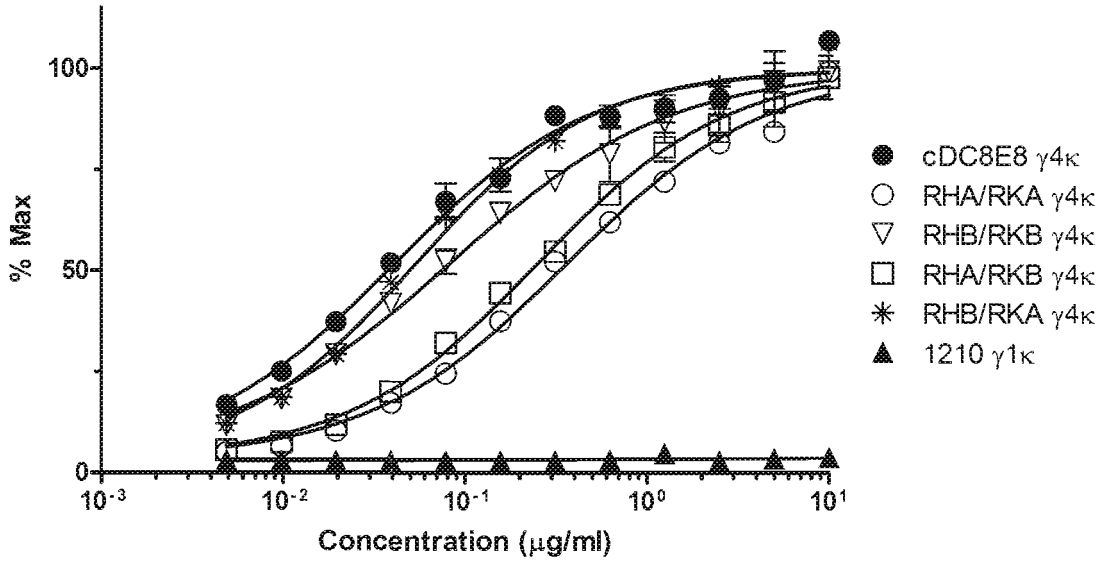
Fig.8

Kabat Number	* * **** . . . * * **** . . . . . ****** * * * **** . . . . . *
DC8E8_Heavy	QVQLQQSGPELVKPGTSVKMPCKASGYIFTdyvisWVKQRTGQGLEWIGeifprsgstyynekfkgKATLTADKSSNTAYMQLSSVTSEDSAVYFCARdyygtsfamdyWGQGTSVTVSS
M65092	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSsyaisWVRQAPGQGLEWMGgiipifgtanyaqkfqgRVTITADKSTSTAYMELSSLRSEDTAVYYCARgstvttgdfdyWGQGTLVTVSS
RHA	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSdyvisWVRQAPGQGLEWMGeifprsgstyynekfkgRVTITADKSTSTAYMELSSLRSEDTAVYYCARdyygtsfamdyWGQGTLVTVSS
RHB	QVQLVQSGPEVKKPGSSVKVPCKASGYIFTdyvisWVKQAPGQGLEWIGeifprsgstyynekfkgKATLTADKSTSTAYMELSSLRSEDTAVYFCARdyygtsfamdyWGQGTLVTVSS
RHC	QVQLVQSGPEVKKPGSSVKVPCKASGGTFSdyvisWVRQAPGQGLEWMGeifprsgstyynekfkgRVTITADKSTSTAYMELSSLRSEDTAVYYCARdyygtsfamdyWGQGTLVTVSS
RHD	QVQLVQSGAEVKKPGSSVKVSCKASGYTFSdyvisWVRQAPGQGLEWMGeifprsgstyynekfkgRVTITADKSTSTAYMELSSLRSEDTAVYYCARdyygtsfamdyWGQGTLVTVSS
RHE	QVQLVQSGAEVKKPGSSVKVSCKASGGIFSdyvisWVRQAPGQGLEWMGeifprsgstyynekfkgRVTITADKSTSTAYMELSSLRSEDTAVYYCARdyygtsfamdyWGQGTLVTVSS
RHF	QVQLVQSGAEVKKPGSSVKVSCKASGGTFTdyvisWVRQAPGQGLEWMGeifprsgstyynekfkgRVTITADKSTSTAYMELSSLRSEDTAVYYCARdyygtsfamdyWGQGTLVTVSS
RHG	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSdyvisWVKQAPGQGLEWMGeifprsgstyynekfkgRVTITADKSTSTAYMELSSLRSEDTAVYYCARdyygtsfamdyWGQGTLVTVSS
RHH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSdyvisWVRQAPGQGLEWIGeifprsgstyynekfkgRVTITADKSTSTAYMELSSLRSEDTAVYYCARdyygtsfamdyWGQGTLVTVSS
RHI	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSdyvisWVRQAPGQGLEWMGeifprsgstyynekfkgKVTITADKSTSTAYMELSSLRSEDTAVYYCARdyygtsfamdyWGQGTLVTVSS
RHJ	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSdyvisWVRQAPGQGLEWMGeifprsgstyynekfkgRATITADKSTSTAYMELSSLRSEDTAVYYCARdyygtsfamdyWGQGTLVTVSS
RHK	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSdyvisWVRQAPGQGLEWMGeifprsgstyynekfkgRVTLTADKSTSTAYMELSSLRSEDTAVYYCARdyygtsfamdyWGQGTLVTVSS
RHL	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSdyvisWVRQAPGQGLEWMGeifprsgstyynekfkgRVTITADKSTSTAYMELSSLRSEDTAVYFCARdyygtsfamdyWGQGTLVTVSS
RHM	QVQLVQSGAEVKKPGSSVKVSCKASGYIFSdyvisWVRQAPGQGLEWMGeifprsgstyynekfkgRVTITADKSTSTAYMELSSLRSEDTAVYYCARdyygtsfamdyWGQGTLVTVSS

Fig.9

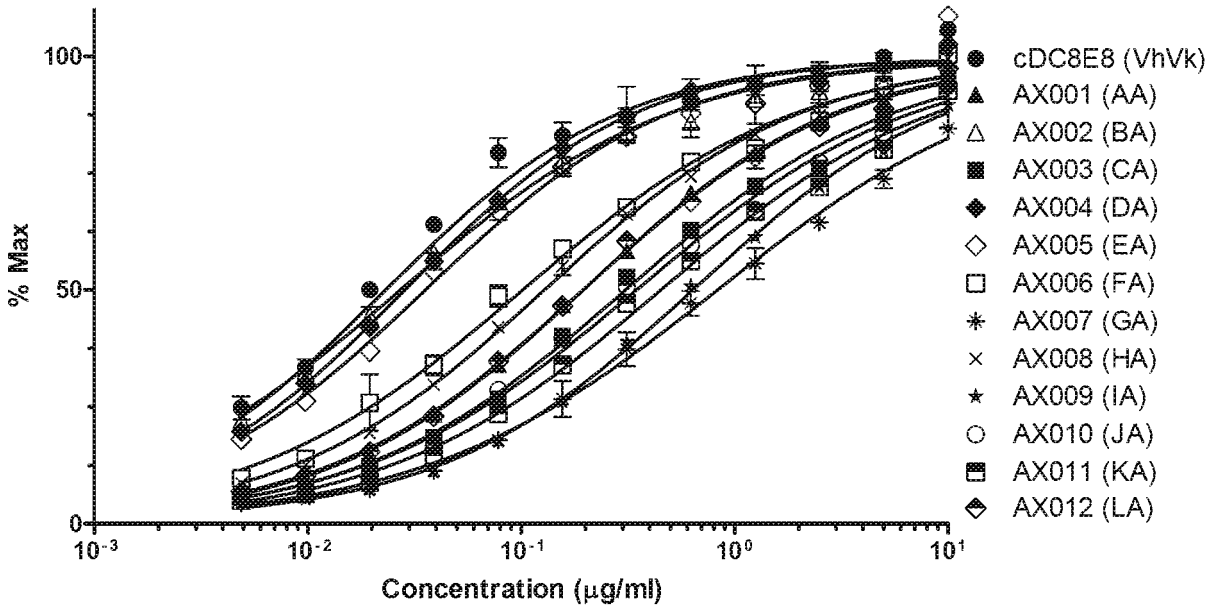
Kabat Number	****** ********** ** **** ********** **** ***** ********** ** **********
DC8E8_Kappa	DIVMSQSPSSLAVSAGEKVTMSCksqsllnsrtrknylawyqqkpgqspkllvwastresgvpdrftgsgsgtdftltissvqaedlavyyckqsfylrtfgggtkldik
X72449	DIVMTQSPLSLPVTPGEPASISCrssqslhi-ngynylawylqkpgqspqllvysnrasgvpdrftgsgsgtdftlkisrveaedvgvyyckqglqtpftfgqgtkvdik
RKA	DIVMTQSPLSLPVTPGEPASISCksqsllnsrtrknylawylqkpgqspqllvwastresgvpdrftgsgsgtdftlkisrveaedvgvyyckqsfylrtfgqgtkveik
RKB	DIVMSQSPASLPVTPGEPASISCksqsllnsrtrknylawylqkpgqspqllvwastresgvpdrfsgsgsgtdftlkisrvkaedvgvyyckqsfylrtfgqgtkveik

Fig.10



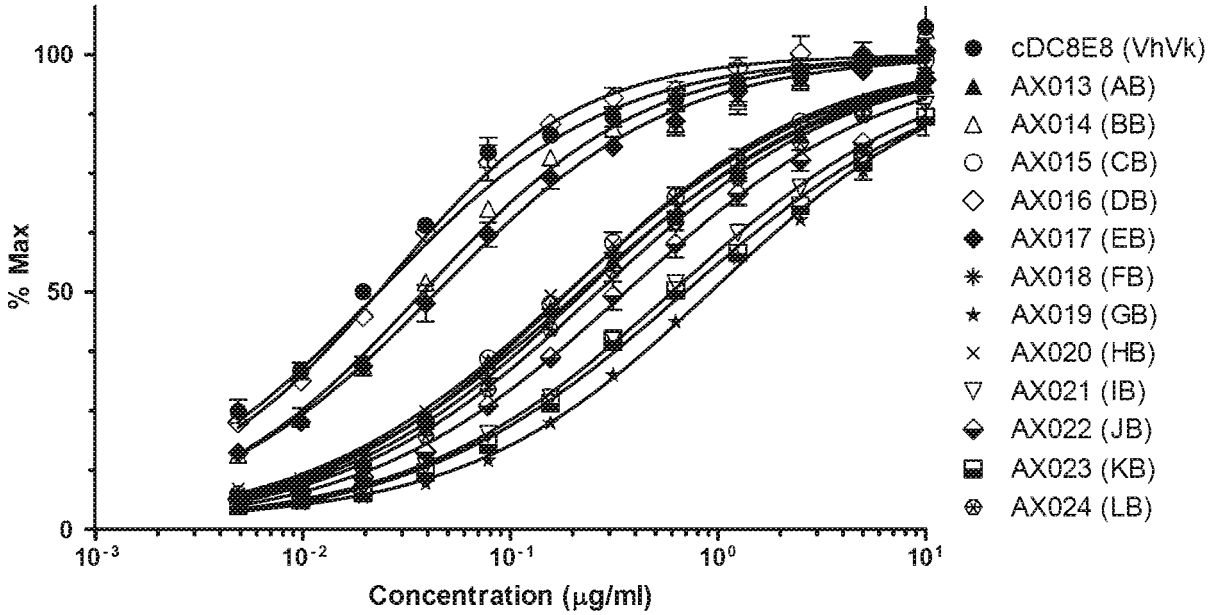
	EC50 (μg/ml)					
	cDC8E8	RHA/RKA	RHB/RKB	RHA/RKB	RHB/RKA	1210 γ1κ
γ1κ	0.02915	0.1884	0.02694	0.2216	0.07770	NA
γ4κ	0.04068	0.3596	0.08151	0.2479	0.05328	NA

Fig.11



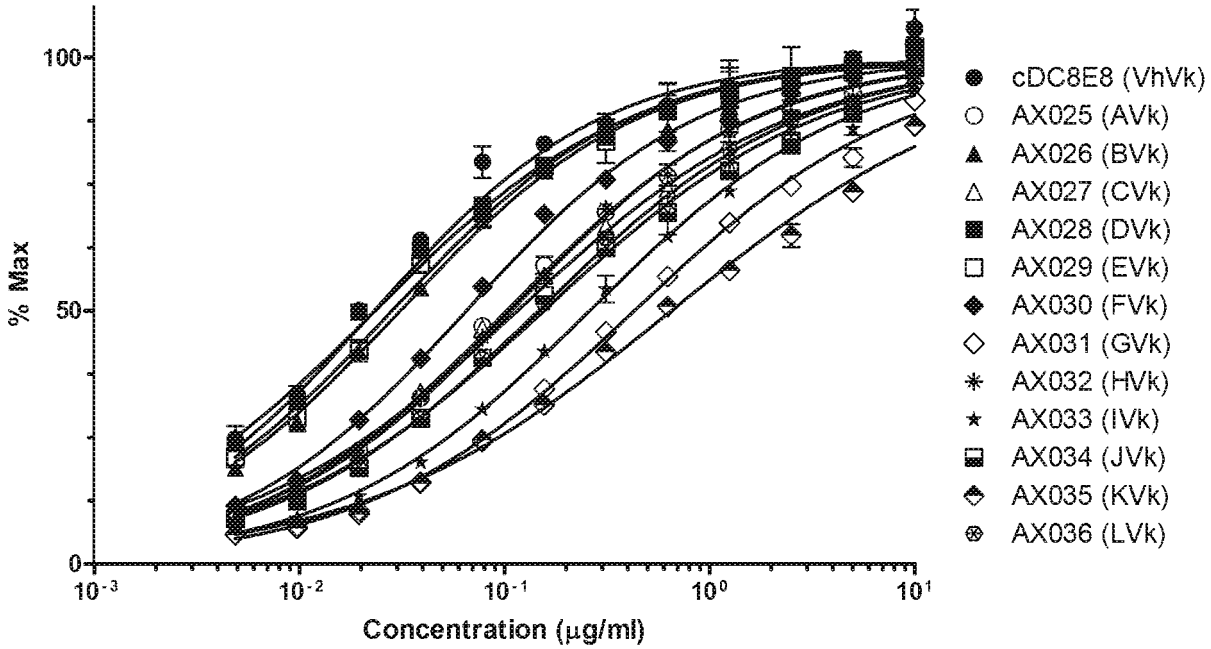
Name	Chain Composition		EC50 (µg/ml)
cDC8E8	VH	VK	0.0199
AX001	RHA	RKA	0.1951
AX002	RHB	RKA	0.0271
AX003	RHC	RKA	0.3083
AX004	RHD	RKA	0.0285
AX005	RHE	RKA	0.0356
AX006	RHF	RKA	0.1015
AX007	RHG	RKA	0.8311
AX008	RHH	RKA	0.1286
AX009	RHI	RKA	0.6491
AX010	RHJ	RKA	0.3471
AX011	RHK	RKA	0.4510
AX012	RHL	RKA	0.1945

Fig.12



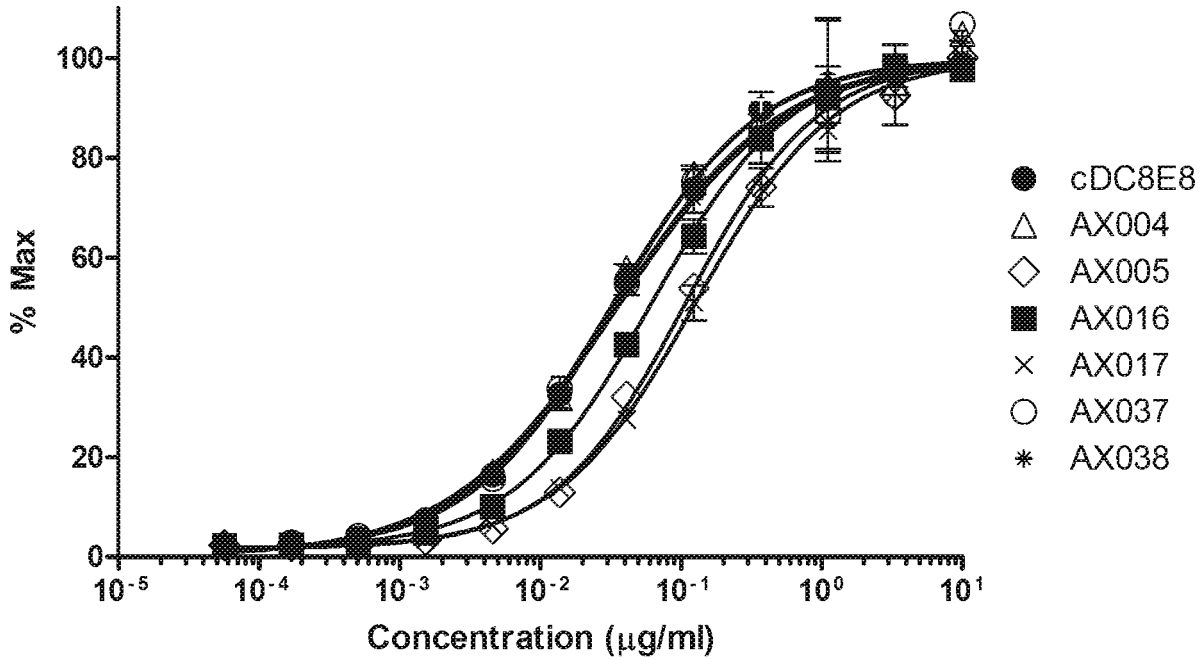
Name	Chain Composition		EC50 (µg/ml)
cDC8E8	VH	VK	0.0199
AX013	RHA	RKB	0.2152
AX014	RHB	RKB	0.0379
AX015	RHC	RKB	0.1907
AX016	RHD	RKB	0.0262
AX017	RHE	RKB	0.0443
AX018	RHF	RKB	0.2264
AX019	RHG	RKB	0.9673
AX020	RHH	RKB	0.1877
AX021	RHI	RKB	0.6141
AX022	RHJ	RKB	0.3593
AX023	RHK	RKB	0.6941
AX024	RHL	RKB	0.2634

Fig.13



Name	Chain Composition		EC50 (µg/ml)
cDC8E8	VH	VK	0.0199
AX025	RHA	Vk	0.1024
AX026	RHB	Vk	0.0310
AX027	RHC	Vk	0.1156
AX028	RHD	Vk	0.0234
AX029	RHE	Vk	0.0283
AX030	RHF	Vk	0.0652
AX031	RHG	Vk	0.4299
AX032	RHH	Vk	0.1126
AX033	RHI	Vk	0.2599
AX034	RHJ	Vk	0.1556
AX035	RHK	Vk	0.6510
AX036	RHL	Vk	0.1463

Fig.14



Name	Chain Composition		EC50 (µg/ml)
cDC8E8	VH	VK	0.0338
AX004	RHD	RKA	0.0322
AX005	RHE	RKA	0.1074
AX016	RHD	RKB	0.0615
AX017	RHE	RKB	0.1265
AX037	RHM	RKA	0.0346
AX038	RHM	RKB	0.0352

Fig.15

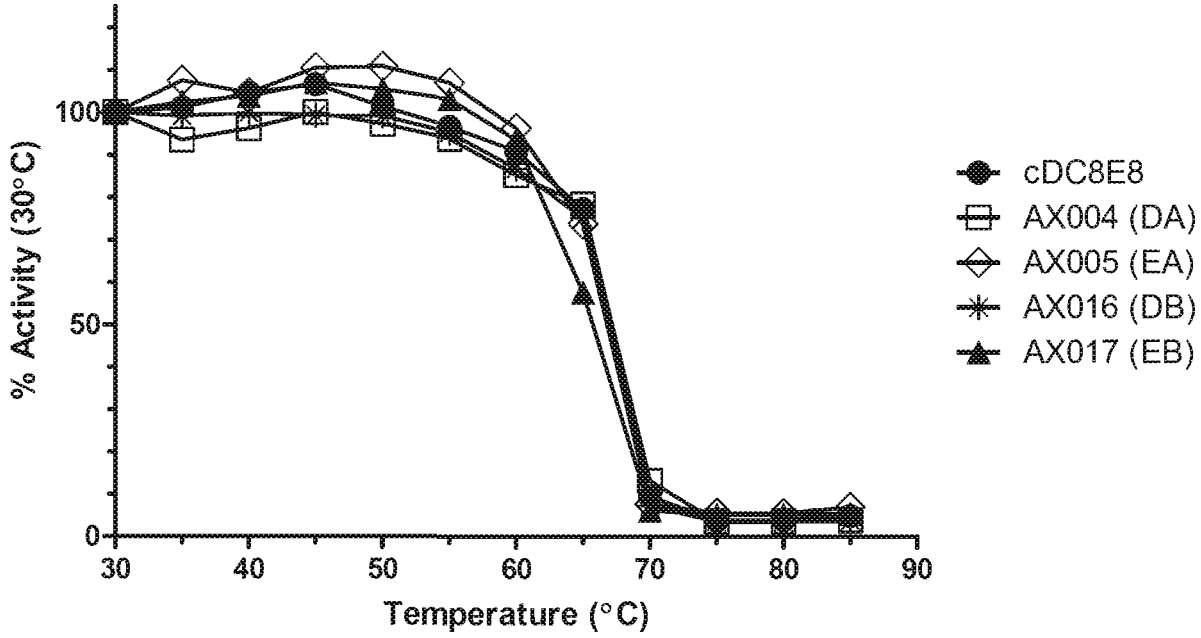
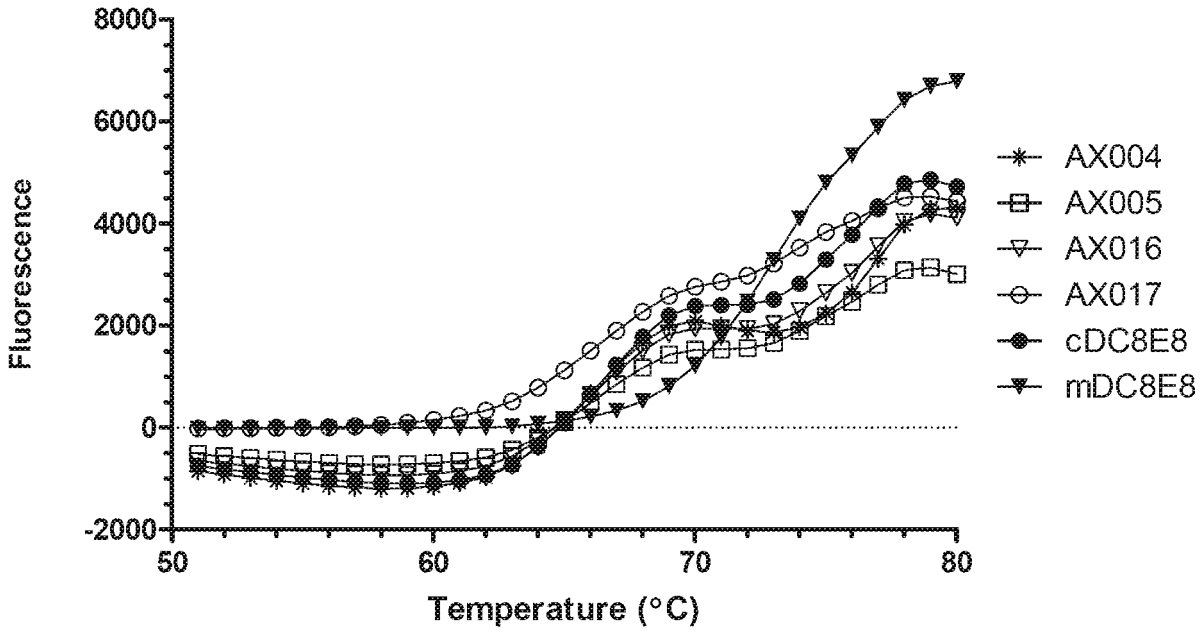
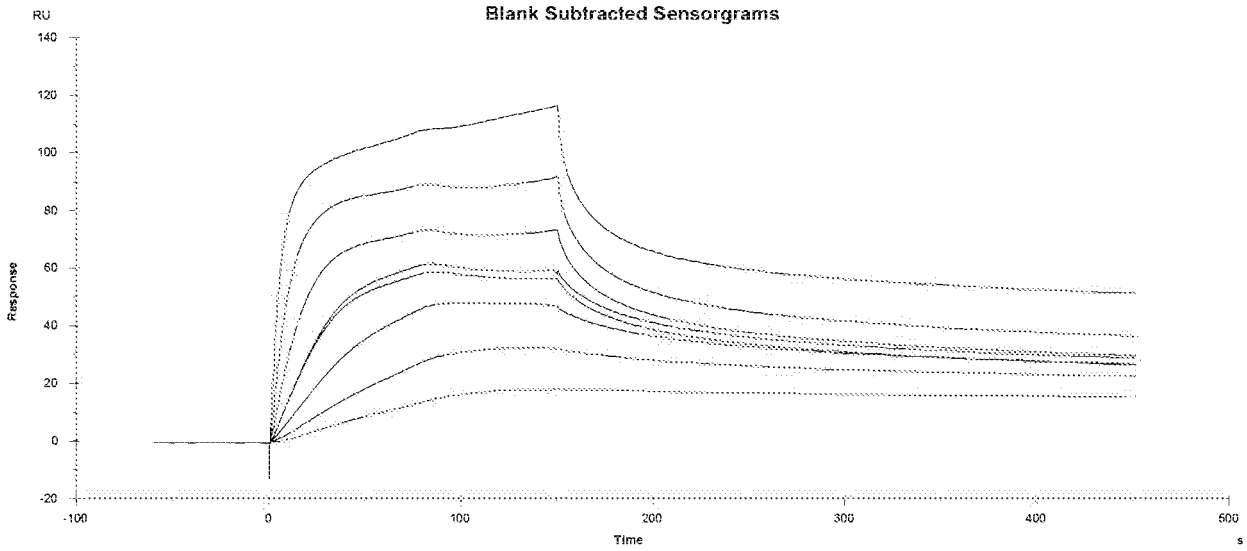

