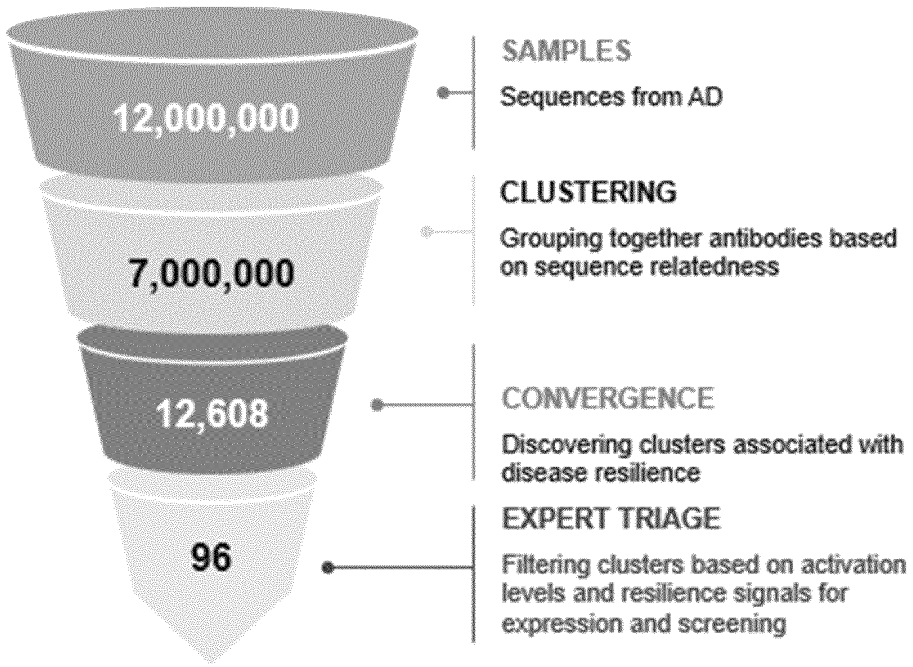

12,000,000
7,000,000
12,608
96
SAMPLES
Sequences from AD
CLUSTERING
Grouping together antibodies based on sequence relatedness
CONVERGENCE
Discovering clusters associated with disease resilience
EXPERT TRIAGE
Filtering clusters based on activation levels and resilience signals for expression and screening

Fig. 1A

CDR1
CDR2
CDR3
Known HTT binder
SU540
SU540
SU540
SU540 (ATL5061)
SU585 (ATL5060)
SU540
SU540
EVQLVESGGGLVKPGGSLTISCAASGFTFSNAWMNWVRQAPGKGLEWVGHIRTQAEGGTSDYAAPVK
GRFTISRDDSKNTLYLQMNSLKTEDTAVYYCIPPPYYYYGLDVWGQGTTVTVSS

Fig. 1B

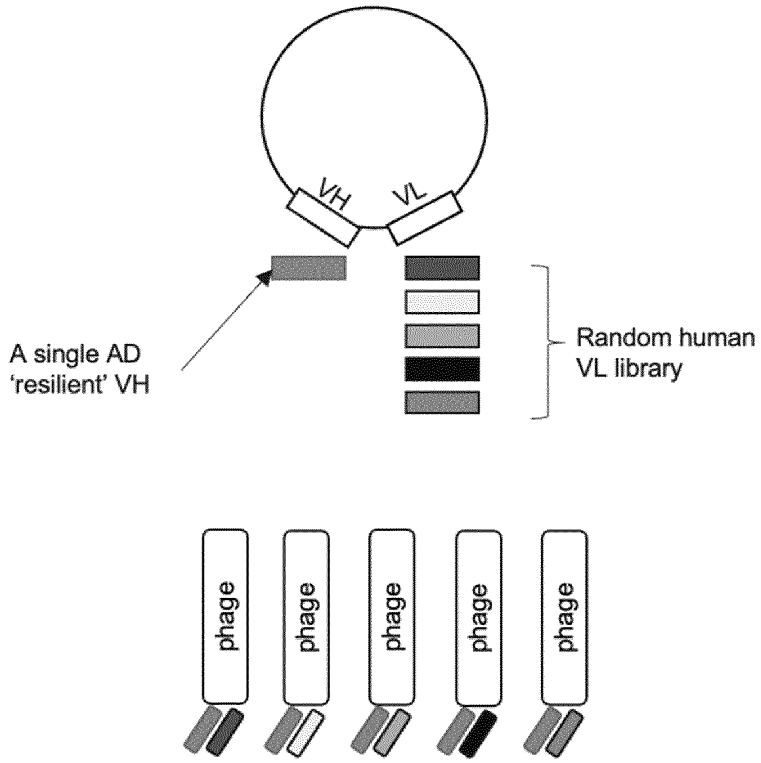

VH
VL
A single AD
'resilient' VH
Random human
VL library
phage
phage
phage
phage
phage

Fig. 2A

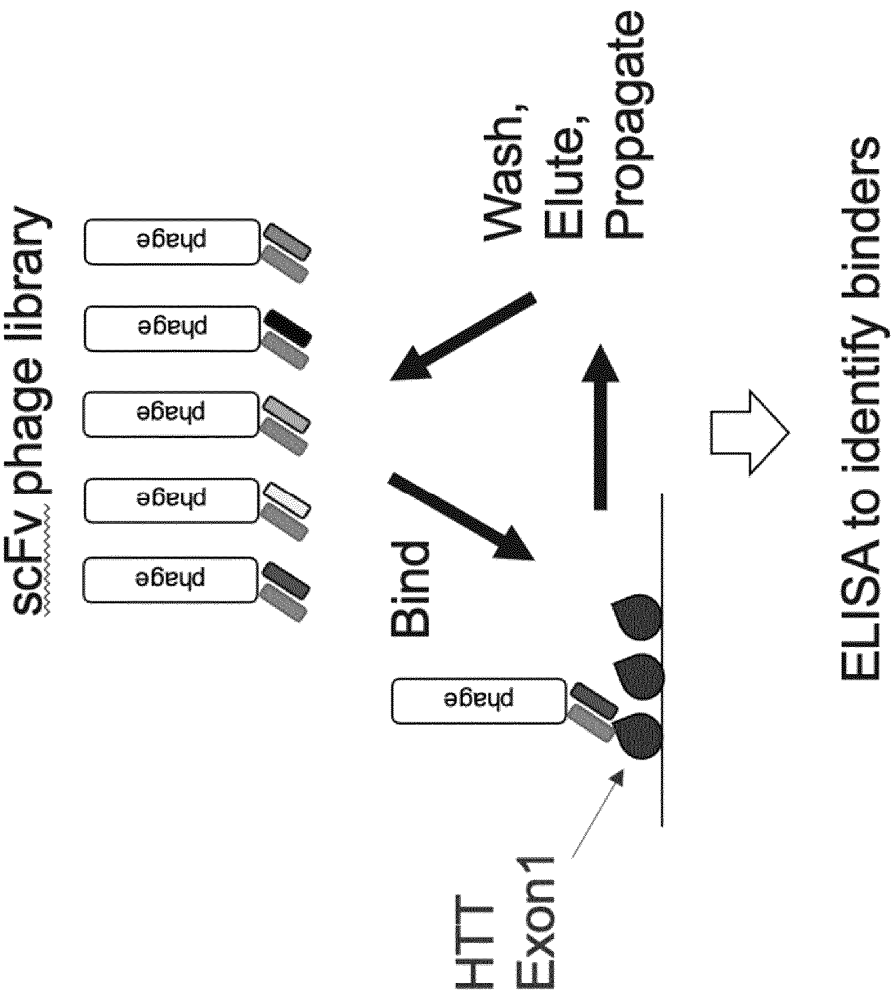

scFv phage library
phage
phage
phage
phage
phage
Bind
Wash,
Elute,
Propagate
phage
HTT
Exon1
ELISA to identify binders

Fig. 2B

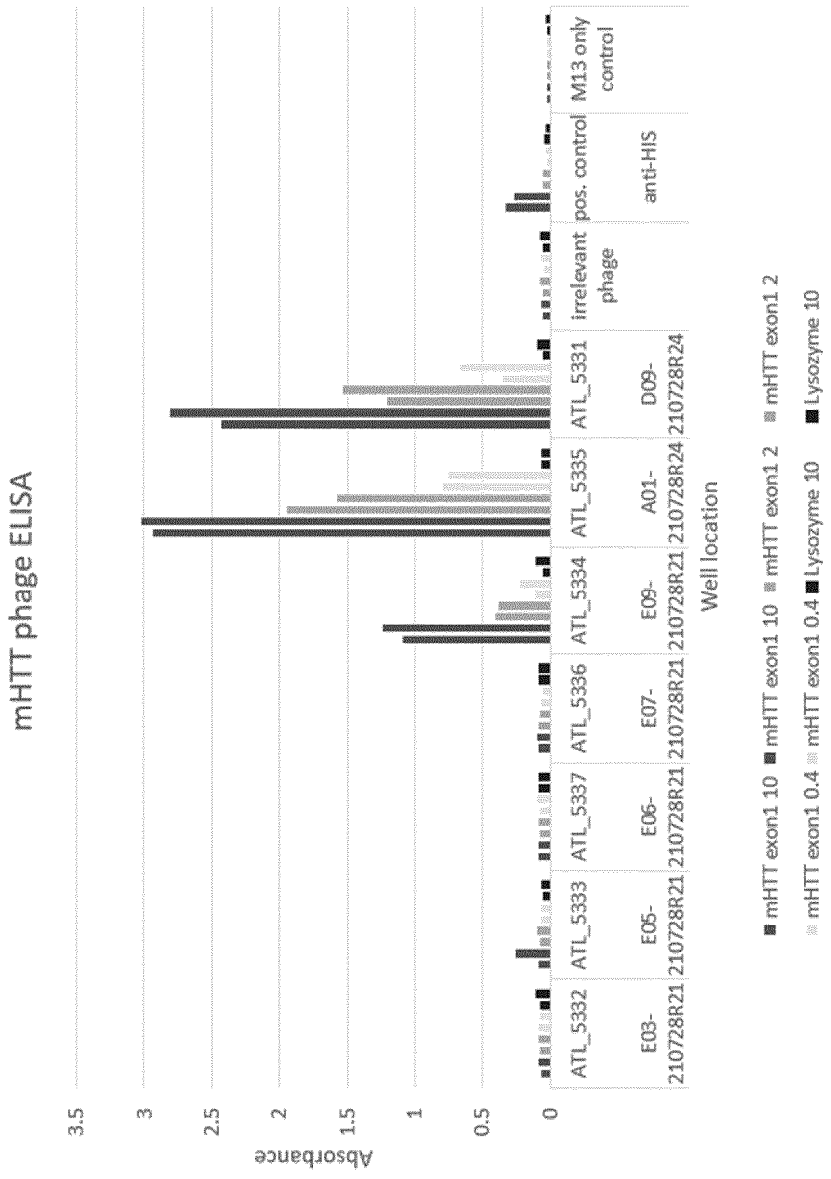

mHTT phage ELISA
Absorbance
3.5
3
2.5
2
1.5
1
0.5
0
ATL_5332
E03-210728R21
ATL_5333
E05-210728R21
ATL_5337
E06-210728R21
ATL_5336
E07-210728R21
ATL_5334
E09-210728R21
ATL_5335
A01-210728R24
ATL_5331
D09-210728R24
irrelevant phage
pos. control anti-HIS
M13 only control
Well location
mHTT exon1 10
mHTT exon1 10
mHTT exon1 2
mHTT exon1 2
mHTT exon1 0.4
Lysozyme 10
Lysozyme 10

Fig. 3A

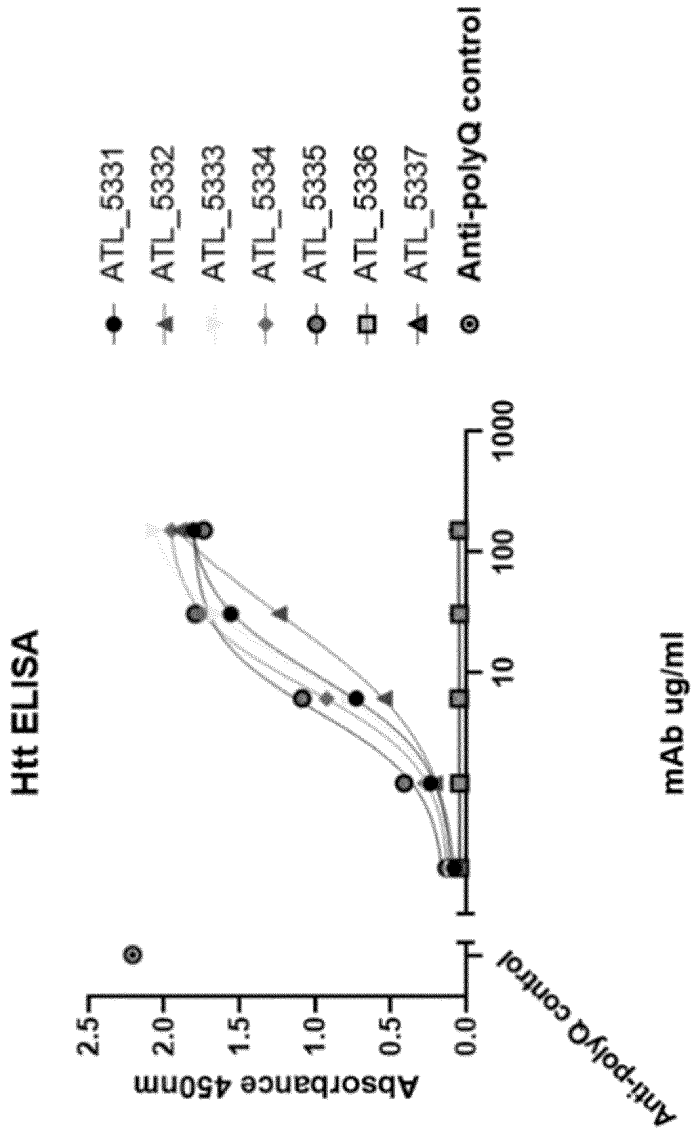

Htt ELISA
Absorbance 450nm
2.5
2.0
1.5
1.0
0.5
0.0
Anti-polyQ control
10
100
1000
mAb ug/ml
ATL_5331
ATL_5332
ATL_5333
ATL_5334
ATL_5335
ATL_5336
ATL_5337
Anti-polyQ control

Fig. 3B

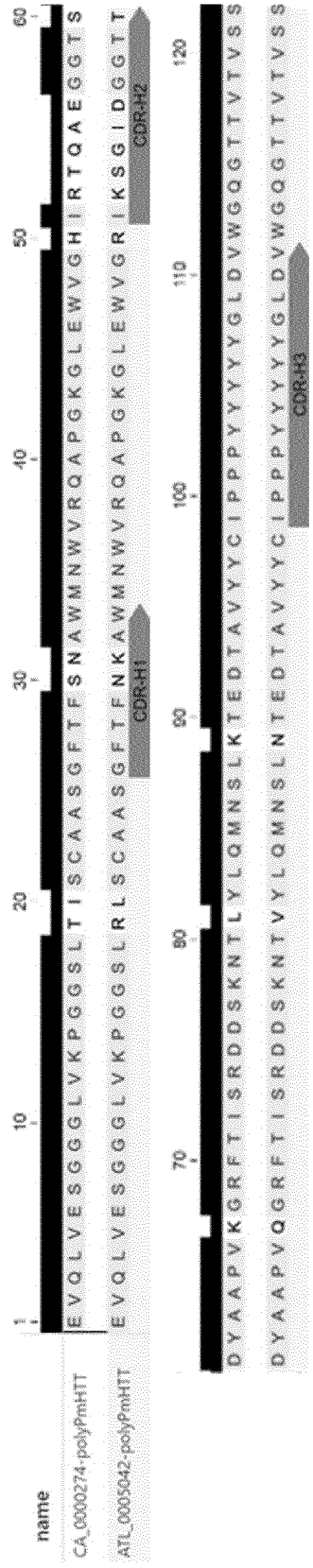

name
CA_0000274-polyPmHTT
ATL_0005042-polyPmHTT
CDR-H1
CDR-H2
CDR-H3

Fig. 4A

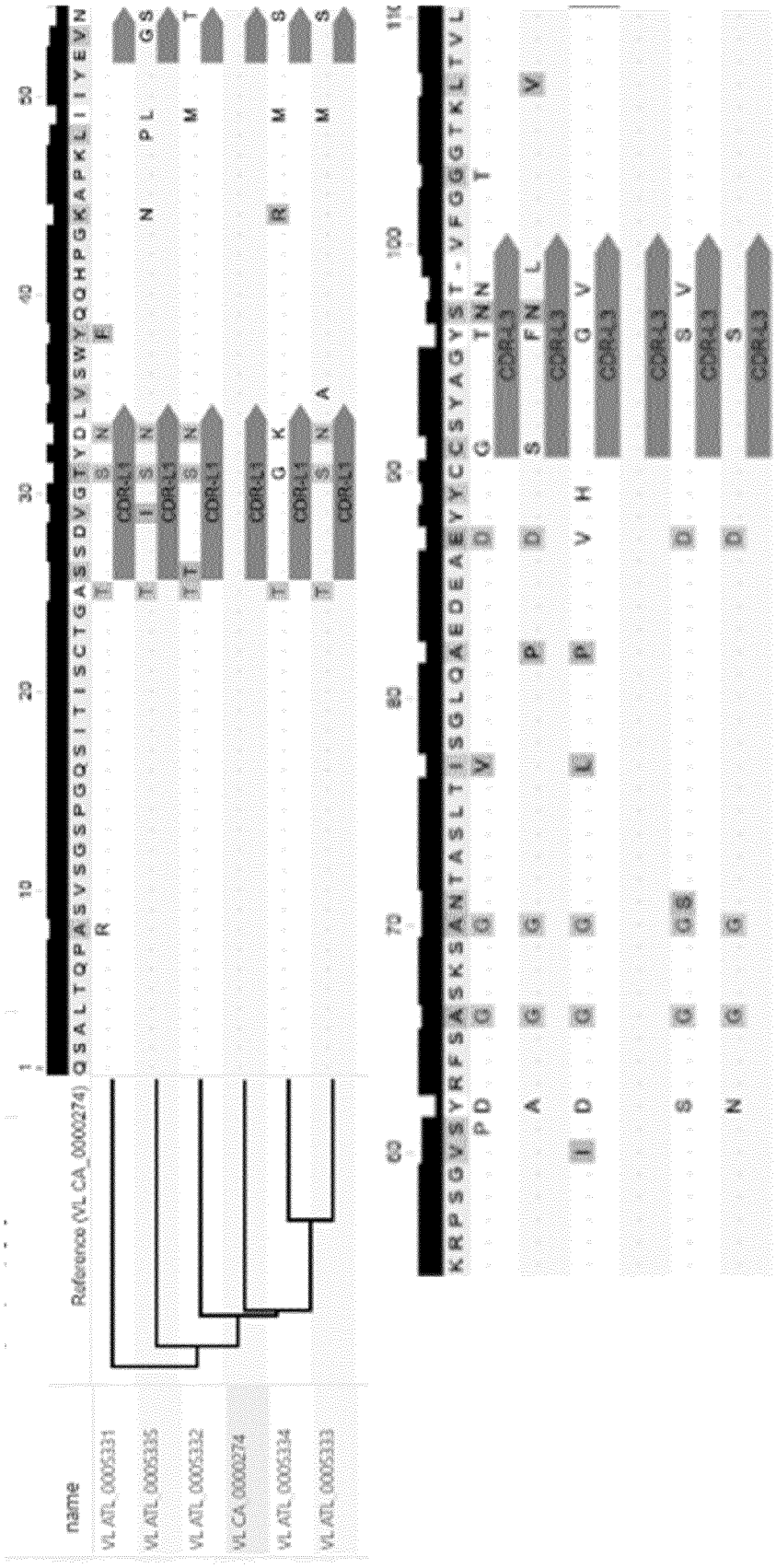

name
Reference (VL CA_0000274)
VL ATL_0005331
VL ATL_0005335
VL ATL_0005332
VL CA_0000274
VL ATL_0005334
VL ATL_0005333
CDR-L3
CDR-L1

Fig. 4B

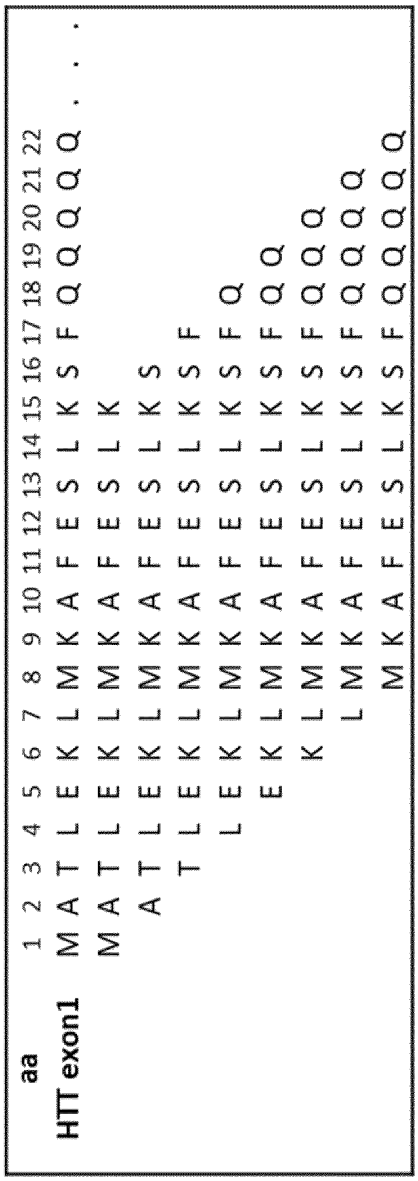
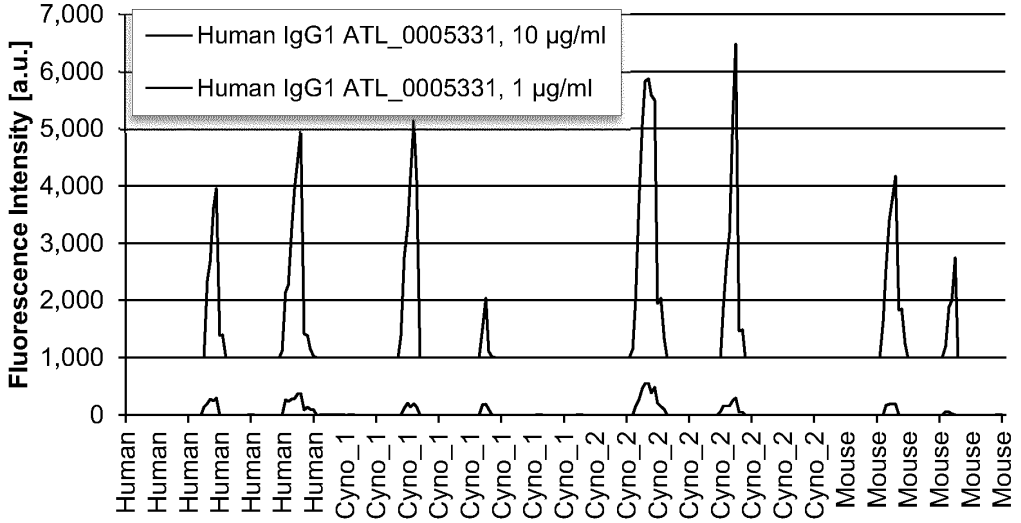

aa
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
HTT exon1
M A T L E K L M K A F E S L K S F Q Q Q Q . . .
M A T L E K L M K A F E S L K S F Q Q Q Q Q Q
A T L E K L M K A F E S L K S Q Q Q Q Q Q
T L E K L M K A F E S L K S F Q Q Q Q Q Q
L E K L M K A F E S L K S F Q Q Q Q Q Q
E K L M K A F E S L K S F Q Q Q Q Q Q
K L M K A F E S L K S F Q Q Q Q Q Q
L M K A F E S L K S F Q Q Q Q Q Q
M K A F E S L K S F Q Q Q Q Q Q

Fig. 5



HUMAN

MATLEKLMKAFESLKSFQQQQQQQQQ**QQQQQQQQQPPPPPPPPPPPQL**PQPP**PQAQPLLPQPQ PPPPPPPPPPGPAV**AEEPLHR

CYNO_1

MATLEKLMKAFESLKSFQQQ**QQQQQQQQQPPPPPPPPPPPP**QLPQPP**QAQPMLPQPQPPPPP PR**HHPARLWLRSRCTDQRKNFQLPRKTV

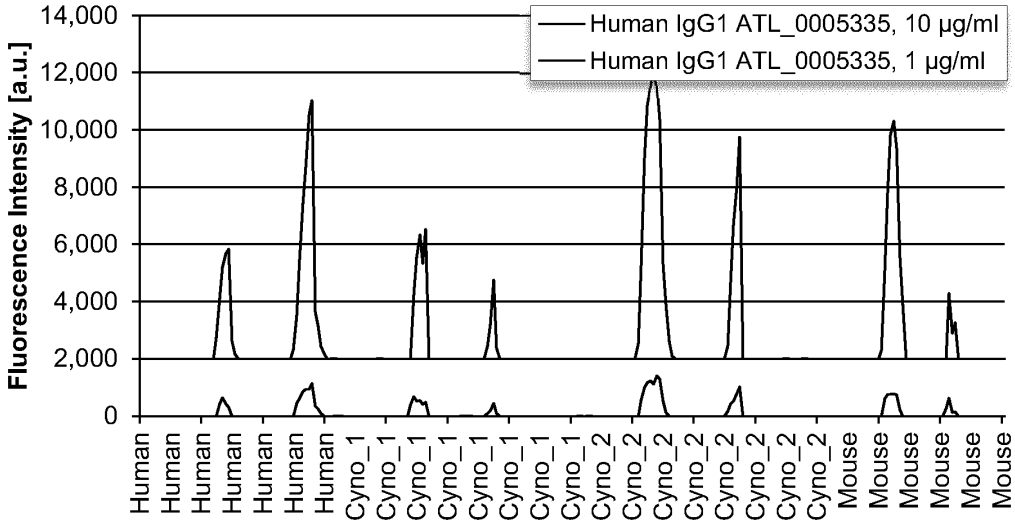
CYNO_2

MATLEKLMKAFESLKSFQQ**QQQQQQQQQQQPPPPPPPPPPPPQLP**QPP**QAQPMLPQPQPPPP PPPPPPGP**AVAEEPLHRPKKELSATKKDRVNH

MOUSE

MATLEKLMKAFESLKSFQQQ**QQQQPPPQAPPPPPPPPPPQPPQPPPQGQPPPPPPPLP**GPA EEPLHR

Fig. 6



HUMAN

MATLEKLMKAFESLKSFQQQQQQQQQ**QQQQQQQQPPPPPPPPPPPQL**PQPP**PQAQPLLPQPQ PPPPPPPPPPGPAV**AEEPLHR

CYNO_1

MATLEKLMKAFESLKSFQQQ**QQQQQQQQPPPPPPPPPPPP**QLPQP**PQAQPMLPQPQPPPPP PR**HHPARLWLRSRCTDQRKNFQLPRKTV

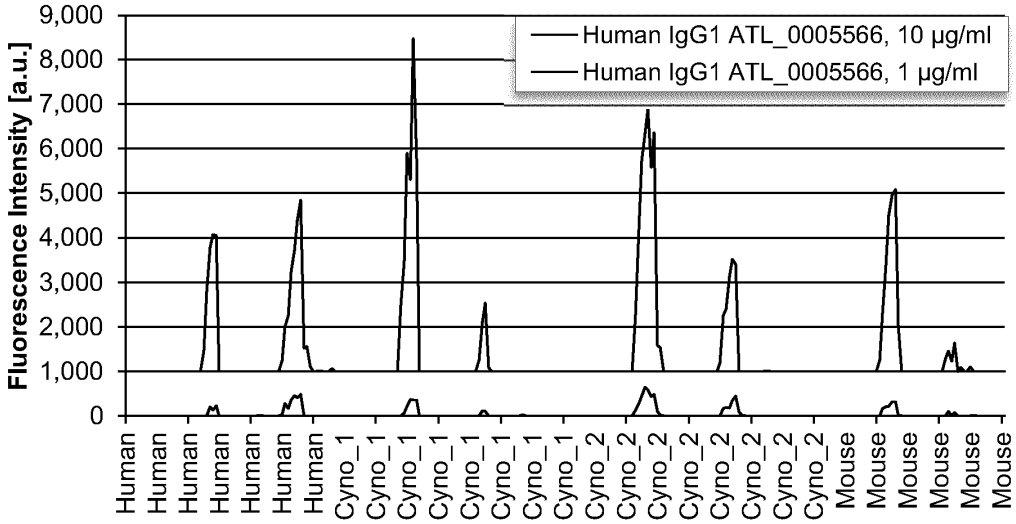
CYNO_2

MATLEKLMKAFESLKSFQQ**QQQQQQQQQQPPPPPPPPPPPQLPQ**PPQ**AQPMLPQPQPPPP PPPPPP**GPAVAEEPLHRPKKELSATKKDRVNH

MOUSE

MATLEKLMKAFESLKSFQQ**QQQQQPPPQAPPPPPPPPPPQPPQPPPQGQPPPPPPPLP**GPA EEPLHR

Fig. 7



HUMAN

MATLEKLMKAFESLKSFQQQQQQQQQ**QQQQQQQQPPPPPPPPPPP**PQLPQPP**PQAQPLLPQPQP PPPPPPPPPGPA**VAEEPLHR

CYNO_1

MATLEKLMKAFESLKSFQQQ**QQQQQQQQPPPPPPPPPPP**PQLPQP**PQAQPMLPQPQPPPPPP R**HHPARLWLRSRCTDQRKNFQLPRKTV

CYNO_2

MATLEKLMKAFESLKSFQQQ**QQQQQQQQQPPPPPPPPPPPQL**PQPP**QAQPMLPQPQPPPPP PPPPPG**PAVAEEPLHRPKKELSATKKDRVNH

MOUSE

MATLEKLMKAFESLKSFQQ**QQQQQPPPQAPPPPPPPPPPQPPQPPPQGQPPPPPPPLP**GPAE EPLHR

Fig. 8

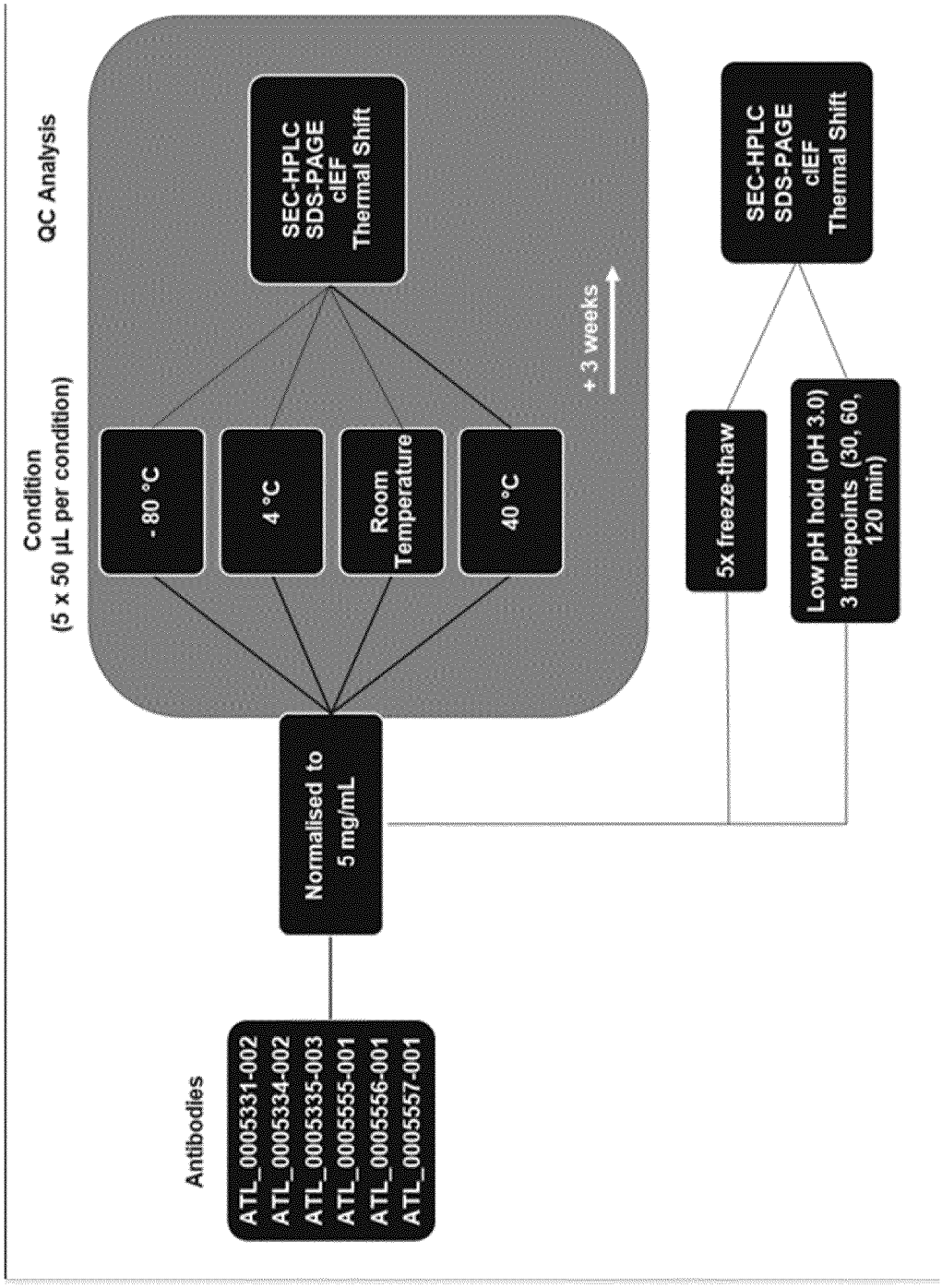

Antibodies
ATL_0005331-002
ATL_0005334-002
ATL_0005335-003
ATL_0005555-001
ATL_0005556-001
ATL_0005557-001
Normalised to 5 mg/mL
Condition (5 x 50 µL per condition)
- 80 °C
4 °C
Room Temperature
40 °C
+ 3 weeks
QC Analysis
SEC-HPLC
SDS-PAGE
cIEF
Thermal Shift
5x freeze-thaw
Low pH hold (pH 3.0) 3 timepoints (30, 60, 120 min)
SEC-HPLC
SDS-PAGE
cIEF
Thermal Shift

