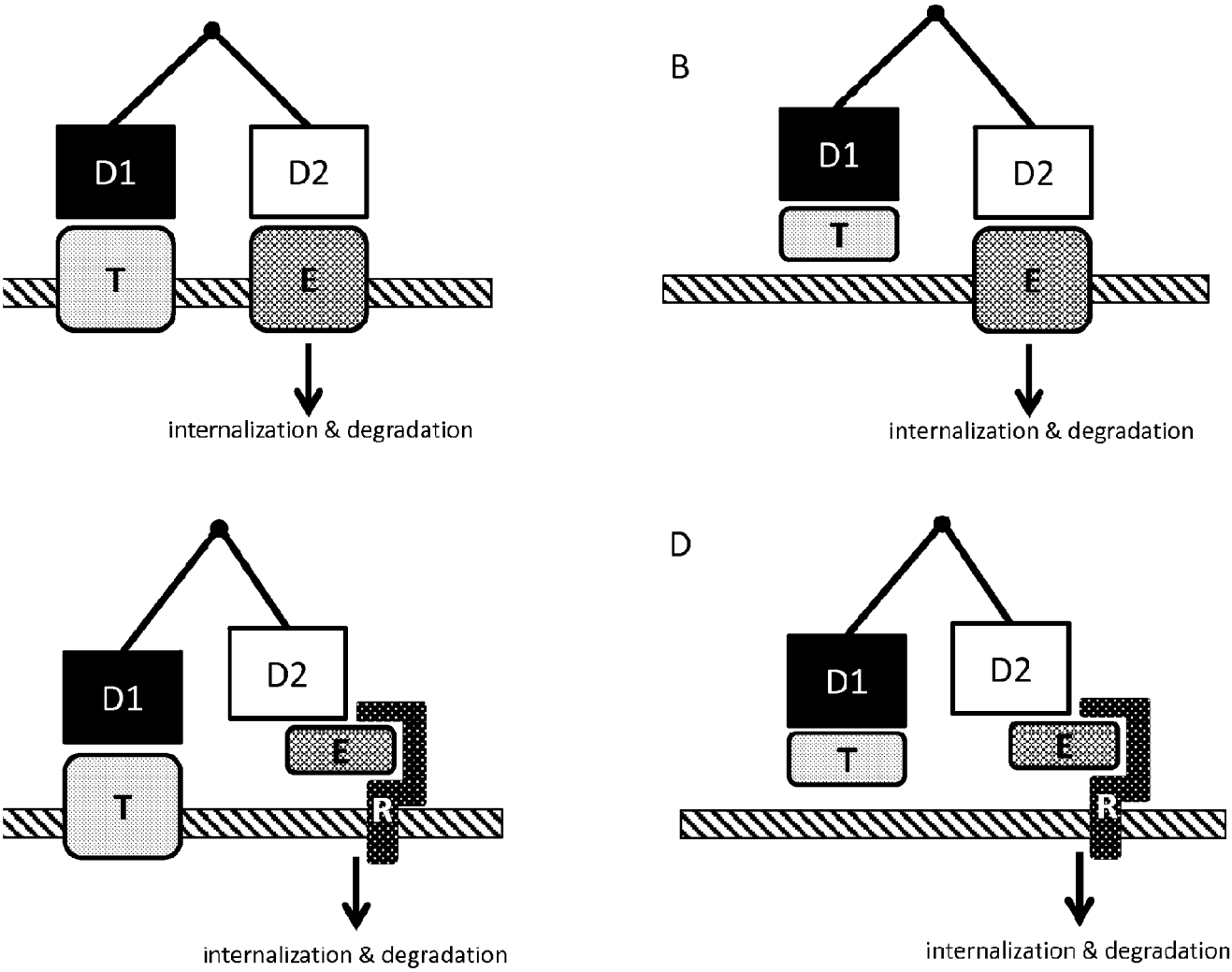

D1
D2
T
E
internalization & degradation
B
D1
D2
T
E
internalization & degradation
D1
D2
T
E
R
internalization & degradation
D
D1
D2
T
E
R
internalization & degradation

