A

Htau N-terminal

Met A E P R Q E F E V Met E D H A G T Y G L G D R K D Q G G Y T Met H Q D Q E G

D T D A G L K E S P L Q T P T E D G S E E P G S E T S D A K S T P T A E D V T A P L V D E G

A P G K Q A A A Q P H T E I P E G T T A E E A G I G D T P S L E D E A A G H V T Q A R

Met V S K S K D G

B

Htau C-terminal

Met P D L K N V K S K I G S T E N L K H Q P G G G K V Q I I N K K L D L S N V Q S K C

G S K D N I K H V P G G G S V Q I V Y K P V D L S K V T S K C G S L G N I H H K P G G G Q

V E V K S E K L D F K D R V Q S K I G S L D N I T H V P G G G N K K I E T H K L T F R E N A

K A K T D H G A E I V Y K S P V V S G D T S P R H L S N V S S T G S I D Met V D S P Q L A

T L A D E V S A S L G Q A G L

FIG. 1

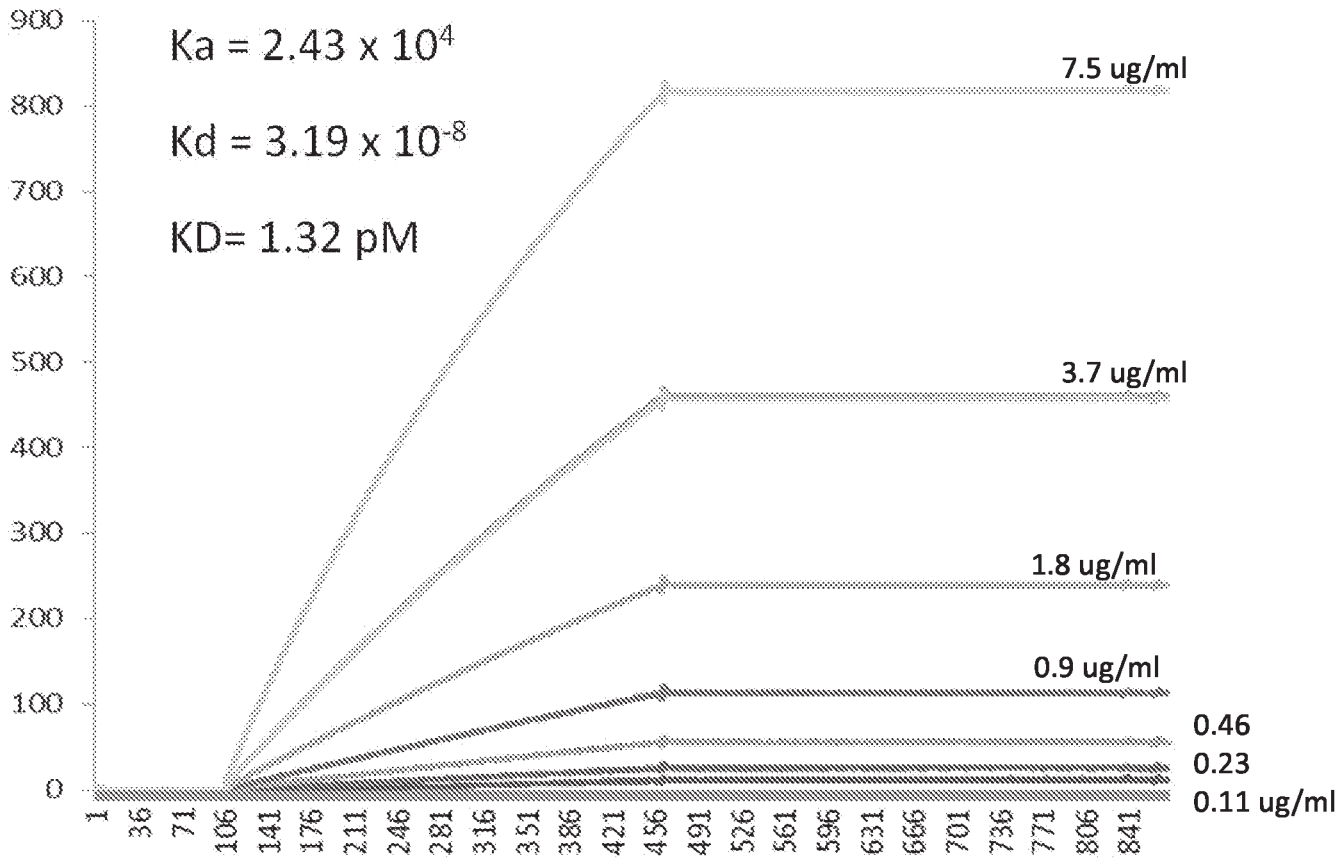

Ka = 2.43 x 10^4
Kd = 3.19 x 10^-8
KD= 1.32 pM
7.5 ug/ml
3.7 ug/ml
1.8 ug/ml
0.9 ug/ml
0.46
0.23
0.11 ug/ml
900
800
700
600
500
400
300
200
100
0
1
36
71
106
141
176
211
246
281
316
351
386
421
456
491
526
561
596
631
666
701
736
771
806
841

FIG. 2A

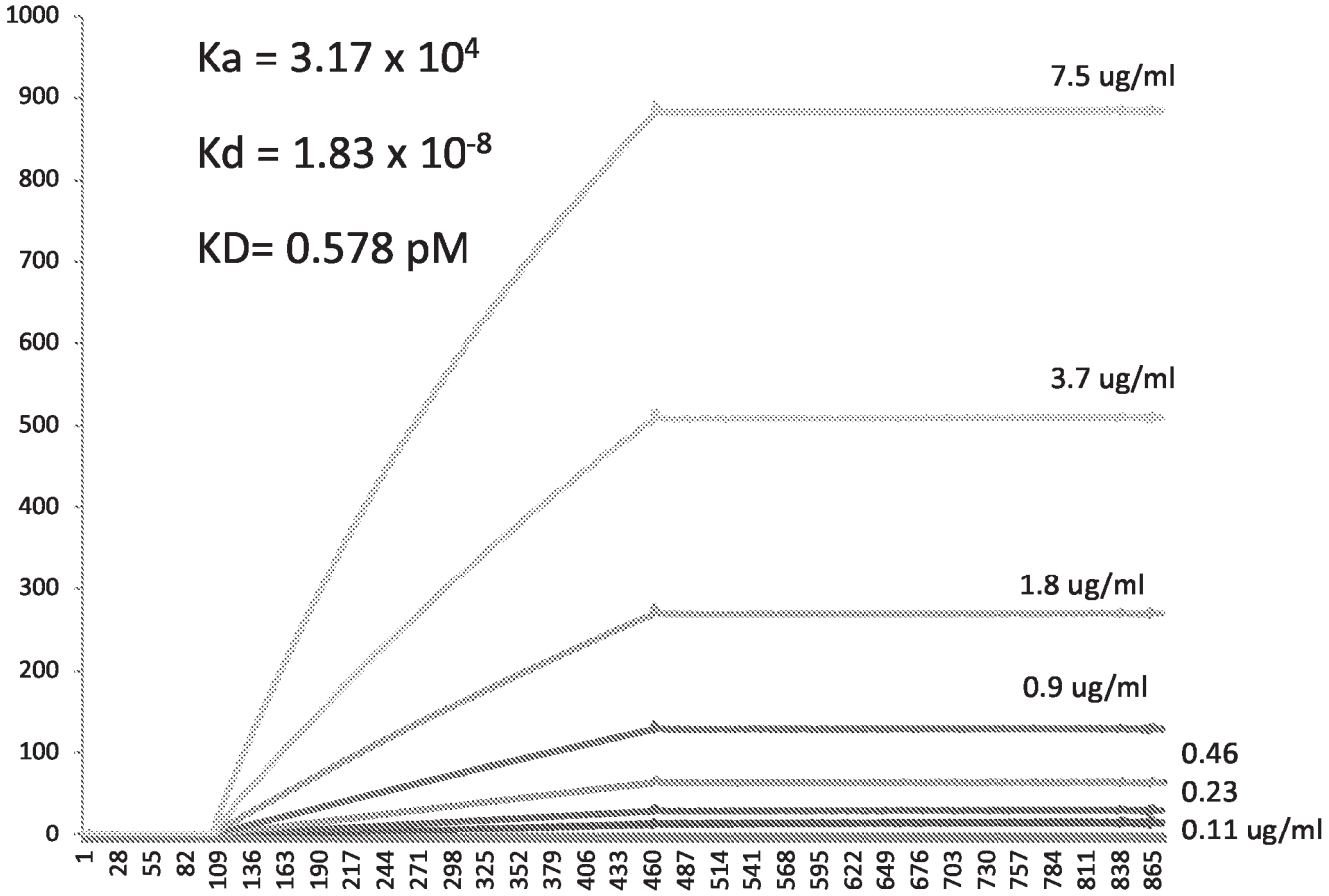

Ka = 3.17 x 10^4
Kd = 1.83 x 10^-8
KD= 0.578 pM
7.5 ug/ml
3.7 ug/ml
1.8 ug/ml
0.9 ug/ml
0.46
0.23
0.11 ug/ml
1000
900
800
700
600
500
400
300
200
100
0
1
28
55
82
109
136
163
190
217
244
271
298
325
352
379
406
433
460
487
514
541
568
595
622
649
676
703
730
757
784
811
838
865

FIG. 2B

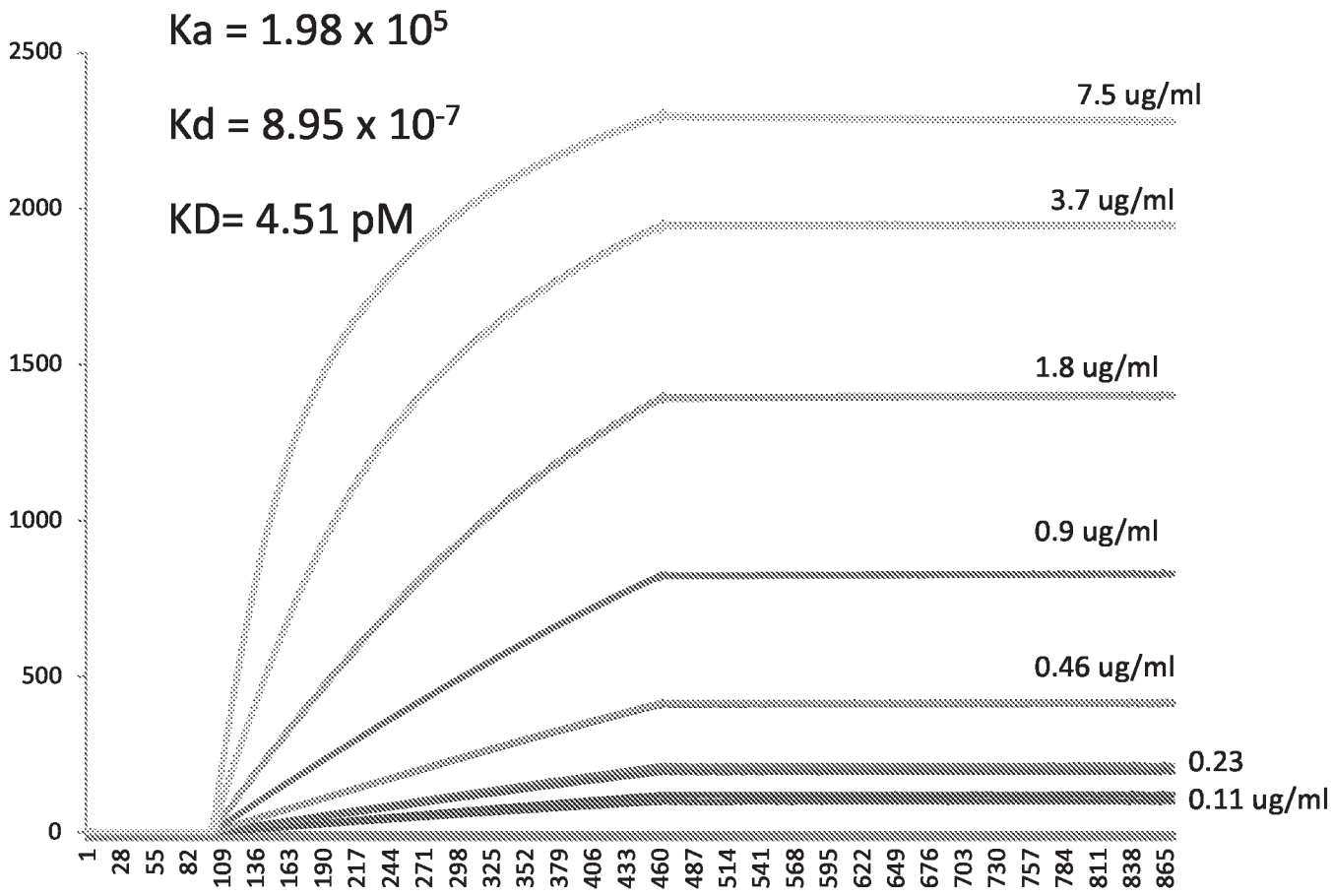

Ka = 1.98 x 10^5
Kd = 8.95 x 10^-7
KD= 4.51 pM
2500
2000
1500
1000
500
0
1
28
55
82
109
136
163
190
217
244
271
298
325
352
379
406
433
460
487
514
541
568
595
622
649
676
703
730
757
784
811
838
865
7.5 ug/ml
3.7 ug/ml
1.8 ug/ml
0.9 ug/ml
0.46 ug/ml
0.23
0.11 ug/ml

FIG. 3A

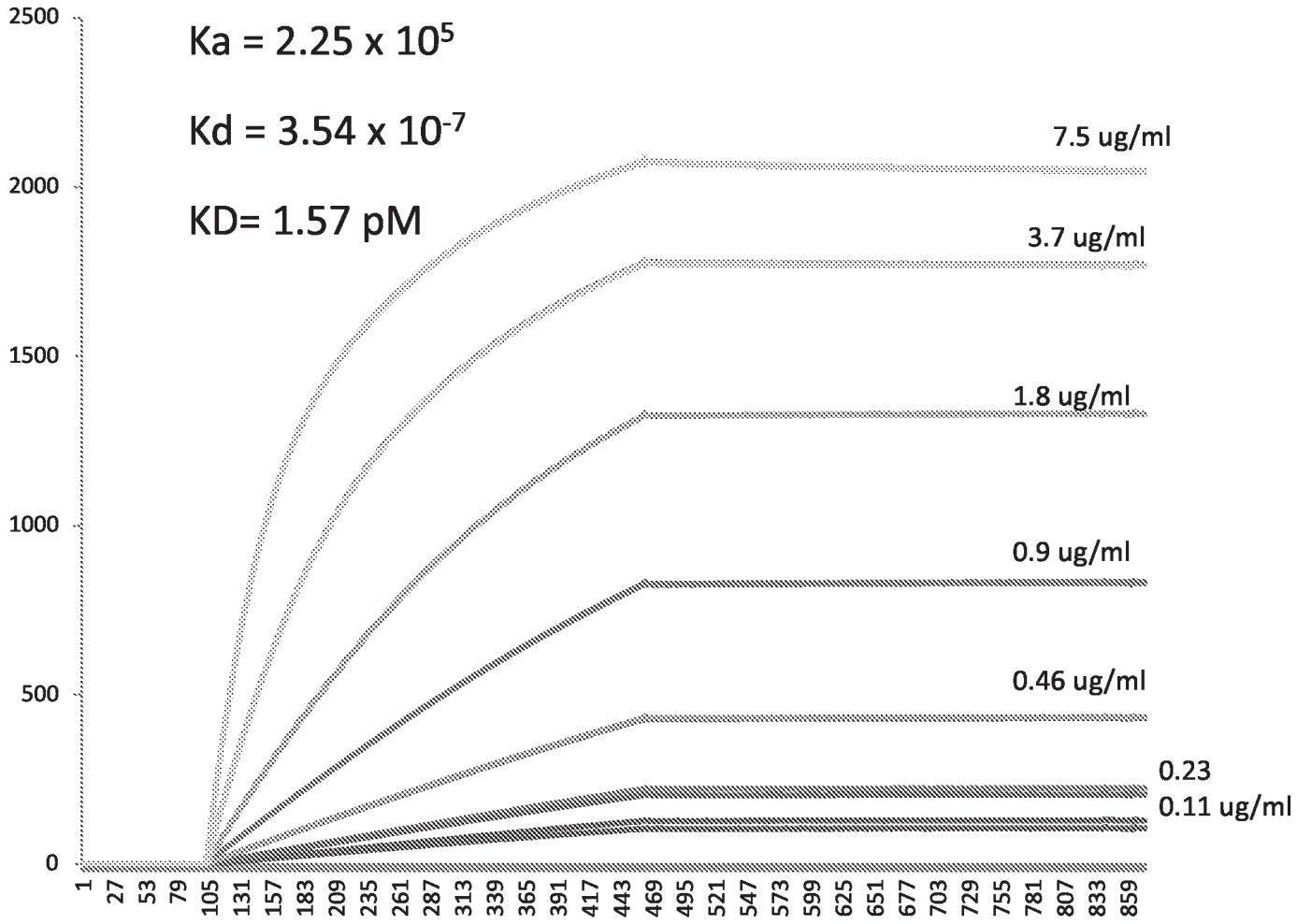

Ka = 2.25 x 10^5
Kd = 3.54 x 10^-7
KD= 1.57 pM
7.5 ug/ml
3.7 ug/ml
1.8 ug/ml
0.9 ug/ml
0.46 ug/ml
0.23
0.11 ug/ml
2500
2000
1500
1000
500
0
1
27
53
79
105
131
157
183
209
235
261
287
313
339
365
391
417
443
469
495
521
547
573
599
625
651
677
703
729
755
781
807
833
859

FIG. 3B

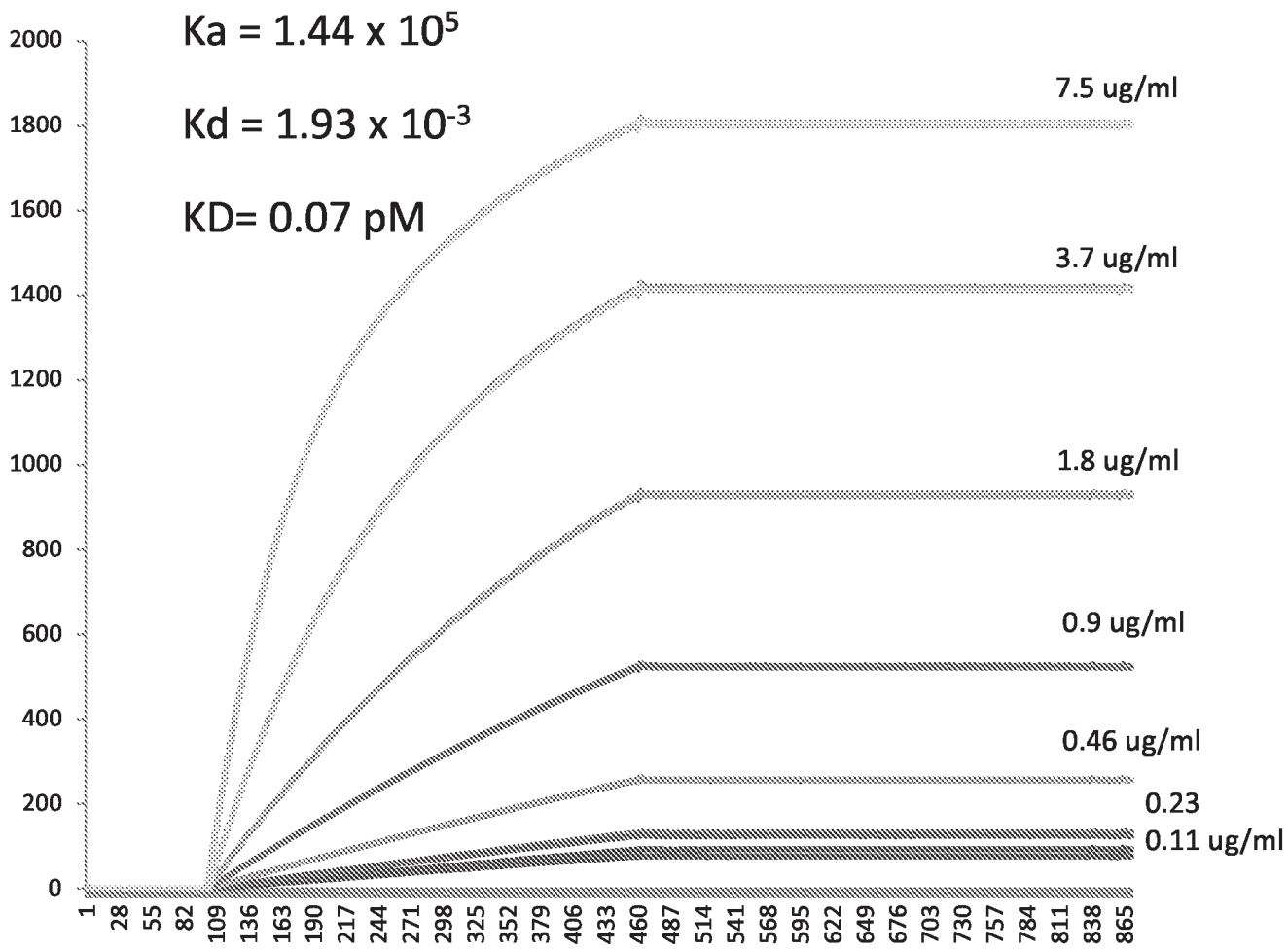

Ka = 1.44 x 10^5
Kd = 1.93 x 10^-3
KD= 0.07 pM
7.5 ug/ml
3.7 ug/ml
1.8 ug/ml
0.9 ug/ml
0.46 ug/ml
0.23
0.11 ug/ml
2000
1800
1600
1400
1200
1000
800
600
400
200
0
1 28 55 82 109 136 163 190 217 244 271 298 325 352 379 406 433 460 487 514 541 568 595 622 649 676 703 730 757 784 811 838 865

FIG. 4A

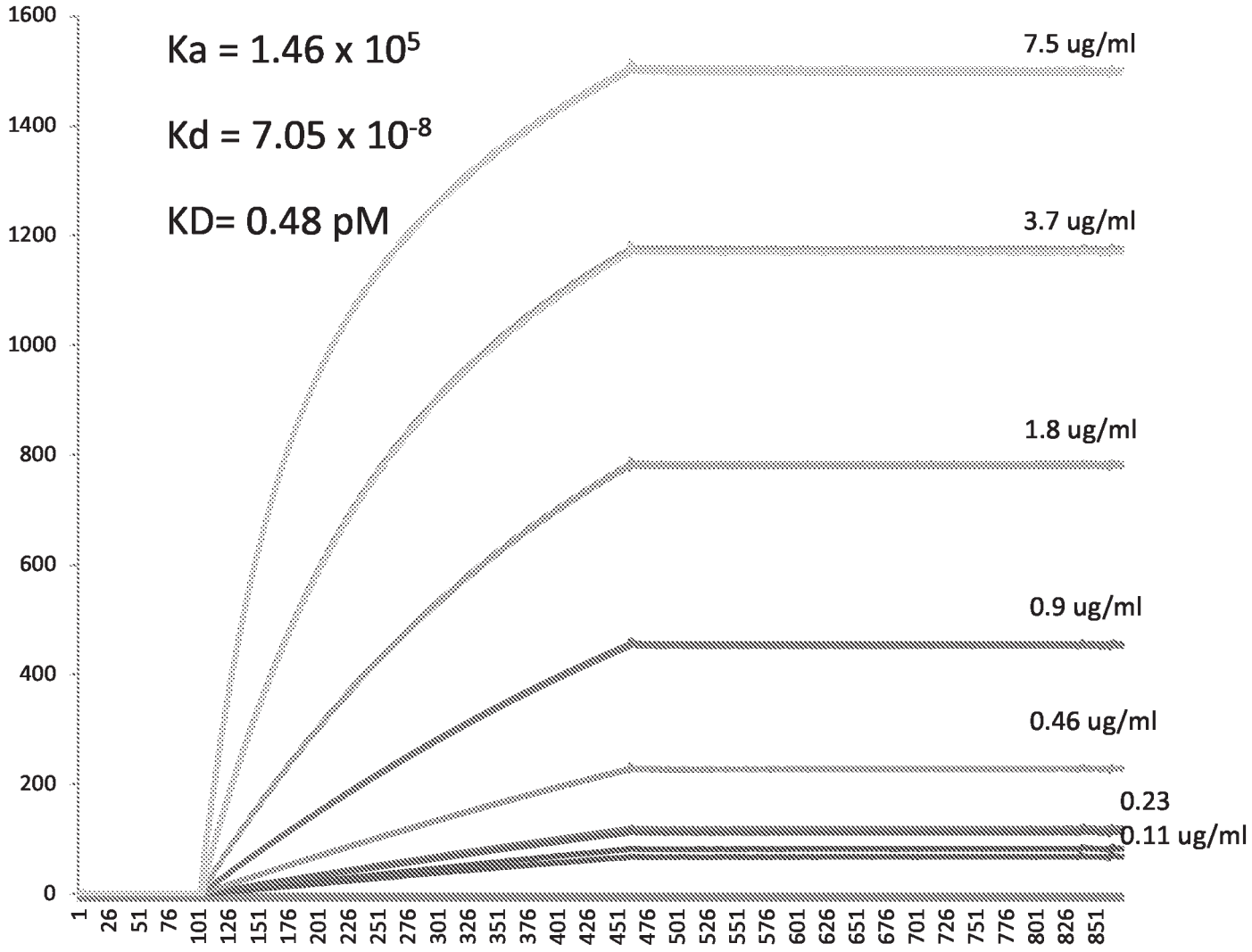

Ka = 1.46 x 10^5
Kd = 7.05 x 10^-8
KD= 0.48 pM
7.5 ug/ml
3.7 ug/ml
1.8 ug/ml
0.9 ug/ml
0.46 ug/ml
0.23
0.11 ug/ml
1600
1400
1200
1000
800
600
400
200
0
1
26
51
76
101
126
151
176
201
226
251
276
301
326
351
376
401
426
451
476
501
526
551
576
601
626
651
676
701
726
751
776
801
826
851

FIG. 4B

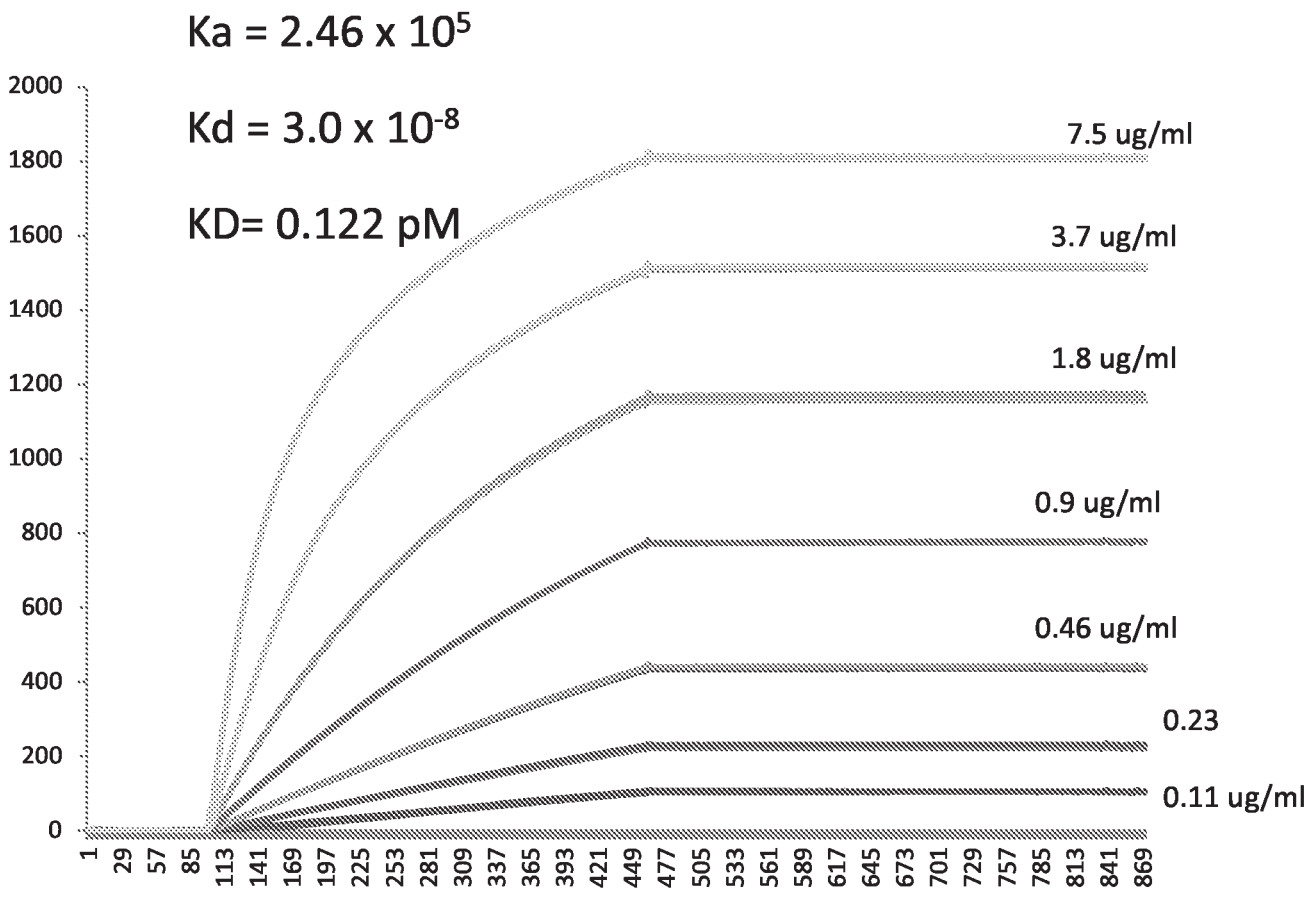

Ka = 2.46 x 10^5
Kd = 3.0 x 10^-8
KD= 0.122 pM
7.5 ug/ml
3.7 ug/ml
1.8 ug/ml
0.9 ug/ml
0.46 ug/ml
0.23
0.11 ug/ml
2000
1800
1600
1400
1200
1000
800
600
400
200
0
1 29 57 85 113 141 169 197 225 253 281 309 337 365 393 421 449 477 505 533 561 589 617 645 673 701 729 757 785 813 841 869

FIG. 5A

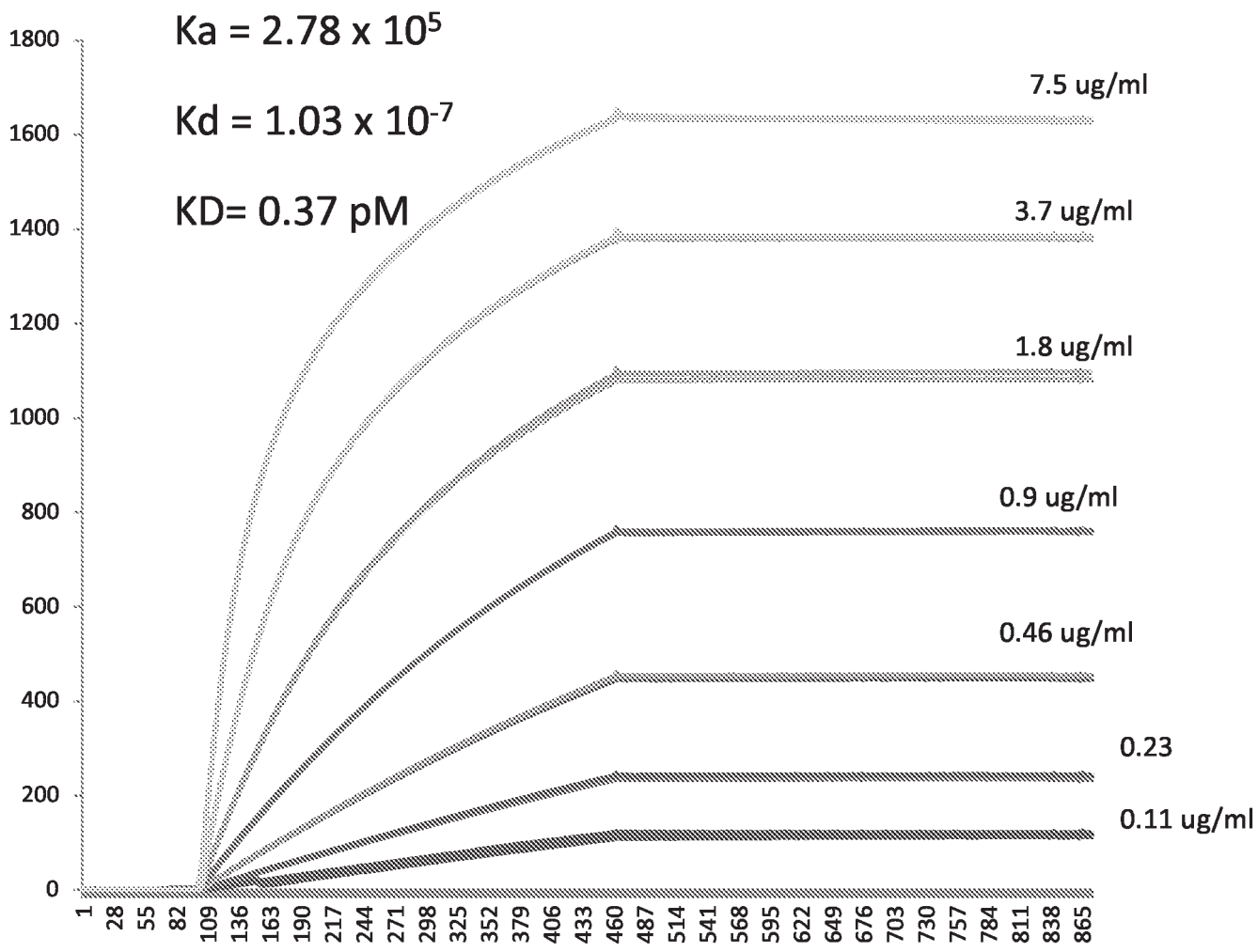

Ka = 2.78 x 10^5
Kd = 1.03 x 10^-7
KD= 0.37 pM
7.5 ug/ml
3.7 ug/ml
1.8 ug/ml
0.9 ug/ml
0.46 ug/ml
0.23
0.11 ug/ml
1800
1600
1400
1200
1000
800
600
400
200
0
1 28 55 82 109 136 163 190 217 244 271 298 325 352 379 406 433 460 487 514 541 568 595 622 649 676 703 730 757 784 811 838 865

FIG. 5B

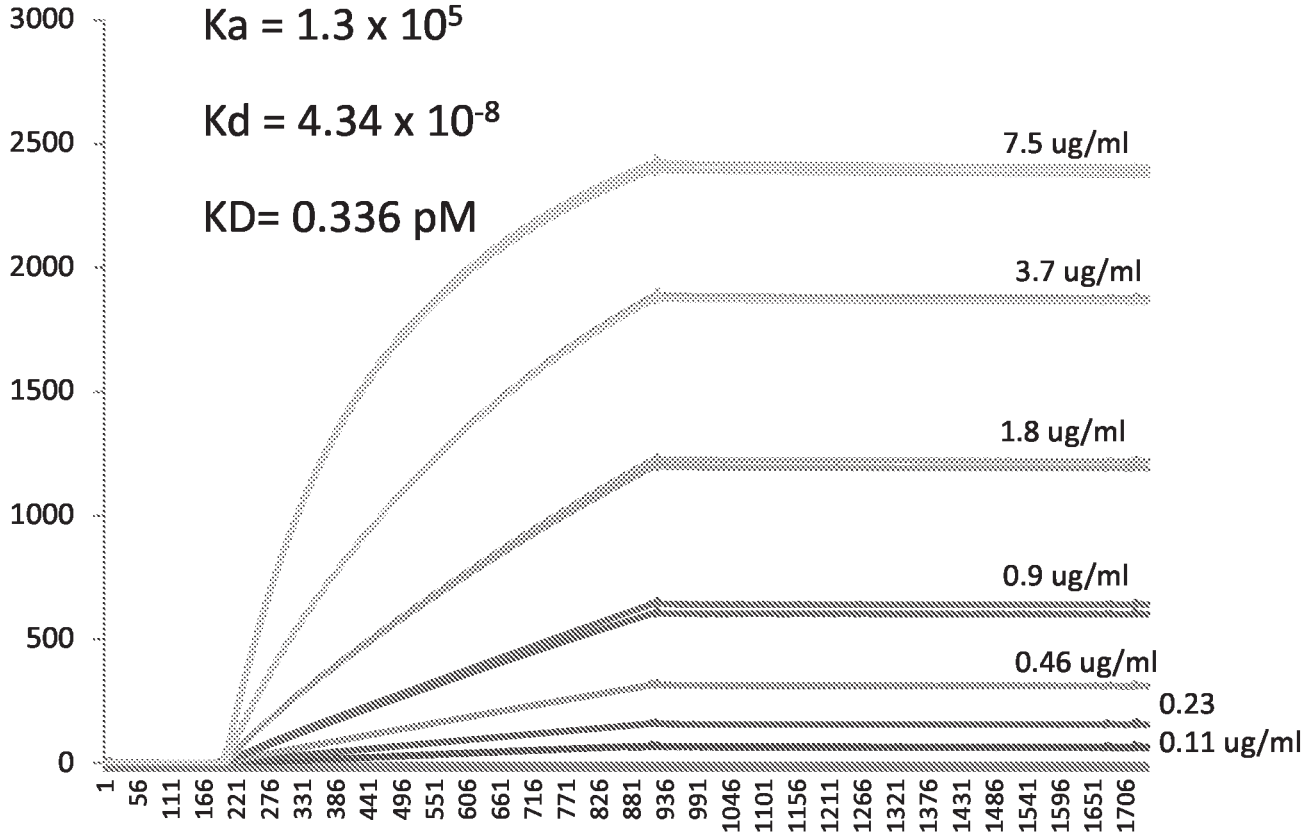

Ka = 1.3 x 10^5
Kd = 4.34 x 10^-8
KD= 0.336 pM
7.5 ug/ml
3.7 ug/ml
1.8 ug/ml
0.9 ug/ml
0.46 ug/ml
0.23
0.11 ug/ml
3000
2500
2000
1500
1000
500
0
1
56
111
166
221
276
331
386
441
496
551
606
661
716
771
826
881
936
991
1046
1101
1156
1211
1266
1321
1376
1431
1486
1541
1596
1651
1706

FIG. 6A

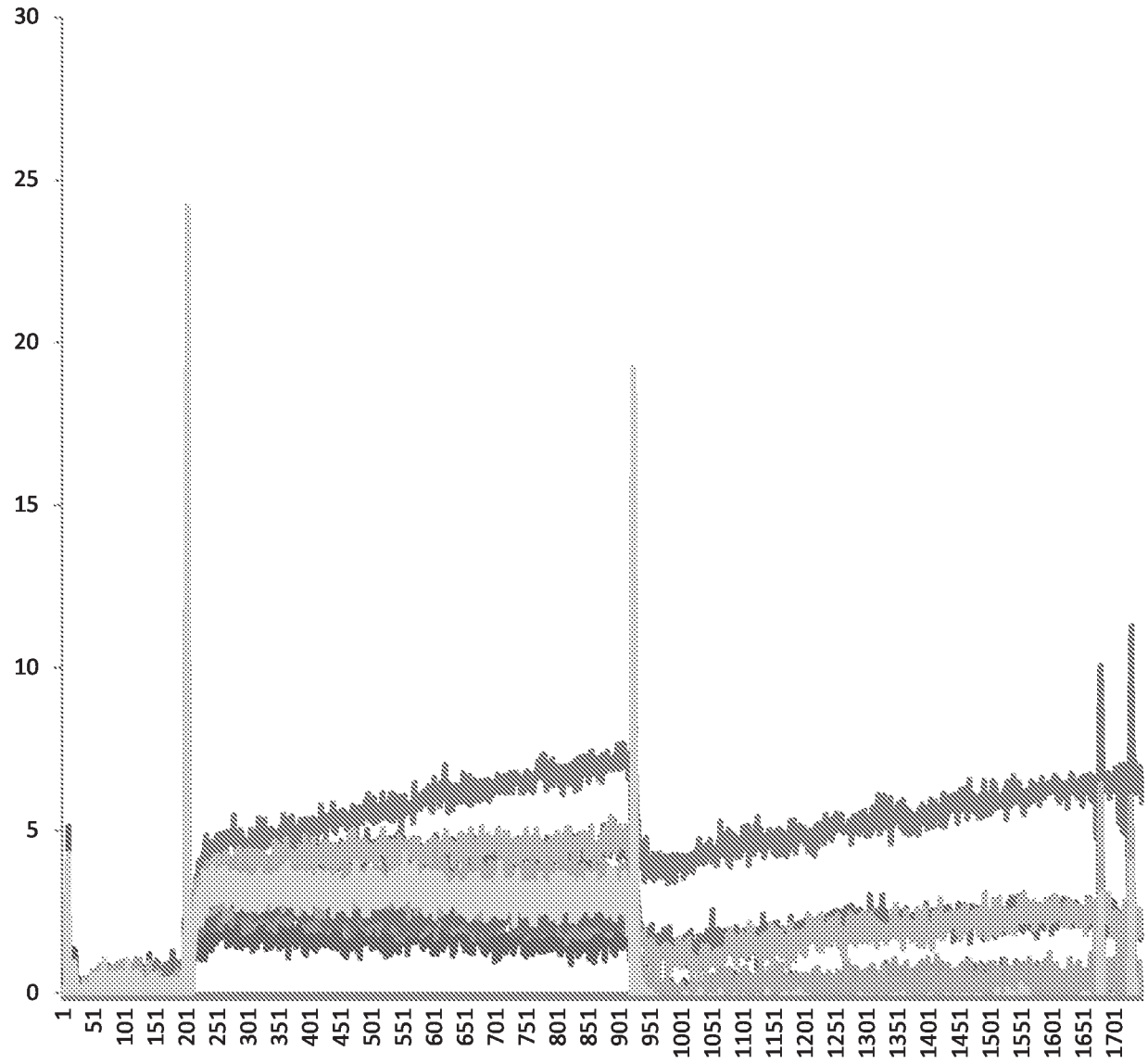

30
25
20
15
10
5
0
1
51
101
151
201
251
301
351
401
451
501
551
601
651
701
751
801
851
901
951
1001
1051
1101
1151
1201
1251
1301
1351
1401
1451
1501
1551
1601
1651
1701

FIG. 6B

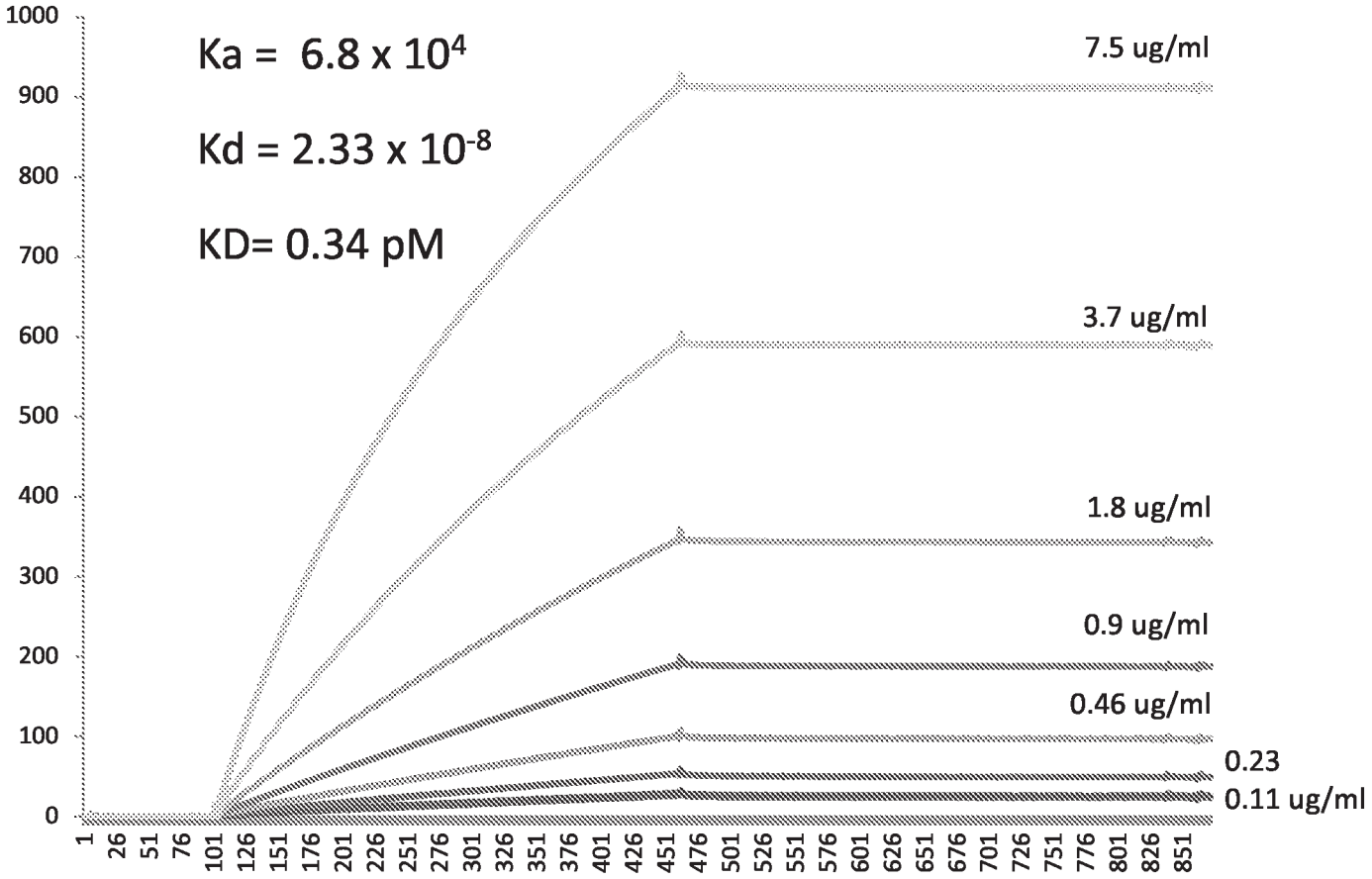

Ka = 6.8 x 10^4
Kd = 2.33 x 10^-8
KD= 0.34 pM
7.5 ug/ml
3.7 ug/ml
1.8 ug/ml
0.9 ug/ml
0.46 ug/ml
0.23
0.11 ug/ml
1000
900
800
700
600
500
400
300
200
100
0
1
26
51
76
101
126
151
176
201
226
251
276
301
326
351
376
401
426
451
476
501
526
551
576
601
626
651
676
701
726
751
776
801
826
851