% Activity (30°C)
100
50
0
30
40
50
60
70
80
90
Temperature (°C)
cDC8E8
AX004 (DA)
AX005 (EA)
AX016 (DB)
AX017 (EB)

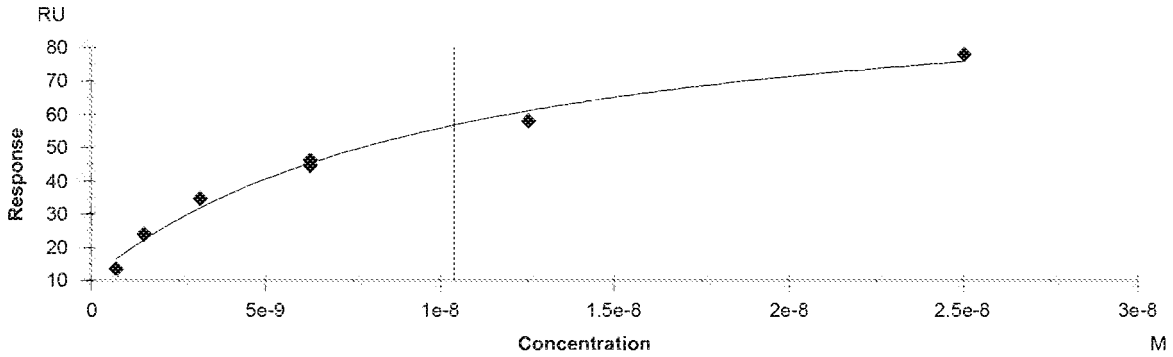
Fig.16



	AX004	AX005	AX016	AX017	cDC8E8	mDC8E8
Tm (rounded)	70	70	70	69	70	73
Maximum	4300.9046	3135.43837	4187.99894	4529.31902	4857.25689	6791.01988
Minimum	-1193.26152	-725.47317	-936.2542	-28.01788	-1098.6411	-25.13077
Max - Min	5494.16612	3860.91154	5124.25314	4557.3369	5955.89801	6816.15065
Slope	4.414670596	3.678766181	3.965288376	3.348855489	3.62506314	2.02029628

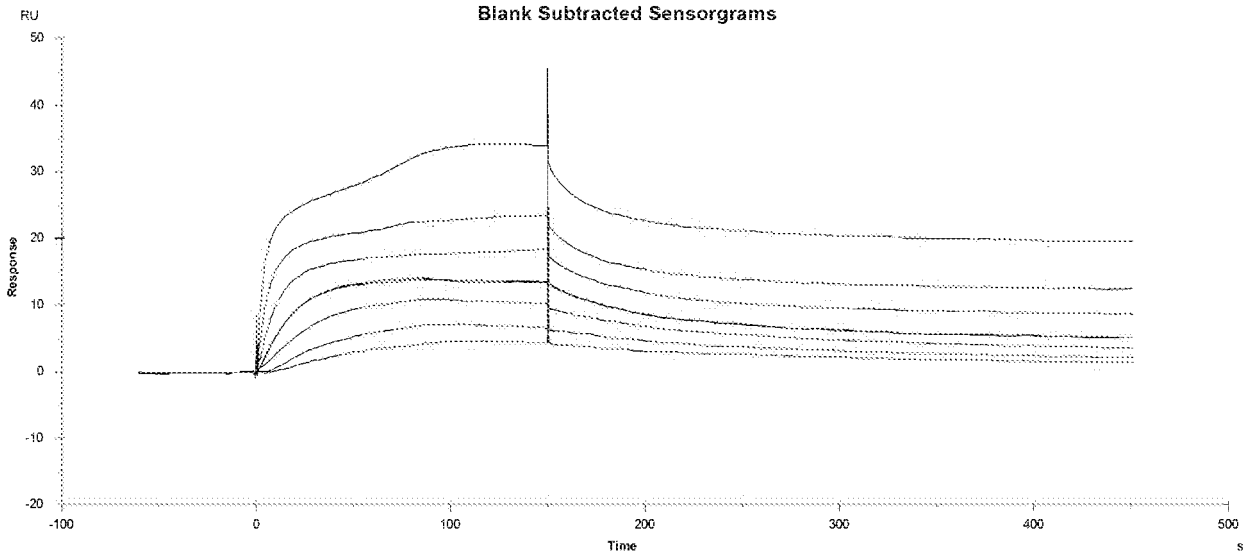
Fig.17

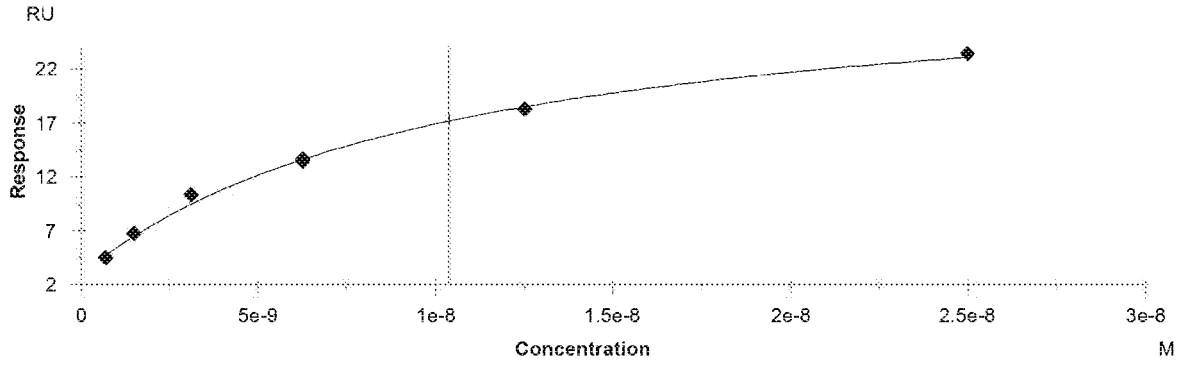




KD (M)	Rmax (RU)	offset (RU)	Chi² (RU²)
1.040×10^{-8}	92.43	10.61	8.39

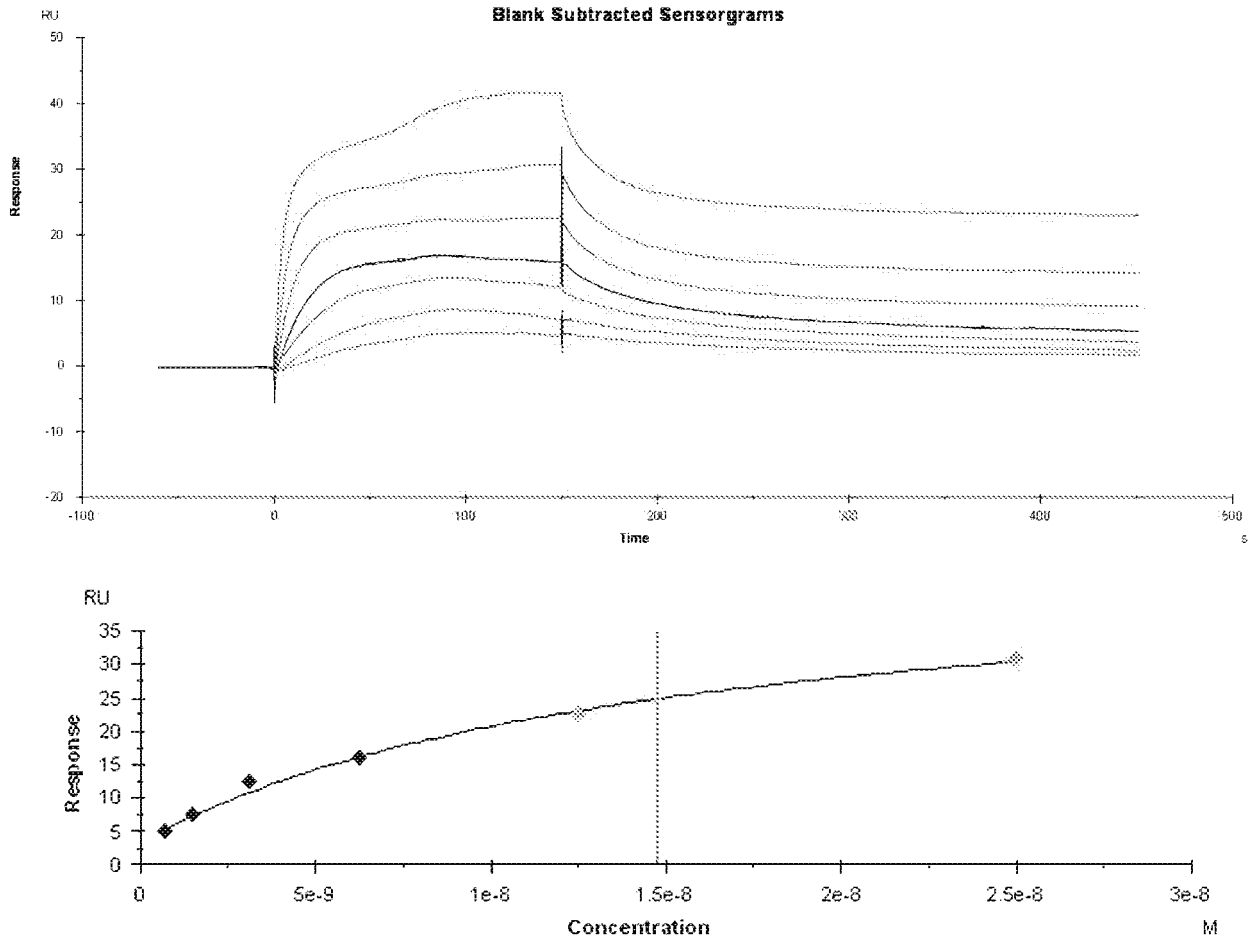
Fig.18





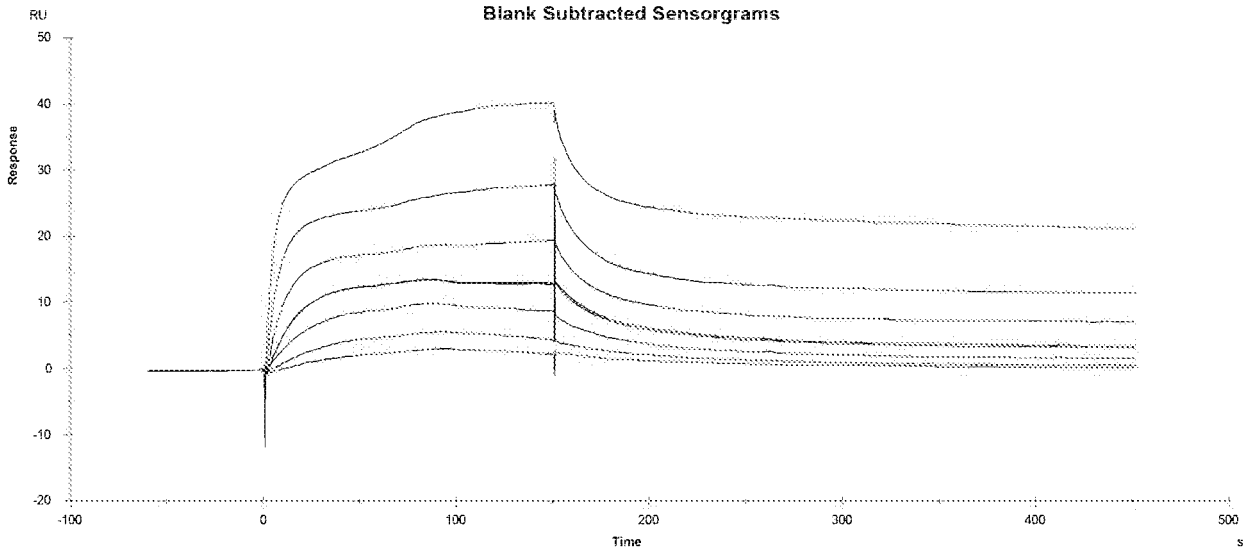
KD (M)	Rmax (RU)	offset (RU)	Chi² (RU²)
$1.037x10^{-8}$	28.56	2.921	0.226

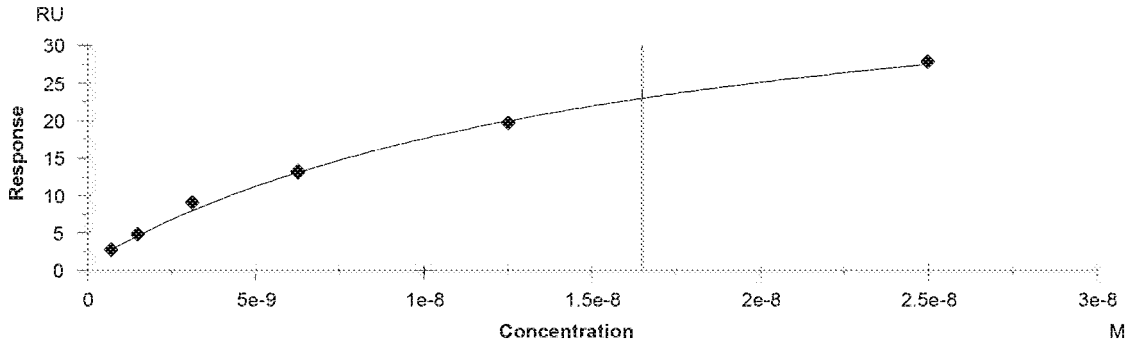
Fig.19



KD (M)	Rmax (RU)	offset (RU)	Chi² (RU²)
$1.473x10^{-8}$	43.02	3.320	0.668

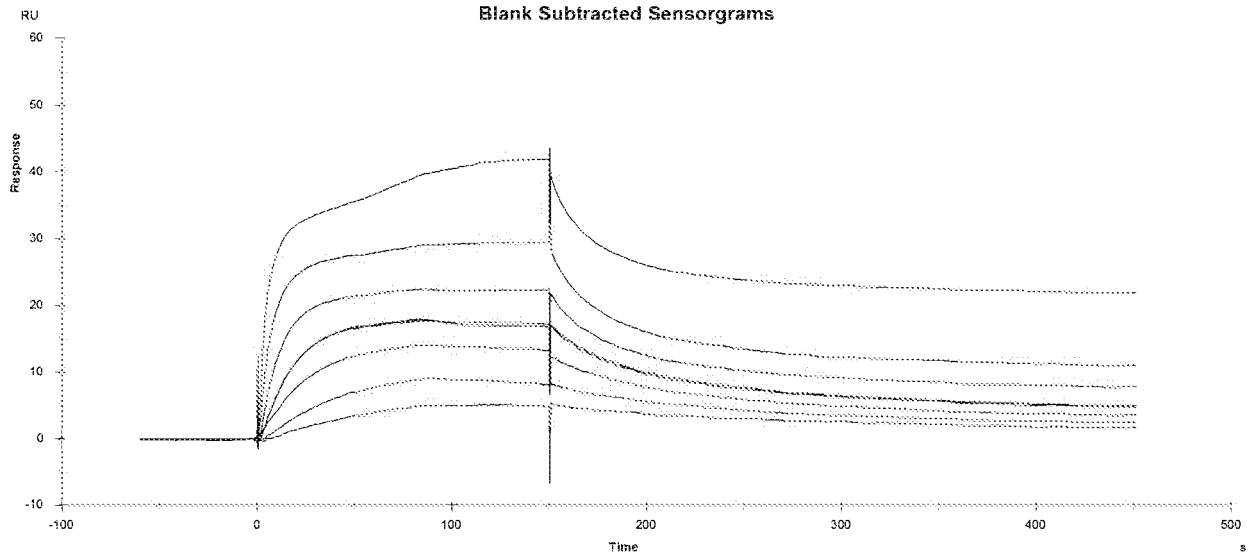
Fig.20

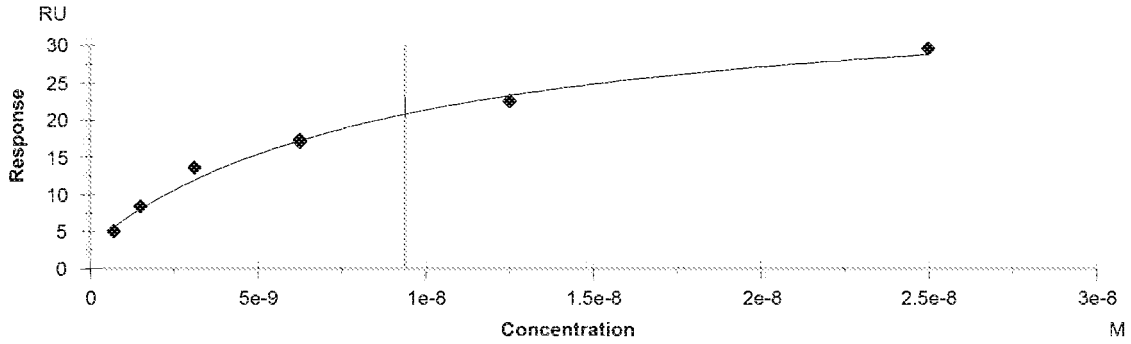




KD (M)	Rmax (RU)	offset (RU)	Chi² (RU²)
1.649×10^{-8}	43.96	1.011	0.292

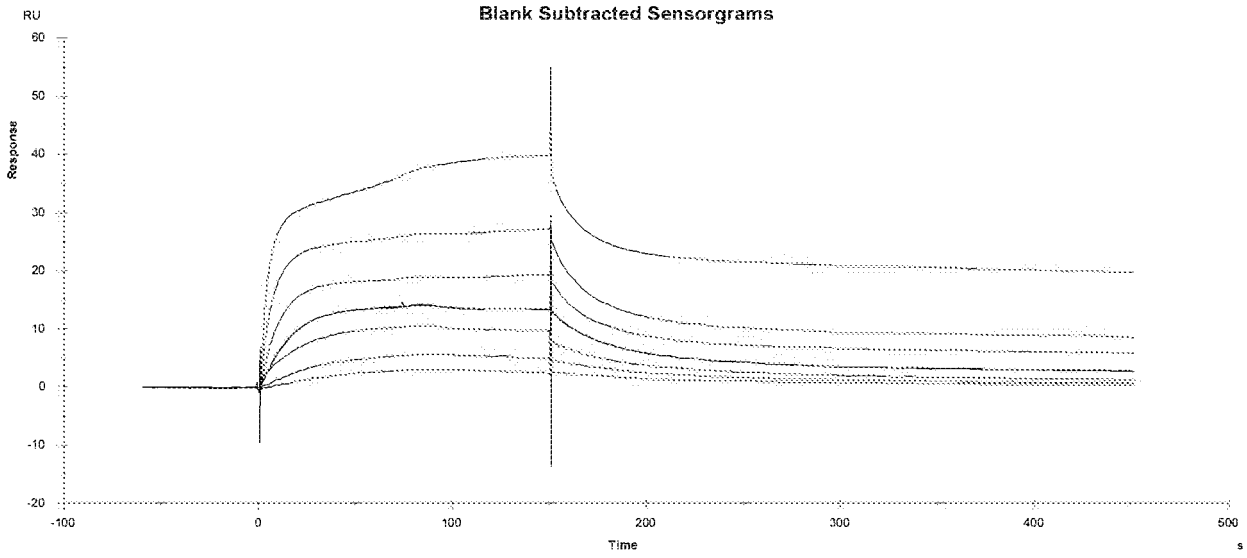
Fig.21

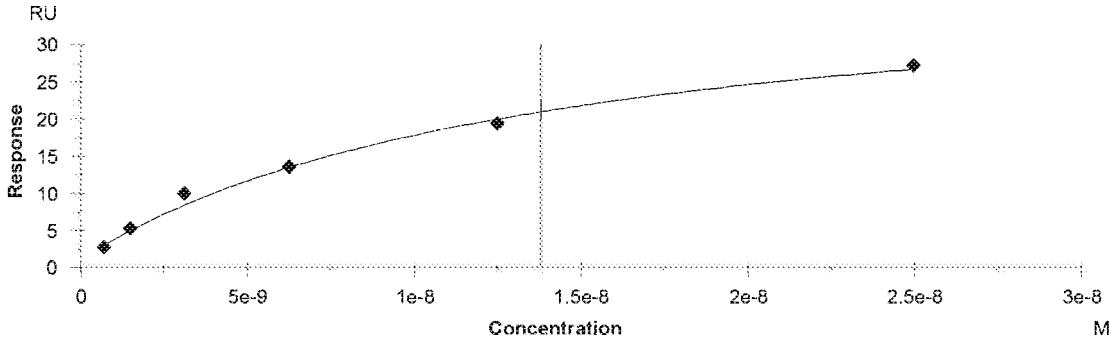




KD (M)	Rmax (RU)	offset (RU)	Chi² (RU²)
$9.386x10^{-9}$	35.18	3.184	0.987

Fig.22





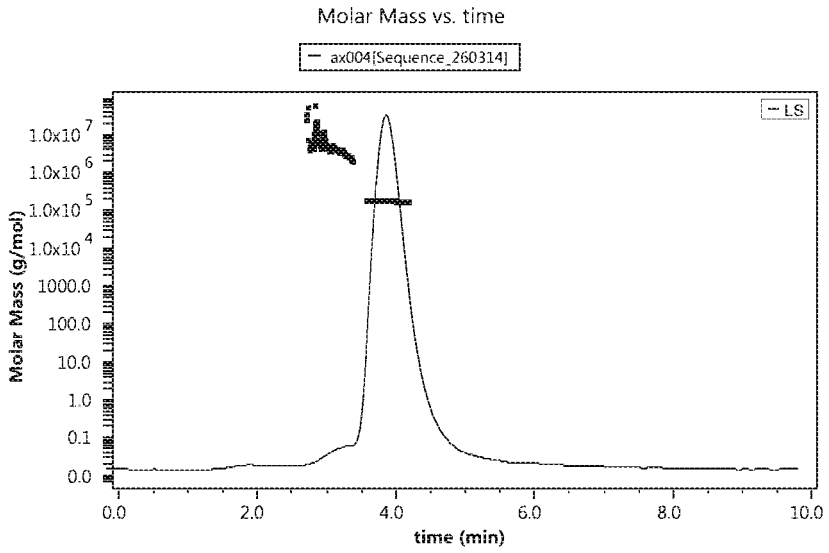
KD (M)	Rmax (RU)	offset (RU)	Chi² (RU²)
$1.381x10^{-8}$	39.68	1.130	0.685