Figure 1

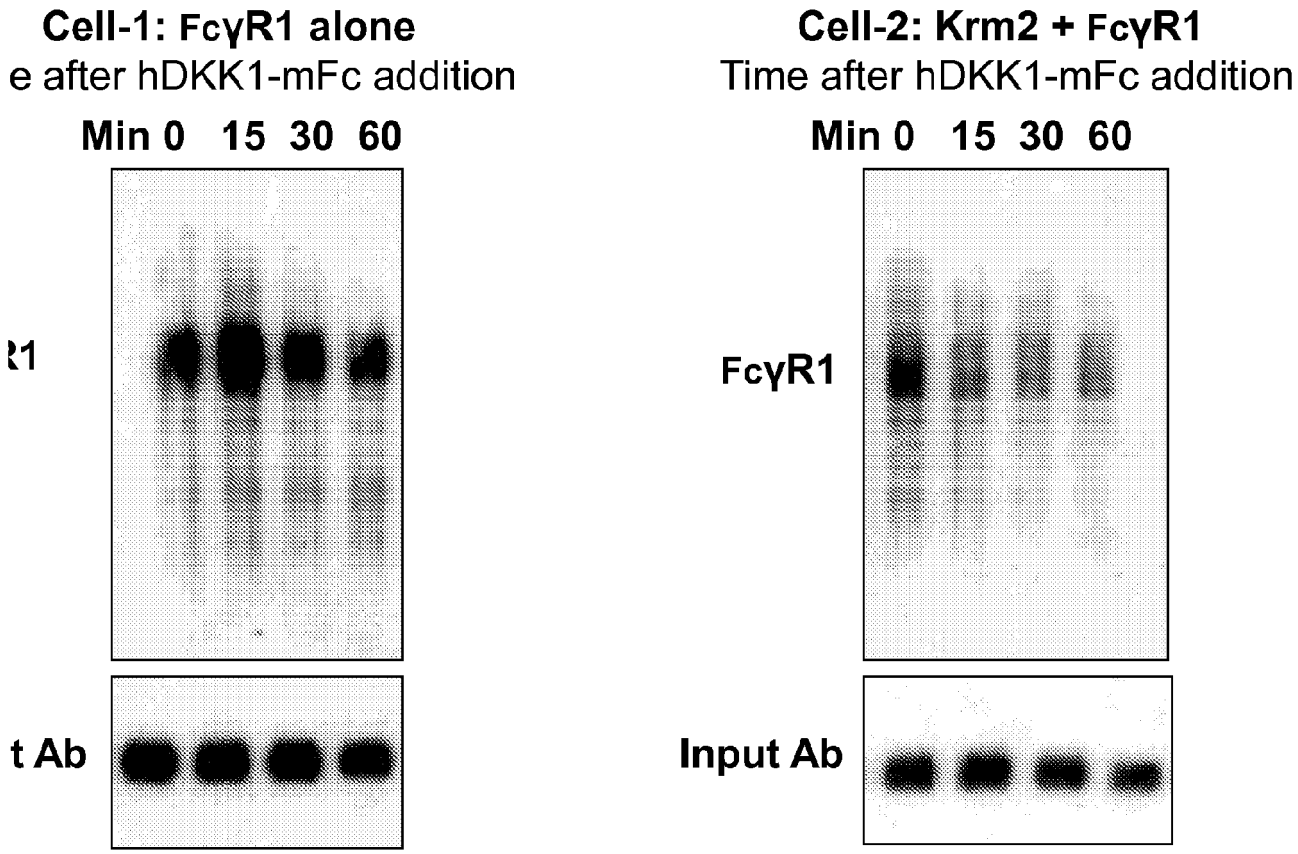

Cell-1: FcγR1 alone
e after hDKK1-mFc addition
Min 0 15 30 60
R1
t Ab
Cell-2: Krm2 + FcγR1
Time after hDKK1-mFc addition
Min 0 15 30 60
FcγR1
Input Ab