FIG. 7A

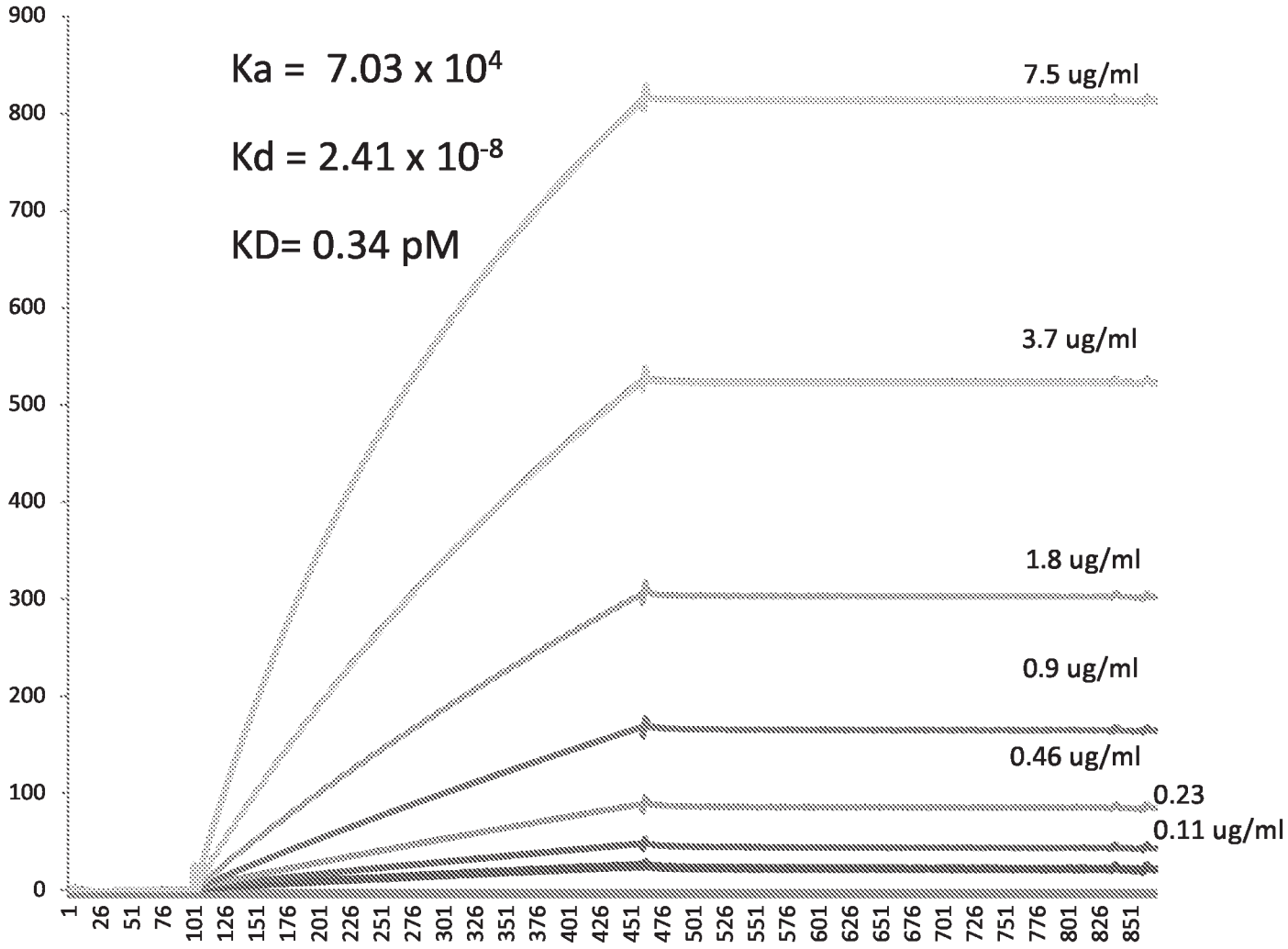

Ka = 7.03 x 10^4
Kd = 2.41 x 10^-8
KD= 0.34 pM
7.5 ug/ml
3.7 ug/ml
1.8 ug/ml
0.9 ug/ml
0.46 ug/ml
0.23
0.11 ug/ml
900
800
700
600
500
400
300
200
100
0
1
26
51
76
101
126
151
176
201
226
251
276
301
326
351
376
401
426
451
476
501
526
551
576
601
626
651
676
701
726
751
776
801
826
851

FIG. 7B

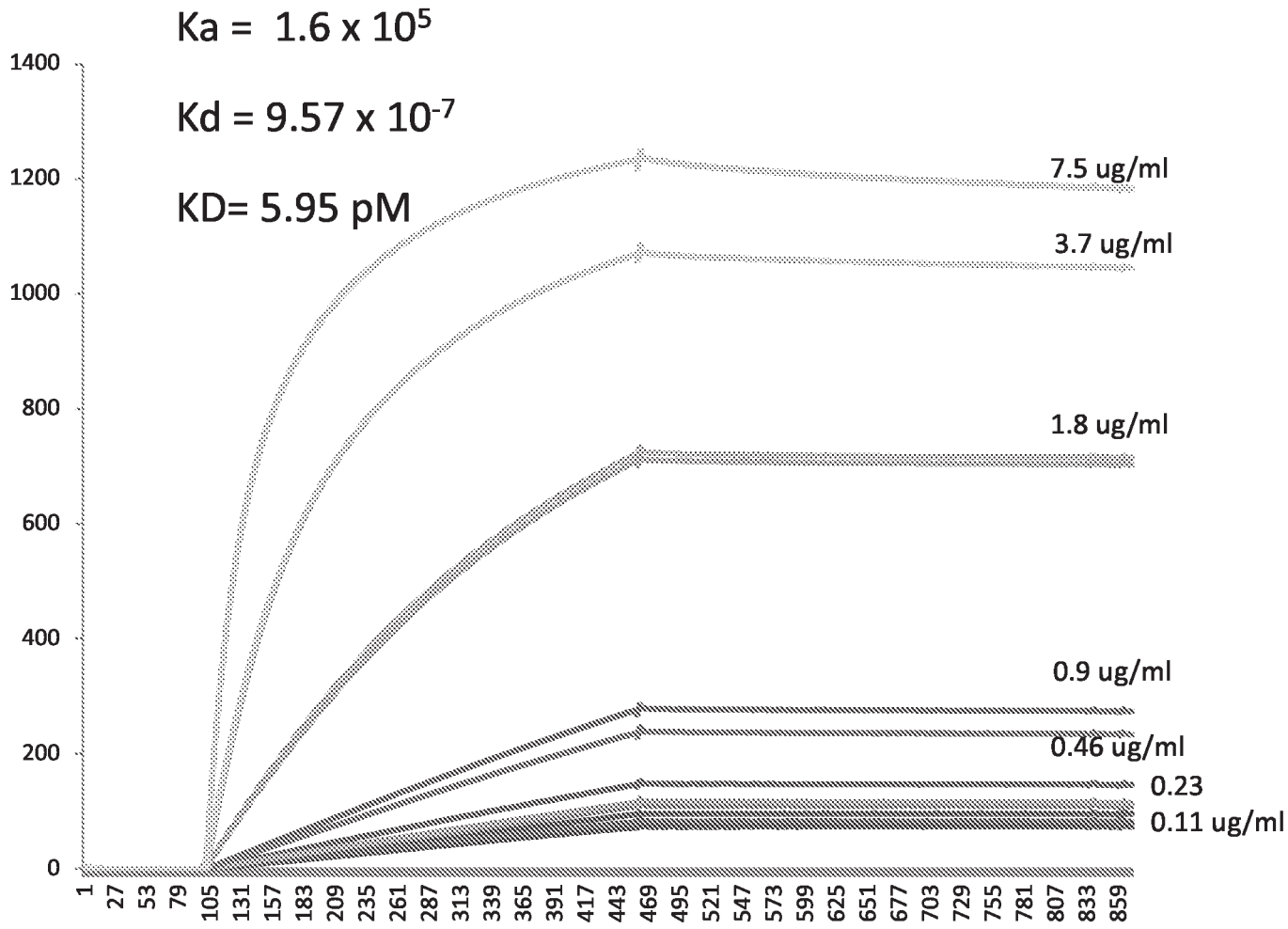

Ka = 1.6 x 10^5
Kd = 9.57 x 10^-7
KD= 5.95 pM
7.5 ug/ml
3.7 ug/ml
1.8 ug/ml
0.9 ug/ml
0.46 ug/ml
0.23
0.11 ug/ml
1400
1200
1000
800
600
400
200
0
1
27
53
79
105
131
157
183
209
235
261
287
313
339
365
391
417
443
469
495
521
547
573
599
625
651
677
703
729
755
781
807
833
859

FIG. 8A

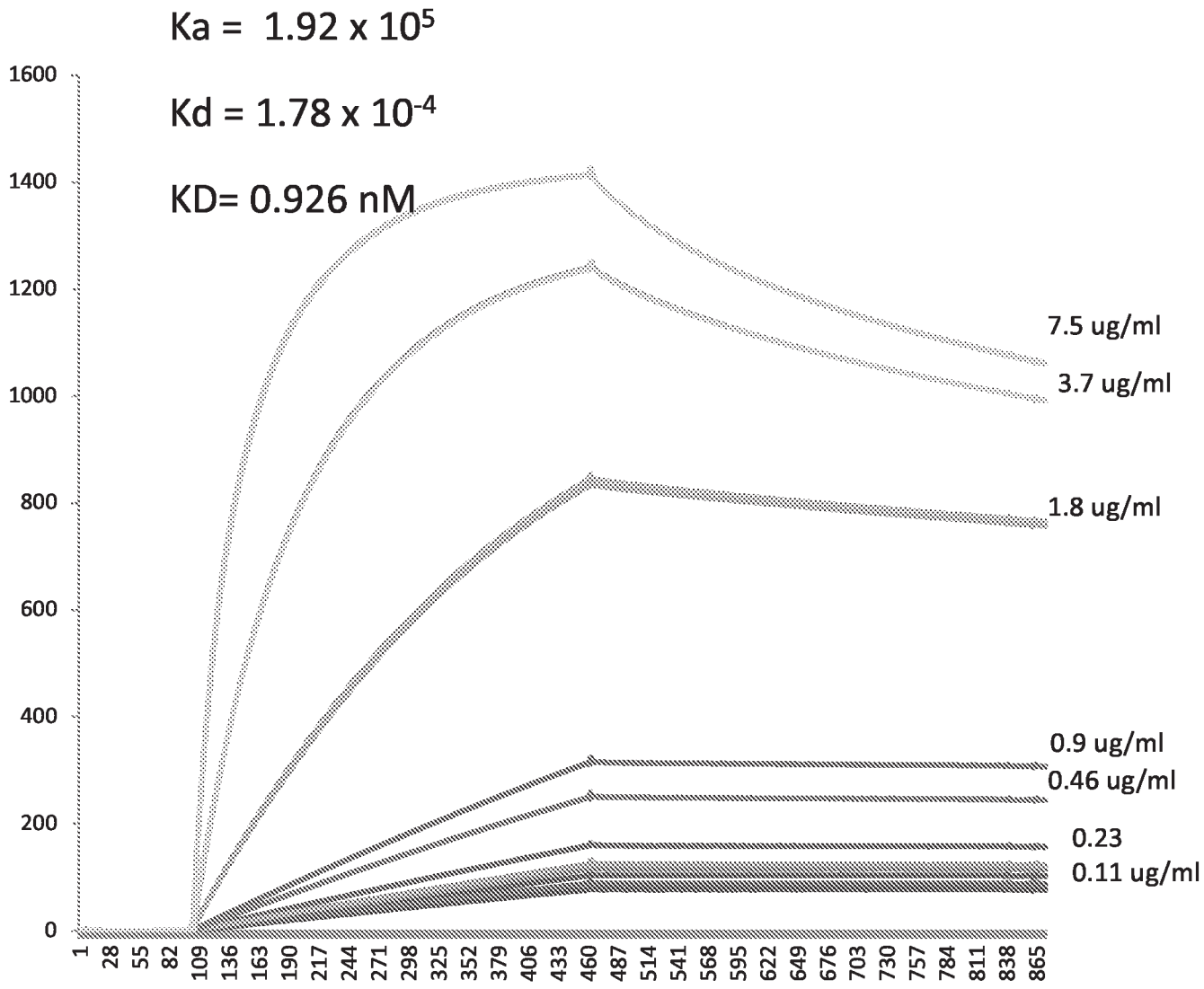

Ka = 1.92 x 10^5
Kd = 1.78 x 10^-4
KD= 0.926 nM
1600
1400
1200
1000
800
600
400
200
0
1
28
55
82
109
136
163
190
217
244
271
298
325
352
379
406
433
460
487
514
541
568
595
622
649
676
703
730
757
784
811
838
865
7.5 ug/ml
3.7 ug/ml
1.8 ug/ml
0.9 ug/ml
0.46 ug/ml
0.23
0.11 ug/ml

FIG. 8B

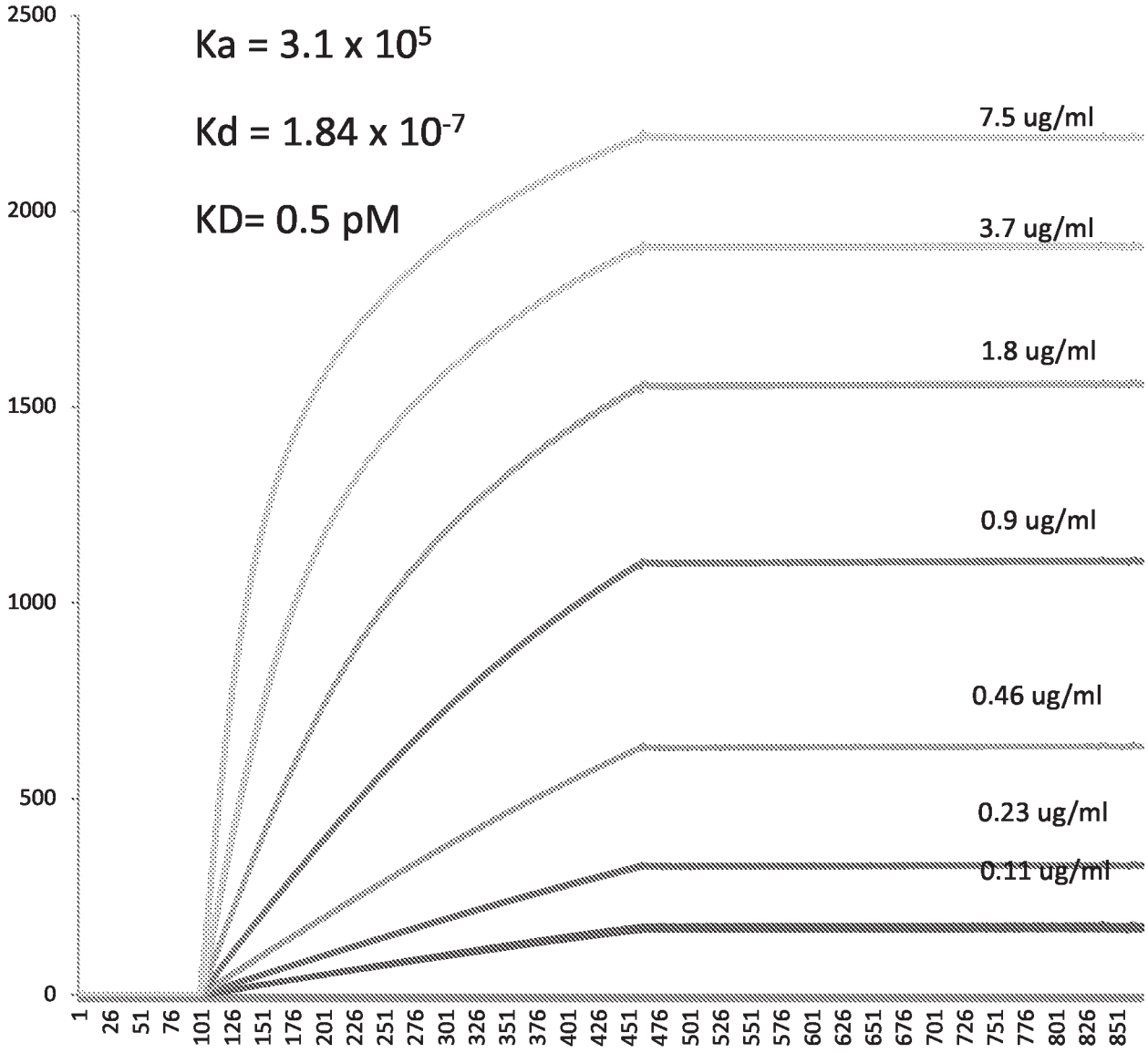

Ka = 3.1 x 10^5
Kd = 1.84 x 10^-7
KD= 0.5 pM
7.5 ug/ml
3.7 ug/ml
1.8 ug/ml
0.9 ug/ml
0.46 ug/ml
0.23 ug/ml
0.11 ug/ml
2500
2000
1500
1000
500
0
1 26 51 76 101 126 151 176 201 226 251 276 301 326 351 376 401 426 451 476 501 526 551 576 601 626 651 676 701 726 751 776 801 826 851

FIG. 9A

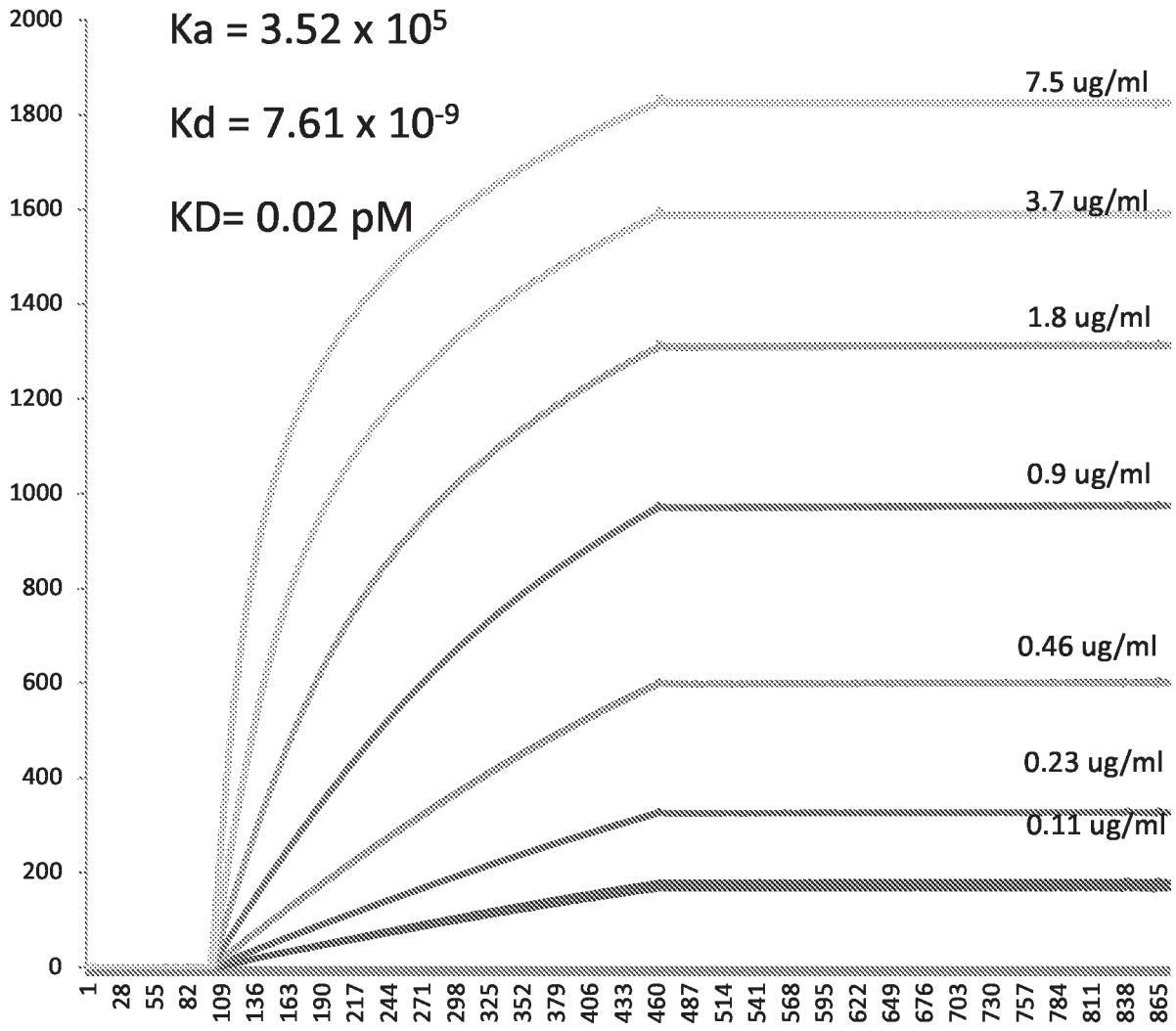

Ka = 3.52 x 10^5
Kd = 7.61 x 10^-9
KD= 0.02 pM
7.5 ug/ml
3.7 ug/ml
1.8 ug/ml
0.9 ug/ml
0.46 ug/ml
0.23 ug/ml
0.11 ug/ml
2000
1800
1600
1400
1200
1000
800
600
400
200
0
1 28 55 82 109 136 163 190 217 244 271 298 325 352 379 406 433 460 487 514 541 568 595 622 649 676 703 730 757 784 811 838 865

FIG. 9B

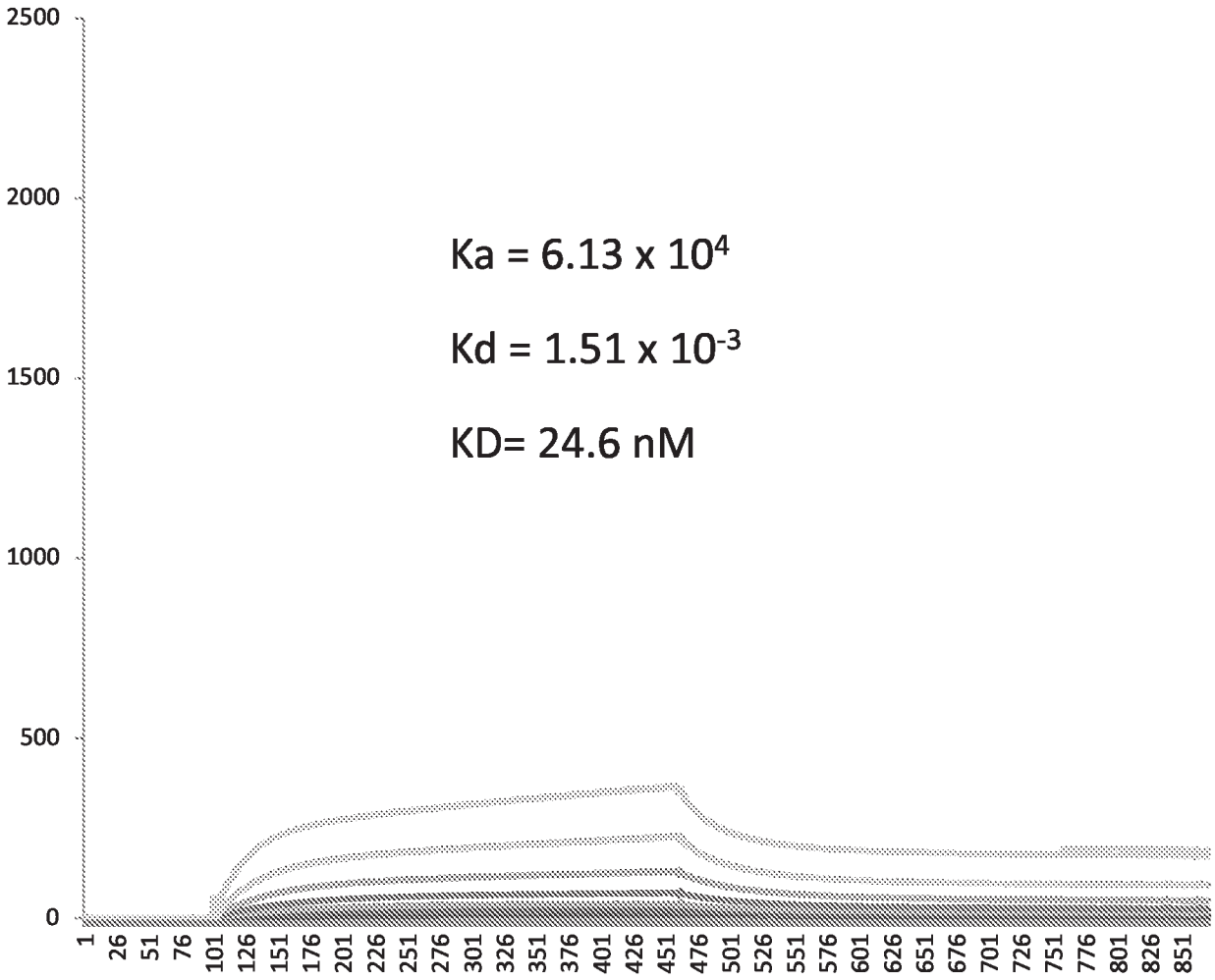

2500
2000
1500
1000
500
0
Ka = 6.13 x 10^4
Kd = 1.51 x 10^-3
KD= 24.6 nM
1
26
51
76
101
126
151
176
201
226
251
276
301
326
351
376
401
426
451
476
501
526
551
576
601
626
651
676
701
726
751
776
801
826
851

FIG. 10A

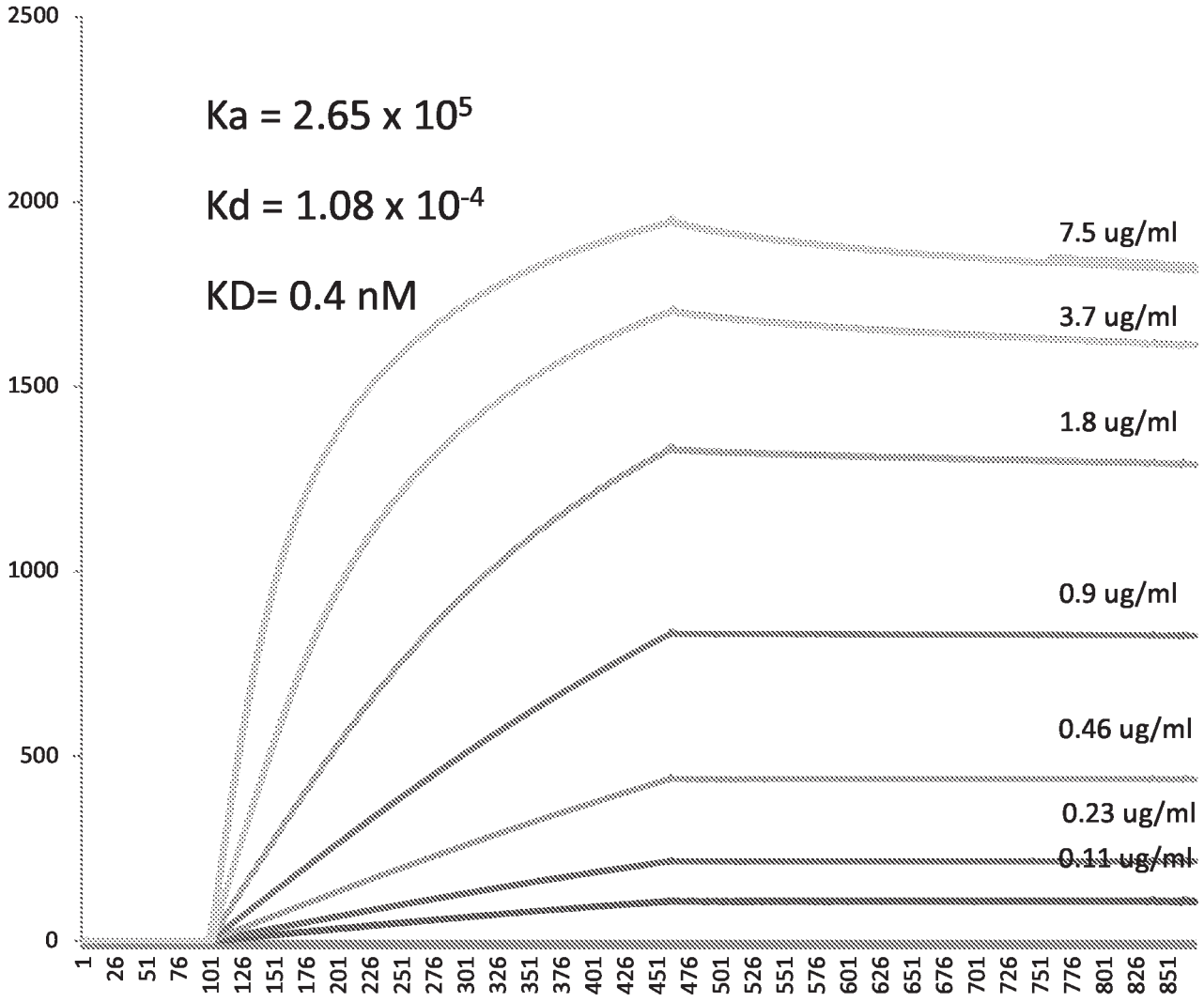

Ka = 2.65 x 10^5
Kd = 1.08 x 10^-4
KD= 0.4 nM
7.5 ug/ml
3.7 ug/ml
1.8 ug/ml
0.9 ug/ml
0.46 ug/ml
0.23 ug/ml
0.11 ug/ml
2500
2000
1500
1000
500
0
1
26
51
76
101
126
151
176
201
226
251
276
301
326
351
376
401
426
451
476
501
526
551
576
601
626
651
676
701
726
751
776
801
826
851

FIG. 10B

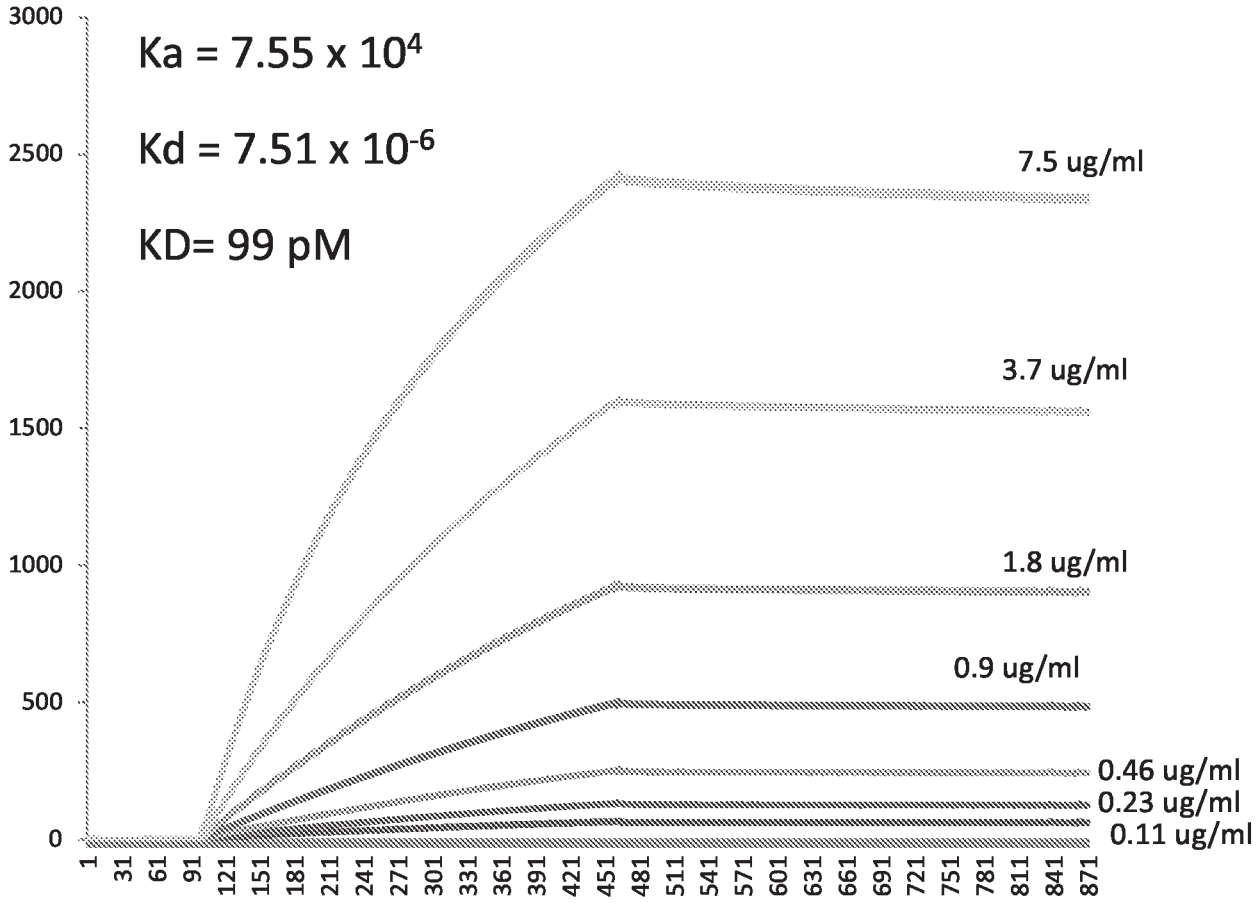

Ka = 7.55 x 10^4
Kd = 7.51 x 10^-6
KD= 99 pM
7.5 ug/ml
3.7 ug/ml
1.8 ug/ml
0.9 ug/ml
0.46 ug/ml
0.23 ug/ml
0.11 ug/ml
3000
2500
2000
1500
1000
500
0
1
31
61
91
121
151
181
211
241
271
301
331
361
391
421
451
481
511
541
571
601
631
661
691
721
751
781
811
841
871

FIG. 11A

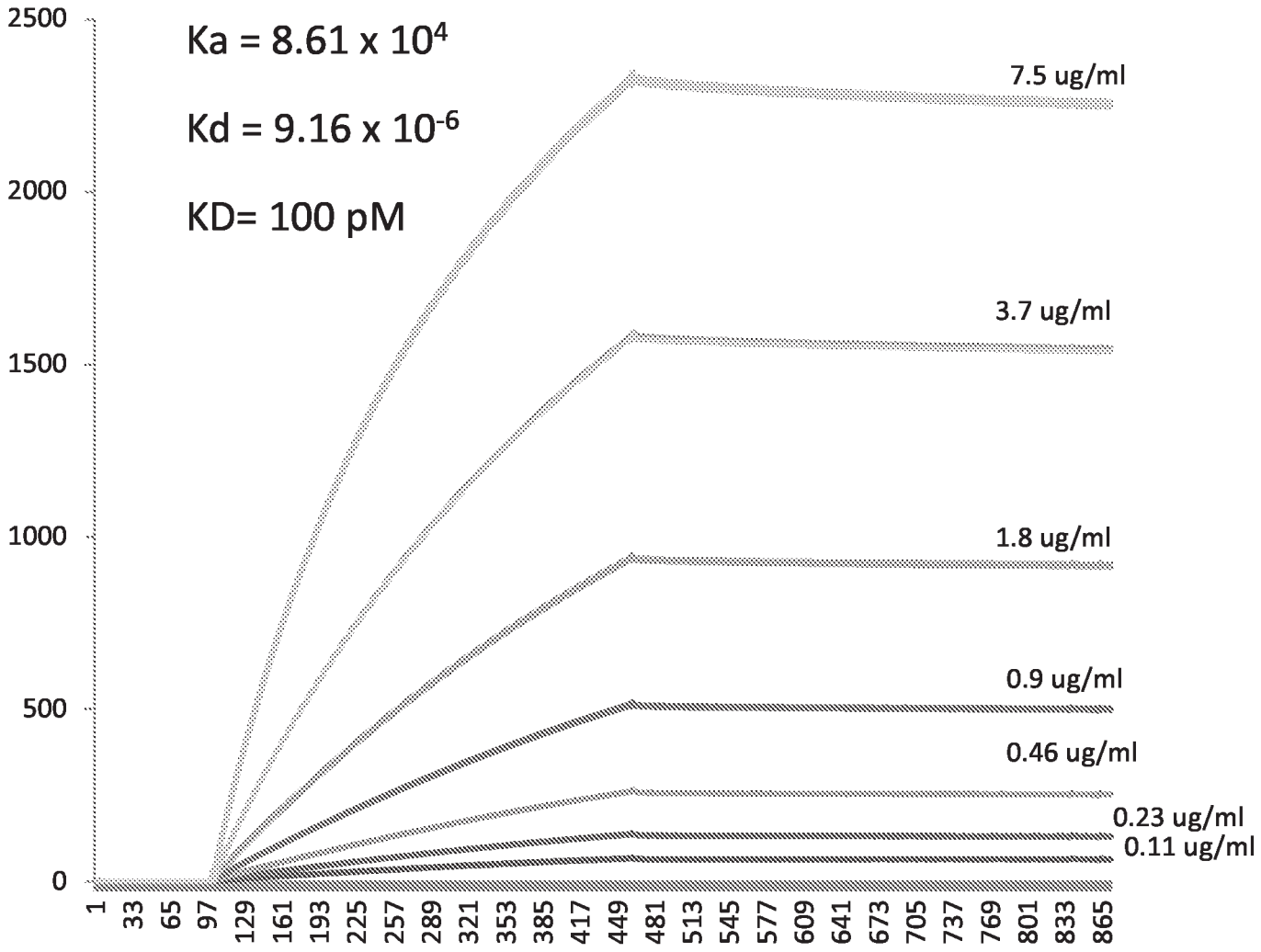

Ka = 8.61 x 10^4
Kd = 9.16 x 10^-6
KD= 100 pM
7.5 ug/ml
3.7 ug/ml
1.8 ug/ml
0.9 ug/ml
0.46 ug/ml
0.23 ug/ml
0.11 ug/ml
2500
2000
1500
1000
500
0
1
33
65
97
129
161
193
225
257
289
321
353
385
417
449
481
513
545
577
609
641
673
705
737
769
801
833
865

FIG. 11B

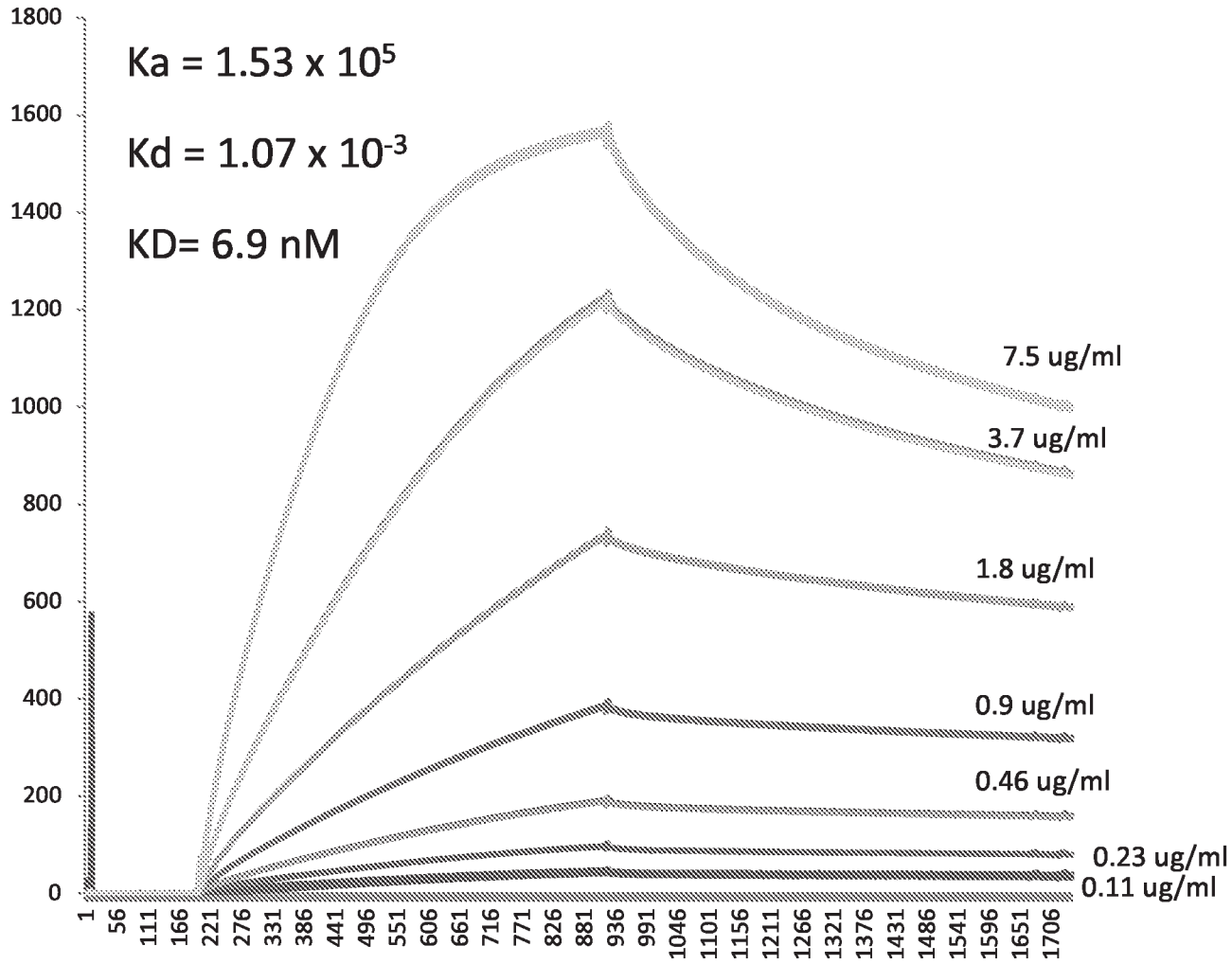

Ka = 1.53 x 10^5
Kd = 1.07 x 10^-3
KD= 6.9 nM
7.5 ug/ml
3.7 ug/ml
1.8 ug/ml
0.9 ug/ml
0.46 ug/ml
0.23 ug/ml
0.11 ug/ml
1800
1600
1400
1200
1000
800
600
400
200
0
1
56
111
166
221
276
331
386
441
496
551
606
661
716
771
826
881
936
991
1046
1101
1156
1211
1266
1321
1376
1431
1486
1541
1596
1651
1706

FIG. 12A

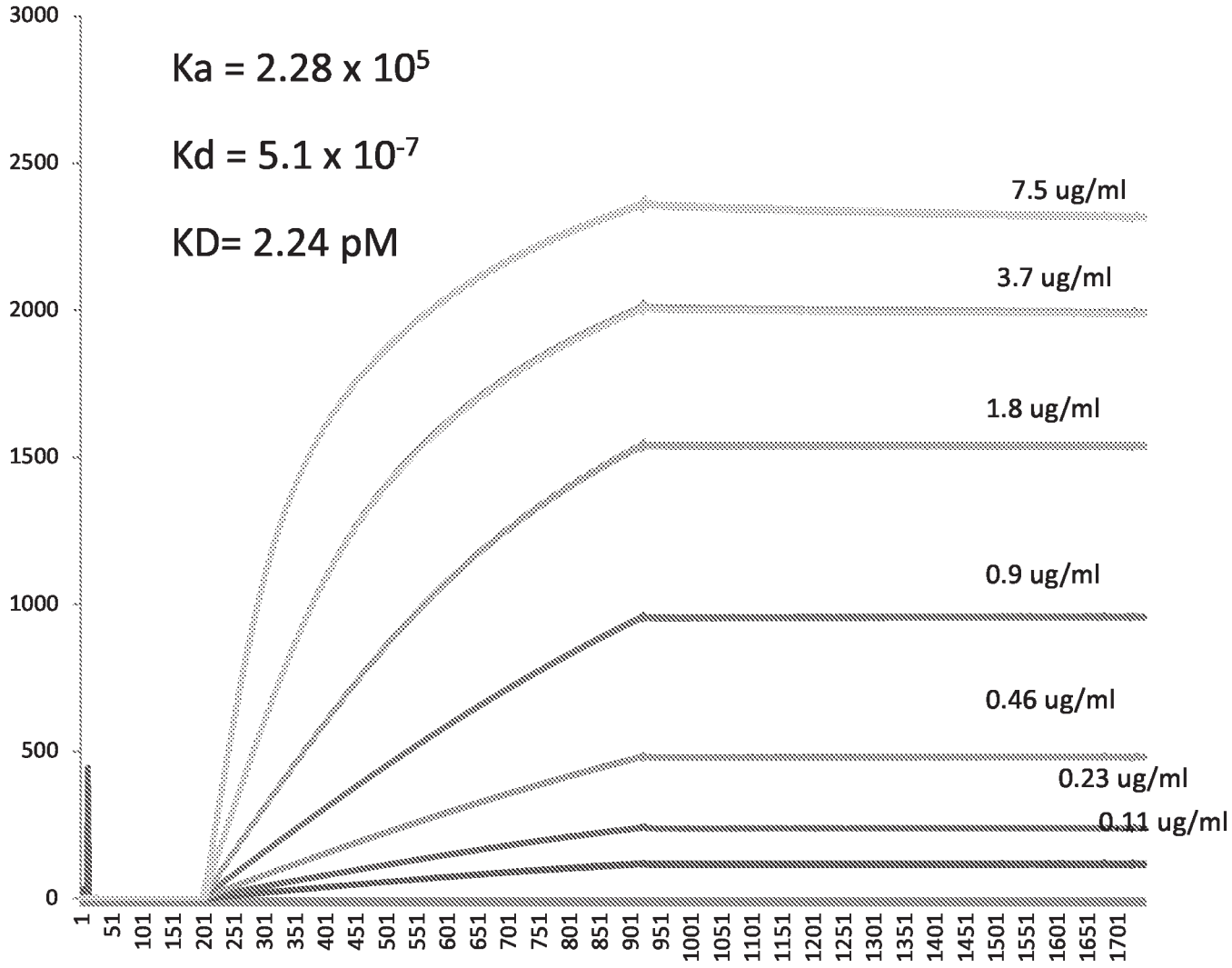

Ka = 2.28 x 10^5
Kd = 5.1 x 10^-7
KD= 2.24 pM
7.5 ug/ml
3.7 ug/ml
1.8 ug/ml
0.9 ug/ml
0.46 ug/ml
0.23 ug/ml
0.11 ug/ml
3000
2500
2000
1500
1000
500
0
1
51
101
151
201
251
301
351
401
451
501
551
601
651
701
751
801
851
901
951
1001
1051
1101
1151
1201
1251
1301
1351
1401
1451
1501
1551
1601
1651
1701

FIG. 12B

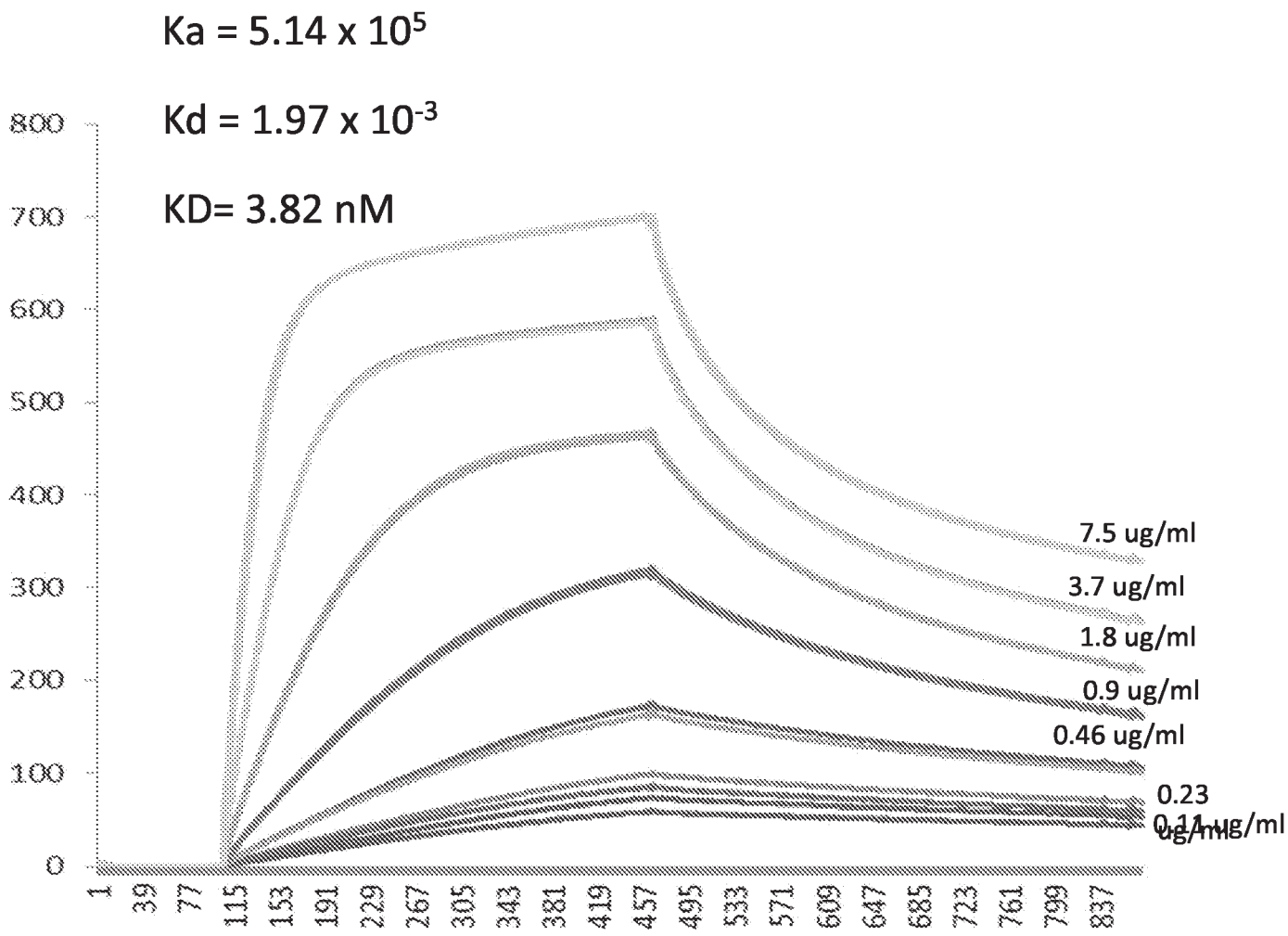

Ka = 5.14 x 10^5
Kd = 1.97 x 10^-3
KD= 3.82 nM
800
700
600
500
400
300
200
100
0
1
39
77
115
153
191
229
267
305
343
381
419
457
495
533
571
609
647
685
723
761
799
837
7.5 ug/ml
3.7 ug/ml
1.8 ug/ml
0.9 ug/ml
0.46 ug/ml
0.23
0.11 ug/ml