Fig.23

	KD (M)	Rmax (RU)	offset (RU)	Chi² (RU²)
mDC8E8	$1.040x10^{-8}$	92.43	10.61	8.39
cDC8E8	$1.037x10^{-8}$	28.56	2.921	0.226
AX004	$1.473x10^{-8}$	43.02	3.320	0.668
AX005	$1.649x10^{-8}$	43.96	1.011	0.292
AX016	$9.386x10^{-9}$	35.18	3.184	0.987
AX017	$1.381x10^{-8}$	39.68	1.130	0.685

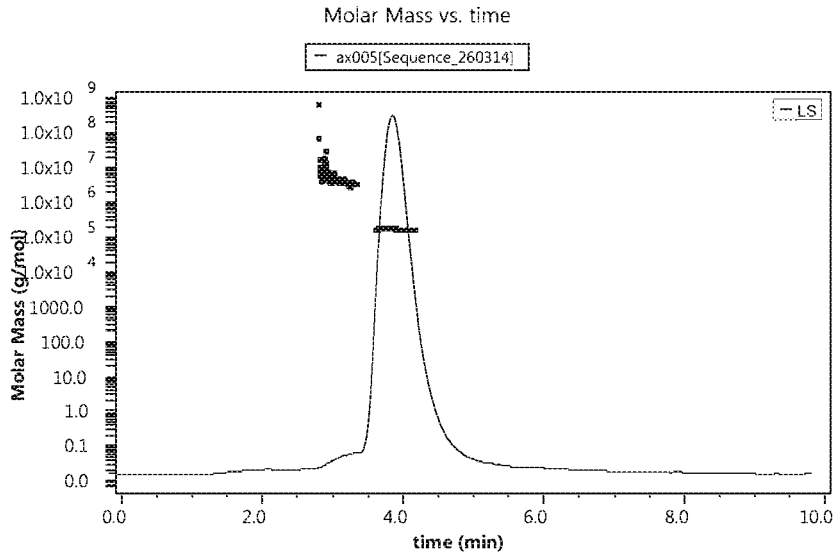
Fig.24

Fig.24A



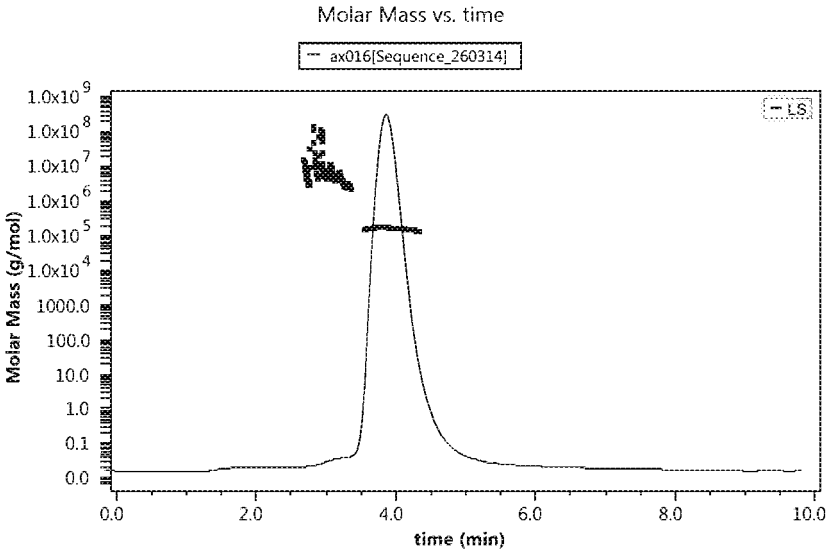
Peak	Mw (kDa)	Polydispersity	Mass fraction (%)
1	169.8	1.001	99.6

Fig.24B



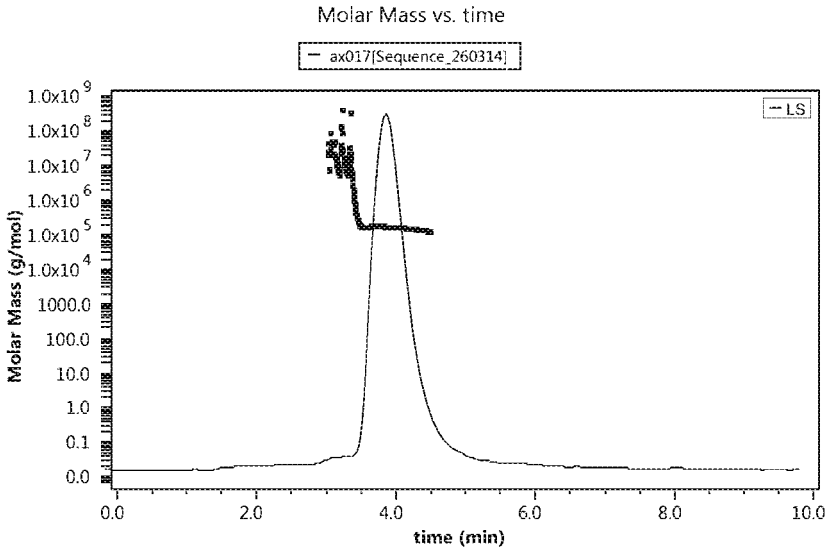
Peak	Mw (kDa)	Polydispersity	Mass fraction (%)
1	165.9	1.001	99.7

Fig.24C



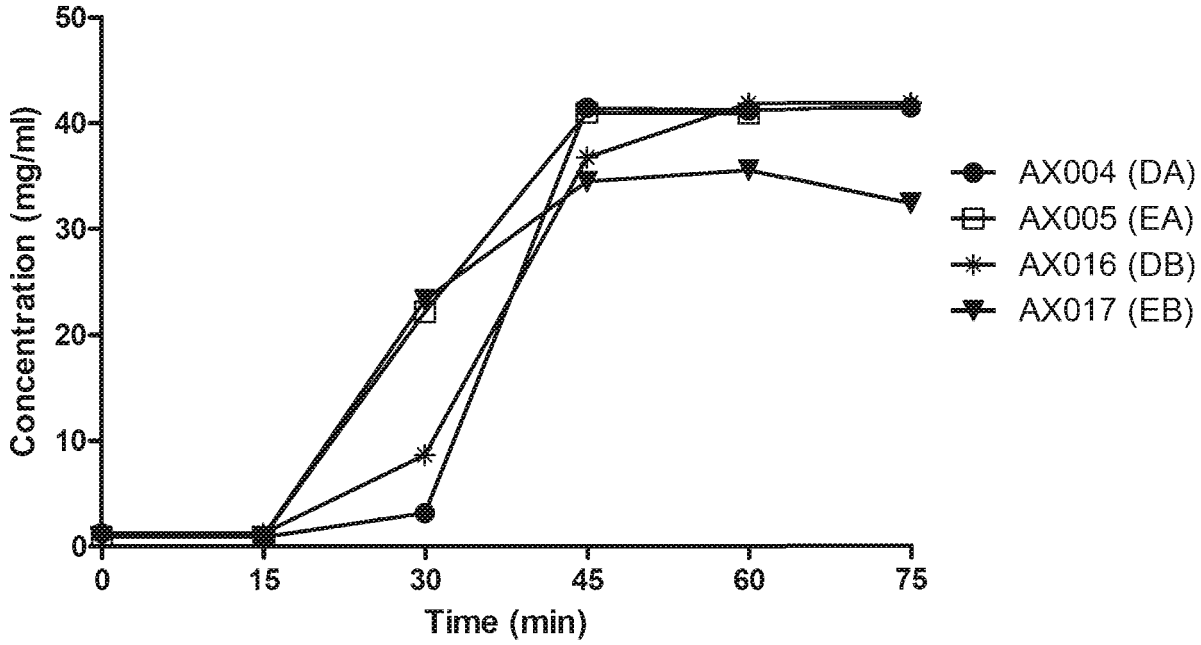
Peak	Mw (kDa)	Polydispersity	Mass fraction (%)
1	161.6	1.004	99.8

Fig.24D



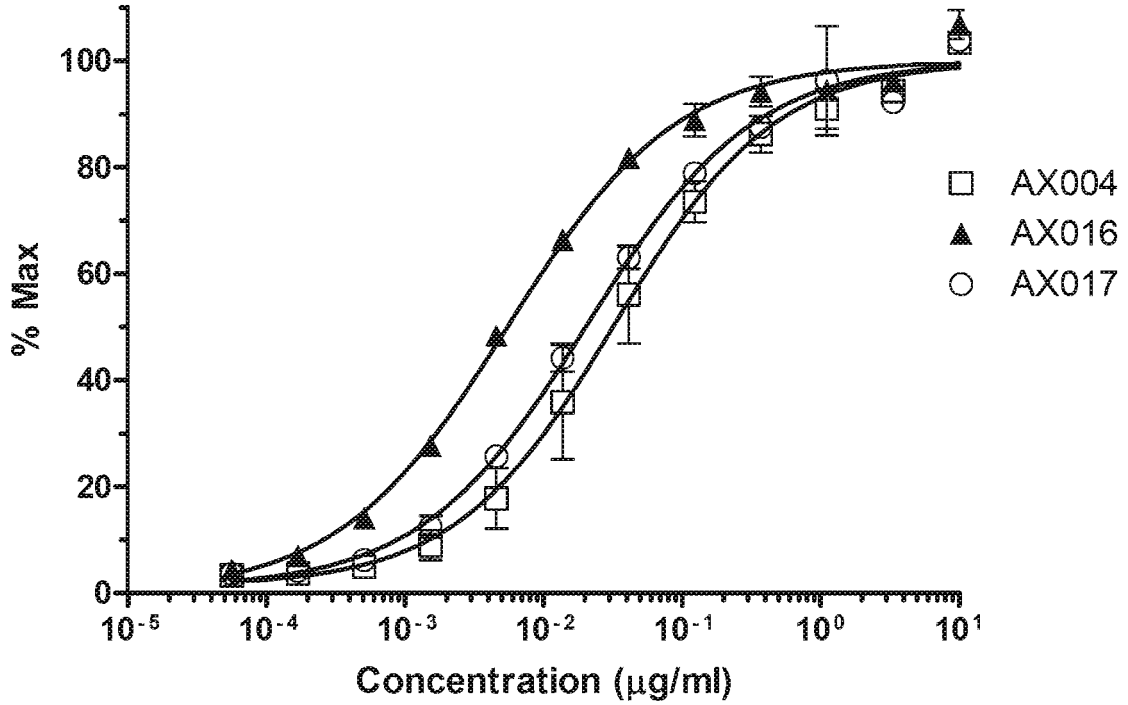
Peak	Mw (kDa)	Polydispersity	Mass fraction (%)
1	160.0	1.008	99.9

Fig.25



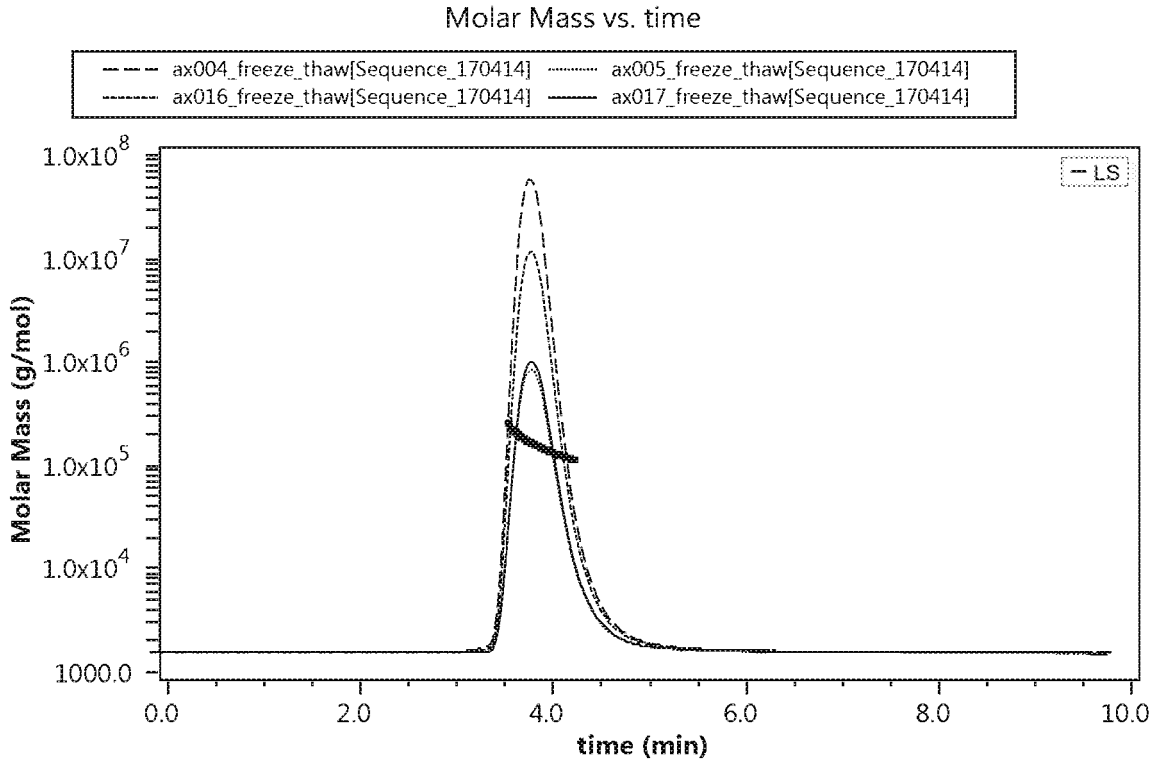
Time (min)	*Concentration(mg/ml)* AX004	AX005	AX016	AX017
0	1.248	0.935	1.281	0.961
15	0.900	0.906	1.252	0.969
30	3.175	22.156	8.643	23.296
45	41.455	40.965	36.767	34.497
60	41.204	40.906	41.856	35.545
75	41.447	ND	41.864	32.385

Fig.26



	AX004	AX016	AX017
EC_{50}	0.03287	0.005483	0.02067

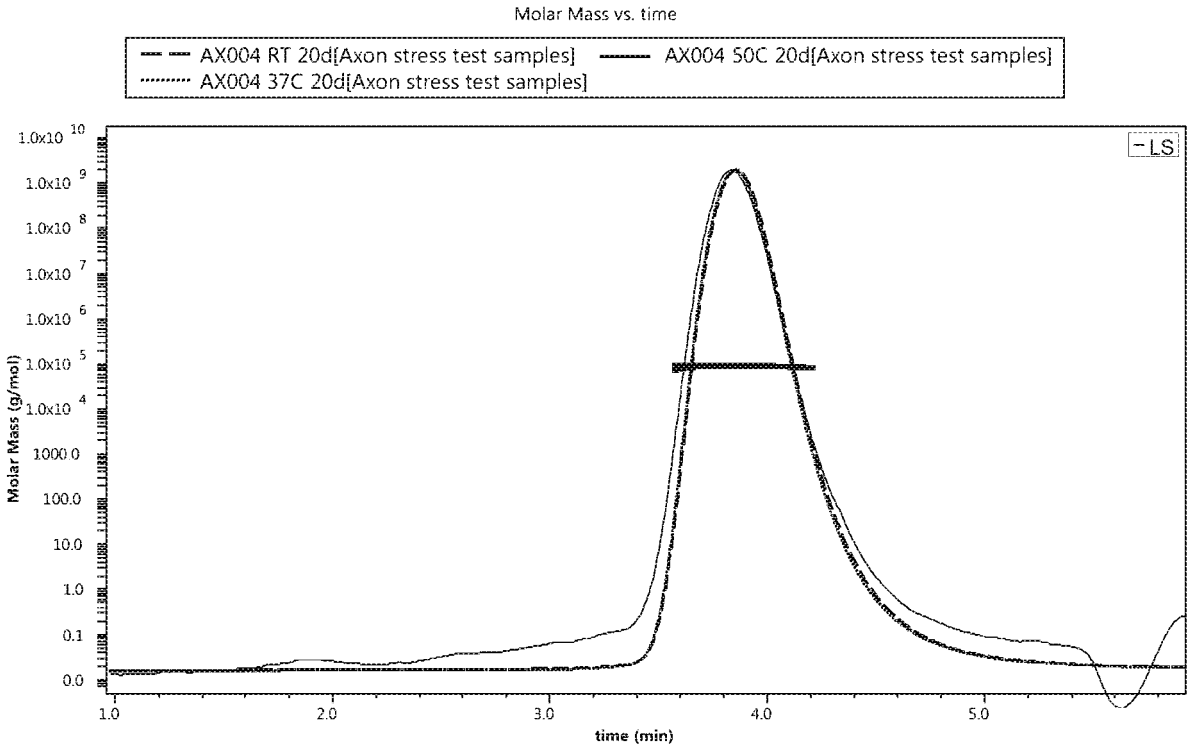
Fig.27



Sample	Sample Concentration (mg/ml)	Mw (kDa)	Polydispersity (< 1.05 is acceptable)	Mass fraction (%)
Ax004_freeze_thaw	1.25	160.0 (± 0.3 %)	1.033 (± 0.5 %)	> 99.5
Ax005_freeze_thaw	0.94	159.9 (± 0.3 %)	1.037 (± 0.4 %)	> 99.5
Ax016_freeze_thaw	1.28	157.6 (± 0.3 %)	1.039 (± 0.5 %)	> 99.5
Ax017_freeze_thaw	0.96	155.8 (± 0.3 %)	1.037 (± 0.4 %)	> 99.5

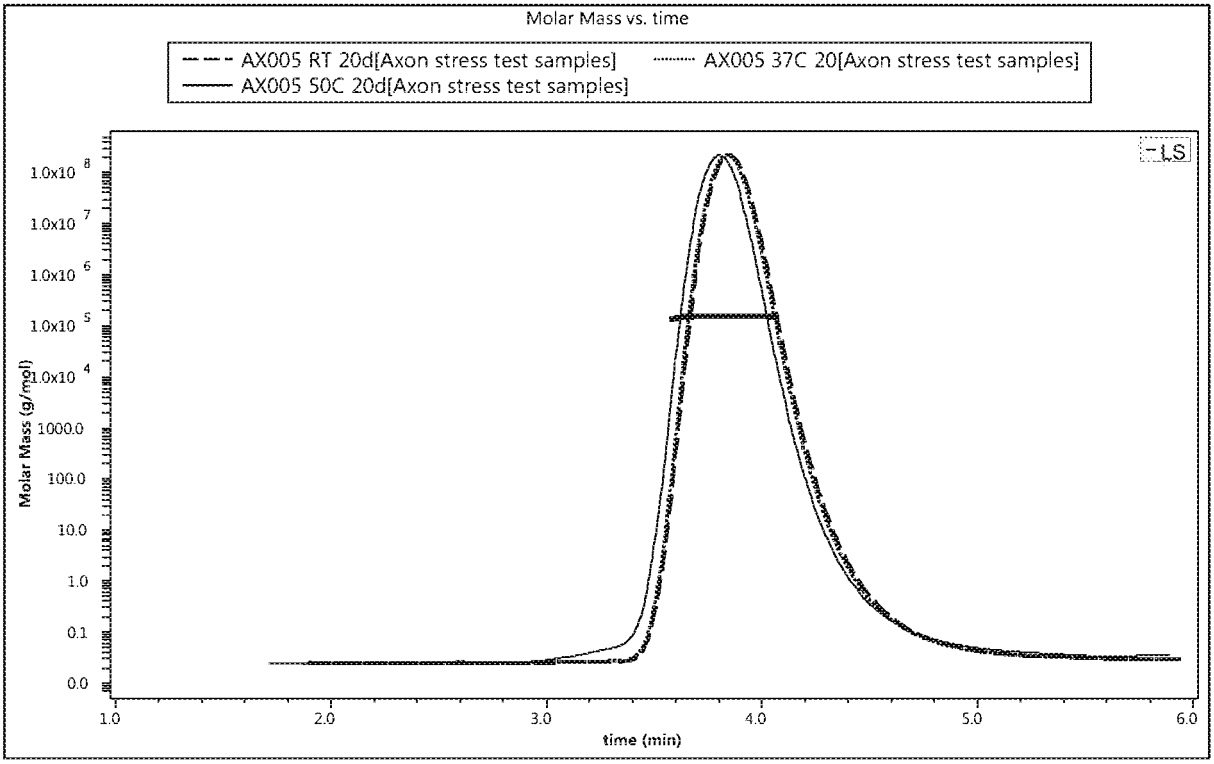
Fig.28

Fig.28A



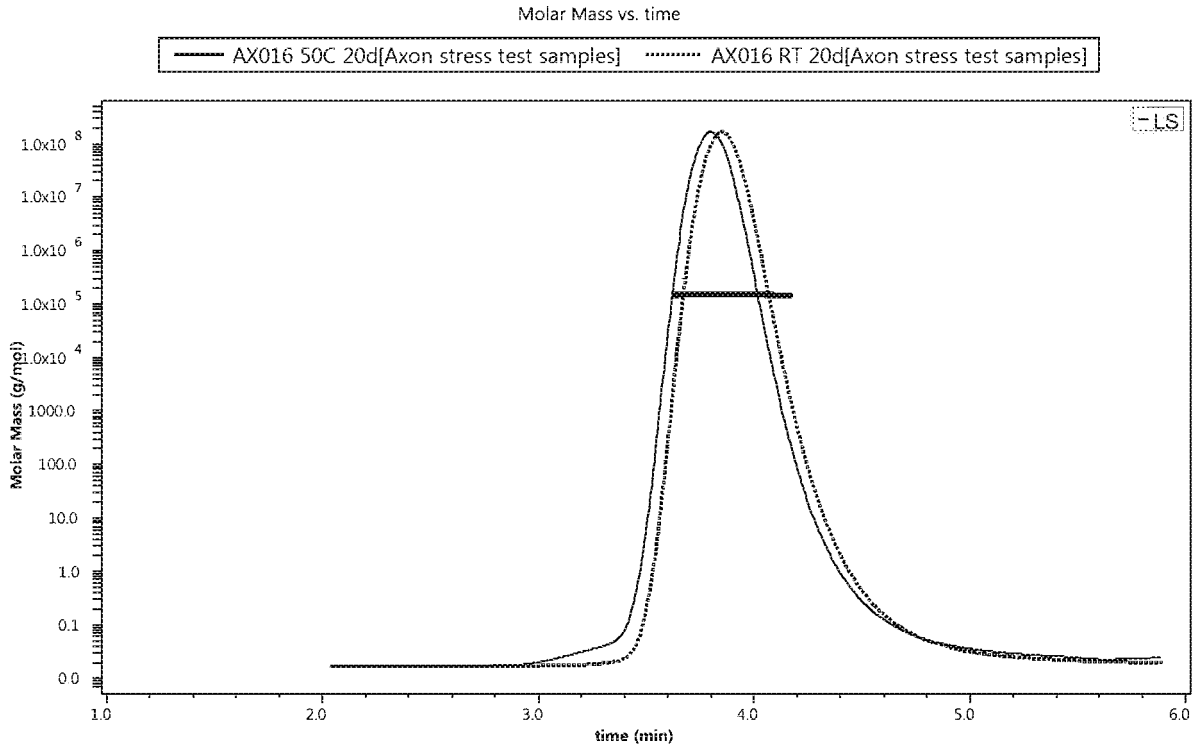
	Mw (kDa)	Polydispersity (Mw/Mn)	Mass Fraction (%)
AX004 RT 20d	146.7 ±0.4	1.014 ±0.004	100.0
AX004 37°C 20d	143.4 ±0.4	1.026 ±0.004	99.7
AX004 50°C 20d	152.4 ±2.4	1.023 ±0.026	99.4