Figure 2

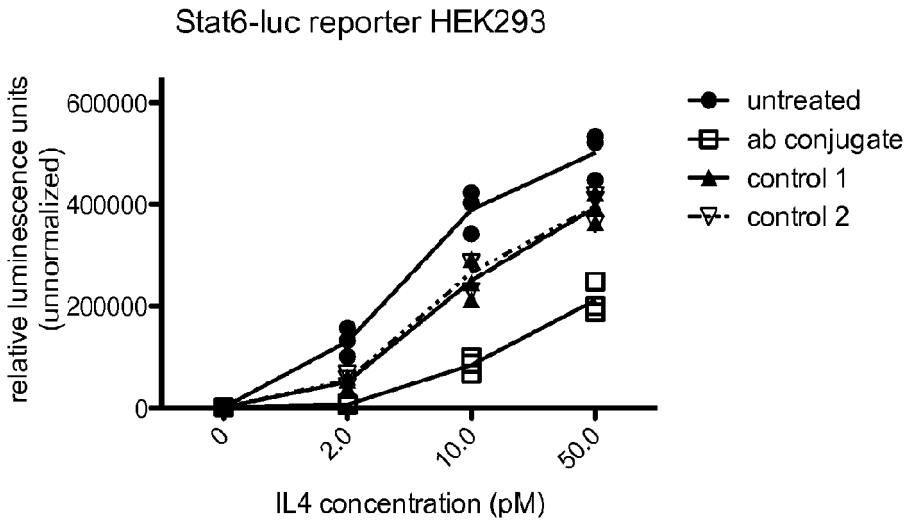

Stat6-luc reporter HEK293
relative luminescence units (unnormalized)
600000
400000
200000
0
0
2.0
10.0
50.0
IL4 concentration (pM)
untreated
ab conjugate
control 1
control 2

Figure 3

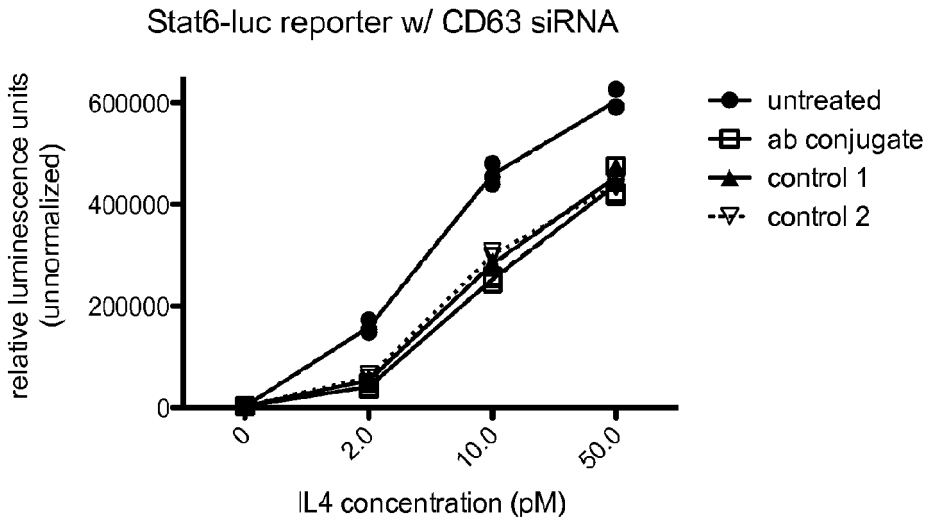

Stat6-luc reporter w/ CD63 siRNA
relative luminescence units (unnormalized)
600000
400000
200000
0
0
2.0
10.0
50.0
IL4 concentration (pM)
untreated
ab conjugate
control 1
control 2