FIG. 13A

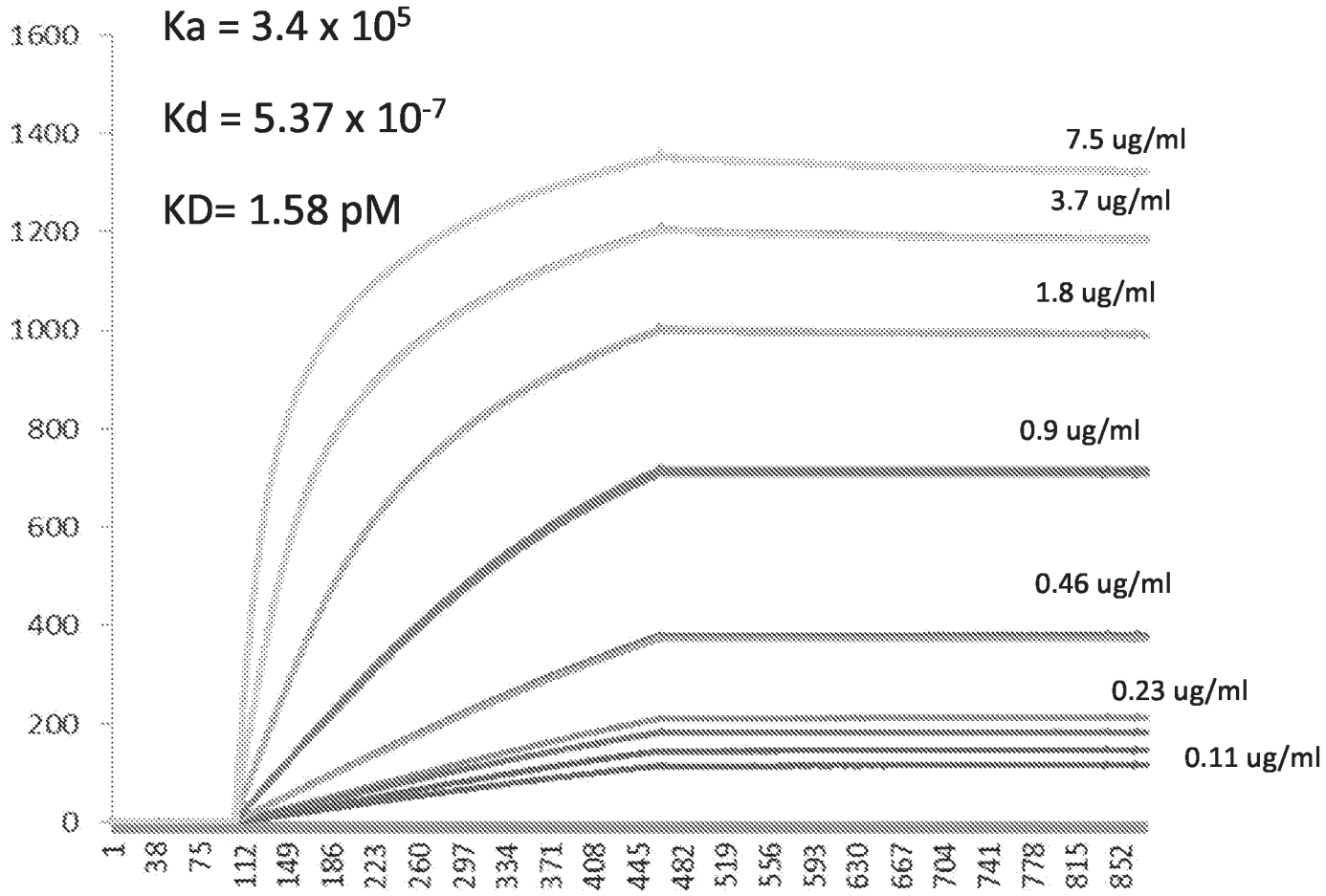

Ka = 3.4 x 10^5
Kd = 5.37 x 10^-7
KD= 1.58 pM
7.5 ug/ml
3.7 ug/ml
1.8 ug/ml
0.9 ug/ml
0.46 ug/ml
0.23 ug/ml
0.11 ug/ml
1600
1400
1200
1000
800
600
400
200
0
1
38
75
112
149
186
223
260
297
334
371
408
445
482
519
556
593
630
667
704
741
778
815
852

FIG. 13B

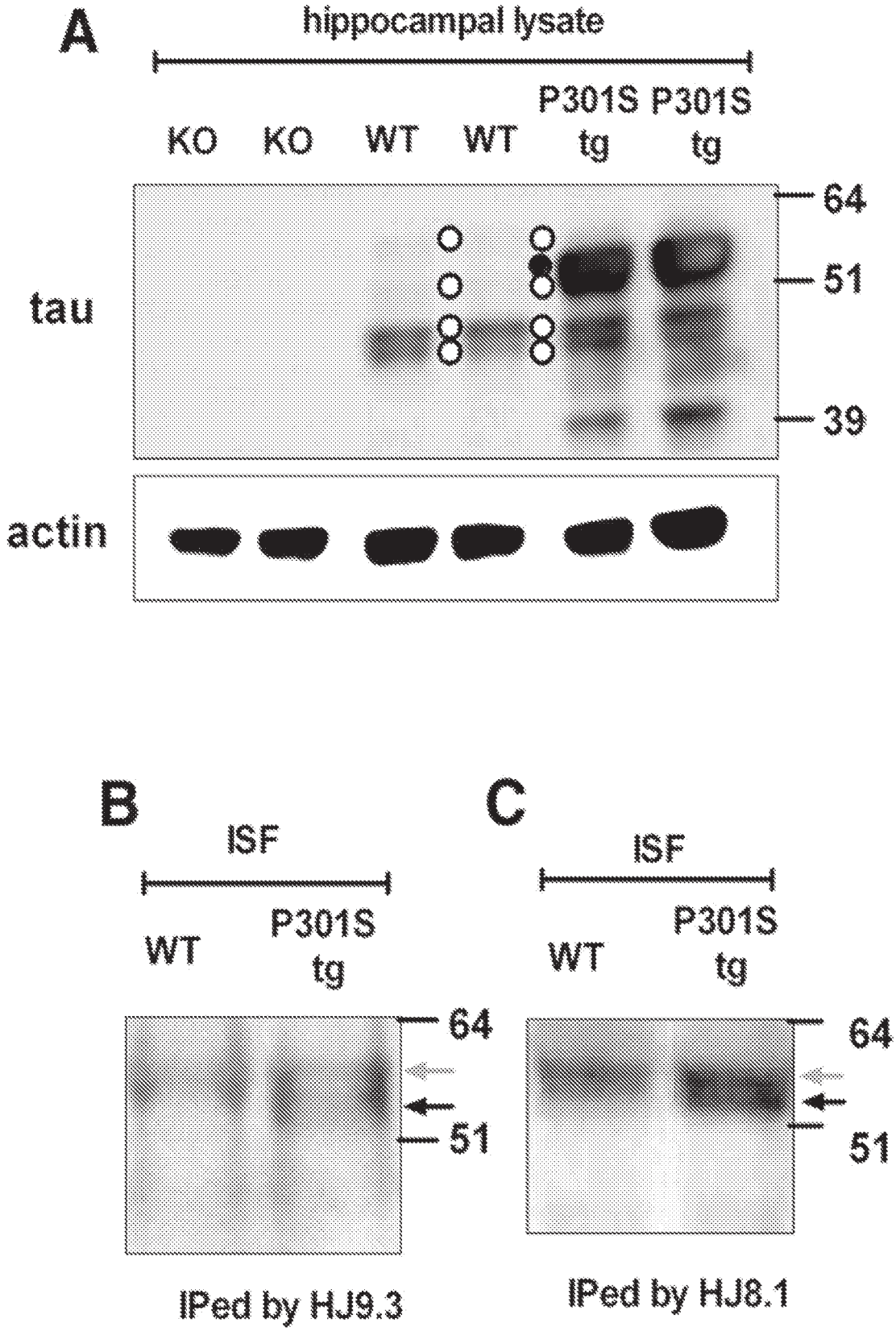

A
hippocampal lysate
KO
KO
WT
WT
P301S tg
P301S tg
tau
actin
64
51
39
B
ISF
WT
P301S tg
64
51
IPed by HJ9.3
C
ISF
WT
P301S tg
64
51
IPed by HJ8.1

FIG. 14

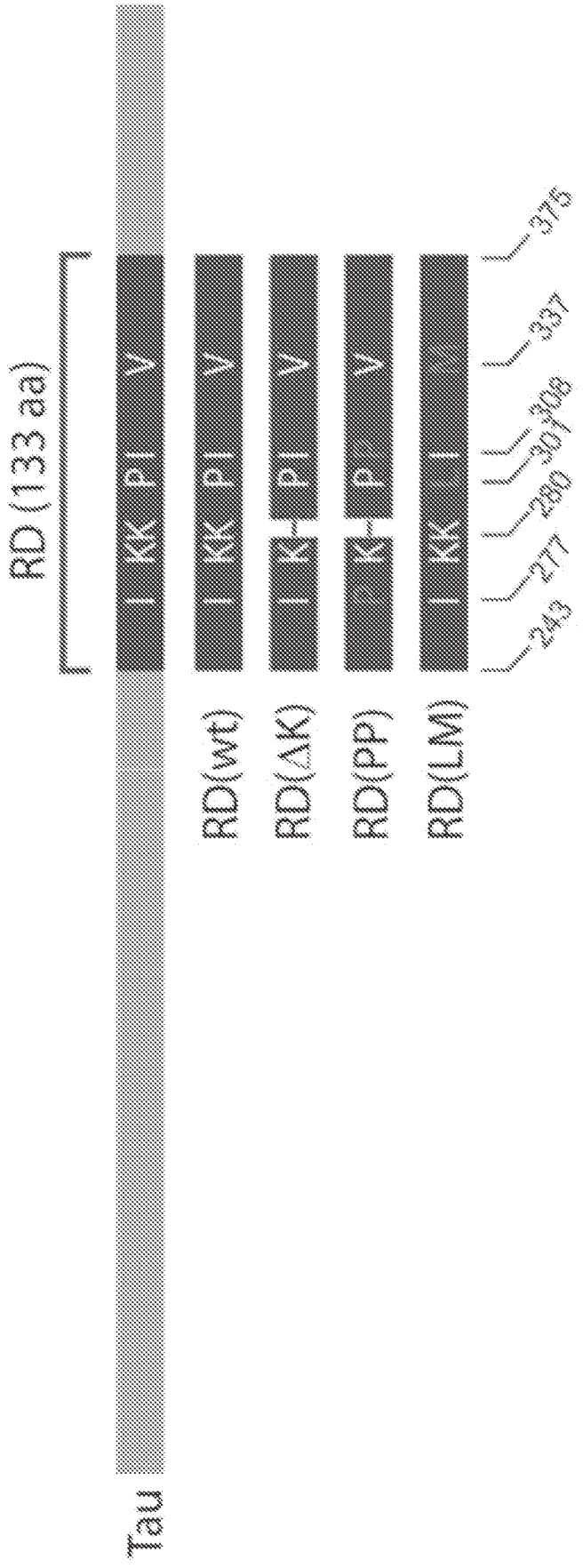

RD (133 aa)
Tau
RD(wt)
RD(ΔK)
RD(PP)
RD(LM)
I KK PI V
I KK PI V
I KH PI V
I KH P V
I KK I
243
277
280
301
308
337
375

FIG. 15A

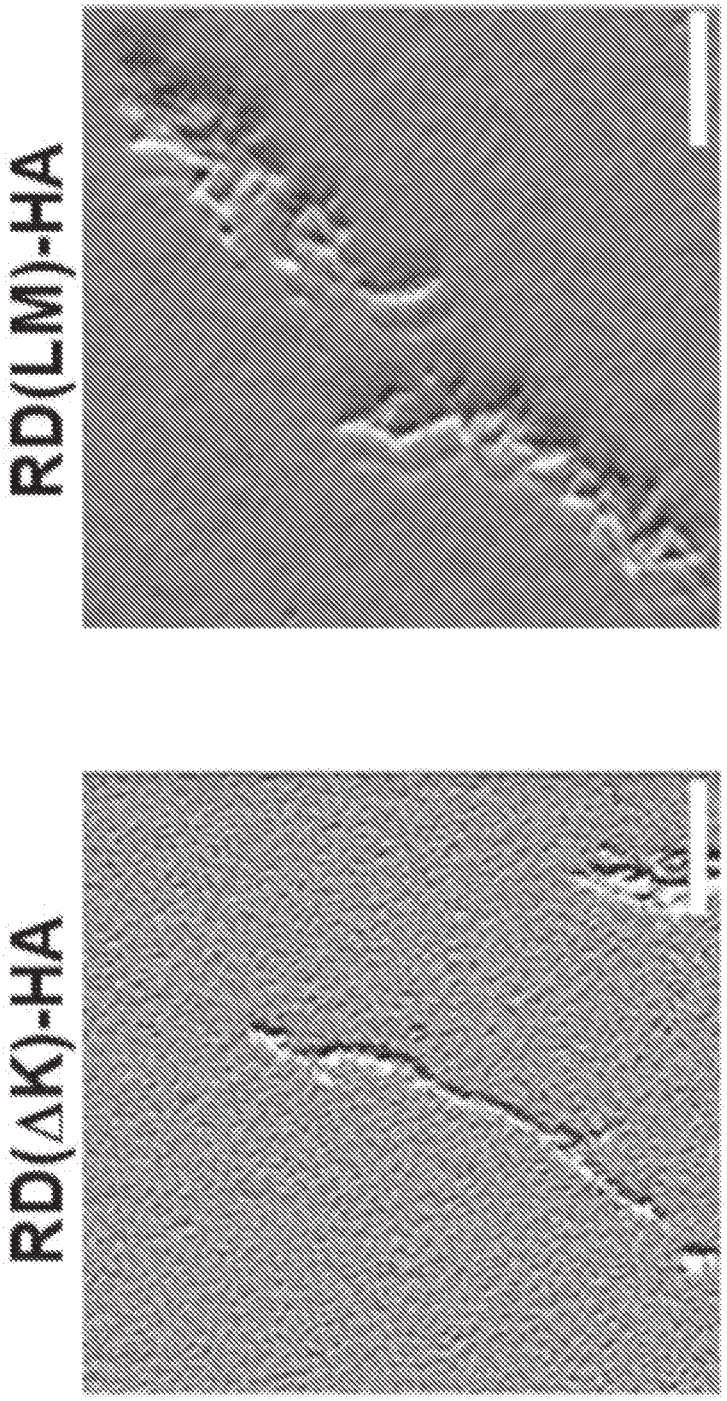


FIG. 15B

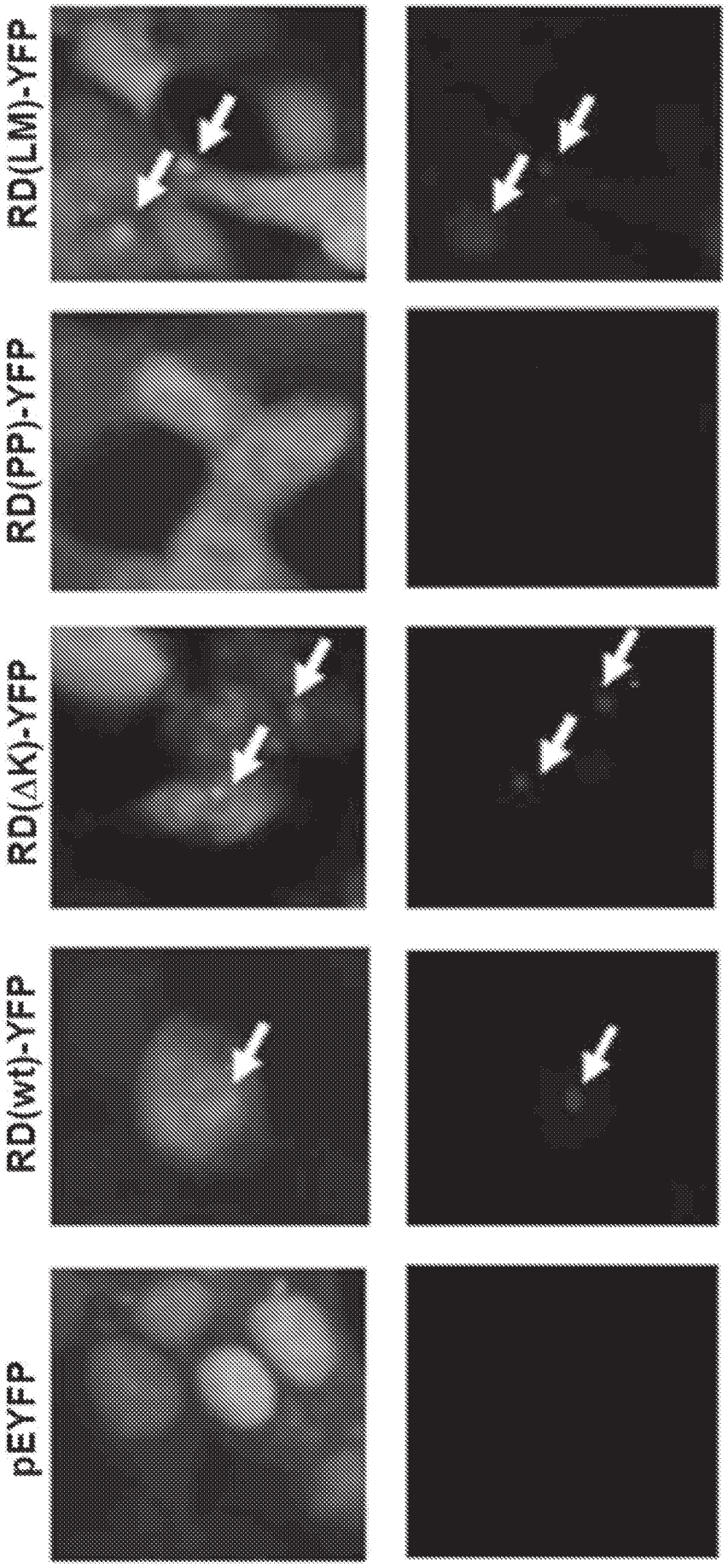


FIG. 15C

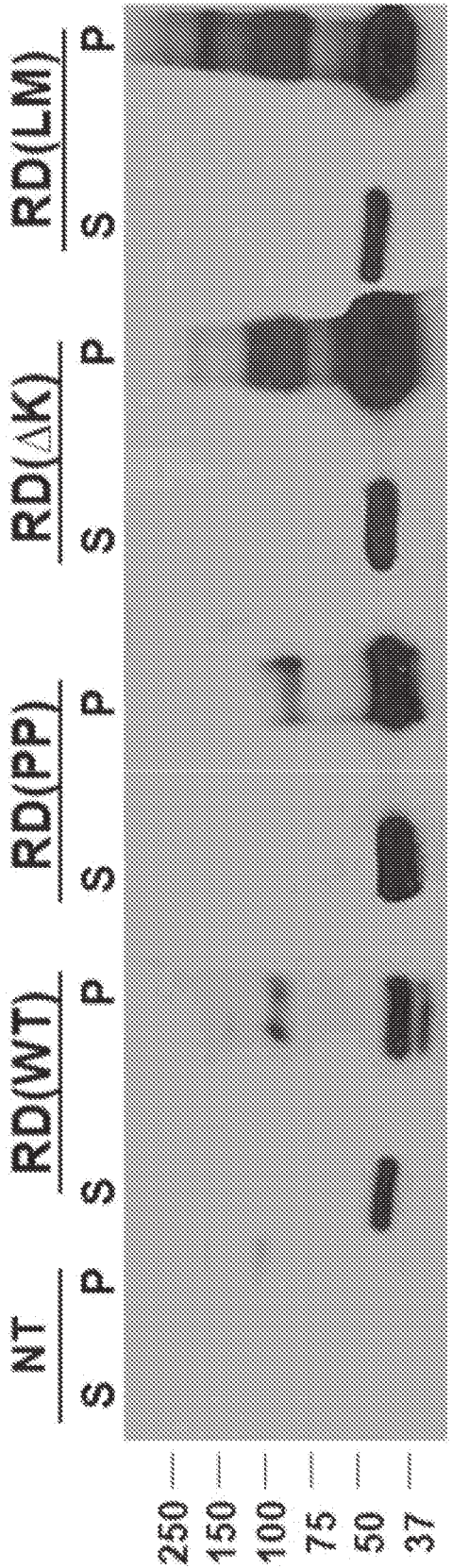


FIG. 15D

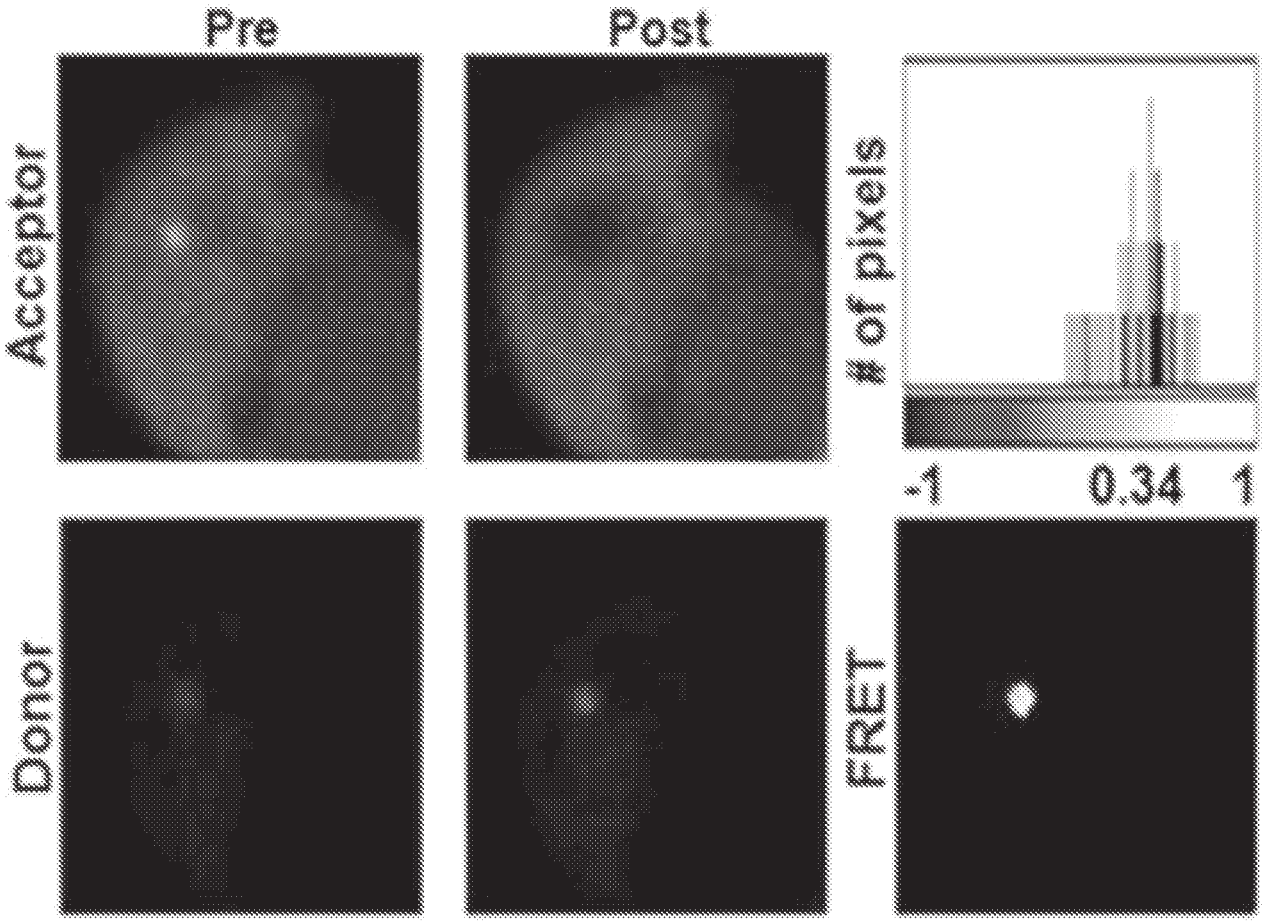


FIG. 16A

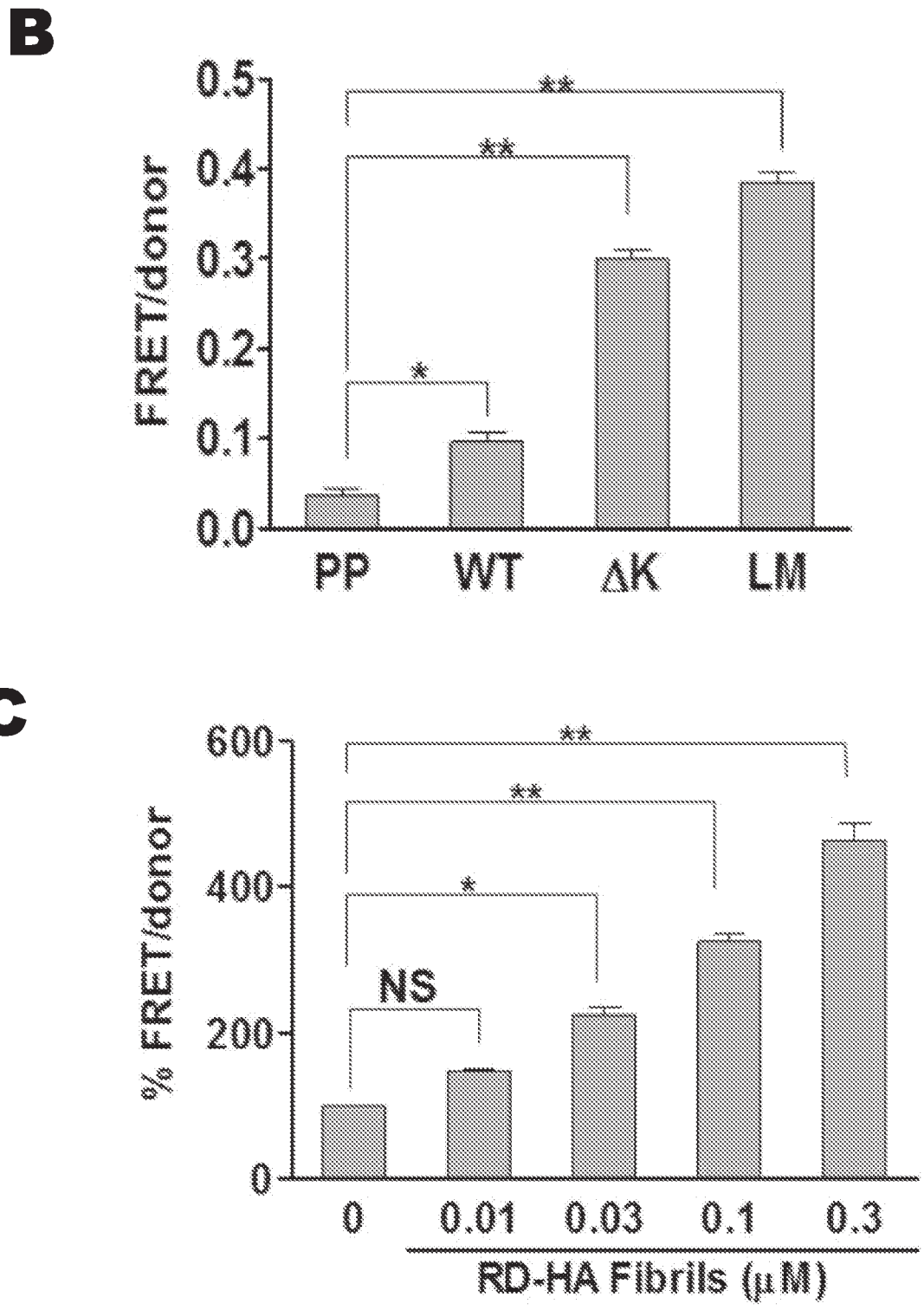

B
FRET/donor
0.5
0.4
0.3
0.2
0.1
0.0
**
**
*
PP
WT
ΔK
LM
C
% FRET/donor
600
400
200
0
**
**
*
NS
0
0.01
0.03
0.1
0.3
RD-HA Fibrils (μM)

FIG. 16

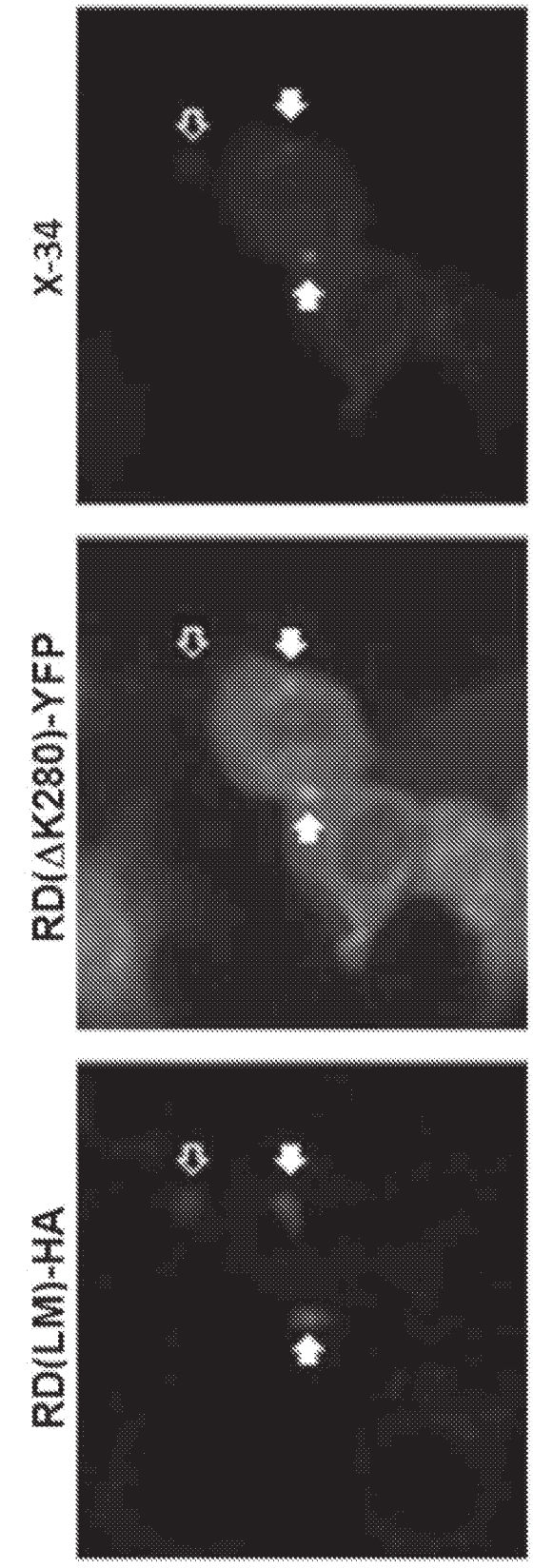


FIG. 17A

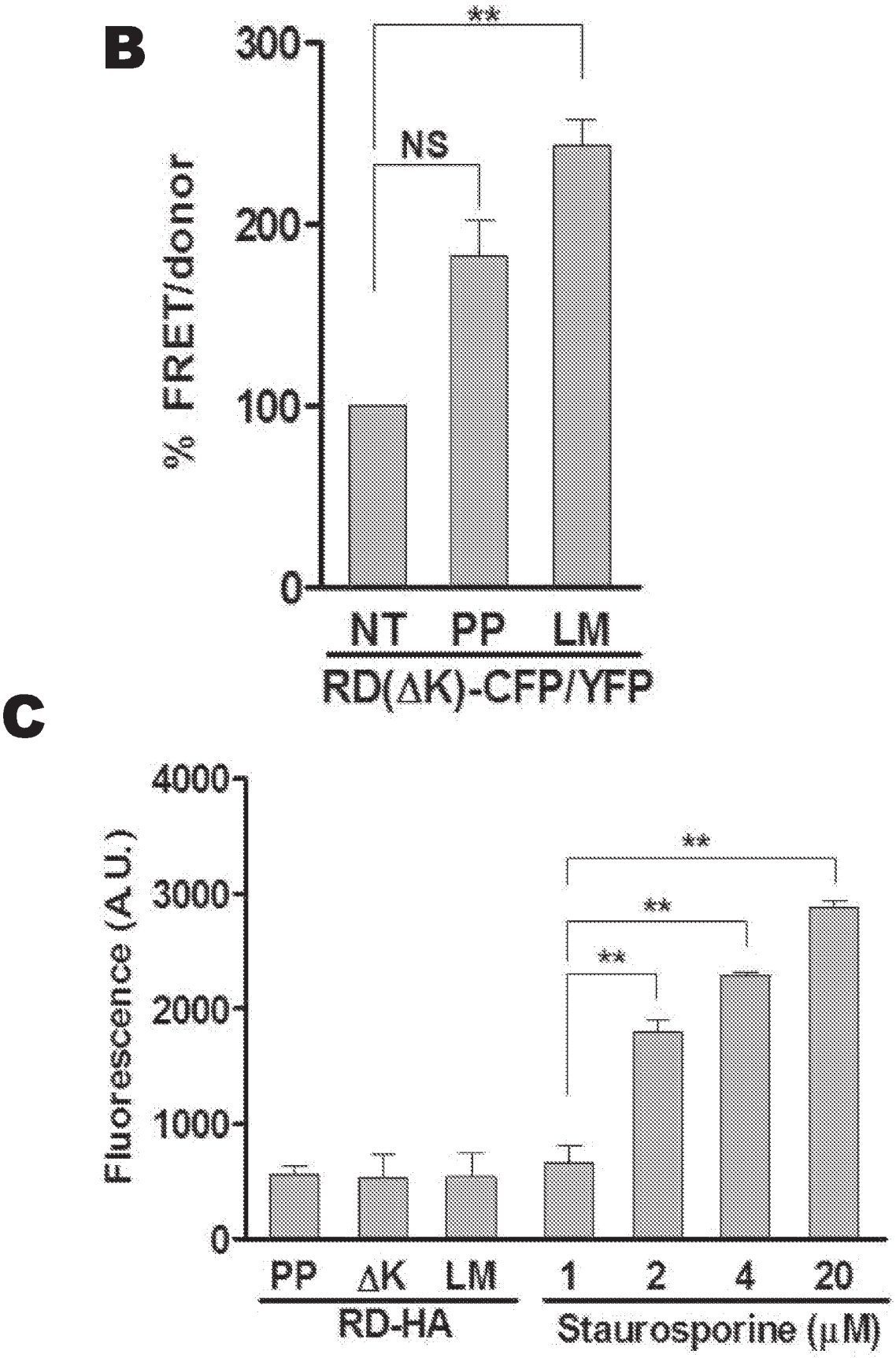

B
300
200
100
0
% FRET/donor
**
NS
NT
PP
LM
RD(ΔK)-CFP/YFP
C
4000
3000
2000
1000
0
Fluorescence (A.U.)
**
**
**
PP
ΔK
LM
1
2
4
20
RD-HA
Staurosporine (μM)

FIG. 17

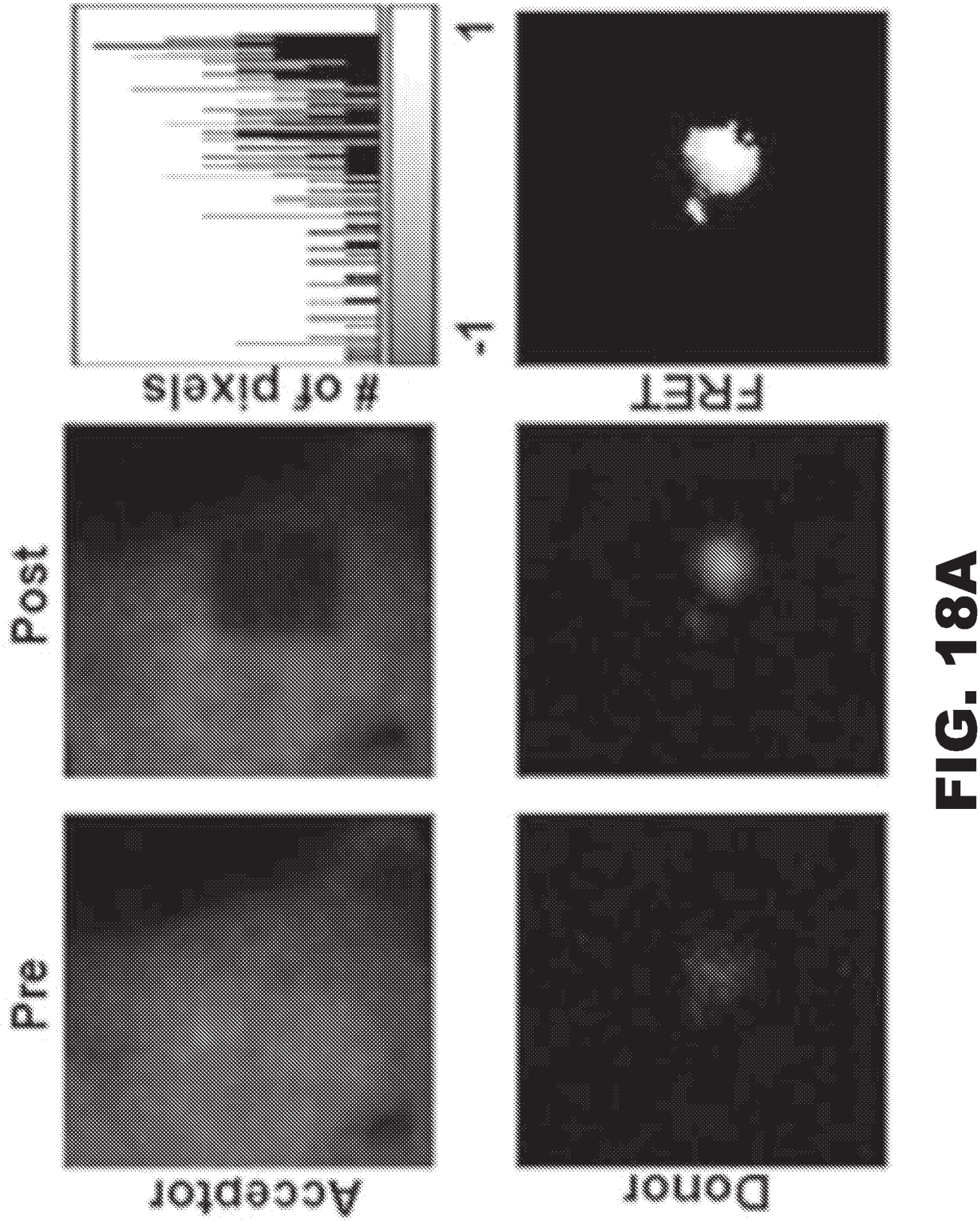


FIG. 18A

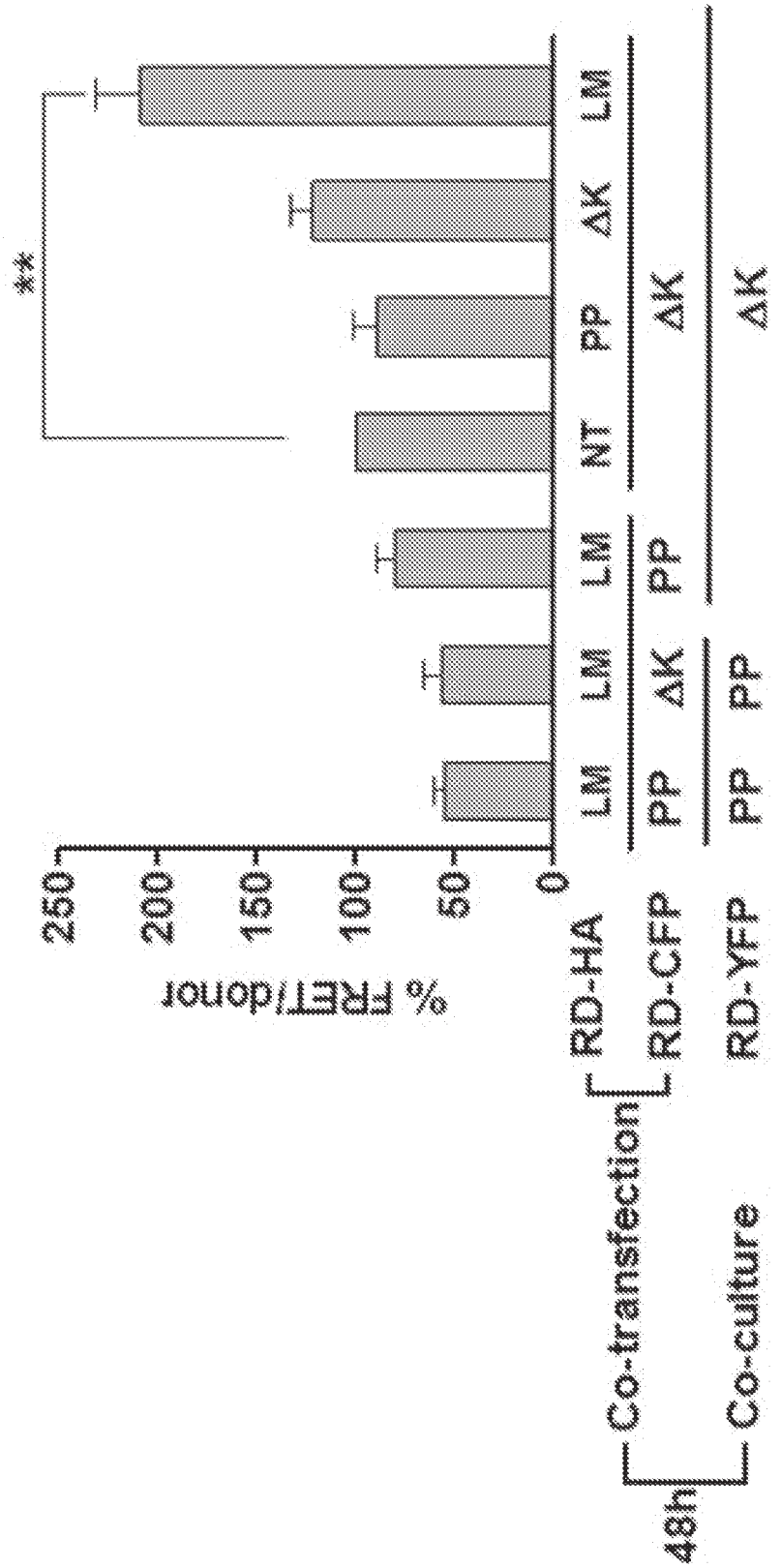

48h
Co-transfection
Co-culture
RD-HA
RD-CFP
RD-YFP
LM
LM
PP
ΔK
LM
LM
PP
ΔK
PP
PP
NT
PP
ΔK
LM
**
% FRET/donor
0
50
100
150
200
250

FIG. 18B

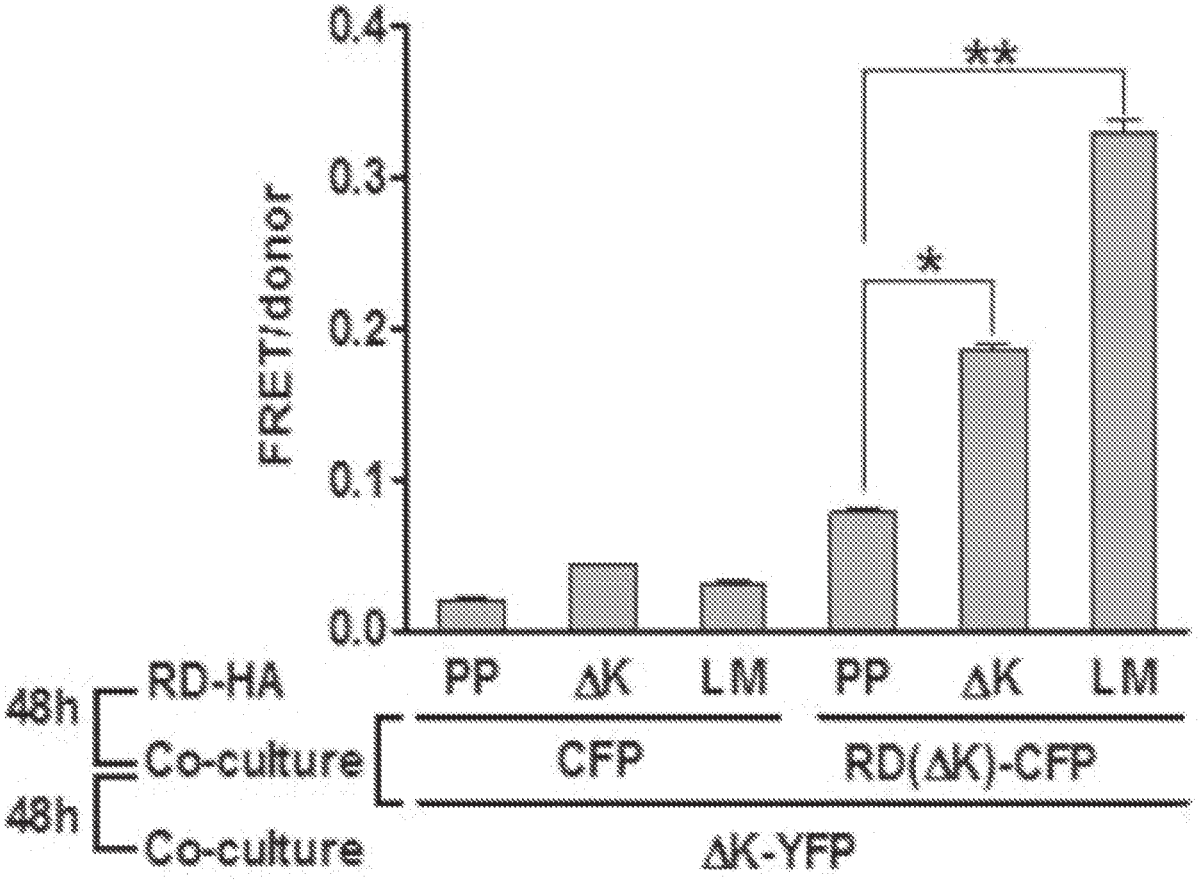
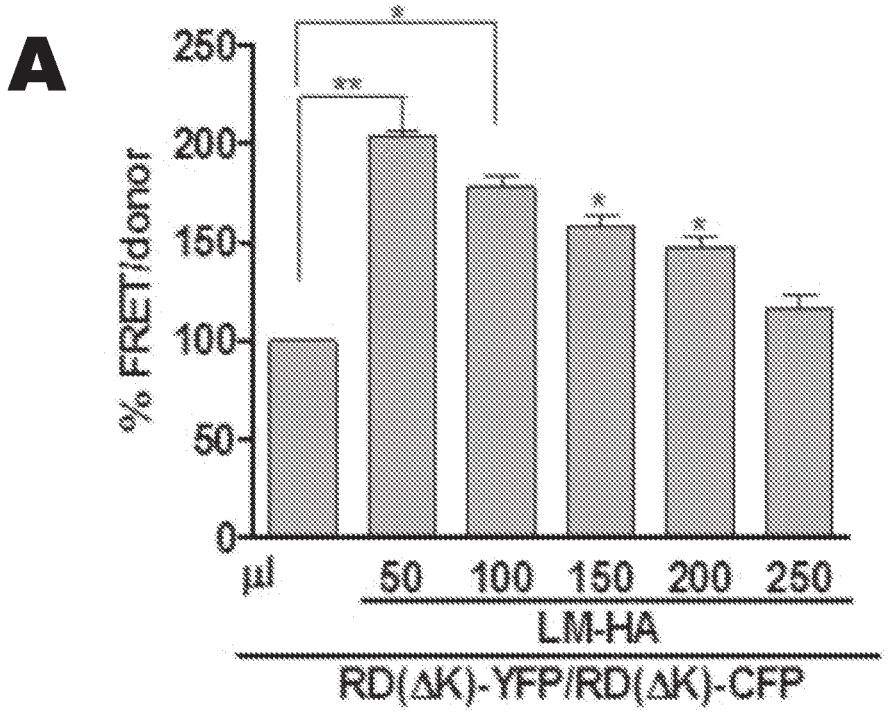