Fig. 9

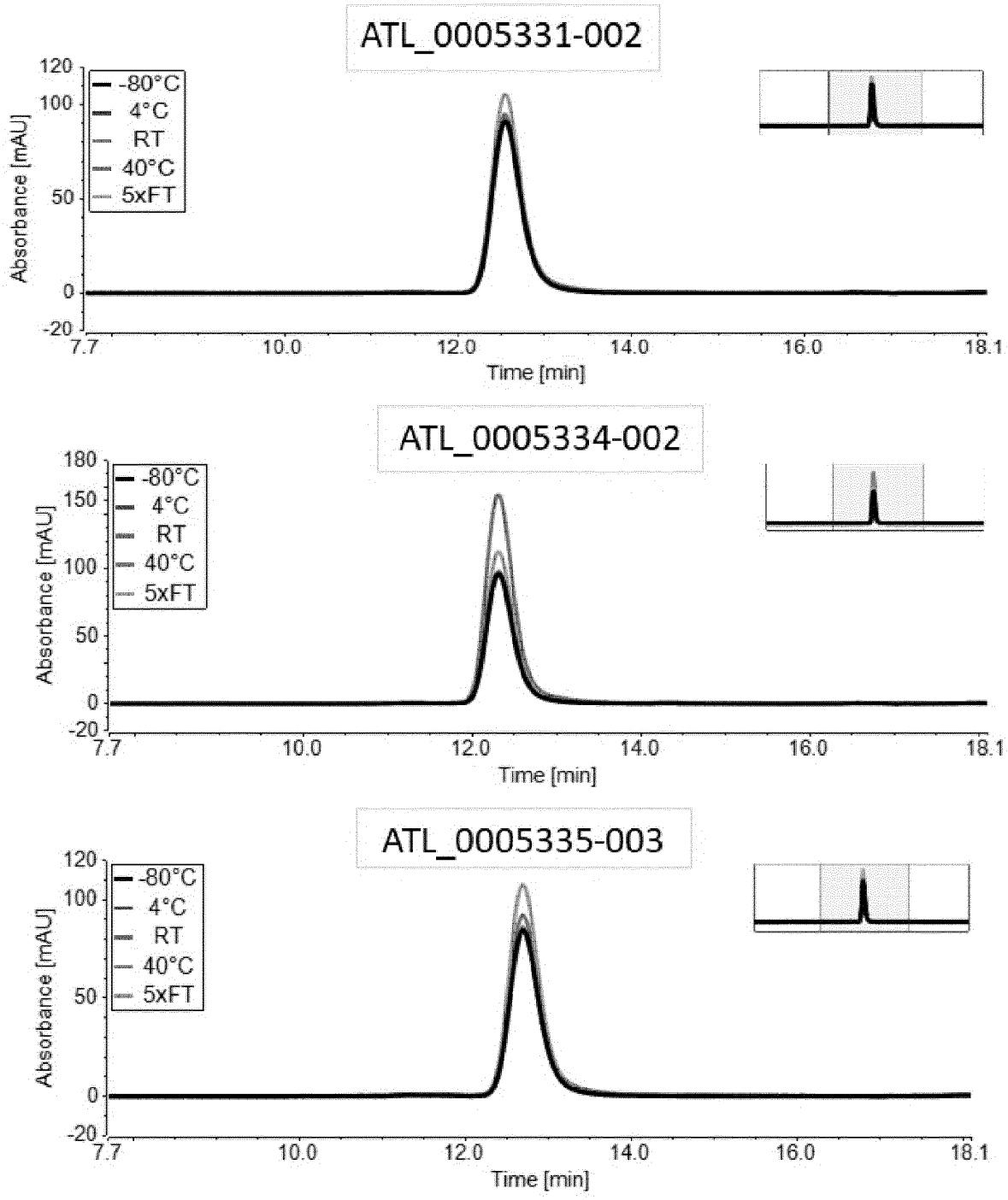

ATL_0005331-002
-80°C
4°C
RT
40°C
5xFT
Absorbance [mAU]
Time [min]
ATL_0005334-002
-80°C
4°C
RT
40°C
5xFT
Absorbance [mAU]
Time [min]
ATL_0005335-003
-80°C
4°C
RT
40°C
5xFT
Absorbance [mAU]
Time [min]

Fig.10A

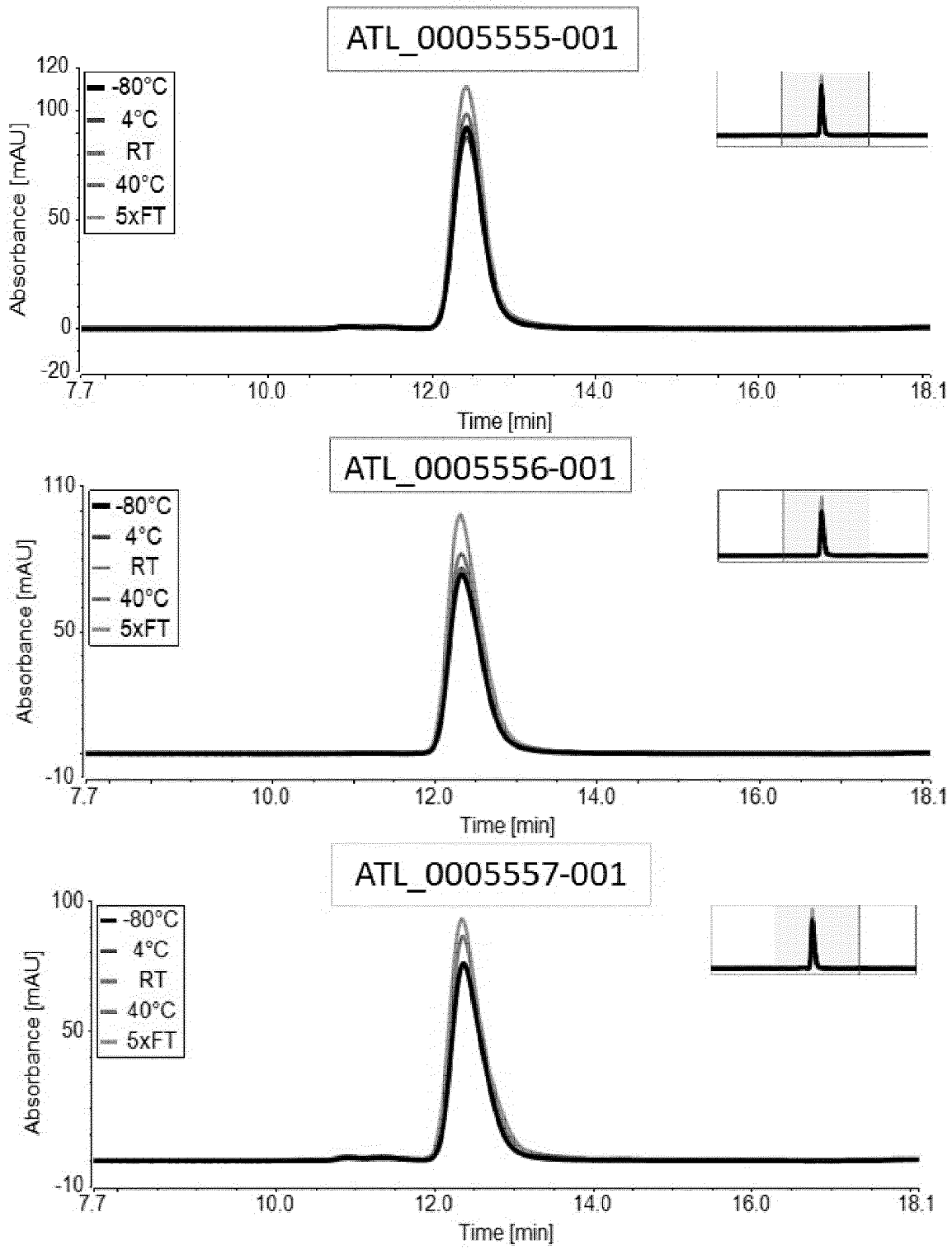

ATL_0005555-001
-80°C
4°C
RT
40°C
5xFT
Absorbance [mAU]
120
100
50
0
-20
7.7
10.0
12.0
14.0
16.0
18.1
Time [min]
ATL_0005556-001
-80°C
4°C
RT
40°C
5xFT
Absorbance [mAU]
110
50
-10
7.7
10.0
12.0
14.0
16.0
18.1
Time [min]
ATL_0005557-001
-80°C
4°C
RT
40°C
5xFT
Absorbance [mAU]
100
50
-10
7.7
10.0
12.0
14.0
16.0
18.1
Time [min]

Fig.10B

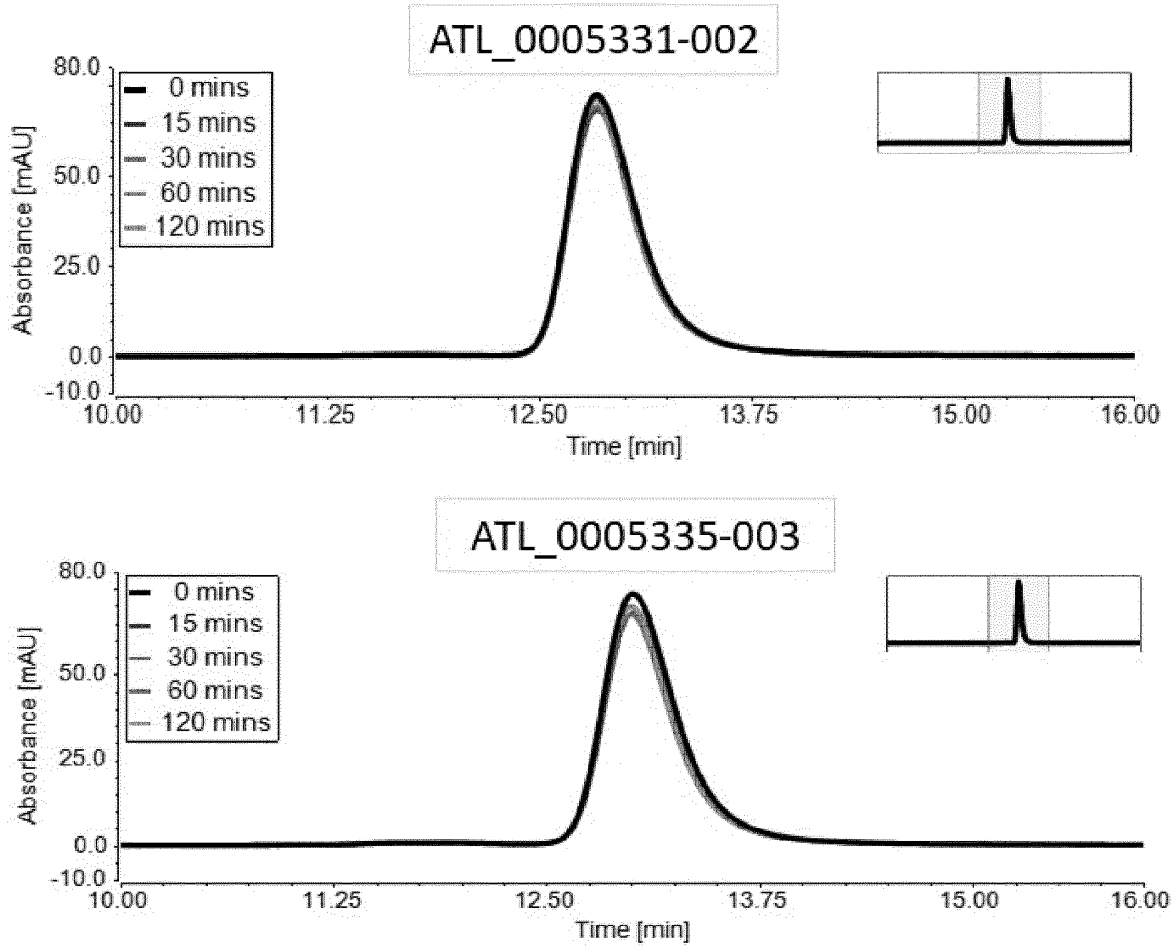

ATL_0005331-002
0 mins
15 mins
30 mins
60 mins
120 mins
Absorbance [mAU]
80.0
50.0
25.0
0.0
-10.0
10.00
11.25
12.50
13.75
15.00
16.00
Time [min]
ATL_0005335-003
0 mins
15 mins
30 mins
60 mins
120 mins
Absorbance [mAU]
80.0
50.0
25.0
0.0
-10.0
10.00
11.25
12.50
13.75
15.00
16.00
Time [min]

Fig. 11

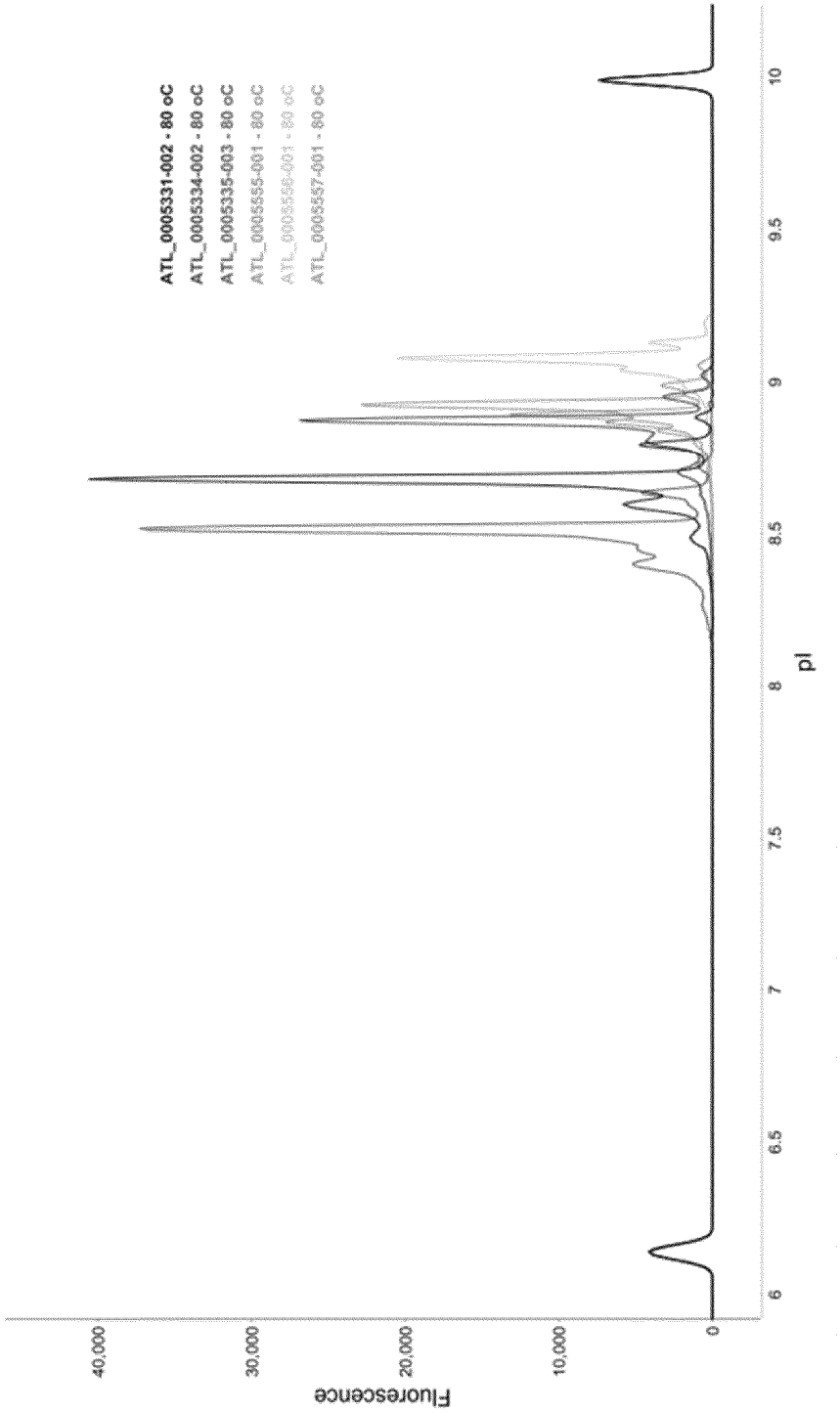

ATL_0005331-002 - 80 oC
ATL_0005334-002 - 80 oC
ATL_0005335-003 - 80 oC
ATL_0005555-001 - 80 oC
ATL_0005556-001 - 80 oC
ATL_0005557-001 - 80 oC
Fluorescence
40,000
30,000
20,000
10,000
0
6
6.5
7
7.5
8
8.5
9
9.5
10
pI

Fig.12A

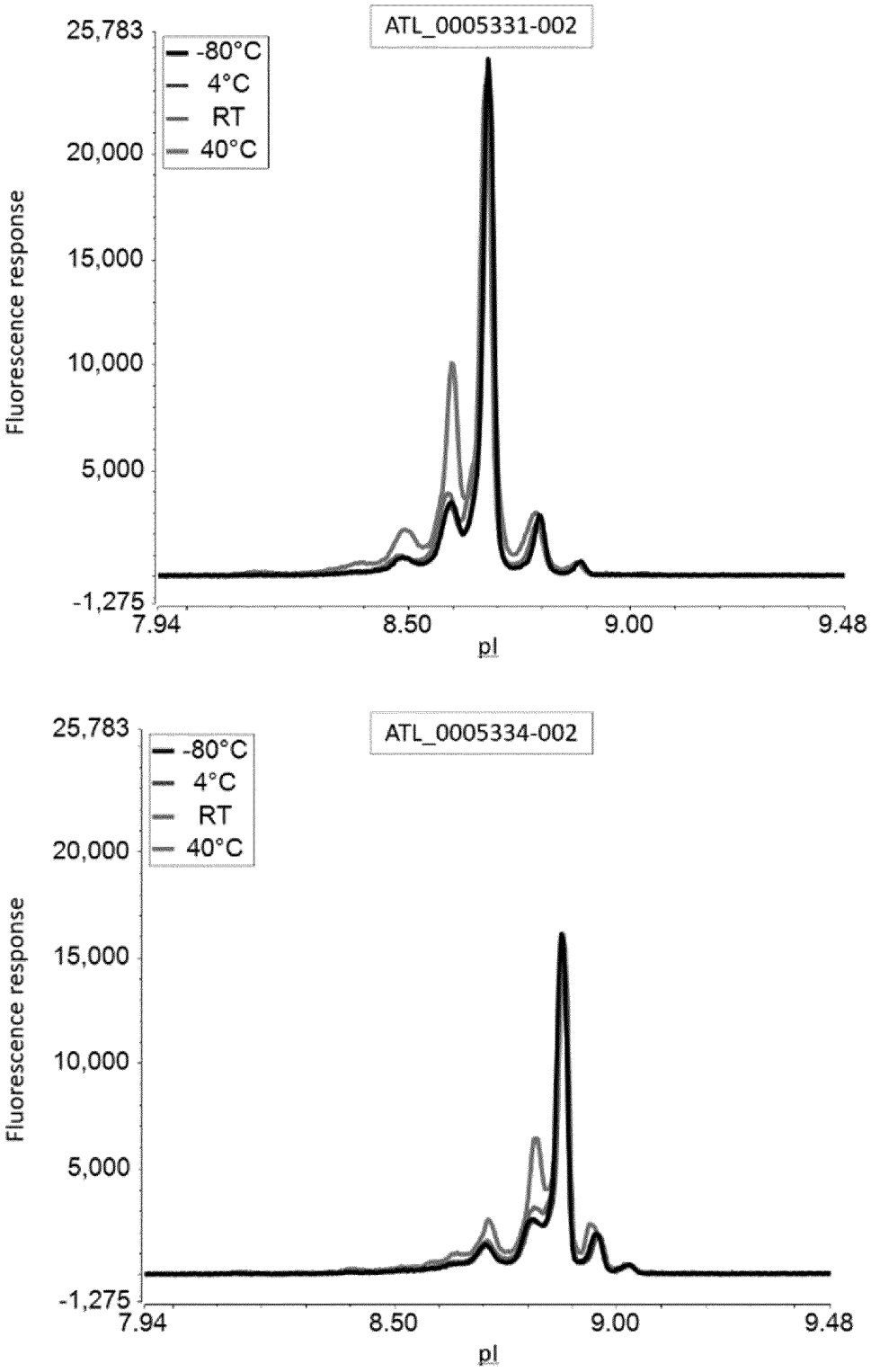

ATL_0005331-002
-80°C
4°C
RT
40°C
25,783
20,000
15,000
10,000
5,000
-1,275
Fluorescence response
7.94
8.50
9.00
9.48
pI
ATL_0005334-002
-80°C
4°C
RT
40°C
25,783
20,000
15,000
10,000
5,000
-1,275
Fluorescence response
7.94
8.50
9.00
9.48
pI

Fig.12B-1

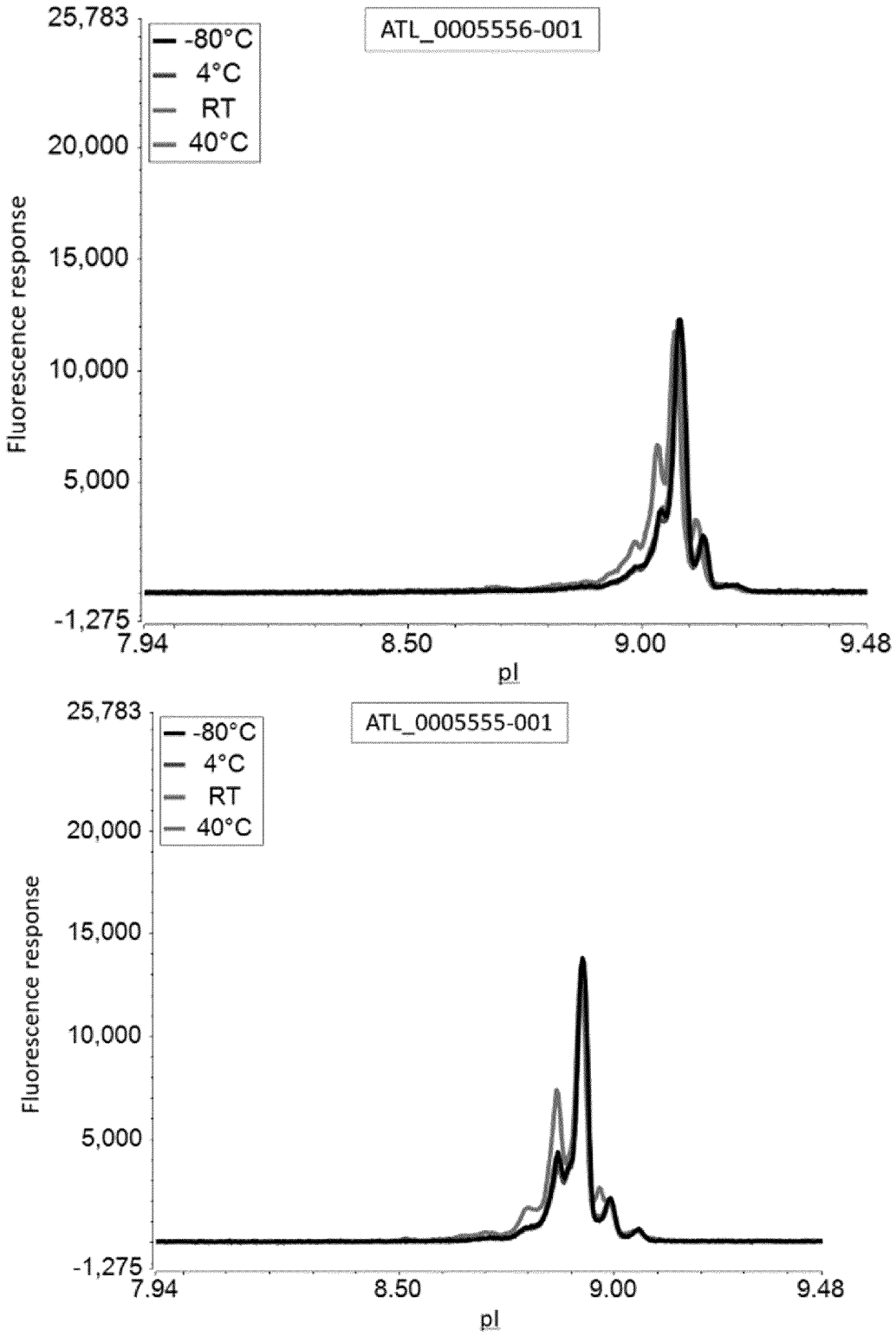

ATL_0005556-001
-80°C
4°C
RT
40°C
25,783
20,000
15,000
10,000
5,000
-1,275
Fluorescence response
7.94
8.50
9.00
9.48
pI
ATL_0005555-001
-80°C
4°C
RT
40°C
25,783
20,000
15,000
10,000
5,000
-1,275
Fluorescence response
7.94
8.50
9.00
9.48
pI

Fig.12B-2

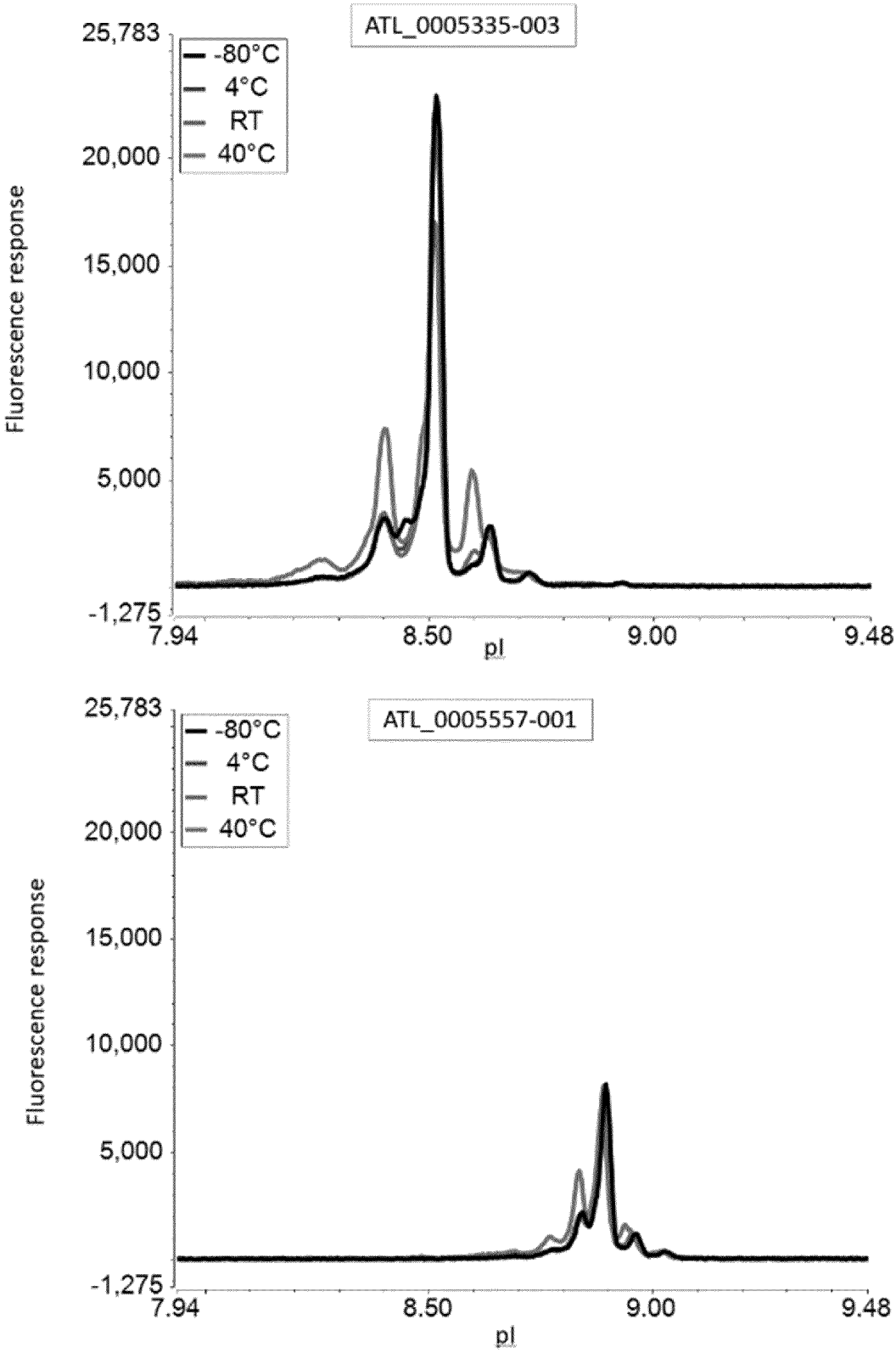

ATL_0005335-003
-80°C
4°C
RT
40°C
25,783
20,000
15,000
10,000
5,000
-1,275
Fluorescence response
7.94
8.50
9.00
9.48
pI
ATL_0005557-001
-80°C
4°C
RT
40°C
25,783
20,000
15,000
10,000
5,000
-1,275
Fluorescence response
7.94
8.50
9.00
9.48
pI

Fig.12B-3

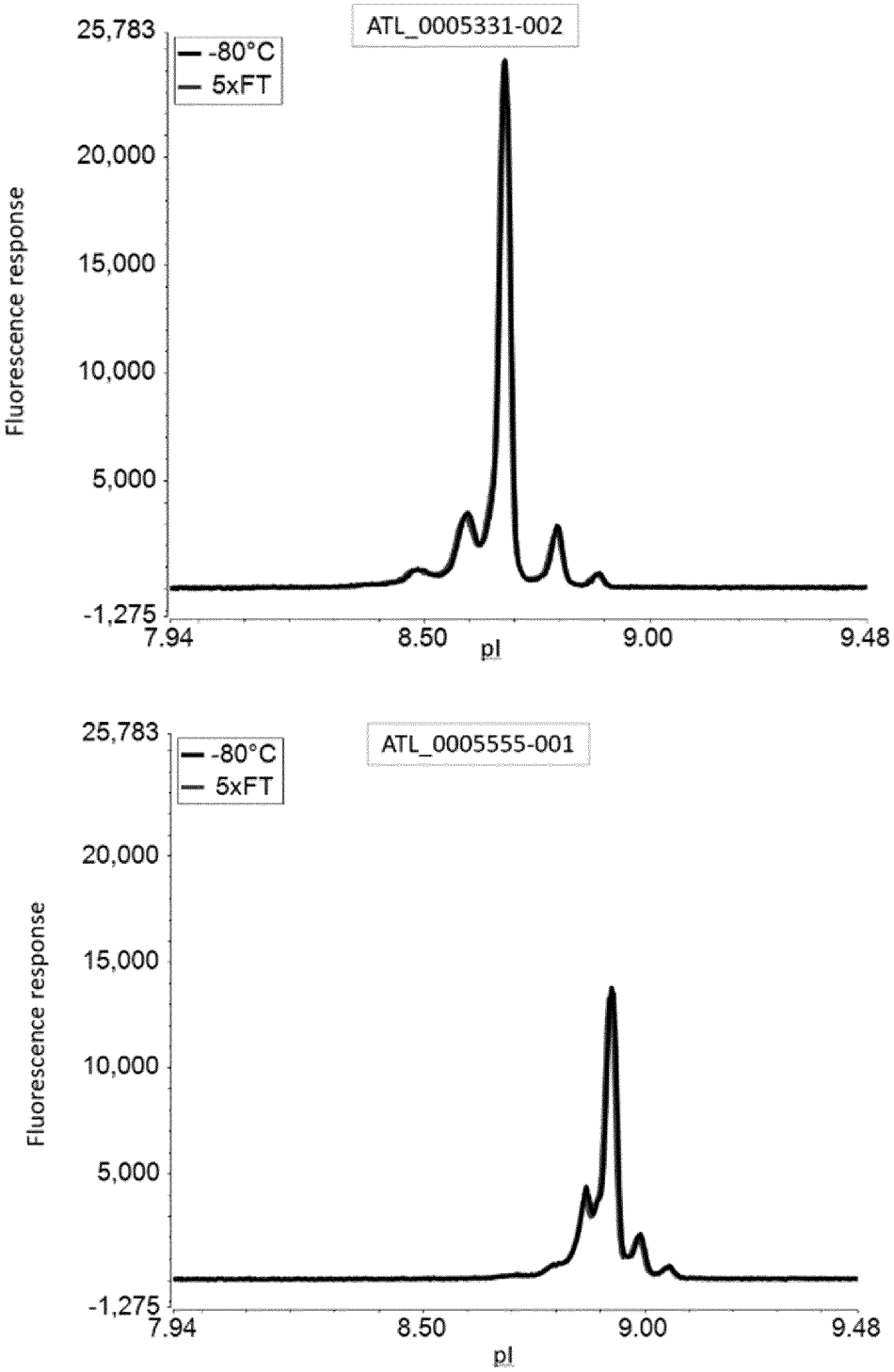

ATL_0005331-002
-80°C
5xFT
25,783
20,000
15,000
10,000
5,000
-1,275
Fluorescence response
7.94
8.50
9.00
9.48
pI
ATL_0005555-001
-80°C
5xFT
25,783
20,000
15,000
10,000
5,000
-1,275
Fluorescence response
7.94
8.50
9.00
9.48
pI