Figure 4

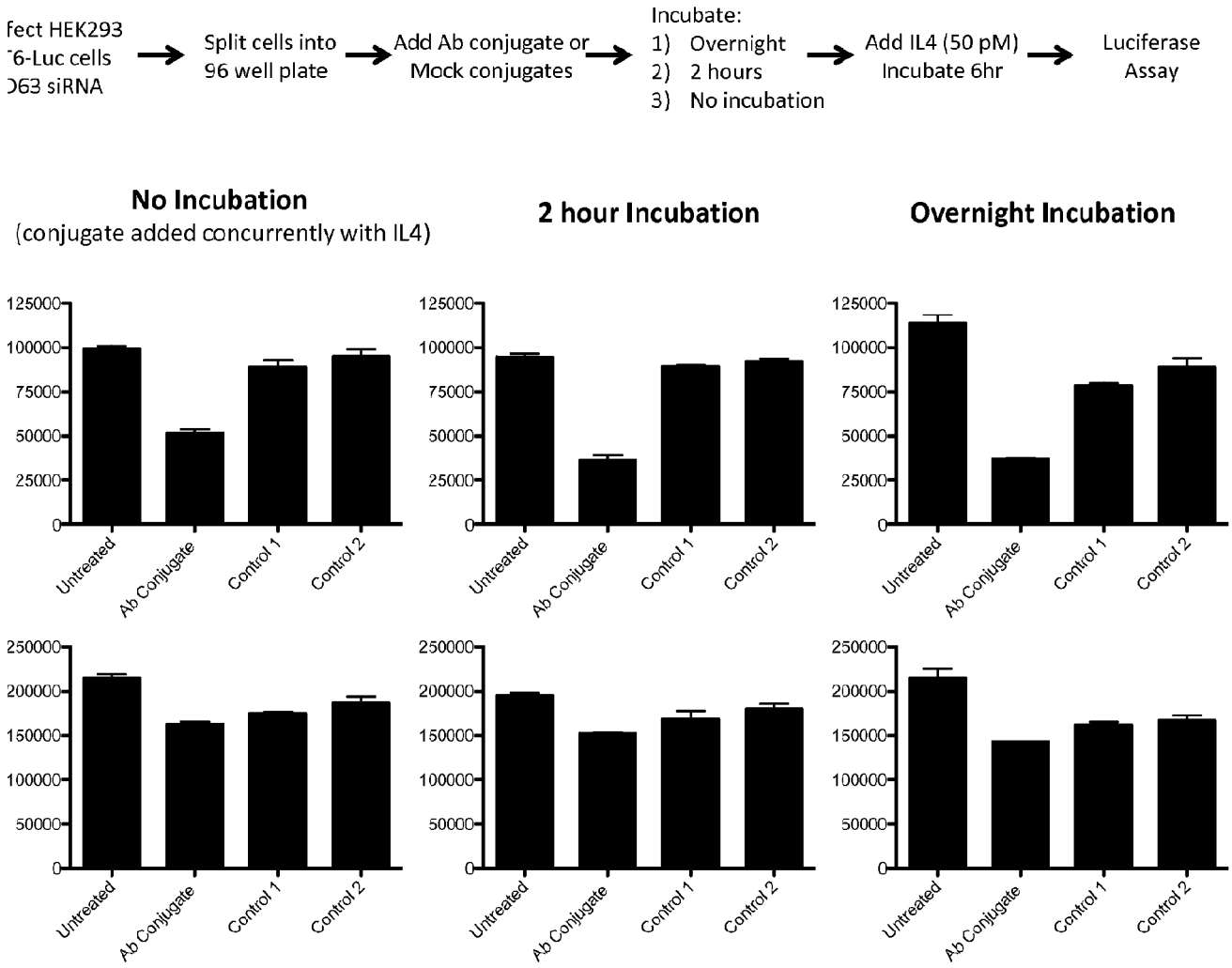
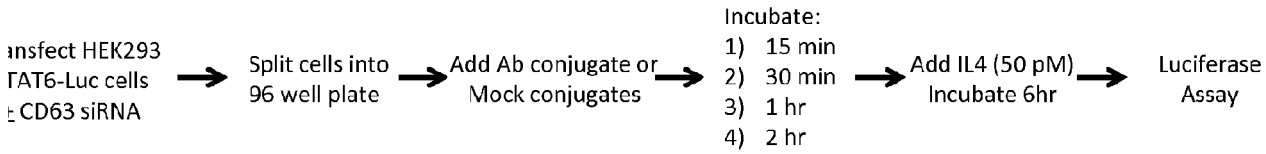