FRET/donor
0.4
0.3
0.2
0.1
0.0
**
*
PP
ΔK
LM
PP
ΔK
LM
48h
RD-HA
Co-culture
CFP
RD(ΔK)-CFP
48h
Co-culture
ΔK-YFP

FIG. 18C


A
250
200
150
100
50
0
% FRET/donor
*
**
*
*
μl
50 100 150 200 250
LM-HA
RD(ΔK)-YFP/RD(ΔK)-CFP

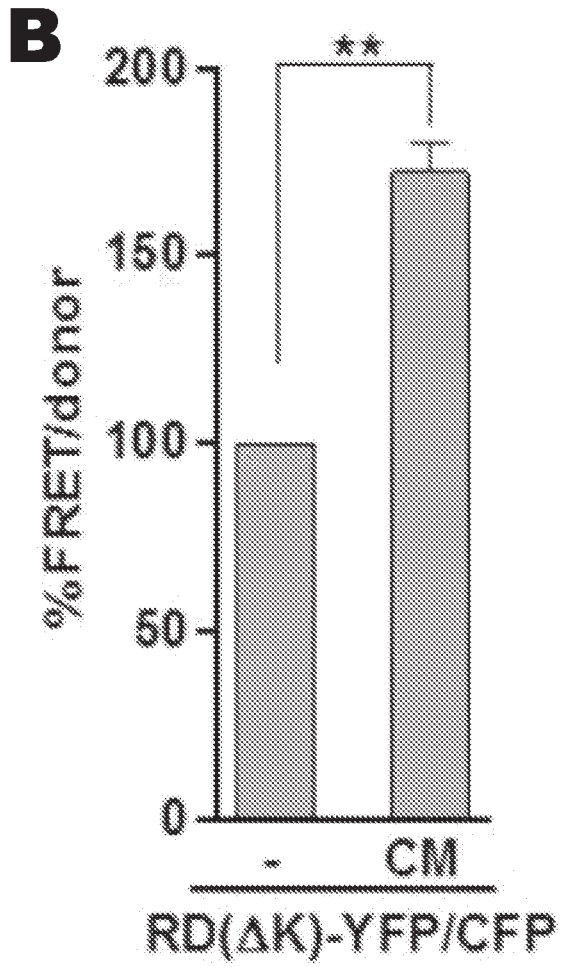
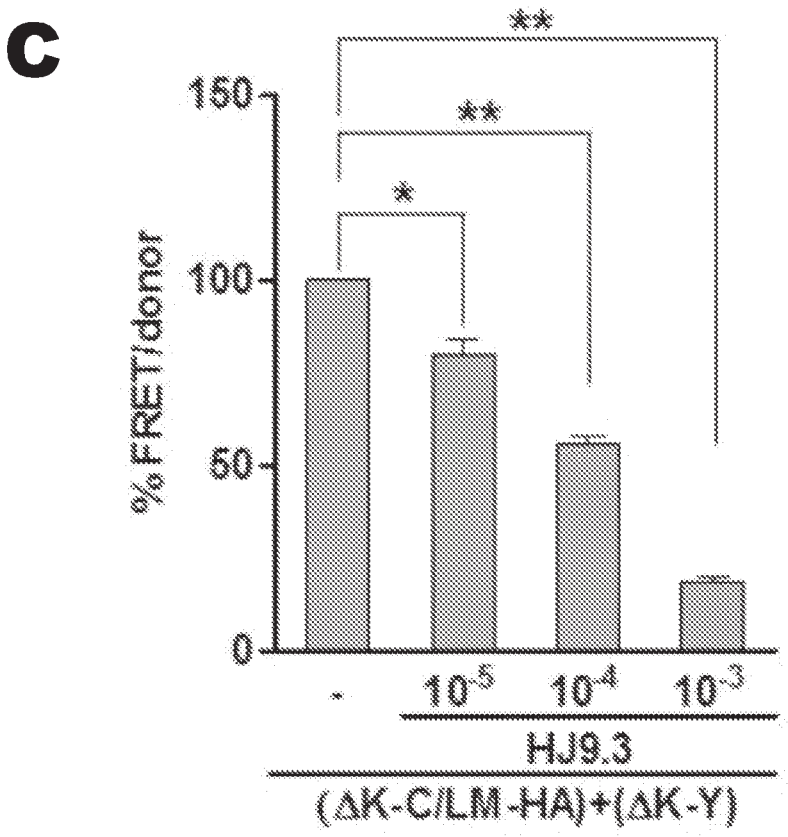

B
200
150
100
50
0
%FRET/donor
**
-
CM
RD(ΔK)-YFP/CFP

FIG. 19


C
**
**
*
150
100
50
0
% FRET/donor
-
10-5
10-4
10-3
HJ9.3
(ΔK-C/LM-HA)+(ΔK-Y)

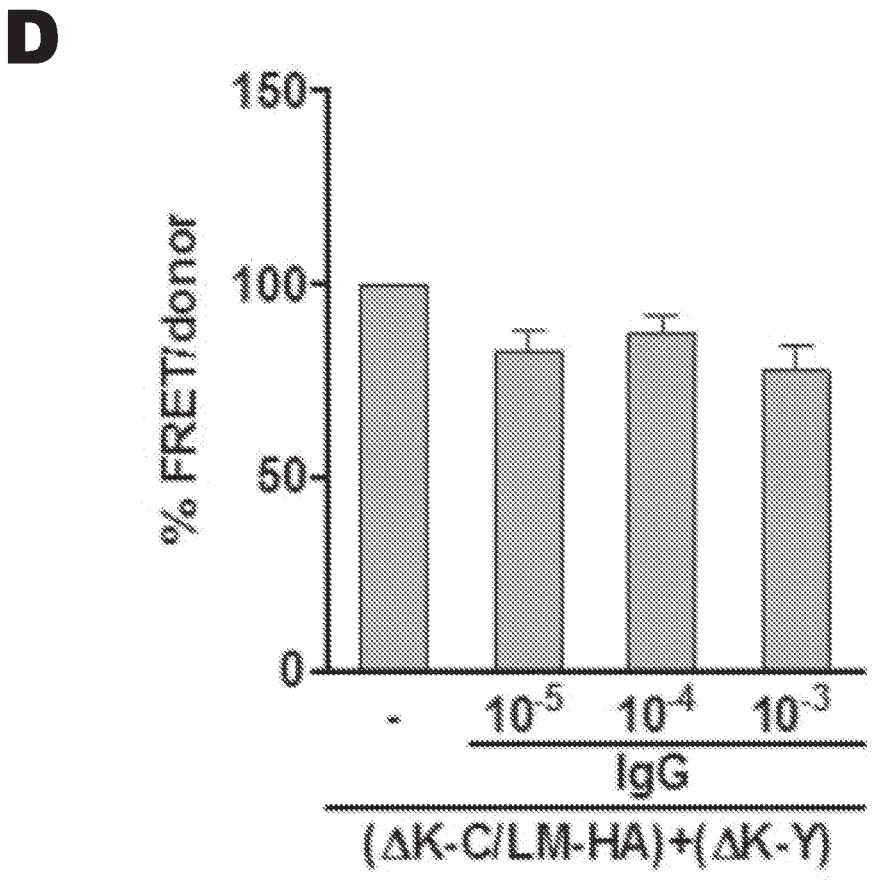
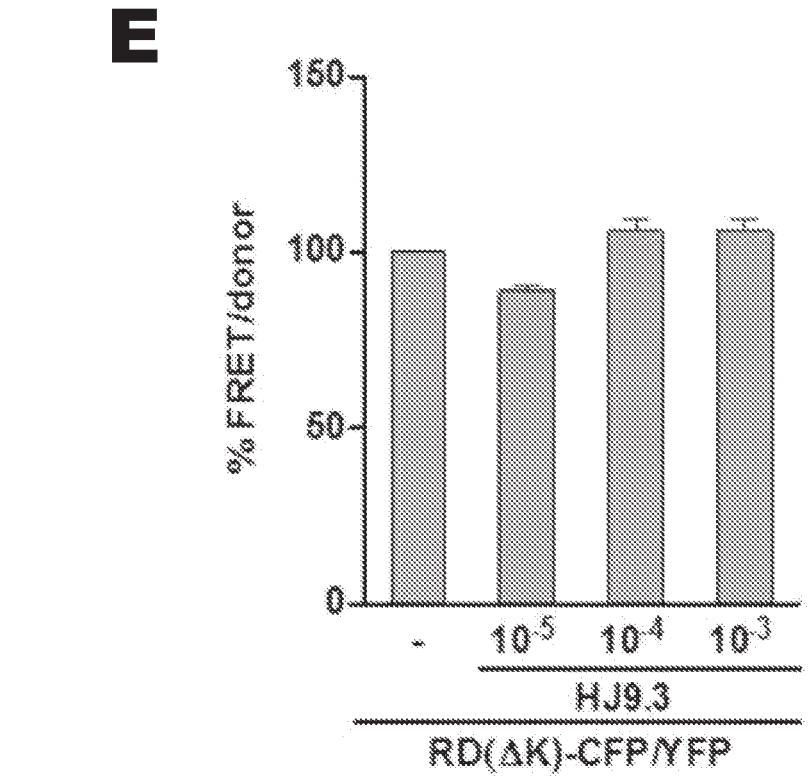

D
150
100
50
0
% FRET/donor
-
10-5
10-4
10-3
IgG
(ΔK-C/LM-HA)+(ΔK-Y)

FIG. 19


E
150
100
50
0
% FRET/donor
-
10-5
10-4
10-3
HJ9.3
RD(ΔK)-CFP/YFP

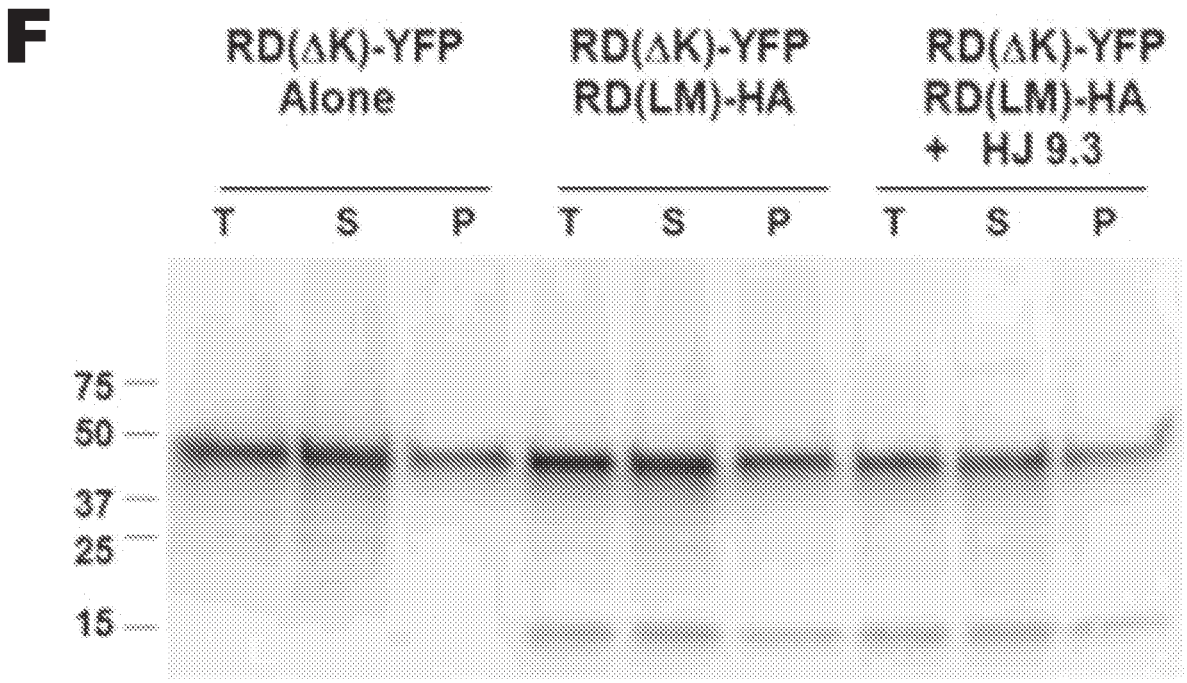
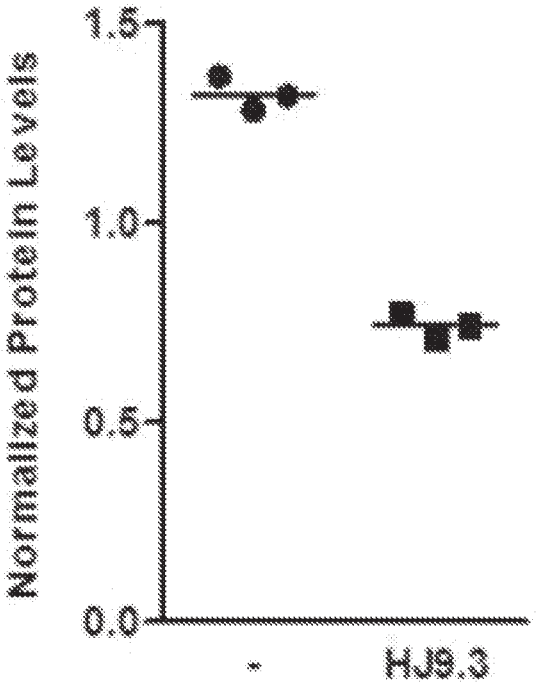

F
RD(ΔK)-YFP
Alone
RD(ΔK)-YFP
RD(LM)-HA
RD(ΔK)-YFP
RD(LM)-HA
+ HJ 9.3
T S P T S P T S P
75
50
37
25
15

FIG. 19

G


Normalized Protein Levels
1.5
1.0
0.5
0.0
-
HJ9.3

H

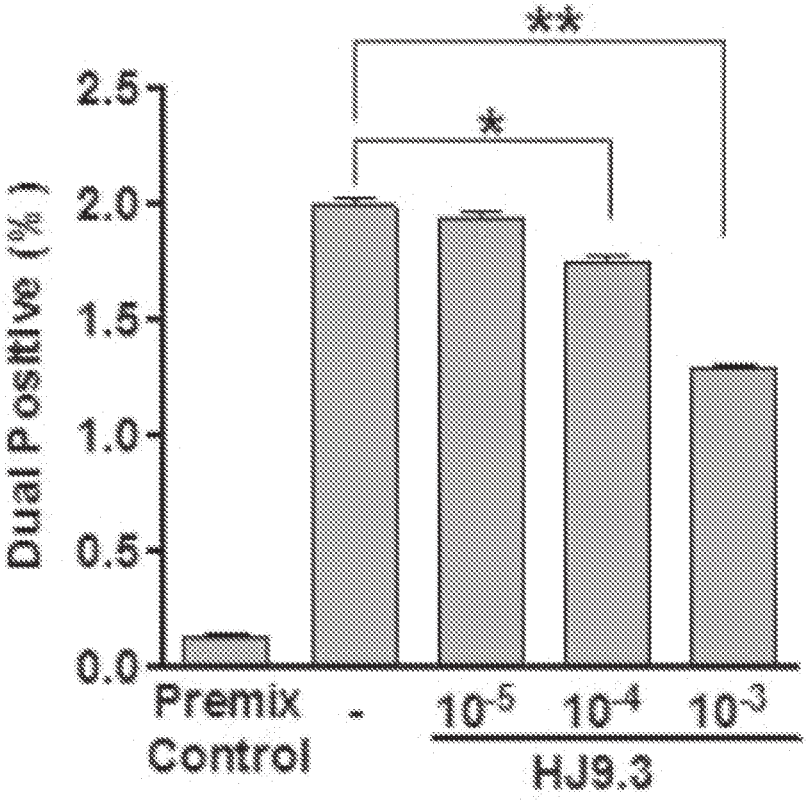

**
*
Dual Positive (%)
2.5
2.0
1.5
1.0
0.5
0.0
Premix Control
-
10-5
10-4
10-3
HJ9.3

FIG. 19

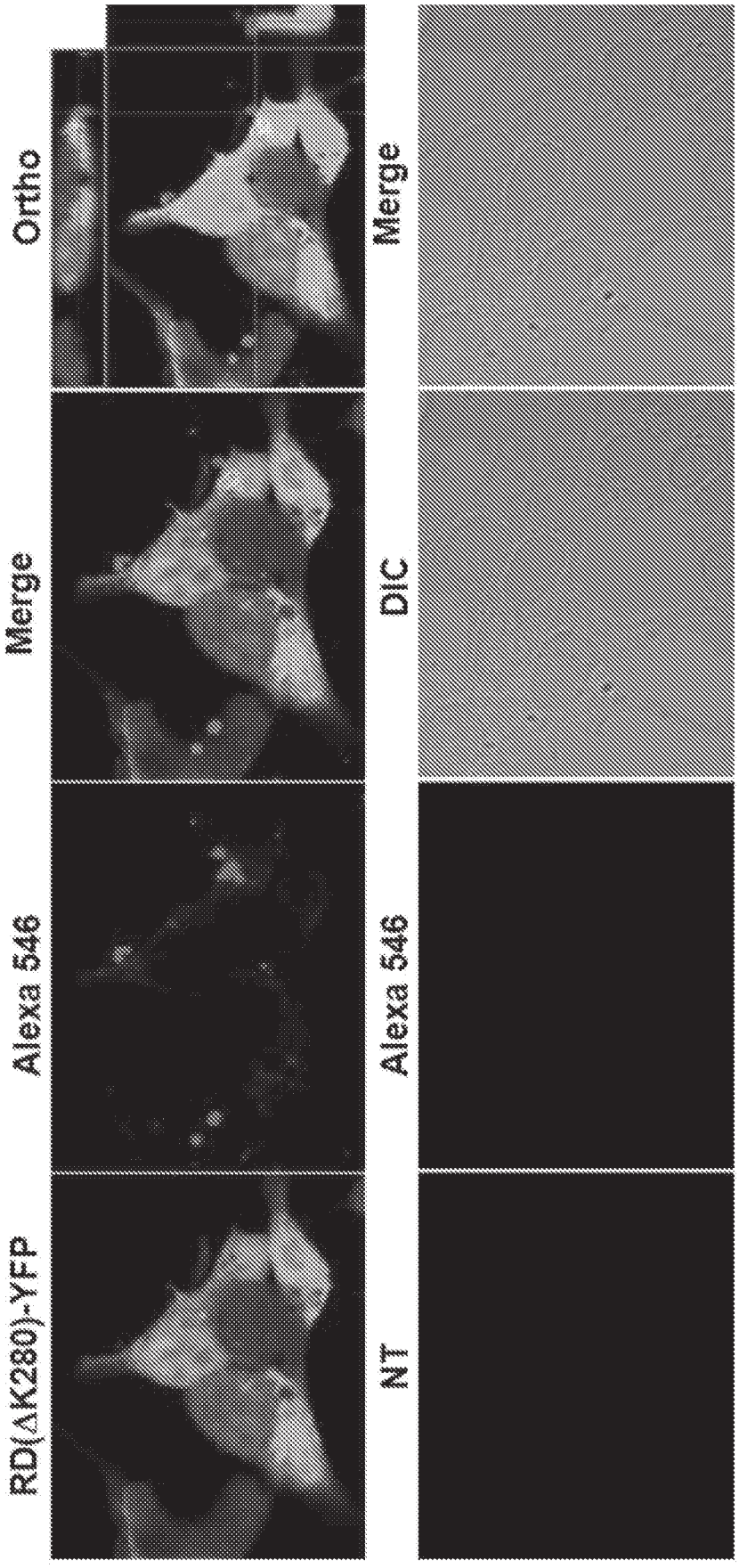


FIG. 20

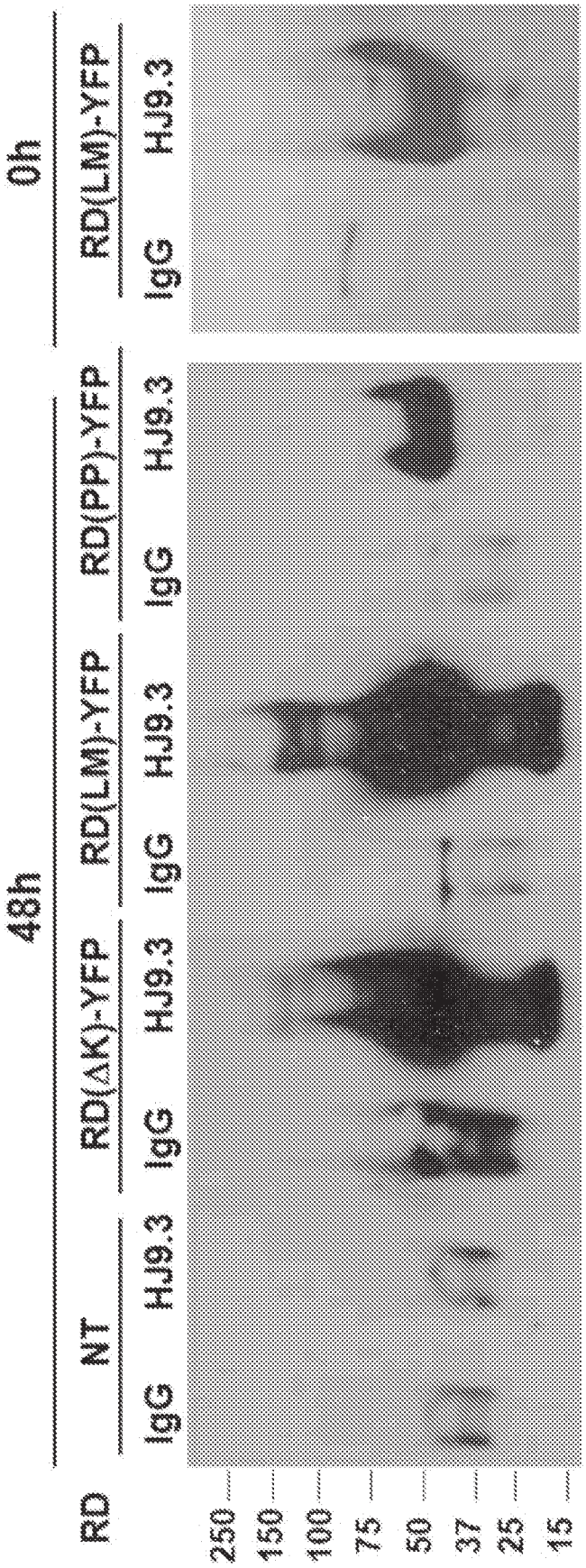
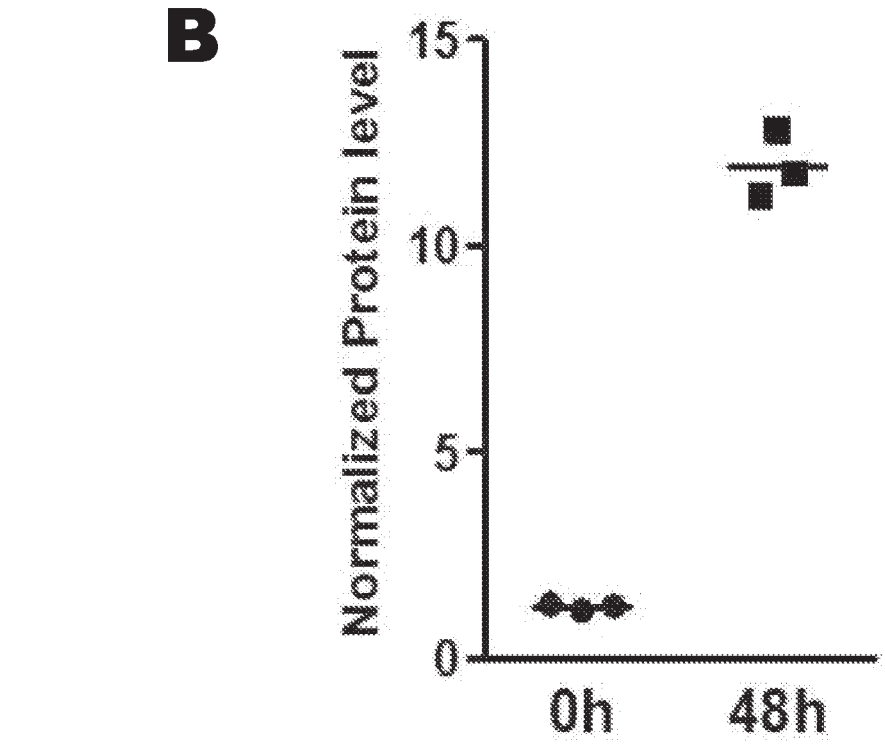

48h
0h
RD
NT
RD(ΔK)-YFP
RD(LM)-YFP
RD(PP)-YFP
RD(LM)-YFP
IgG
HJ9.3
IgG
HJ9.3
IgG
HJ9.3
IgG
HJ9.3
250
150
100
75
50
37
25
15

FIG. 21A


B
Normalized Protein level
15
10
5
0
0h
48h

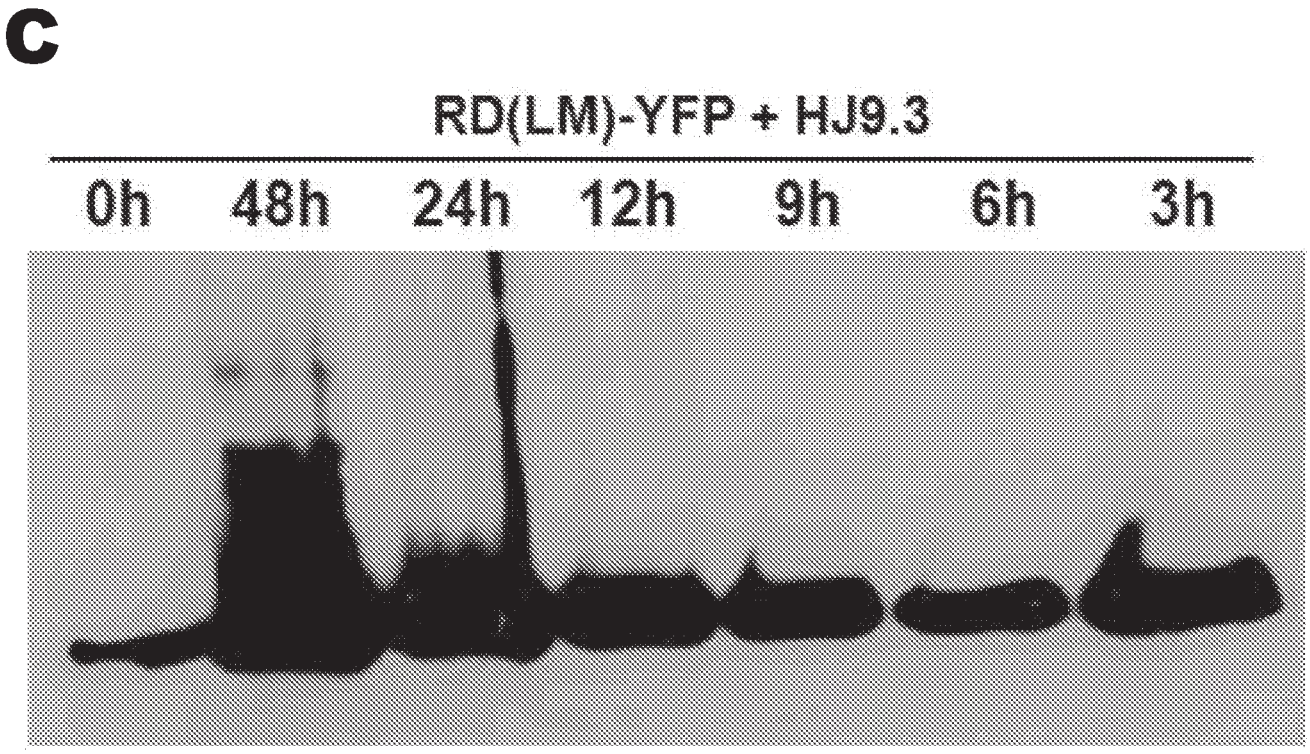

C
RD(LM)-YFP + HJ9.3
0h
48h
24h
12h
9h
6h
3h

FIG. 21

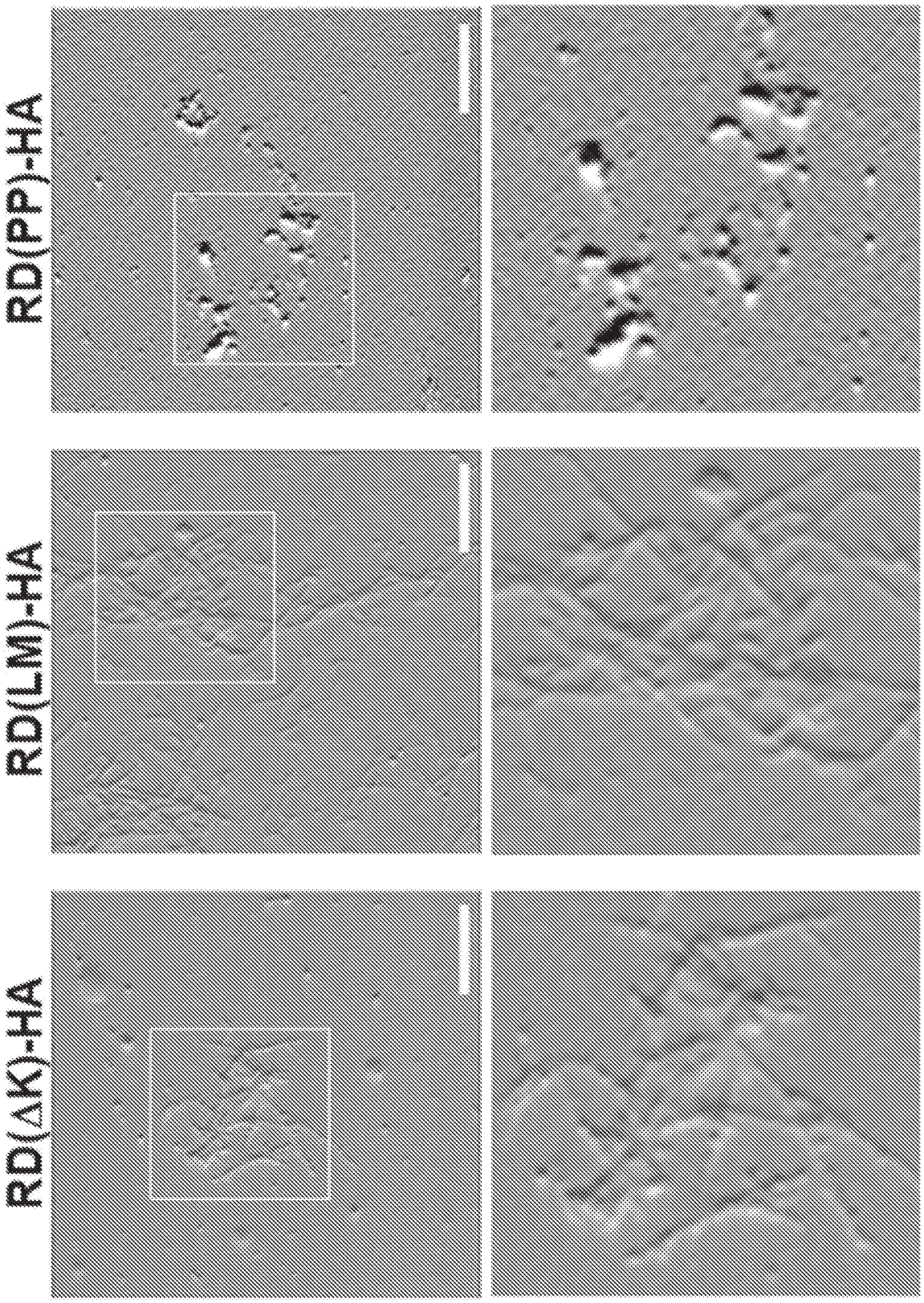


FIG. 21D

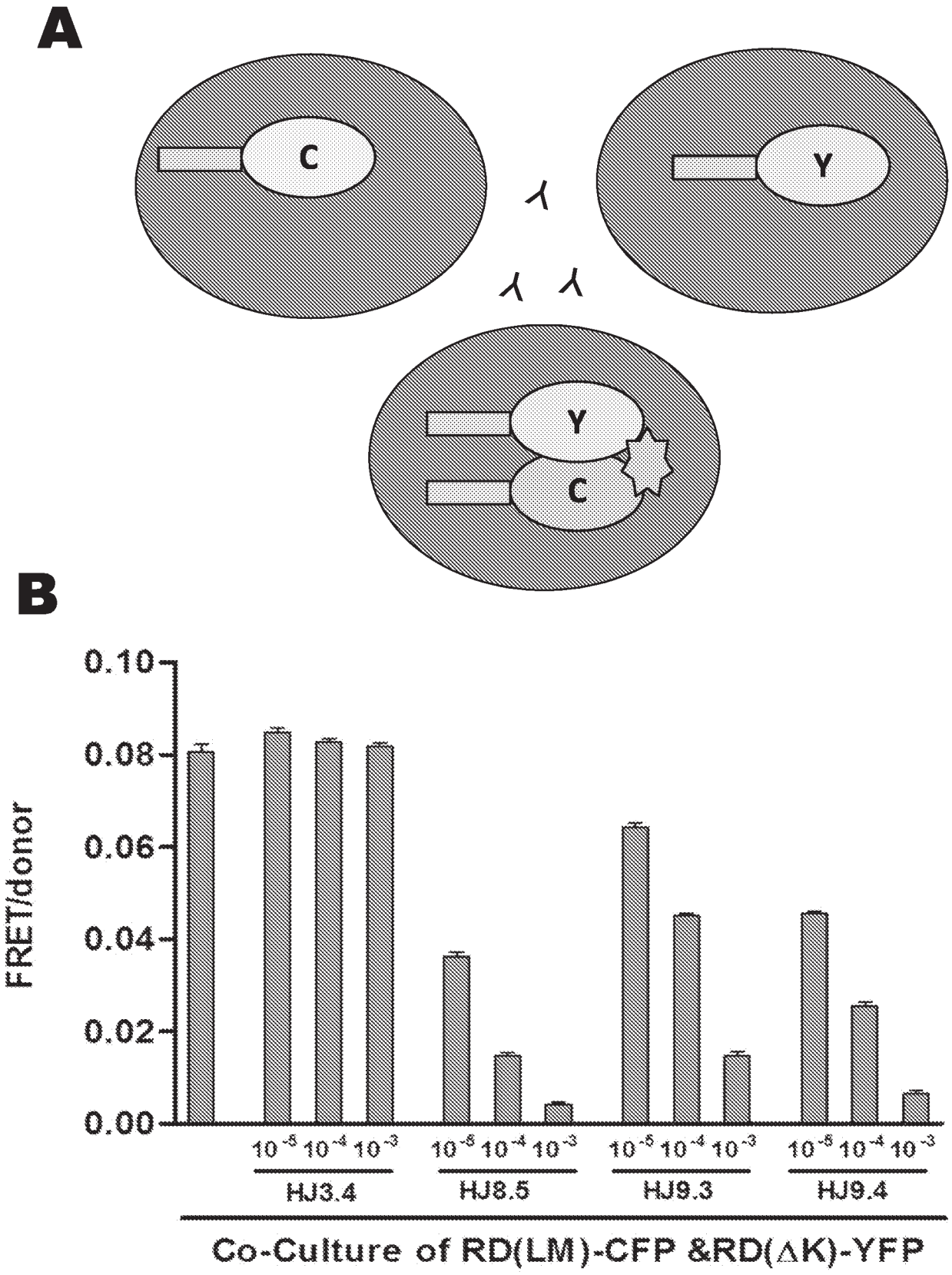

A
C
Y
Y
C
B
FRET/donor
0.10
0.08
0.06
0.04
0.02
0.00
10-6 10-4 10-3
HJ3.4
10-6 10-4 10-3
HJ8.5
10-6 10-4 10-3
HJ9.3
10-6 10-4 10-3
HJ9.4
Co-Culture of RD(LM)-CFP &RD(ΔK)-YFP

FIG. 22

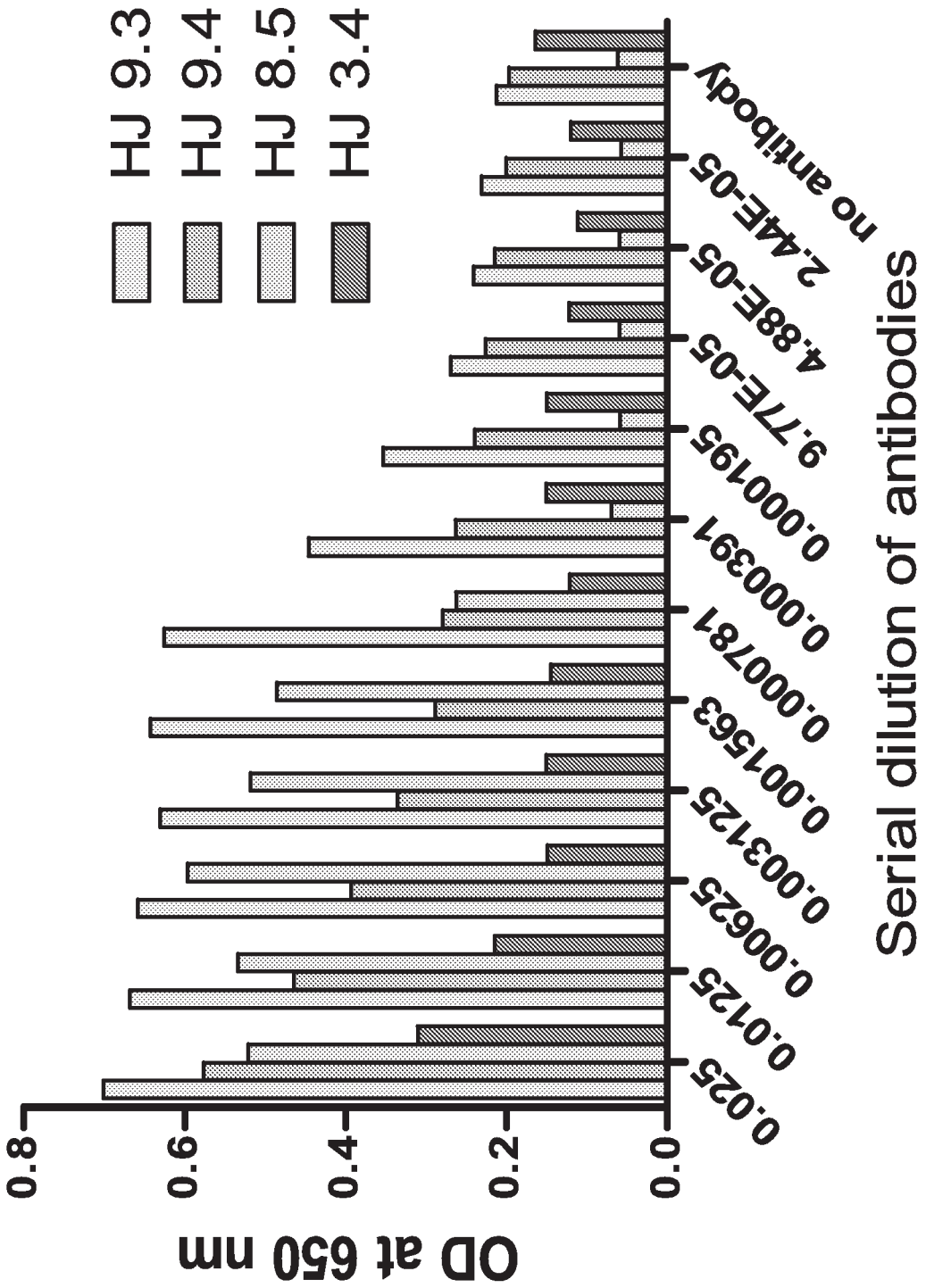

HJ 9.3
HJ 9.4
HJ 8.5
HJ 3.4
OD at 650 nm
0.0
0.2
0.4
0.6
0.8
0.025
0.0125
0.00625
0.003125
0.001563
0.000781
0.000391
0.000195
9.77E-05
4.88E-05
2.44E-05
no antibody
Serial dilution of antibodies

FIG. 22C

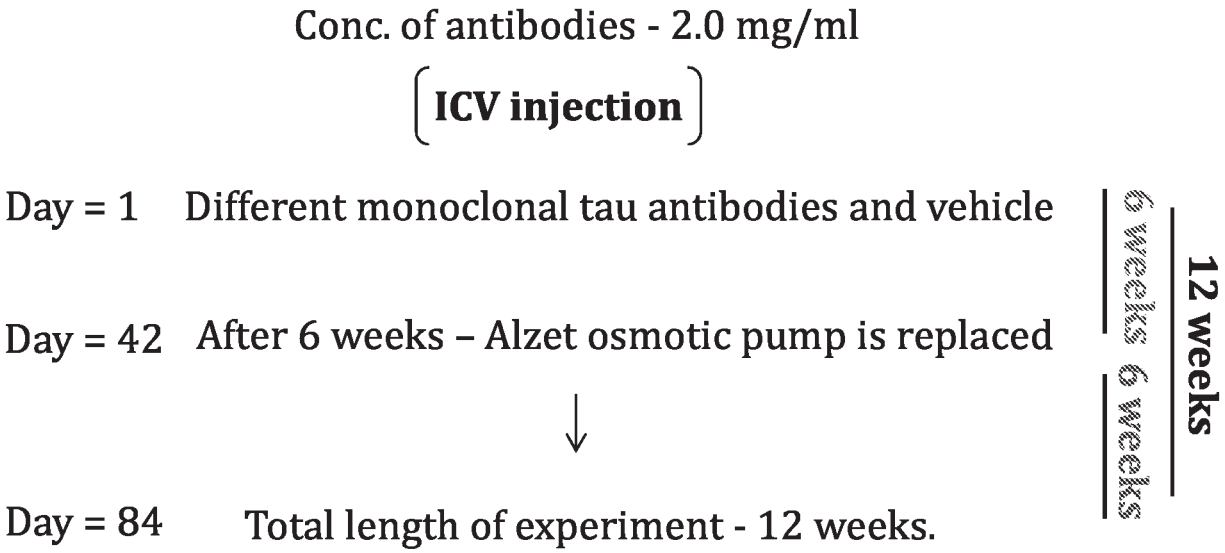
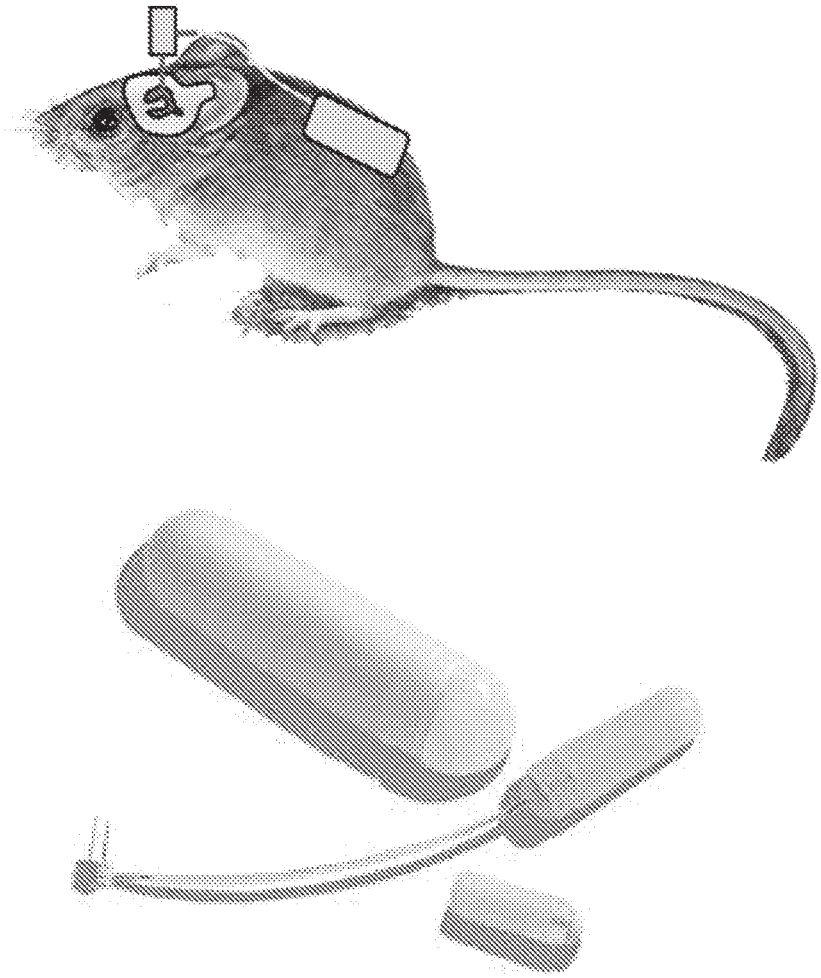

Conc. of antibodies - 2.0 mg/ml
ICV injection
Day = 1 Different monoclonal tau antibodies and vehicle
Day = 42 After 6 weeks – Alzet osmotic pump is replaced
Day = 84 Total length of experiment - 12 weeks.
6 weeks
6 weeks
12 weeks