Fig.28B



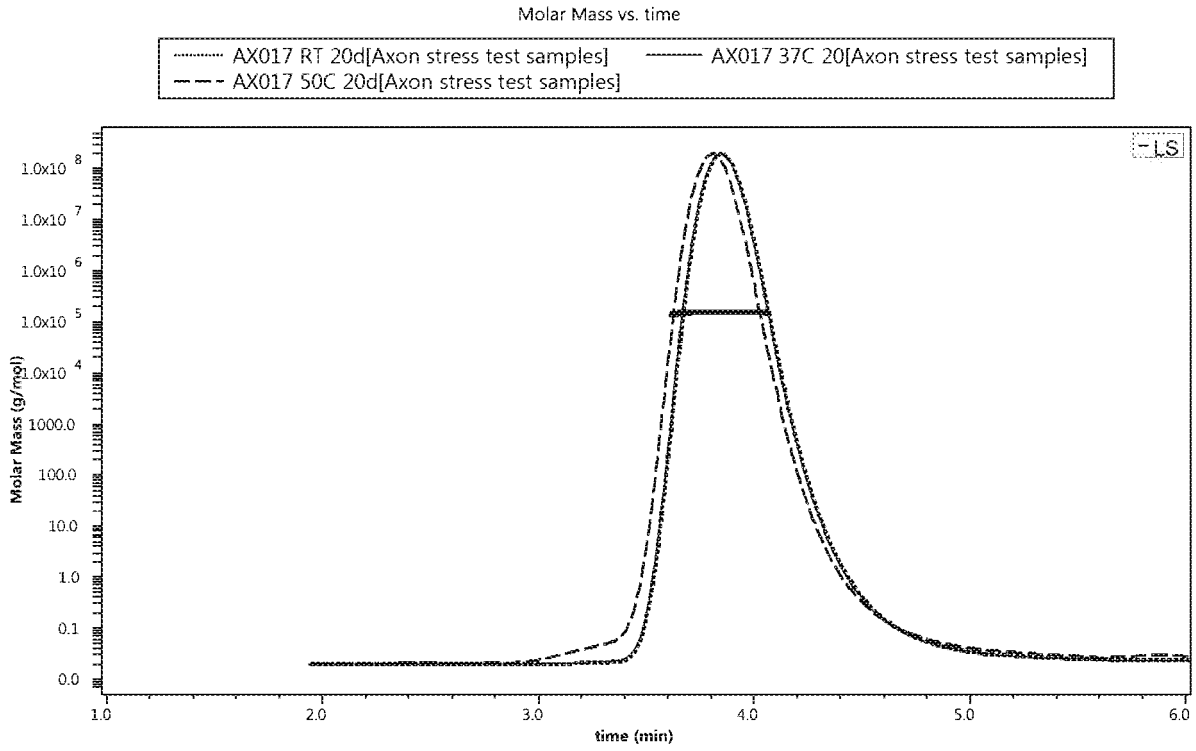
	Mw (kDa)	Polydispersity (Mw/Mn)	Mass Fraction (%)
AX005 RT 20d	145.0 ±0.4	1.013 ±0.005	100.0
AX005 37°C 20d	143.6 ±0.4	1.016 ±0.004	99.9
AX005 50°C 20d	146.3 ±0.3	1.009 ±0.003	99.4

Fig.28C



	Mw (kDa)	Polydispersity (Mw/Mn)	Mass Fraction (%)
AX016 RT 20d	144.0 ±0.4	1.018 ±0.004	99.9
AX016 37°C 20d	N/A	N/A	N/A
AX016 50°C 20d	145.6 ±0.3	1.012 ±0.004	99.3

Fig.28D



	Mw (kDa)	Polydispersity (Mw/Mn)	Mass Fraction (%)
AX017 RT 20d	143.3 ±0.4	1.017 ±0.004	100.0
AX017 37°C 20d	143.2 ±0.3	1.016 ±0.004	99.9
AX017 50°C 20d	146.1 ±0.4	1.009 ±0.004	99.2

Fig.29

Fig.29A

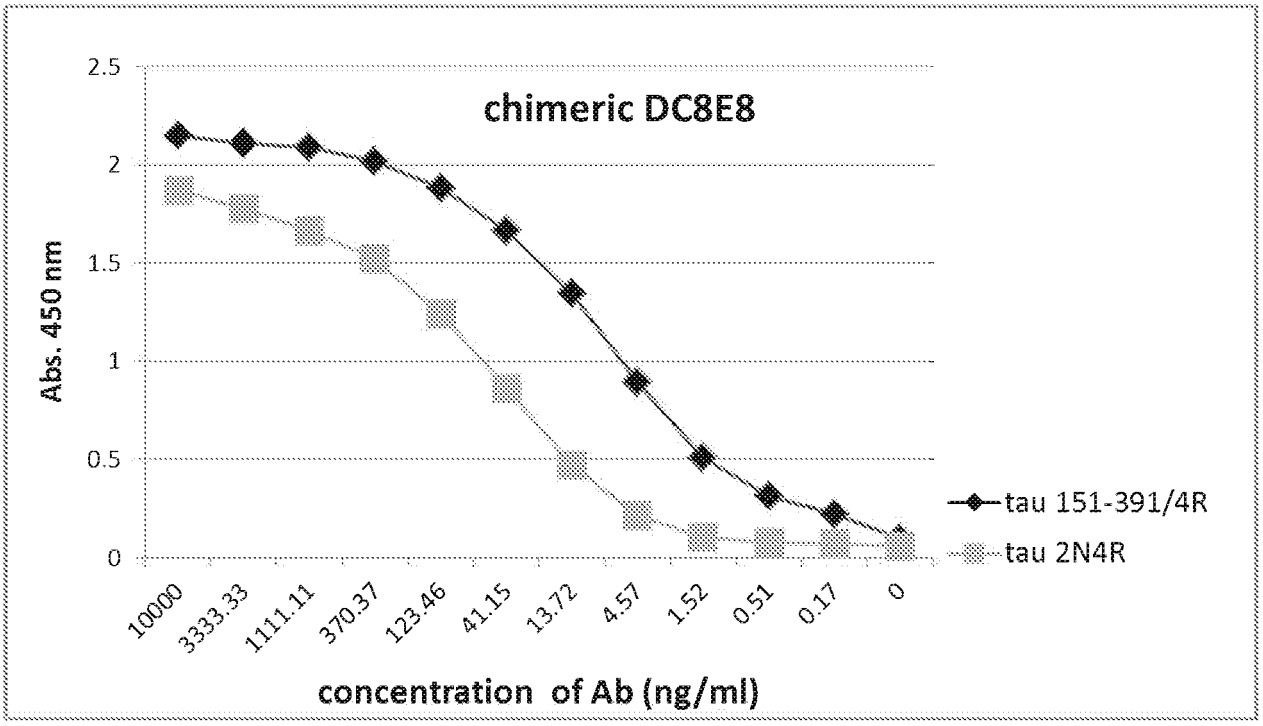


Fig.29B

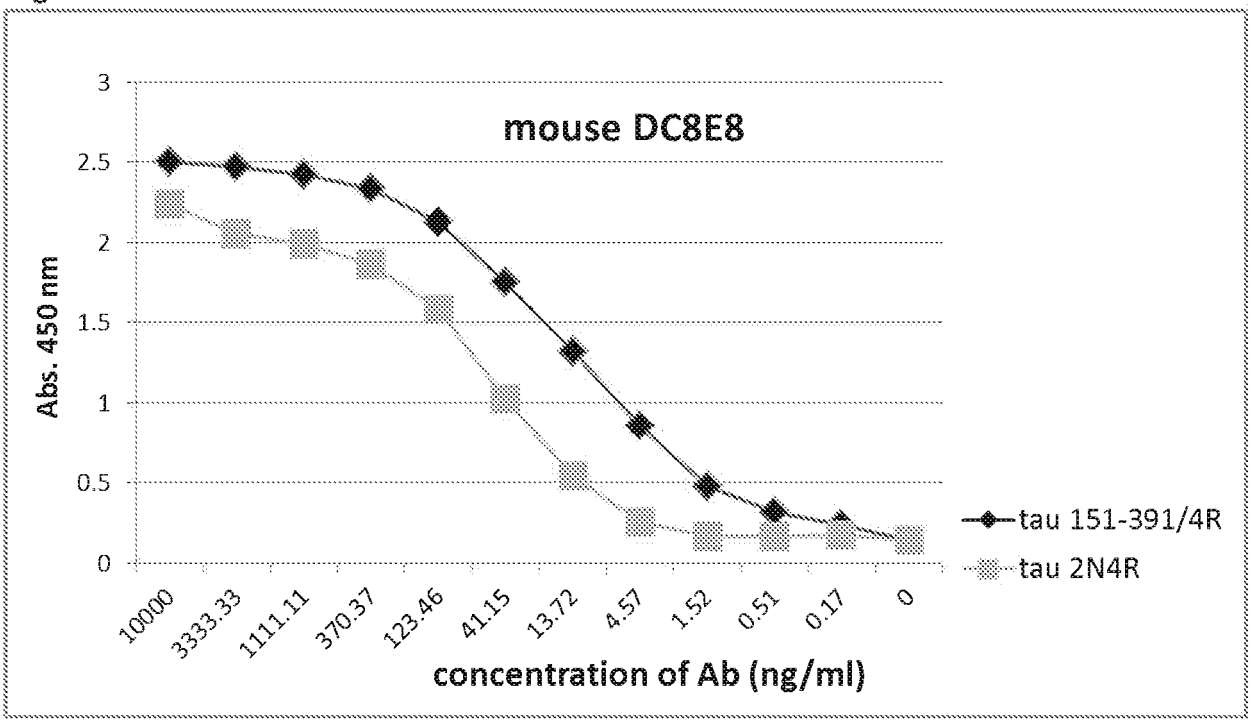
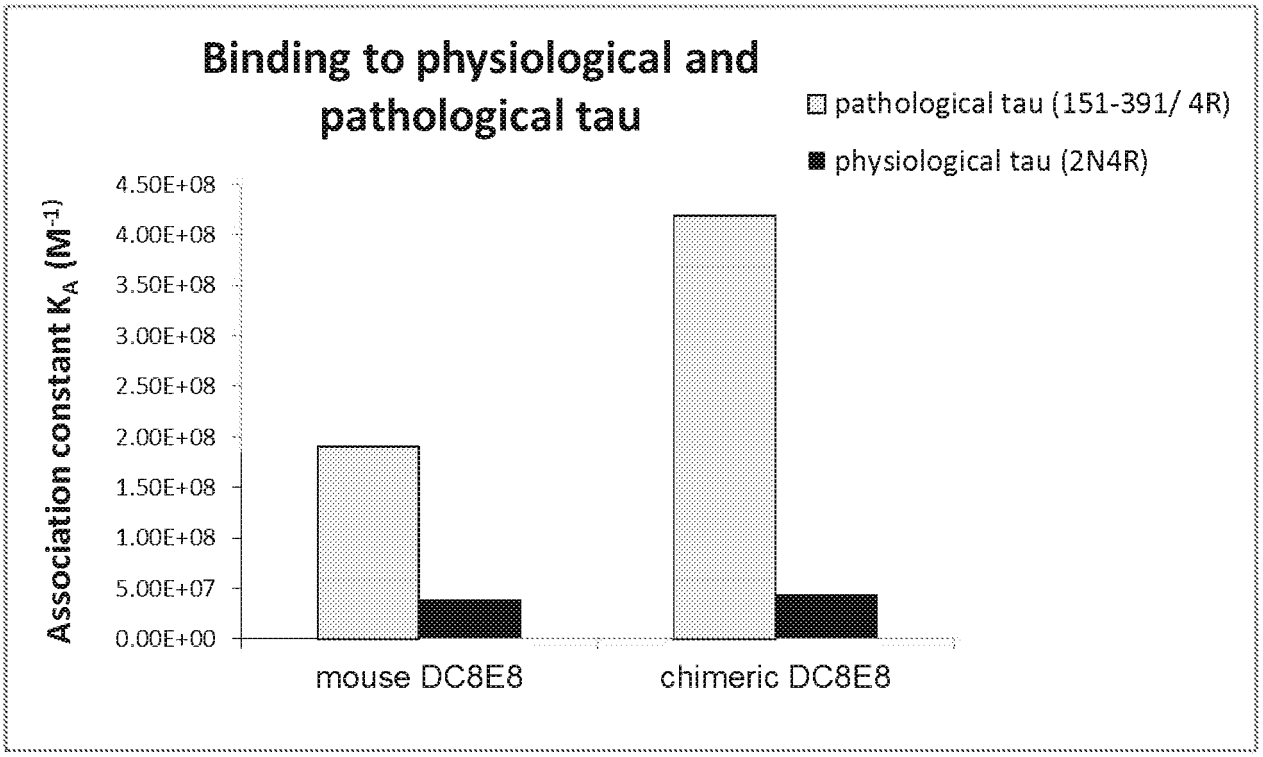


Fig.29C

EC50 (ng/ml) Ab	Chimeric DC8E8	Mouse DC8E8
Tau 151-391/4R	10.1	15.7
Tau 2N4R	52.7	52.4

Fig.30



K_A (M^{-1}) Ab	Chimeric DC8E8	Mouse DC8E8
Tau 151-391/4R	4.2E+08	1.9E+08
Tau 2N4R	4.4E+07	3.9E+07

Fig.31

Fig.31A

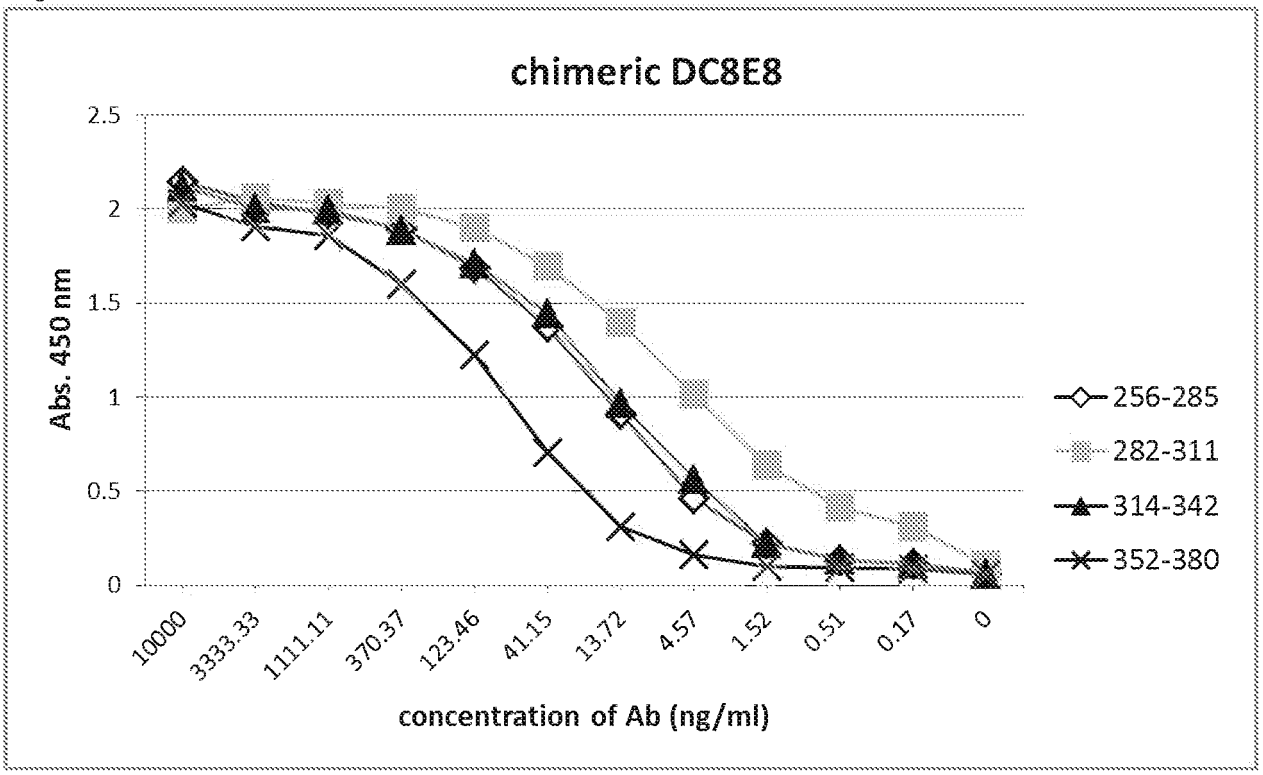


Fig.31B

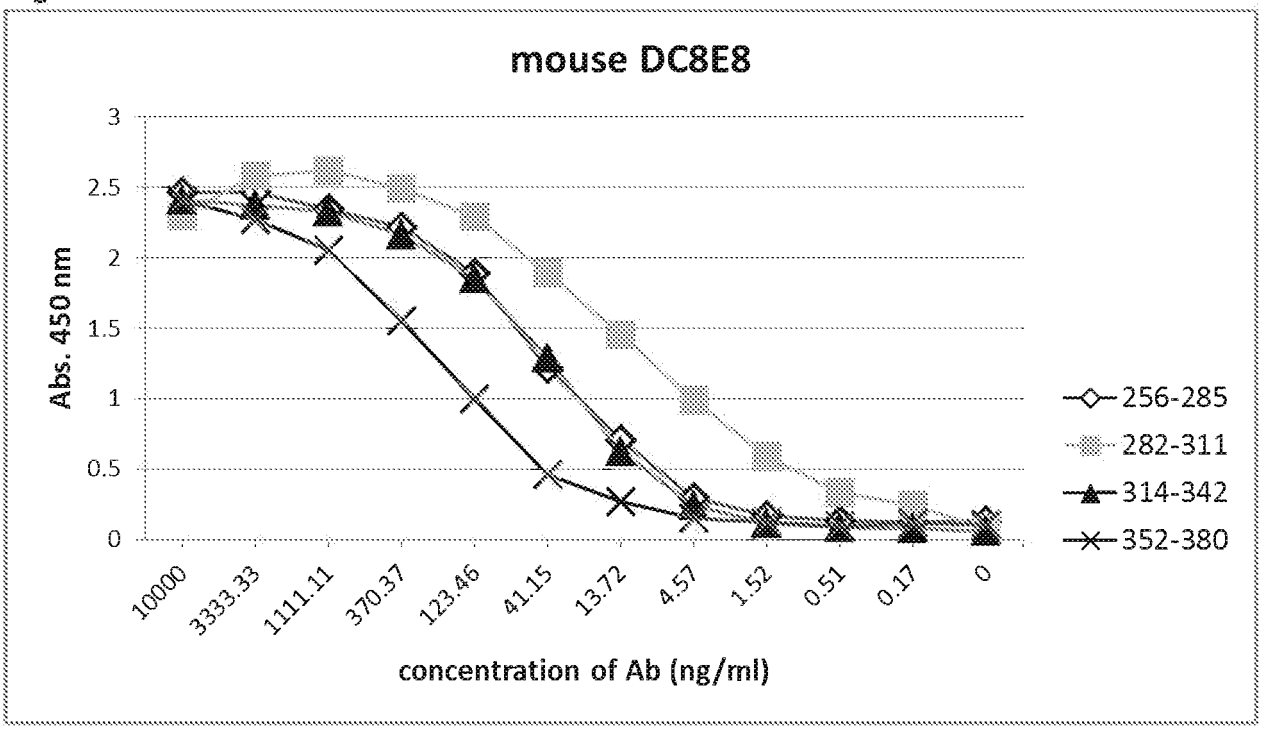


Fig.31C

EC50 (ng/ml) Antibodies	Chimeric DC8E8	Mouse DC8E8
Tau peptide 256-285	21.2	43.33
Tau peptide 282-311	7.31	11.76
Tau peptide 314-342	17.28	38.97
Tau peptide 352-380	86.96	212.8

Fig.32

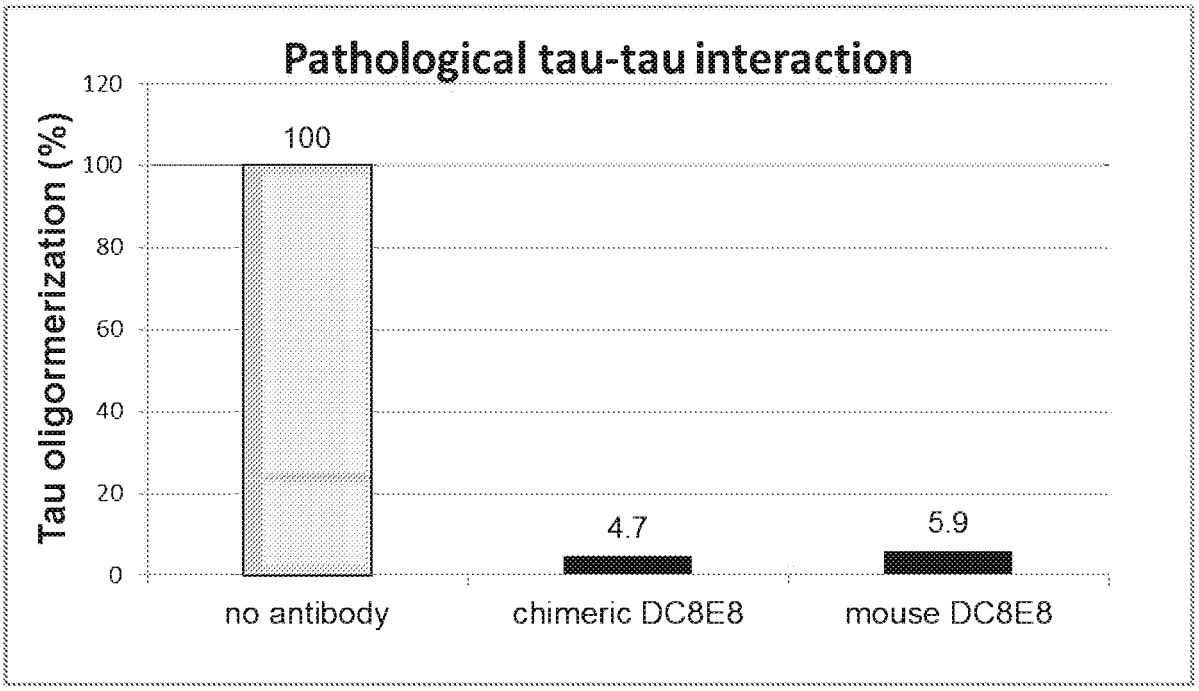

Pathological tau-tau interaction
Tau oligormerization (%)
120
100
80
60
40
20
0
100
4.7
5.9
no antibody
chimeric DC8E8
mouse DC8E8