fect HEK293
6-Luc cells
063 siRNA
Split cells into
96 well plate
Add Ab conjugate or
Mock conjugates
Incubate:
1) Overnight
2) 2 hours
3) No incubation
Add IL4 (50 pM)
Incubate 6hr
Luciferase
Assay
No Incubation
(conjugate added concurrently with IL4)
2 hour Incubation
Overnight Incubation
125000
100000
75000
50000
25000
0
250000
200000
150000
100000
50000
0
Untreated
Ab Conjugate
Control 1
Control 2

Figure 5


ınsfect HEK293
ΓAT6-Luc cells
ᵵ CD63 siRNA
Split cells into
96 well plate
Add Ab conjugate or
Mock conjugates
Incubate:
1) 15 min
2) 30 min
3) 1 hr
4) 2 hr
Add IL4 (50 pM)
Incubate 6hr
Luciferase
Assay

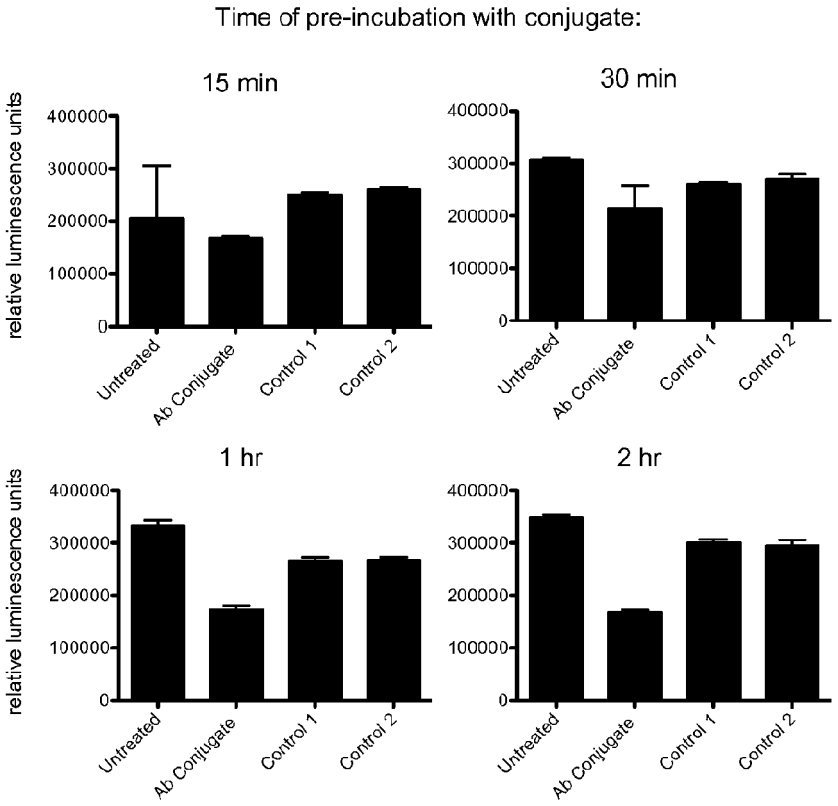

Time of pre-incubation with conjugate:
15 min
30 min
1 hr
2 hr
relative luminescence units
400000
300000
200000
100000
0
Untreated
Ab Conjugate
Control 1
Control 2