FIG. 23A



Alzet osmotic pump

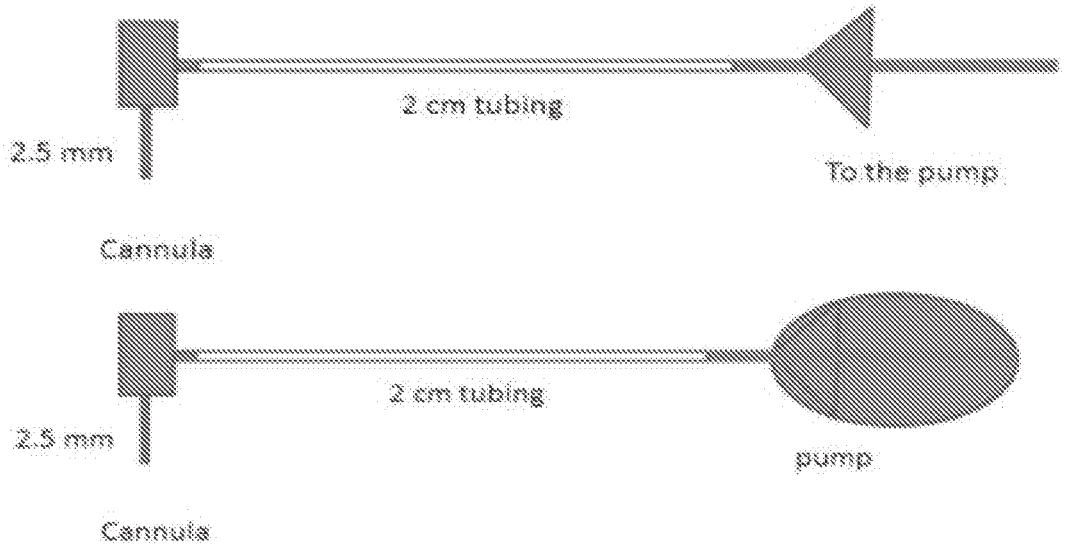


FIG. 23B

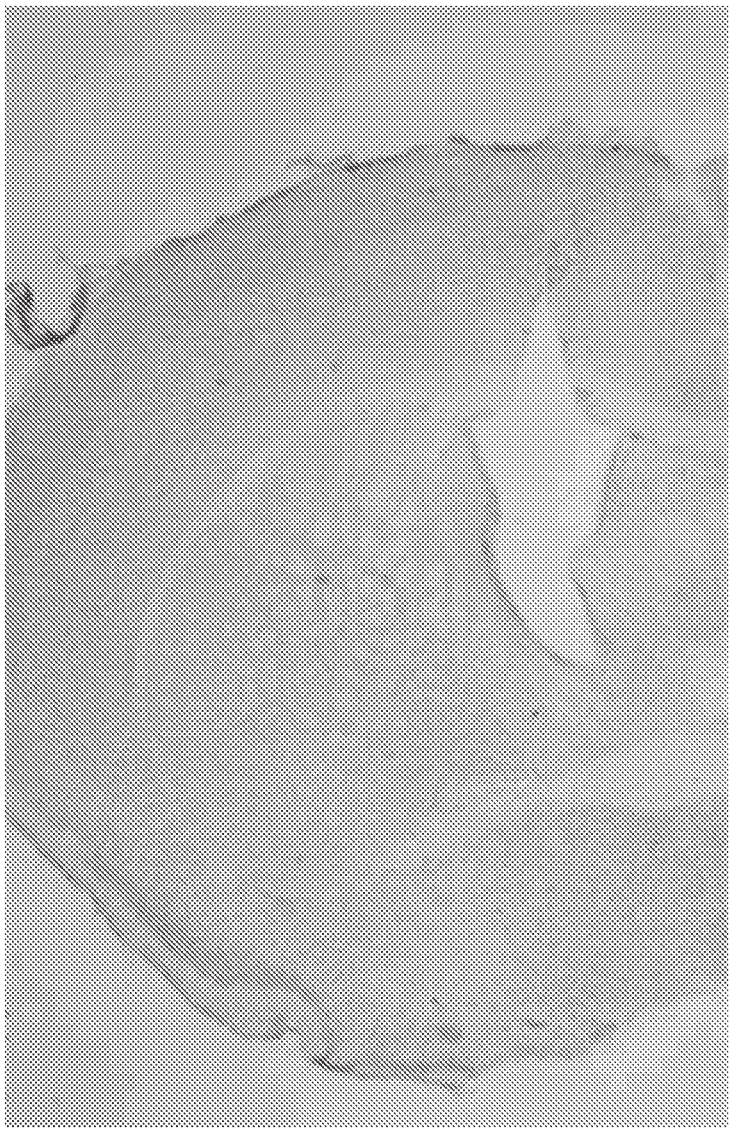


FIG. 23C

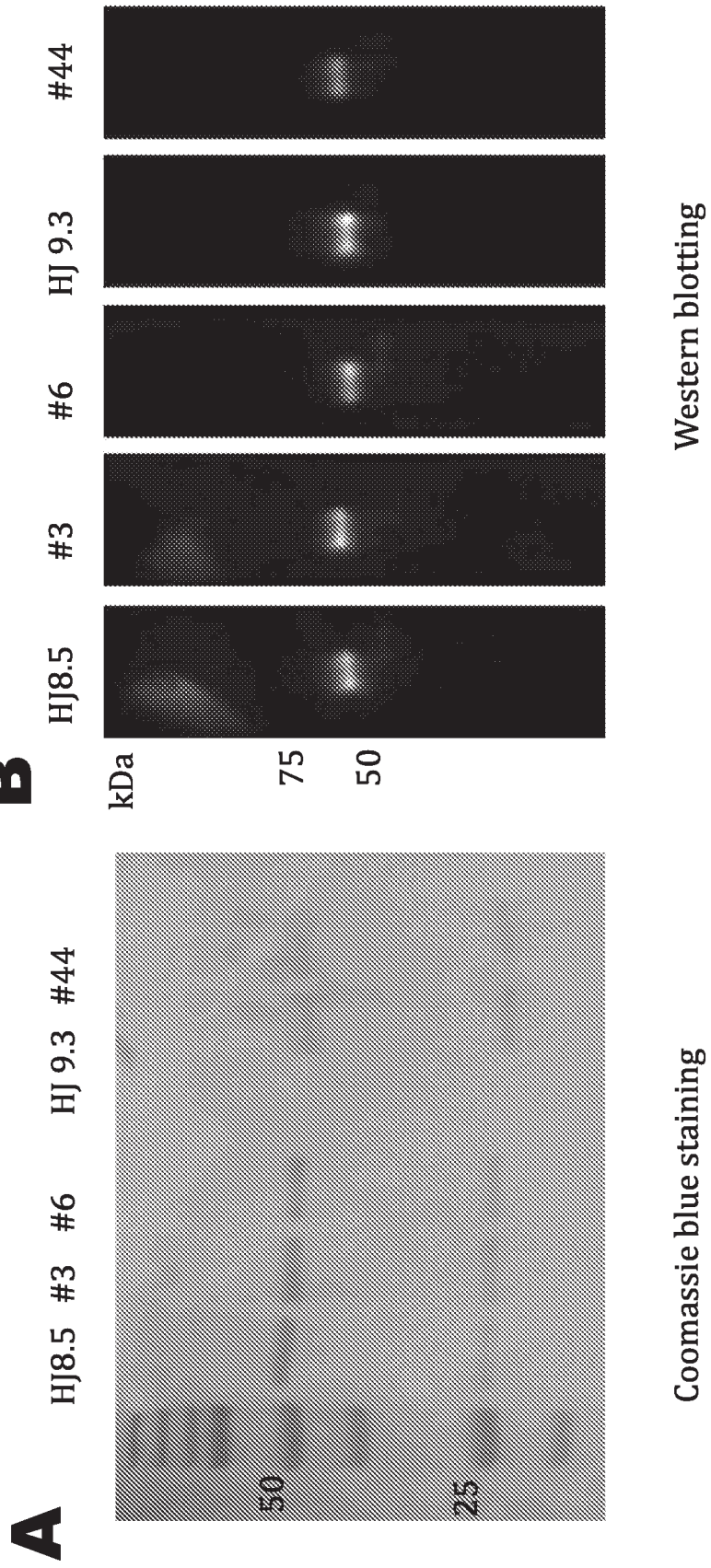

A
HJ8.5
#3
#6
HJ 9.3
#44
50
25
Coomassie blue staining
B
HJ8.5
#3
#6
HJ 9.3
#44
kDa
75
50
Western blotting

FIG. 24

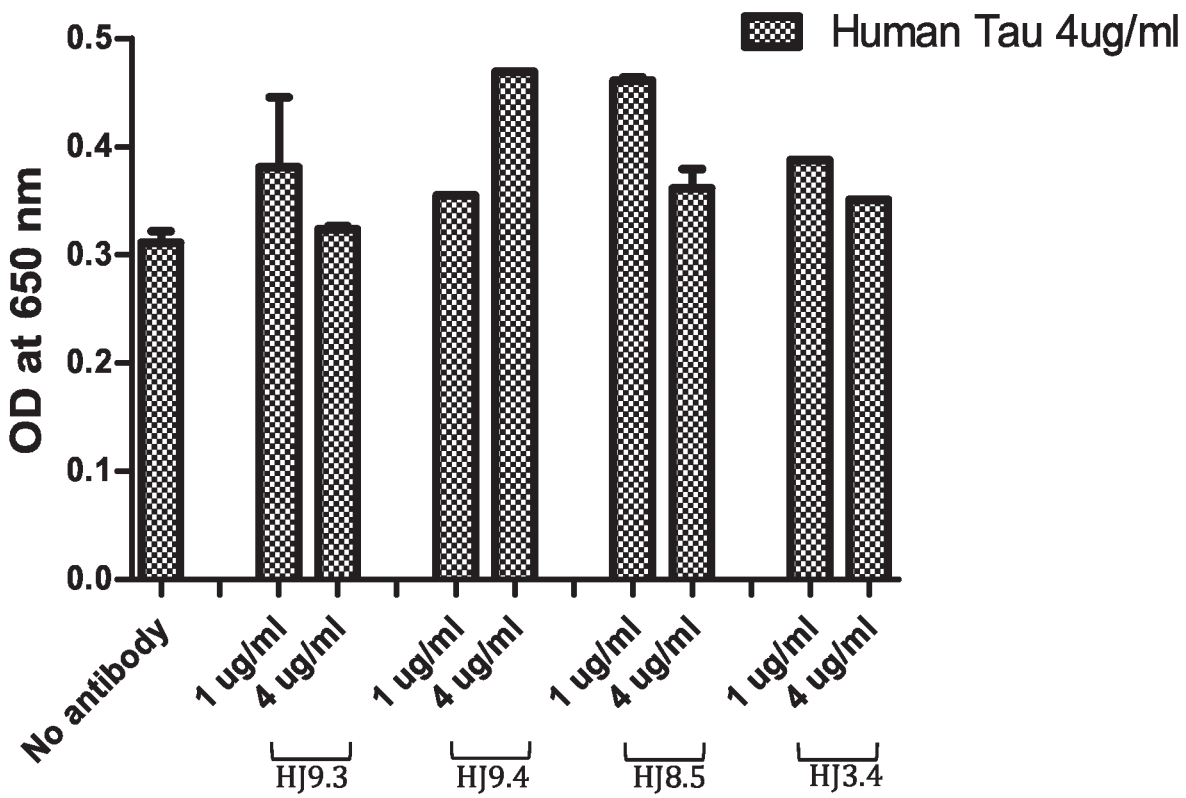

Human Tau 4ug/ml
OD at 650 nm
0.5
0.4
0.3
0.2
0.1
0.0
No antibody
1 ug/ml
4 ug/ml
1 ug/ml
4 ug/ml
1 ug/ml
4 ug/ml
1 ug/ml
4 ug/ml
HJ9.3
HJ9.4
HJ8.5
HJ3.4

FIG. 25

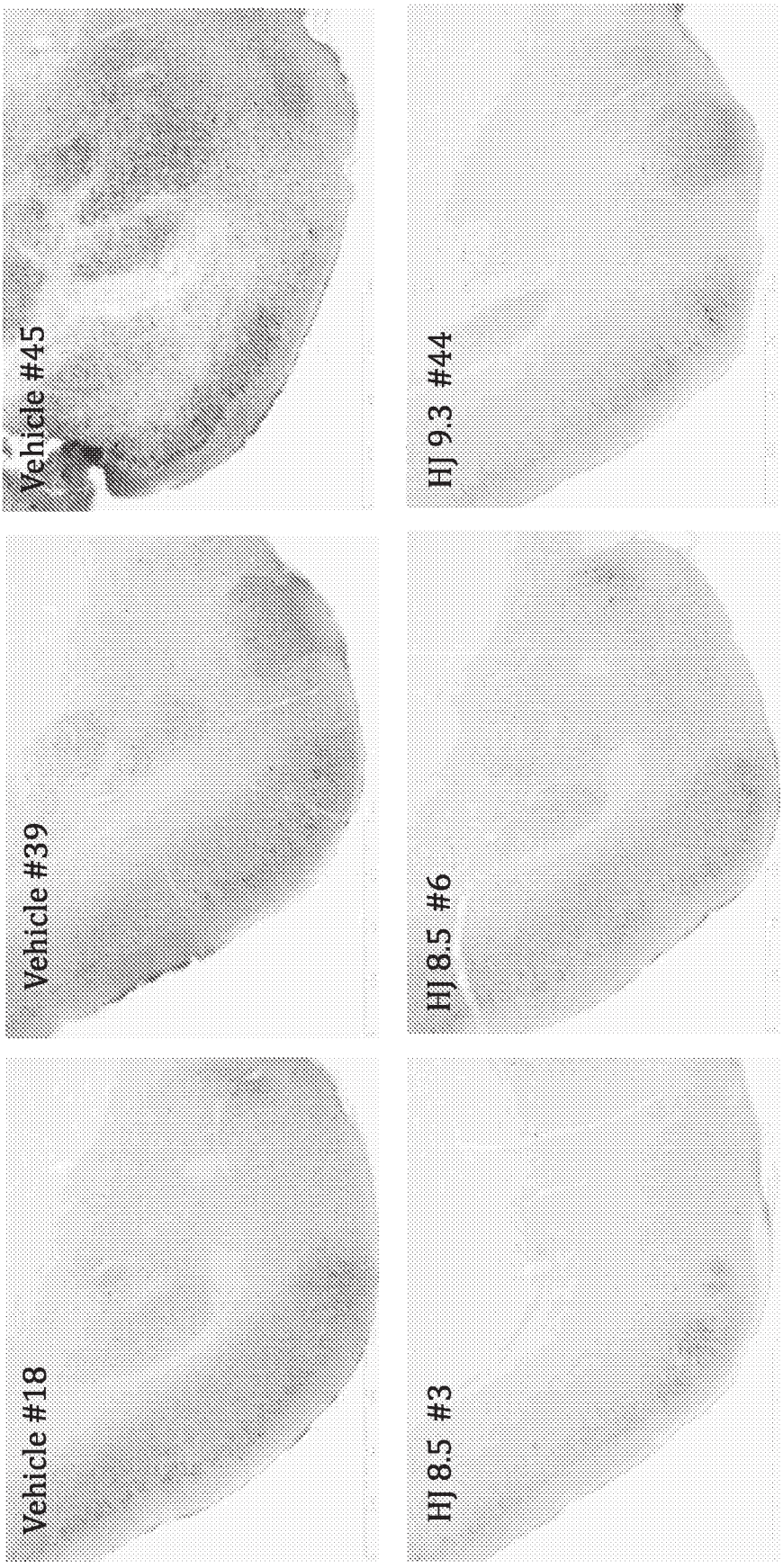
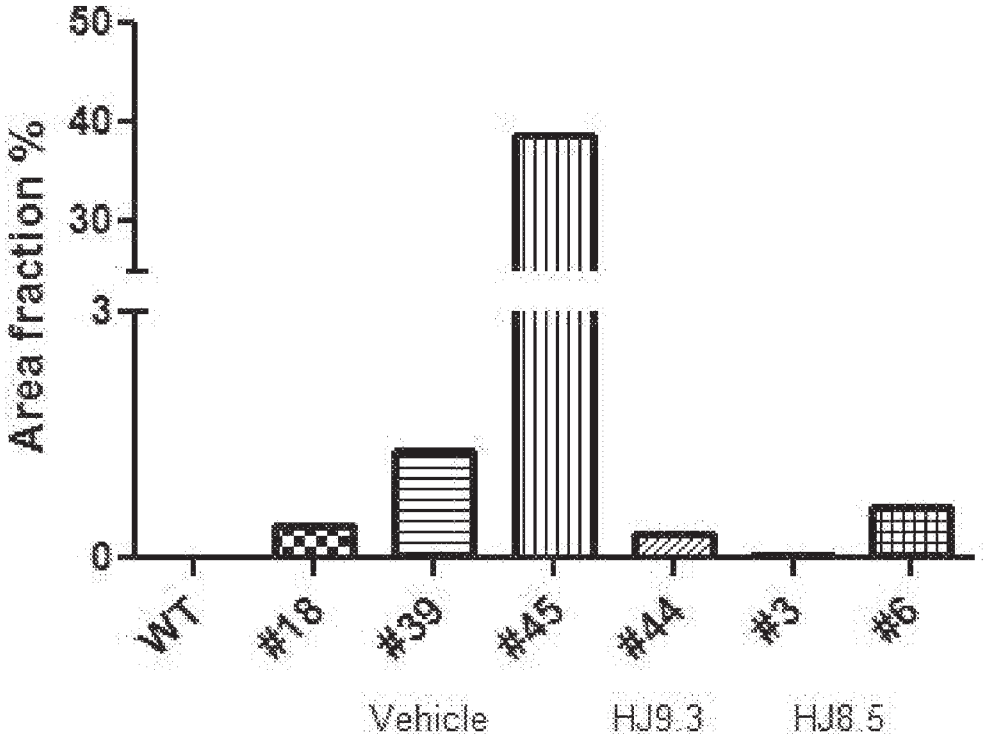


FIG. 26

A


Area fraction %
50
40
30
3
0
WT
#18
#39
#45
#44
#3
#6
Vehicle
HJ9.3
HJ8.5

B

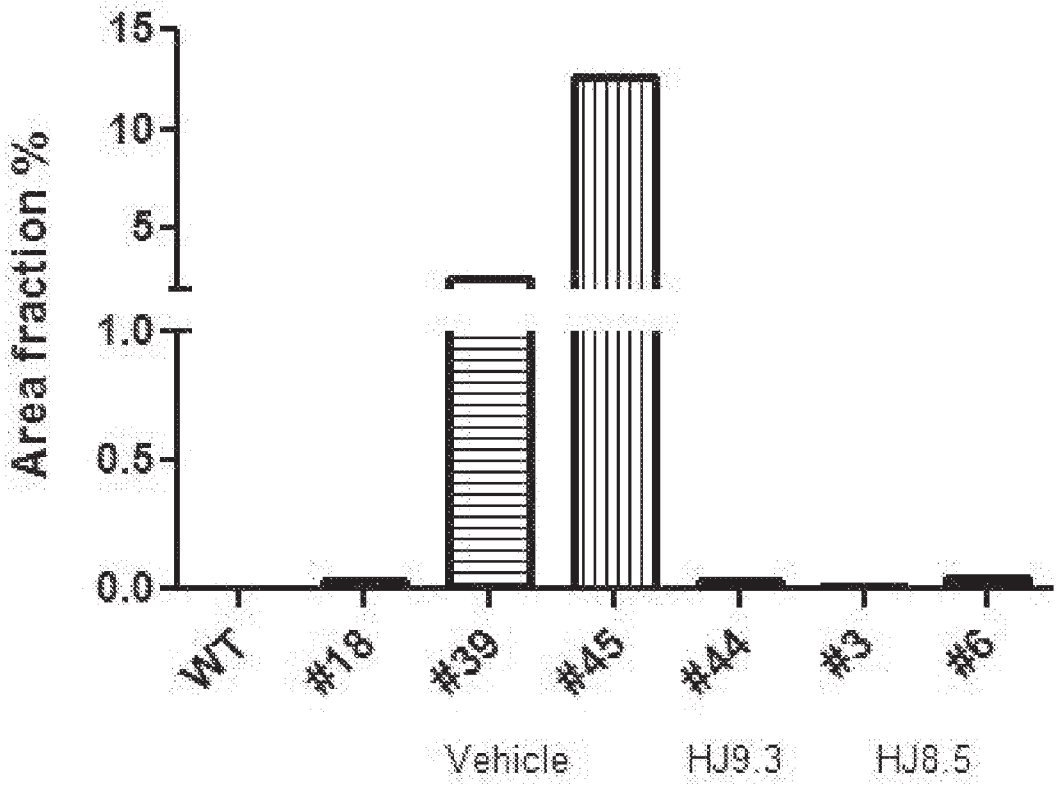

Area fraction %
15
10
5
1.0
0.5
0.0
WT
#18
#39
#45
#44
#3
#6
Vehicle
HJ9.3
HJ8.5

FIG. 27

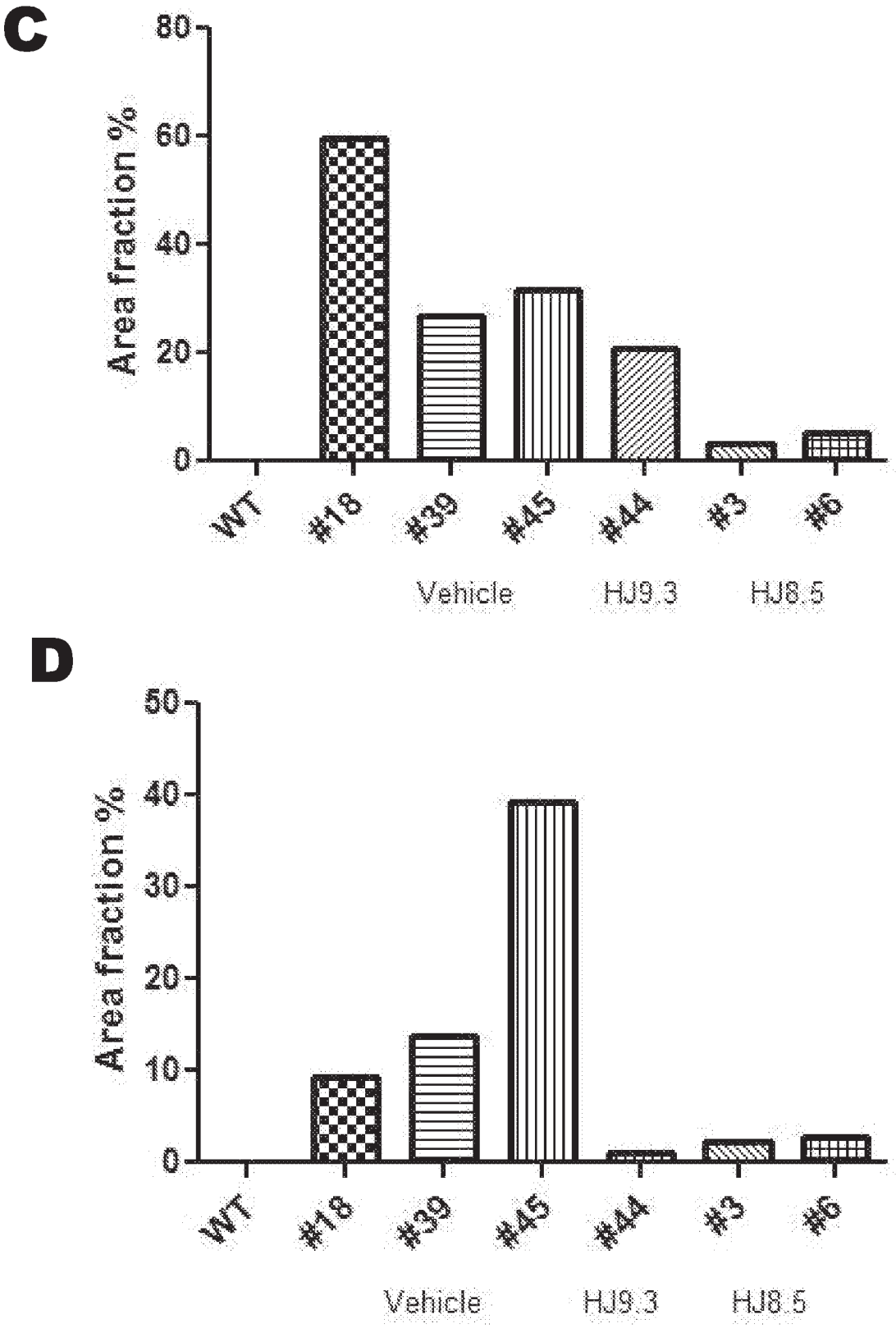

C
Area fraction %
80
60
40
20
0
WT
#18
#39
#45
#44
#3
#6
Vehicle
HJ9.3
HJ8.5
D
Area fraction %
50
40
30
20
10
0
WT
#18
#39
#45
#44
#3
#6
Vehicle
HJ9.3
HJ8.5

FIG. 27

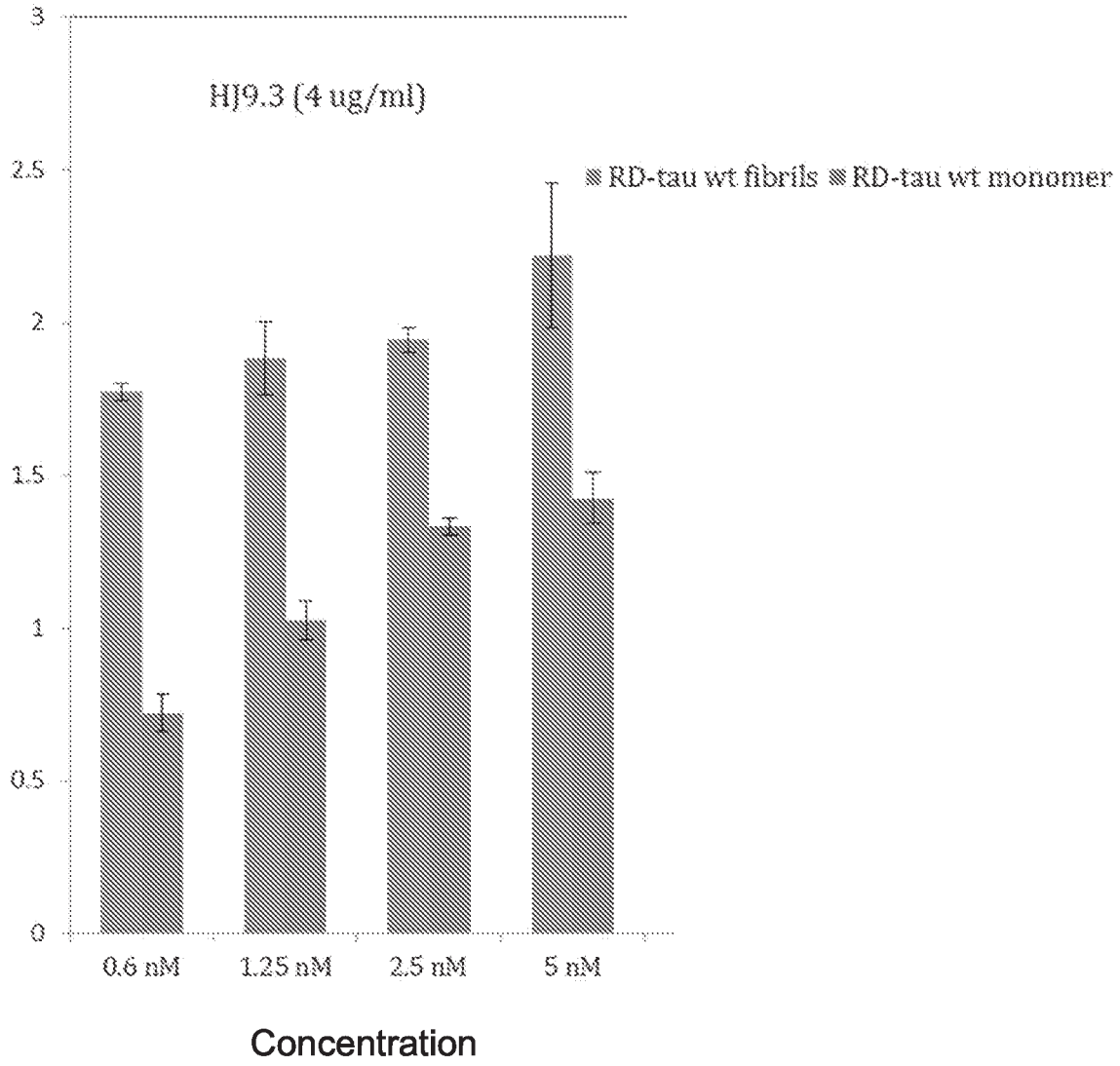

HJ9.3 (4 ug/ml)
RD-tau wt fibrils
RD-tau wt monomer
3
2.5
2
1.5
1
0.5
0
0.6 nM
1.25 nM
2.5 nM
5 nM
Concentration

FIG. 28

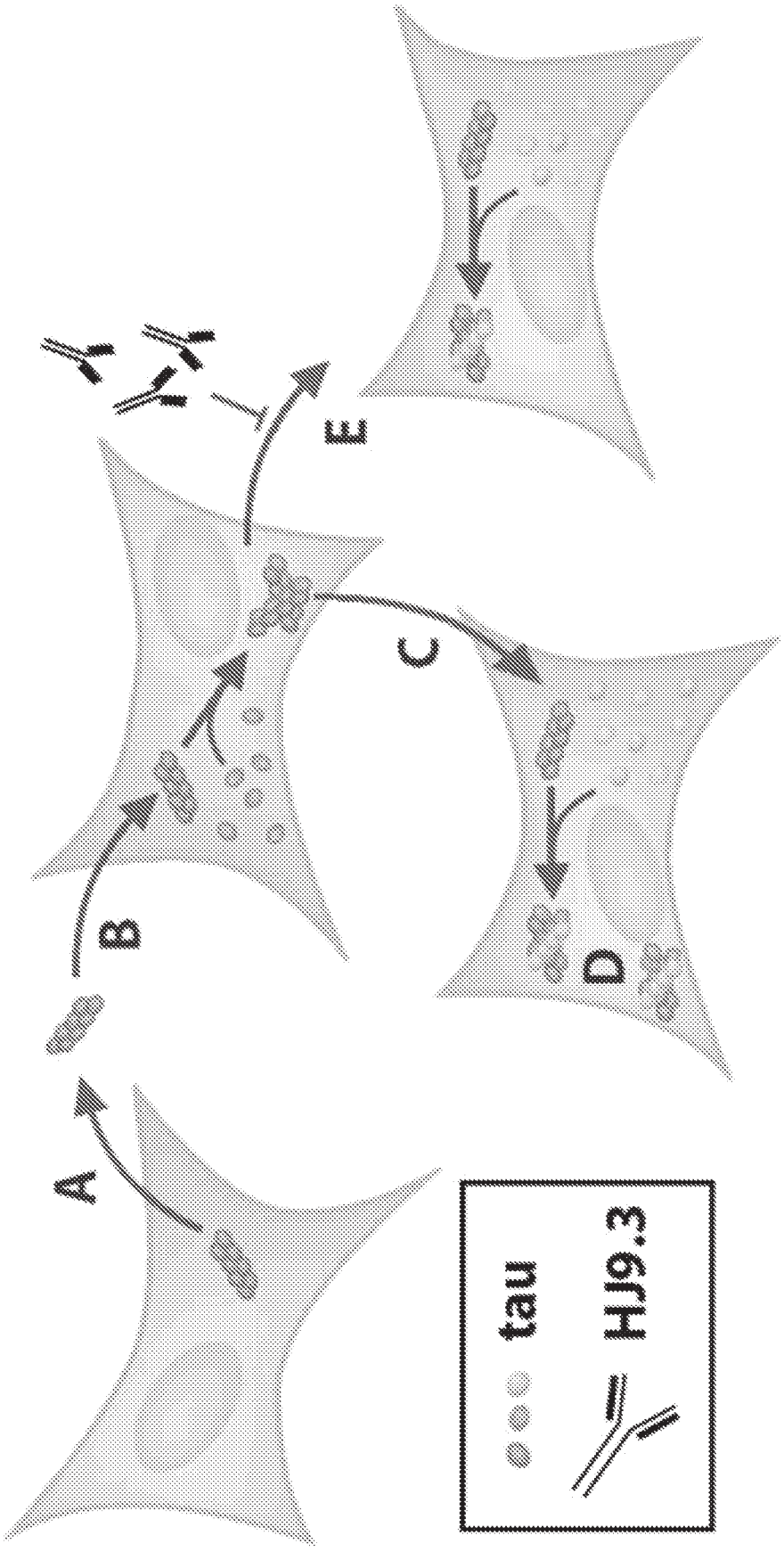


FIG. 29

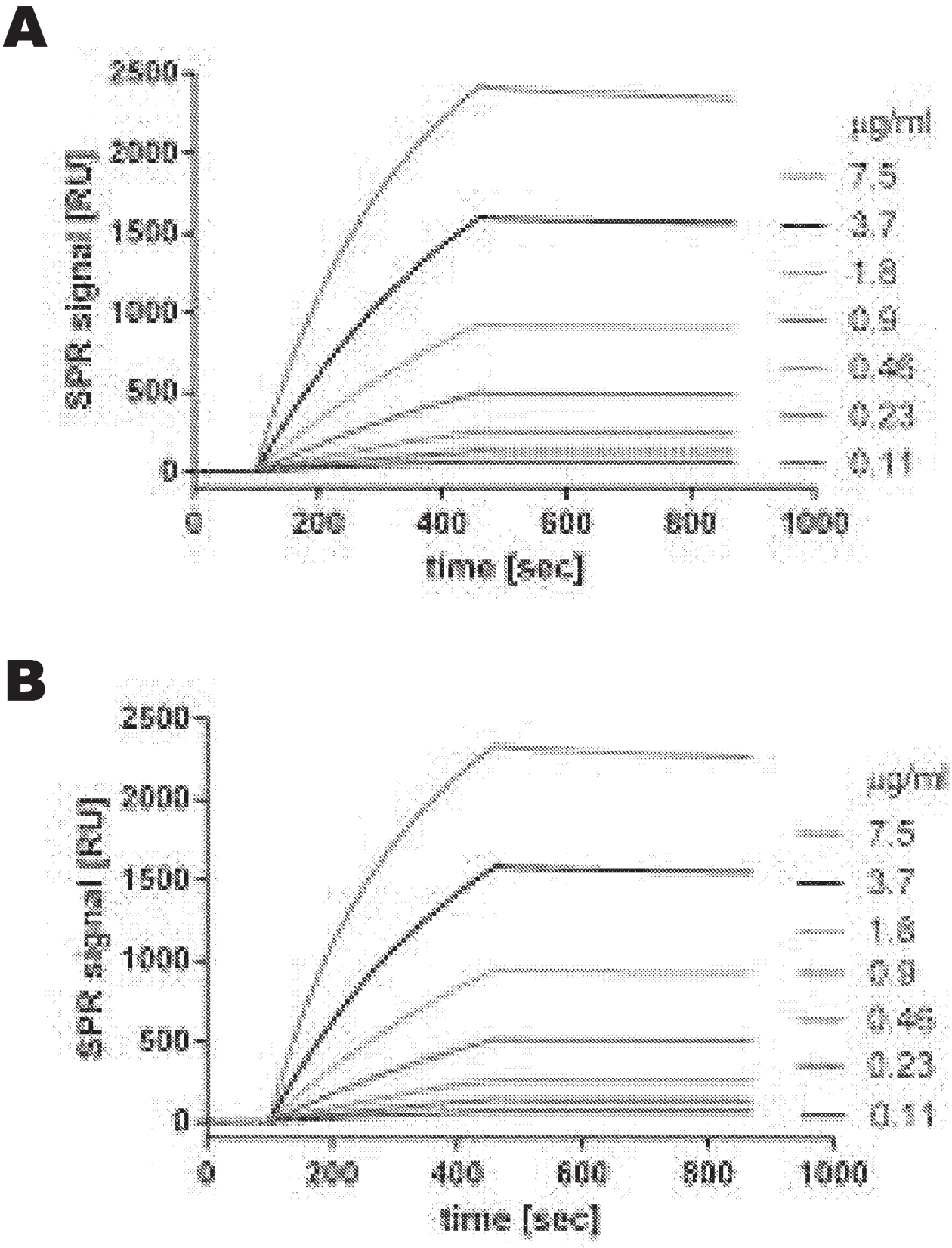
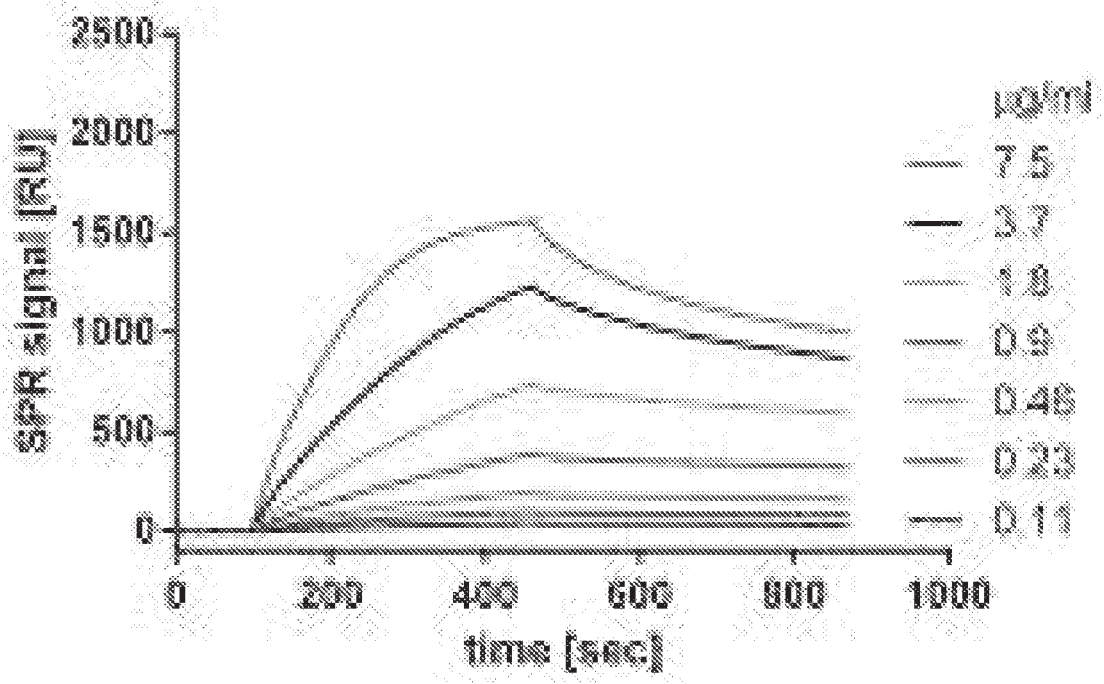

A
2500
2000
1500
1000
500
0
SPR signal [RU]
0
200
400
600
800
1000
time [sec]
μg/ml
7.5
3.7
1.8
0.9
0.45
0.23
0.11
B
2500
2000
1500
1000
500
0
SPR signal [RU]
0
200
400
600
800
1000
time [sec]
μg/ml
7.5
3.7
1.8
0.9
0.45
0.23
0.11

FIG. 30

C


SPR signal [RU]
2500
2000
1500
1000
500
0
0
200
400
600
800
1000
time [sec]
μg/ml
7.5
3.7
1.8
0.9
0.46
0.23
0.11

D

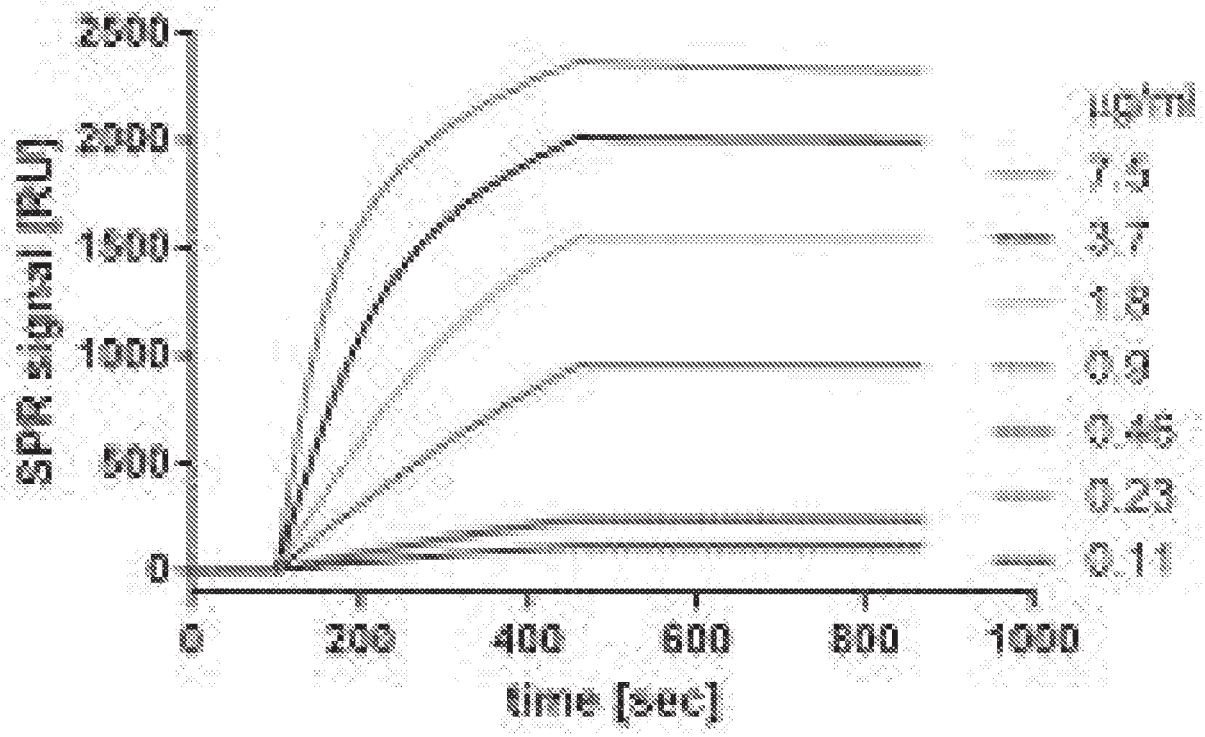

SPR signal [RU]
2500
2000
1500
1000
500
0
0
200
400
600
800
1000
time [sec]
μg/ml
7.5
3.7
1.8
0.9
0.46
0.23
0.11

FIG. 30

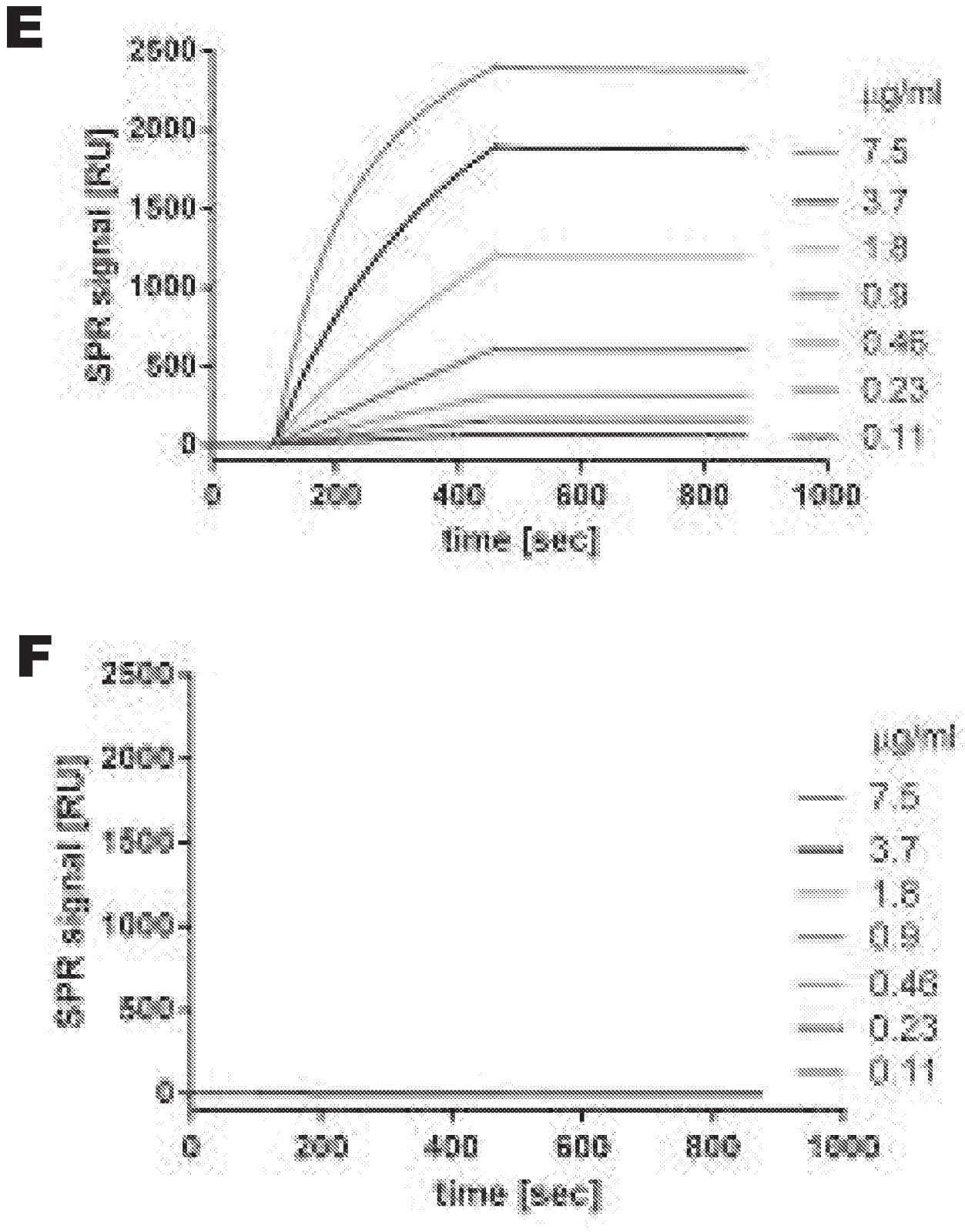

E
2500
2000
1500
1000
500
0
SPR signal [RU]
0
200
400
600
800
1000
time [sec]
μg/ml
7.5
3.7
1.8
0.9
0.46
0.23
0.11
F
2500
2000
1500
1000
500
0
SPR signal [RU]
0
200
400
600
800
1000
time [sec]
μg/ml
7.5
3.7
1.8
0.9
0.46
0.23
0.11

FIG. 30

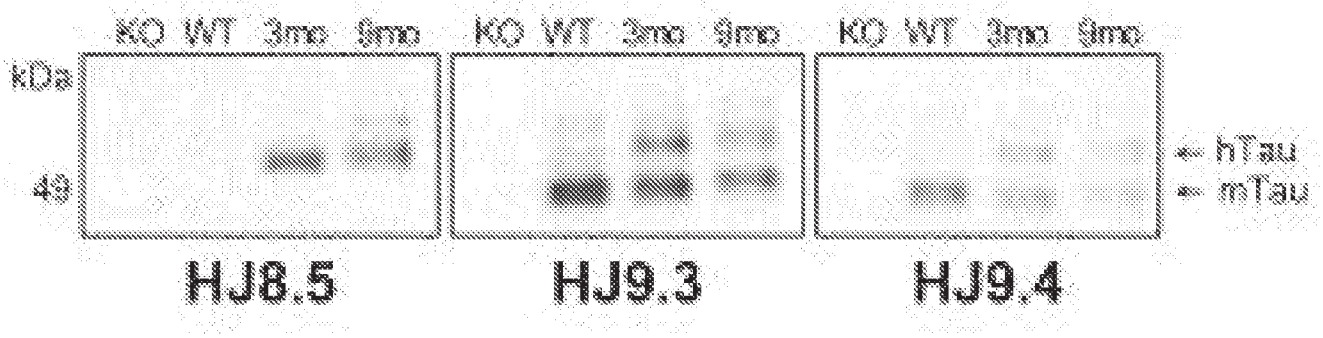

KO WT 3mo 9mo
KO WT 3mo 9mo
KO WT 3mo 9mo
kDa
49
hTau
mTau
HJ8.5
HJ9.3
HJ9.4

FIG. 30G

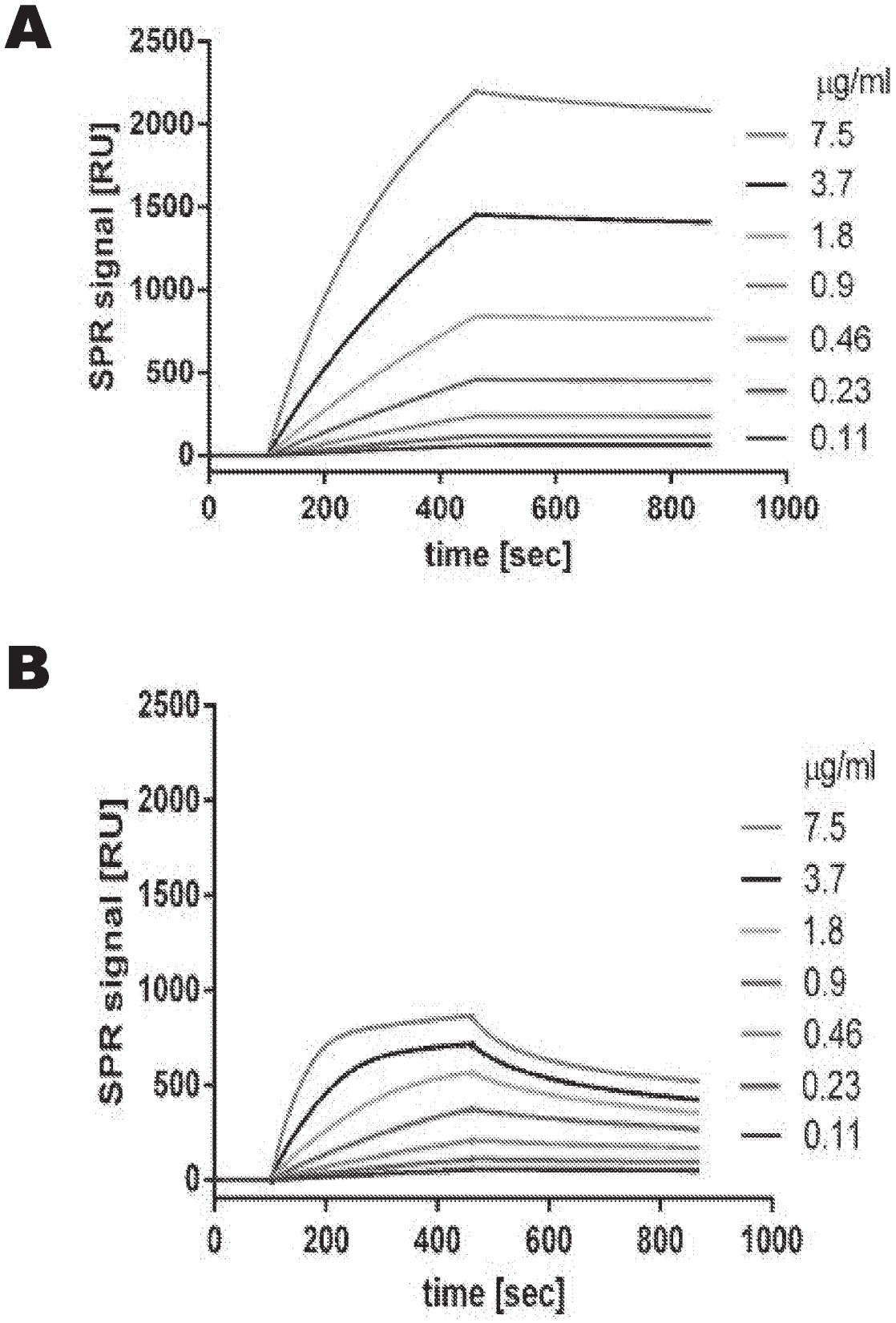

A
2500
2000
1500
1000
500
0
SPR signal [RU]
0
200
400
600
800
1000
time [sec]
µg/ml
7.5
3.7
1.8
0.9
0.46
0.23
0.11
B
2500
2000
1500
1000
500
0
SPR signal [RU]
0
200
400
600
800
1000
time [sec]
µg/ml
7.5
3.7
1.8
0.9
0.46
0.23
0.11