Fig. 12C-1

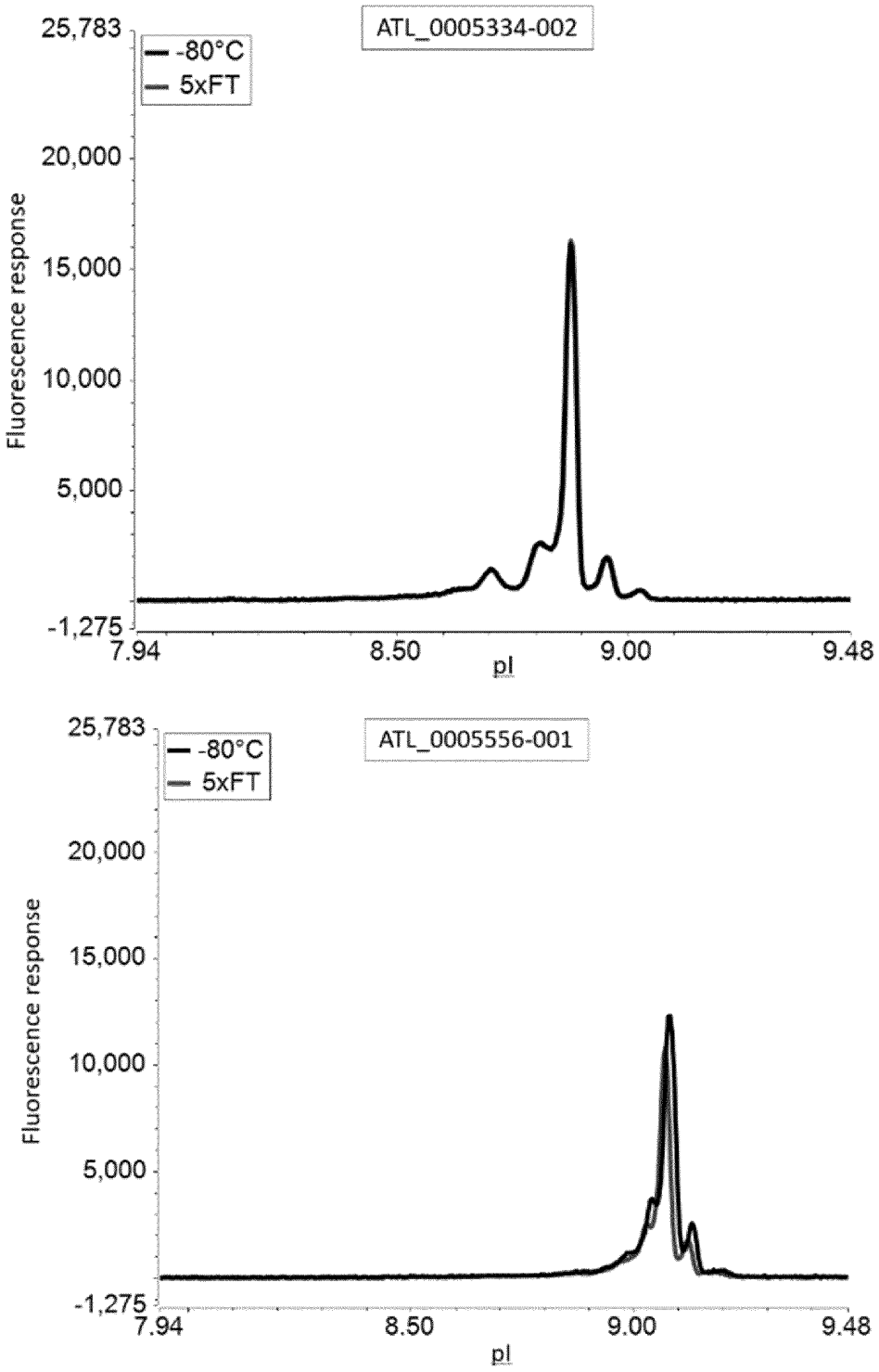

ATL_0005334-002
-80°C
5xFT
25,783
20,000
15,000
10,000
5,000
-1,275
Fluorescence response
7.94
8.50
9.00
9.48
pI
ATL_0005556-001
-80°C
5xFT
25,783
20,000
15,000
10,000
5,000
-1,275
Fluorescence response
7.94
8.50
9.00
9.48
pI

Fig. 12C-2

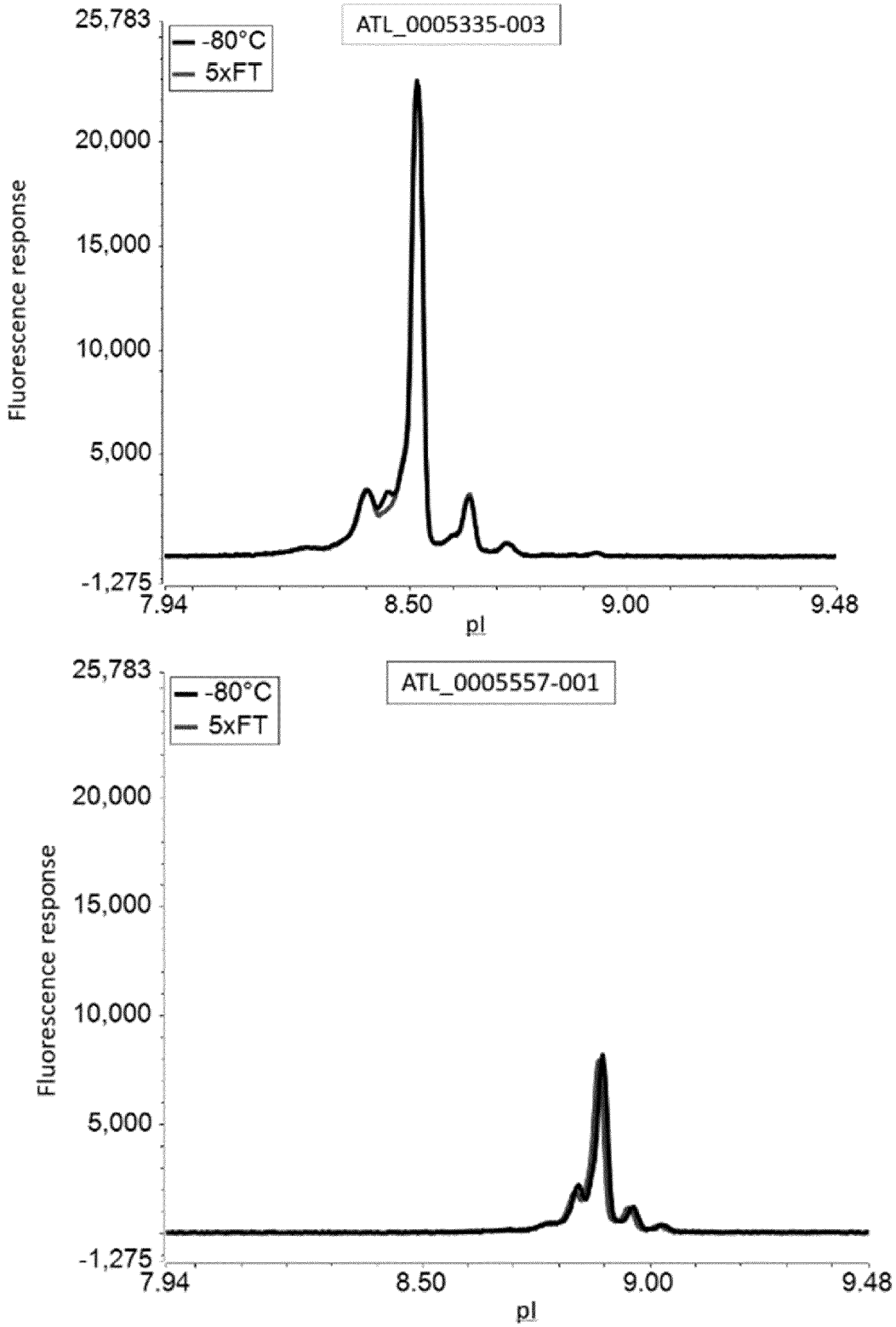

ATL_0005335-003
-80°C
5xFT
25,783
20,000
15,000
10,000
5,000
-1,275
Fluorescence response
7.94
8.50
9.00
9.48
pI
ATL_0005557-001
-80°C
5xFT
25,783
20,000
15,000
10,000
5,000
-1,275
Fluorescence response
7.94
8.50
9.00
9.48
pI

Fig. 12C-3

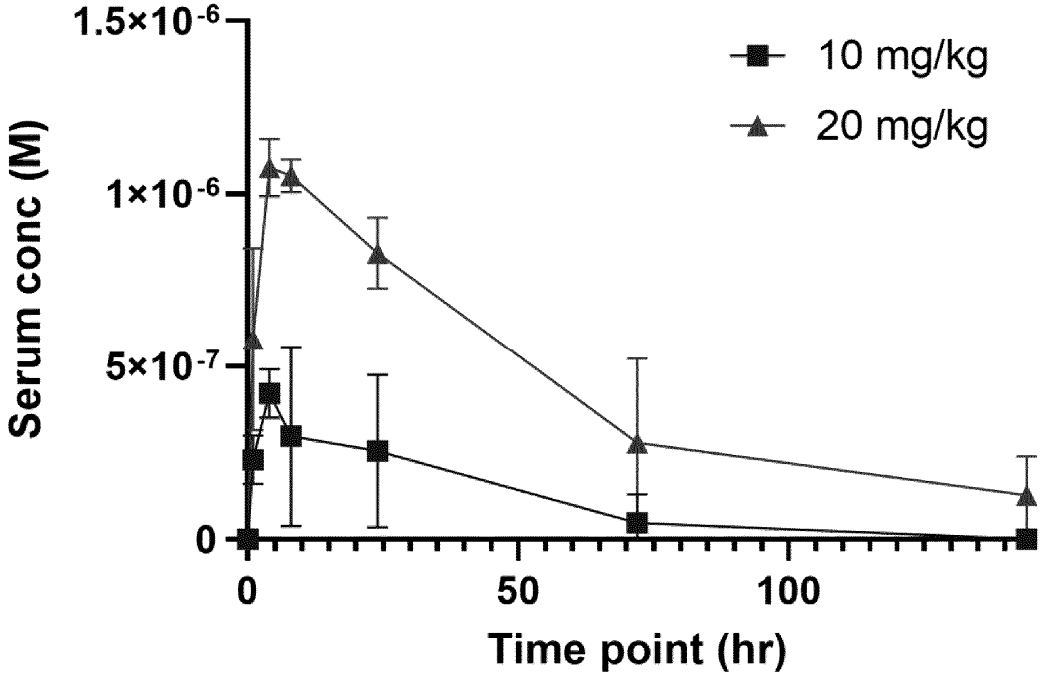

1.5×10-6
1×10-6
5×10-7
0
Serum conc (M)
10 mg/kg
20 mg/kg
0
50
100
Time point (hr)

Fig.13

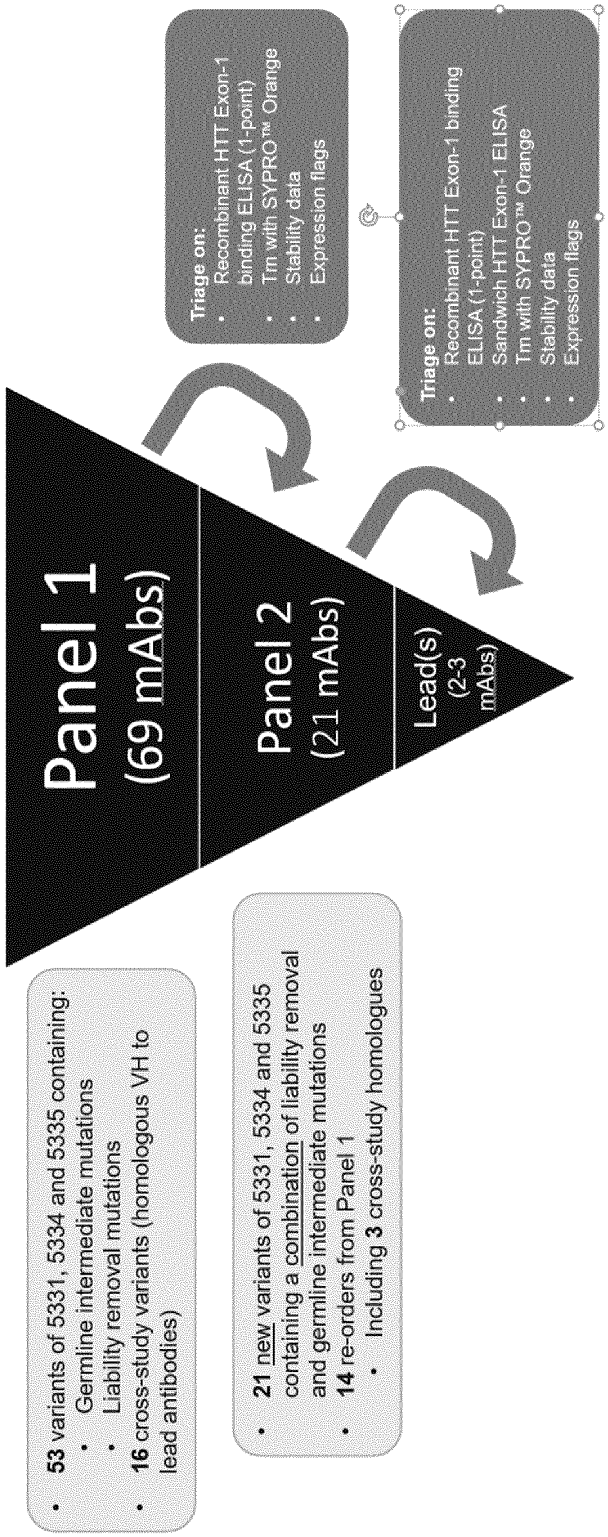

Panel 1
(69 mAbs)
Panel 2
(21 mAbs)
Lead(s)
(2-3
mAbs)
• 53 variants of 5331, 5334 and 5335 containing:
• Germline intermediate mutations
• Liability removal mutations
• 16 cross-study variants (homologous VH to lead antibodies)
• 21 new variants of 5331, 5334 and 5335 containing a combination of liability removal and germline intermediate mutations
• 14 re-orders from Panel 1
• Including 3 cross-study homologues
Triage on:
• Recombinant HTT Exon-1 binding ELISA (1-point)
• Tm with SYPRO™ Orange
• Stability data
• Expression flags
Triage on:
• Recombinant HTT Exon-1 binding ELISA (1-point)
• Sandwich HTT Exon-1 ELISA
• Tm with SYPRO™ Orange
• Stability data
• Expression flags

Fig. 14

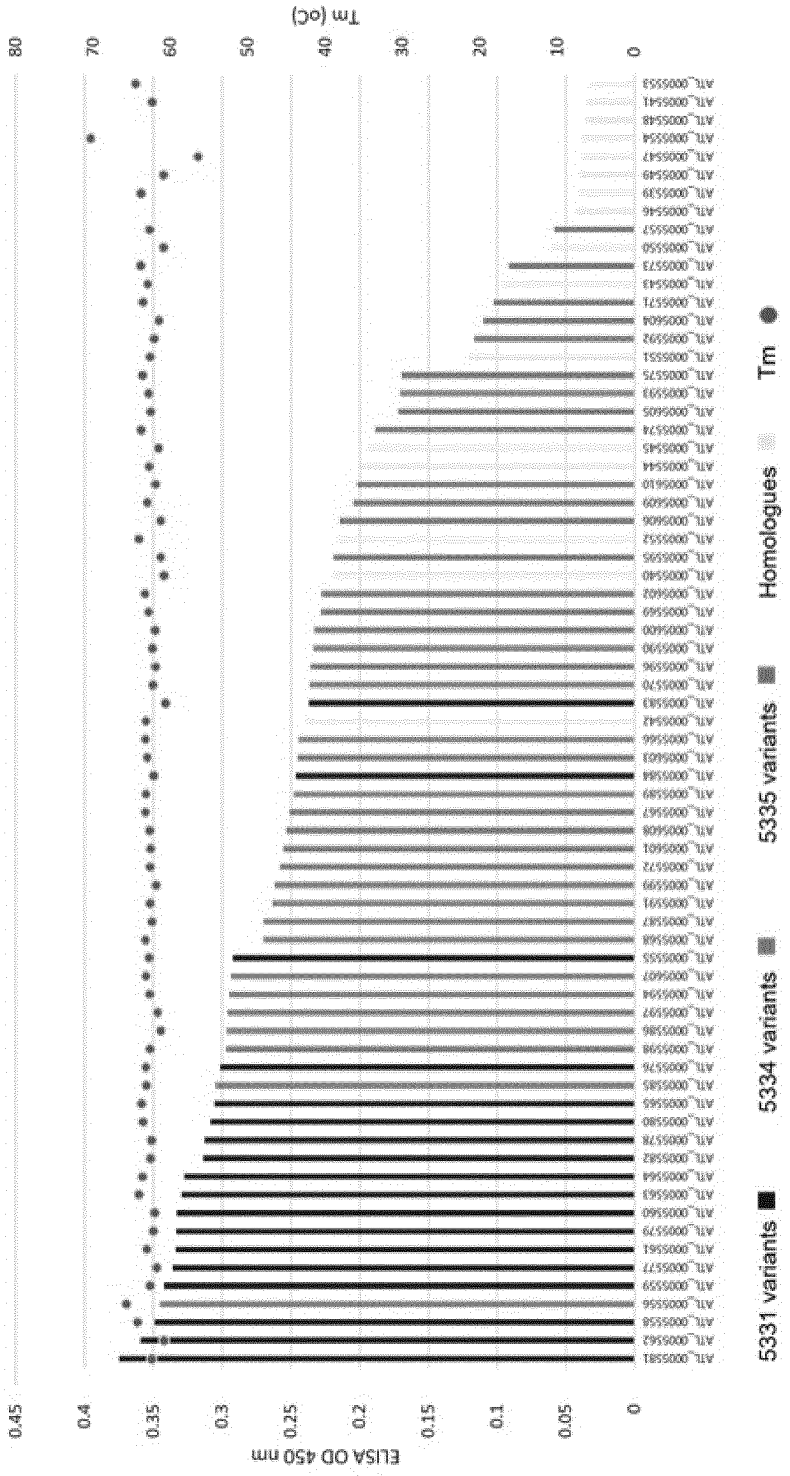

ELISA OD 450 nm
Tm (oC)
5331 variants
5334 variants
5335 variants
Homologues
Tm

Fig. 15

	ATL_0005895
Bottom	-0.05698
Top	0.6816
LogEC50	-8.527
HillSlope	0.7655
EC50	2.974e-009

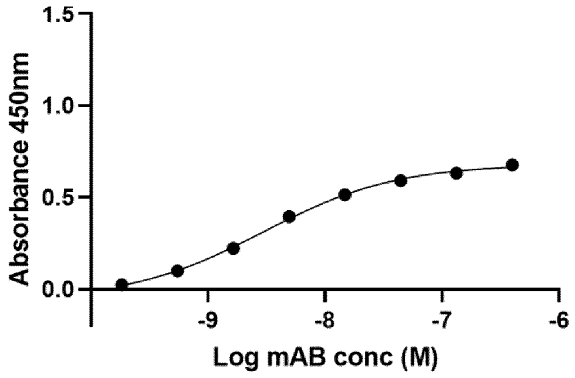


Fig.16A

	ATL_0005901
Bottom	-0.02020
Top	0.7104
LogEC50	-8.253
HillSlope	0.8102
EC50	5.588e-009

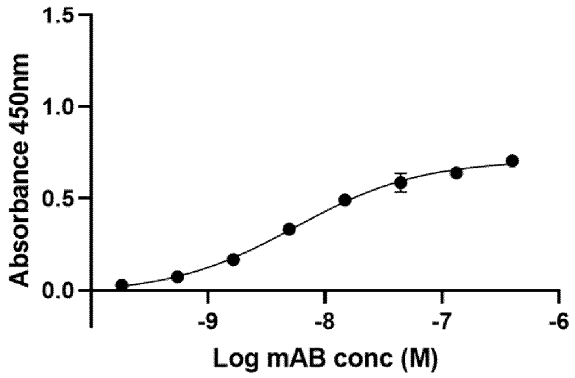


Fig.16B

	ATL_0005567
Bottom	-0.07271
Top	1.041
LogEC50	Fail. No top of curve
HillSlope	0.4813
EC50	Fail. No top of curve

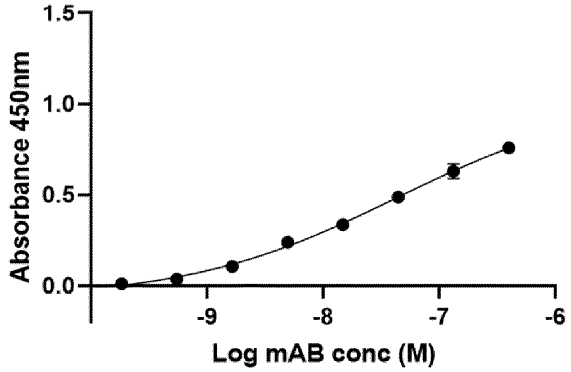


Fig.16C

	5895
Bottom	-0.01077
Top	0.9430
LogEC50	-8.408
HillSlope	1.603
EC50	3.908e-009

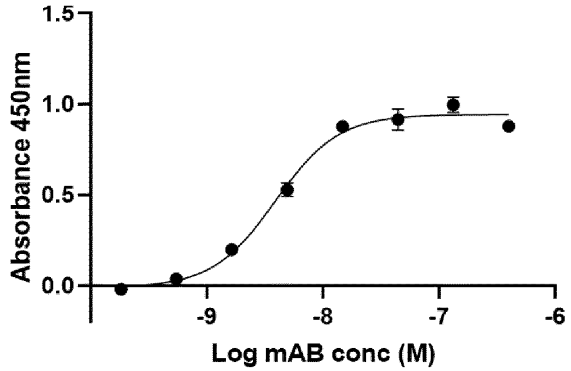


Fig.16D

	5901
Bottom	-0.01233
Top	0.9526
LogEC50	-8.345
HillSlope	1.536
EC50	4.519e-009

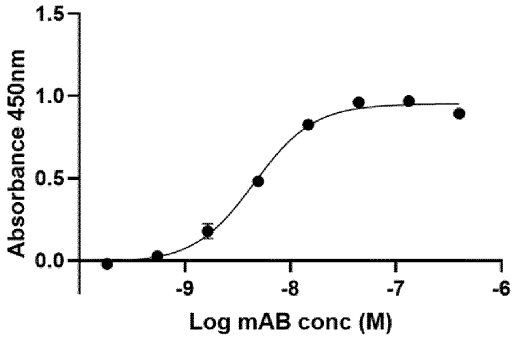


Fig.16E

	5567
Bottom	-0.04582
Top	0.7791
LogEC50	-8.016
HillSlope	0.9248
EC50	9.635e-009

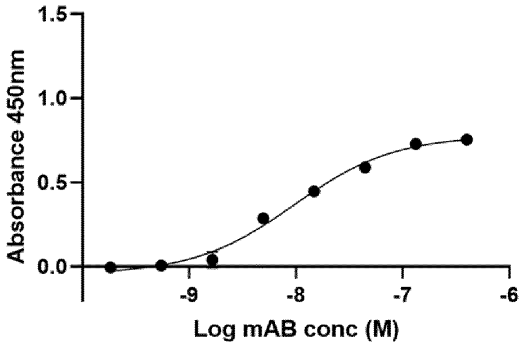


Fig.16F

	5059
Bottom	-0.007806
Top	0.9844
LogEC50	-7.714
HillSlope	1.019
EC50	1.931e-008

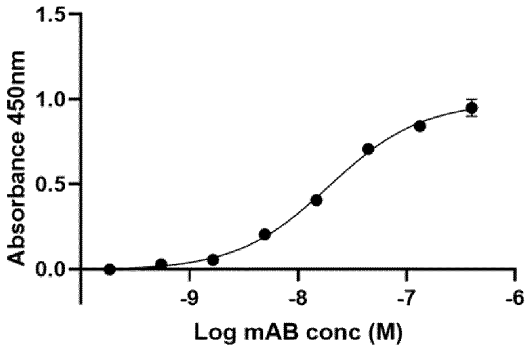


Fig.16G

	5895
Bottom	0.01685
Top	1.298
LogEC50	-8.357
HillSlope	1.578
EC50	4.392e-009

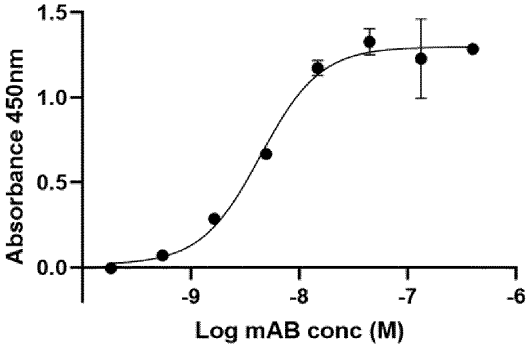


Fig.16H

	5901
Bottom	-0.009701
Top	1.191
LogEC50	-8.326
HillSlope	1.593
EC50	4.726e-009

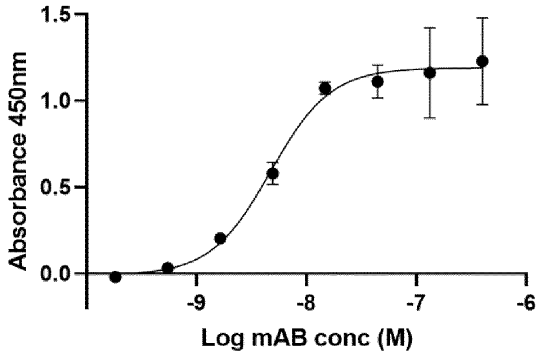


Fig.16I

	5567
Bottom	-0.01397
Top	1.215
LogEC50	-8.226
HillSlope	1.210
EC50	5.946e-009

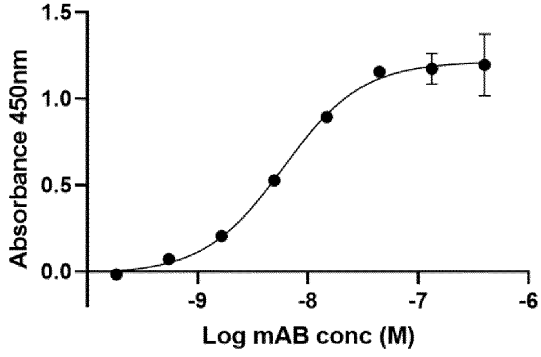


Fig.16J

	ATL_0005895
Bottom	0.1084
Top	1.101
LogEC50	-9.136
HillSlope	1.665
EC50	7.309e-010

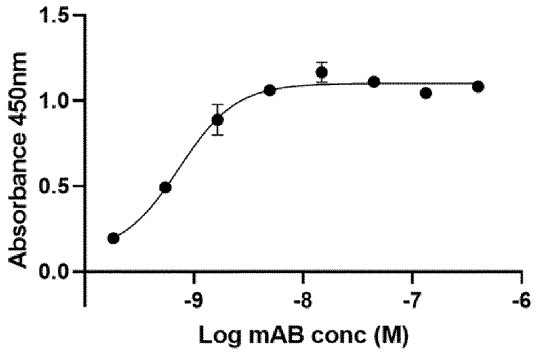


Fig.16K

	ATL_0005901
Bottom	0.1808
Top	1.103
LogEC50	-8.902
HillSlope	1.840
EC50	1.253e-009

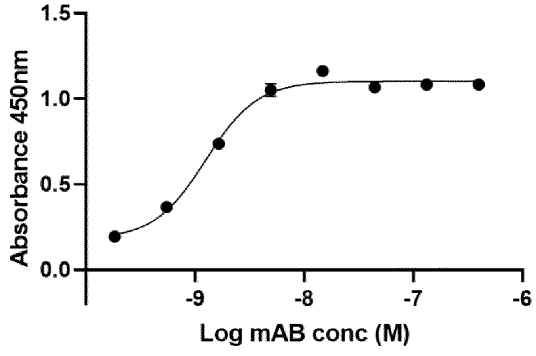


Fig.16L

	ATL_0005567
Bottom	0.01267
Top	1.083
LogEC50	-8.061
HillSlope	1.665
EC50	8.696e-009

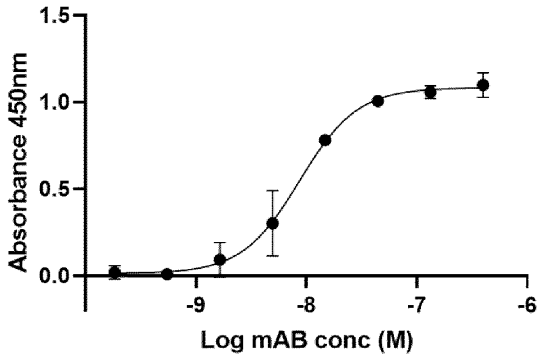


Fig.16M

	ATL_0005059-005
Bottom	-0.03325
Top	1.226
LogEC50	-7.742
HillSlope	1.049
EC50	1.810e-008