Fig.33

Fig.33A

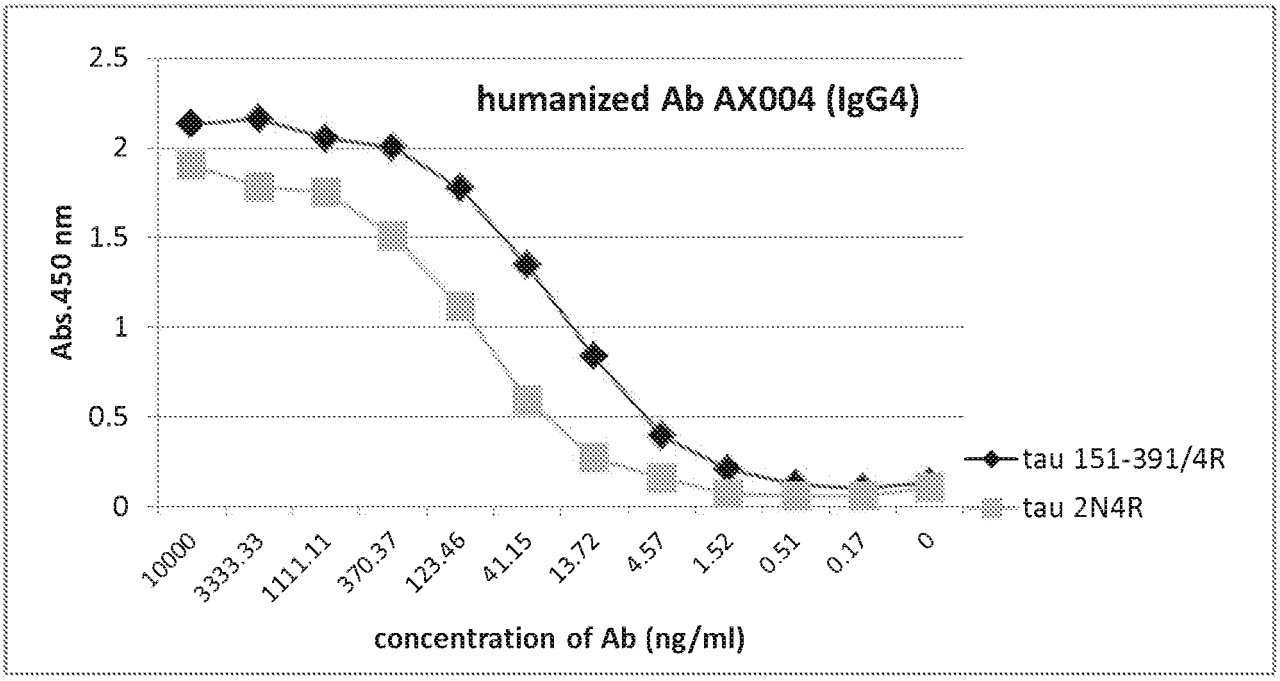


Fig.33B

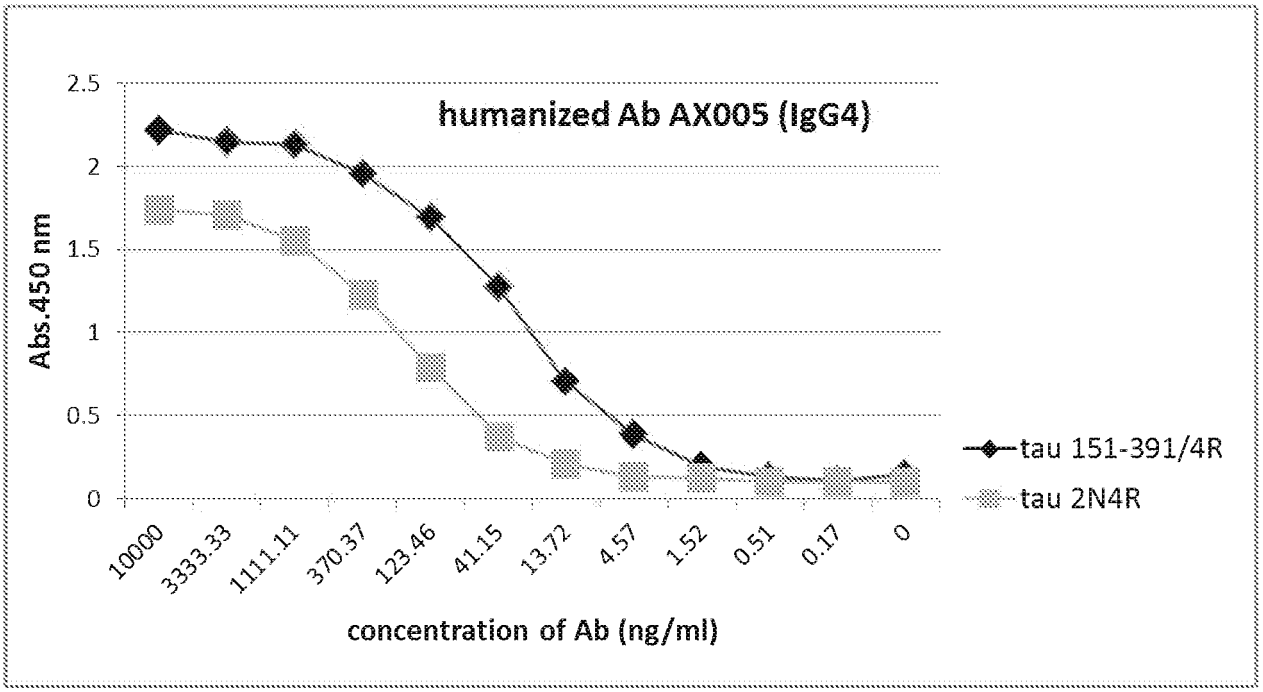


Fig.33C

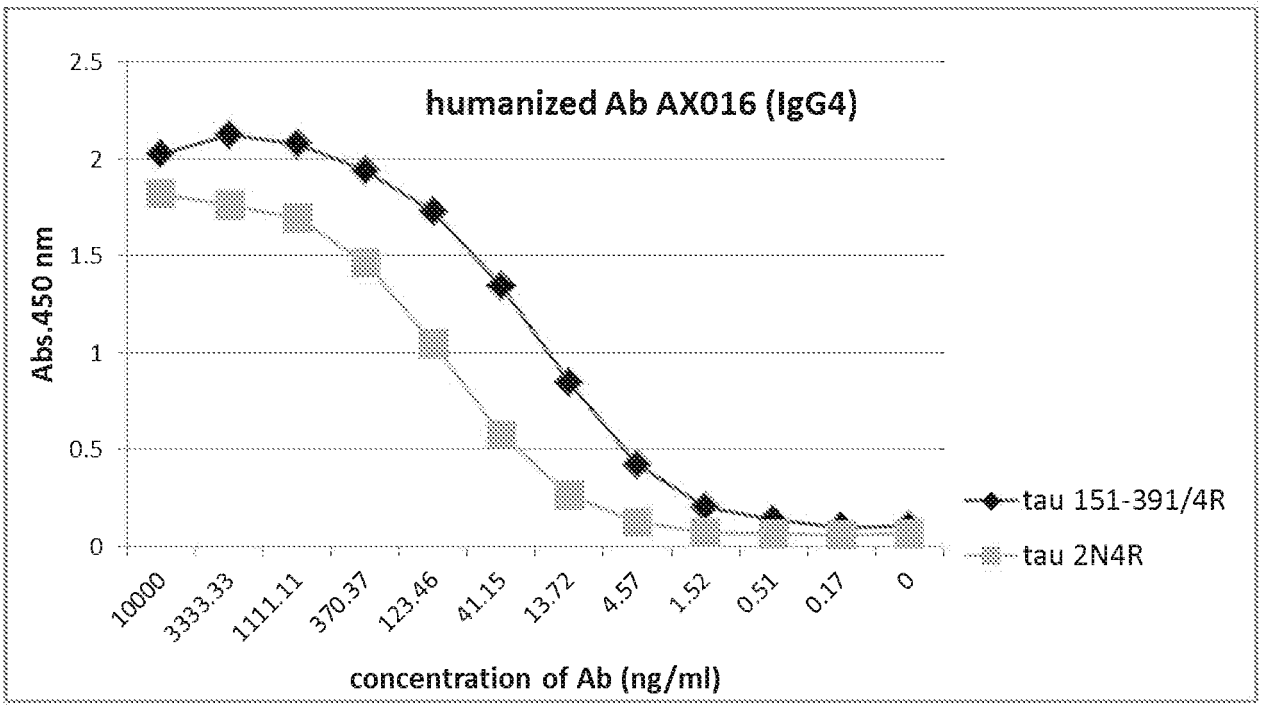


Fig.33D

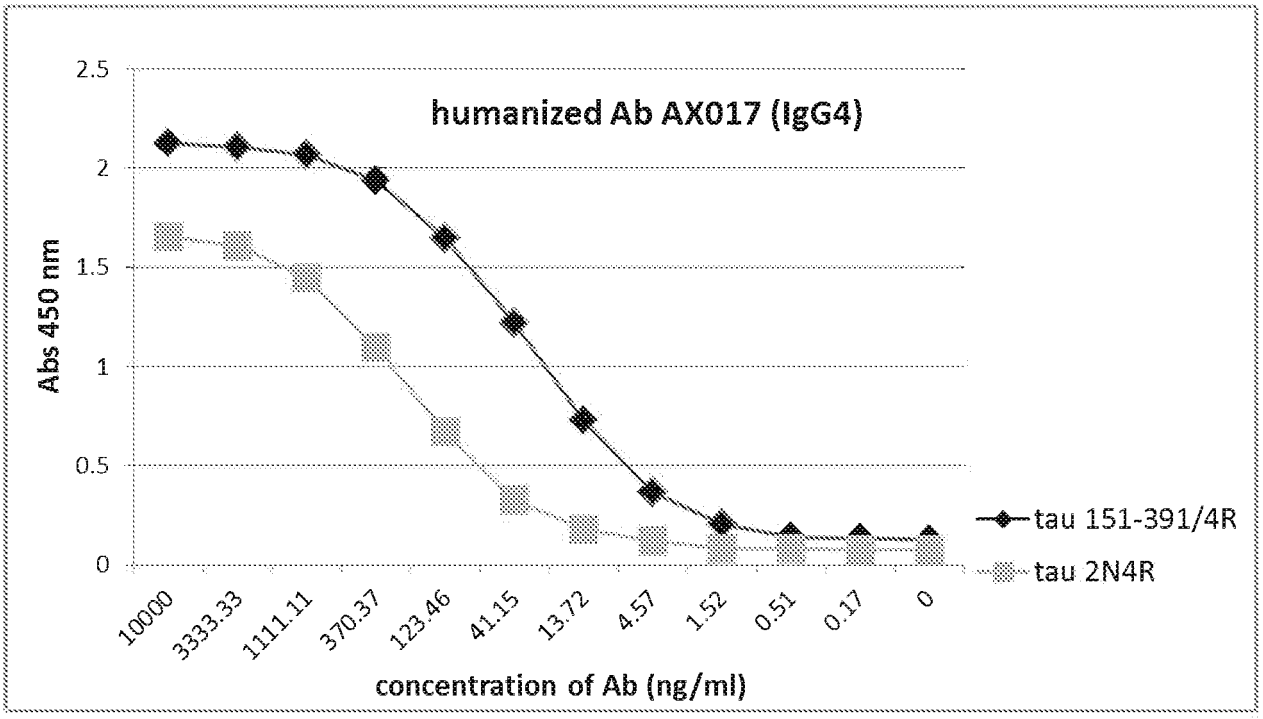


Fig.33E

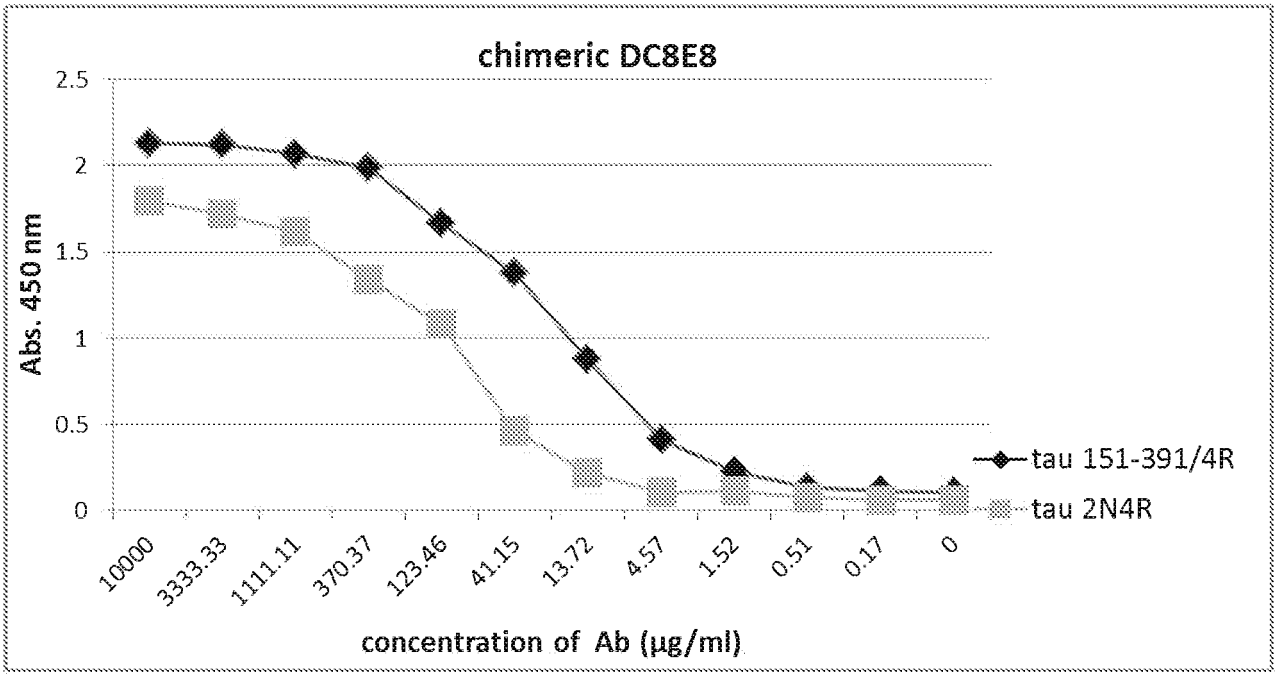


Fig.33F

EC50 (ng/ml) Humanized Ab/IgG4	AX004	AX005	AX016	AX017	Chimeric DC8E8
Tau 151-391/4R	25.19	33.69	23.91	33.96	24.6
Tau 2N4R	93.32	184.1	97.67	215.4	109