FIG. 31

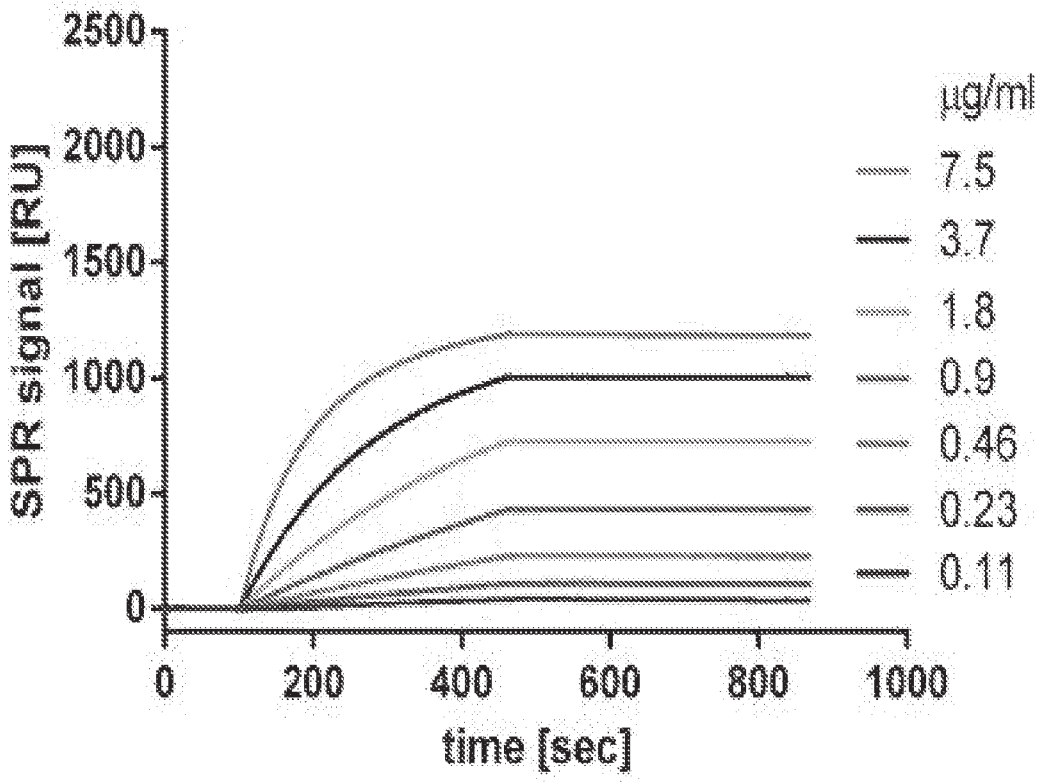

SPR signal [RU]
2500
2000
1500
1000
500
0
0
200
400
600
800
1000
time [sec]
µg/ml
7.5
3.7
1.8
0.9
0.46
0.23
0.11

FIG. 31C

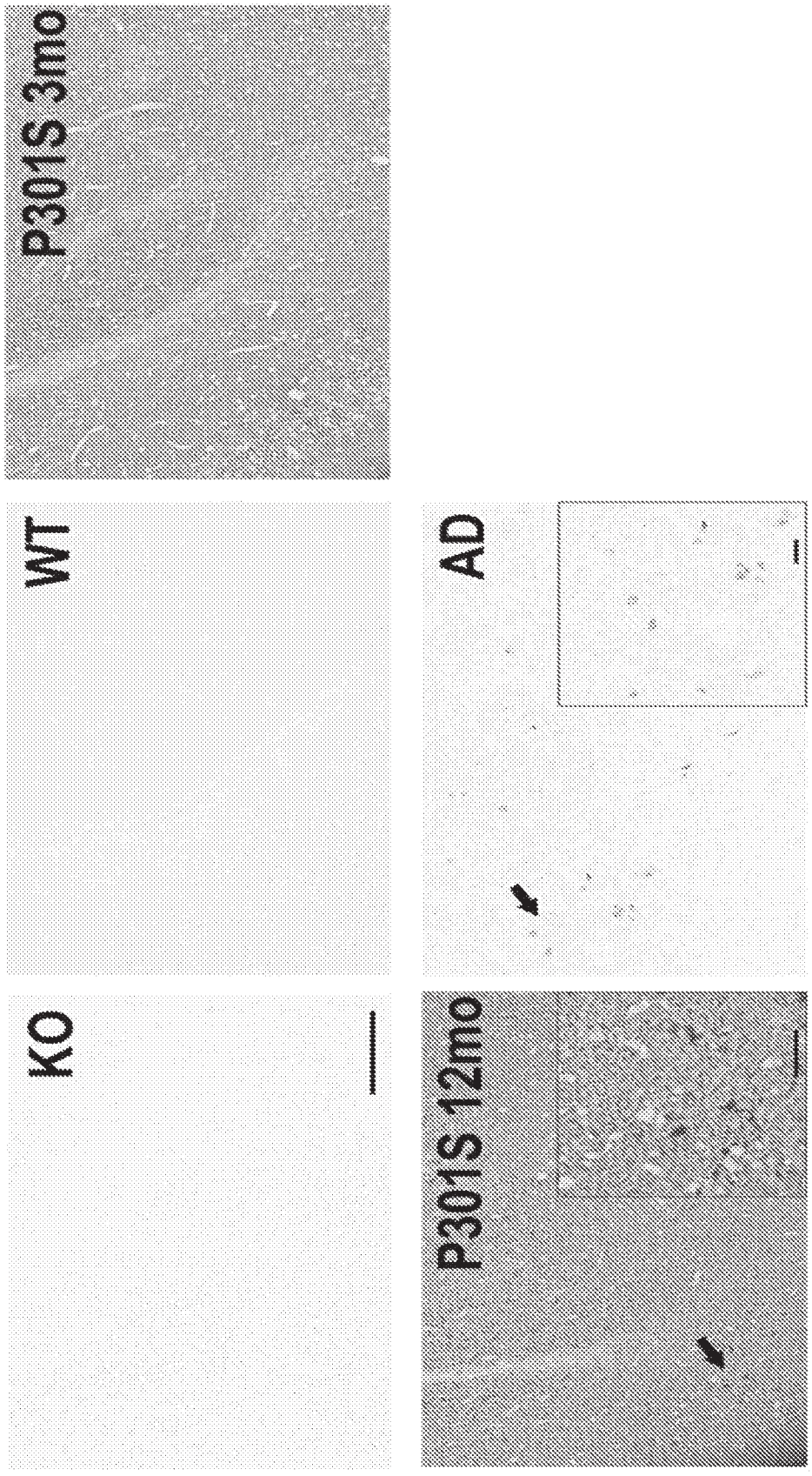


FIG. 32

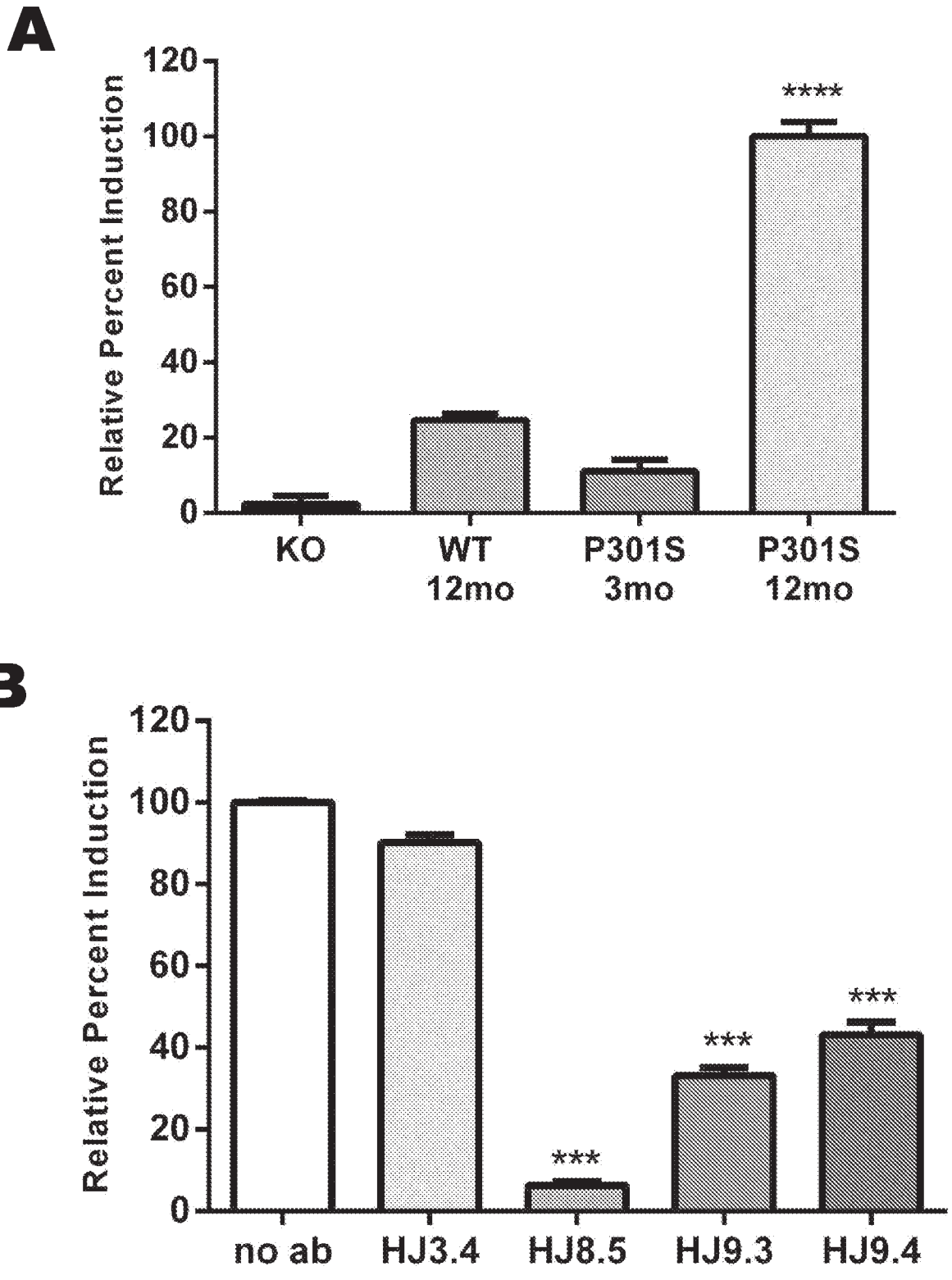

A
Relative Percent Induction
120
100
80
60
40
20
0
****
KO
WT 12mo
P301S 3mo
P301S 12mo
B
Relative Percent Induction
120
100
80
60
40
20
0
***
***
***
no ab
HJ3.4
HJ8.5
HJ9.3
HJ9.4

FIG. 33

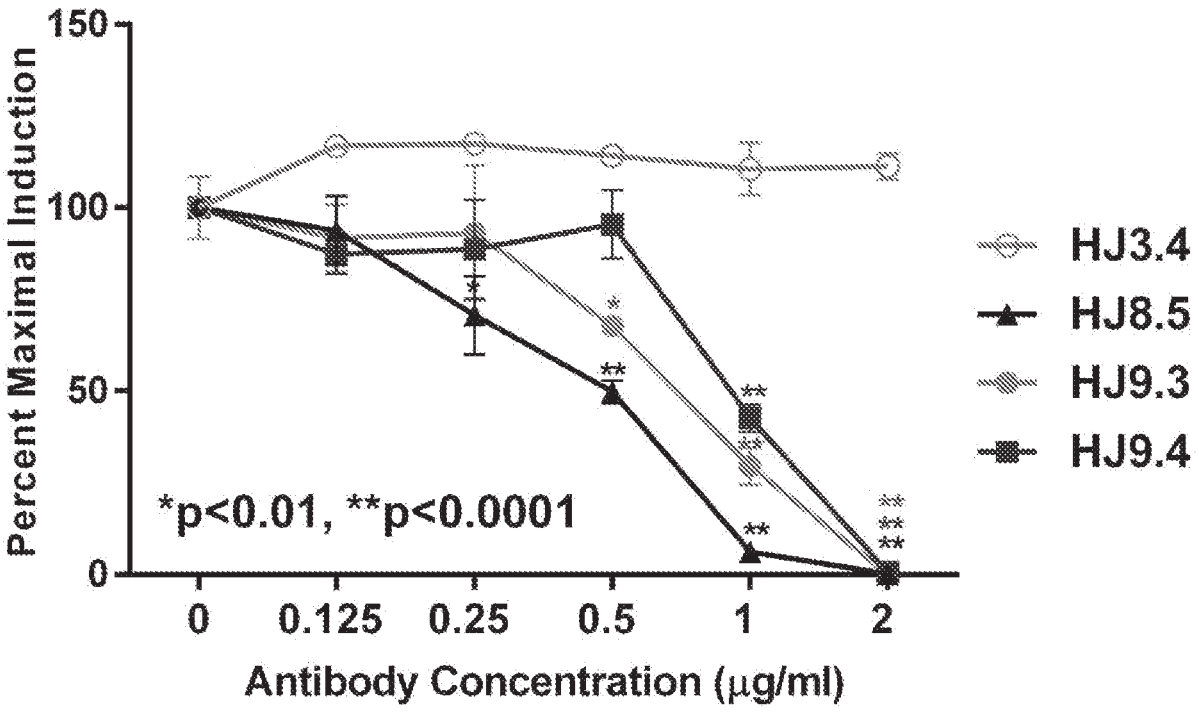

150
100
50
0
Percent Maximal Induction
*p<0.01, **p<0.0001
0
0.125
0.25
0.5
1
2
Antibody Concentration (μg/ml)
HJ3.4
HJ8.5
HJ9.3
HJ9.4

FIG. 33C

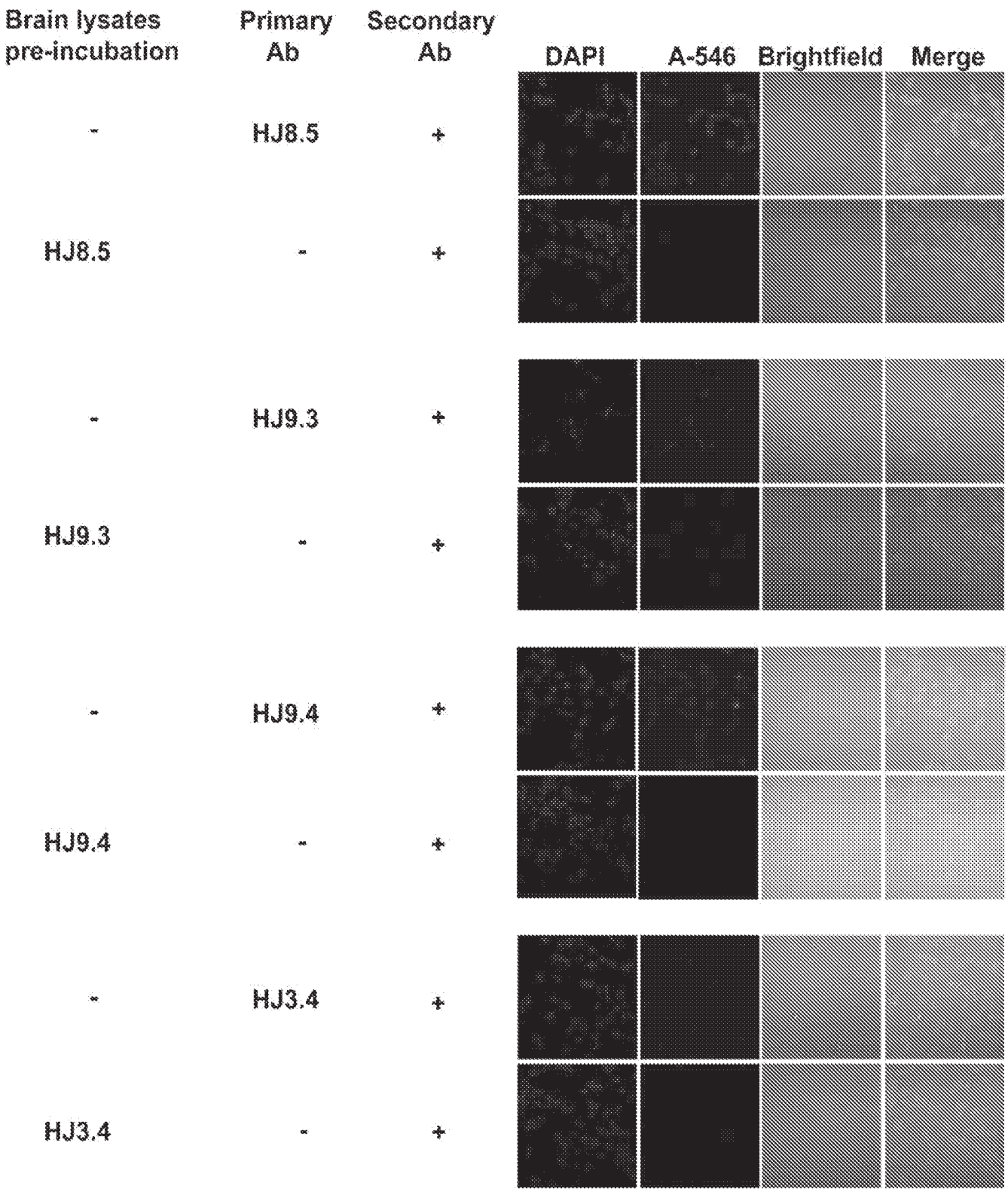
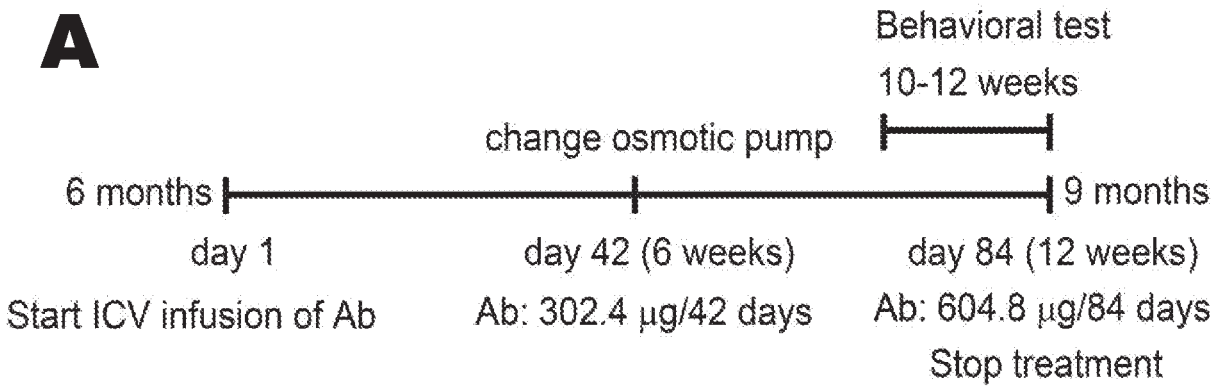

Brain lysates pre-incubation
Primary Ab
Secondary Ab
DAPI
A-546
Brightfield
Merge
-
HJ8.5
+
HJ8.5
-
+
-
HJ9.3
+
HJ9.3
-
+
-
HJ9.4
+
HJ9.4
-
+
-
HJ3.4
+
HJ3.4
-
+

FIG. 34

A



Rate of infusion: 3.6 μl/day = 7.2 μg/day

B



FIG. 35

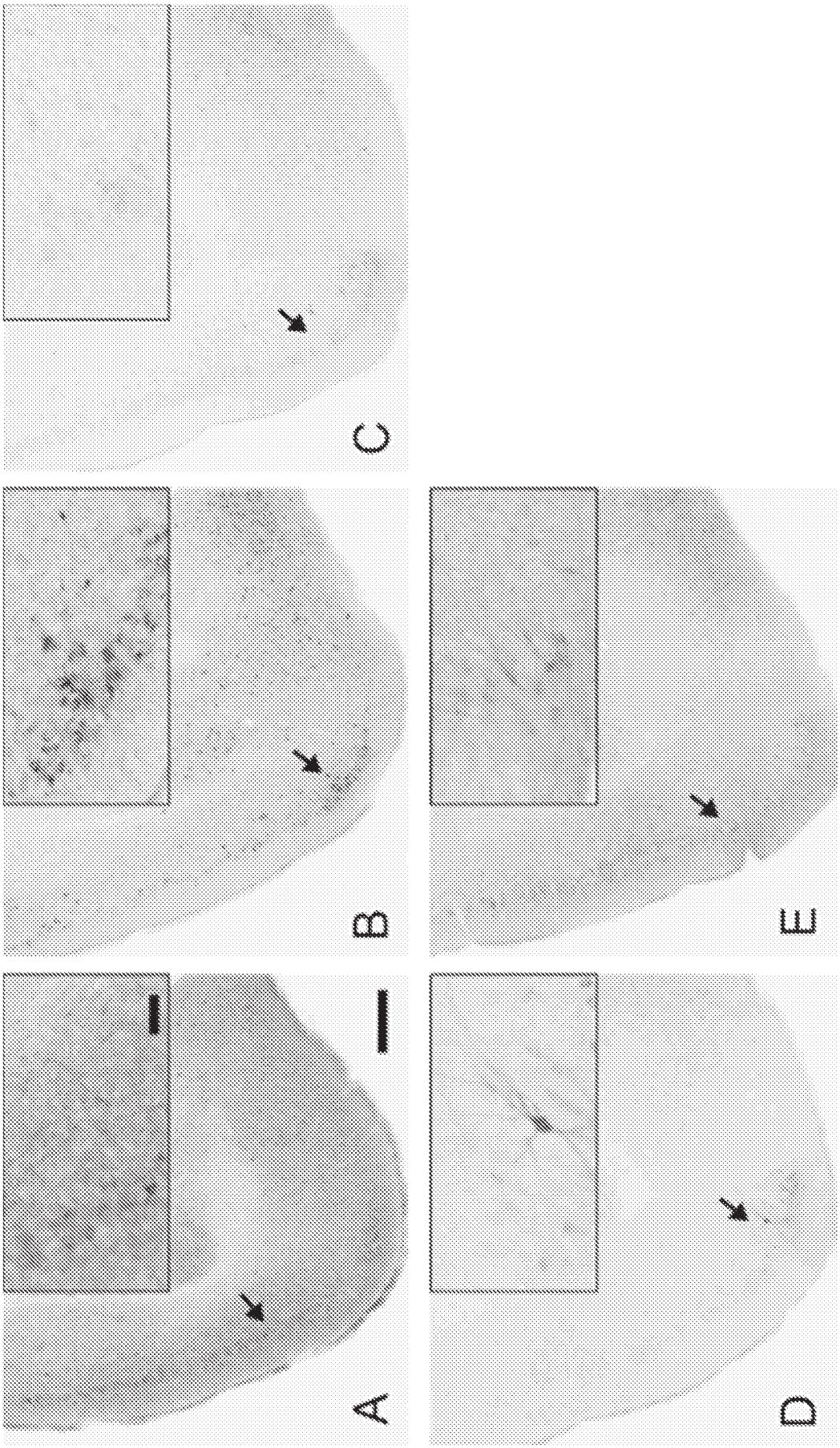


FIG. 36

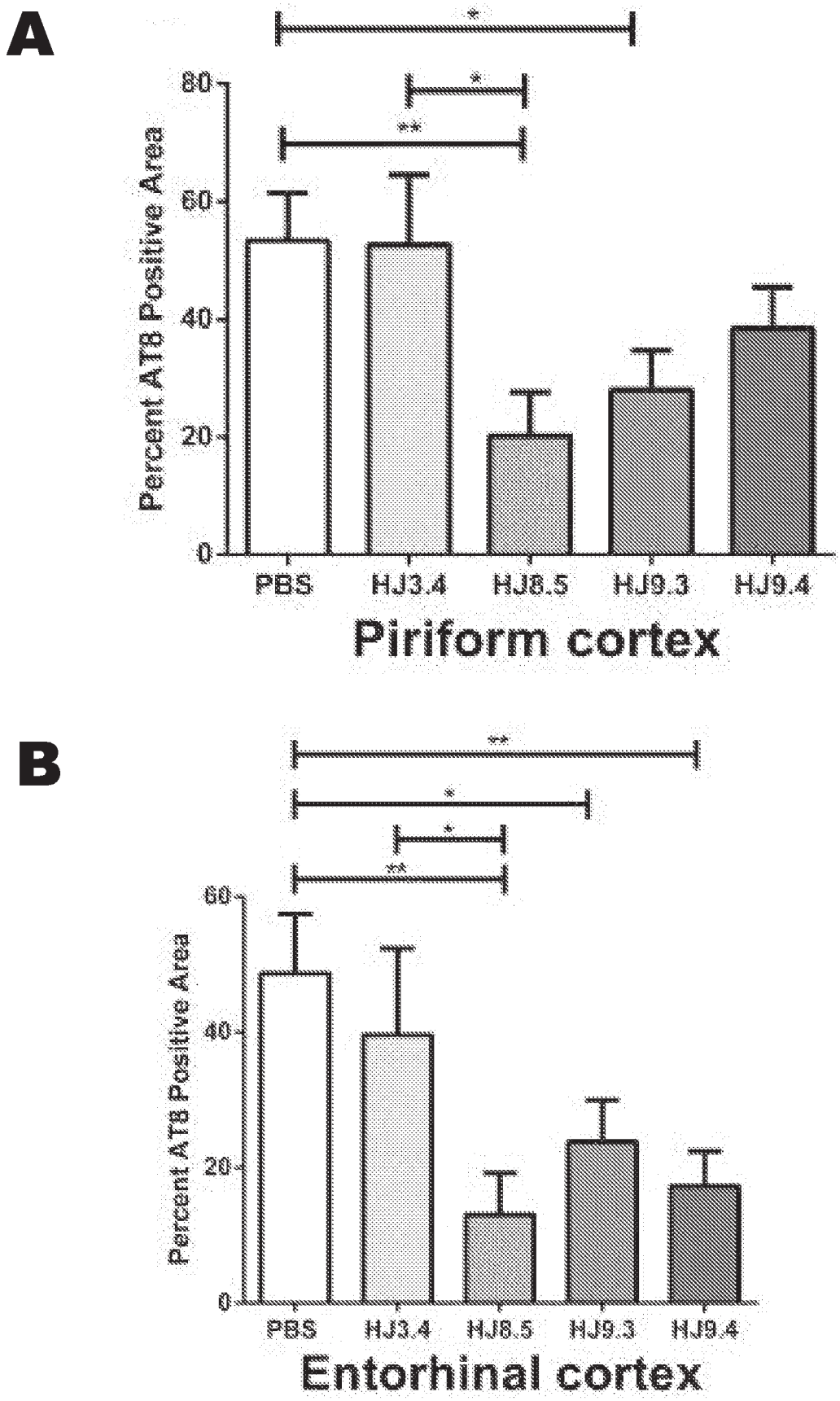
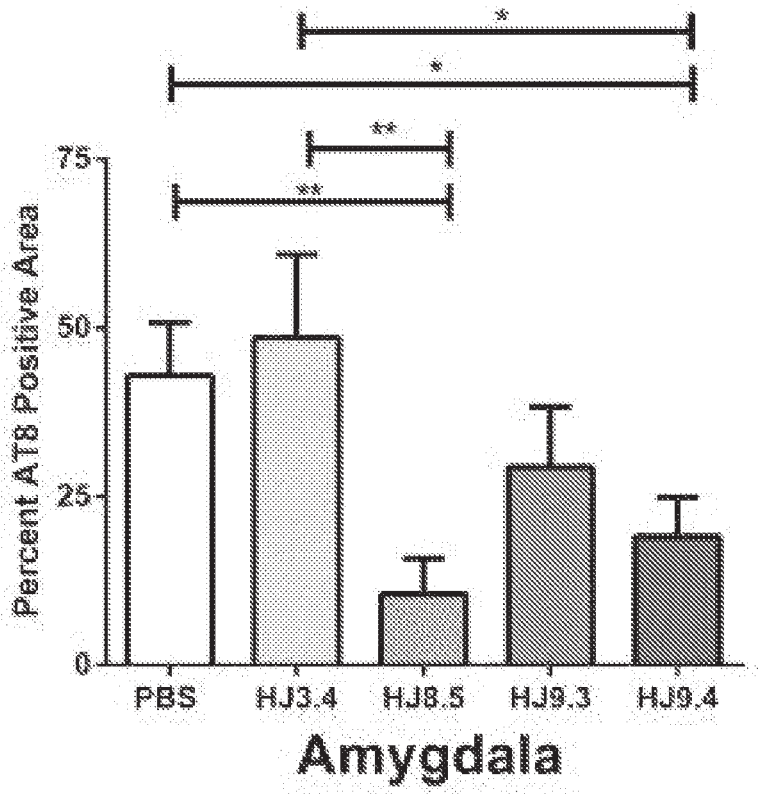

A
Percent AT8 Positive Area
0
20
40
60
80
PBS
HJ3.4
HJ8.5
HJ9.3
HJ9.4
Piriform cortex
B
Percent AT8 Positive Area
0
20
40
60
PBS
HJ3.4
HJ8.5
HJ9.3
HJ9.4
Entorhinal cortex

FIG. 37

C


*
*
**
**
75
50
25
0
Percent AT8 Positive Area
PBS
HJ3.4
HJ8.5
HJ9.3
HJ9.4
Amygdala

D

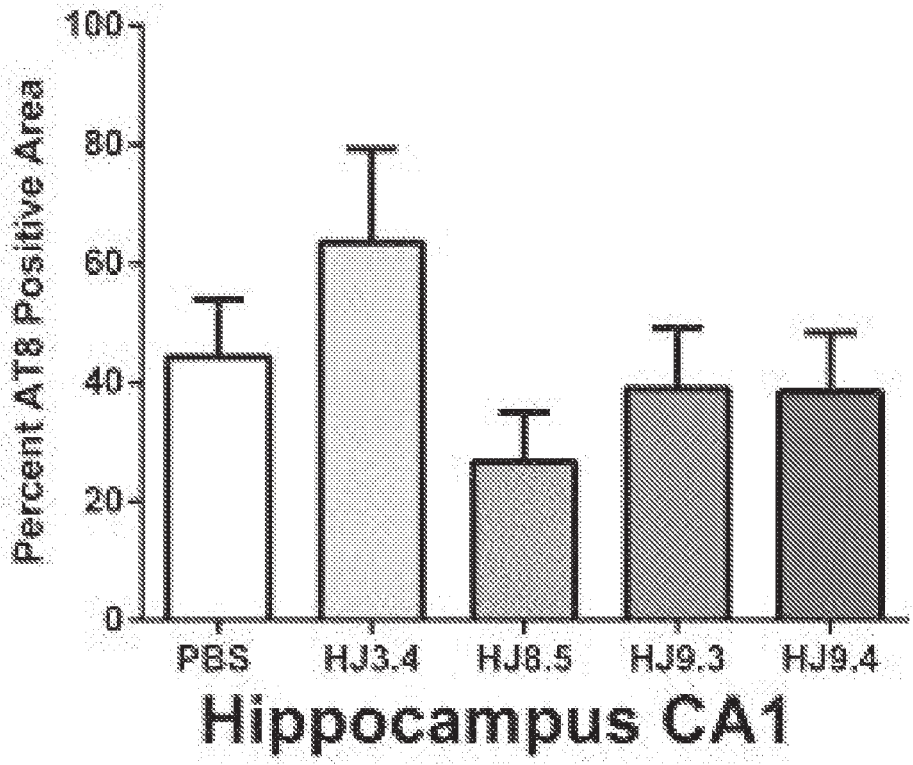
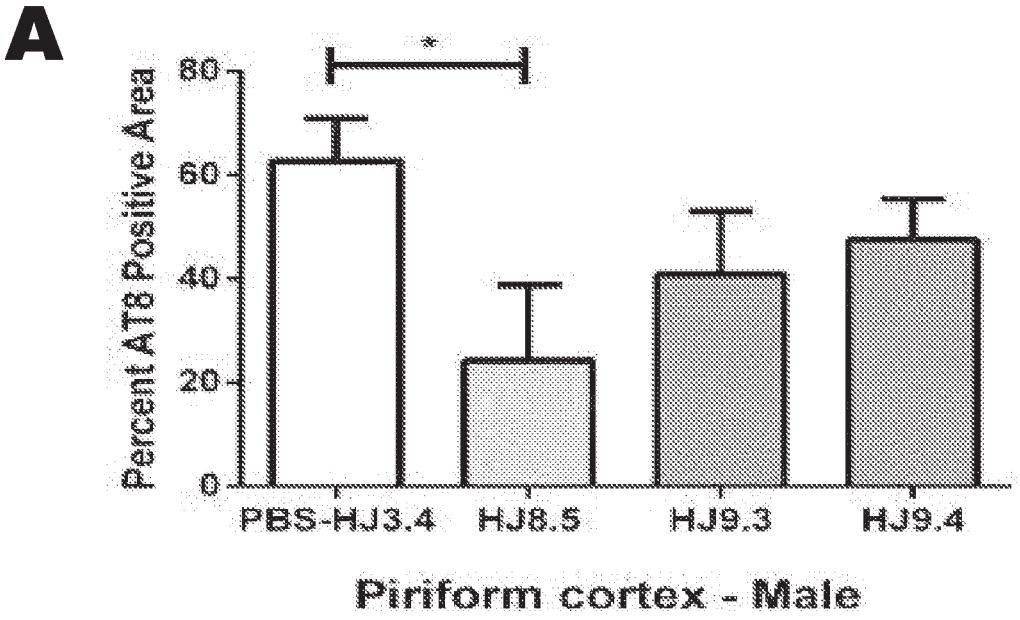

100
80
60
40
20
0
Percent AT8 Positive Area
PBS
HJ3.4
HJ8.5
HJ9.3
HJ9.4
Hippocampus CA1

FIG. 37


A
*
Percent AT8 Positive Area
80
60
40
20
0
PBS-HJ3.4
HJ8.5
HJ9.3
HJ9.4
Piriform cortex - Male

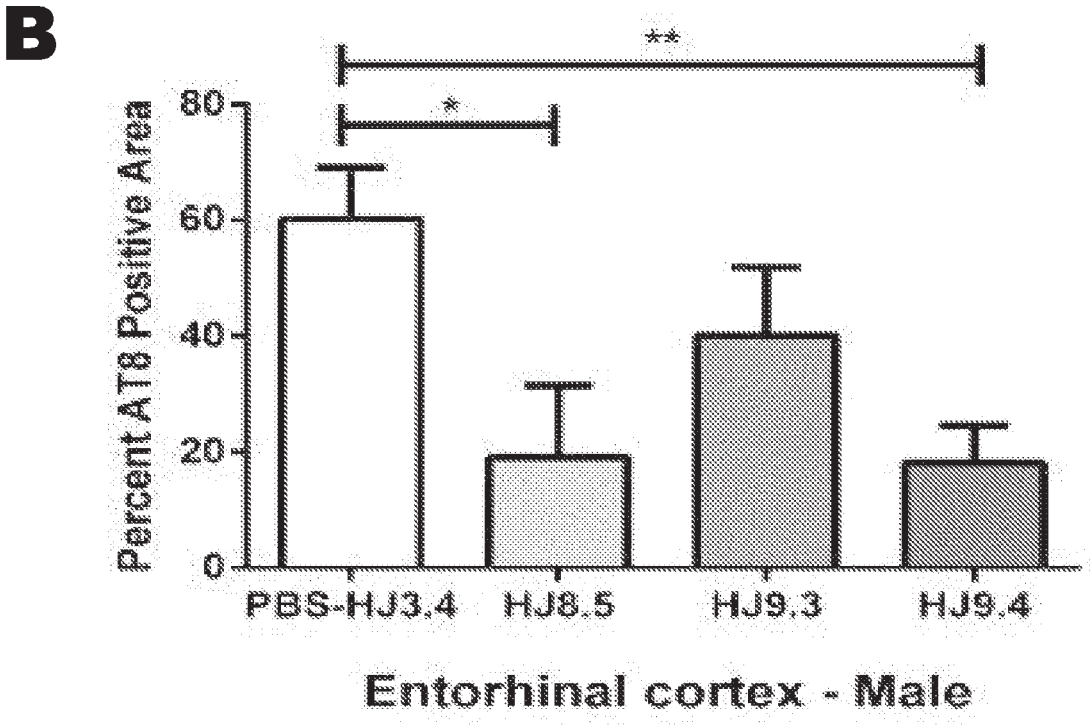
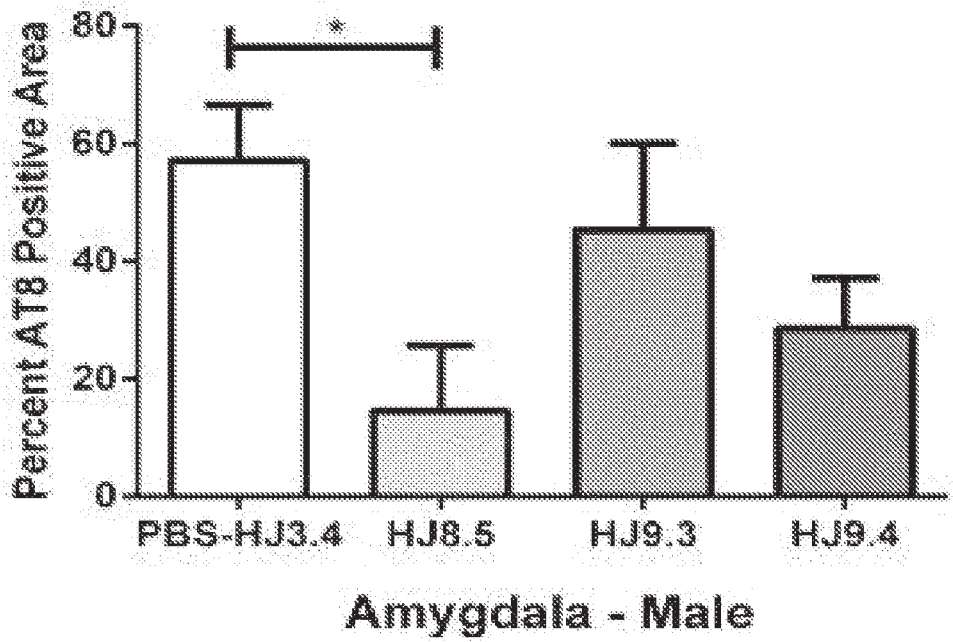

B
**
*
Percent AT8 Positive Area
80
60
40
20
0
PBS-HJ3.4
HJ8.5
HJ9.3
HJ9.4
Entorhinal cortex - Male

FIG. 38

C


Percent AT8 Positive Area
80
60
40
20
0
*
PBS-HJ3.4
HJ8.5
HJ9.3
HJ9.4
Amygdala - Male

D

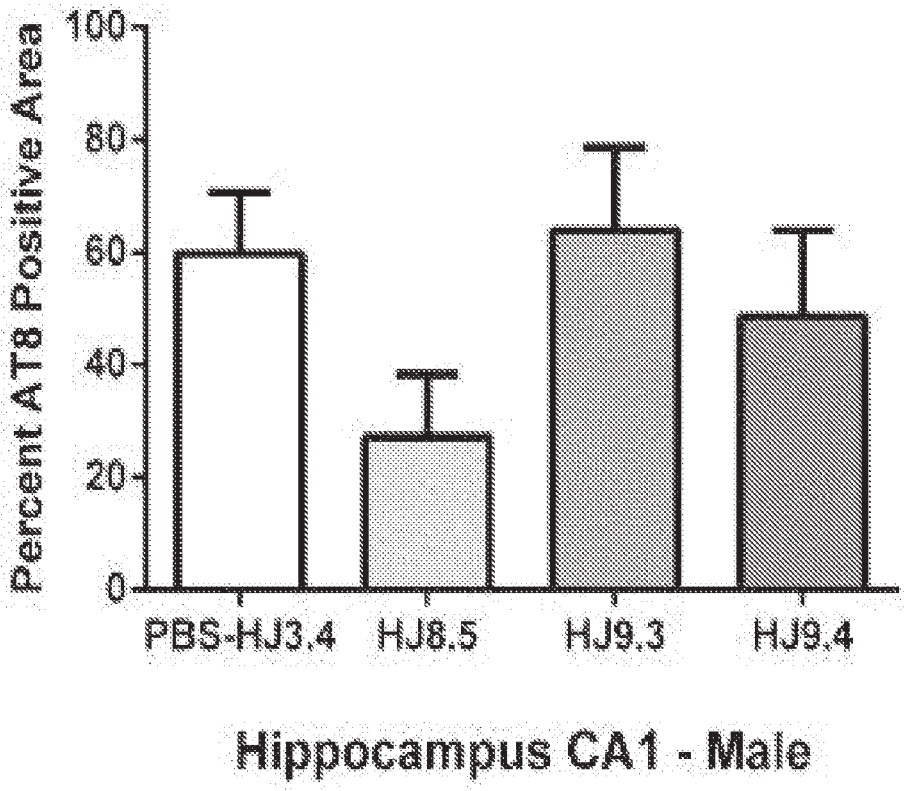
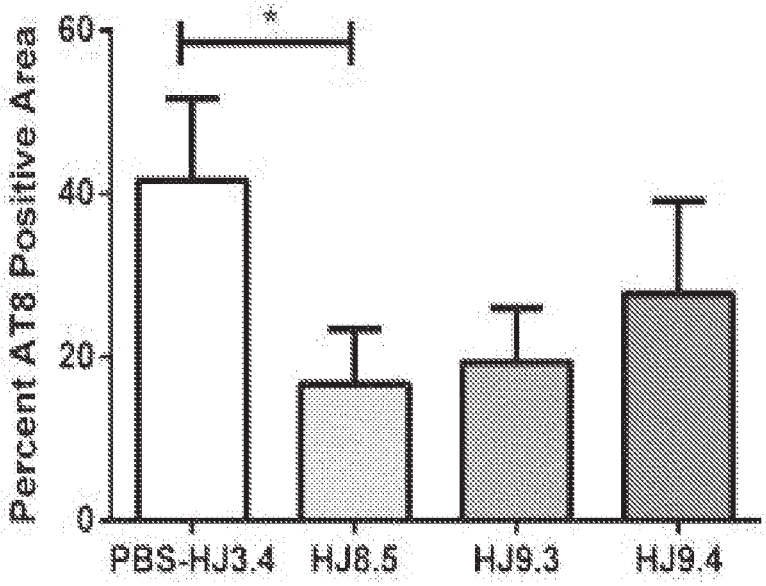

Percent AT8 Positive Area
100
80
60
40
20
0
PBS-HJ3.4
HJ8.5
HJ9.3
HJ9.4
Hippocampus CA1 - Male