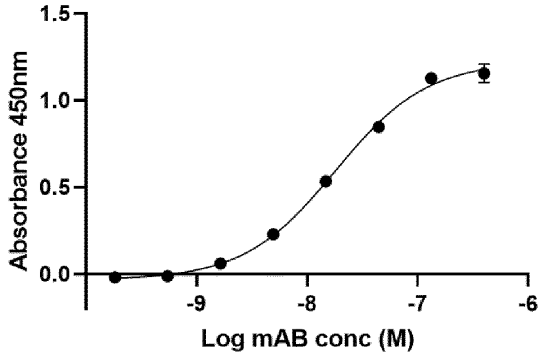


Fig.16N

	5895
Bottom	0.06546
Top	1.190
LogEC50	-8.417
HillSlope	2.110
EC50	3.831e-009

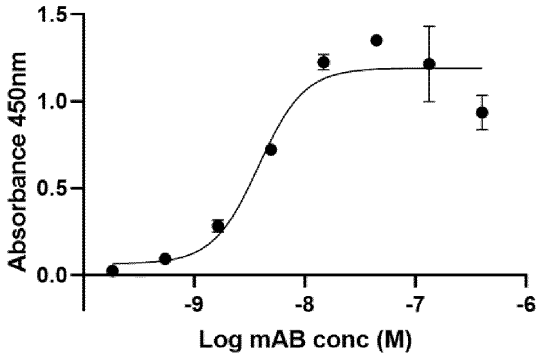


Fig.16O

	5901
Bottom	0.08123
Top	1.138
LogEC50	Fail. Poor curve
HillSlope	2.386
EC50	Fail. Poor curve

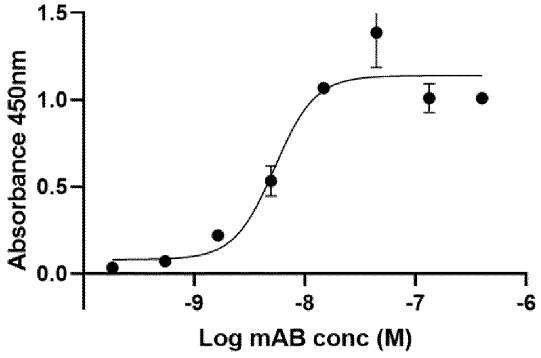


Fig.16P

	5567
Bottom	-0.009242
Top	1.379
LogEC50	-8.184
HillSlope	1.265
EC50	6.548e-009

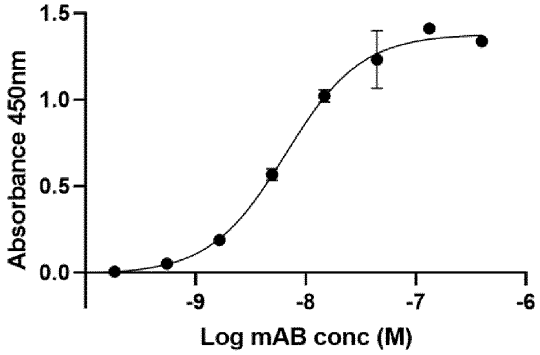


Fig.16Q

	5059
Bottom	0.1737
Top	1.411
LogEC50	-7.790
HillSlope	1.333
EC50	1.621e-008

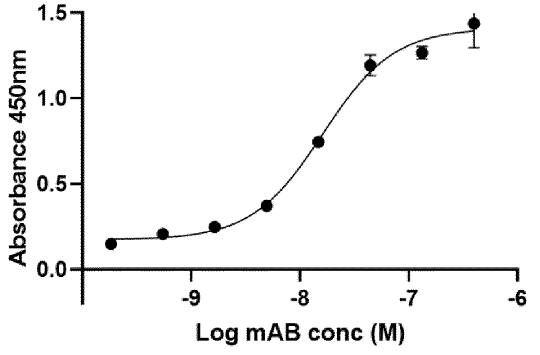


Fig.16R

	5895
Bottom	0.05283
Top	1.062
LogEC50	-8.495
HillSlope	1.719
EC50	3.200e-009

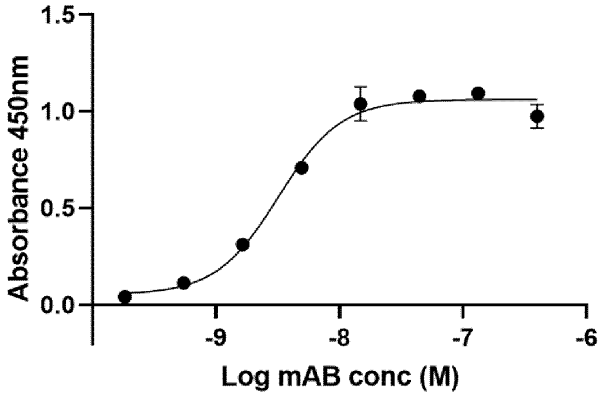


Fig.16S

	5901
Bottom	0.05472
Top	1.066
LogEC50	-8.338
HillSlope	1.731
EC50	4.590e-009

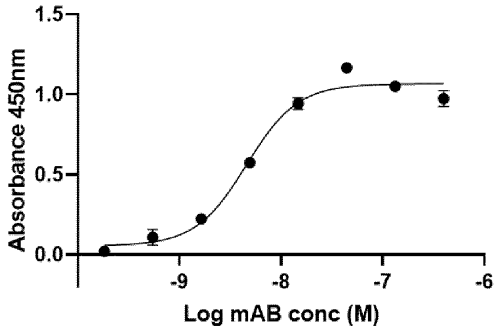


Fig.16T

	5567
Bottom	0.05472
Top	1.066
LogEC50	-8.338
HillSlope	1.731
EC50	4.590e-009

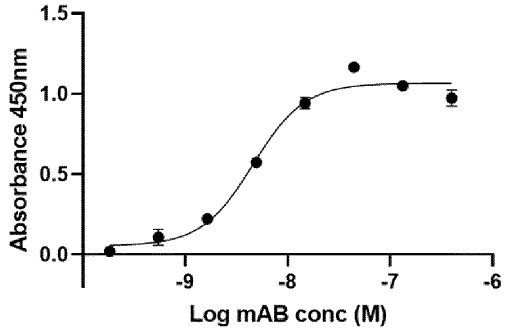


Fig.16U

	5059
Bottom	0.02930
Top	0.9633
LogEC50	-7.757
HillSlope	2.226
EC50	1.751e-008

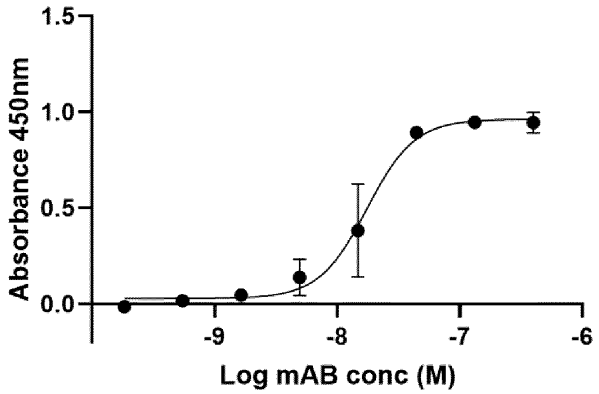


Fig.16V

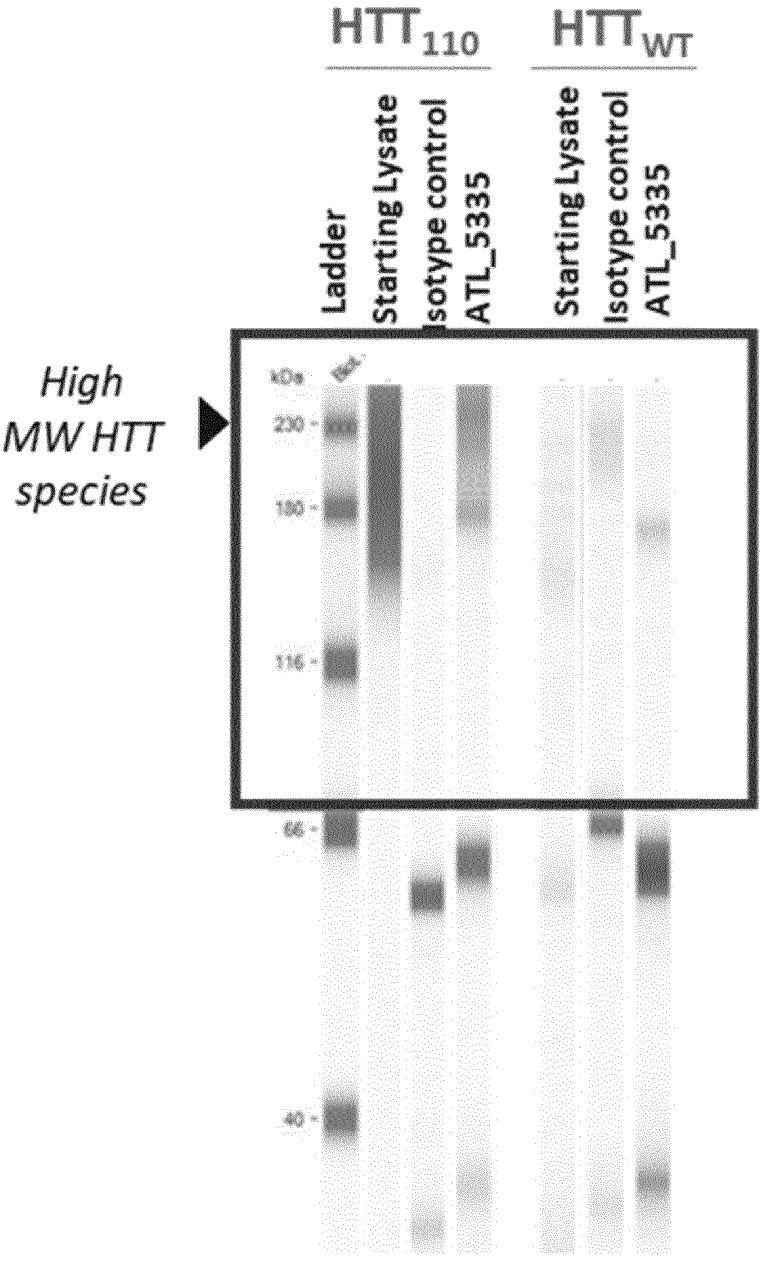

HTT110
HTTWT
Ladder
Starting Lysate
Isotype control ATL_5335
Starting Lysate
Isotype control ATL_5335
High MW HTT species
kDa
230
180
116
66
40

Fig.17A

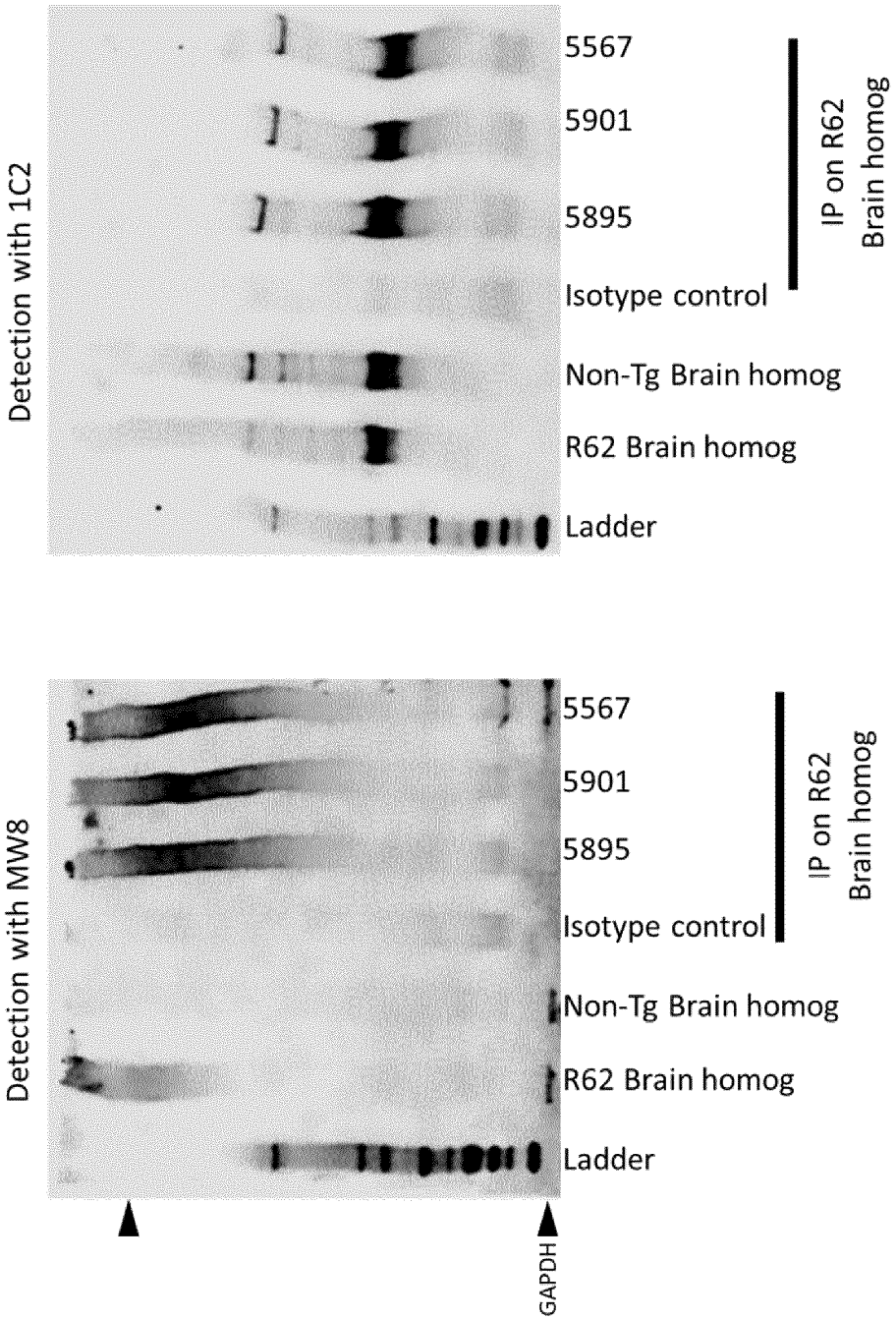

Detection with 1C2
5567
5901
5895
Isotype control
IP on R62 Brain homog
Non-Tg Brain homog
R62 Brain homog
Ladder
Detection with MW8
5567
5901
5895
Isotype control
IP on R62 Brain homog
Non-Tg Brain homog
R62 Brain homog
Ladder
GAPDH

Fig.17B

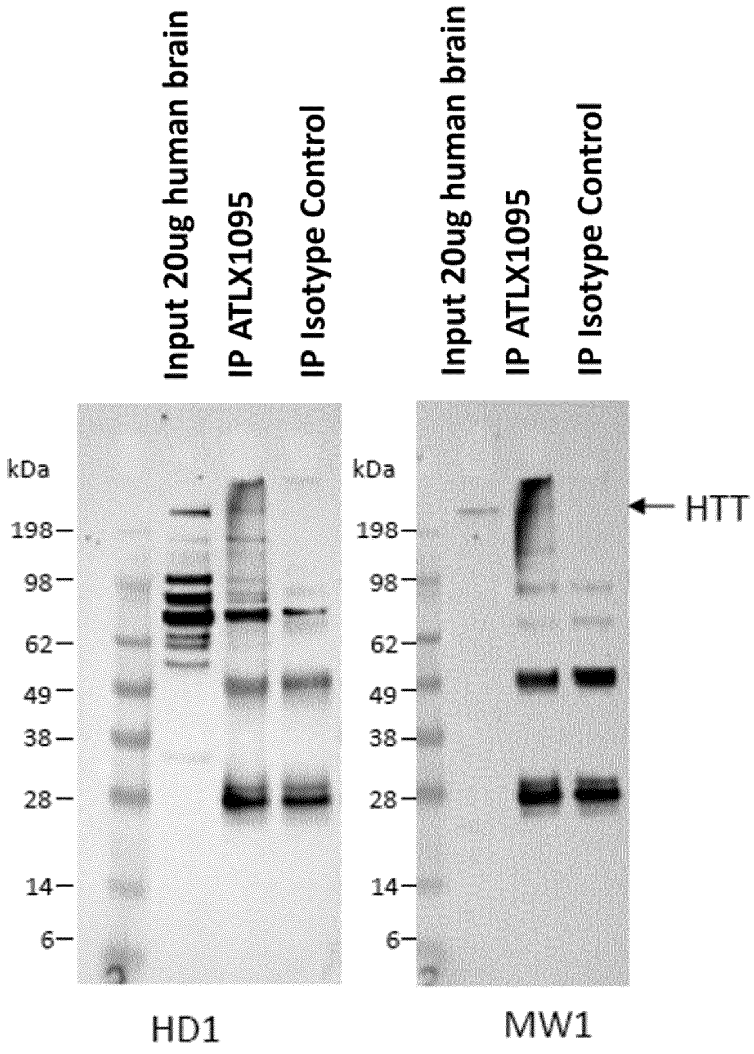

Input 20ug human brain
IP ATLX1095
IP Isotype Control
Input 20ug human brain
IP ATLX1095
IP Isotype Control
kDa
198
98
62
49
38
28
14
6
kDa
198
98
62
49
38
28
14
6
HTT
HD1
MW1

Fig.17C

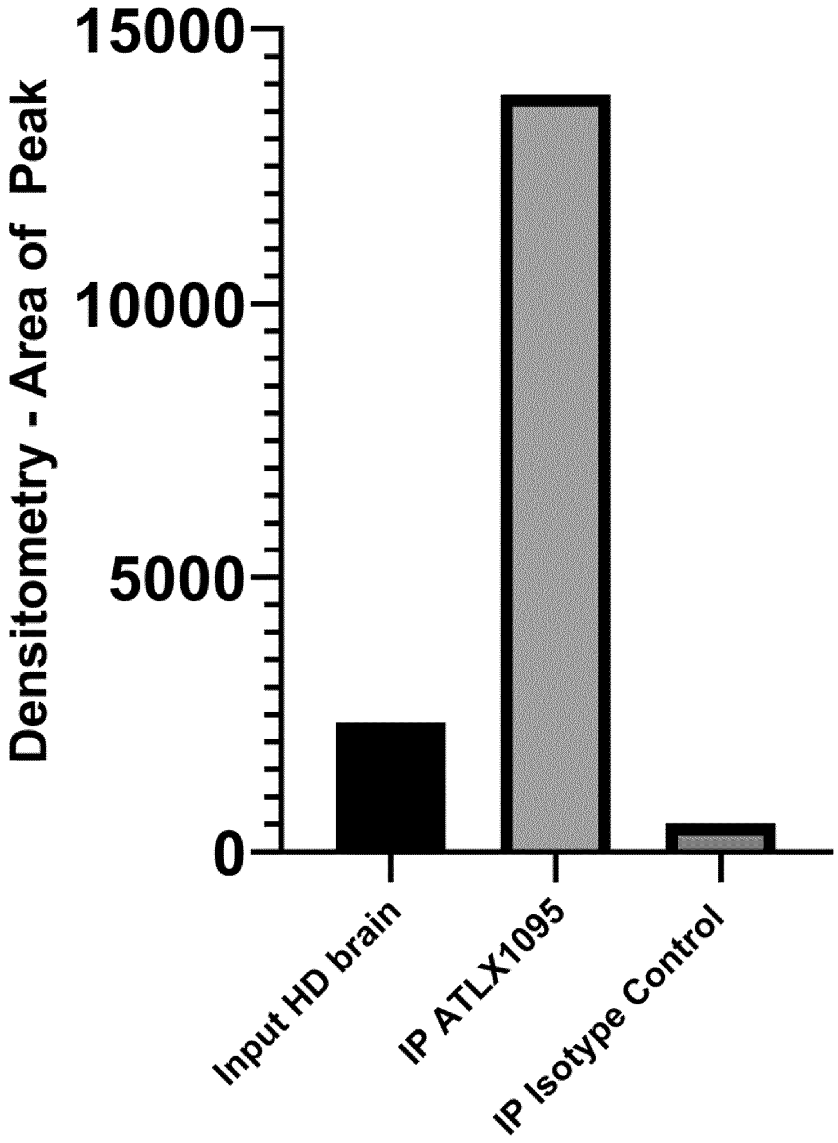

15000
10000
5000
0
Densitometry - Area of Peak
Input HD brain
IP ATLX1095
IP Isotype Control

Fig.17D

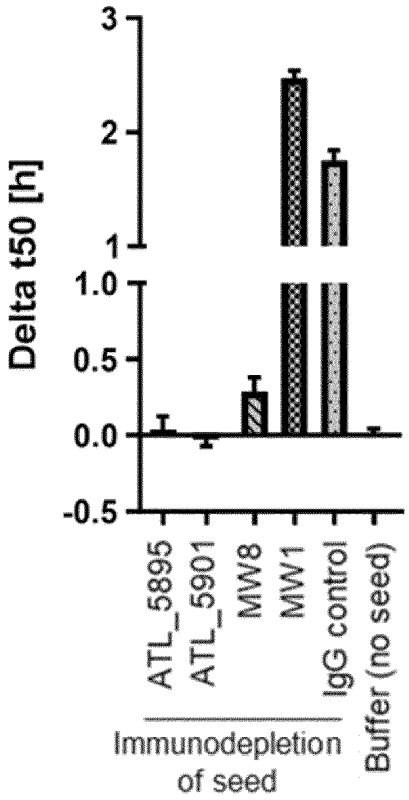

Delta t50 [h]
3
2
1
1.0
0.5
0.0
-0.5
ATL_5895
ATL_5901
MW8
MW1
IgG control
Buffer (no seed)
Immunodepletion of seed

Fig. 18A

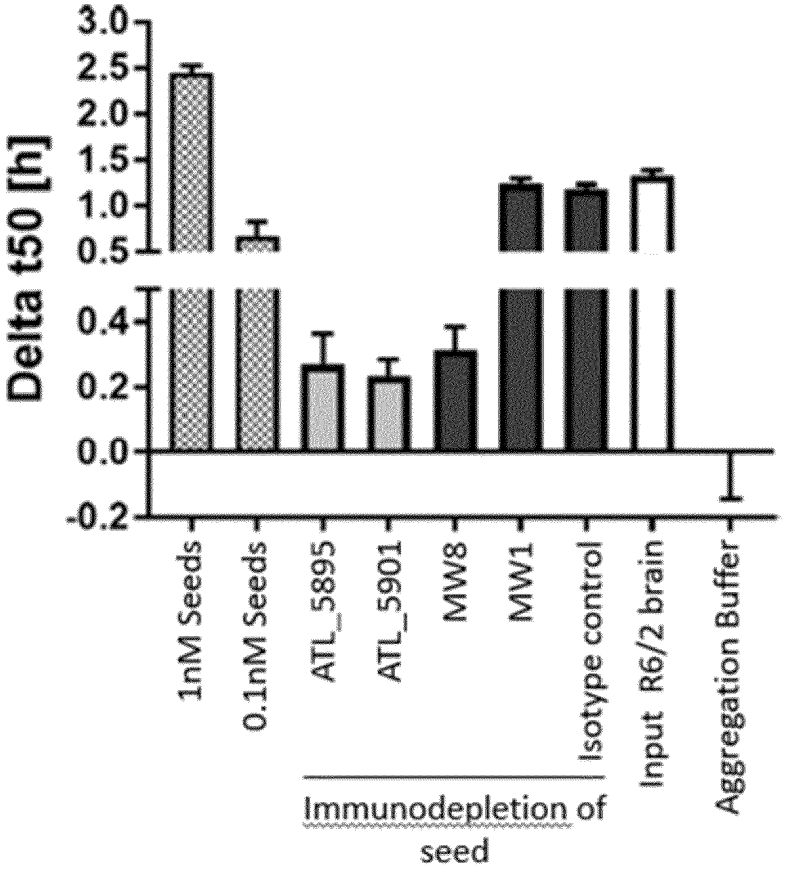

Delta t50 [h]
3.0
2.5
2.0
1.5
1.0
0.5
0.4
0.2
0.0
-0.2
1nM Seeds
0.1nM Seeds
ATL_5895
ATL_5901
MW8
MW1
Isotype control
Input R6/2 brain
Aggregation Buffer
Immunodepletion of seed

Fig. 18B

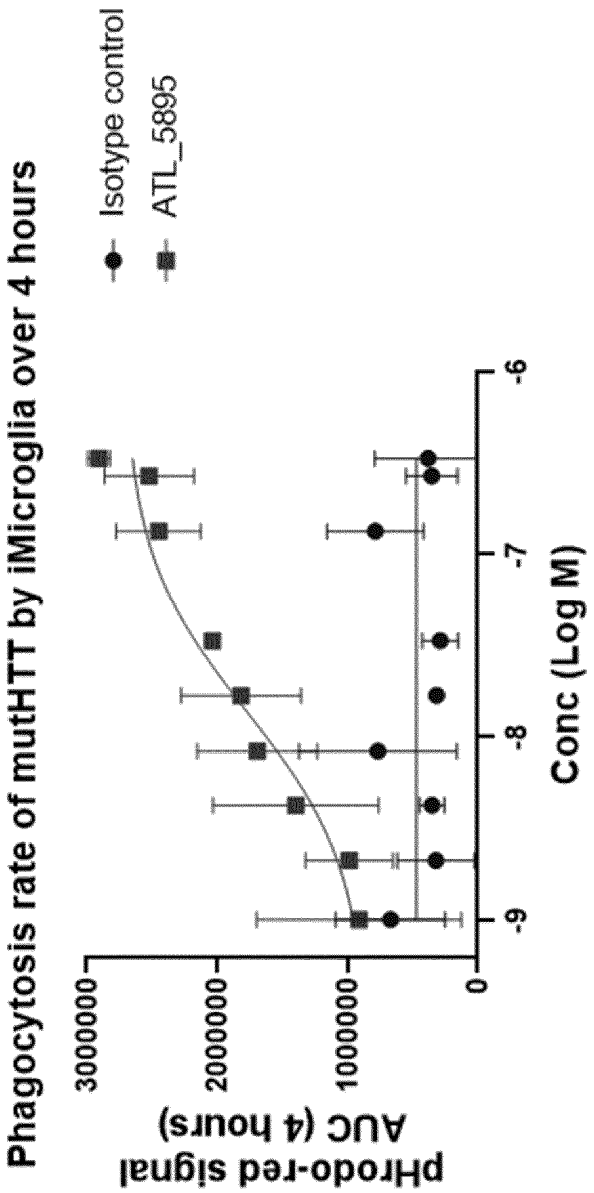

Phagocytosis rate of mutHTT by iMicroglia over 4 hours
Isotype control
ATL_5895
pHrodo-red signal AUC (4 hours)
3000000
2000000
1000000
0
-9
-8
-7
-6
Conc (Log M)

Fig.19

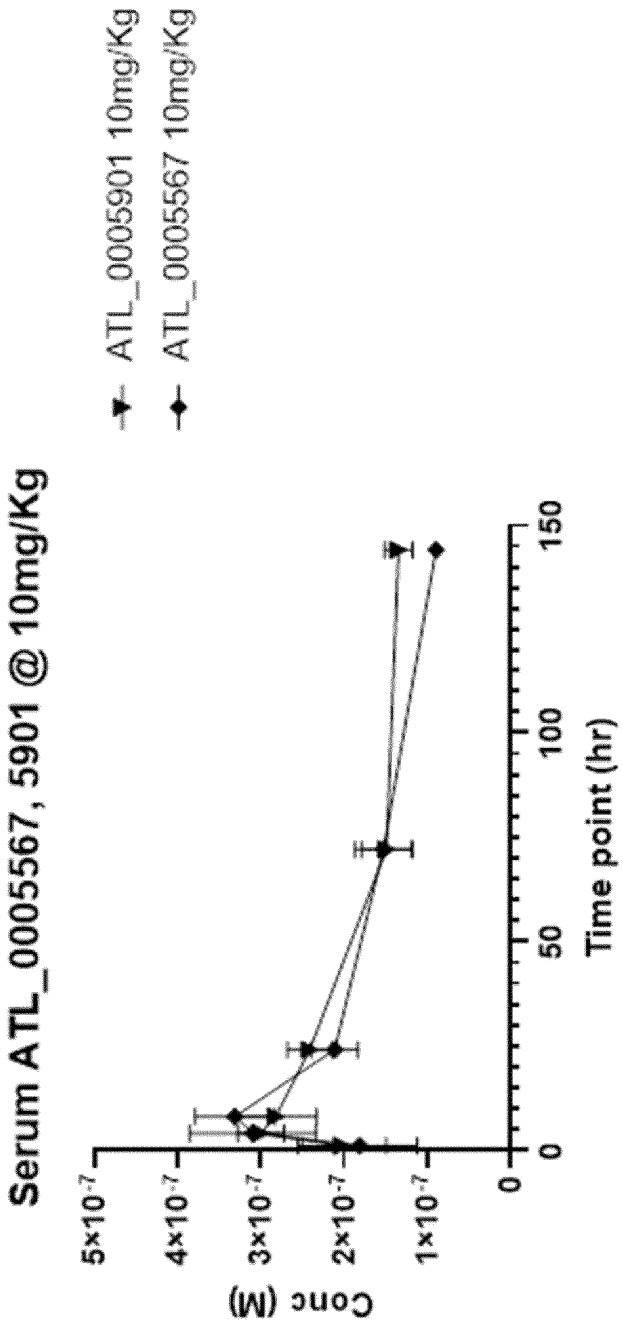

Serum ATL_0005567, 5901 @ 10mg/Kg
ATL_0005901 10mg/Kg
ATL_0005567 10mg/Kg
Conc (M)
5×10⁻⁷
4×10⁻⁷
3×10⁻⁷
2×10⁻⁷
1×10⁻⁷
0
0
50
100
150
Time point (hr)

Fig.20A

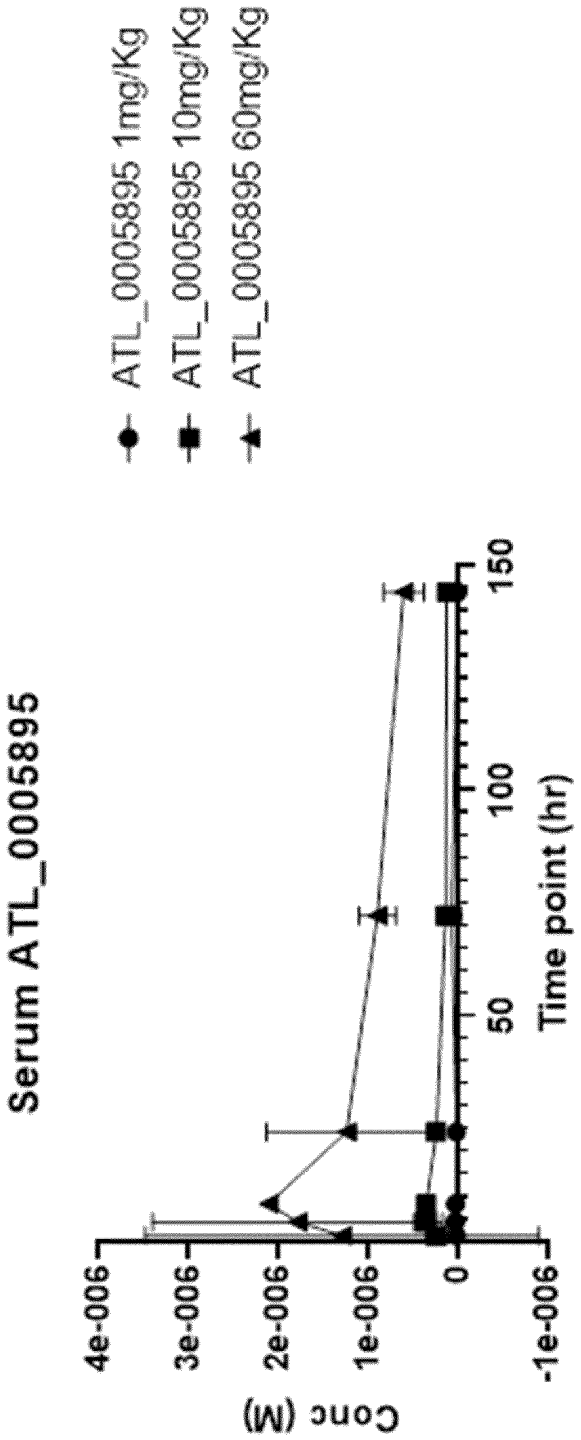

ATL_0005895 1mg/Kg
ATL_0005895 10mg/Kg
ATL_0005895 60mg/Kg
Serum ATL_0005895
Conc (M)
4e-006
3e-006
2e-006
1e-006
0
-1e-006
50
100
150
Time point (hr)

Fig.20B

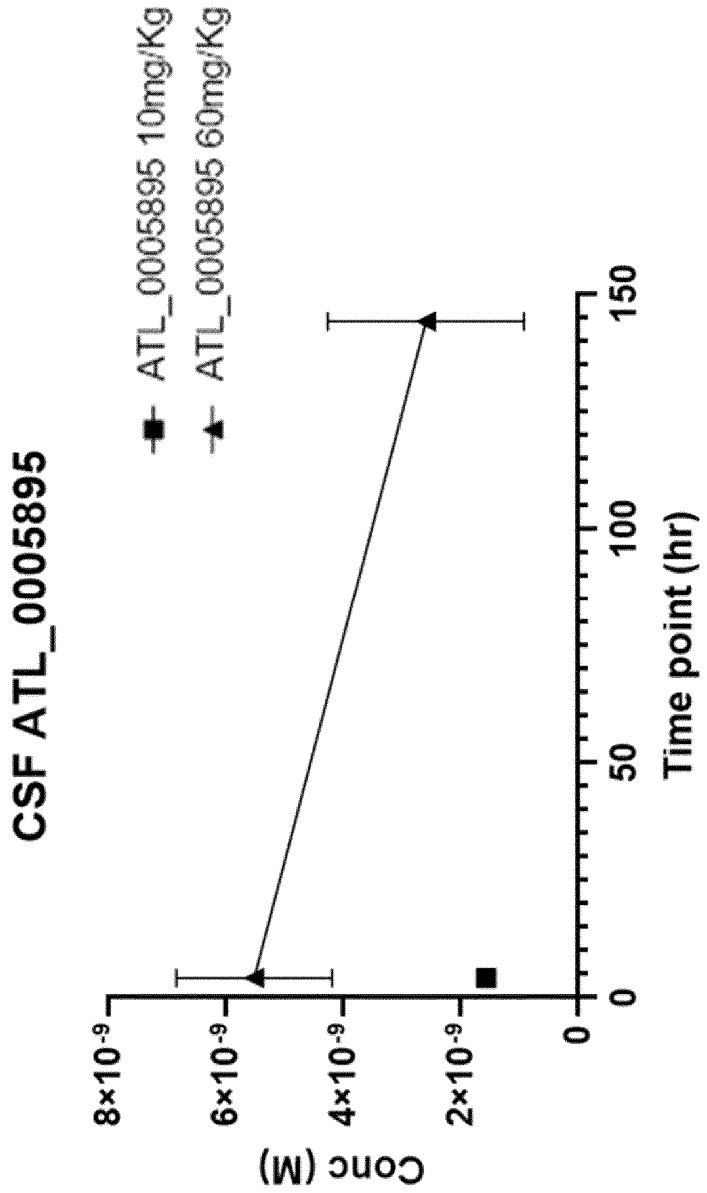

CSF ATL_0005895
ATL_0005895 10mg/Kg
ATL_0005895 60mg/Kg
Conc (M)
8×10-9
6×10-9
4×10-9
2×10-9
0
0
50
100
150
Time point (hr)