Figure 6

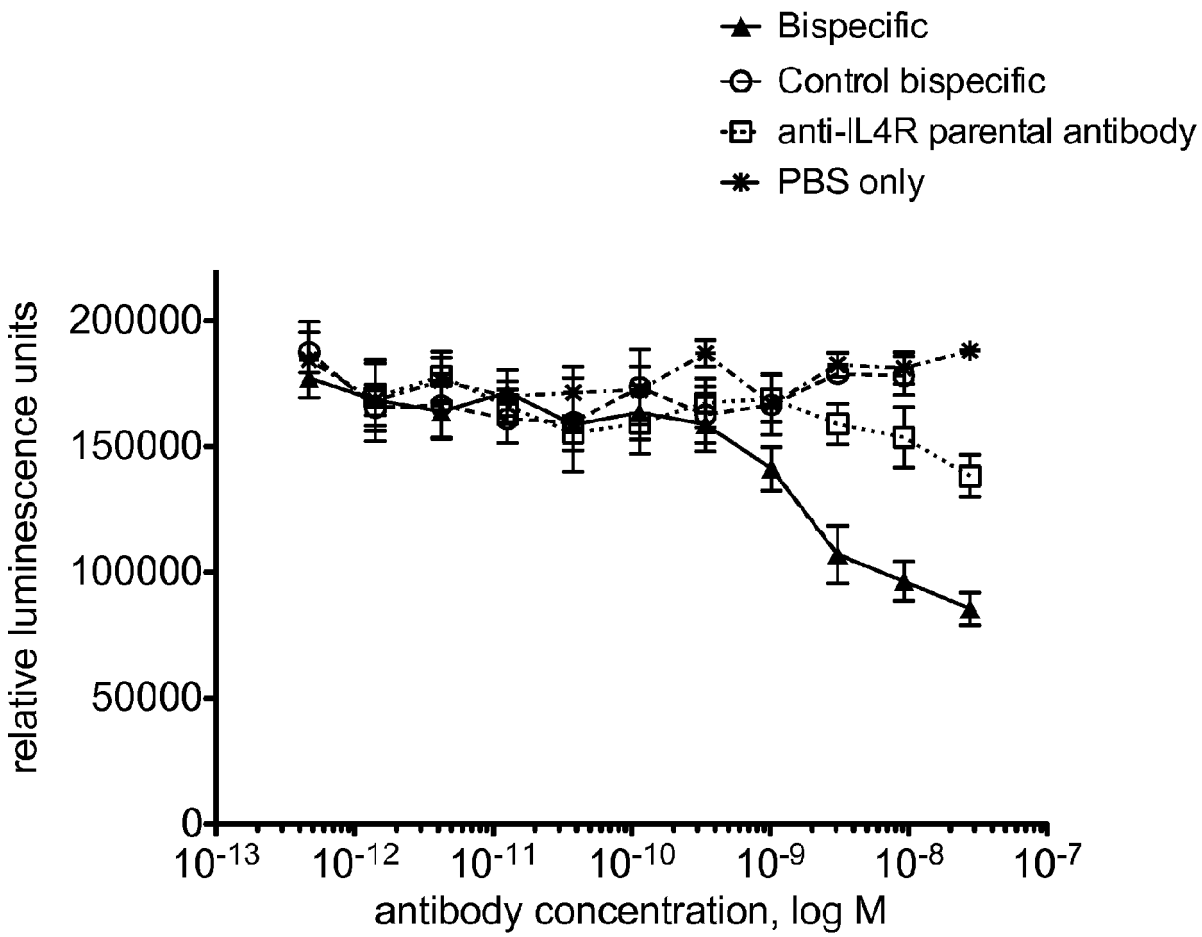

Bispecific
Control bispecific
anti-IL4R parental antibody
PBS only
relative luminescence units
200000
150000
100000
50000
0
10-13
10-12
10-11
10-10
10-9
10-8
10-7
antibody concentration, log M