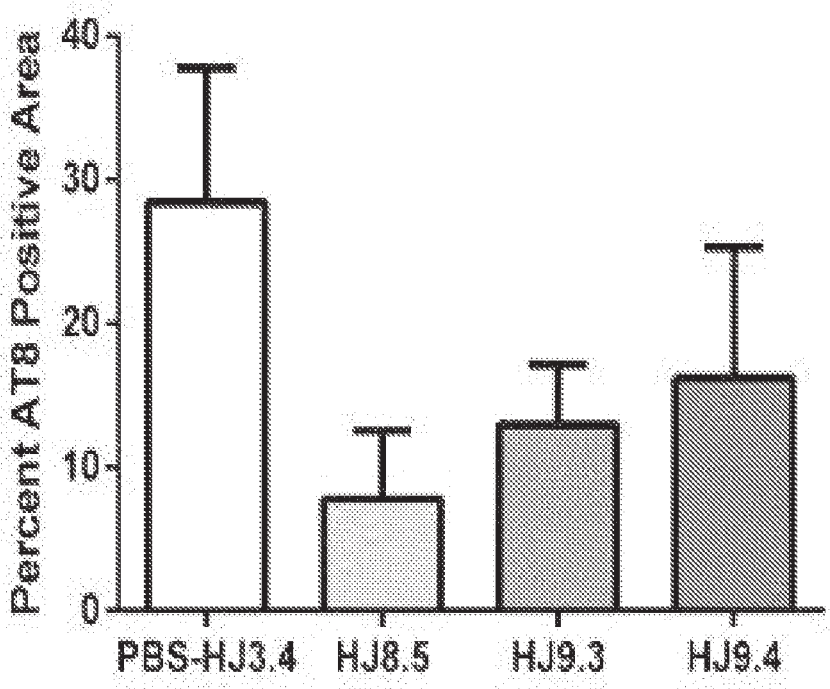
FIG. 38

E



Piriform cortex - Female

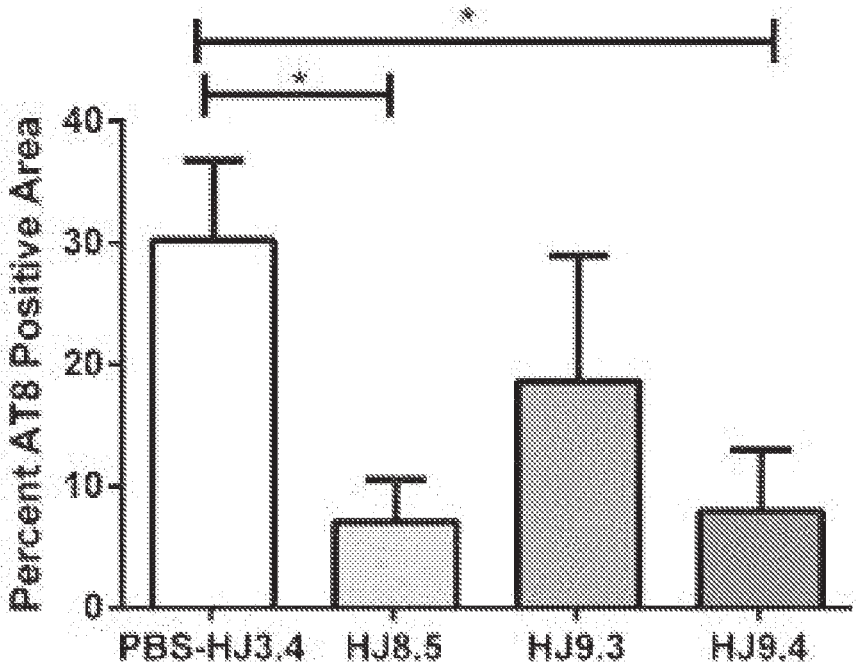
F



Entorhinal cortex - Female

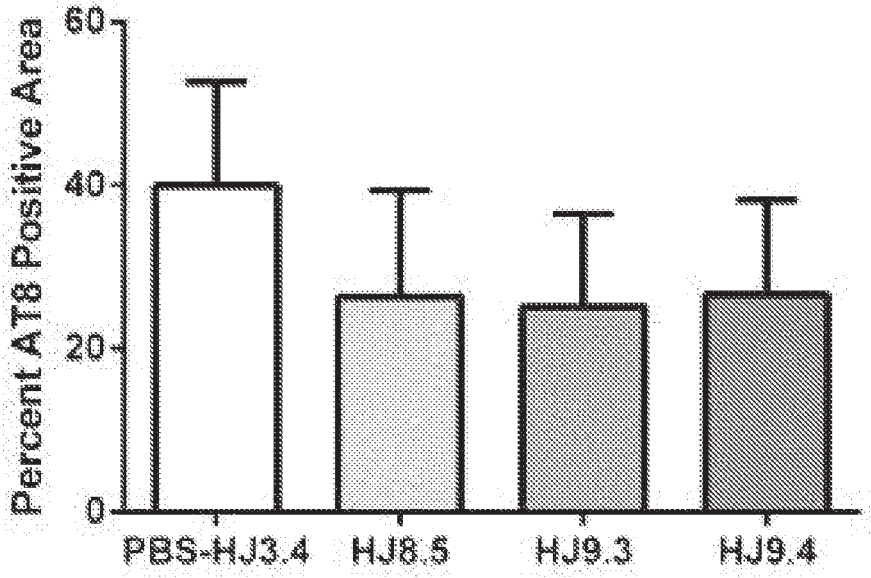
FIG. 38

G



Amygdala - Female

H



Hippocampus CA1 - Female

FIG. 38

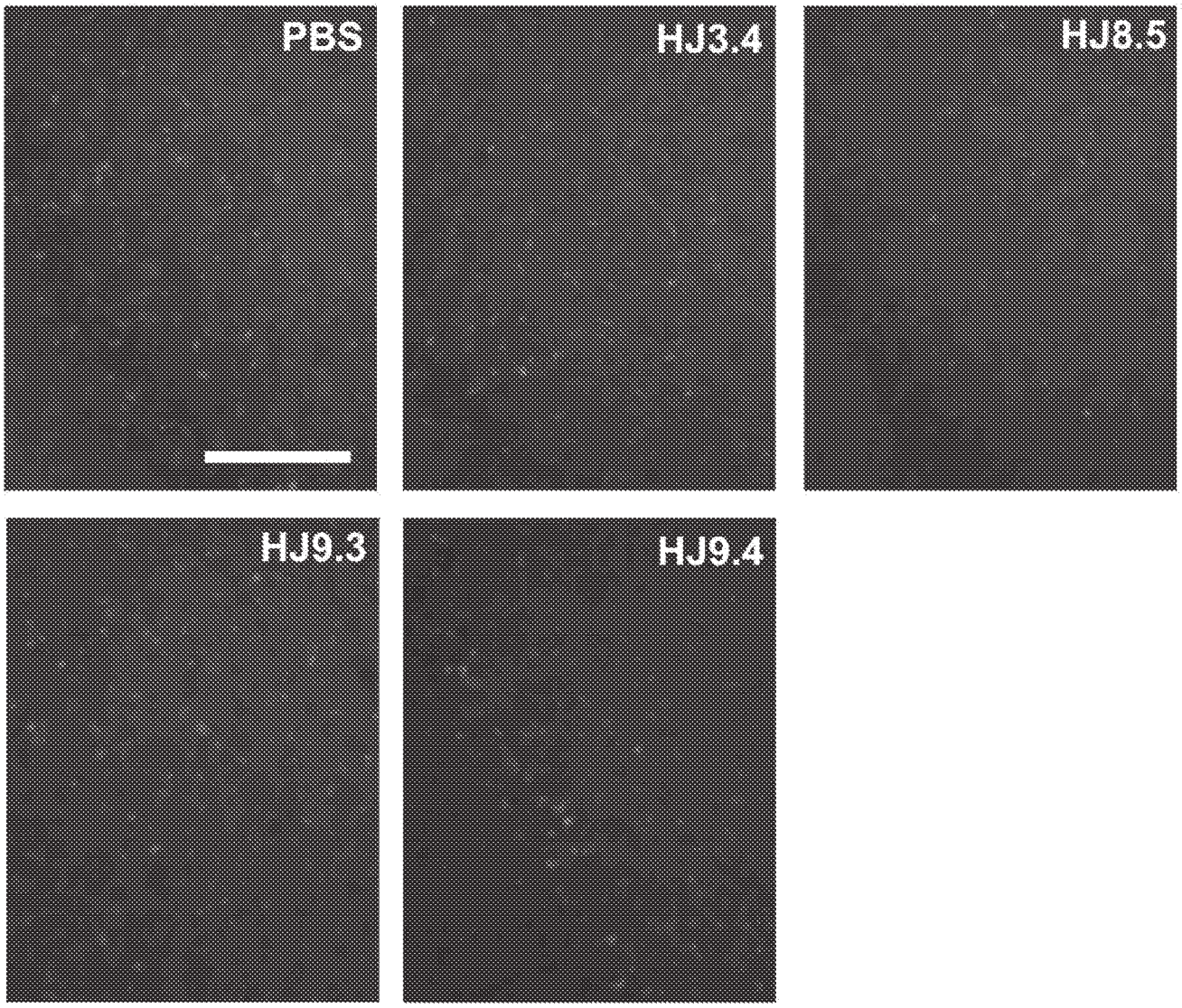


FIG. 39A

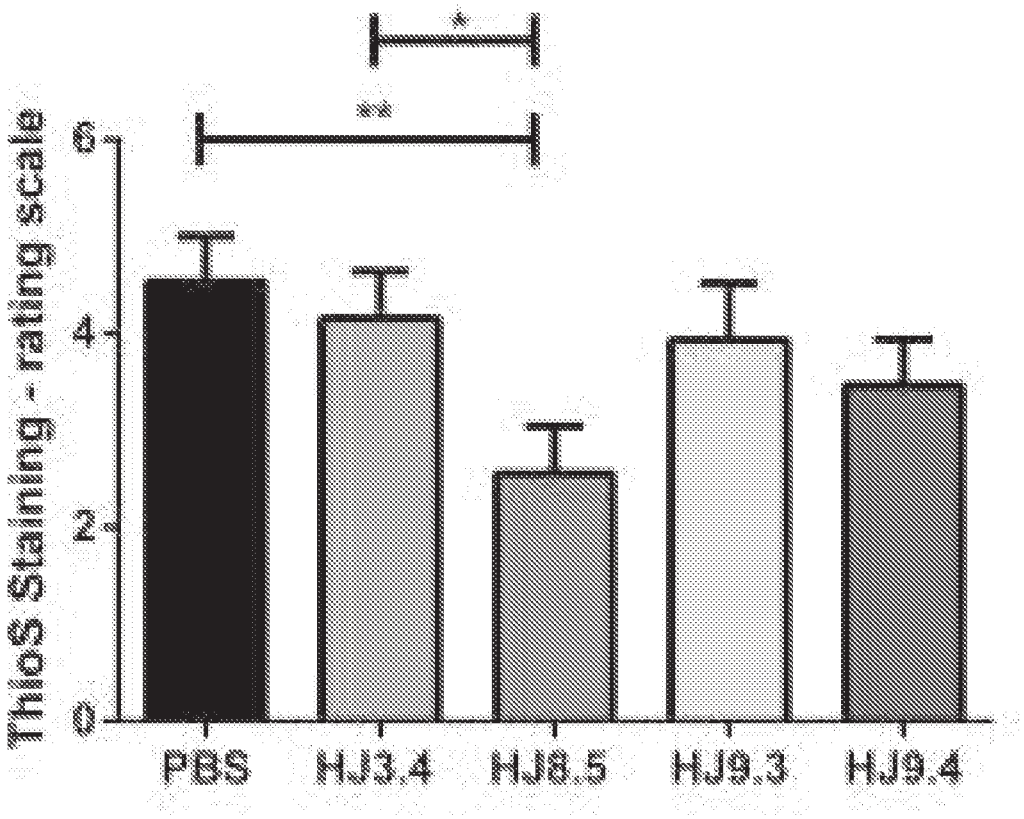


FIG. 39B

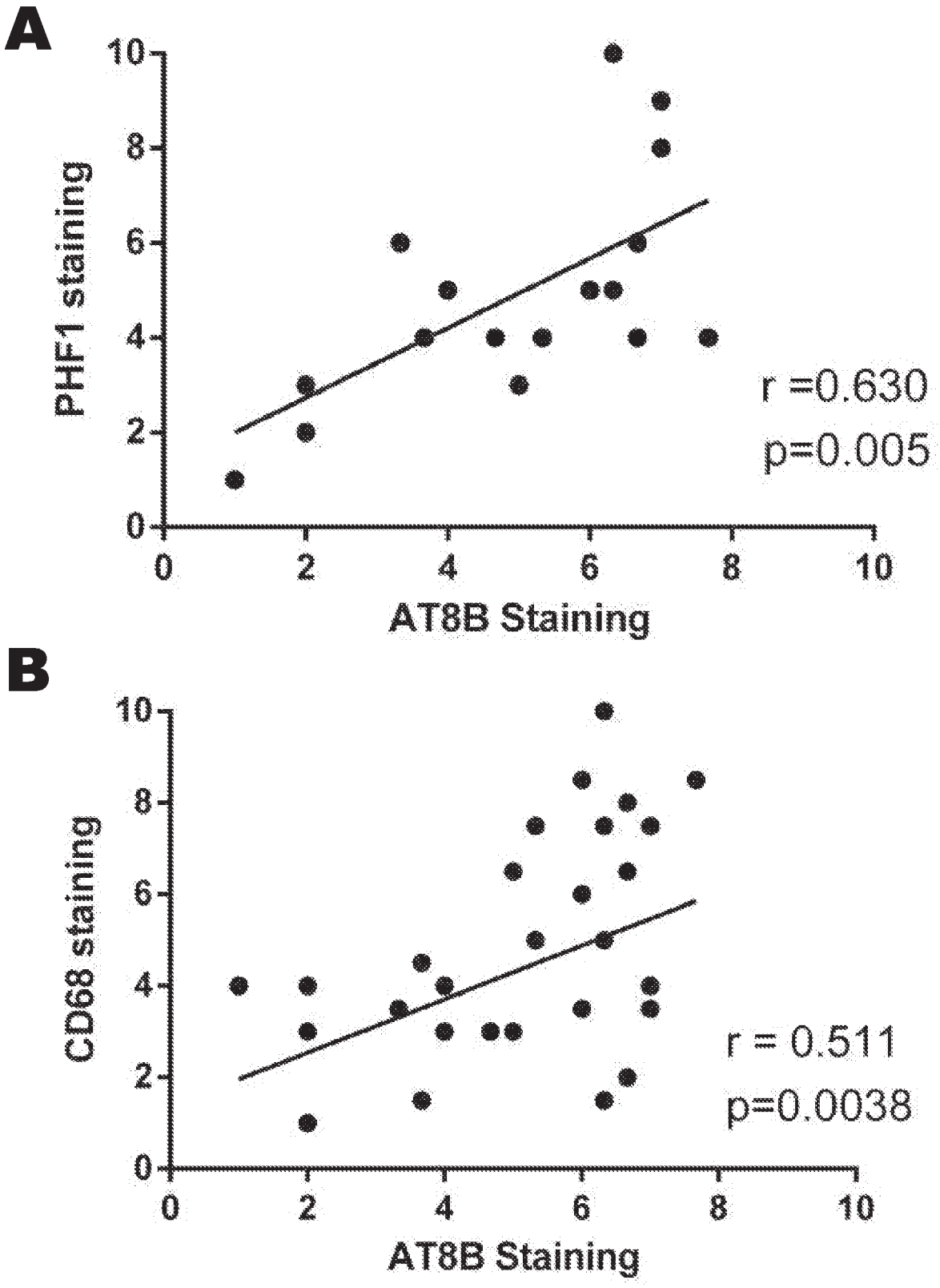

A
PHF1 staining
AT8B Staining
r =0.630
p=0.005
B
CD68 staining
AT8B Staining
r = 0.511
p=0.0038

FIG. 40

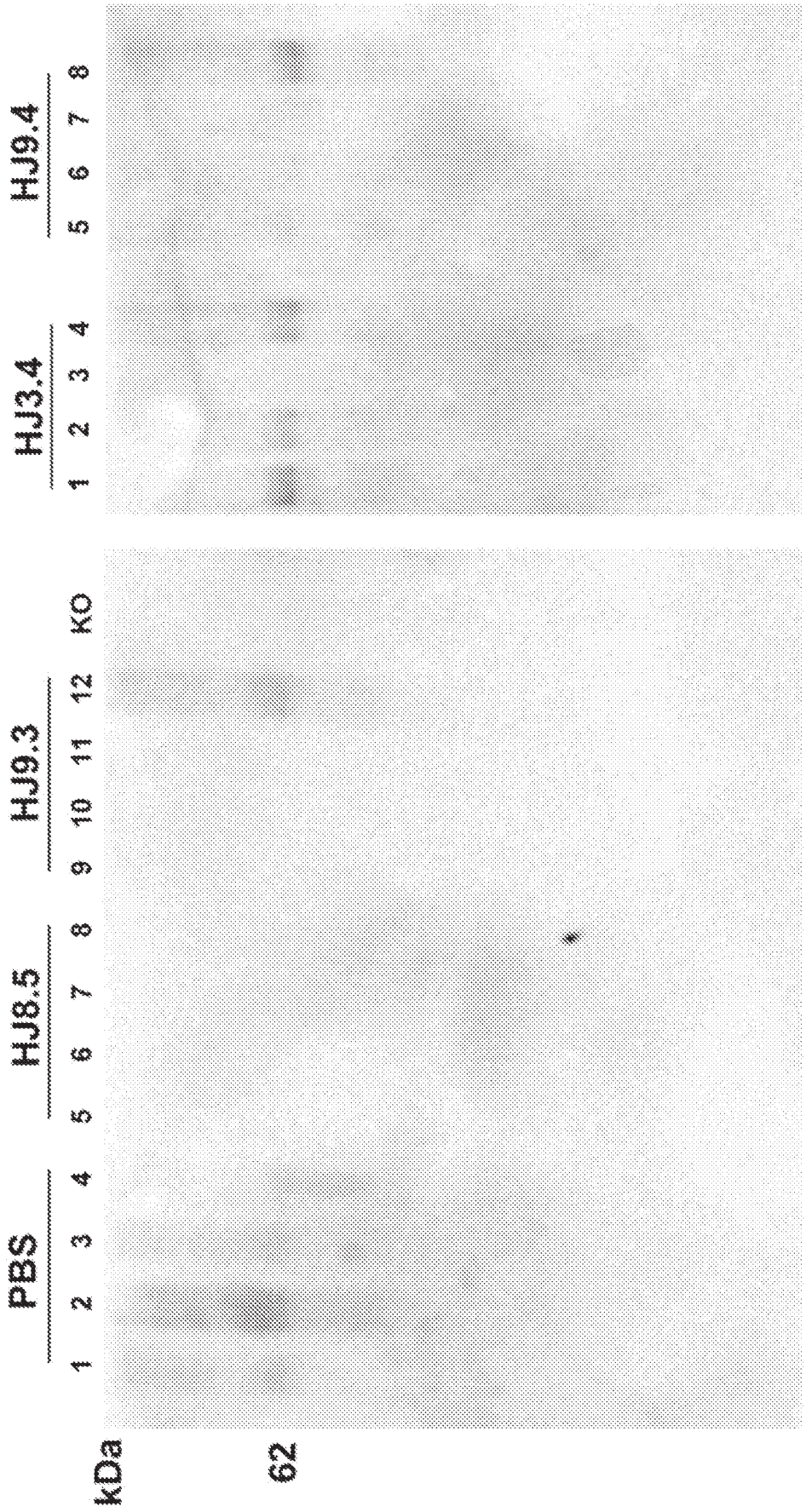


FIG. 40C

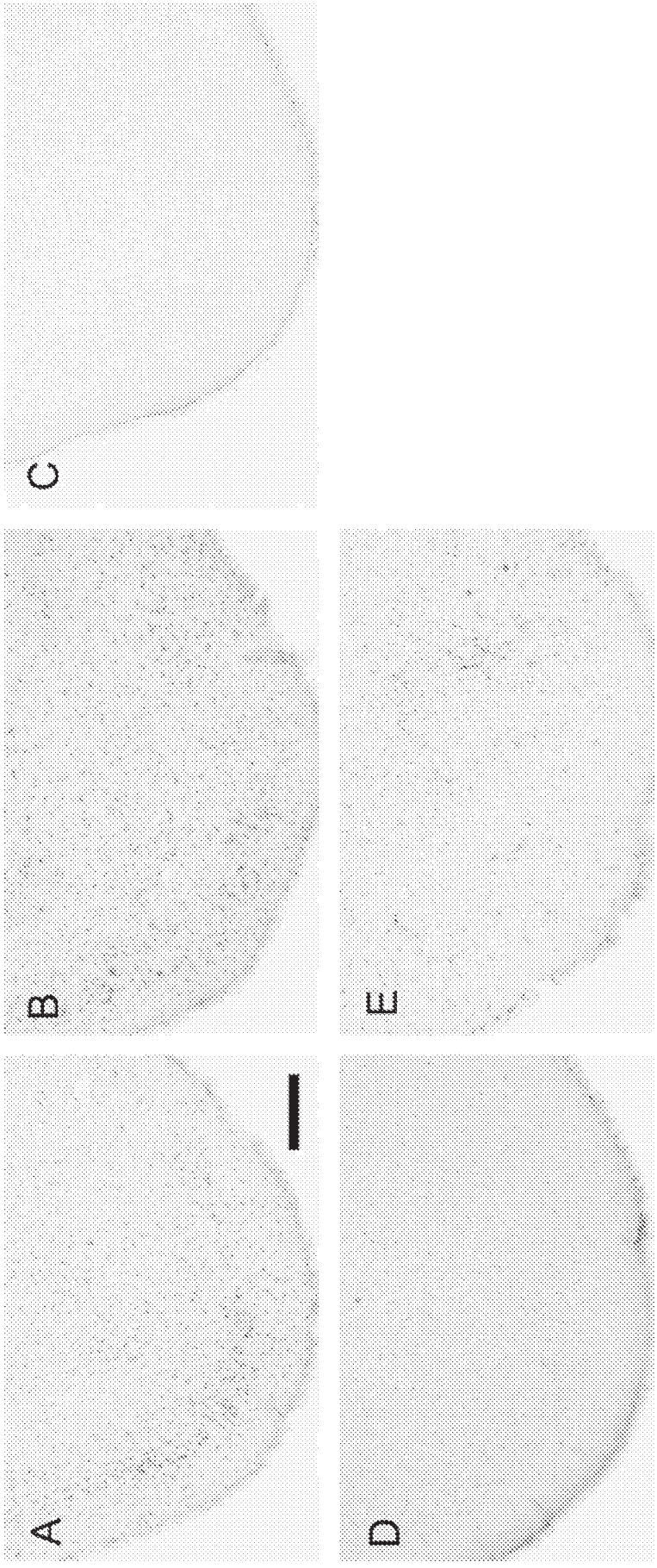


FIG. 41

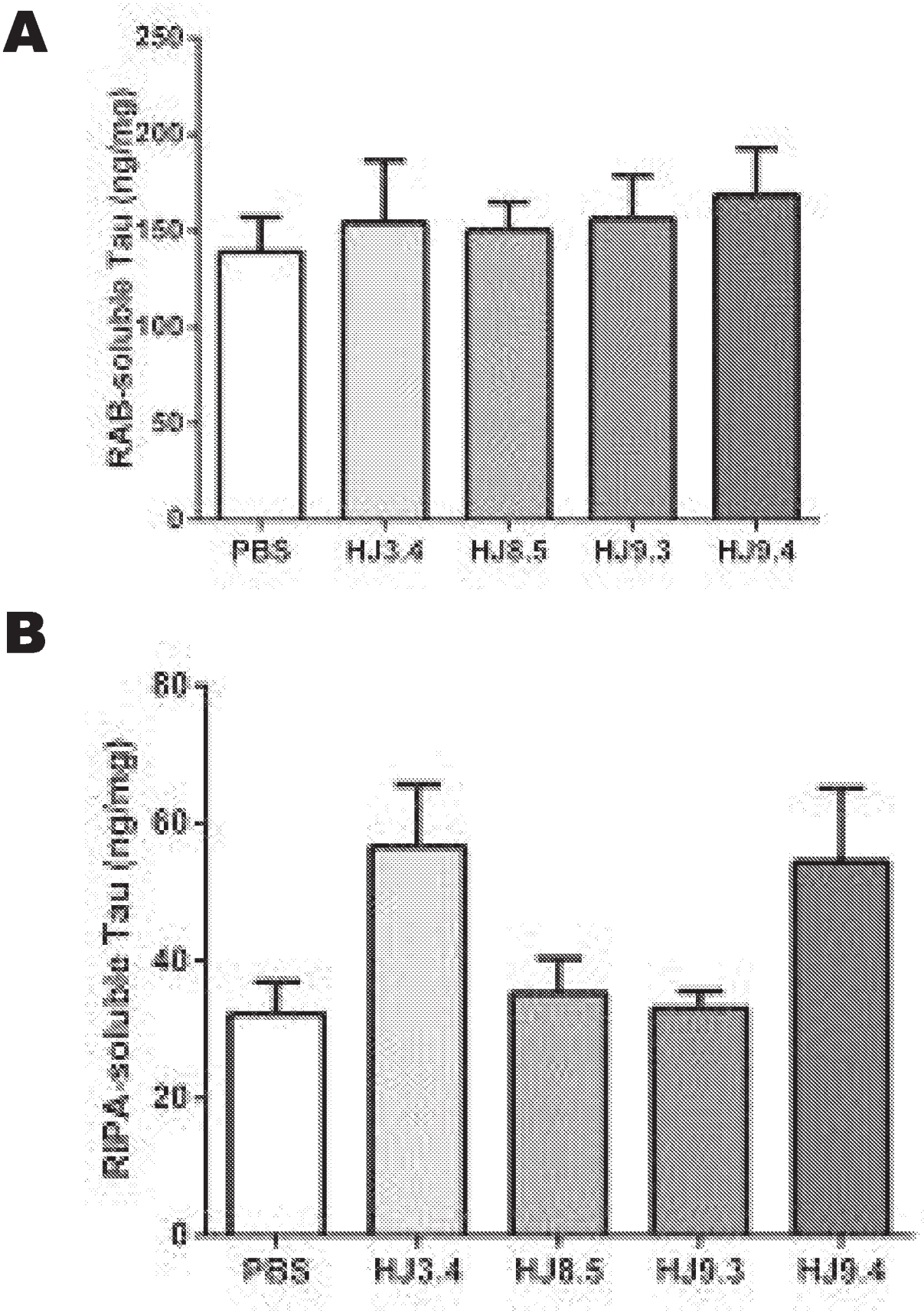

A
RAB-soluble Tau (ng/mg)
0
5
10
15
20
25
PBS
HJ3.4
HJ8.5
HJ9.3
HJ9.4
B
RIPA-soluble Tau (ng/mg)
0
20
40
60
80
PBS
HJ3.4
HJ8.5
HJ9.3
HJ9.4

FIG. 42

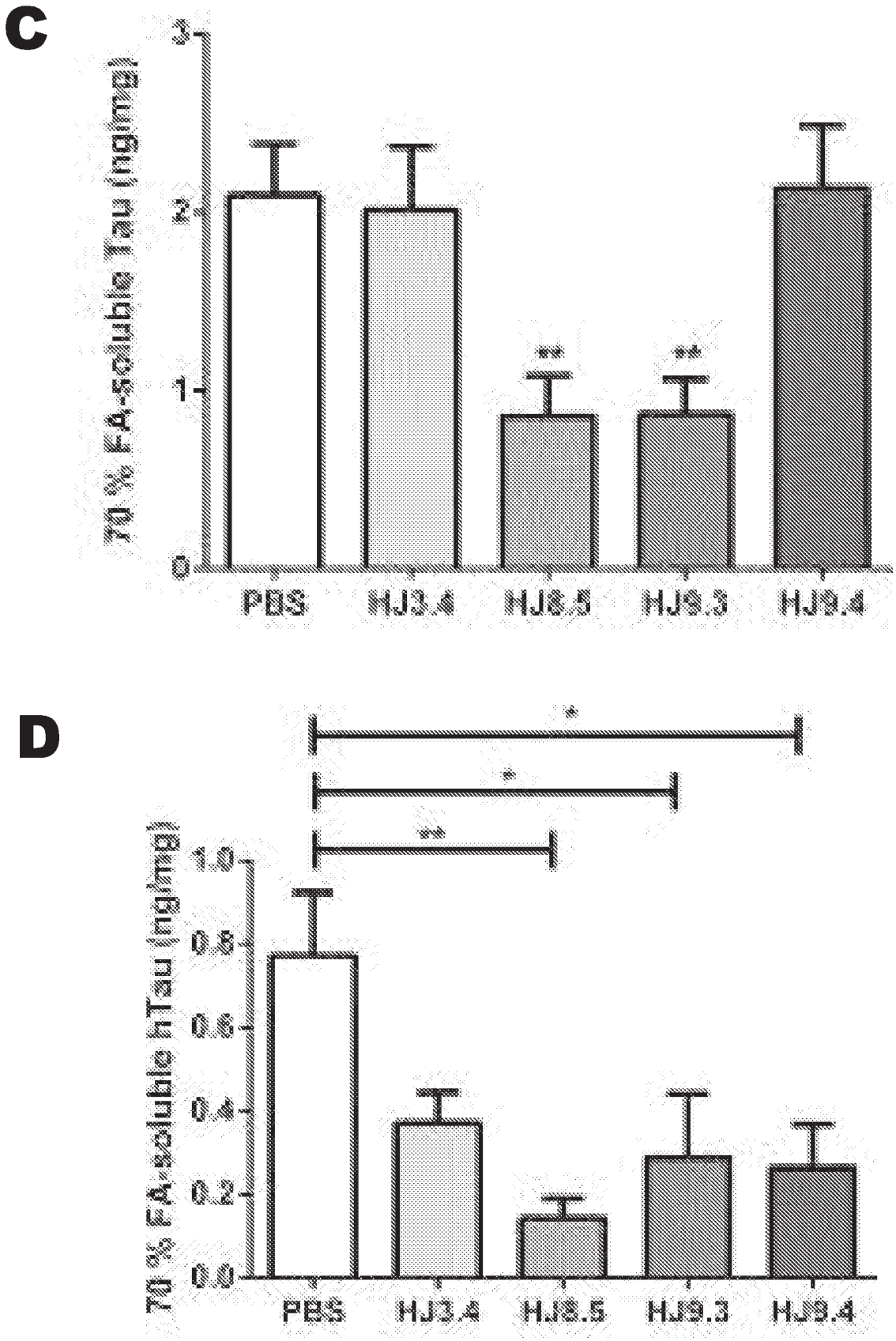

C
70 % FA-soluble Tau (ng/mg)
0
1
2
3
**
**
PBS
HJ3.4
HJ8.5
HJ9.3
HJ9.4
D
70 % FA-soluble hTau (ng/mg)
0.0
0.2
0.4
0.6
0.8
1.0
*
*
**
PBS
HJ3.4
HJ8.5
HJ9.3
HJ9.4

FIG. 42

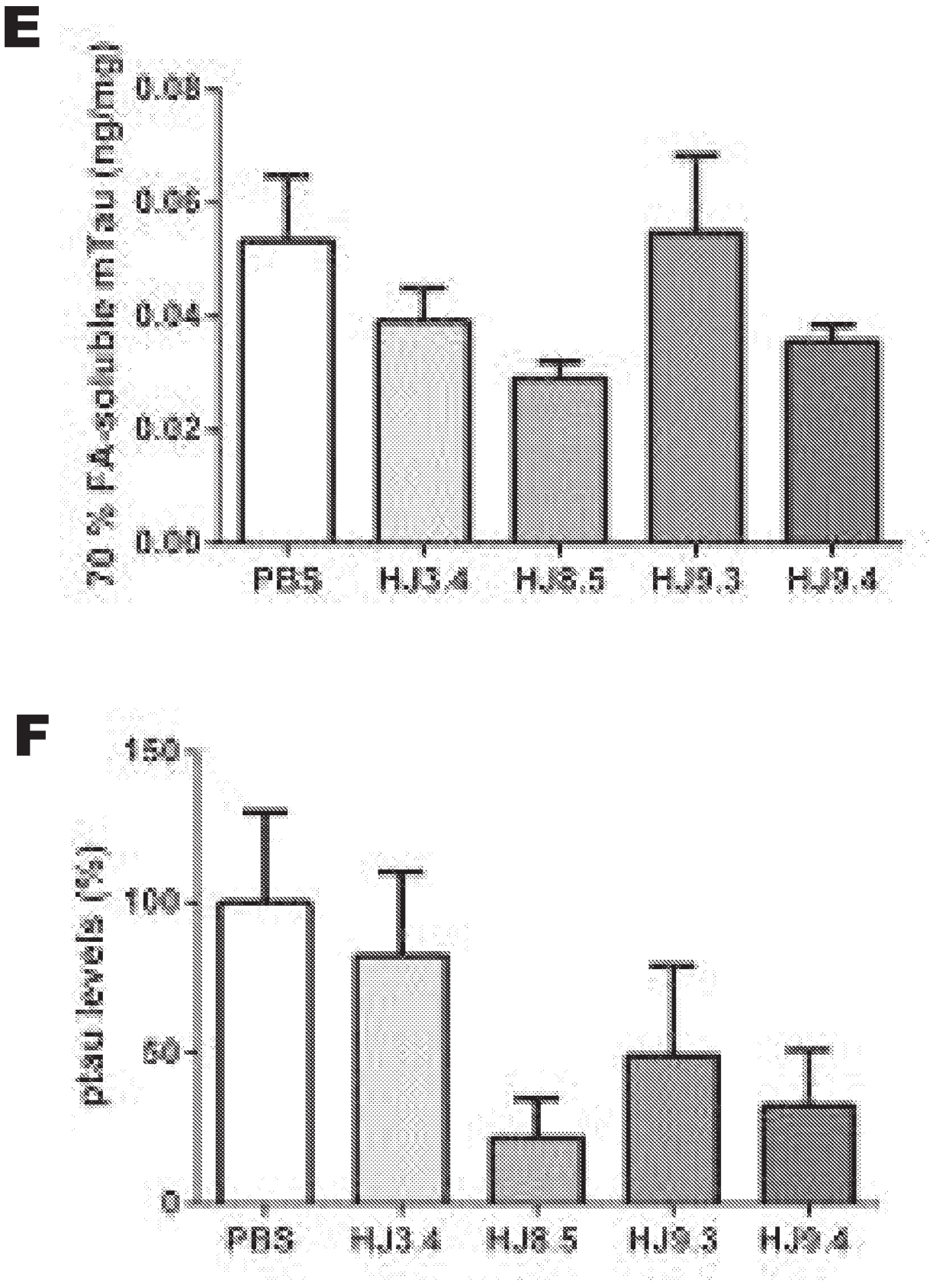
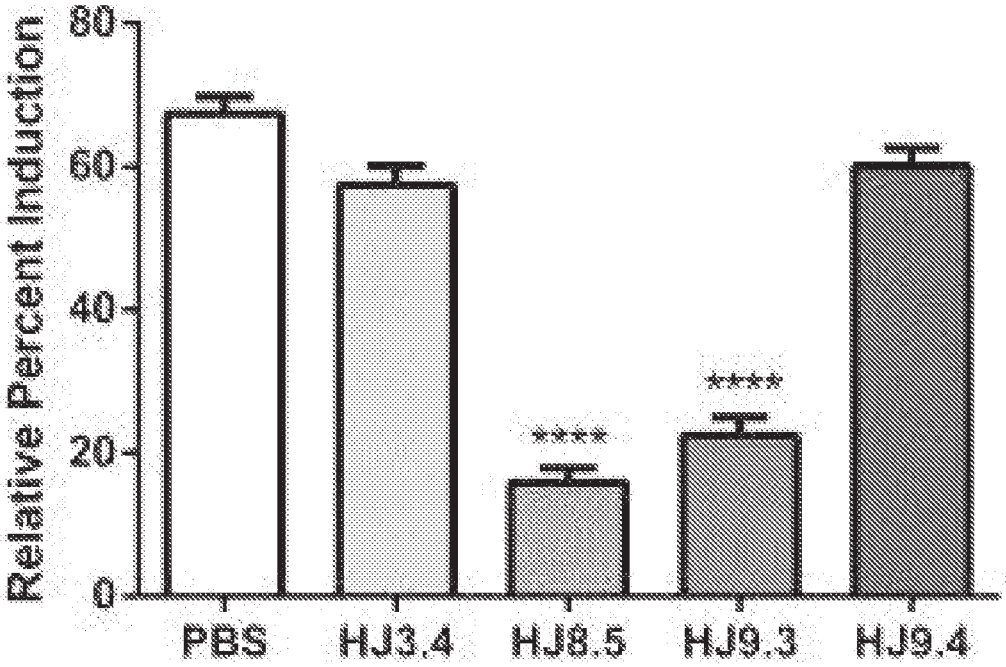

E
70 % FA-soluble mTau (ng/mg)
0.08
0.06
0.04
0.02
0.00
PBS
HJ3.4
HJ8.5
HJ9.3
HJ9.4
F
plau levels (%)
150
100
50
0
PBS
HJ3.4
HJ8.5
HJ9.3
HJ9.4

FIG. 42

A


Relative Percent Induction
80
60
40
20
0
****
****
PBS
HJ3.4
HJ8.5
HJ9.3
HJ9.4

B

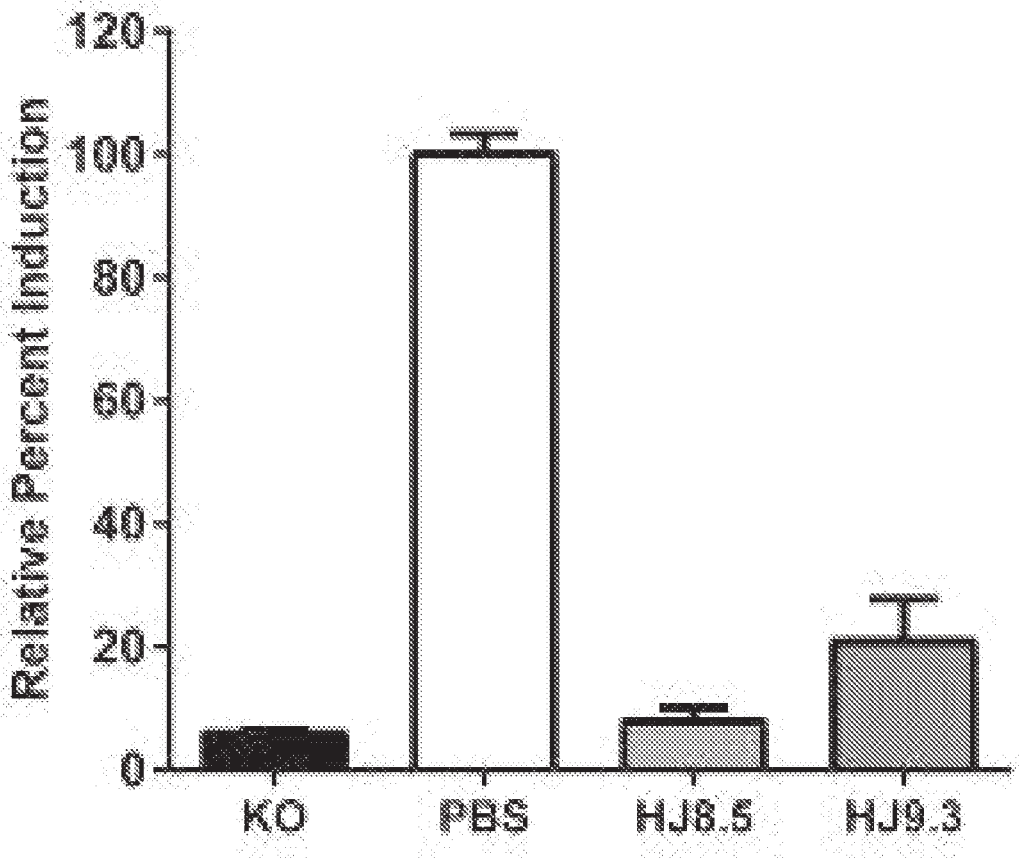
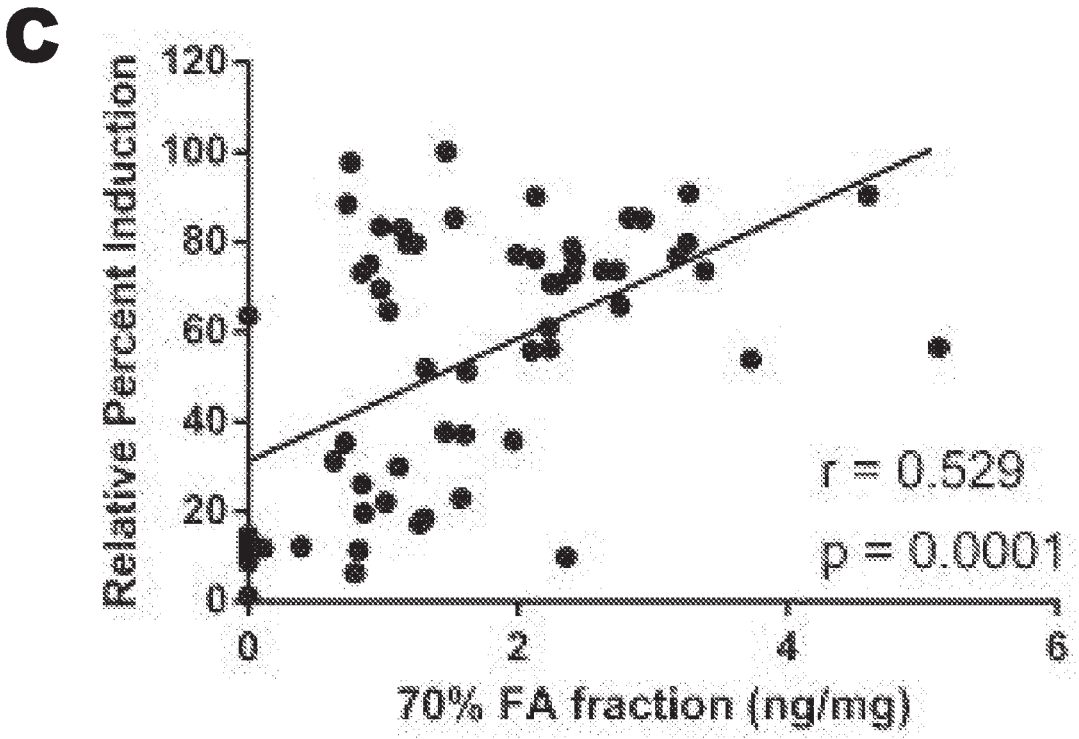

Relative Percent Induction
120
100
80
60
40
20
0
KO
PBS
HJ8.5
HJ9.3

FIG. 43


C
Relative Percent Induction
120
100
80
60
40
20
0
0
2
4
6
r = 0.529
p = 0.0001
70% FA fraction (ng/mg)

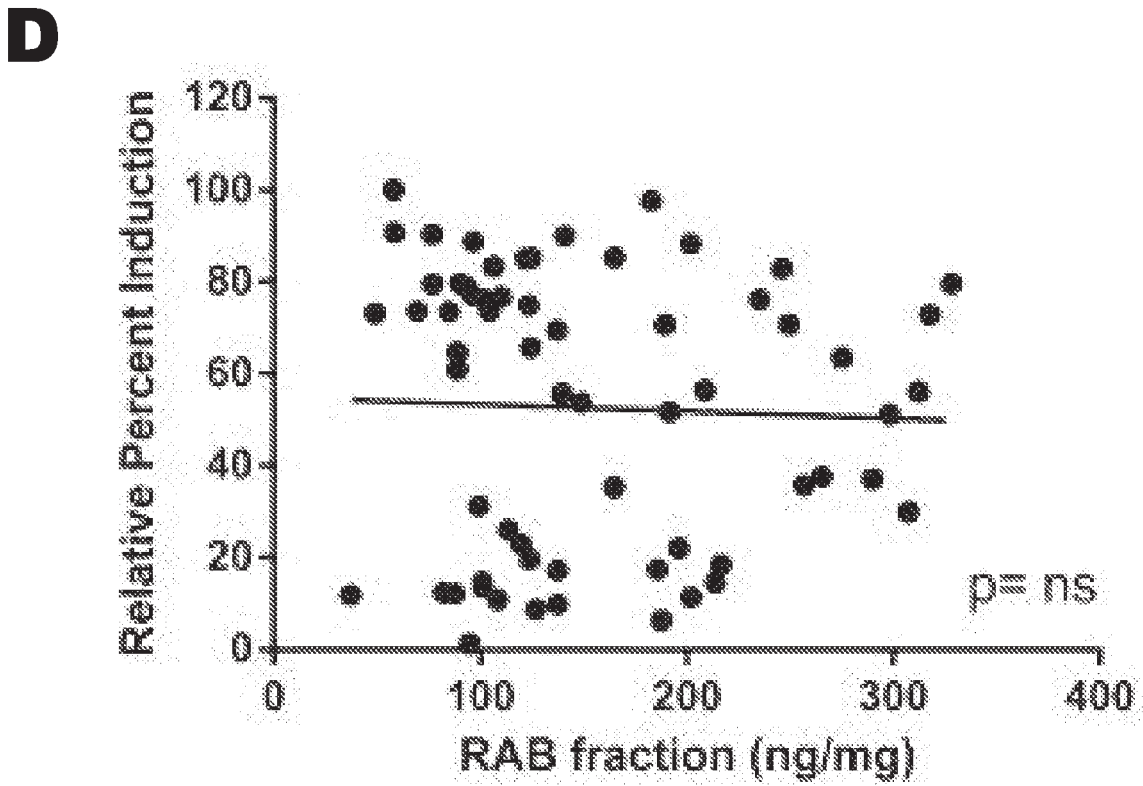

D
Relative Percent Induction
120
100
80
60
40
20
0
0
100
200
300
400
p= ns
RAB fraction (ng/mg)

FIG. 43

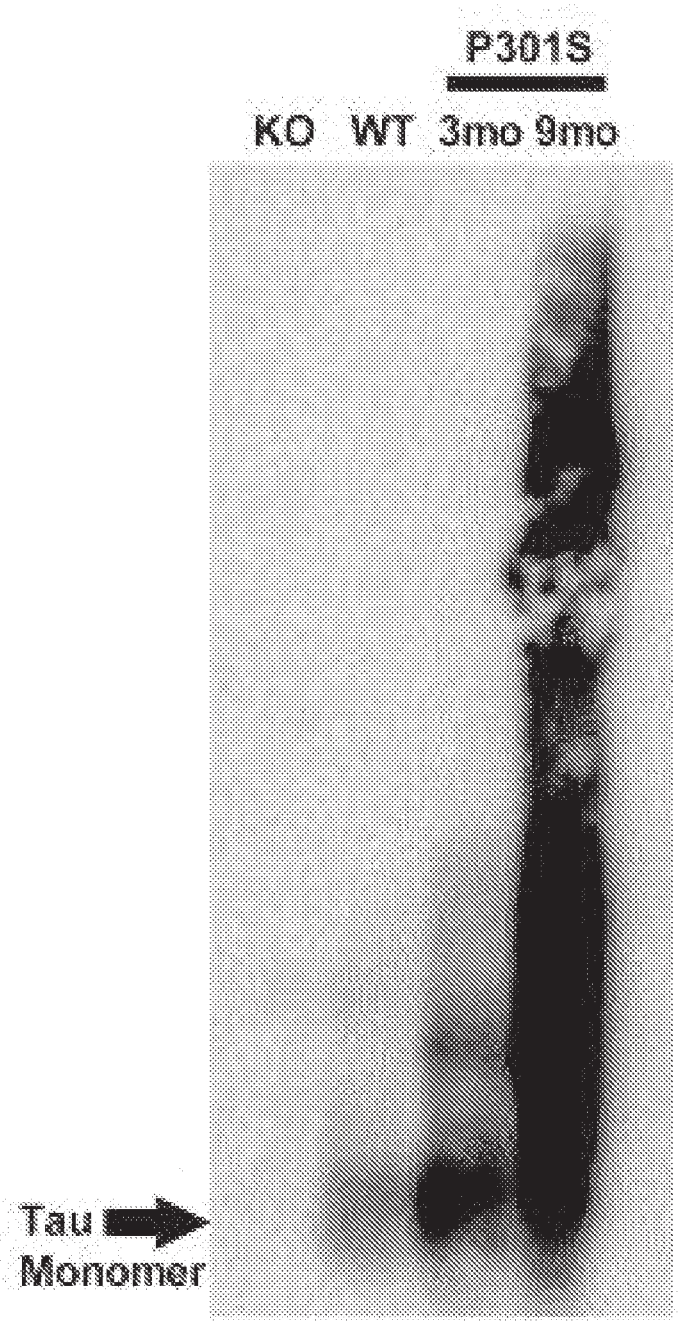


FIG. 43E

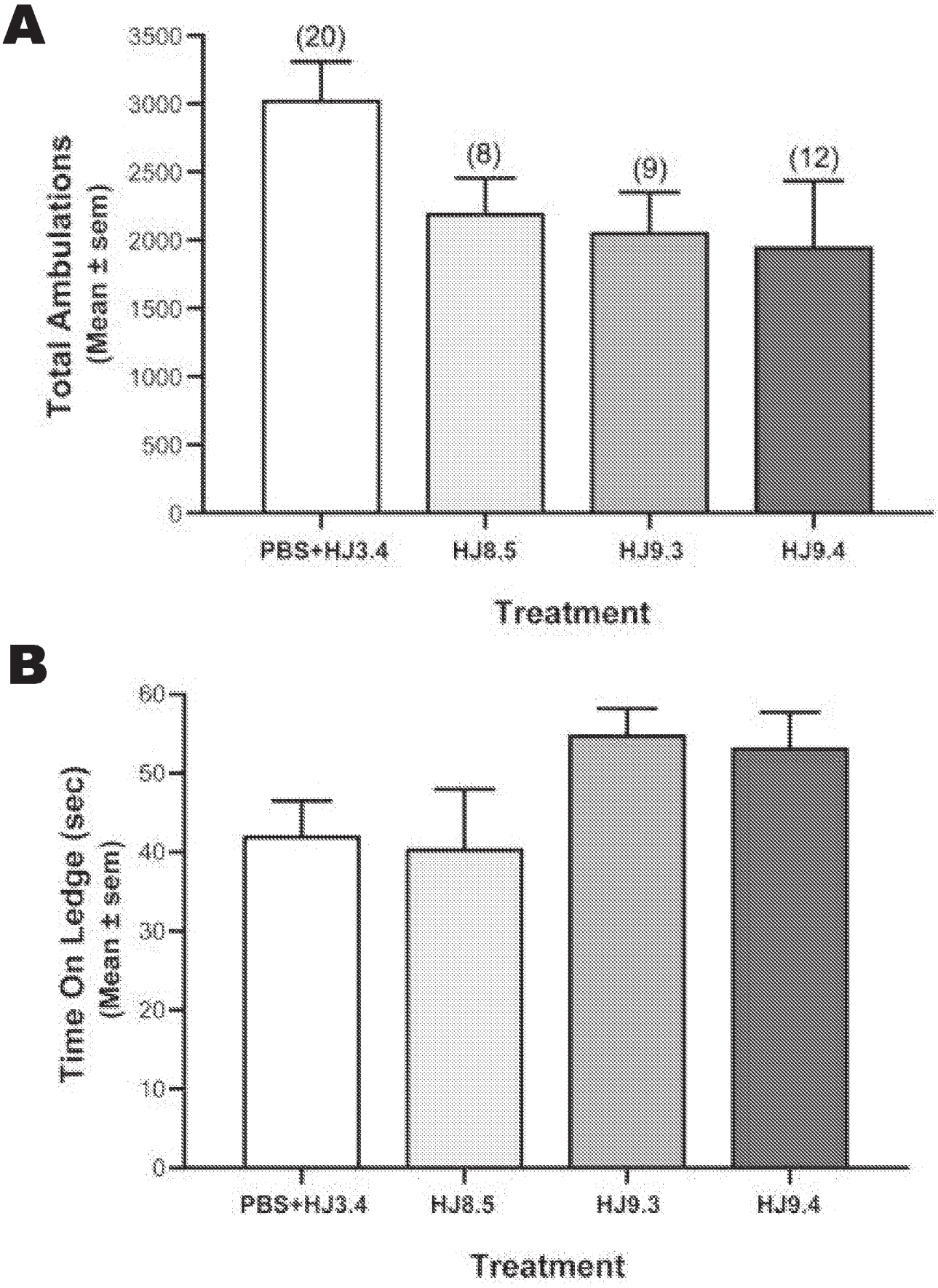

A
Total Ambulations
(Mean ± sem)
3500
3000
2500
2000
1500
1000
500
0
(20)
(8)
(9)
(12)
PBS+HJ3.4
HJ8.5
HJ9.3
HJ9.4
Treatment
B
Time On Ledge (sec)
(Mean ± sem)
60
50
40
30
20
10
0
PBS+HJ3.4
HJ8.5
HJ9.3
HJ9.4
Treatment