Fig.20C

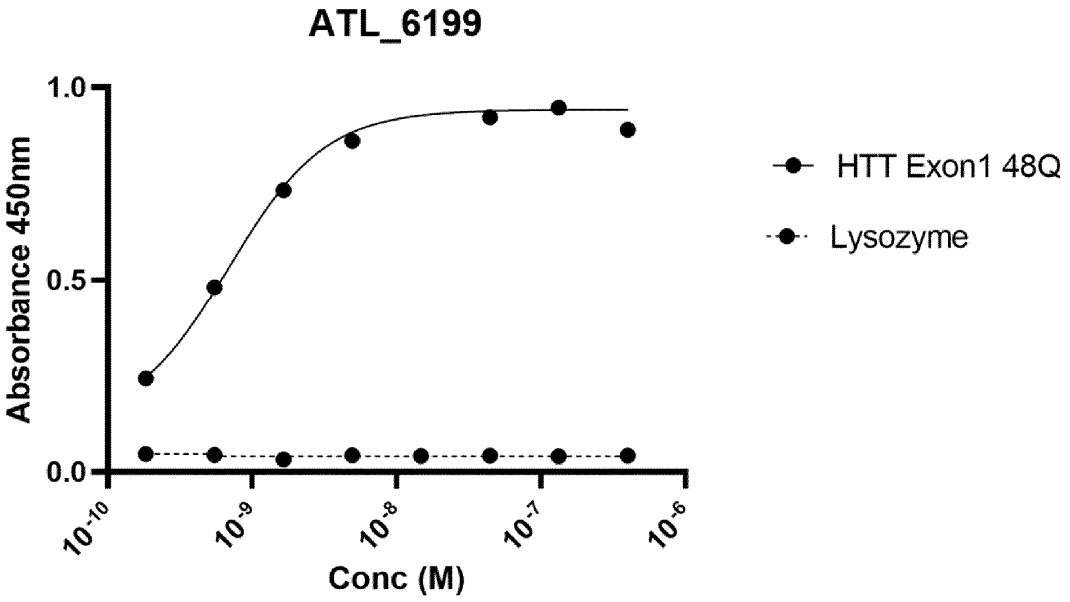


Fig. 21A

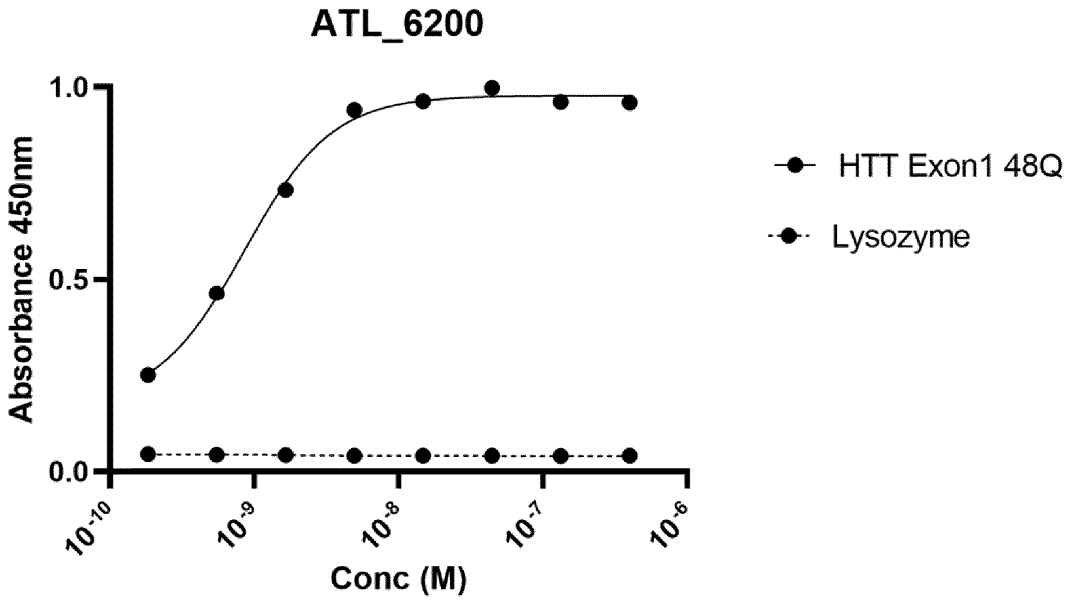


Fig. 21B

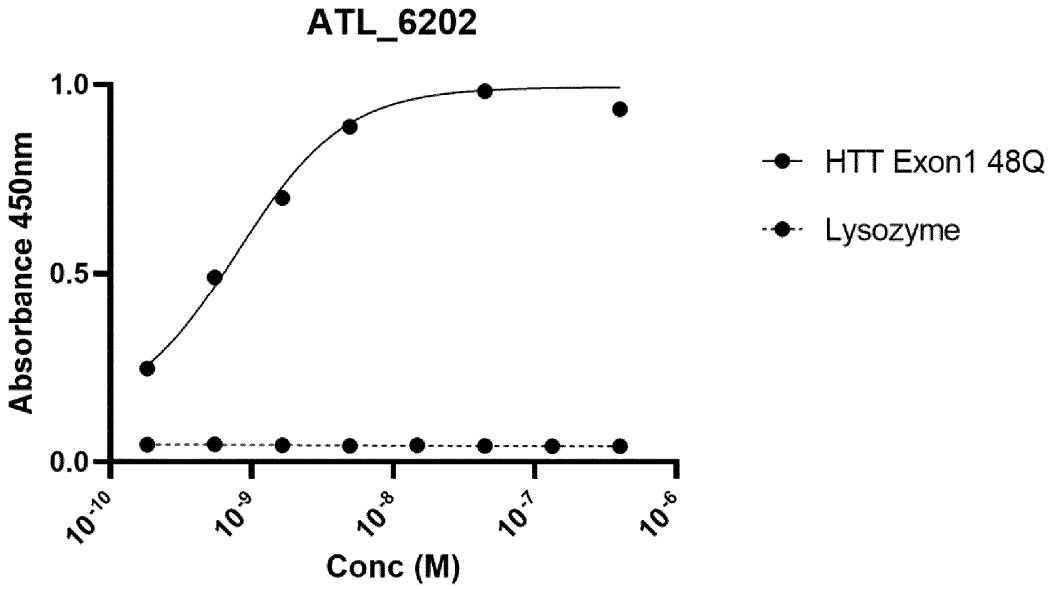


Fig. 21C

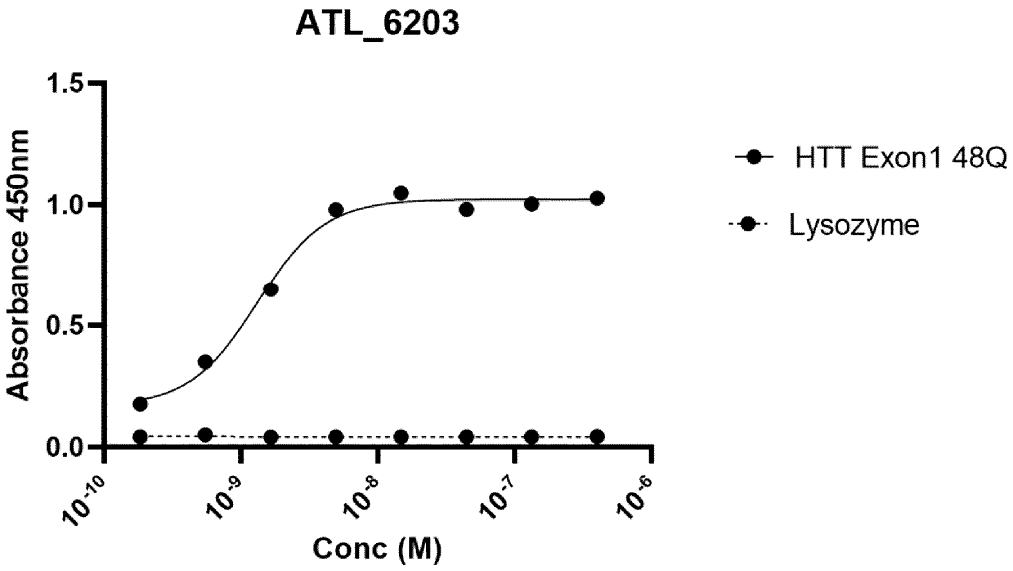


Fig. 21D

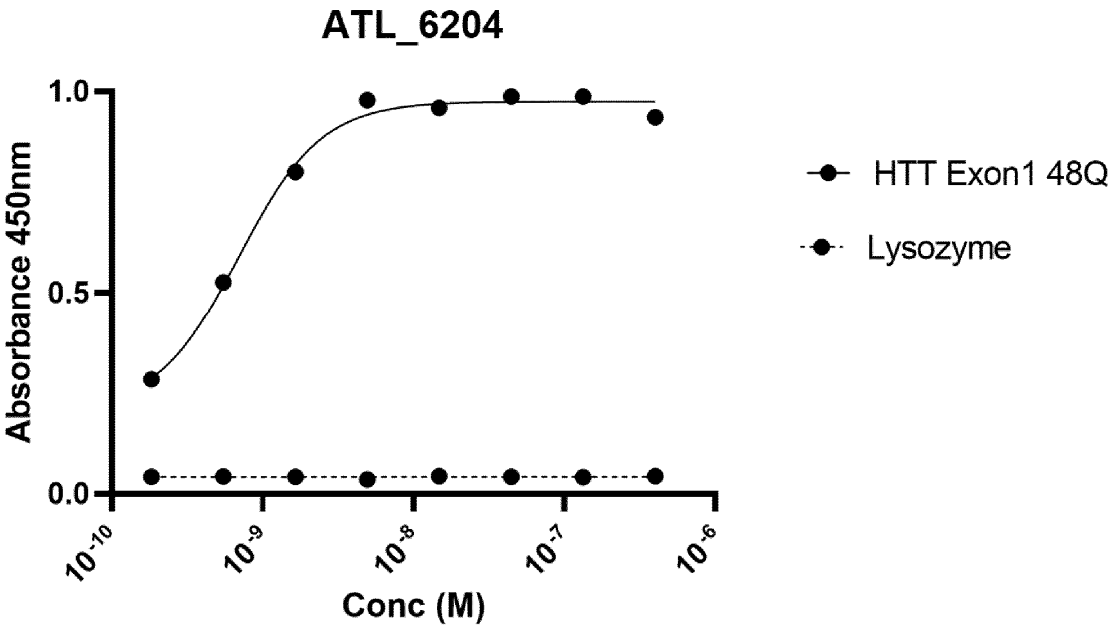


Fig. 21E

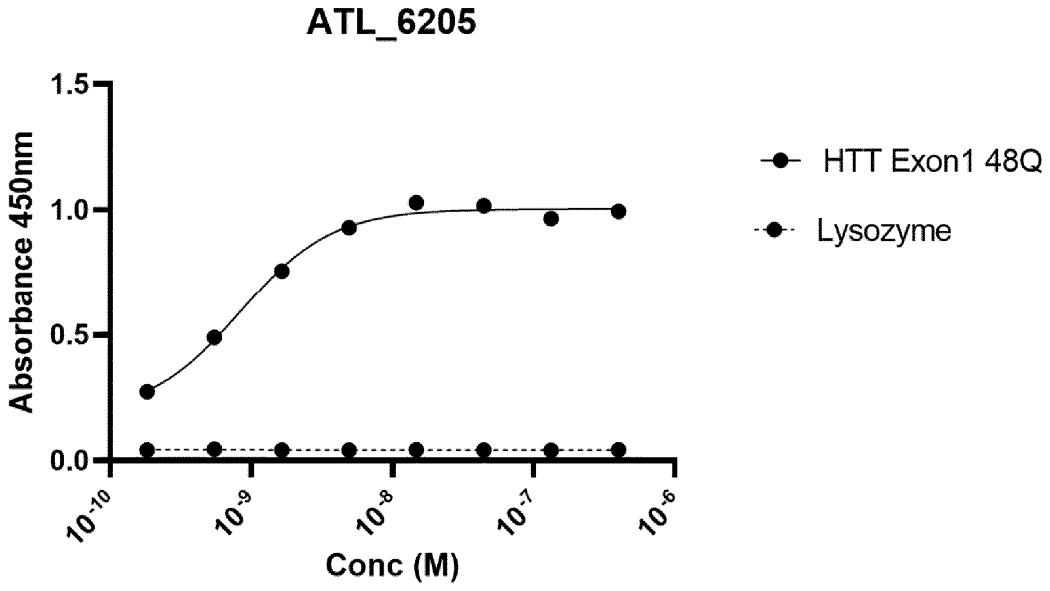


Fig. 21F

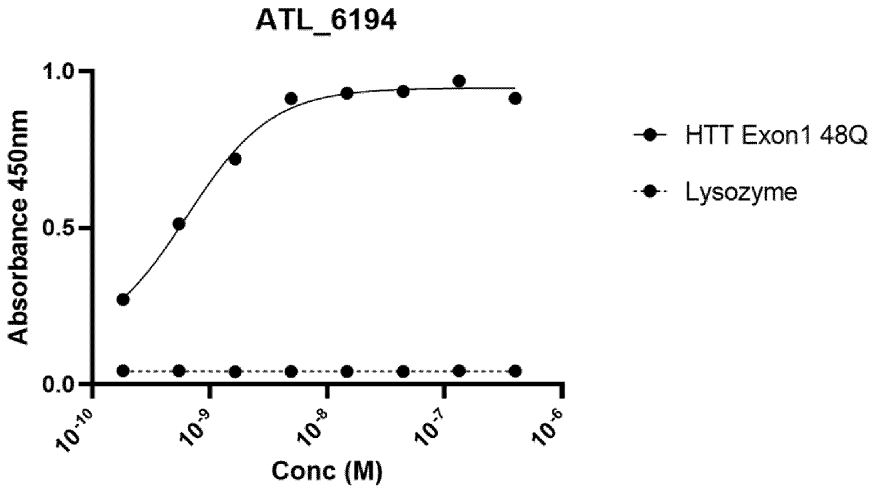


Fig. 21G

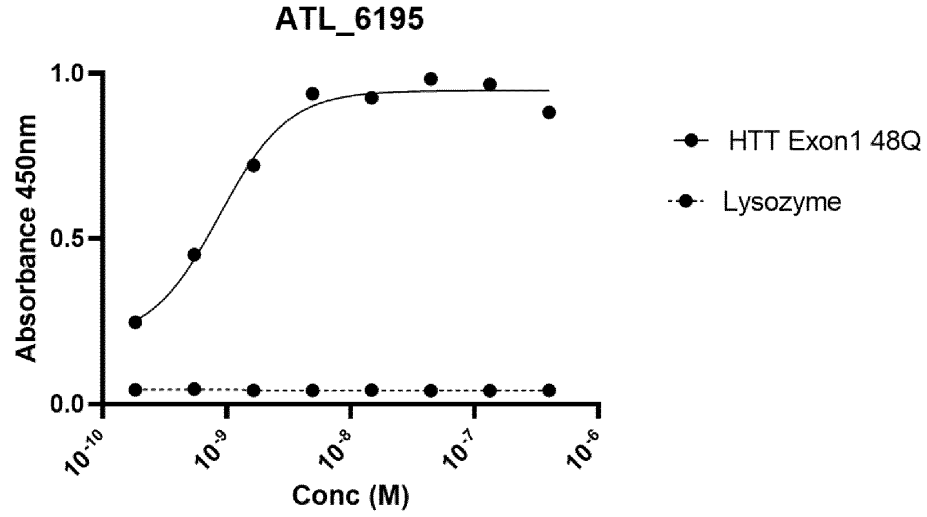


Fig. 21H

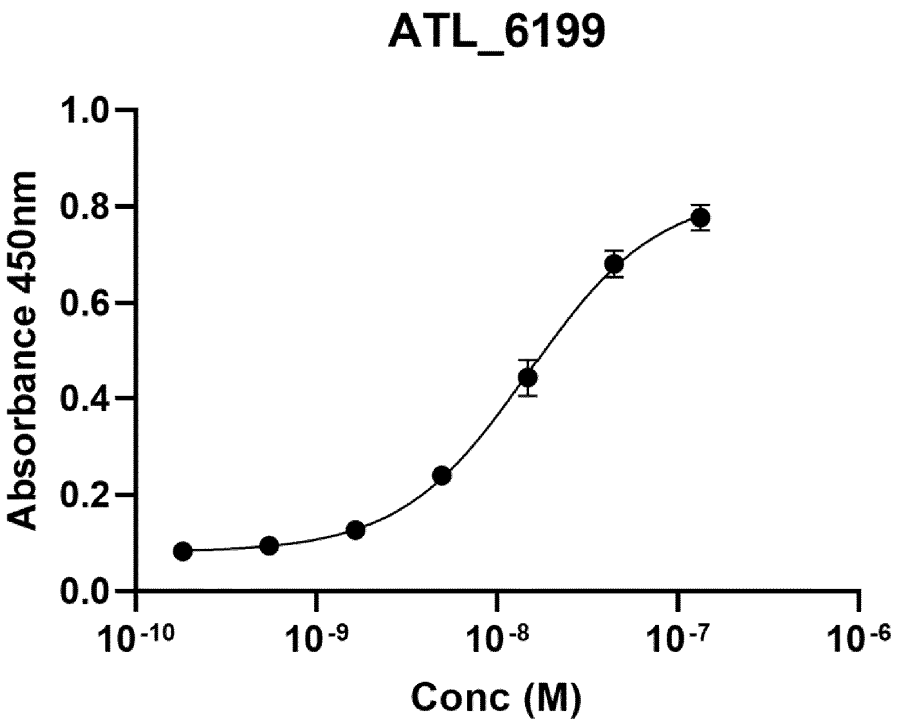


Fig. 22A

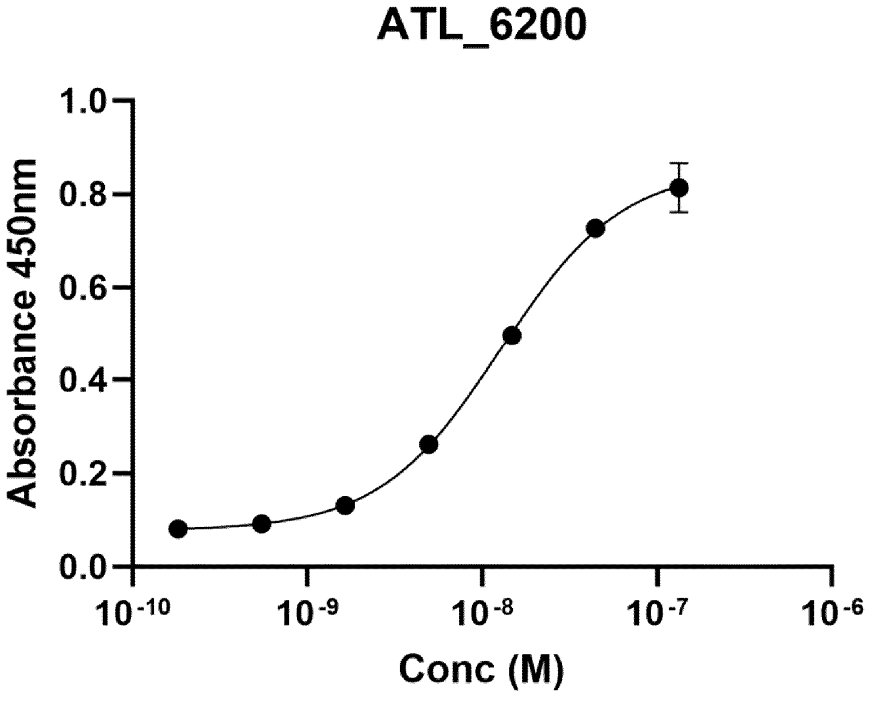


Fig. 22B

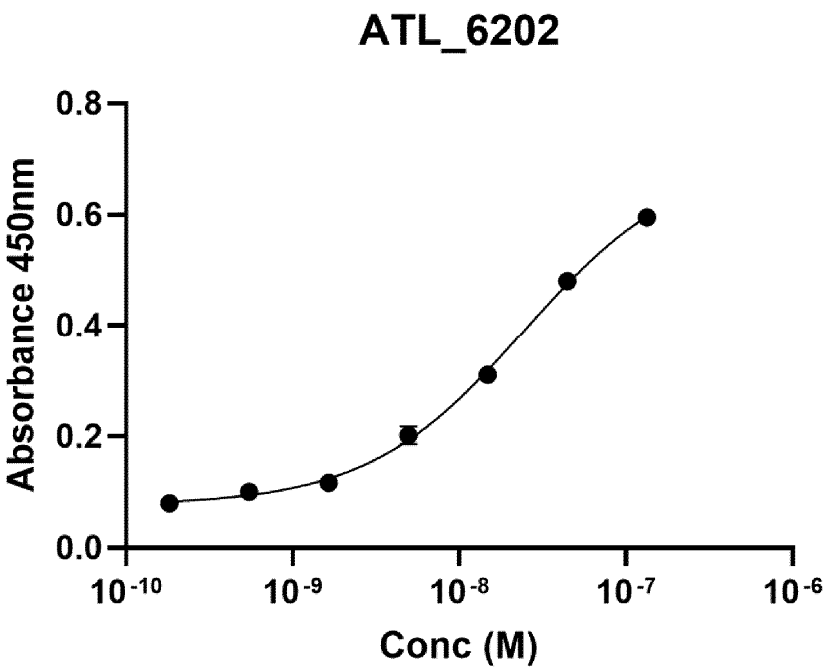


Fig. 22C

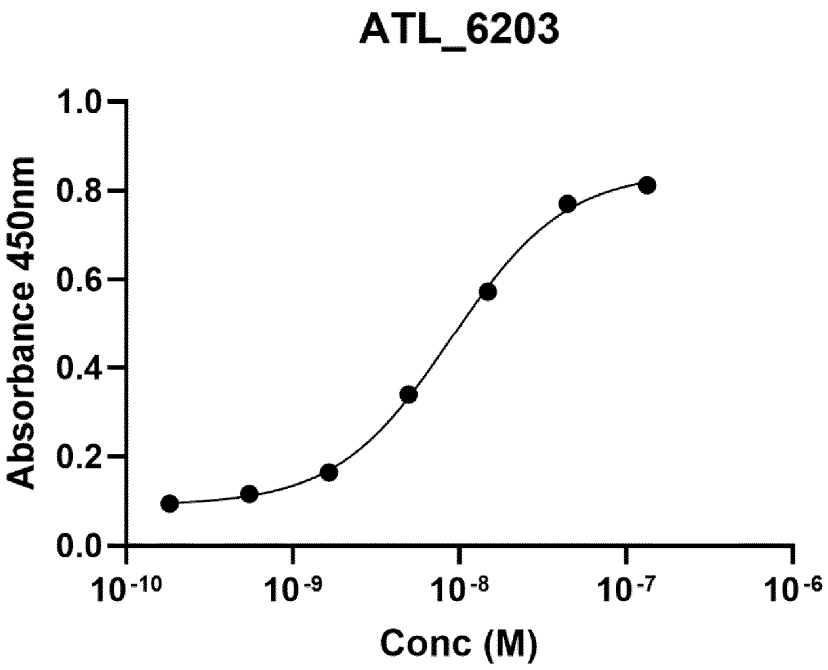


Fig. 22D

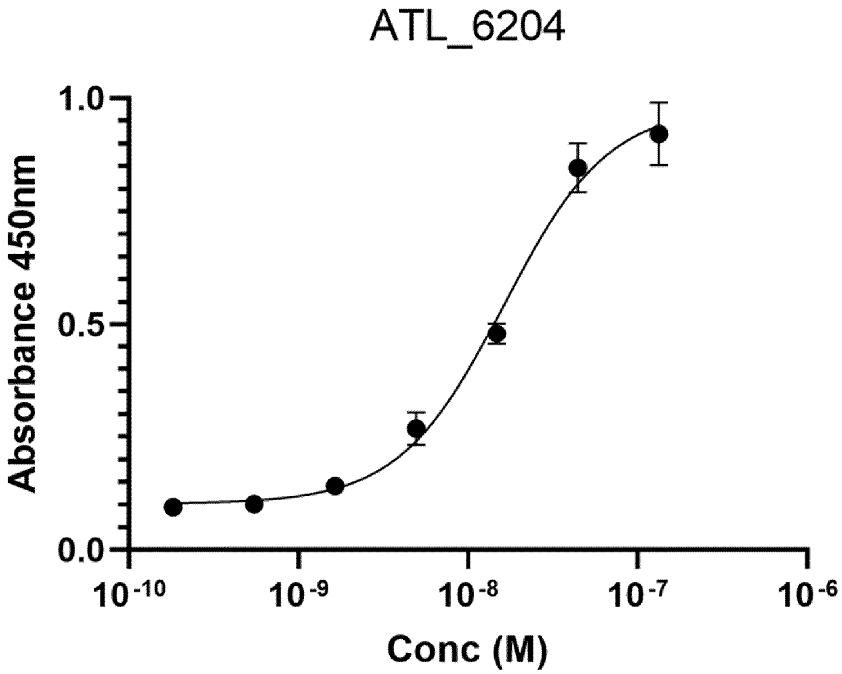


Fig. 22E

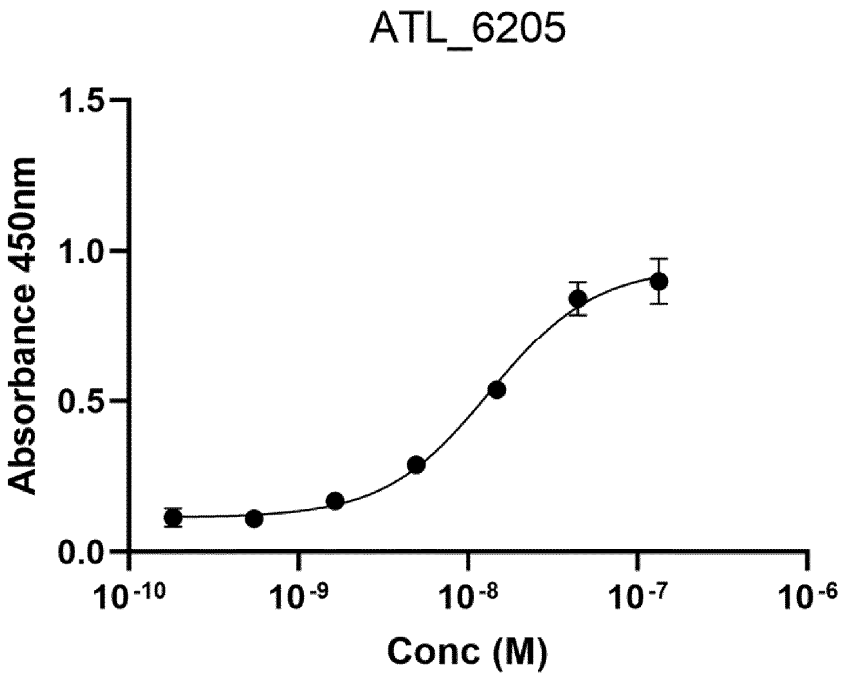


Fig. 22F

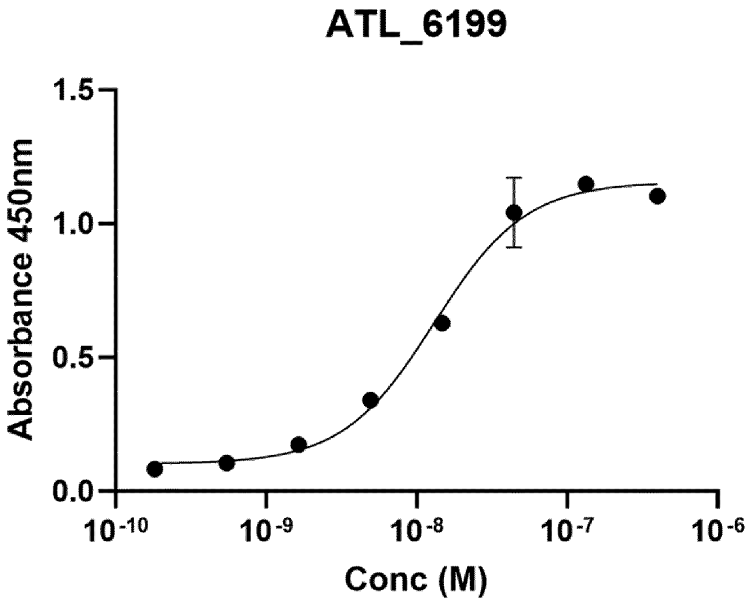


Fig. 22G

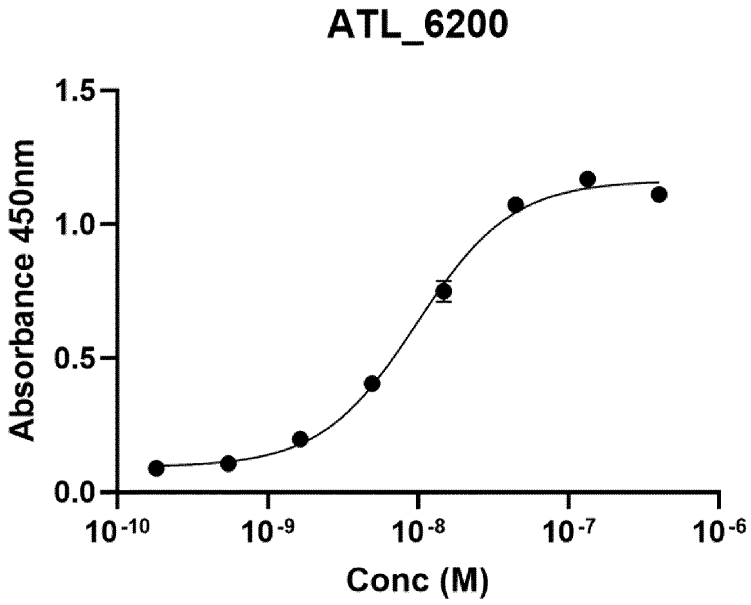


Fig. 22H

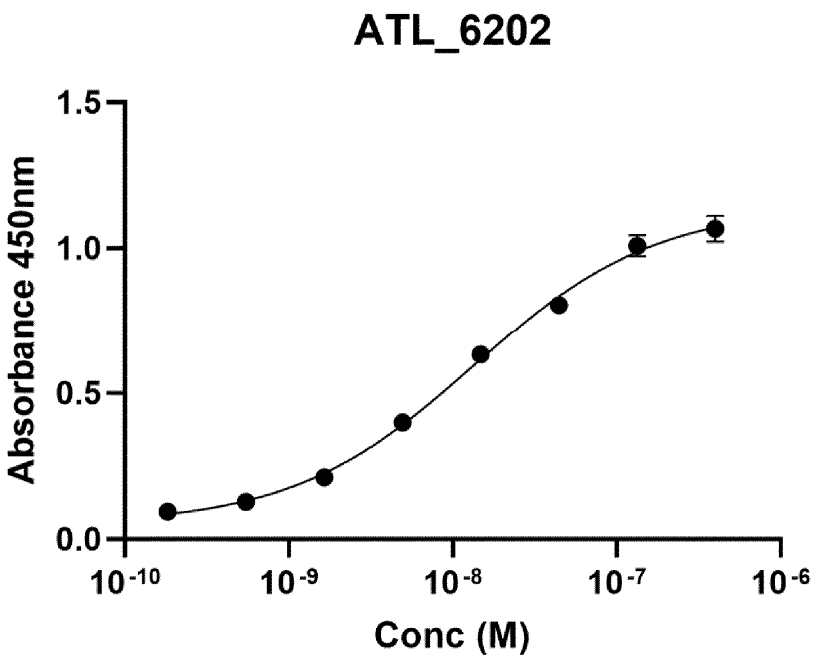


Fig. 22I

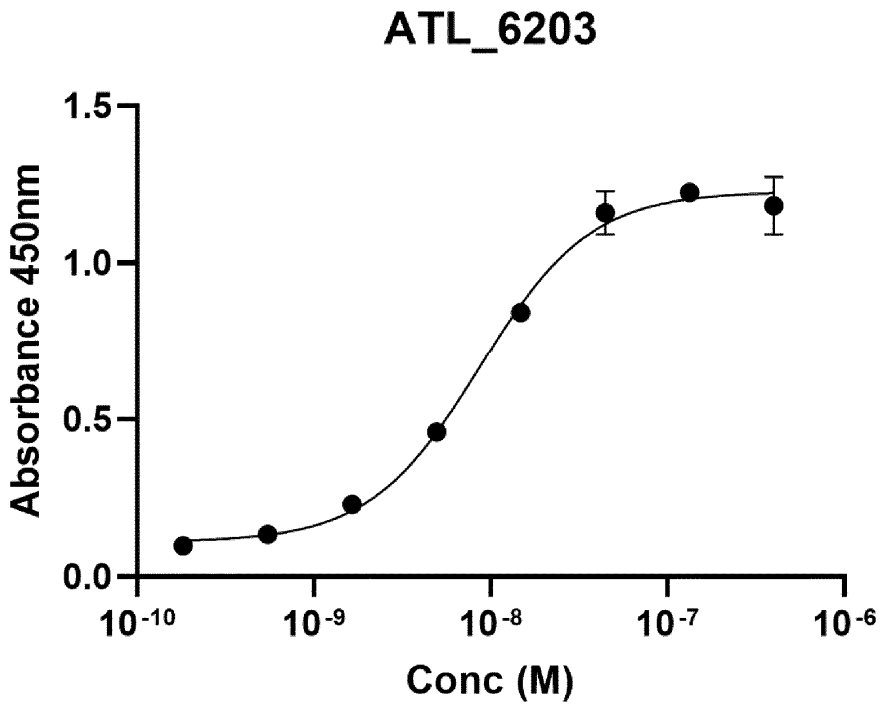


Fig. 22J

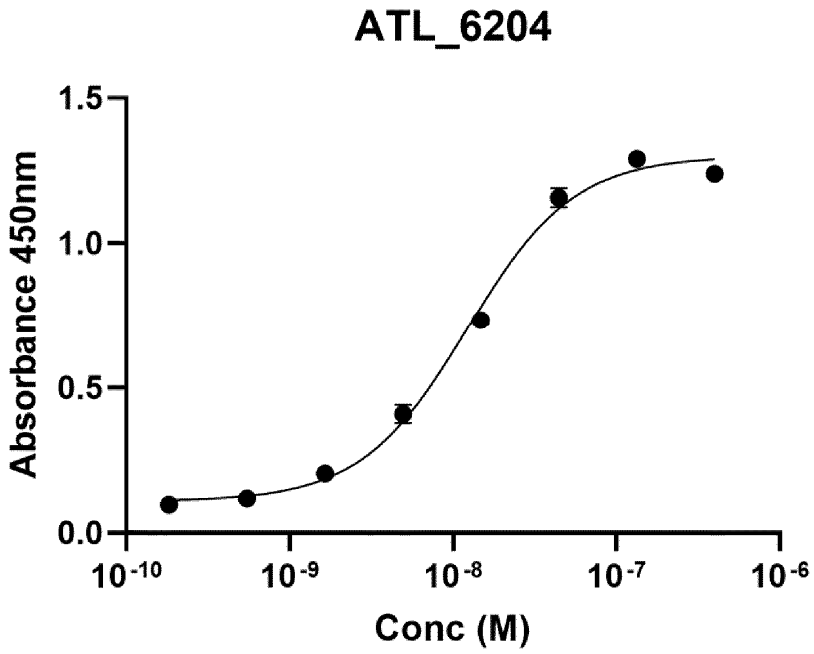


Fig. 22K

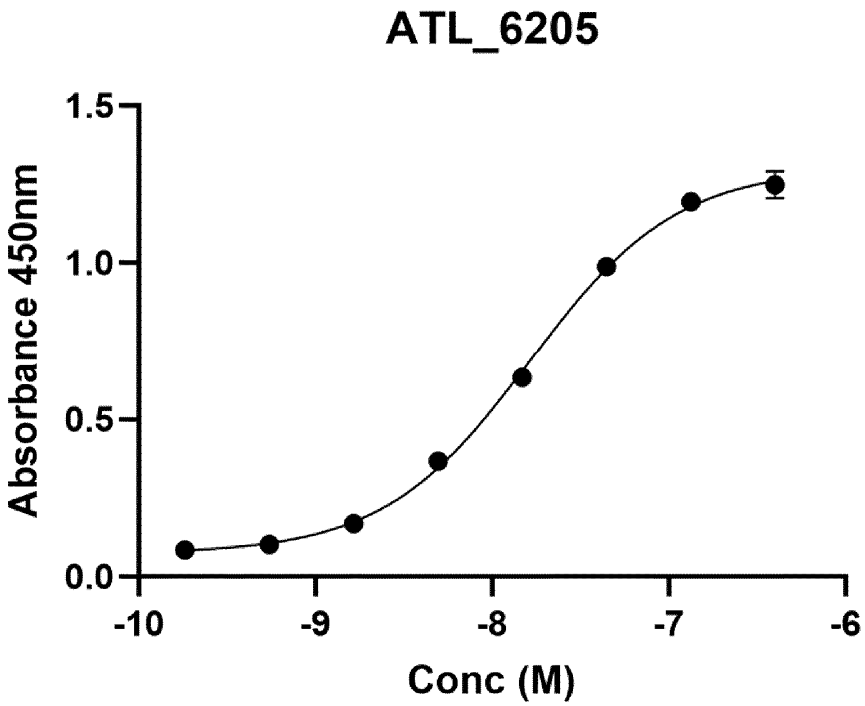


Fig. 22L

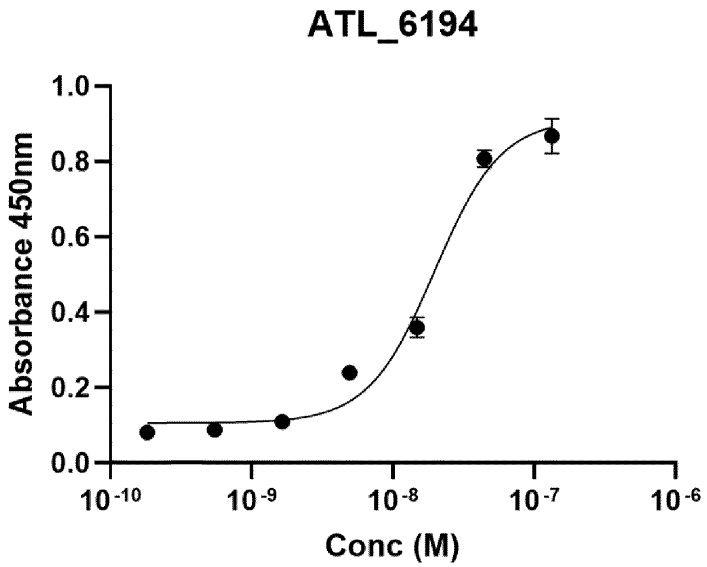


Fig. 22M

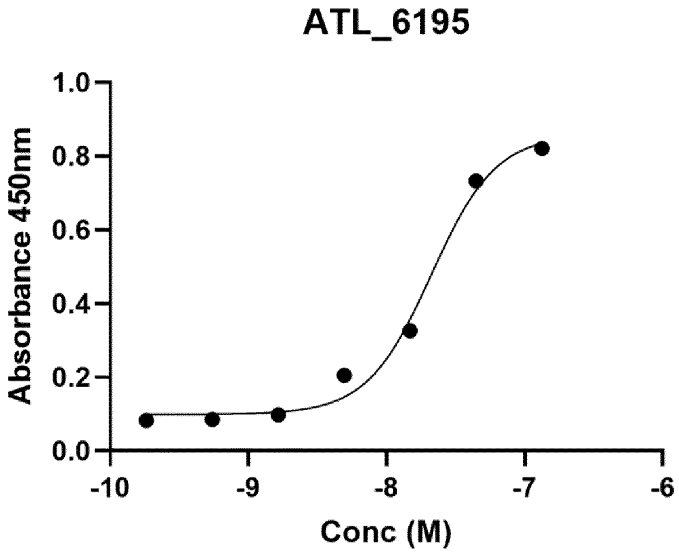


Fig. 22N

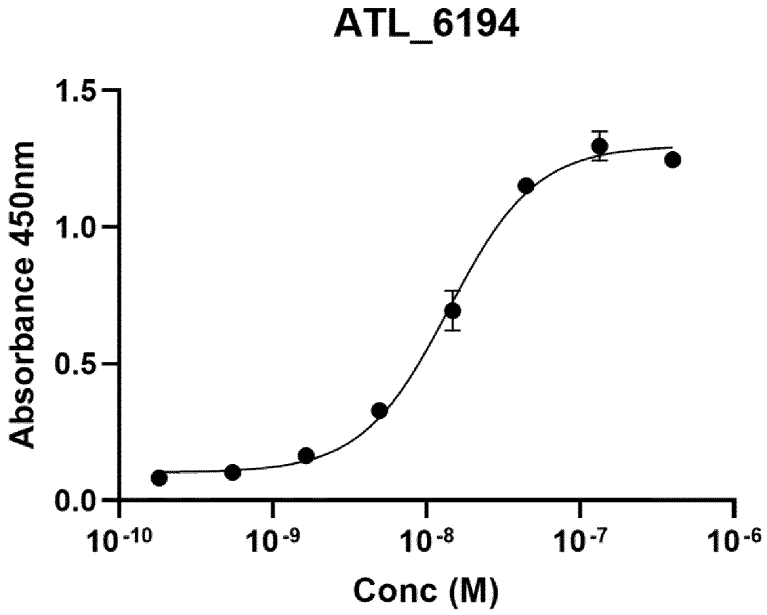


Fig. 22O

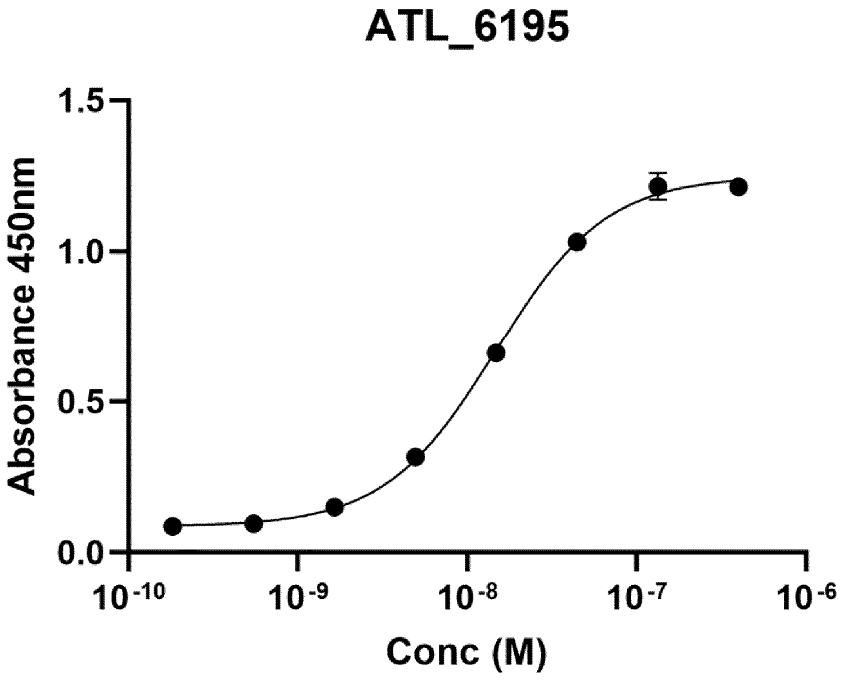


Fig. 22P

ATL_6183

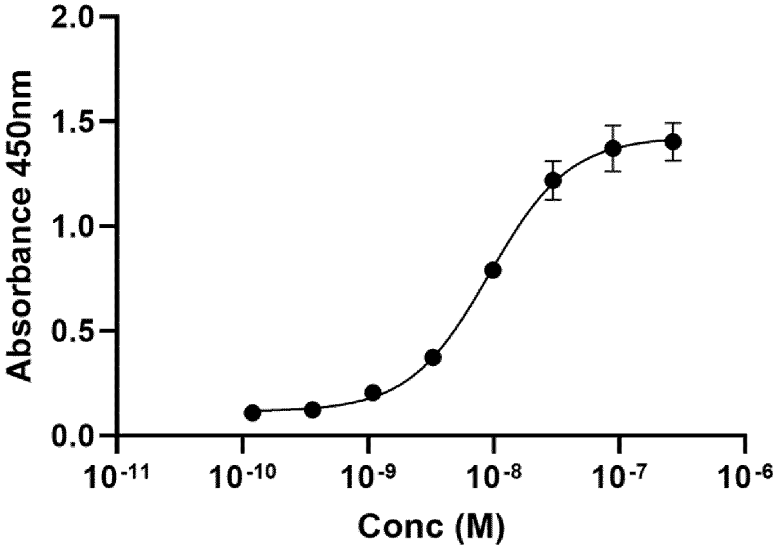


Fig. 23A

ATL_6184

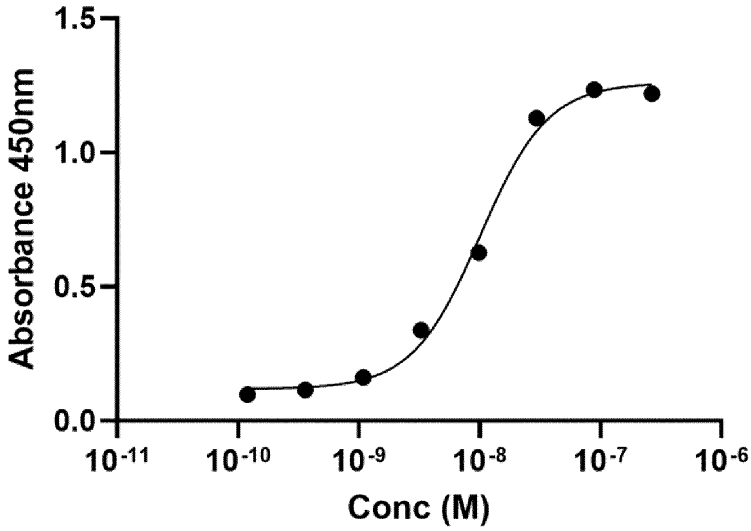


Fig. 23B

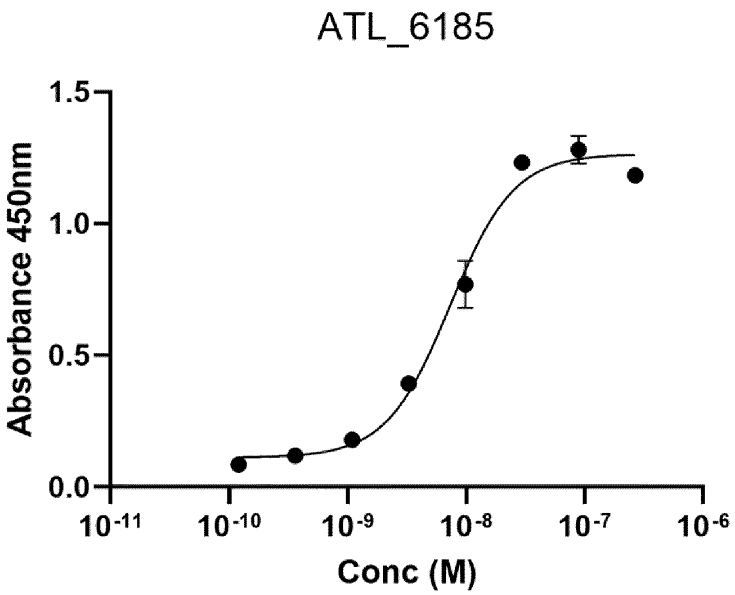


Fig. 23C

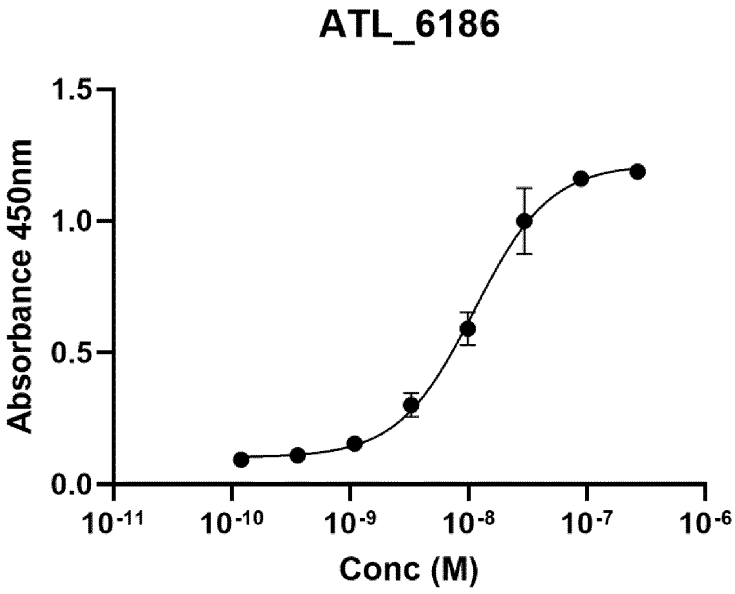


Fig. 23D

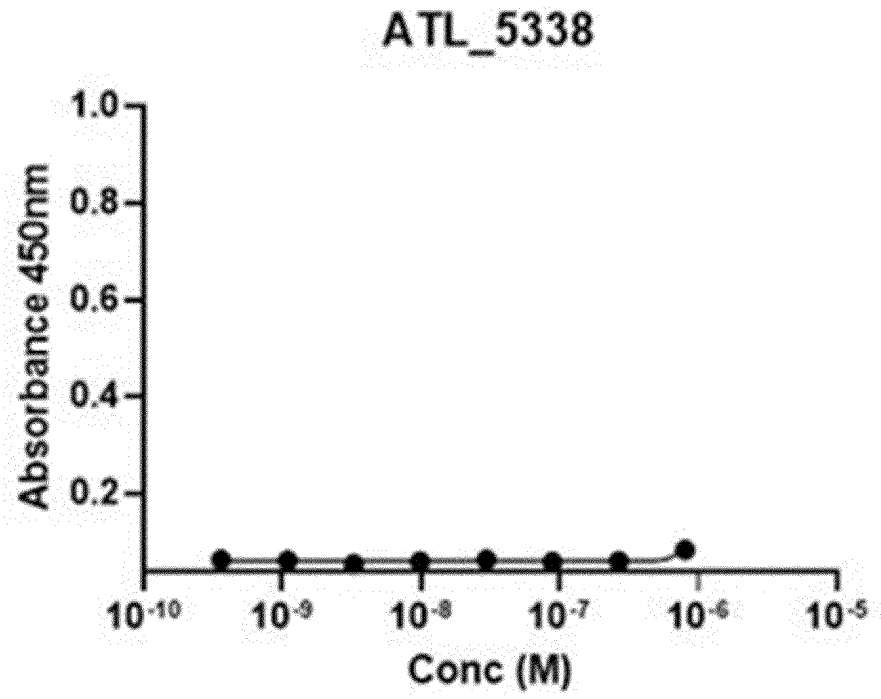

ATL_5338
Absorbance 450nm
1.0
0.8
0.6
0.4
0.2
10-10
10-9
10-8
10-7
10-6
10-5
Conc (M)

Fig. 23E

Antibody	HFW1	HCDR1	HFW2	HCDR2
ATL_0005577	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMN	WVRQAPGKGLEWVG	RIKSGIDAGTTDYAAPVQG
ATL_0005891	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMN	WVRQAPGKGLEWVG	RIKSGIDAGTTDYAAPVQG
ATL_0005586	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMN	WVRQAPGKGLEWVG	RIKSGIDAGTTDYAAPVQG
ATL_0005890	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMN	WVRQAPGKGLEWVG	RIKSGIDAGTTDYAAPVQG
ATL_0005559	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMN	WVRQAPGKGLEWVG	RIKSGIDGGTTDYAAPVQG
ATL_0005572	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMN	WVRQAPGKGLEWVG	RIKSGIDGGTTDYAAPVQG
ATL_0005567	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMN	WVRQAPGKGLEWVG	RIKSGIDGGTTDYAAPVQG
ATL_0005335	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMN	WVRQAPGKGLEWVG	RIKSGIDGGTTDYAAPVQG
ATL_0005901	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMS	WVRQAPGKGLEWVG	RIKSGIDAGTTDYAAPVKG
ATL_0005563	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMN	WVRQAPGKGLEWVG	RIKSGIDGGTTDYAAPVQG
ATL_0005896	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMS	WVRQAPGKGLEWVG	RIKSGIDAGTTDYAAPVKG
ATL_0005894	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMS	WVRQAPGKGLEWVG	RIKSGIDAGTTDYAAPVKG
ATL_0005895	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMS	WVRQAPGKGLEWVG	RIKSGIDAGTTDYAAPVKG
ATL_0005900	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMS	WVRQAPGKGLEWVG	RIKSGIDGGTTDYAAPVKG
ATL_0005331	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMN	WVRQAPGKGLEWVG	RIKSGIDGGTTDYAAPVQG
ATL_0005334	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMN	WVRQAPGKGLEWVG	RIKSGIDGGTTDYAAPVQG
ATL_0005335	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMN	WVRQAPGKGLEWVG	RIKSGIDGGTTDYAAPVQG
ATL_0005555	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMS	WVRQAPGKGLEWVG	RIKSGIDGGTTDYAAPVKG
ATL_0005556	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMS	WVRQAPGKGLEWVG	RIKSGIDGGTTDYAAPVKG
ATL_0005557	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMS	WVRQAPGKGLEWVG	RIKSGIDGGTTDYAAPVKG

Fig.24A-1

Antibody	HFW3	HCDR3	HFW4
ATL_0005577	RFTISRDDSKNTVYLQMNSLNTEDTAVYYCIP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0005891	RFTISRDDSKNTVYLQMNSLNTEDTAVYYCIP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0005586	RFTISRDDSKNTVYLQMNSLNTEDTAVYYCIP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0005890	RFTISRDDSKNTVYLQMNSLNTEDTAVYYCIP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0005559	RFTISRDDSKNTVYLQMNSLNTEDTAVYYCIP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0005572	RFTISRDDSKNTVYLQMNSLNTEDTAVYYCIP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0005567	RFTISRDDSKNTVYLQMNSLNTEDTAVYYCIP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0005335	RFTISRDDSKNTVYLQMNSLNTEDTAVYYCIP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0005901	RFTISRDDSKATLYLQMNSLKTEDTAVYYCIP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0005563	RFTISRDDSKNTVYLQMNSLNTEDTAVYYCIP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0005896	RFTISRDDSKNTLYLQMNSLKTEDTAVYYCIP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0005894	RFTISRDDSKNTLYLQMNSLKTEDTAVYYCIP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0005895	RFTISRDDSKNTLYLQMNSLKTEDTAVYYCIP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0005900	RFTISRDDSKNTLYLQMNSLKTEDTAVYYCIP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0005331	RFTISRDDSKNTVYLQMNSLNTEDTAVYYCIP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0005334	RFTISRDDSKNTVYLQMNSLNTEDTAVYYCIP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0005335	RFTISRDDSKNTVYLQMNSLNTEDTAVYYCIP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0005555	RFTISRDDSKNTLYLQMNSLKTEDTAVYYCIP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0005556	RFTISRDDSKNTLYLQMNSLKTEDTAVYYCIP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0005557	RFTISRDDSKNTLYLQMNSLKTEDTAVYYCIP	PPYYYYYGLDV	WGQGTTVTVSS

Fig.24A-2

Antibody	HFWR1	HCDR1	HFWR2	HCDR2
ATL_0006199	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMS	WVRQAPGKGLEWVG	RIKSGIDAGTTDYAAPVKG
ATL_0006200	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMS	WVRQAPGKGLEWVG	RIKSGIDAGTTDYAAPVKG
ATL_0006202	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMS	WVRQAPGKGLEWVG	RIKSGIDAGTTDYAAPVKG