Fig.34

Fig.34A

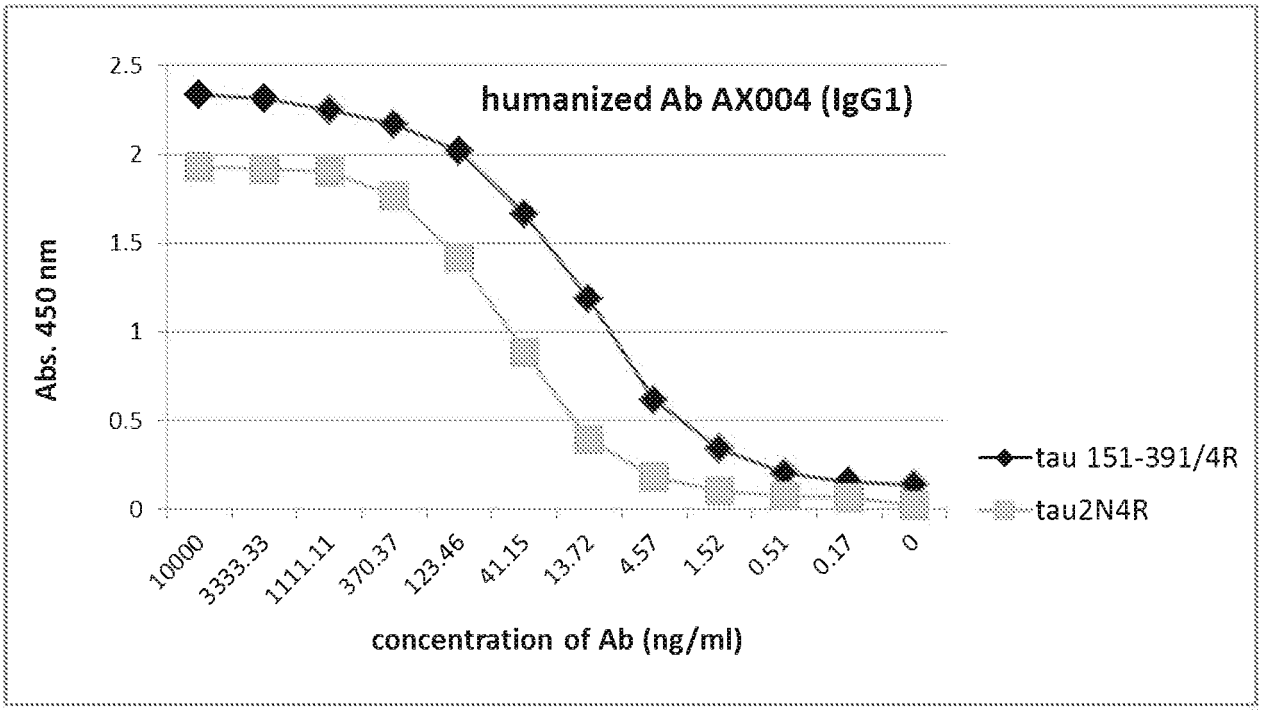


Fig.34B

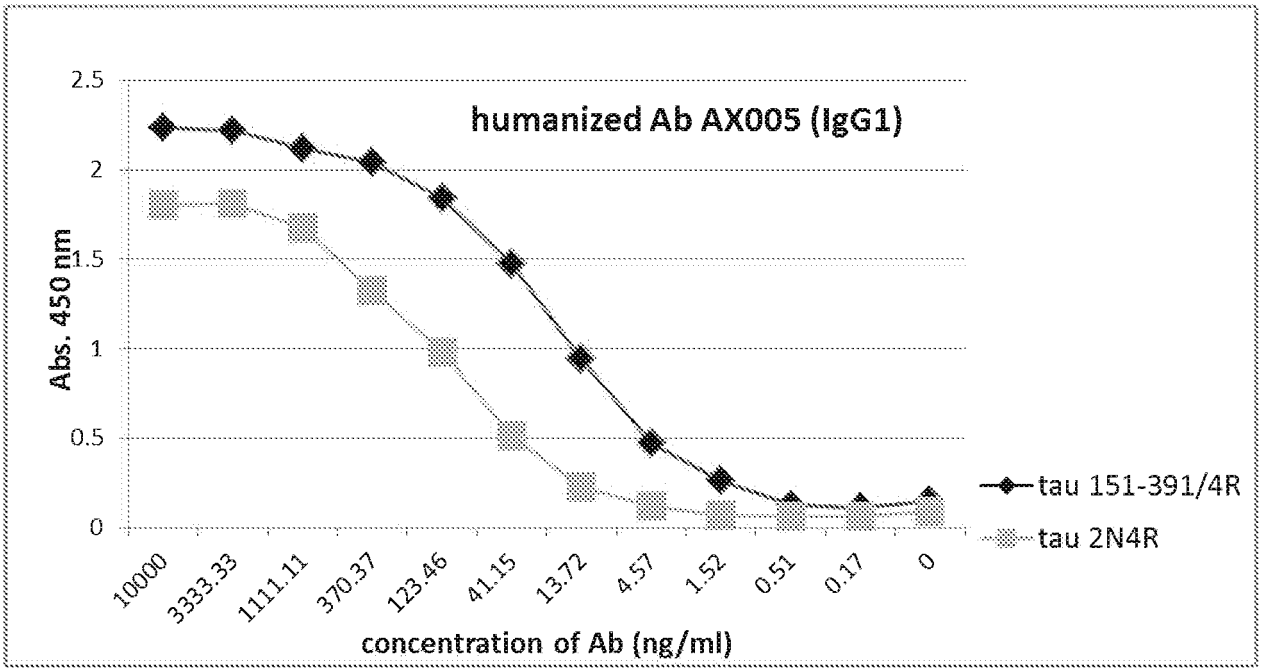


Fig.34C

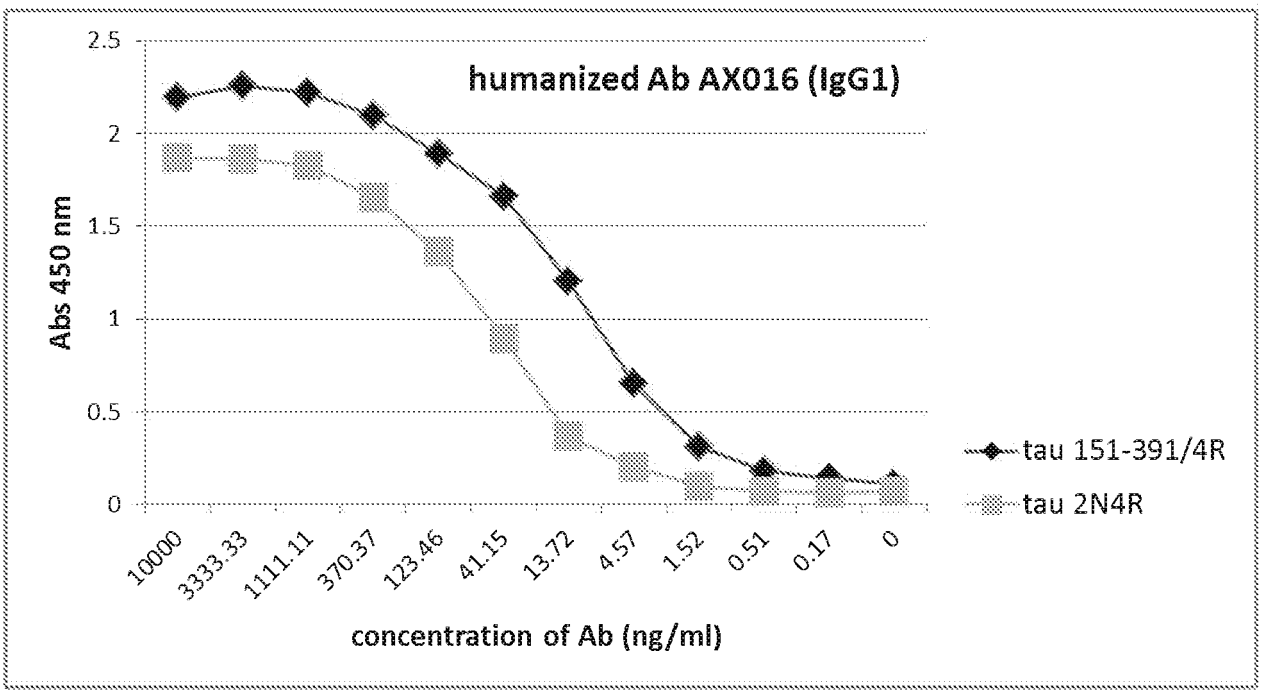


Fig.34D

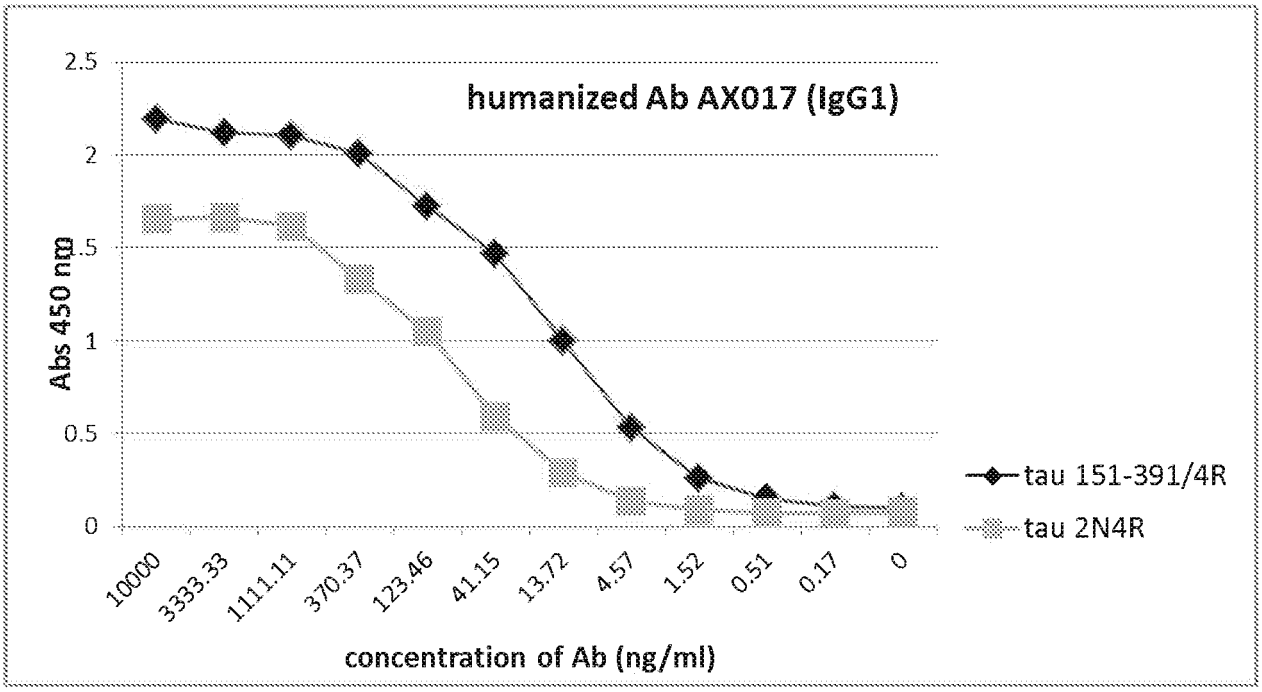
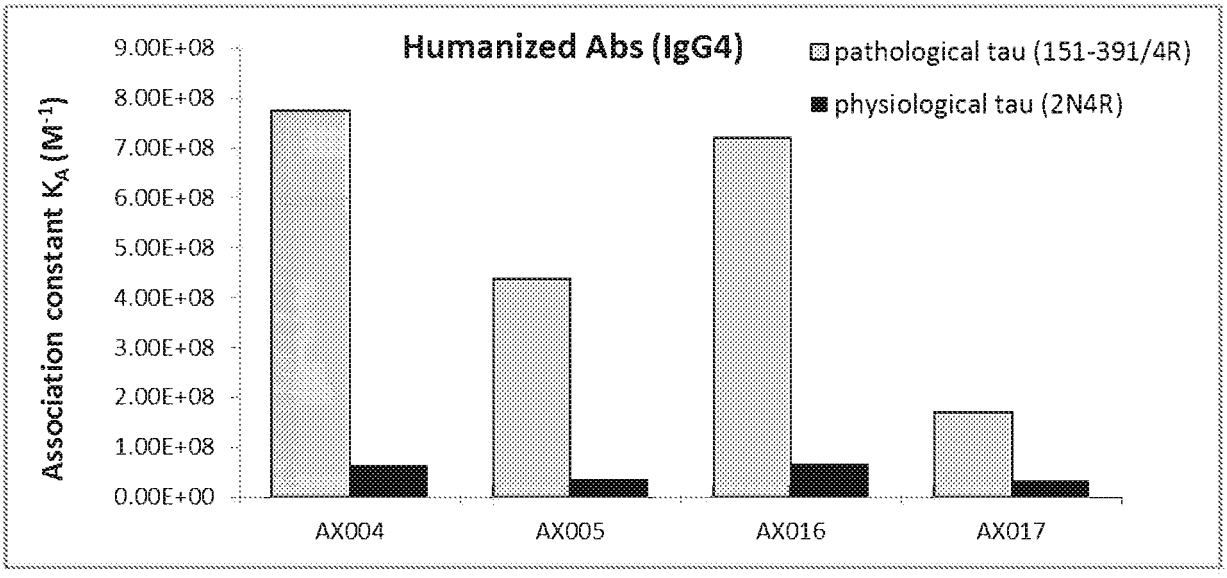


Fig.34E

EC50 (ng/ml) Humanized Ab/IgG1	AX004	AX005	AX016	AX017
Tau 151-391/4R	14.68	20.55	13.71	19.36
Tau 2N4R	53.15	134.5	51.35	91.13

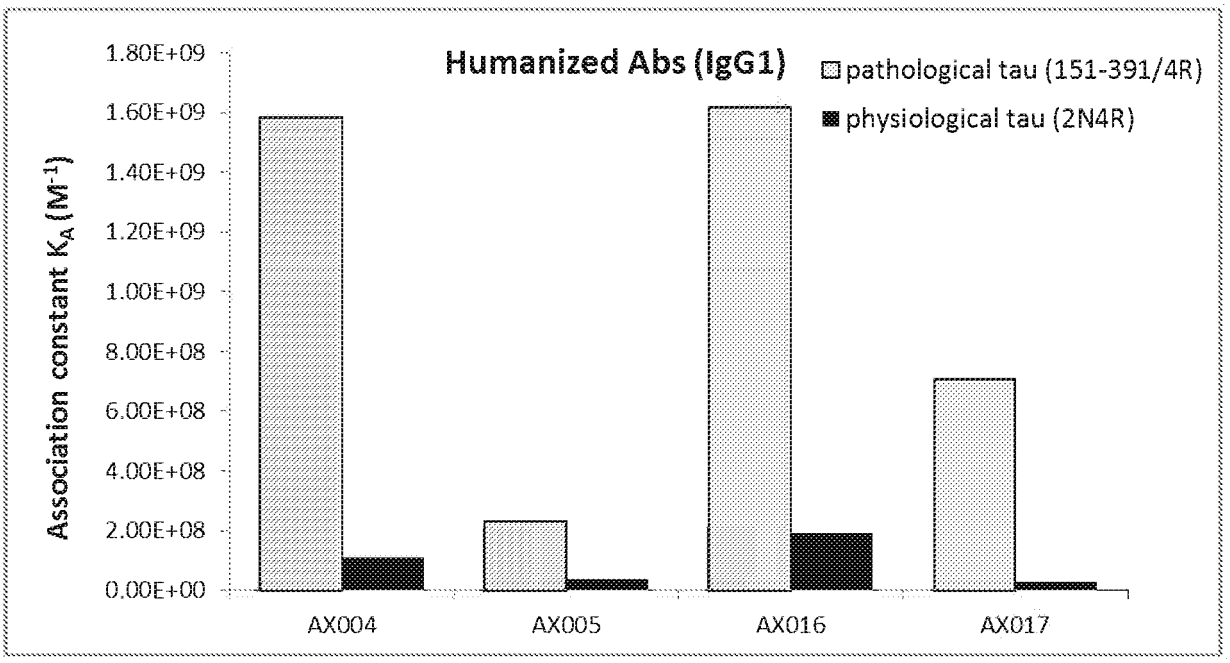
Fig.35

Fig.35A



K_A (M^{-1}) Ab(IgG4)	AX004	AX005	AX016	AX017
Tau 151-391/4R	7.75E+08	4.36E+08	7.2E+08	1.7E+08
Tau 2N4R	6.5E+07	3.5E+07	6.6E+07	3.2E+07

Fig.35B



K_A (M^{-1}) Ab(IgG1)	AX004	AX005	AX016	AX017
Tau 151-391/4R	1.6E+09	2.3E+08	1.6E+09	7.1E+08
Tau 2N4R	1.1E+08	5.7E+07	1.9E+08	2.95E+07

Fig.36

Fig.36A

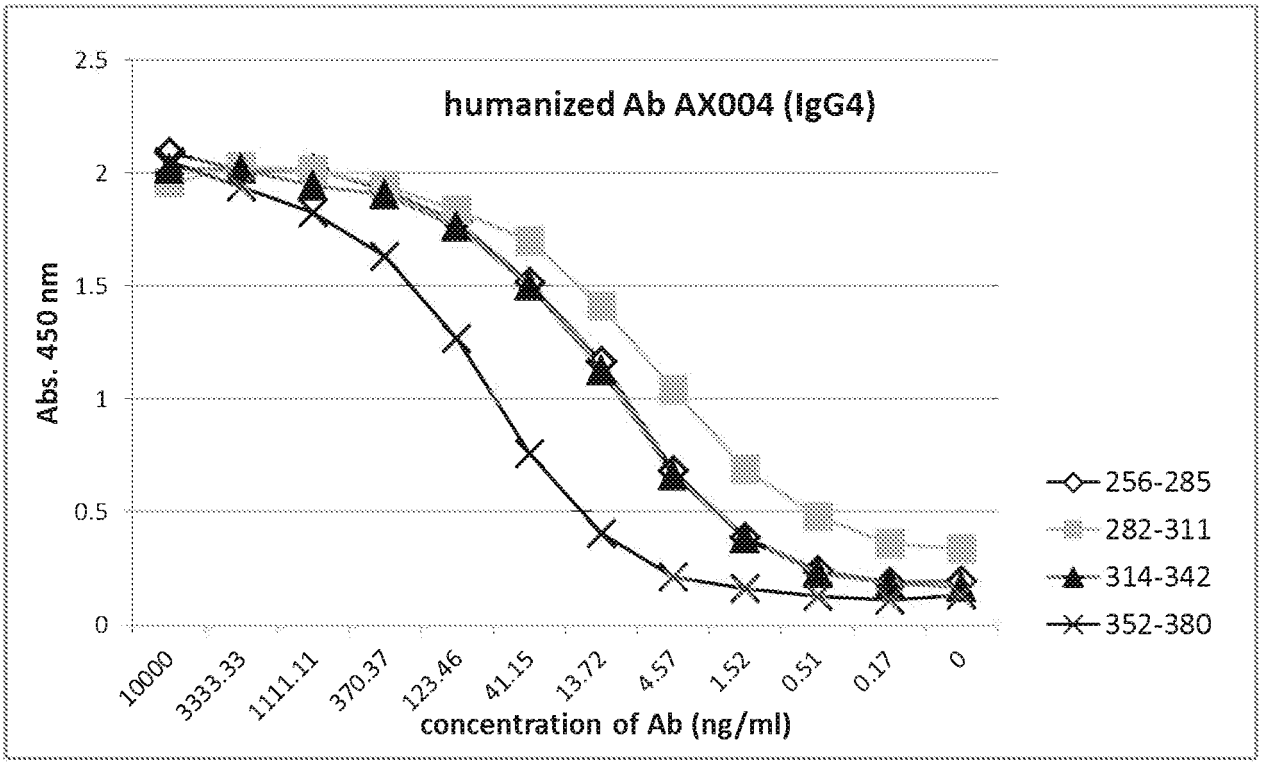


Fig.36B

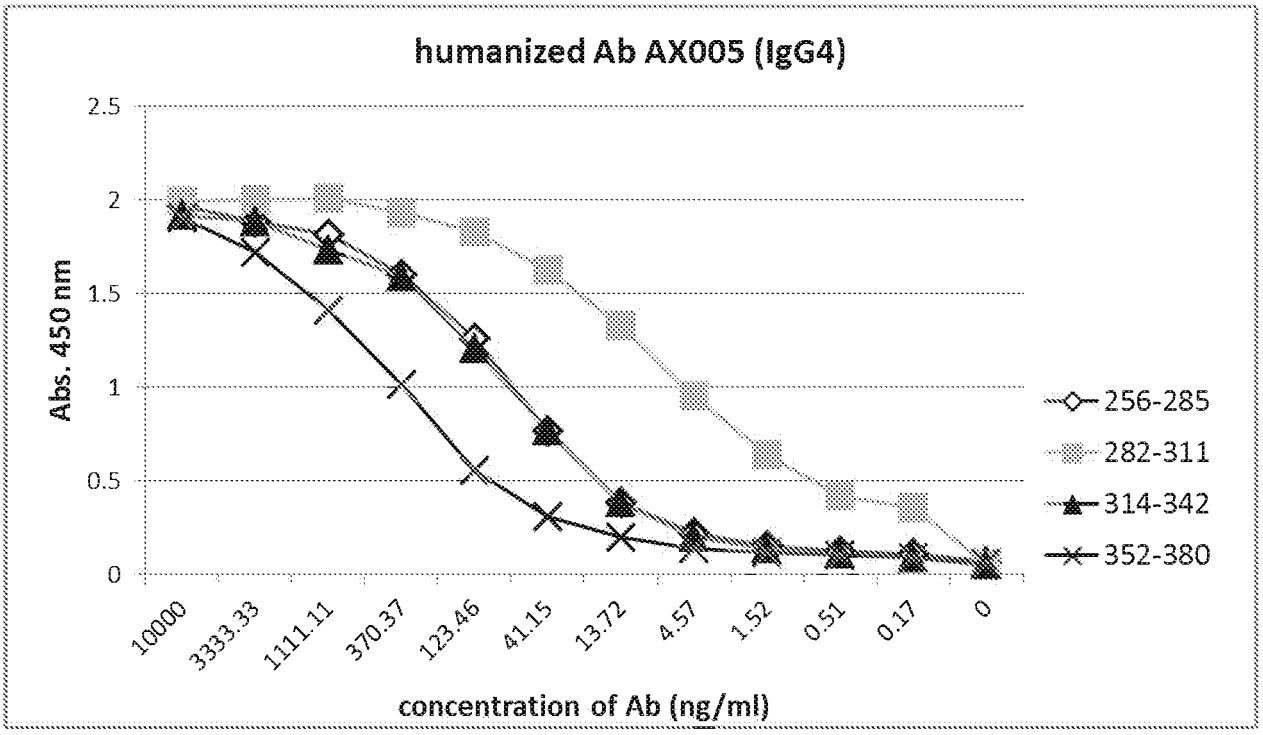


Fig.36C

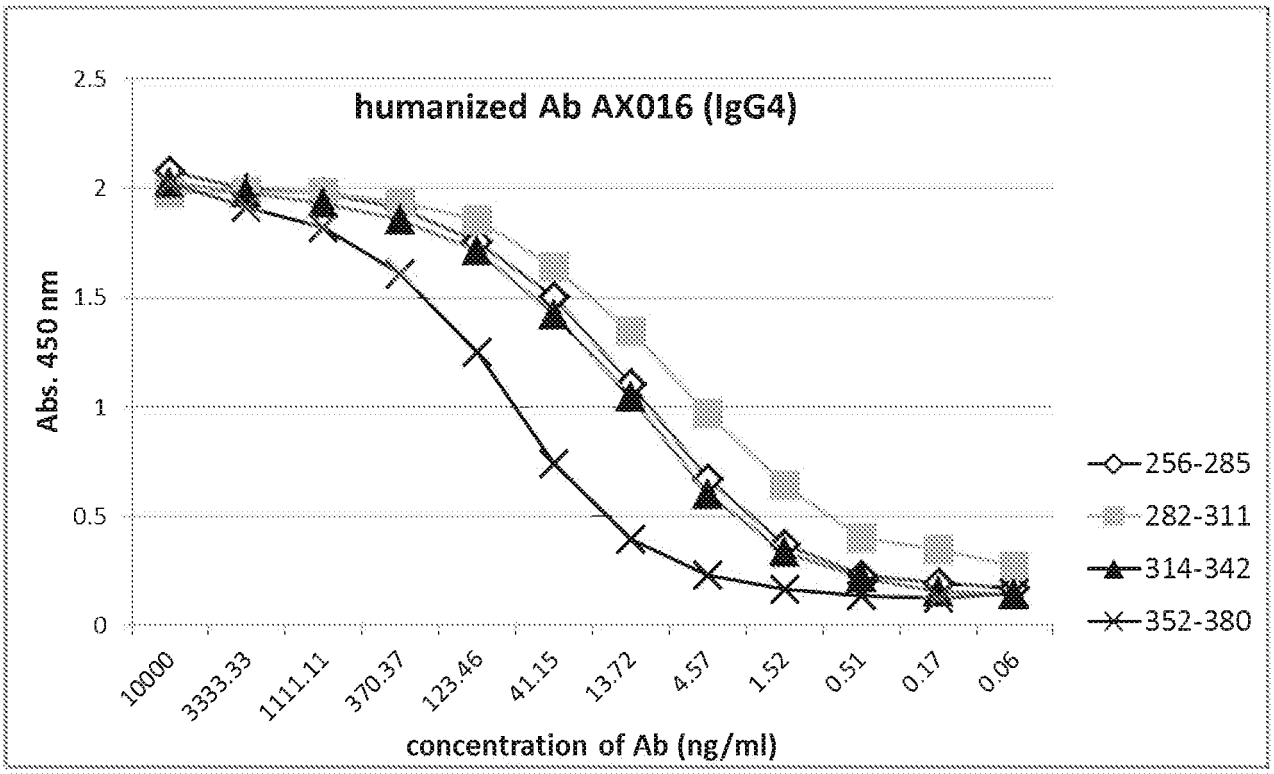


Fig.36D

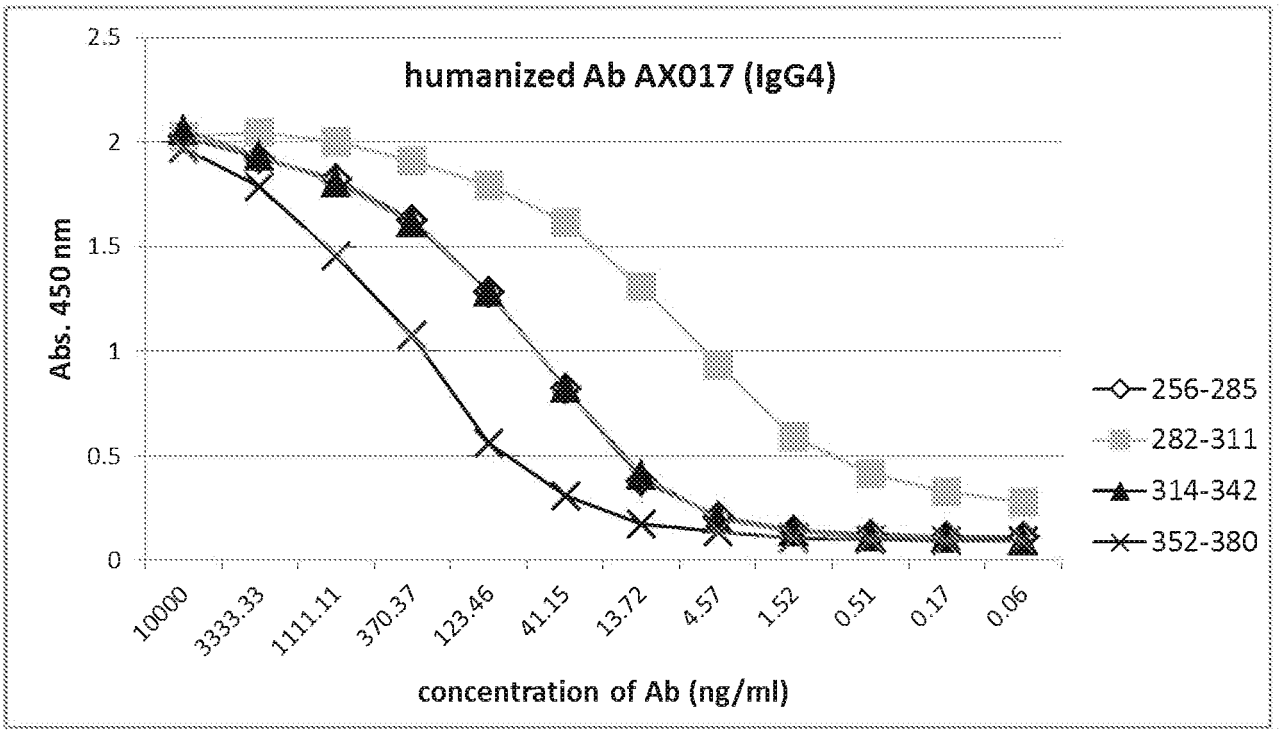


Fig.36E

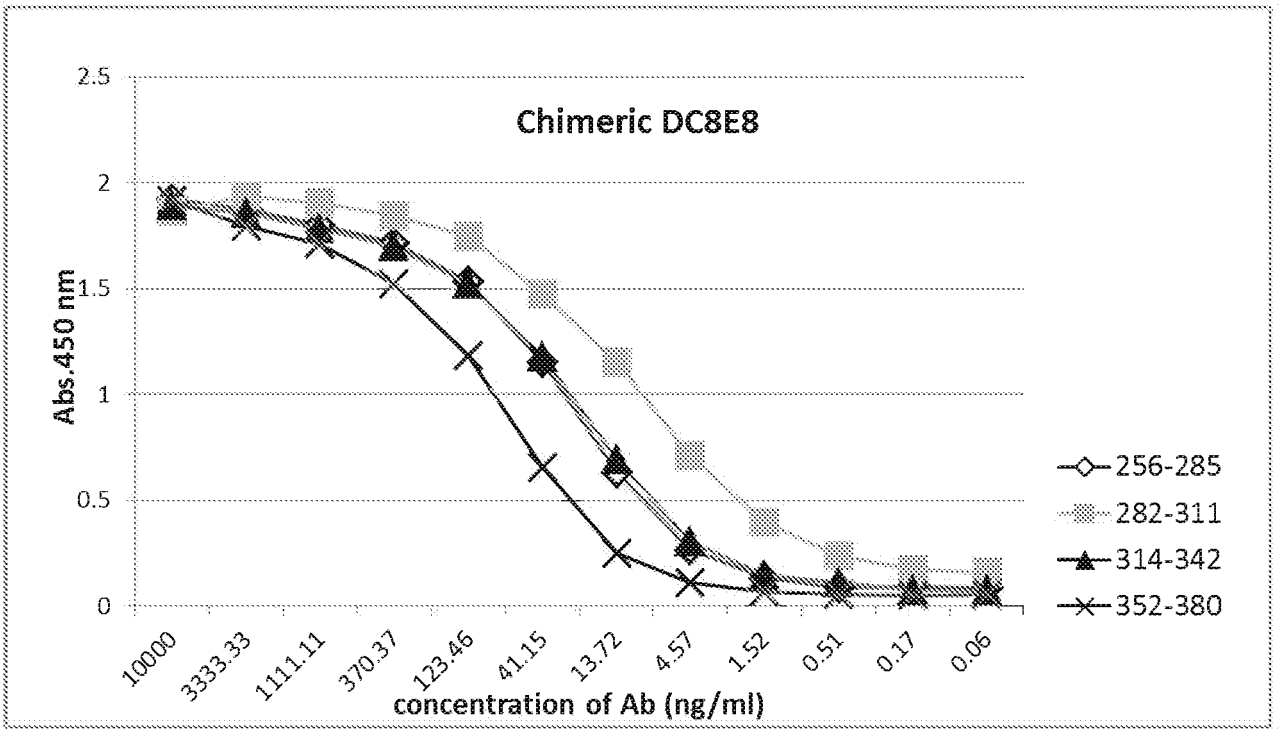


Fig.36F

EC50 (ng/ml) Humanized Ab/IgG4	AX004	AX005	AX016	AX017	Chimeric DC8E8
Tau peptide 256-285	13.18	75.27	13.95	72.47	29.72
Tau peptide 282-311	6.7	8.982	7.558	9.014	8.52
Tau peptide 314-342	13.03	74.47	15.27	72.57	26.47
Tau peptide 352-380	81.37	397.2	85.01	385.3	81.44