Figure 7

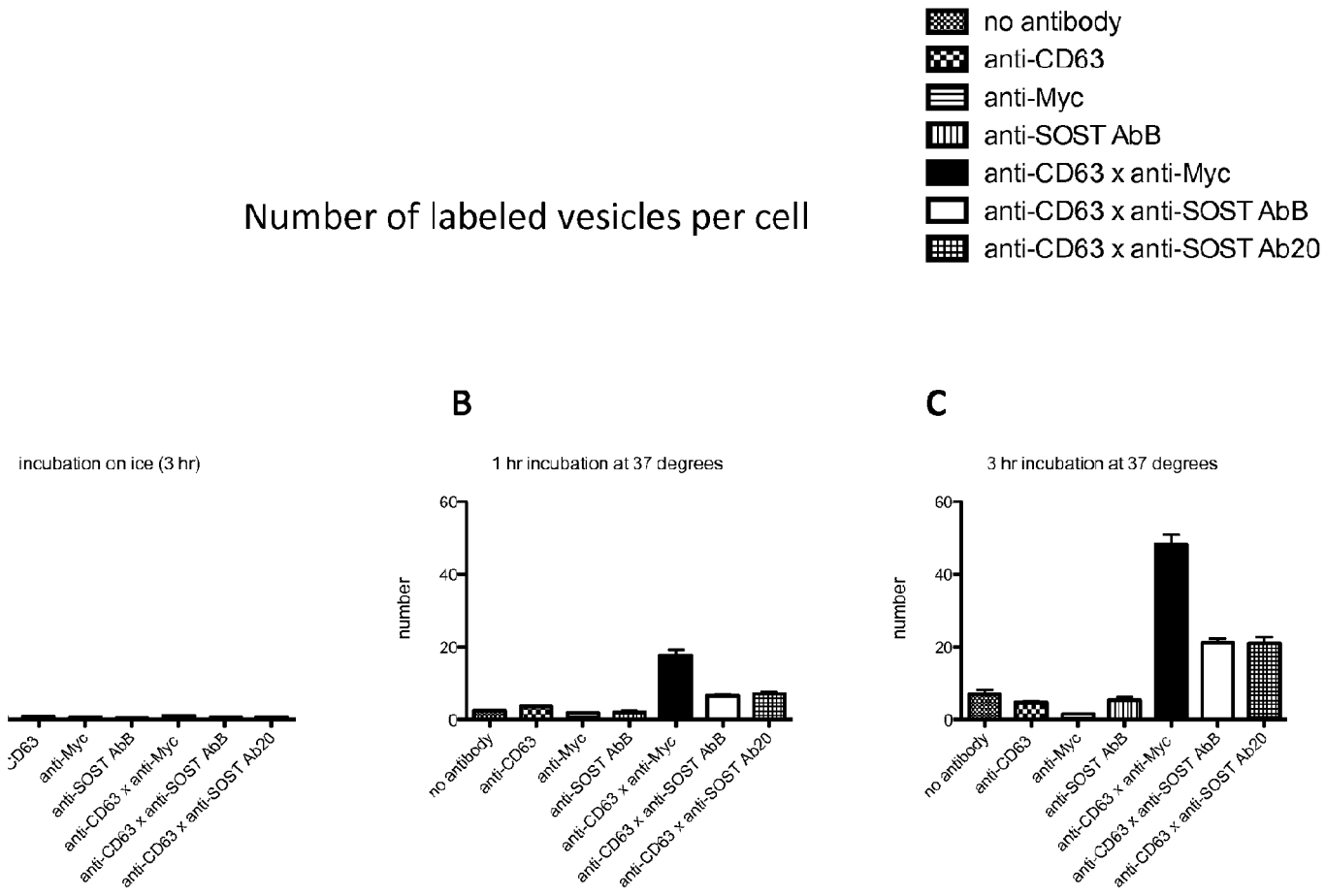

Number of labeled vesicles per cell
no antibody
anti-CD63
anti-Myc
anti-SOST AbB
anti-CD63 x anti-Myc
anti-CD63 x anti-SOST AbB
anti-CD63 x anti-SOST Ab20
B
C
incubation on ice (3 hr)
1 hr incubation at 37 degrees
3 hr incubation at 37 degrees
number
60
40
20
0
anti-Myc
anti-SOST AbB
anti-CD63 x anti-Myc
anti-CD63 x anti-SOST AbB
anti-CD63 x anti-SOST Ab20
no antibody
anti-CD63