ATL_0006203	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMS	WVRQAPGKGLEWVG	RIKSGIDAGTTDYAAPVKG
ATL_0006204	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMS	WVRQAPGKGLEWVG	RIKSGIDAGTTDYAAPVKG
ATL_0006205	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMS	WVRQAPGKGLEWVG	RIKSGIDAGTTDYAAPVKG
ATL_0006183	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMS	WVRQAPGKGLEWVG	RIKSGIDAGTTDYAAPVKG
ATL_0006184	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMS	WVRQAPGKGLEWVG	RIKSGIDAGTTDYAAPVKG
ATL_0006185	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMS	WVRQAPGKGLEWVG	RIKSGIDAGTTDYAAPVKG
ATL_0006186	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMS	WVRQAPGKGLEWVG	RIKSGIDAGTTDYAAPVKG

Antibody	HFWR1	HCDR1	HFWR2	HCDR2
ATL_0006194	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMS	WVRQAPGKGLEWVG	RIKSGIDAGTTDYAAPVKG
ATL_0006195	EVQLVESGGGLVKPGGSLRLSCAASGFTFN	KAWMS	WVRQAPGKGLEWVG	RIKSGIDAGTTDYAAPVKG

Fig.24A-3

Antibody	HFWR3	HCDR3	HFWR4
ATL_0006199	IRFTISRDDSKNTLYLQMNSLKTEDTAVYWCSP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0006200	IRFTISRDDSKNTLYLQMNSLKTEDTAVYYCVP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0006202	IRFTISRDDSKNTLYLQMNSLKTEDTAVYYCSP	PPFYYYYGLDV	WGQGTTVTVSS
ATL_0006203	IRFTISRDDSKNTLYLQMNSLKTEDTAVYYCIP	SPYYYYYGLDV	WGQGTTVTVSS
ATL_0006204	IRFTISRDDSKNTLYLQMNSLKTEDTAVYYCIP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0006205	IRFTISRDDSKNTLYLQMNSLKTEDTAVYWCVP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0006183	IRFTISRDDSKNTLYLQMNSLKTEDTAVYYCTP	PPYYYYGLDV	WGQGTTVTVSS
ATL_0006184	IRFTISRDDSKATLYLQMNSLKTEDTAVYYCTP	PPYYYYGLDV	WGQGTTVTVSS
ATL_0006185	IRFTISRDDSKNTLYLQMNSLKTEDTAVYYCTP	PPYYYYGLNV	WGQGTTVTVSS
ATL_0006186	IRFTISRDDSKATLYLQMNSLKTEDTAVYYCTP	PPYYYYGLNV	WGQGTTVTVSS

Antibody	HFWR3	HCDR3	HFWR4
ATL_0006194	RFTISRDDSKNTLYLQMNSLKTEDTAVYYCVP	PPYYYYYGLDV	WGQGTTVTVSS
ATL_0006195	RFTISRDDSKNTLYLQMNSLKTEDTAVYYCTP	PPYYYYYGLDV	WGQGTTVTVSS

Fig.24A-4

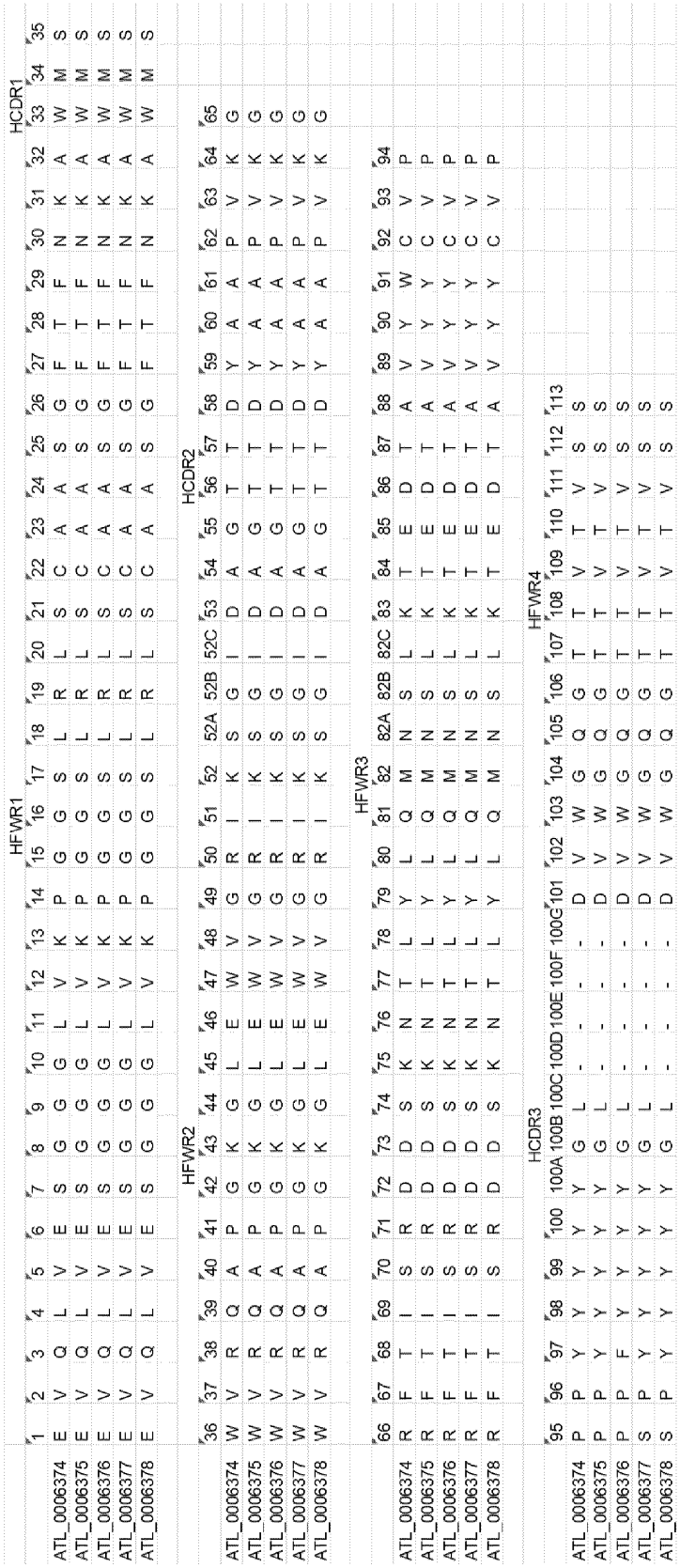


Fig.24A-5

Antibody sequence	LFW1	LCDR1L	LFW2L	LCDR2L
ATL_0005577	QSALTQPRSVSGSPGQSITISC	TGTSSDVGSYNLVS	WFQQHPGKAPKLIIY	EVNKRPS
ATL_0005891	QSALTQPRSVSGSPGQSVTISC	TGTSSDVGSYNLVS	WYQQHPGKAPKLIIY	EVNKRPS
ATL_0005586	QSALTQPASVSGSPGQSITISC	TGTSSDVGGYKLVS	WYQQHPGRAPKLMIY	EVSKRPS
ATL_0005890	QSALTQPRSVSGSPGQSVTISC	TGTSSDVGSYNLVS	WYQQHPGKAPKLMIY	EVNKRPS
ATL_0005559	QSALTQPRSVSGSPGQSITISC	TGTSSDVGSYNLVS	WFQQHPGKAPKLIIY	EVNKRPS
ATL_0005572	QSALTQPASVSGSPGQSITISC	TGTSSDIGSYNLVS	WYQQHPGKAPKPLIY	EGSKRPS
ATL_0005567	QSALTQPASVSGSPGQSITISC	TGTSSDIGSYNLVS	WYQQHPGNAPKPLIY	EGSKRPS
ATL_0005335	QSALTQPASVSGSPGQSITISC	TGTSSDIGSYNLVS	WYQQHPGNAPKPLIY	EGSKRPS
ATL_0005901	QSALTQPASVSGSPGQSITISC	TGTSSDVGGYKLVS	WYQQHPGRAPKLMIY	EVSKRPS
ATL_0005563	QSALTQPRSVSGSPGQSVTISC	TGTSSDVGSYNLVS	WYQQHPGKAPKLIIY	EVNKRPS
ATL_0005896	QSALTQPRSVSGSPGQSVTISC	TGTSSDVGSYNLVS	WYQQHPGKAPKLMIY	EVNKRPS
ATL_0005894	QSALTQPRSVSGSPGQSVTISC	TGTSSDVGSYNLVS	WYQQHPGKAPKLIIY	EVNKRPS
ATL_0005895	QSALTQPRSVSGSPGQSVTISC	TGTSSDVGSYNLVS	WYQQHPGKAPKLMIY	EVNKRPS
ATL_0005900	QSALTQPASVSGSPGQSITISC	TGTSSDVGGYKLVS	WYQQHPGRAPKLMIY	EVSKRPS
ATL_0005331	QSALTQPRSVSGSPGQSITISC	TGTSSDVGSYNLVS	WFQQHPGKAPKLIIY	EVNKRPS
ATL_0005334	QSALTQPASVSGSPGQSITISC	TGTSSDVGGYKLVS	WYQQHPGRAPKLMIY	EVSKRPS
ATL_0005335	QSALTQPASVSGSPGQSITISC	TGTSSDIGSYNLVS	WYQQHPGNAPKPLIY	EGSKRPS
ATL_0005555	QSALTQPRSVSGSPGQSVTISC	TGTSSDVGSYNLVS	WYQQHPGKAPKLMIY	EVNKRPS
ATL_0005556	QSALTQPASVSGSPGQSITISC	TGTSSDVGGYKLVS	WYQQHPGRAPKLMIY	EVSKRPS
ATL_0005557	QSALTQPASVSGSPGQSITISC	TGTSSDIGSYNLVS	WYQQHPGKAPKLMIY	EGSKRPS

Fig.24B-1

Antibody sequence	LFW3L	LCDR3L	LFW4L
ATL_0005577	GVPDRFSGSKSGNTASLTVSGLQAEDEADYYC	GSYAGTNNV	FGTGTKLTVL
ATL_0005891	GVPDRFSGSKSGNTASLTISGLQAEDEADYYC	GSYAGTNNV	FGTGTKVTVL
ATL_0005586	GVSSRFSGSKSGSTASLTISGLQAEDEADYYC	SSYAGSSVV	FGGGTKLTVL
ATL_0005890	GVPDRFSGSKSGNTASLTISGLQAEDEADYYC	GSYAGTNNV	FGTGTKVTVL
ATL_0005559	GVPDRFSGSKSGATASLTVSGLQAEDEADYYC	GSYAGTNNV	FGTGTKLTVL
ATL_0005572	GVSNRFSGSKSGNTASLTISGLQAEDEADYYC	SSYAGFNTLV	FGGGTKLTVL
ATL_0005567	GVSARFSGSKSGNTASLTISGLQPEDEADYYC	SSYAGFSTLV	FGGGTKVTVL
ATL_0005335	GVSARFSGSKSGNTASLTISGLQPEDEADYYC	SSYAGFNTLV	FGGGTKVTVL
ATL_0005901	GVSSRFSGSKSGSTASLTISGLQAEDEADYYC	SSYAGSSVV	FGGGTKLTVL
ATL_0005563	GVPDRFSGSKSGNTASLTISGLQAEDEADYYC	GSYAGTNNV	FGTGTKVTVL
ATL_0005896	GVPDRFSGSKSGATASLTISGLQAEDEADYYC	GSYAGTNNV	FGTGTKVTVL
ATL_0005894	GVPDRFSGSKSGATASLTISGLQAEDEADYYC	GSYAGTANV	FGTGTKVTVL
ATL_0005895	GVPDRFSGSKSGATASLTISGLQAEDEADYYC	GSYAGTANV	FGTGTKVTVL
ATL_0005900	GVSSRFSGSKSGSTASLTISGLQAEDEADYYC	SSYAGSSVV	FGGGTKLTVL
ATL_0005331	GVPDRFSGSKSGNTASLTVSGLQAEDEADYYC	GSYAGTNNV	FGTGTKLTVL
ATL_0005334	GVSSRFSGSKSGSTASLTISGLQAEDEADYYC	CSYAGSSVV	FGGGTKLTVL
ATL_0005335	GVSARFSGSKSGNTASLTISGLQPEDEADYYC	SSYAGFNTLV	FGGGTKVTVL
ATL_0005555	GVPDRFSGSKSGNTASLTISGLQAEDEADYYC	GSYAGTNNV	FGTGTKVTVL
ATL_0005556	GVSSRFSGSKSGSTASLTISGLQAEDEADYYC	CSYAGSSVV	FGGGTKLTVL
ATL_0005557	GVSNRFSGSKSGNTASLTISGLQAEDEADYYC	SSYAGFNTLV	FGGGTKLTVL

Fig.24B-2

Antibody	LFWR1	LCDR1	LFWR2	LCDR2
ATL_0006199	QSALTQPRSVSGSPGQSVTISC	TGTSSDVGSYNLVS	WYQQHPGKAPKLMIY	EVNKRPS
ATL_0006200	QSALTQPRSVSGSPGQSVTISC	TGTSSDVGSYNLVS	WYQQHPGKAPKLMIY	EVNKRPS
ATL_0006202	QSALTQPRSVSGSPGQSVTISC	TGTSSDVGSYNLVS	WYQQHPGKAPKLMIY	EVNKRPS
ATL_0006203	QSALTQPRSVSGSPGQSVTISC	TGTSSDVGSYNLVS	WYQQHPGKAPKLMIY	EVNKRPS
ATL_0006204	QSALTQPRSVSGSPGQSVTISC	TGTSSDVGSYNLVS	WYQQHPGKAPKLMIY	EVNKRPS
ATL_0006205	QSALTQPRSVSGSPGQSVTISC	TGTSSDVGSYNLVS	WYQQHPGKAPKLMIY	EVNKRPS
ATL_0006183	QSALTQPRSVSGSPGQSVTISC	TGTSSDVGSYNLVS	WYQQHPGKAPKLMIY	EVNKRPS
ATL_0006184	QSALTQPASVSGSPGQSITISC	TGTSSDVGGYKLVS	WYQQHPGRAPKLMIY	EVSKRPS
ATL_0006185	QSALTQPRSVSGSPGQSVTISC	TGTSSDVGSYNLVS	WYQQHPGKAPKLMIY	EVNKRPS
ATL_0006186	QSALTQPASVSGSPGQSITISC	TGTSSDVGGYKLVS	WYQQHPGRAPKLMIY	EVSKRPS

Antibody	LFWR1	LCDR1	LFWR2	LCDR2
ATL_0006194	QSALTQPRSVSGSPGQSVTISC	TGTSSDVGSYNLVS	WYQQHPGKAPKLMIY	EVNKRPS
ATL_0006195	QSALTQPRSVSGSPGQSVTISC	TGTSSDVGSYNLVS	WYQQHPGKAPKLMIY	EVNKRPS