Fig.37

Fig.37A

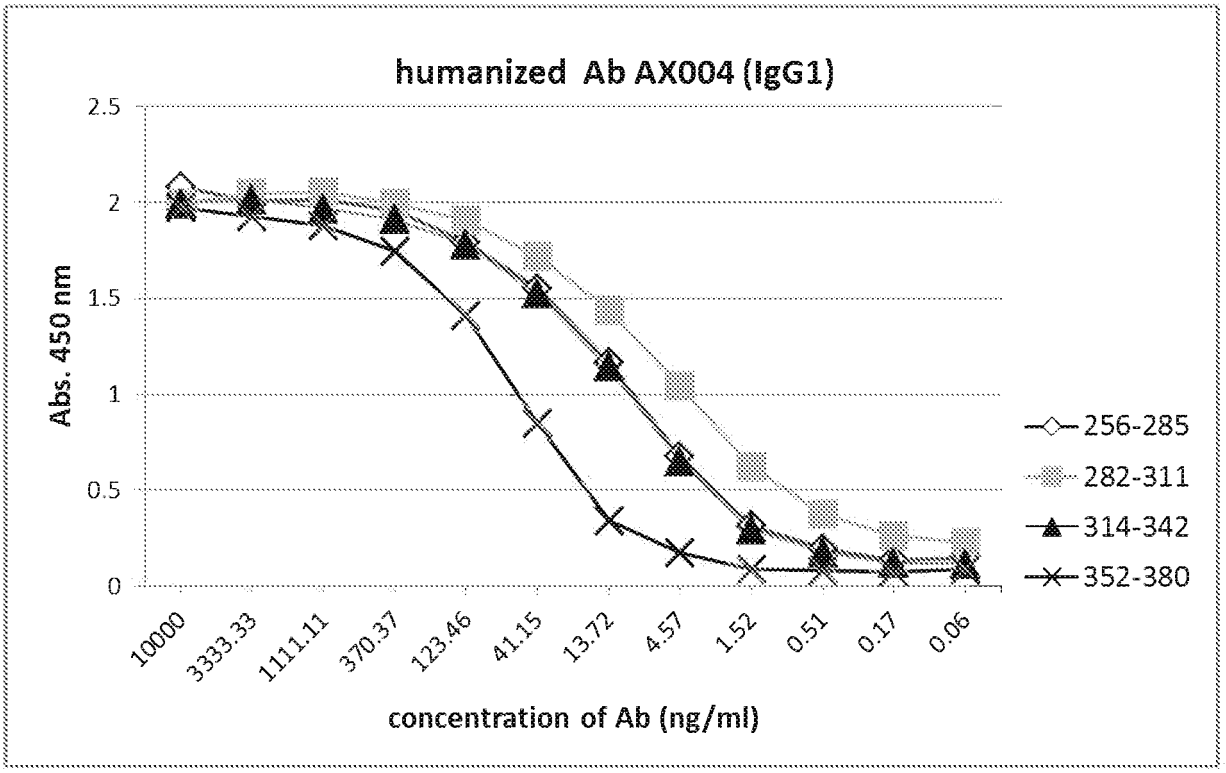


Fig.37B

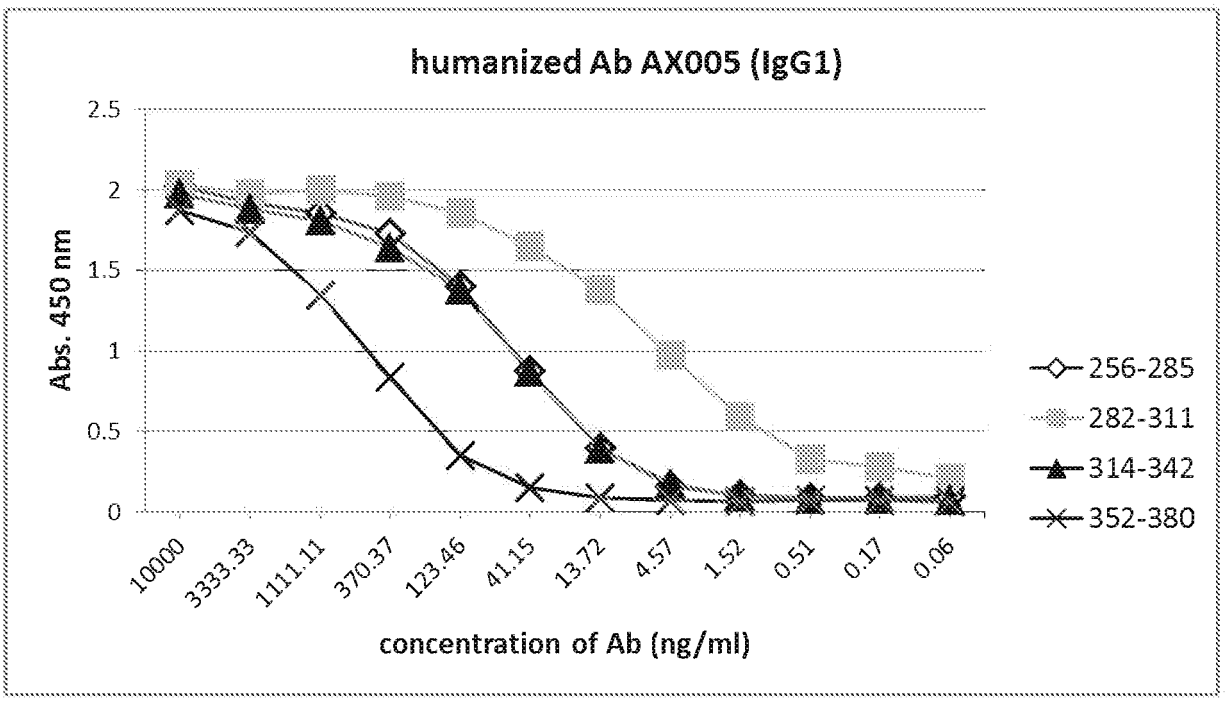


Fig.37C

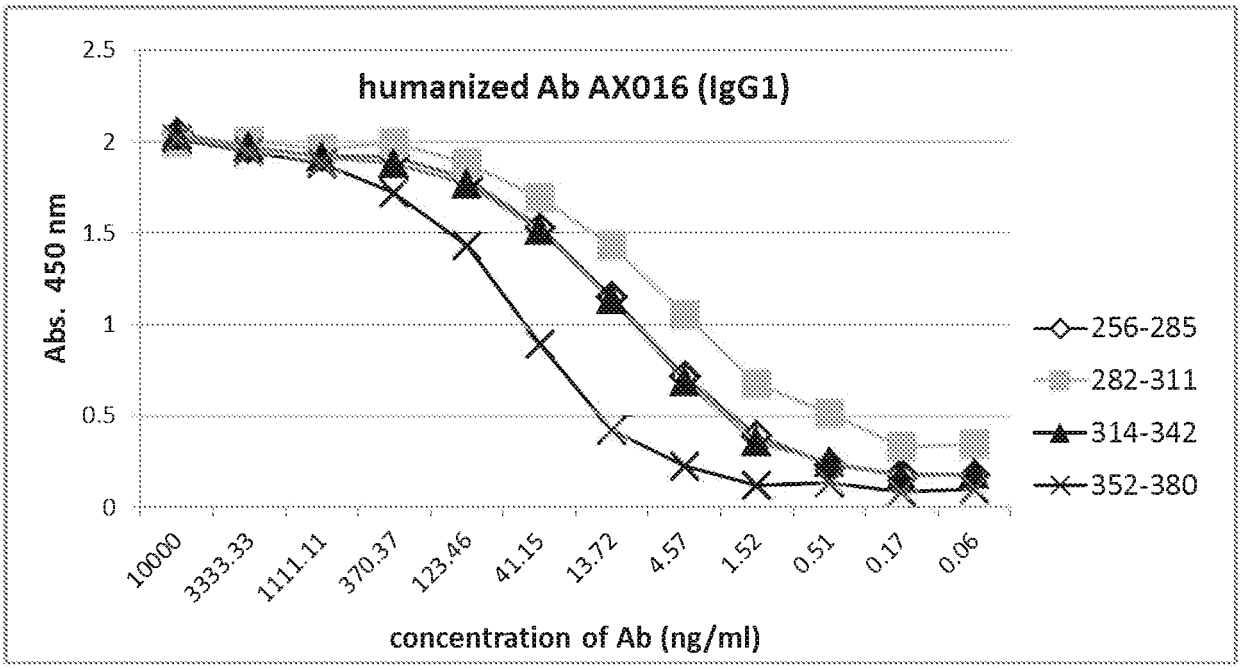


Fig.37D

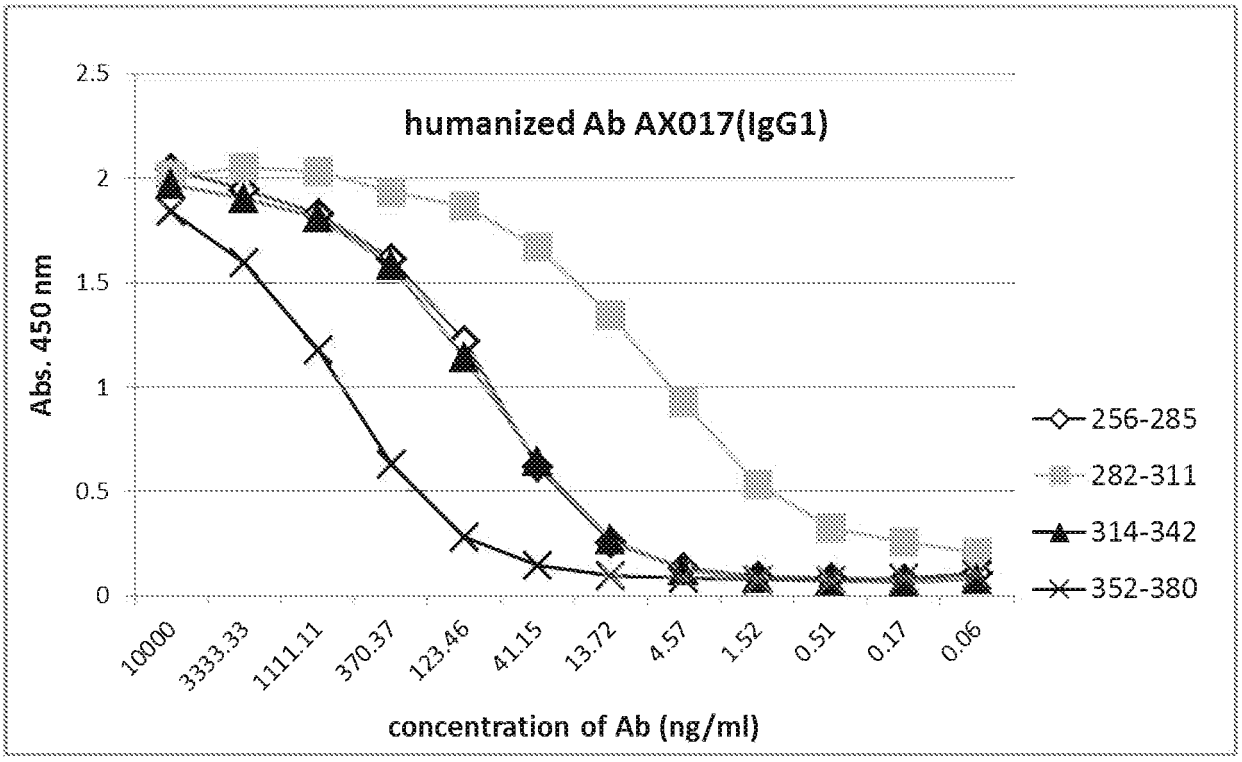


Fig.37E

EC50 (ng/ml) Humanized Ab/IgG1	AX004	AX005	AX016	AX017
Tau peptide 256-285	12.06	58.25	11.7	97.95
Tau peptide 282-311	5.981	6.801	6.474	7.664
Tau peptide 314-342	11.8	56.22	12.16	95.95
Tau peptide 352-380	58.72	578.7	56.63	882.7

Fig.38

Fig.38A

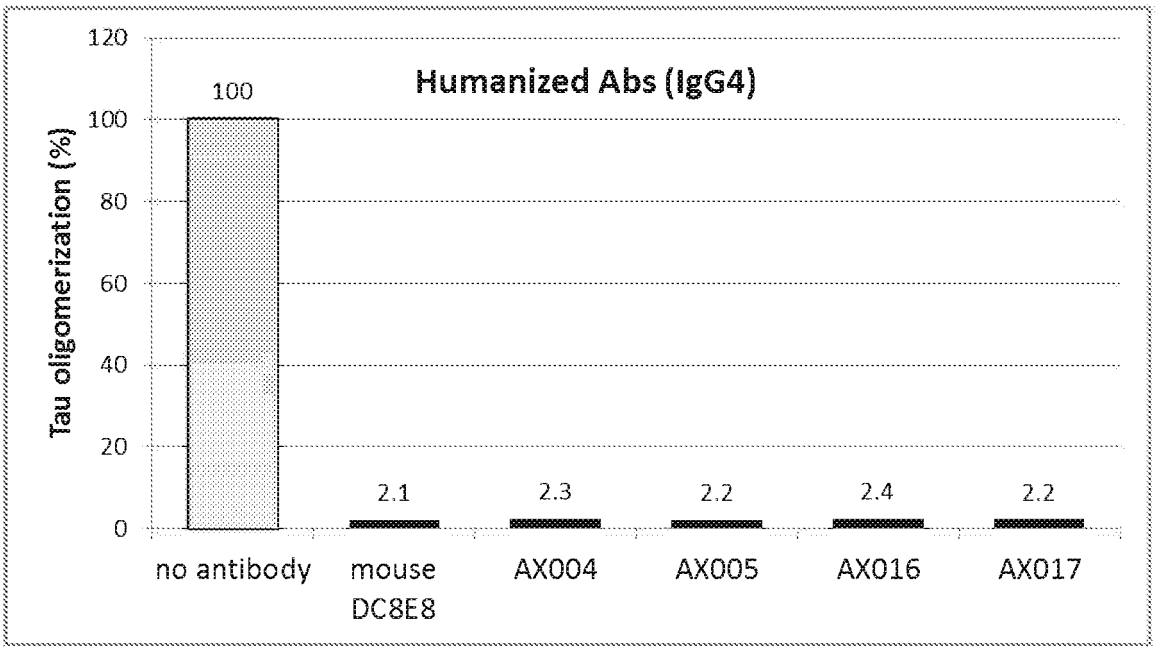
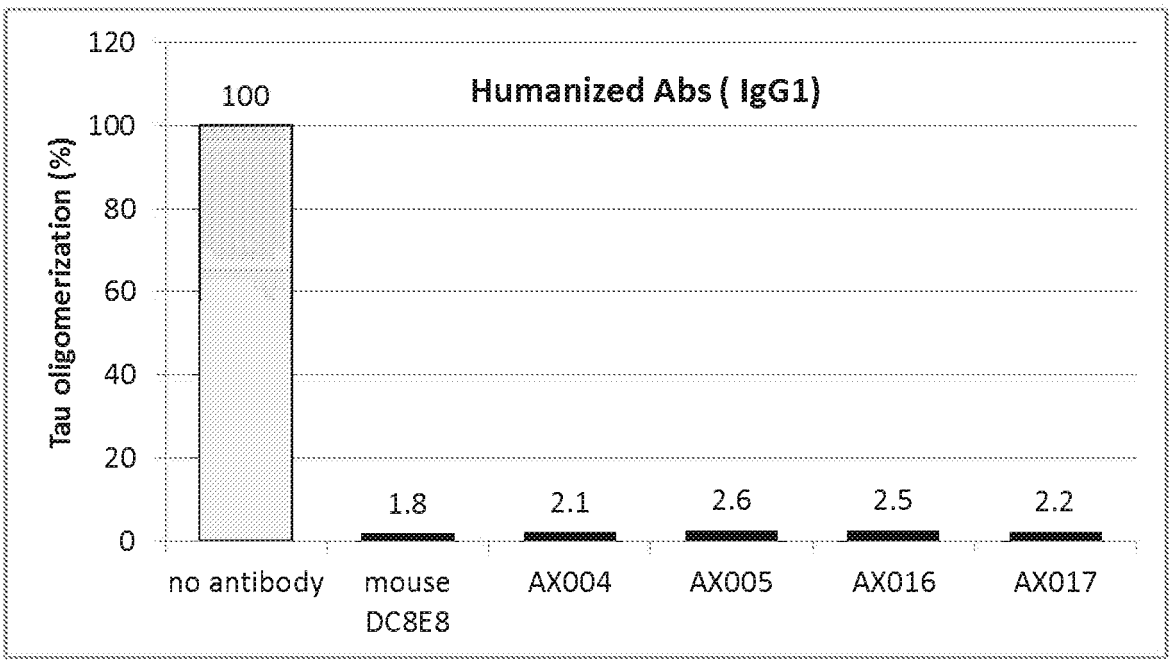


Fig.38B


Humanized Abs (IgG1)
Tau oligomerization (%)
120
100
80
60
40
20
0
100
1.8
2.1
2.6
2.5
2.2
no antibody
mouse DC8E8
AX004
AX005
AX016
AX017