FIG. 44

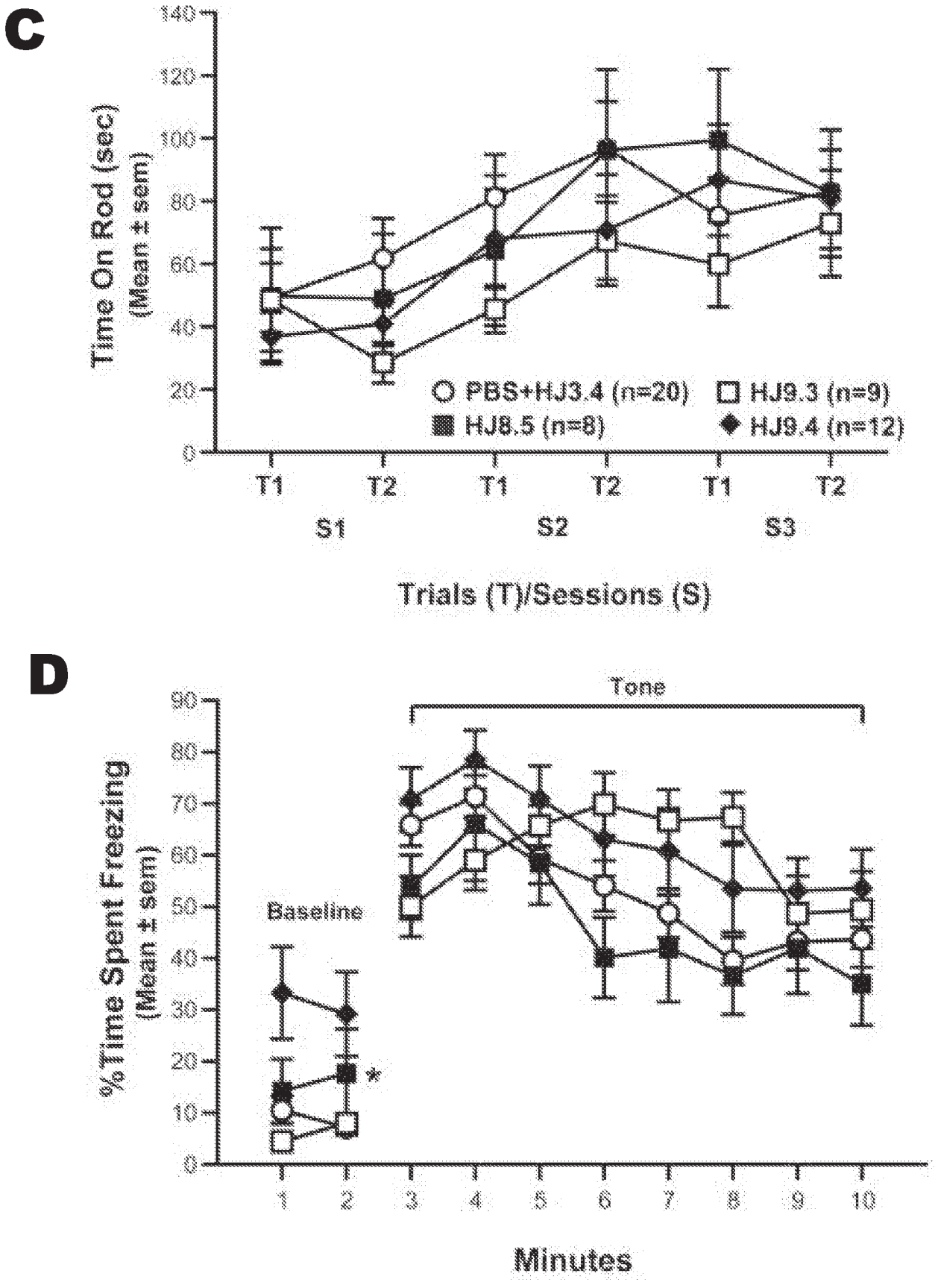
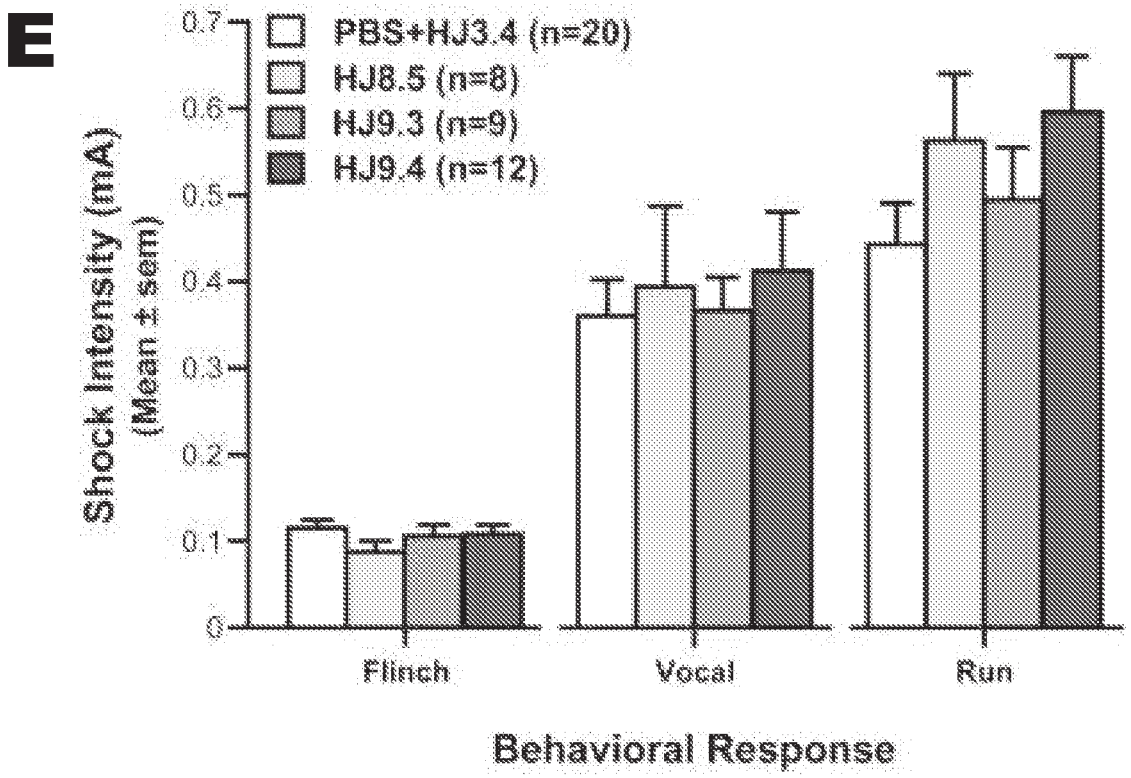

C
Time On Rod (sec)
(Mean ± sem)
140
120
100
80
60
40
20
0
PBS+HJ3.4 (n=20)
HJ3.3 (n=9)
HJ8.5 (n=8)
HJ9.4 (n=12)
T1
T2
T1
T2
T1
T2
S1
S2
S3
Trials (T)/Sessions (S)
D
%Time Spent Freezing
(Mean ± sem)
90
80
70
60
50
40
30
20
10
0
Tone
Baseline
*
1
2
3
4
5
6
7
8
9
10
Minutes

FIG. 44


E
PBS+HJ3.4 (n=20)
HJ8.5 (n=8)
HJ9.3 (n=9)
HJ9.4 (n=12)
Shock Intensity (mA)
(Mean ± sem)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Flinch
Vocal
Run
Behavioral Response

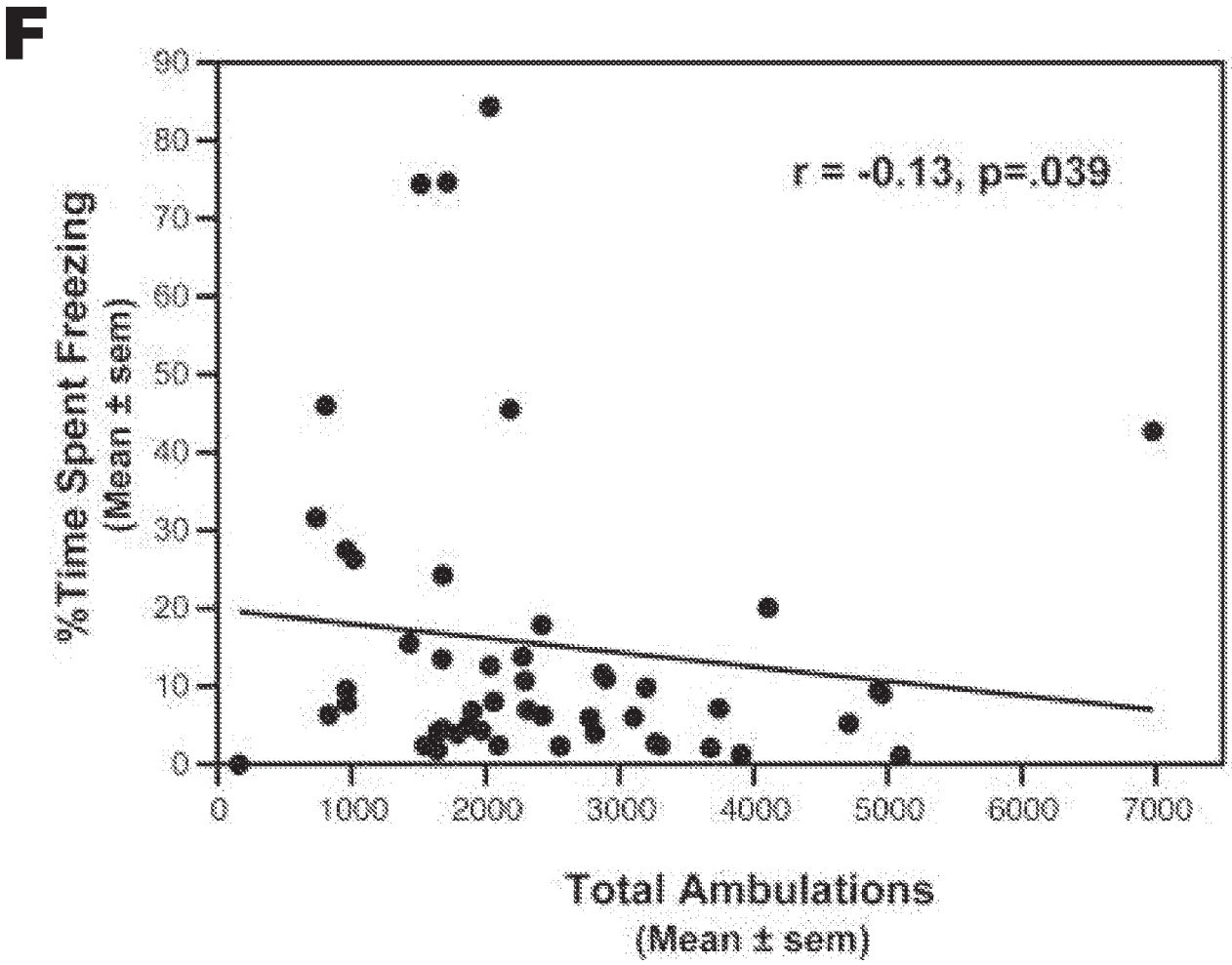

F
r = -0.13, p=.039
% Time Spent Freezing
(Mean ± sem)
90
80
70
60
50
40
30
20
10
0
0
1000
2000
3000
4000
5000
6000
7000
Total Ambulations
(Mean ± sem)

FIG. 44

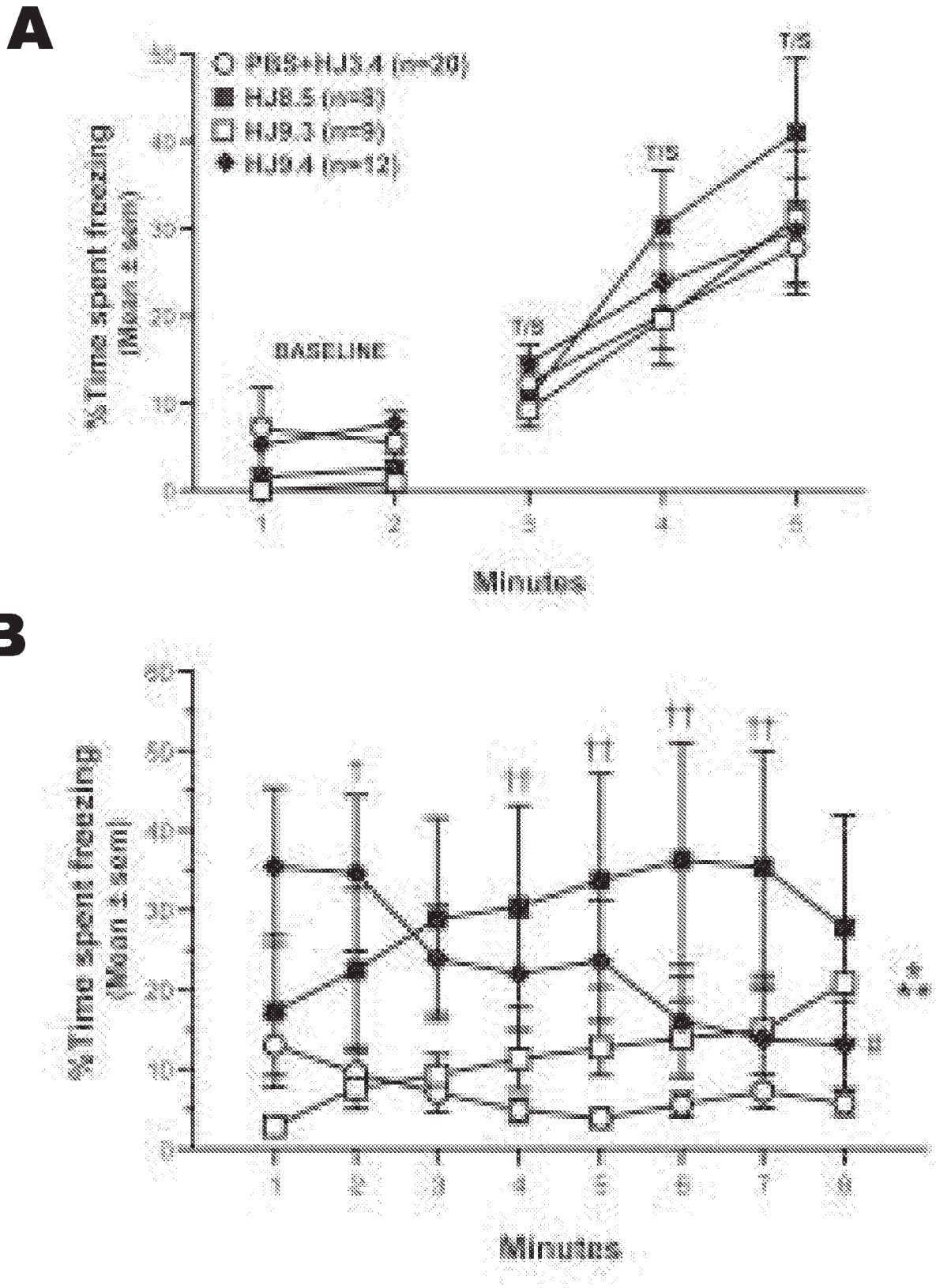

A
PBS+HJ3.4 (n=20)
HJ8.5 (n=8)
HJ9.3 (n=9)
HJ9.4 (n=12)
% Time spent freezing
(Mean ± sem)
BASELINE
Minutes
B
% Time spent freezing
(Mean ± sem)
Minutes

FIG. 45

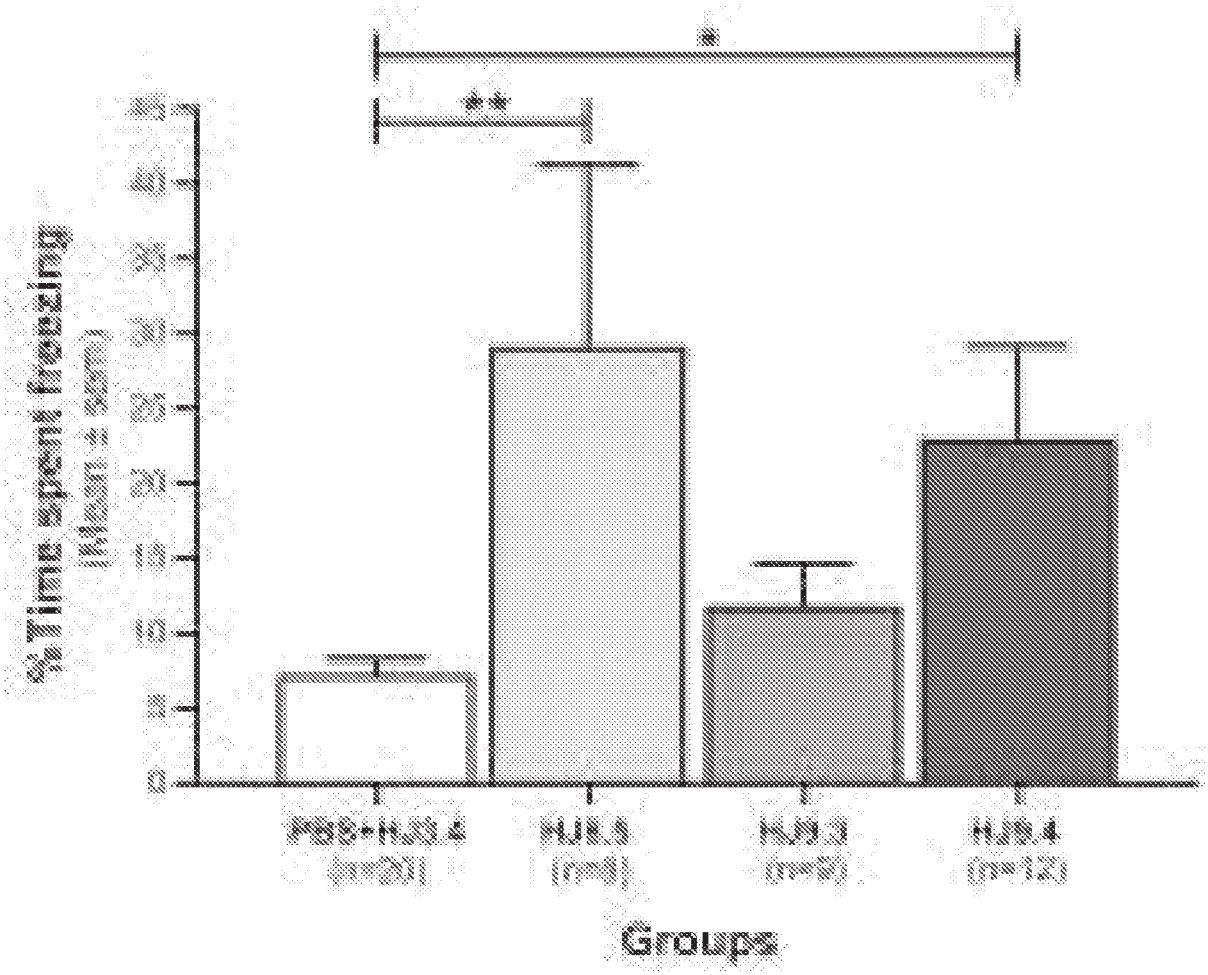

*
**
% Time spent freezing
(Mean ± sem)
0
10
20
30
40
PBS+HJ3.4
(n=20)
HJ3.3
(n=8)
HJ3.4
(n=12)
Groups

FIG. 45C

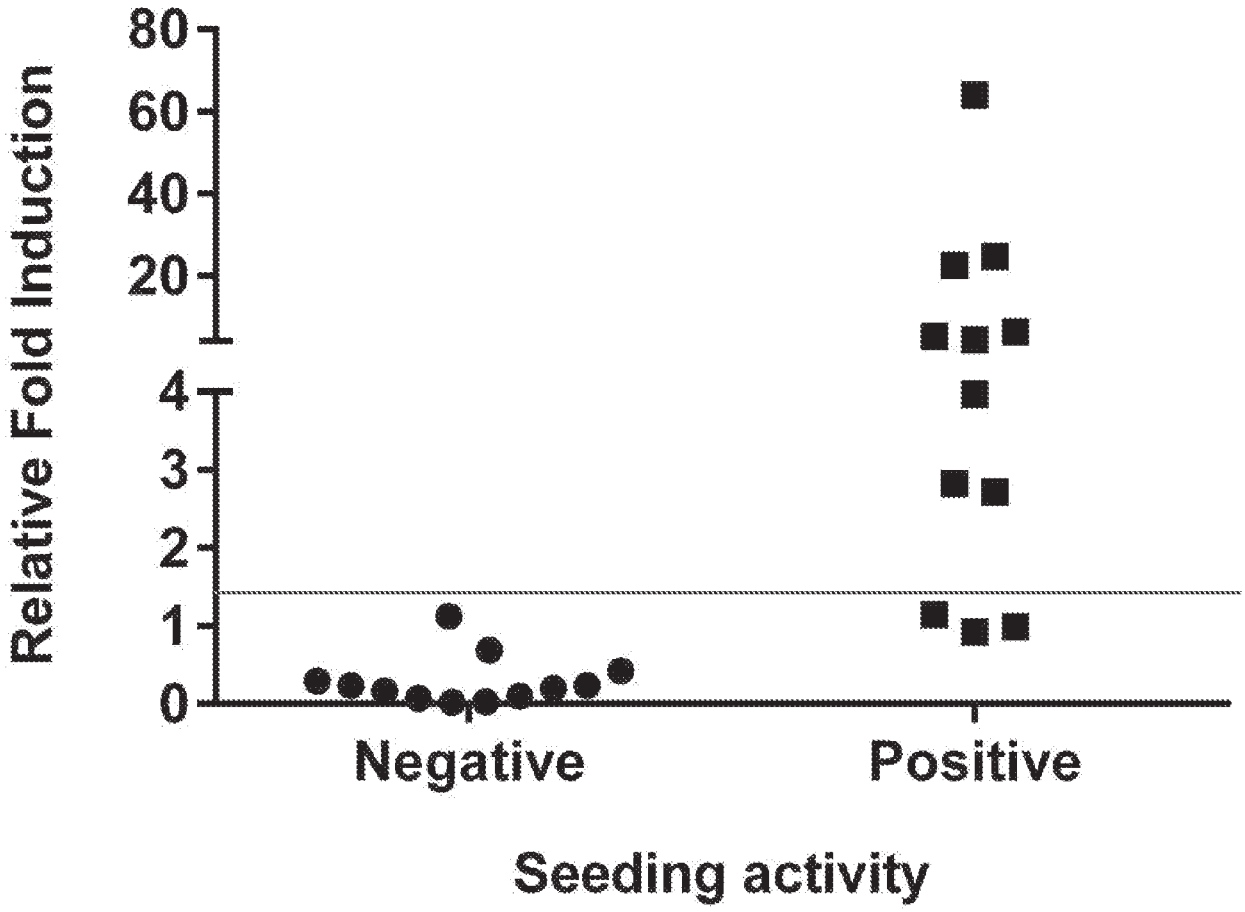

Relative Fold Induction
80
60
40
20
4
3
2
1
0
Negative
Positive
Seeding activity

FIG. 46

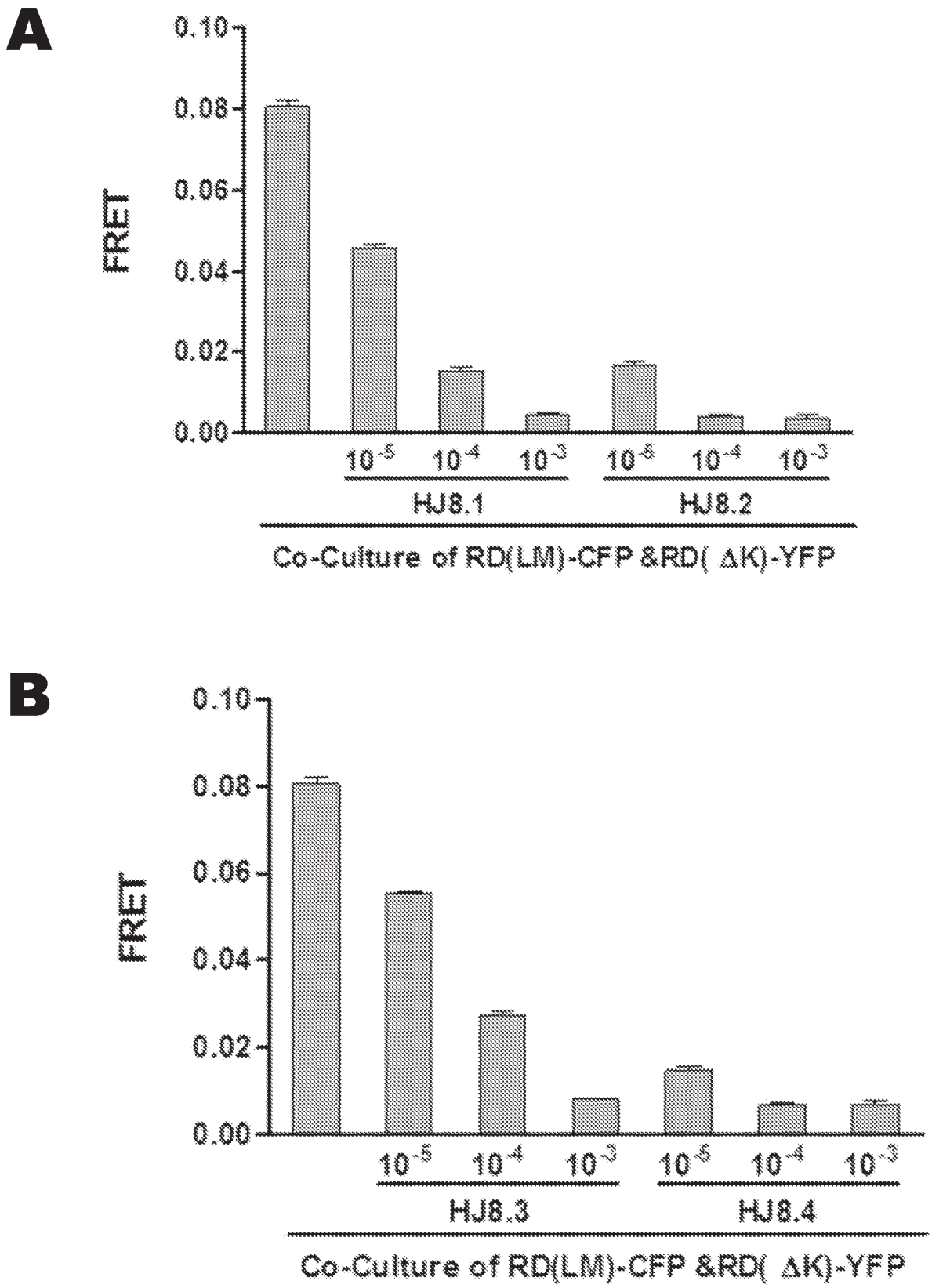
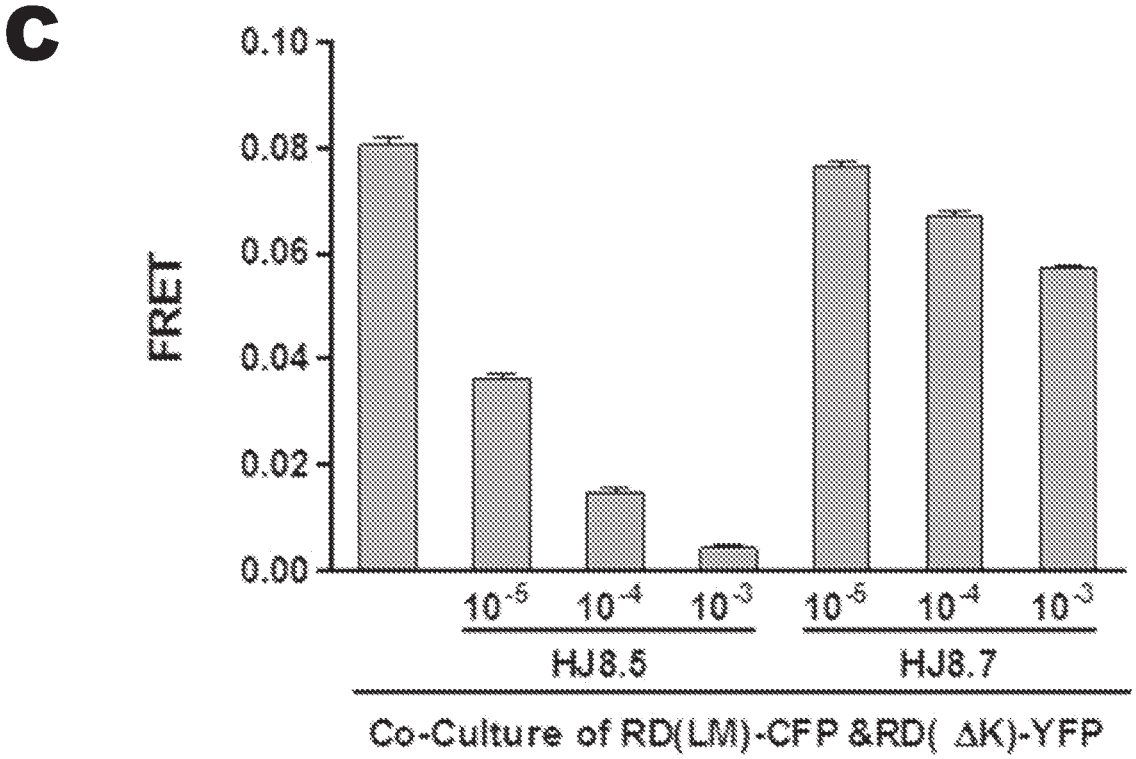

A
FRET
0.10
0.08
0.06
0.04
0.02
0.00
10-5 10-4 10-3 10-5 10-4 10-3
HJ8.1
HJ8.2
Co-Culture of RD(LM)-CFP &RD(ΔK)-YFP
B
FRET
0.10
0.08
0.06
0.04
0.02
0.00
10-5 10-4 10-3 10-5 10-4 10-3
HJ8.3
HJ8.4
Co-Culture of RD(LM)-CFP &RD(ΔK)-YFP

FIG. 47


C
FRET
0.10
0.08
0.06
0.04
0.02
0.00
10-5
10-4
10-3
10-5
10-4
10-3
HJ8.5
HJ8.7
Co-Culture of RD(LM)-CFP &RD(ΔK)-YFP

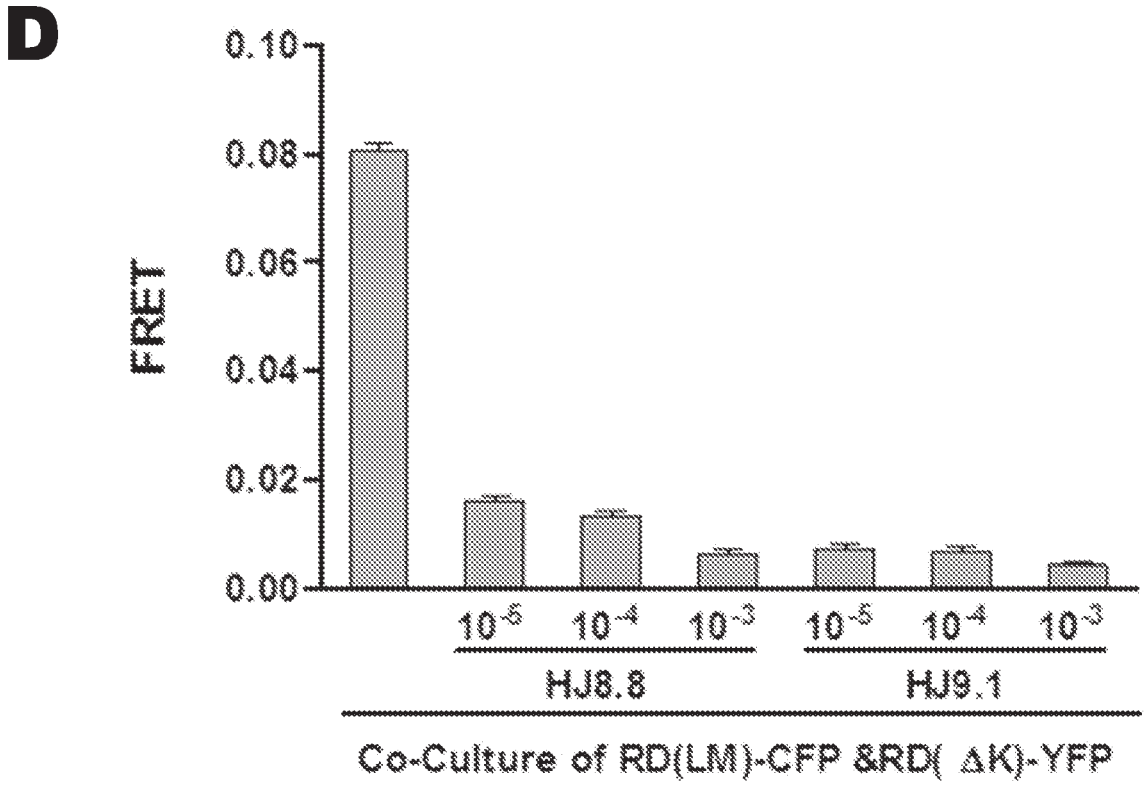

D
FRET
0.10
0.08
0.06
0.04
0.02
0.00
10-5
10-4
10-3
10-5
10-4
10-3
HJ8.8
HJ9.1
Co-Culture of RD(LM)-CFP &RD(ΔK)-YFP

FIG. 47

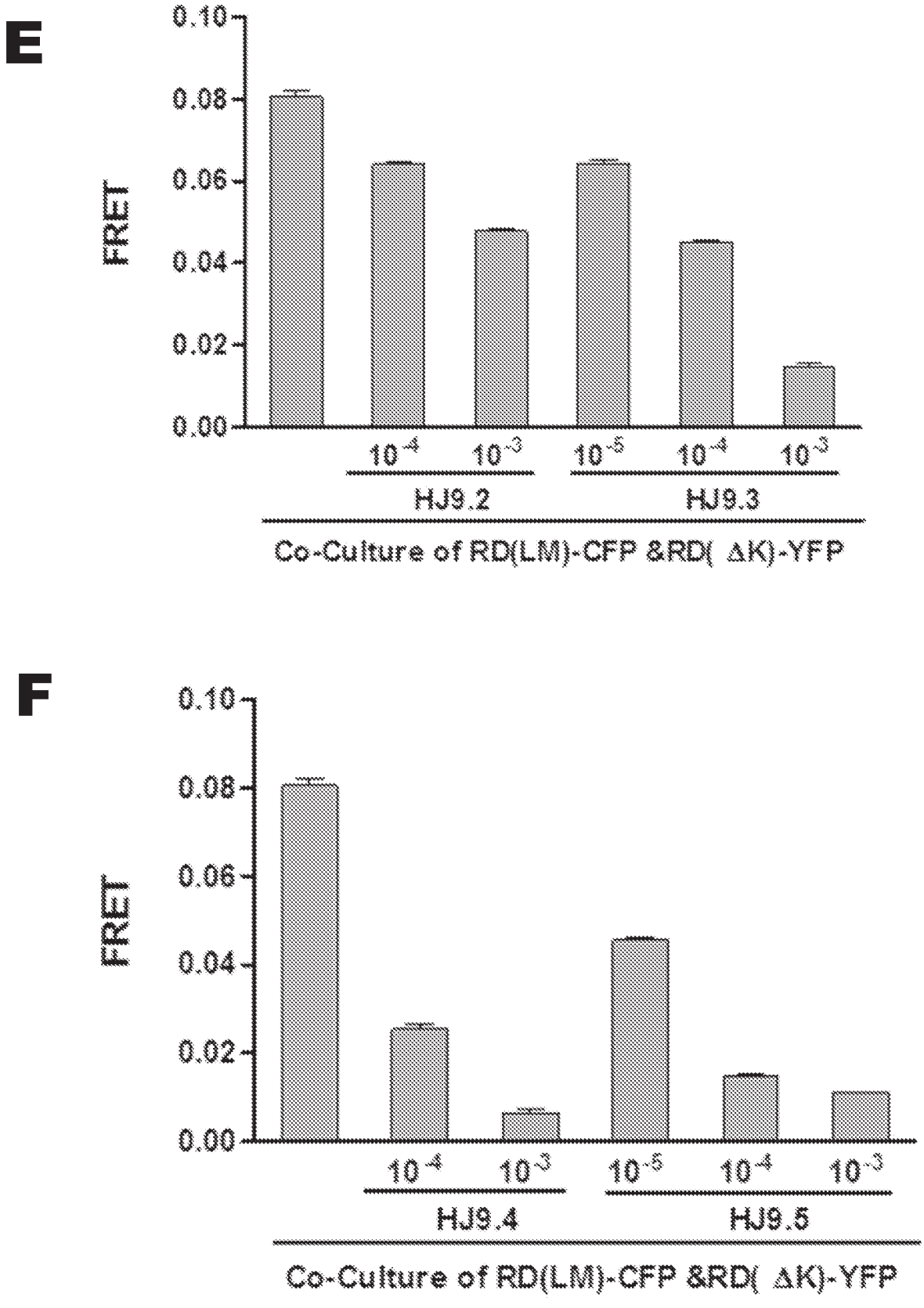

E
FRET
0.10
0.08
0.06
0.04
0.02
0.00
10-4
10-3
10-5
10-4
10-3
HJ9.2
HJ9.3
Co-Culture of RD(LM)-CFP &RD(ΔK)-YFP
F
FRET
0.10
0.08
0.06
0.04
0.02
0.00
10-4
10-3
10-5
10-4
10-3
HJ9.4
HJ9.5
Co-Culture of RD(LM)-CFP &RD(ΔK)-YFP

FIG. 47

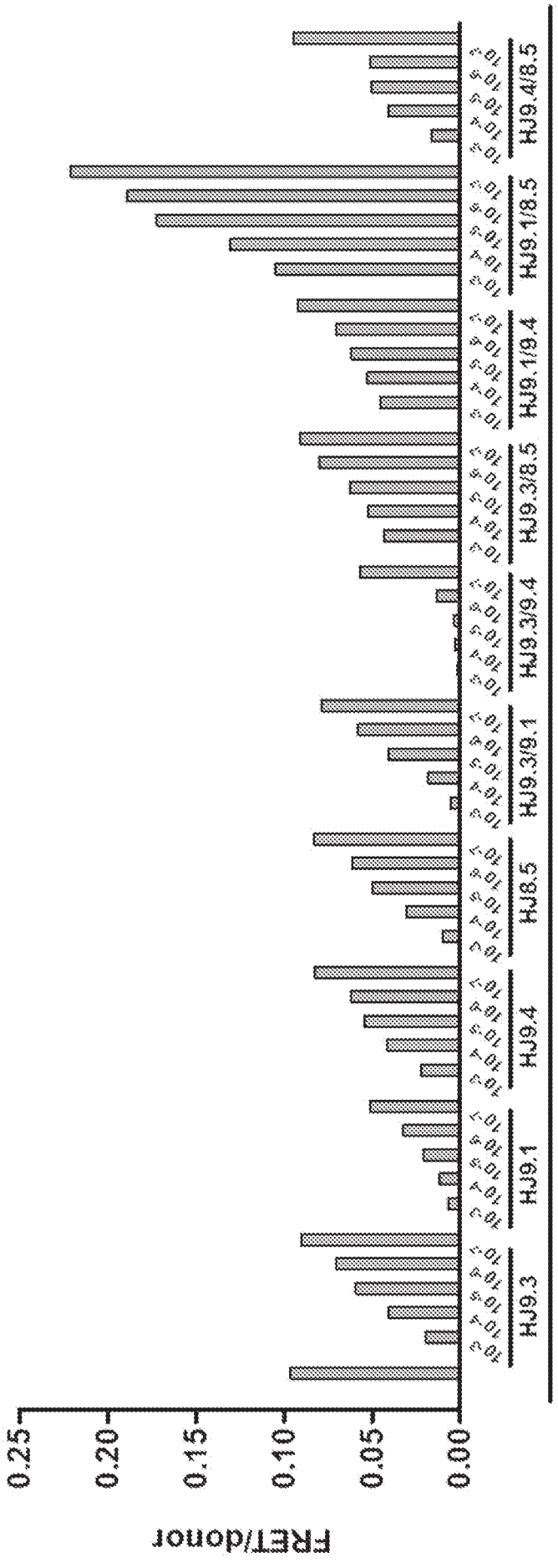

FRET/donor
0.25
0.20
0.15
0.10
0.05
0.00
HJ9.3
HJ9.1
HJ9.4
HJ8.5
HJ9.3/9.1
HJ9.3/9.4
HJ9.3/8.5
HJ9.1/9.4
HJ9.1/8.5
HJ9.4/8.5
Co-Culture of RD(LM)-HA & RD(ΔK)-CFP/YFP

FIG. 48

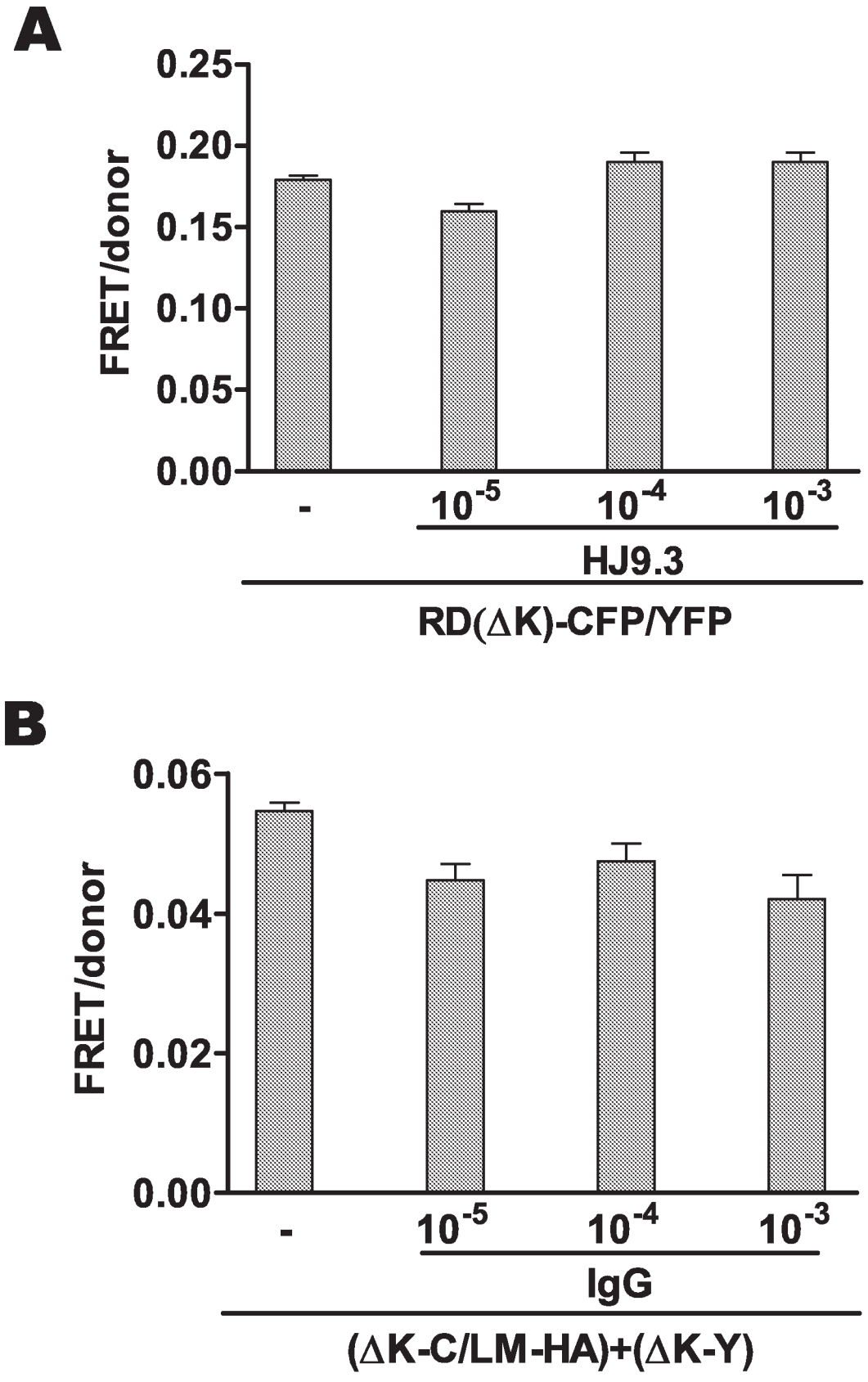

A
0.25
0.20
0.15
0.10
0.05
0.00
FRET/donor
-
10-5
10-4
10-3
HJ9.3
RD(ΔK)-CFP/YFP
B
0.06
0.04
0.02
0.00
FRET/donor
-
10-5
10-4
10-3
IgG
(ΔK-C/LM-HA)+(ΔK-Y)

FIG. 49

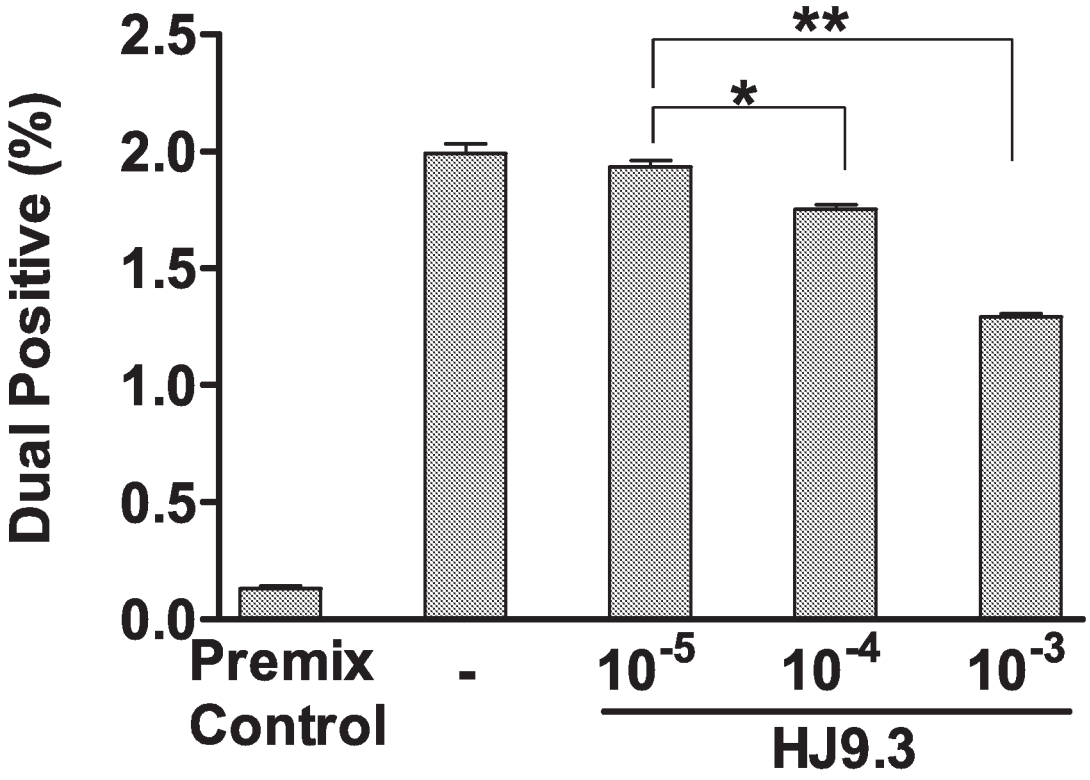

Dual Positive (%)
2.5
2.0
1.5
1.0
0.5
0.0
**
*
Premix Control
-
10-5
10-4
10-3
HJ9.3

FIG. 50