Fig.24B-3

Antibody	LFWR3	LCDR3	LFWR4
ATL_0006199	GVPDRFSGSKSGATASLTISGLQAEDEADYYC	GSYAGTANV	FGTGTKVTVL
ATL_0006200	GVPDRFSGSKSGATASLTISGLQAEDEADYYC	GSYAGTANV	FGTGTKVTVL
ATL_0006202	GVPDRFSGSKSGATASLTISGLQAEDEADYYC	VSYGGTENV	FGTGTKVTVL
ATL_0006203	GVPDRFSGSKSGATASLTISGLQAEDEADYYC	VSYAGTANV	FGTGTKVTVL
ATL_0006204	GVPDRFSGSKSGATASLTISGLQAEDEADYYC	VSFAGTANV	FGTGTKVTVL
ATL_0006205	GVPDRFSGSKSGATASLTISGLQAEDEADYYC	VSYAGTANV	FGTGTKVTVL
ATL_0006183	GVPDRFSGSKSGATASLTISGLQAEDEADYYC	GSYAGTANV	FGTGTKVTVL
ATL_0006184	GVSSRFSGSKSGSTASLTISGLQAEDEADYYC	SSYAGSSVV	FGGGTKLTVL
ATL_0006185	GVPDRFSGSKSGATASLTISGLQAEDEADYYC	GSYAGTANV	FGTGTKVTVL
ATL_0006186	GVSSRFSGSKSGSTASLTISGLQAEDEADYYC	SSYAGSSVV	FGGGTKLTVL

Antibody	LFWR3	LCDR3	LFWR4
ATL_0006194	GVPDRFSGSKSGATASLTISGLQAEDEADYYC	VSYAGTANV	FGTGTKVTVL
ATL_0006195	GVPDRFSGSKSGATASLTISGLQAEDEADYYC	GSYAGTANV	FGTGTKVTVL

Fig.24B-4

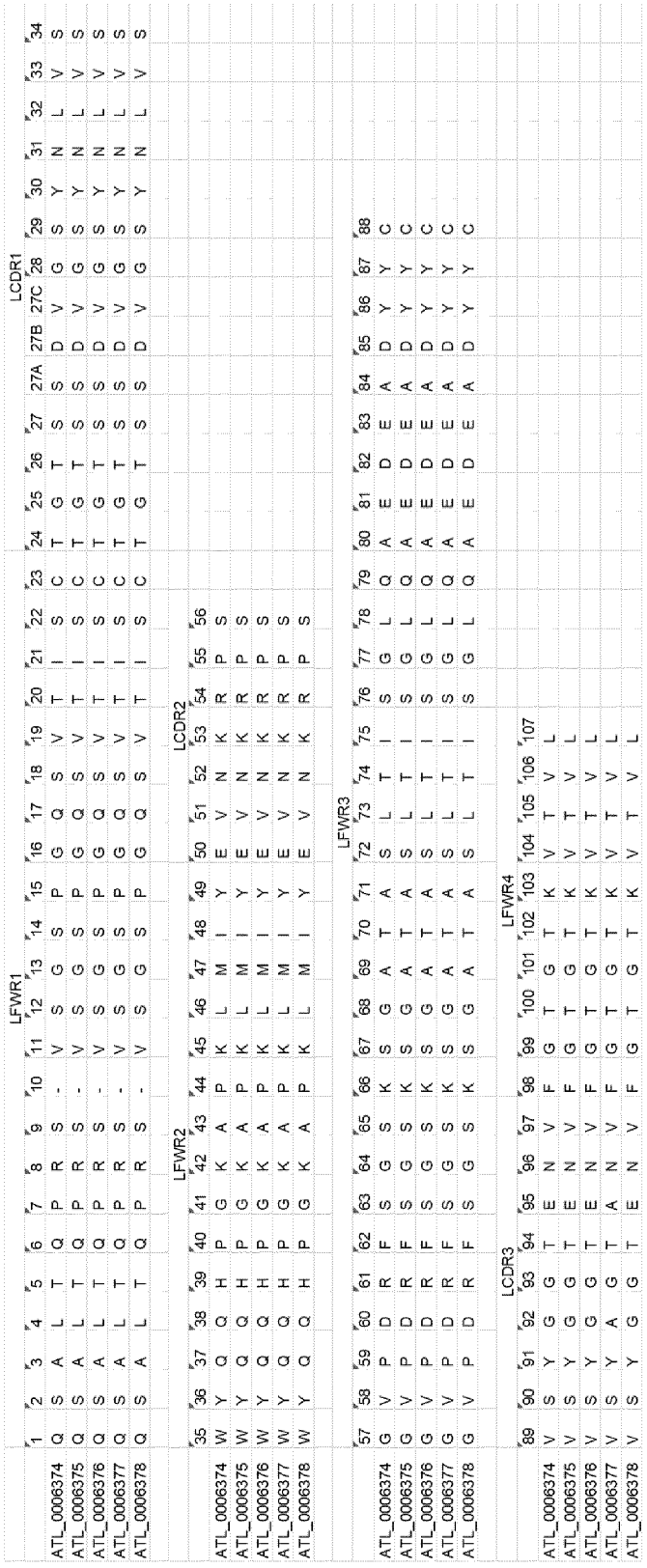


Fig.24B-5

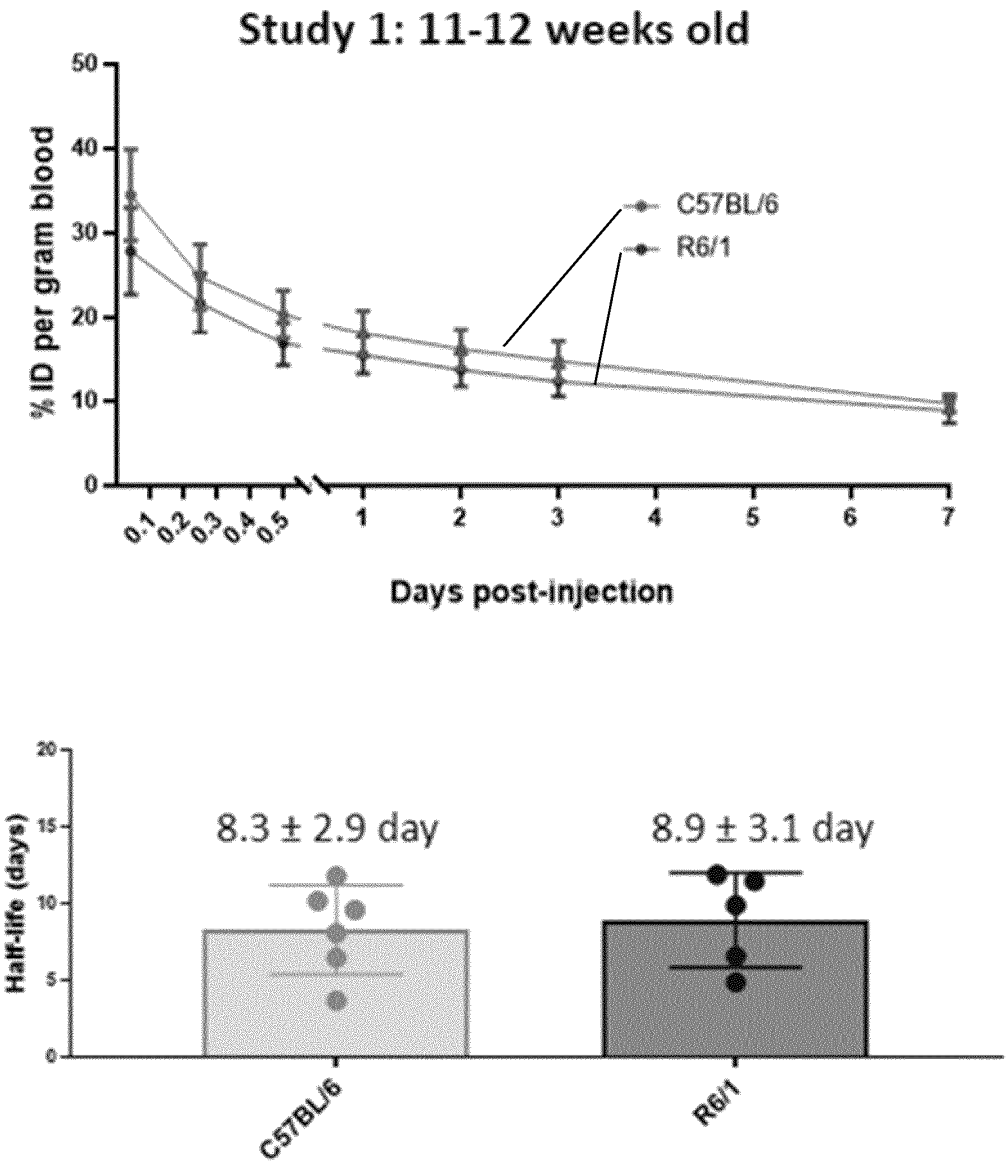

Study 1: 11-12 weeks old
% ID per gram blood
50
40
30
20
10
0
C57BL/6
R6/1
0.1
0.2
0.3
0.4
0.5
1
2
3
4
5
6
7
Days post-injection
Half-life (days)
20
15
10
5
0
8.3 ± 2.9 day
8.9 ± 3.1 day
C57BL/6
R6/1

Fig.25A

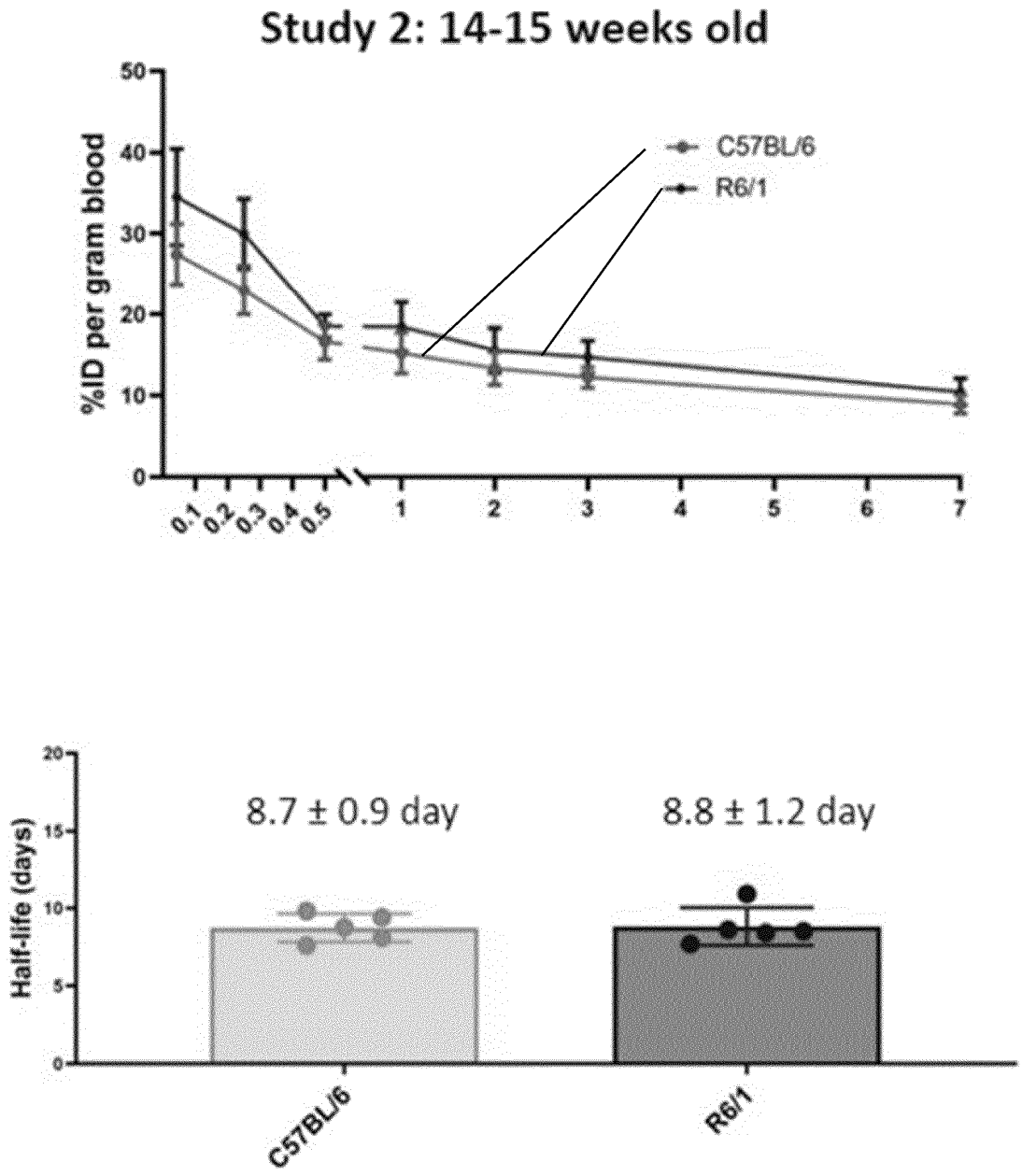

Study 2: 14-15 weeks old
%ID per gram blood
50
40
30
20
10
0
0.1
0.2
0.3
0.4
0.5
1
2
3
4
5
6
7
C57BL/6
R6/1
Half-life (days)
20
15
10
5
0
8.7 ± 0.9 day
8.8 ± 1.2 day
C57BL/6
R6/1

Fig.25B

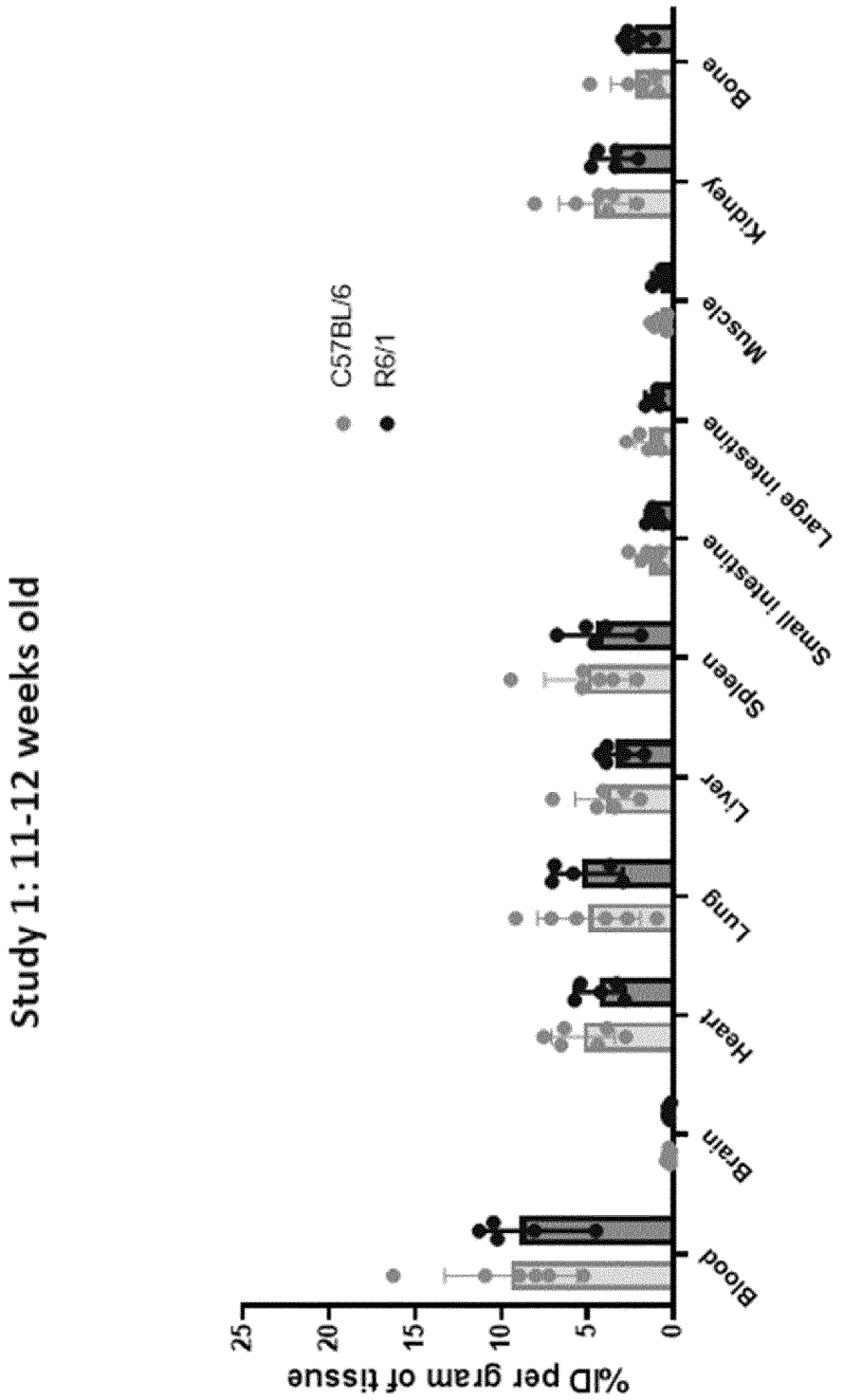

Study 1: 11-12 weeks old
%ID per gram of tissue
25
20
15
10
5
0
C57BL/6
R6/1
Blood
Brain
Heart
Lung
Liver
Spleen
Small intestine
Large intestine
Muscle
Kidney
Bone

Fig.25C

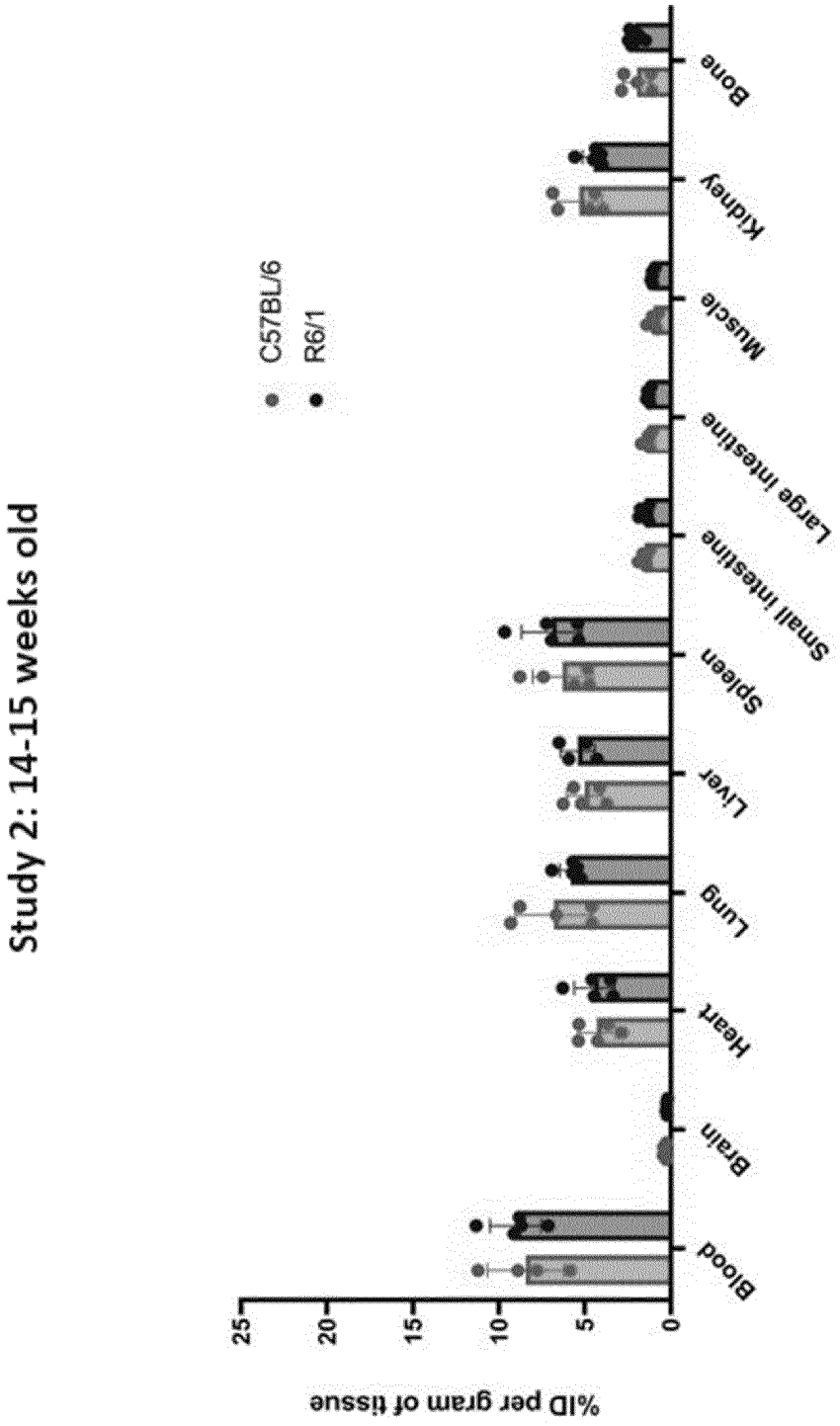

Study 2: 14-15 weeks old
C57BL/6
R6/1
%ID per gram of tissue
25
20
15
10
5
0
Blood
Brain
Heart
Lung
Liver
Spleen
Small intestine
Large intestine
Muscle
Kidney
Bone

Fig.25D

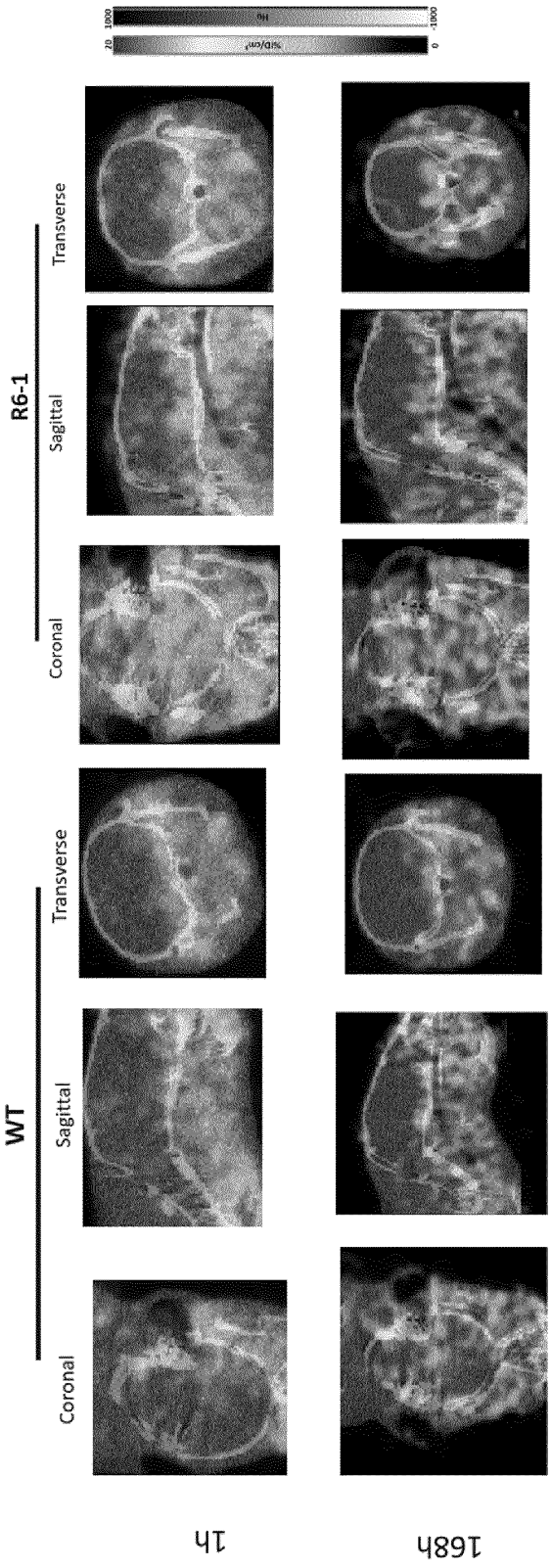

HU
1000
-1000
%ID/cm³
20
0
WT
R6-1
Transverse
Sagittal
Coronal
1h
168h

Fig.25E

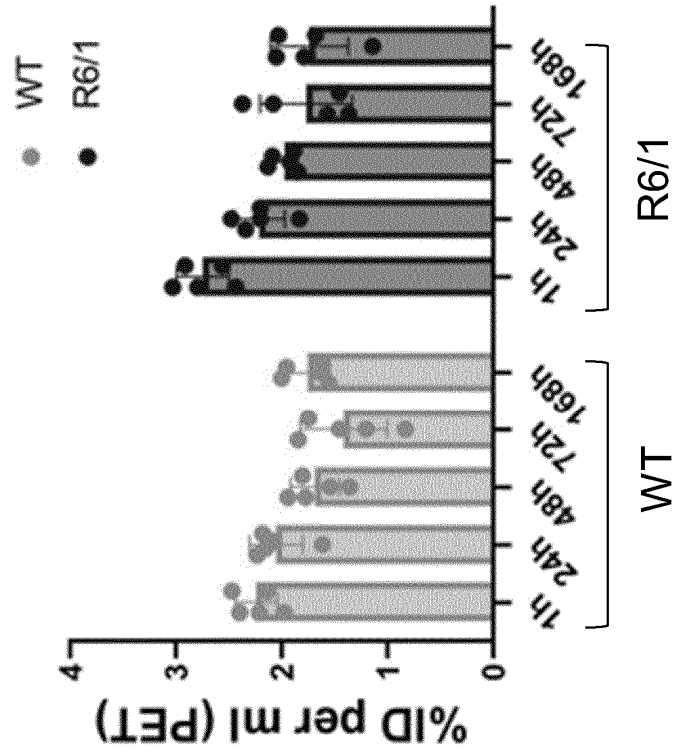

WT
R6/1
%ID per ml (PET)
0
1
2
3
4
1h
24h
48h
72h
168h
WT
1h
24h
48h
72h
168h
R6/1

Fig.25F

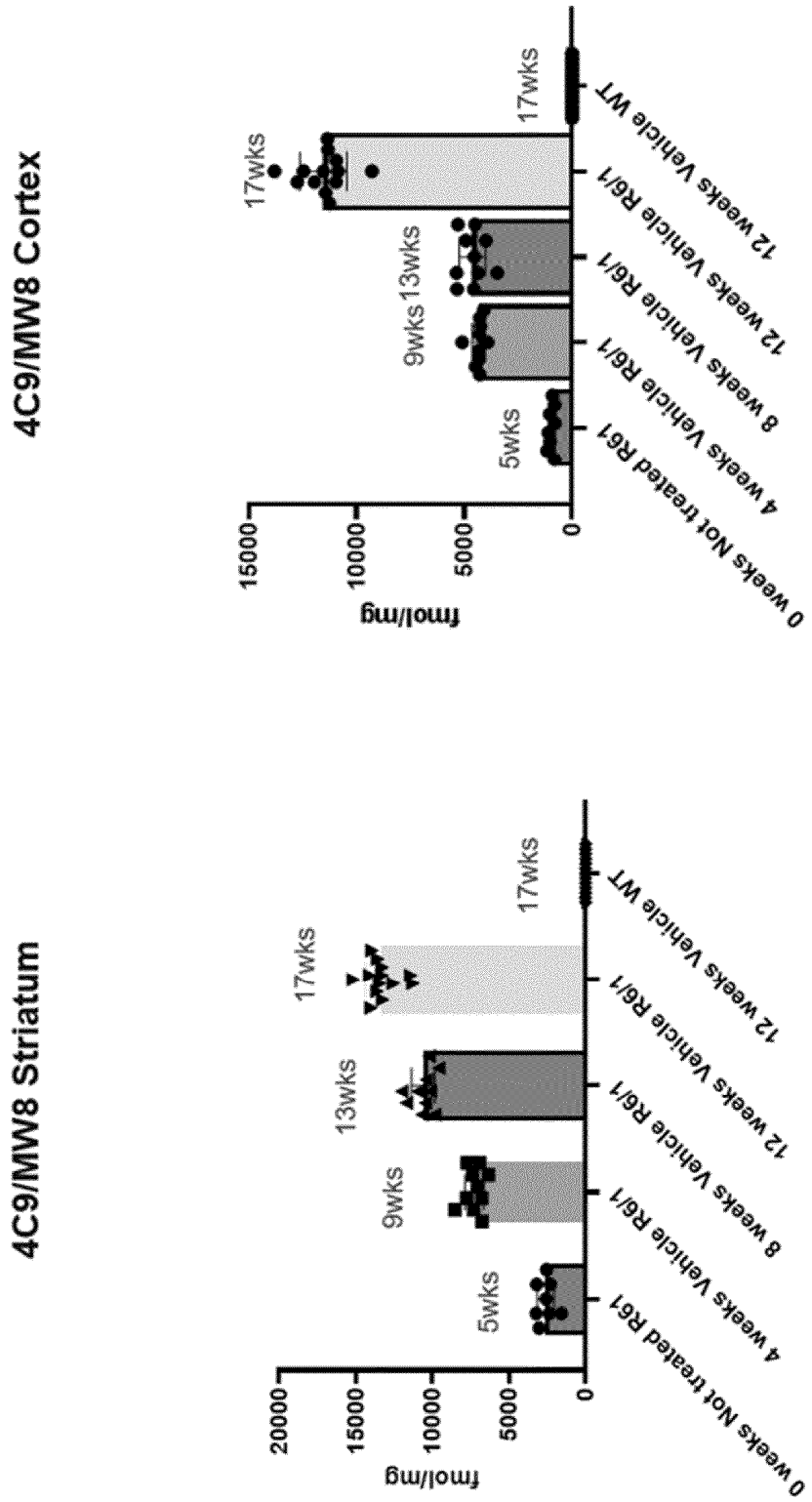

4C9/MW8 Cortex
fmol/mg
15000
10000
5000
0
5wks
9wks
13wks
17wks
17wks
0 weeks Not treated R6/1
4 weeks Vehicle R6/1
8 weeks Vehicle R6/1
12 weeks Vehicle R6/1
12 weeks Vehicle WT
4C9/MW8 Striatum
fmol/mg
20000
15000
10000
5000
0
5wks
9wks
13wks
17wks
17wks
0 weeks Not treated R6/1
4 weeks Vehicle R6/1
8 weeks Vehicle R6/1
12 weeks Vehicle R6/1
12 weeks Vehicle WT

Fig.26A

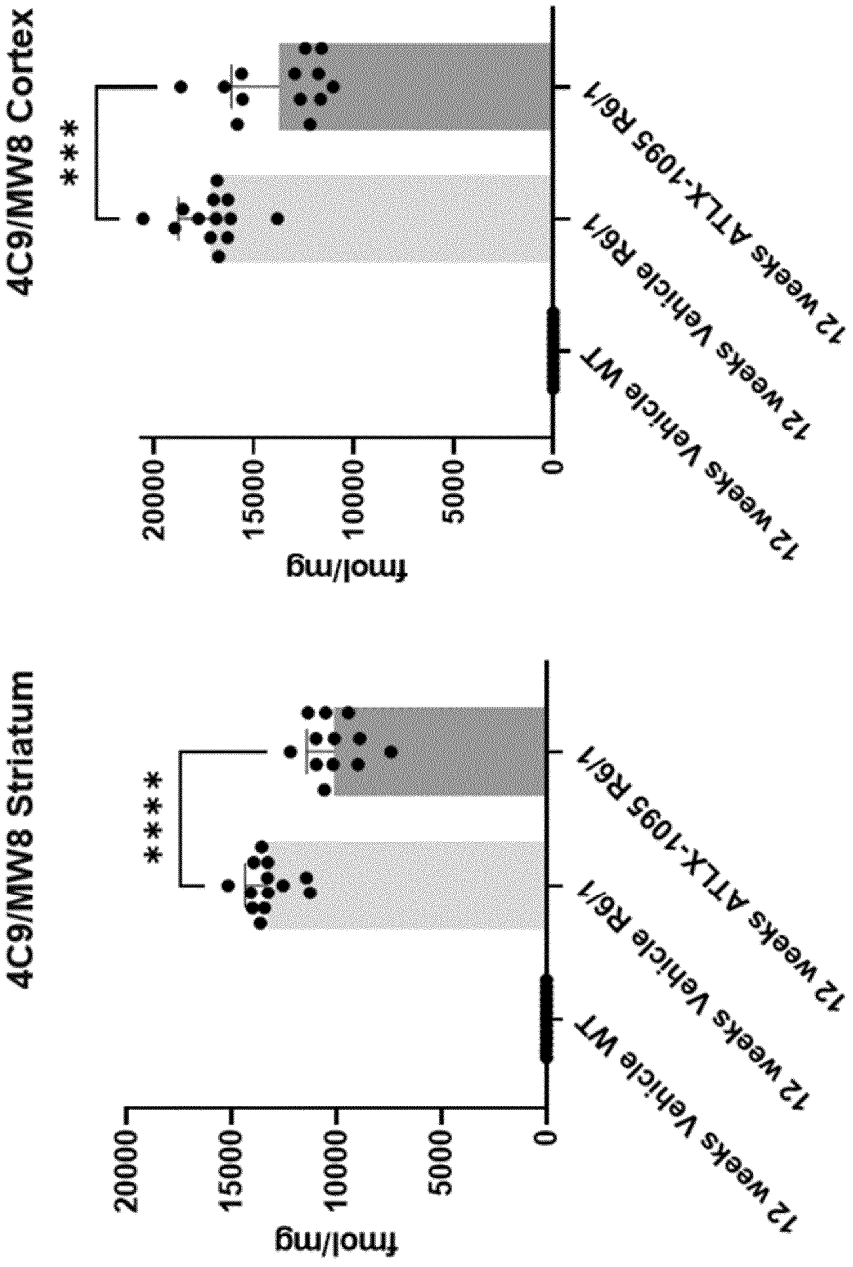

4C9/MW8 Striatum
****
fmol/mg
20000
15000
10000
5000
0
12 weeks Vehicle WT
12 weeks Vehicle R6/1
12 weeks ATLX-1095 R6/1
4C9/MW8 Cortex
***
fmol/mg
20000
15000
10000
5000
0
12 weeks Vehicle WT
12 weeks Vehicle R6/1
12 weeks ATLX-1095 R6/1