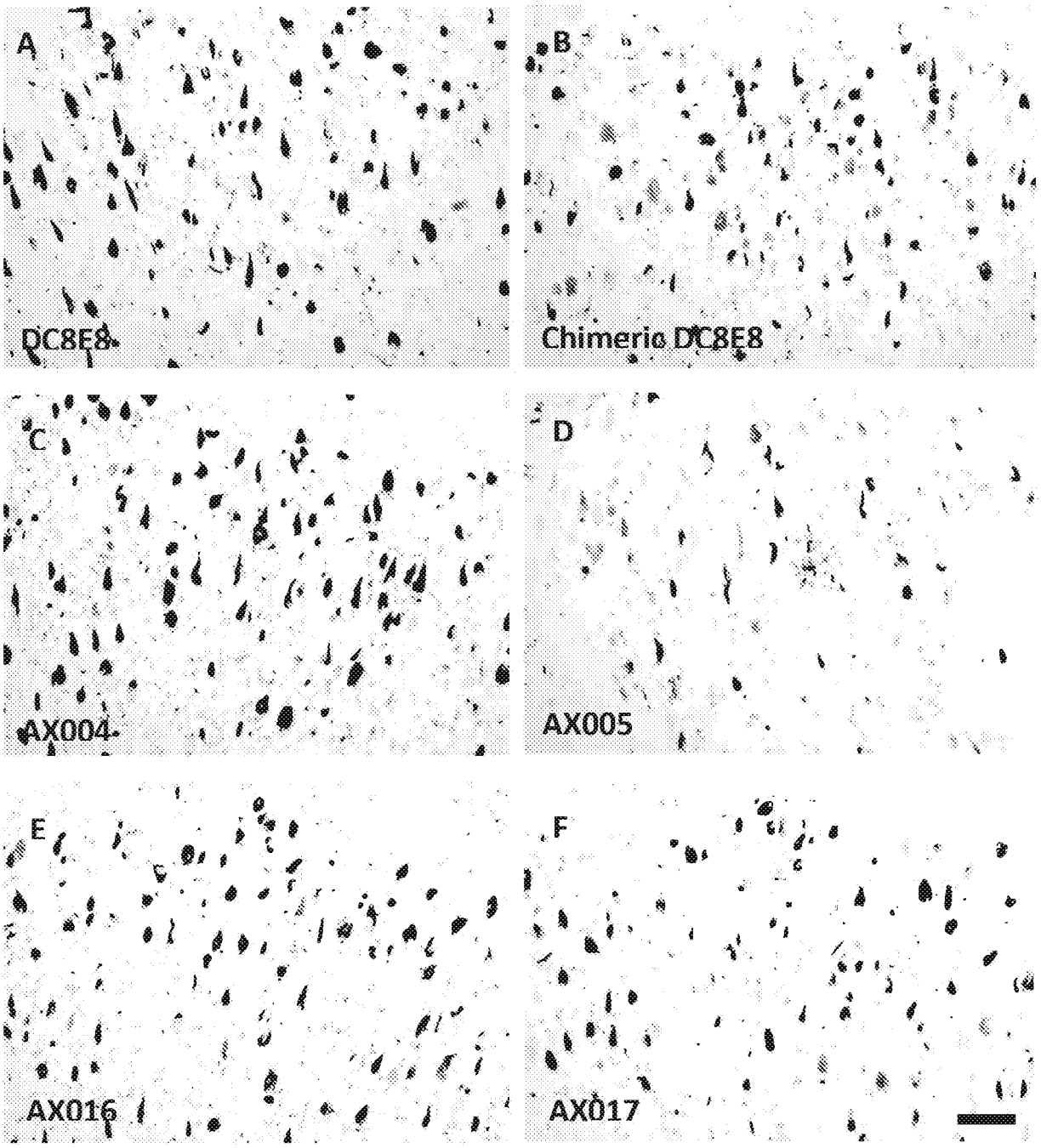


Fig.39

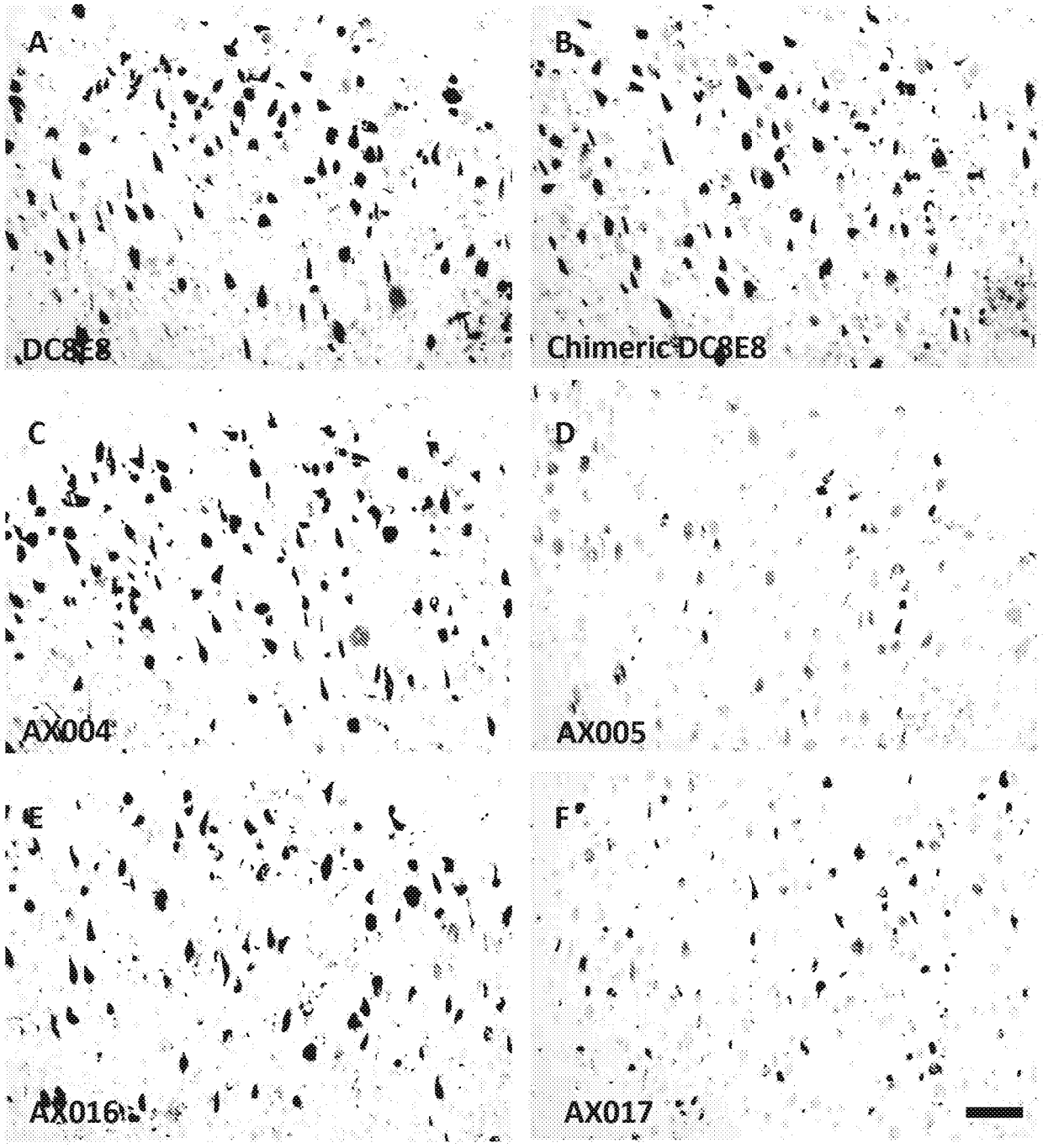


Fig.40

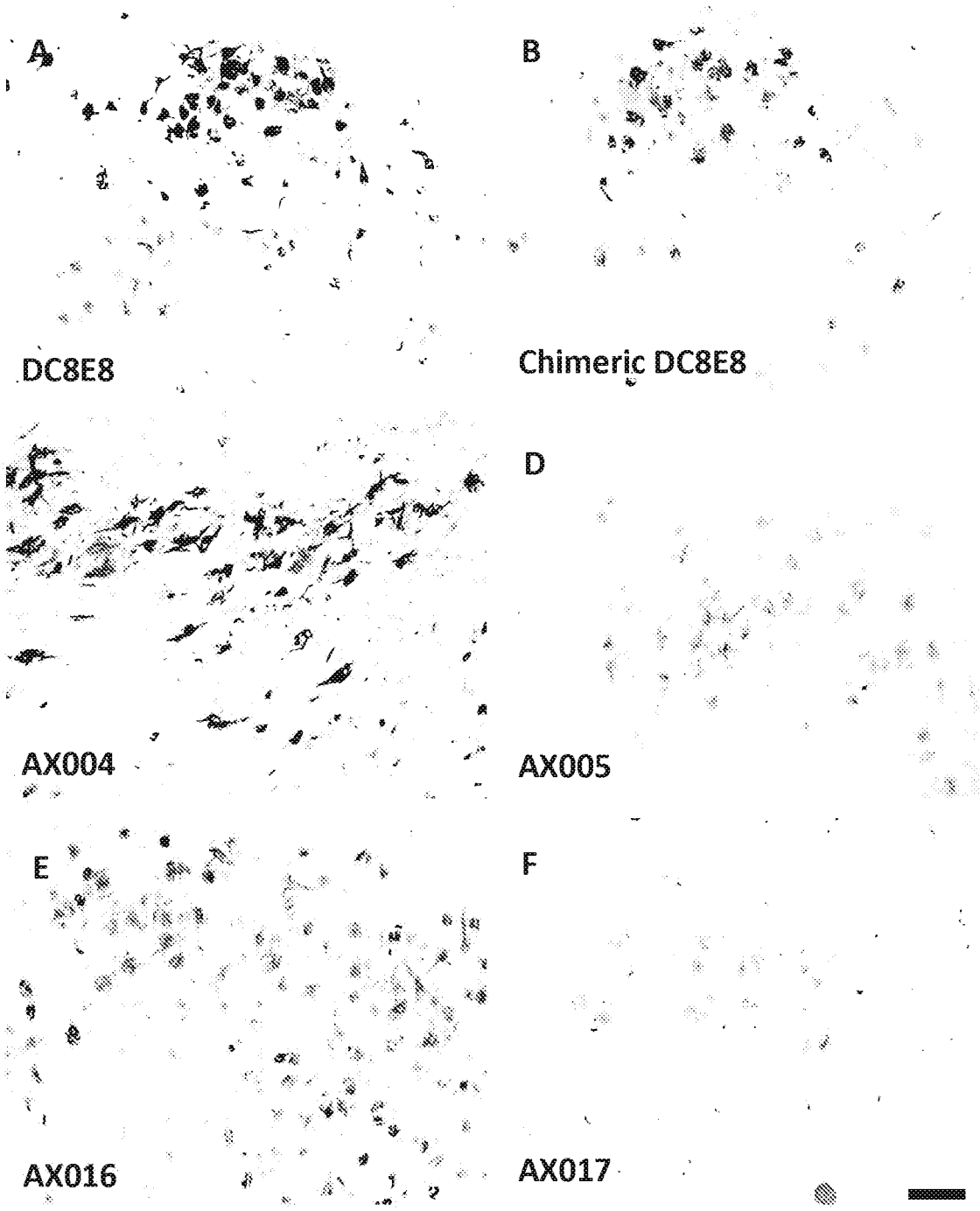


Fig.41

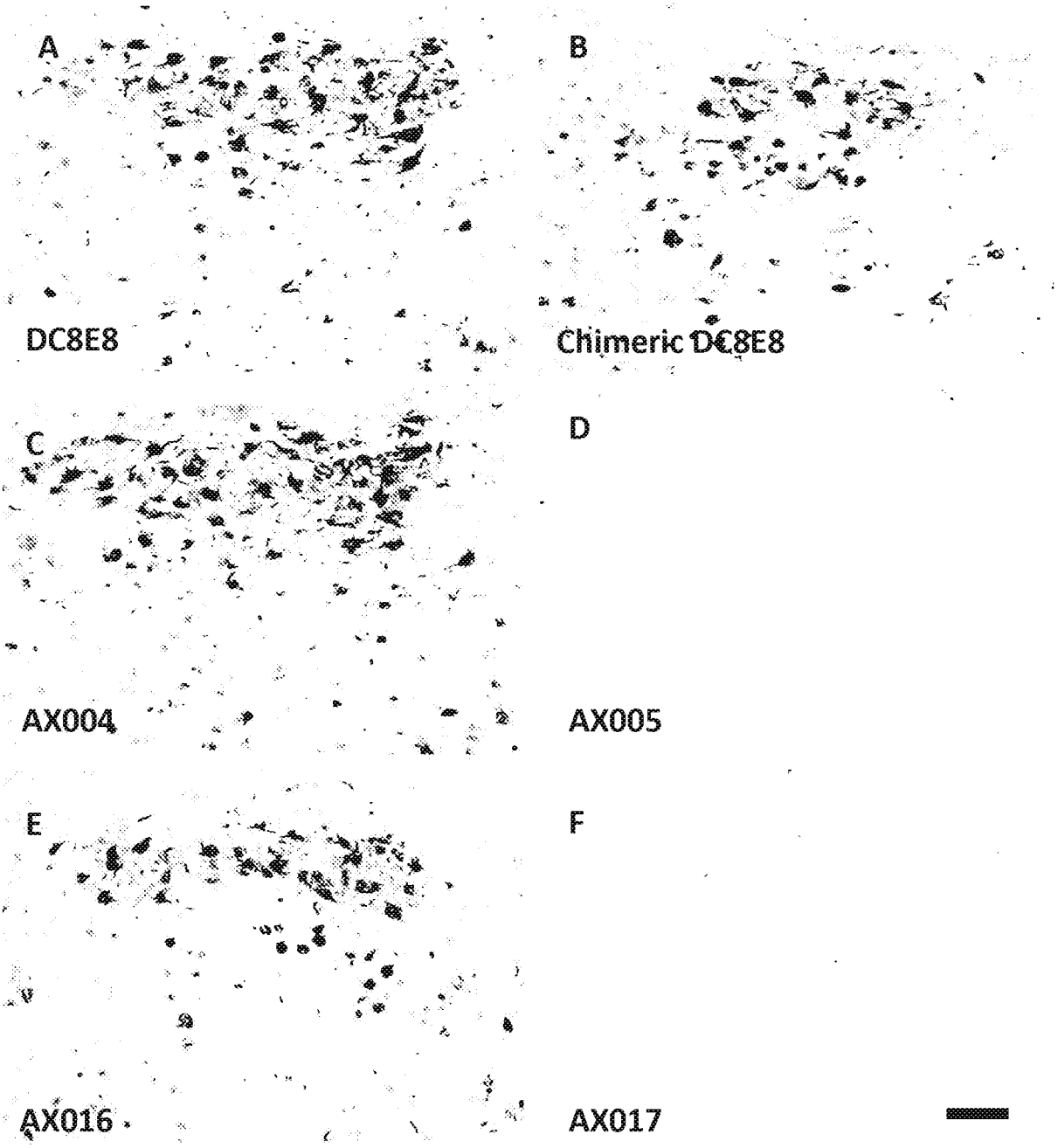


Fig.42

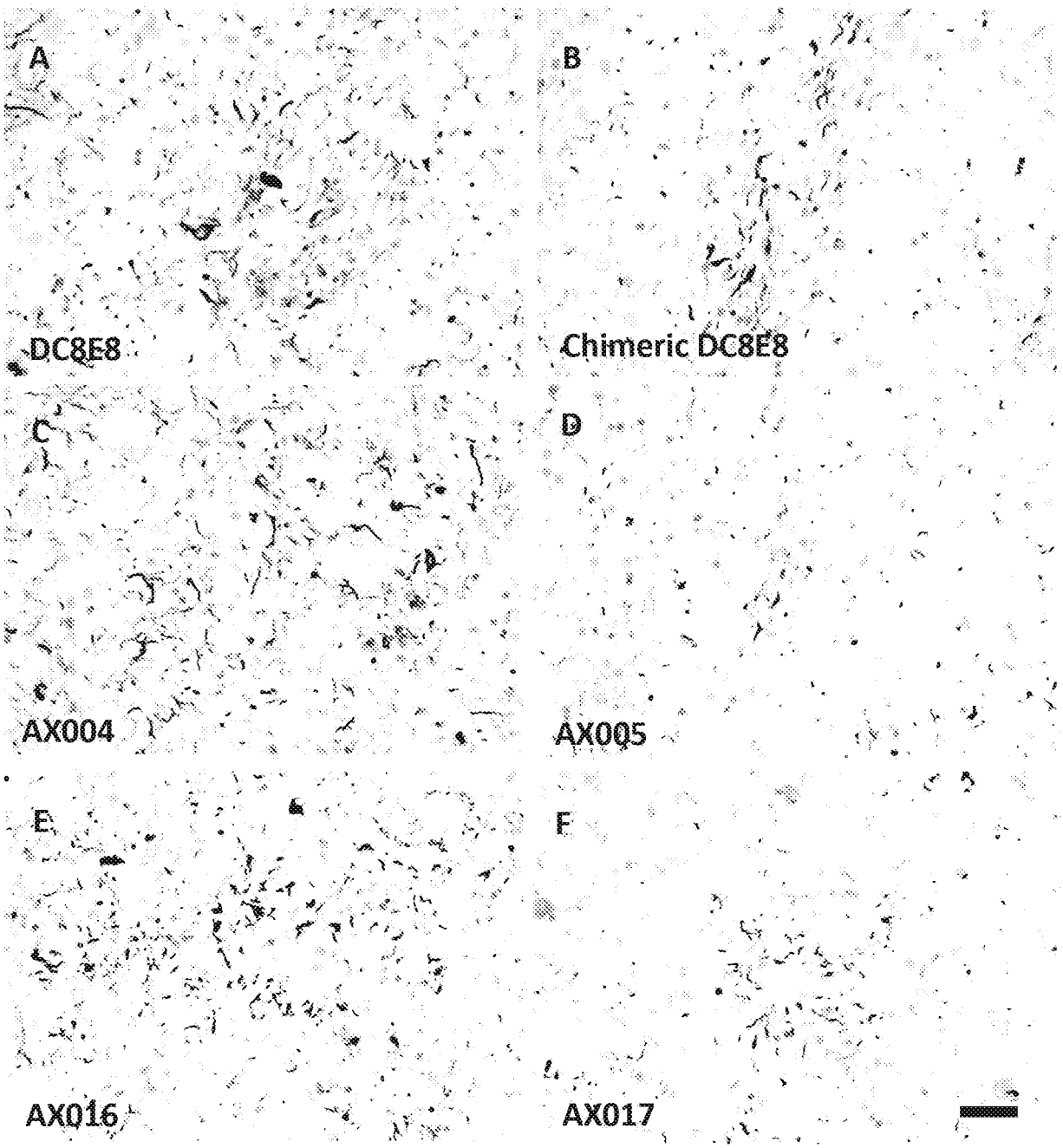


Fig.43

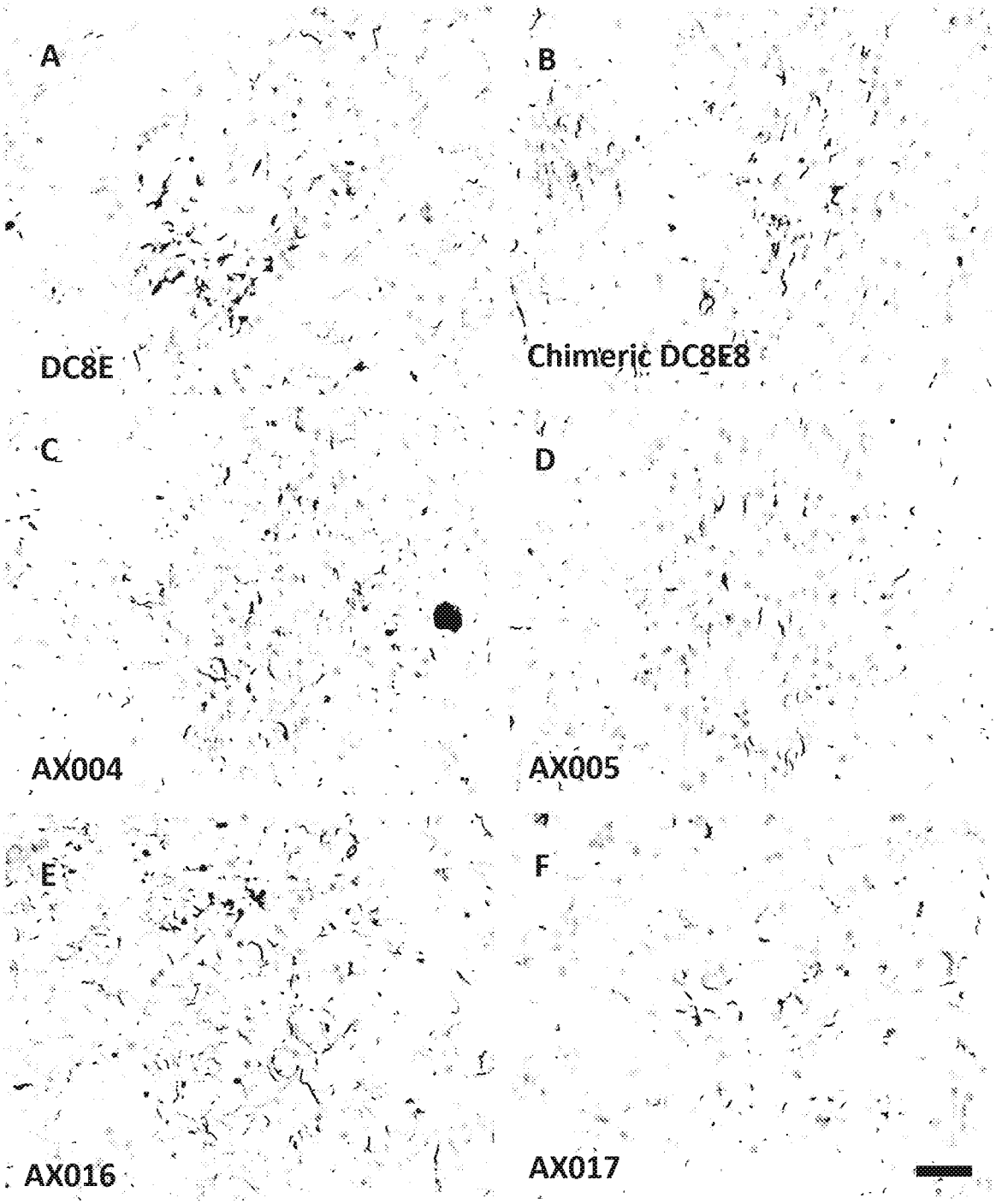


Fig.44

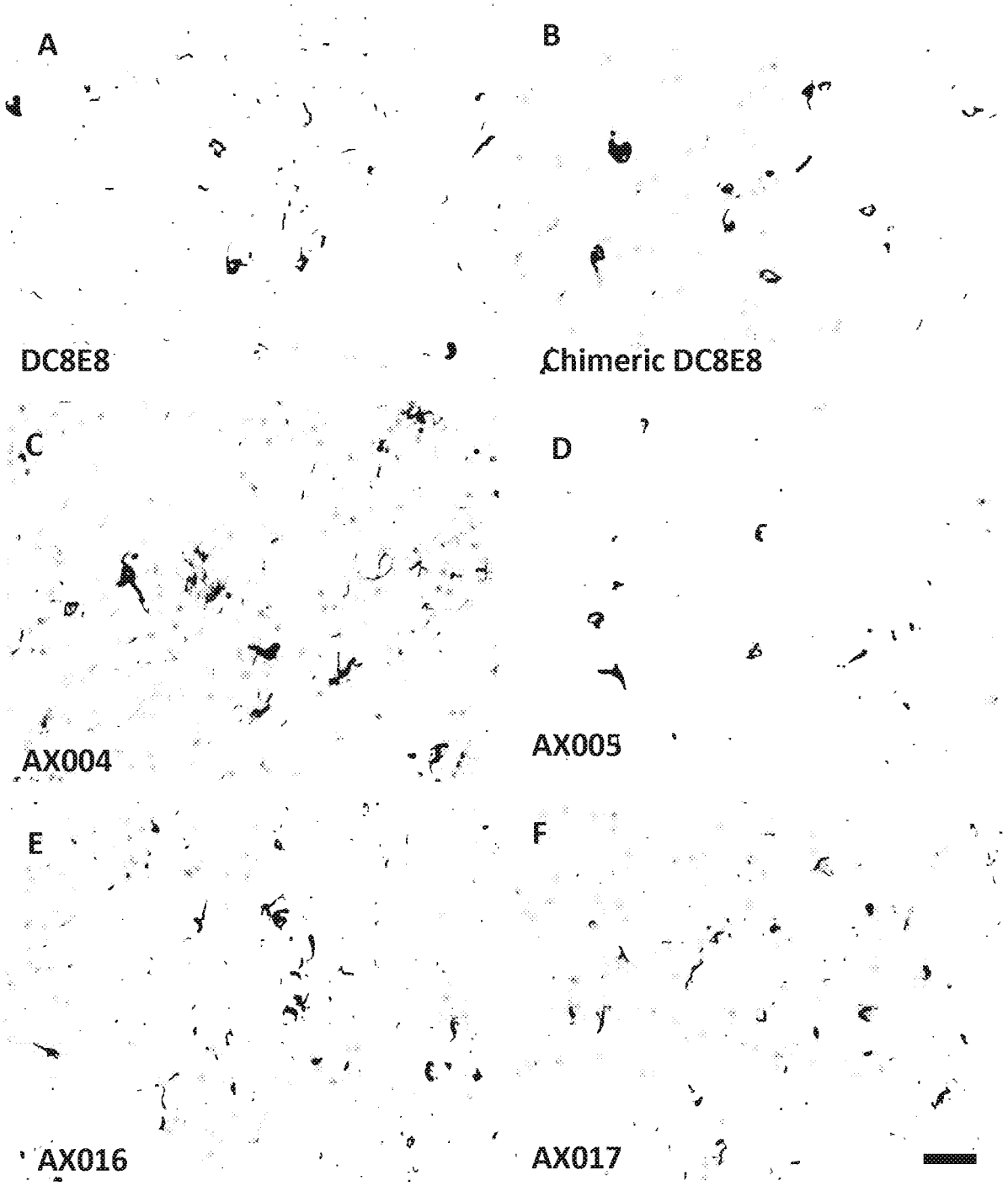


Fig.45

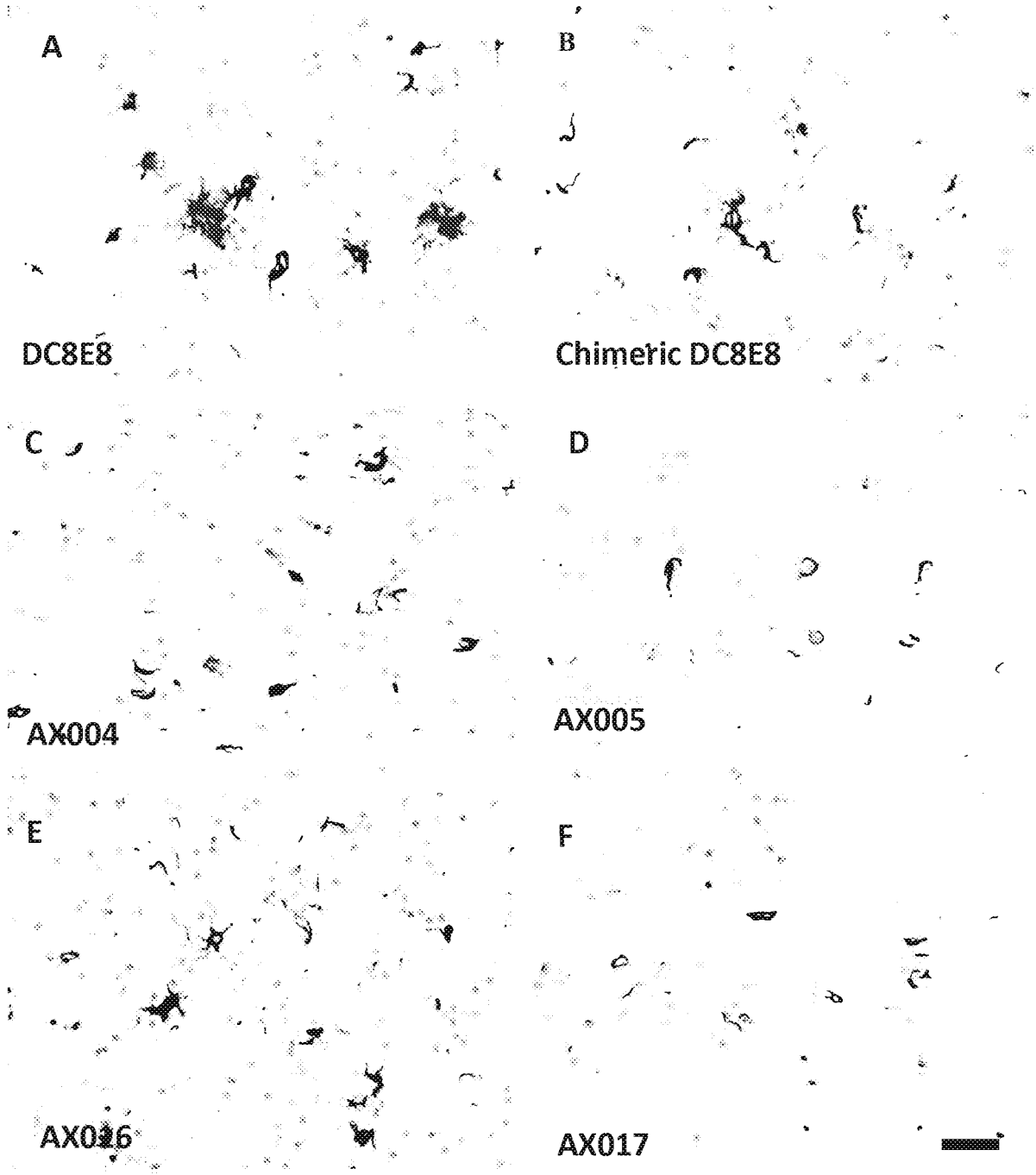


Fig.46