Fig.26B

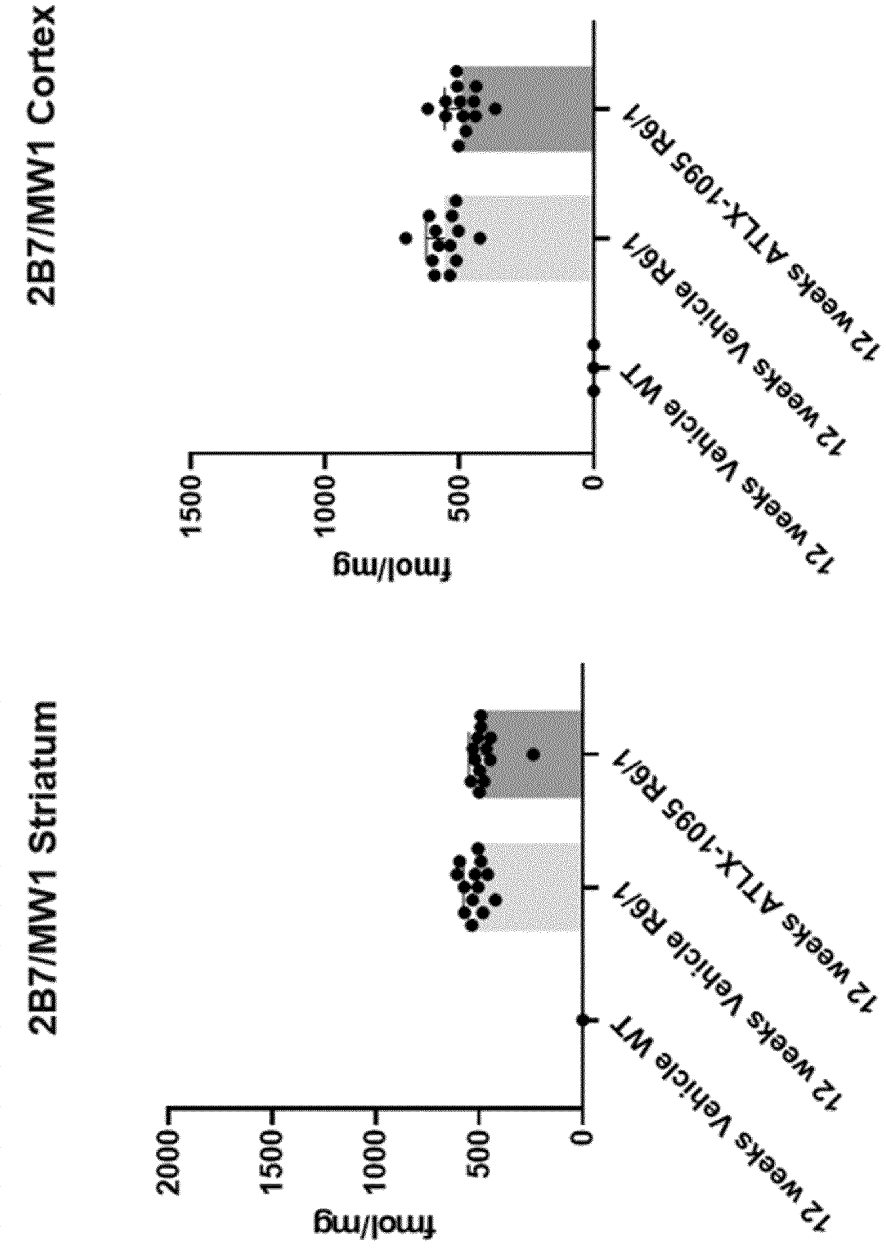

2B7/MW1 Striatum
fmol/mg
2000
1500
1000
500
0
12 weeks Vehicle WT
12 weeks Vehicle R6/1
12 weeks ATLX-1095 R6/1
2B7/MW1 Cortex
fmol/mg
1500
1000
500
0
12 weeks Vehicle WT
12 weeks Vehicle R6/1
12 weeks ATLX-1095 R6/1

Fig.26C

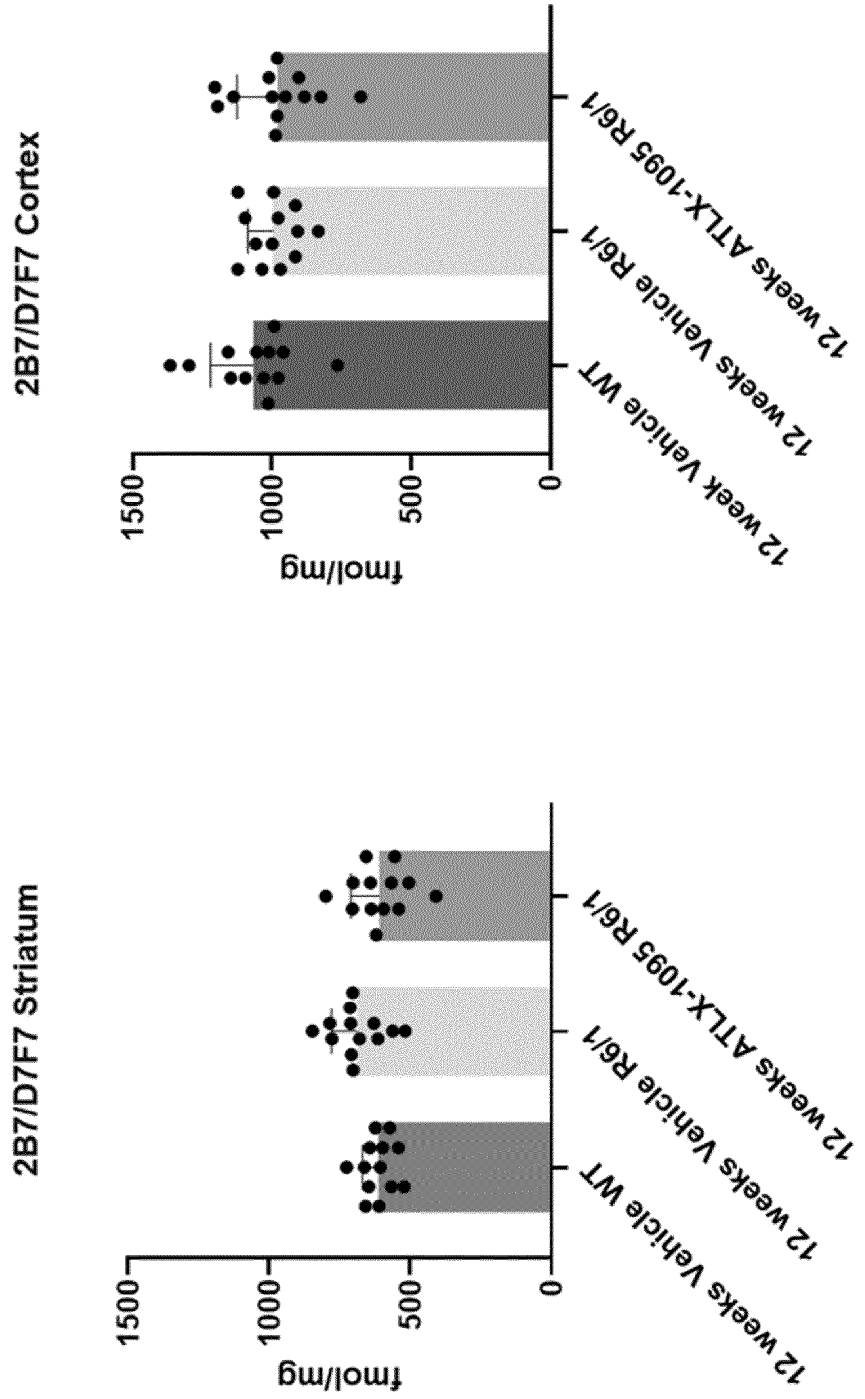

2B7/D7F7 Striatum
fmol/mg
1500
1000
500
0
12 weeks Vehicle WT
12 weeks Vehicle R6/1
12 weeks ATLX-1095 R6/1
2B7/D7F7 Cortex
fmol/mg
1500
1000
500
0
12 week Vehicle WT
12 weeks Vehicle R6/1
12 weeks ATLX-1095 R6/1

Fig.26D

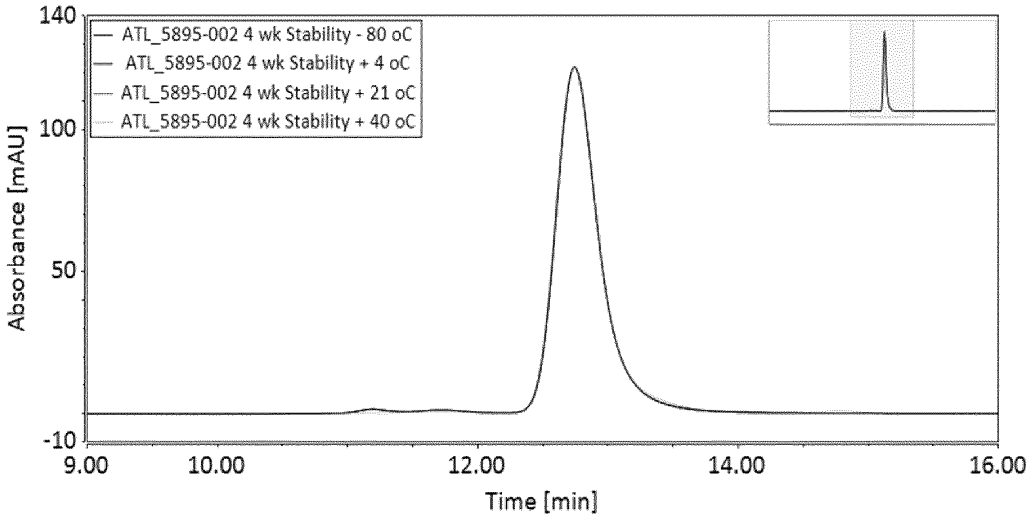


Fig.27A

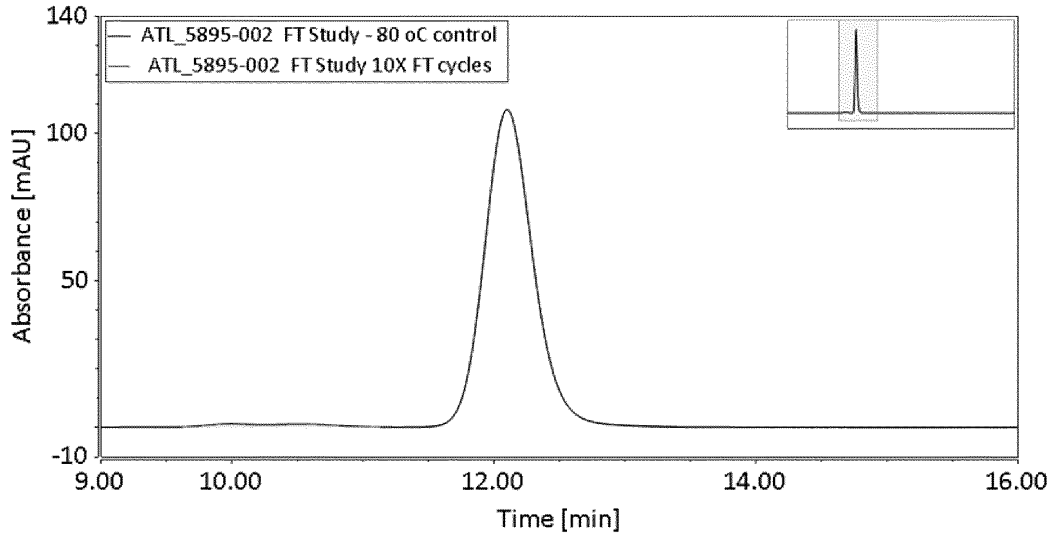


Fig.27B

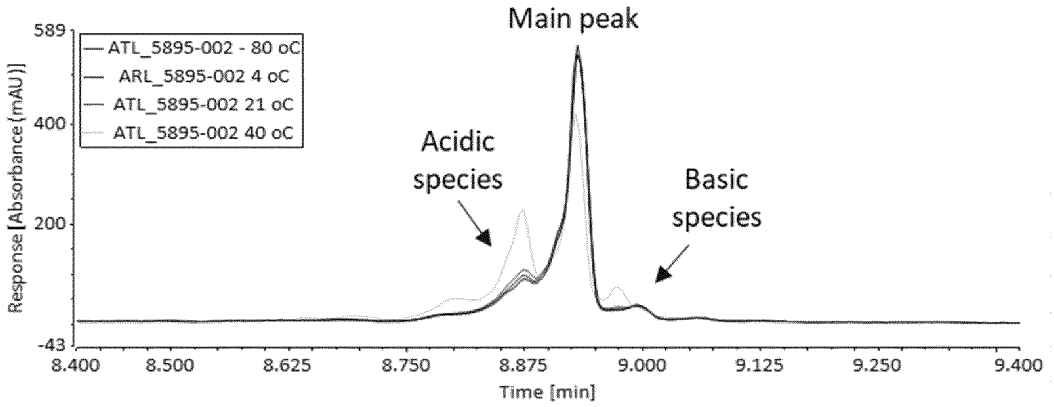


Fig.27C

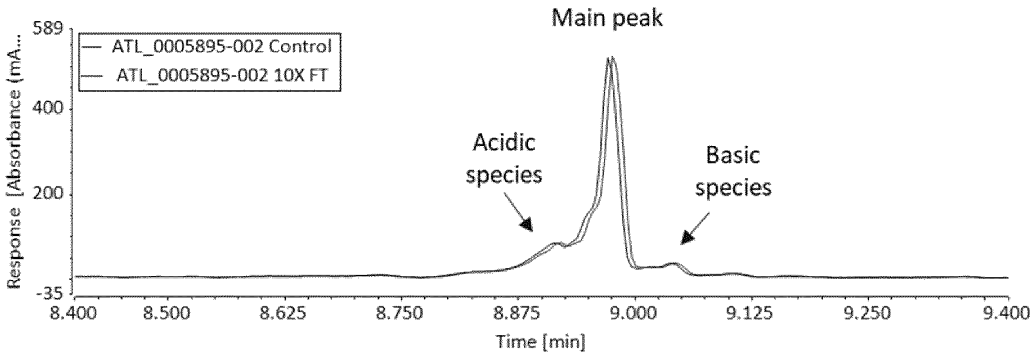


Fig.27D

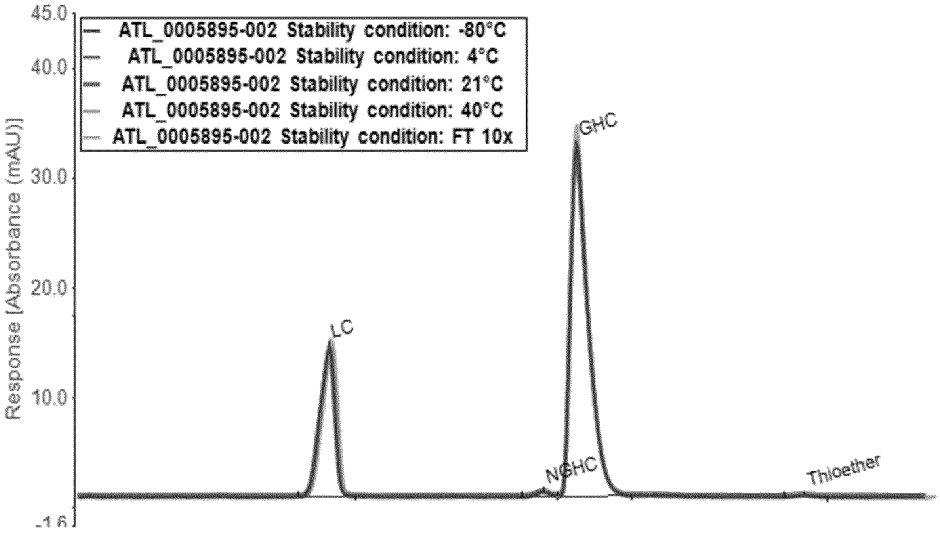


Fig.27E

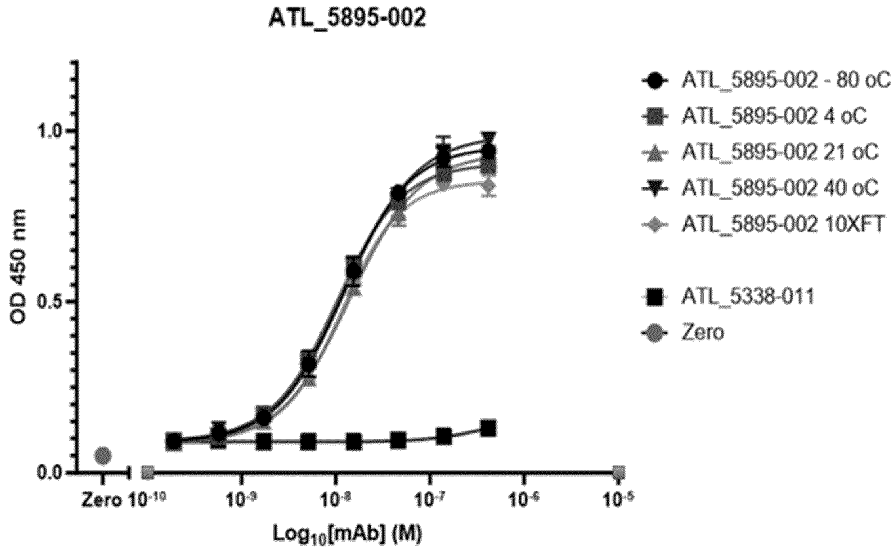
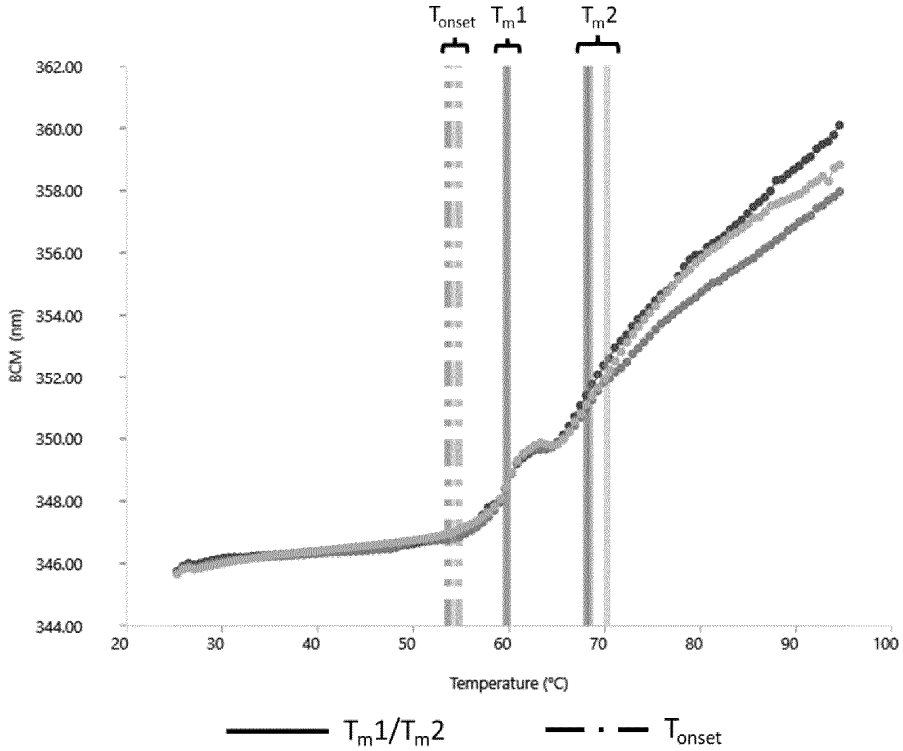


Fig.27F


T_{onset}
T_m1
T_m2
362.00
360.00
358.00
356.00
354.00
352.00
350.00
348.00
346.00
344.00
BCM (nm)
20
30
40
50
60
70
80
90
100
Temperature (°C)
T_m1/T_m2
T_{onset}

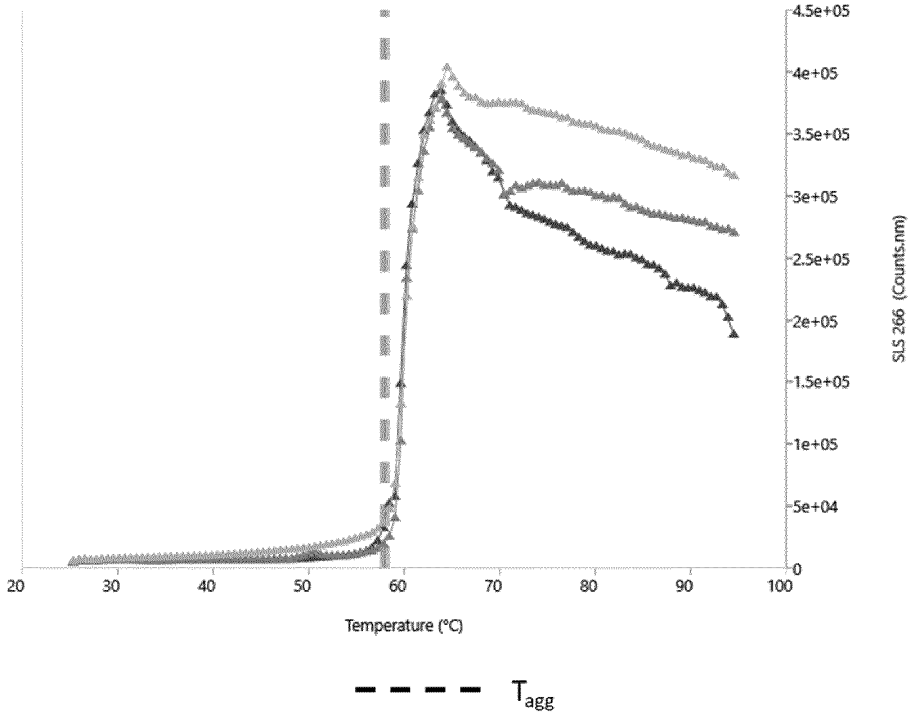

4.5e+05
4e+05
3.5e+05
3e+05
2.5e+05
2e+05
1.5e+05
1e+05
5e+04
0
SLS 266 (Counts.nm)
20
30
40
50
60
70
80
90
100
Temperature (°C)
T_{agg}

Fig.27G

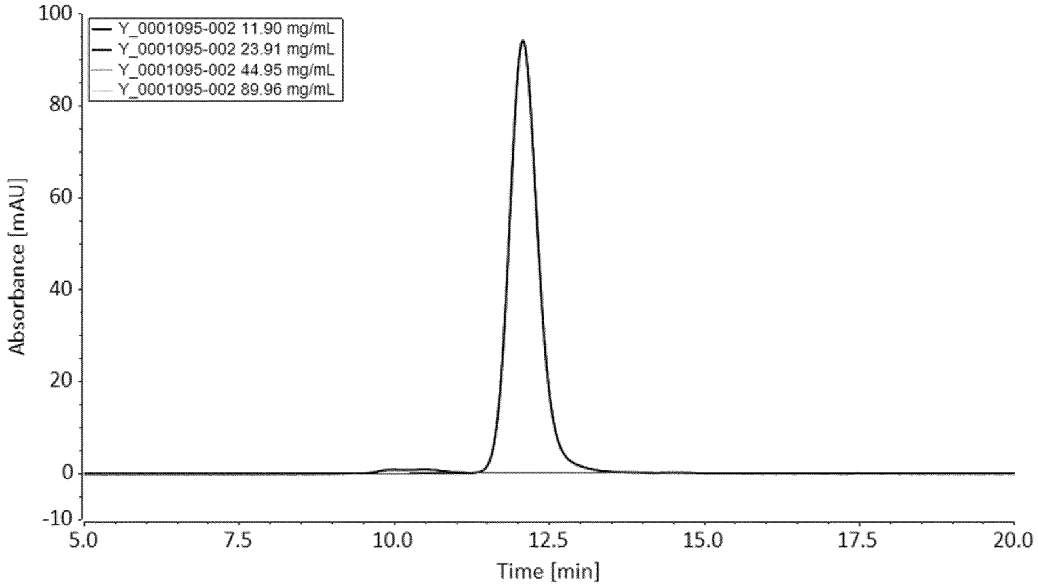


Fig.27H

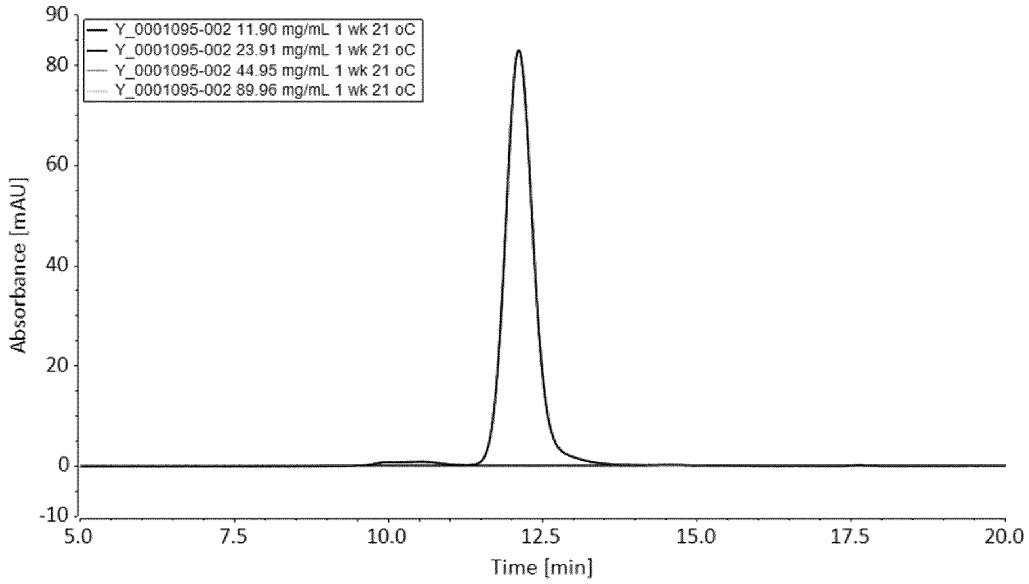


Fig.27I

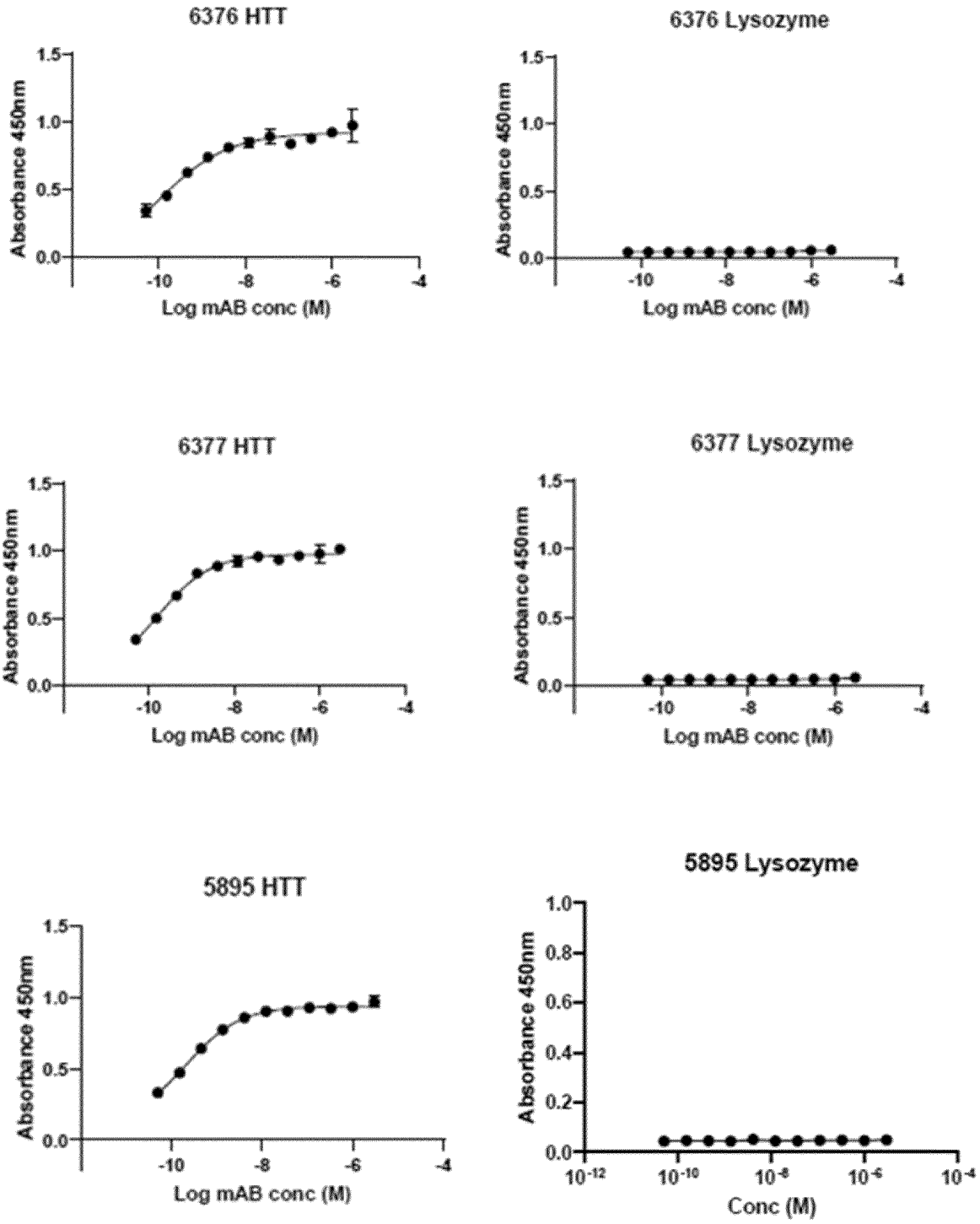

6376 HTT
Absorbance 450nm
1.5
1.0
0.5
0.0
-10
-8
-6
-4
Log mAB conc (M)
6376 Lysozyme
Absorbance 450nm
1.5
1.0
0.5
0.0
-10
-8
-6
-4
Log mAB conc (M)
6377 HTT
Absorbance 450nm
1.5
1.0
0.5
0.0
-10
-8
-6
-4
Log mAB conc (M)
6377 Lysozyme
Absorbance 450nm
1.5
1.0
0.5
0.0
-10
-8
-6
-4
Log mAB conc (M)
5895 HTT
Absorbance 450nm
1.5
1.0
0.5
0.0
-10
-8
-6
-4
Log mAB conc (M)
5895 Lysozyme
Absorbance 450nm
1.0
0.8
0.6
0.4
0.2
0.0
10-12
10-10
10-8
10-6
10-4
Conc (M)

Fig.28

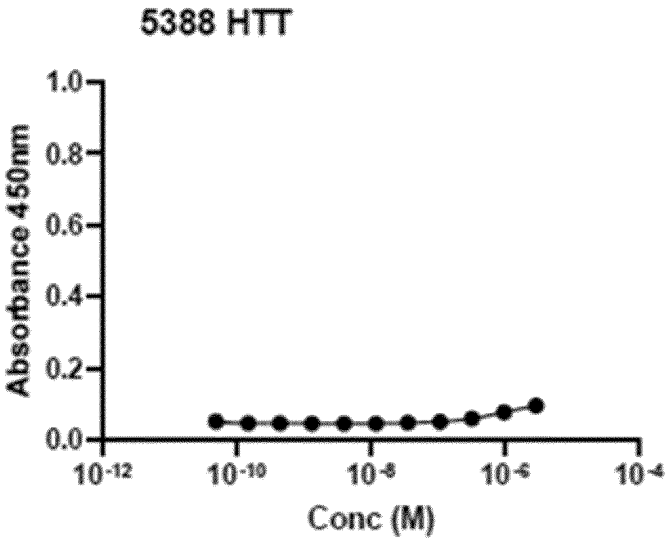


Fig.28 (continued)

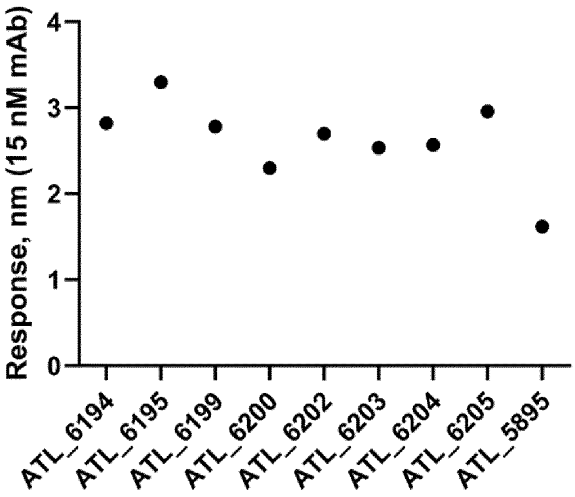


Figure 29A

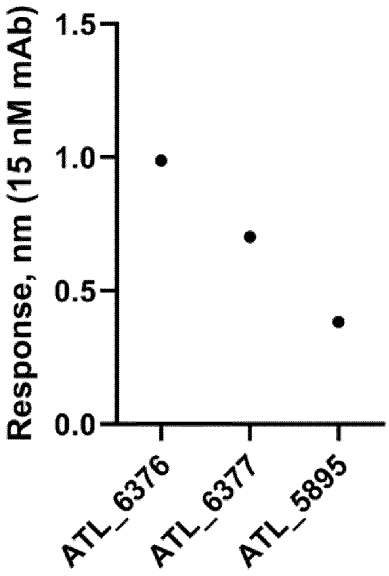


Figure 29B

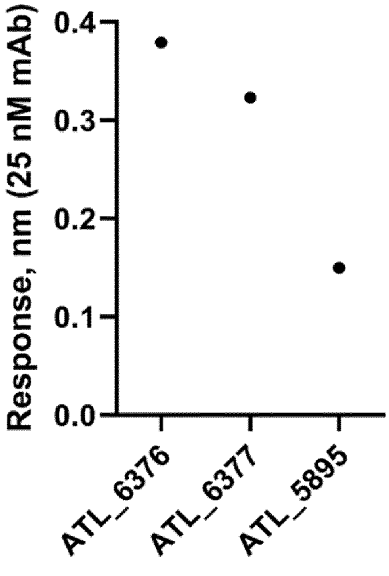


Figure 29C