Figure 8

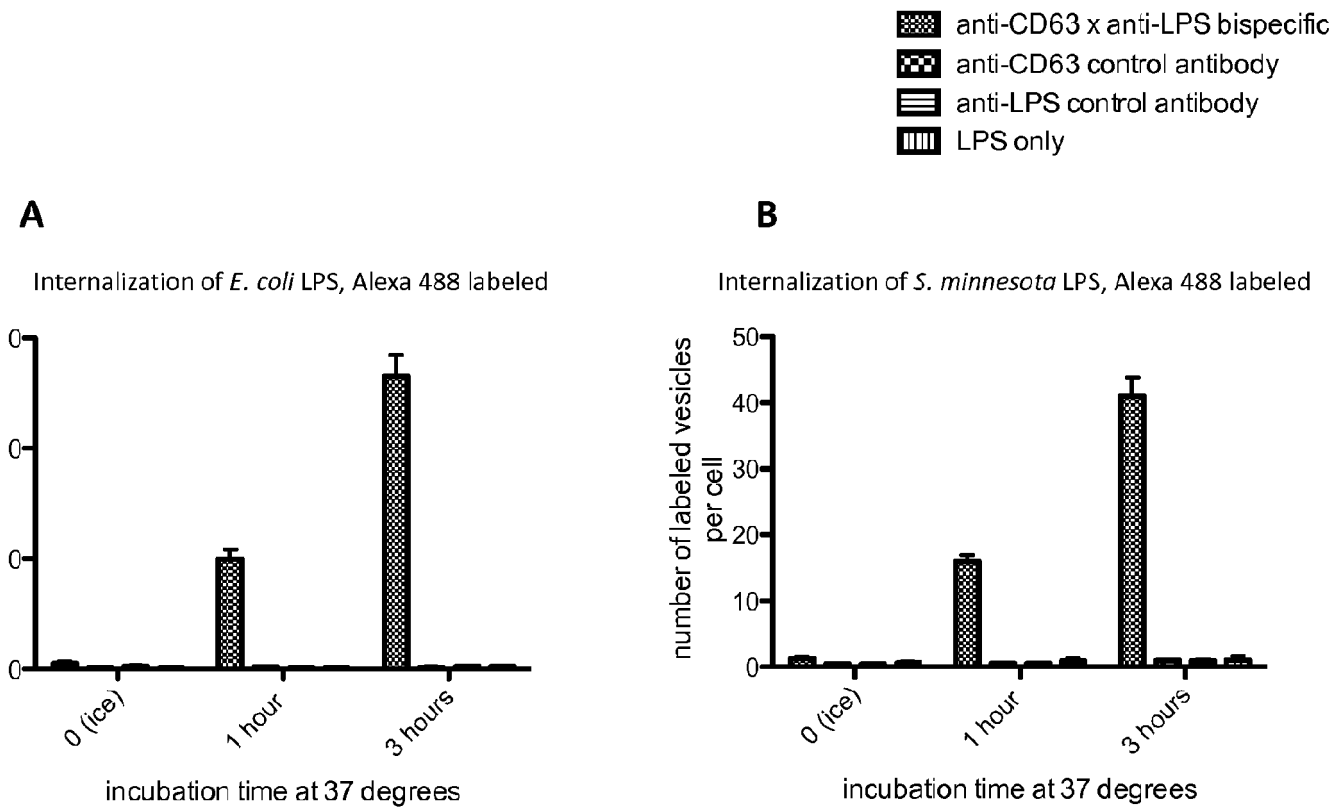

anti-CD63 x anti-LPS bispecific
anti-CD63 control antibody
anti-LPS control antibody
LPS only
A
Internalization of E. coli LPS, Alexa 488 labeled
0
0
0
0
0 (ice)
1 hour
3 hours
incubation time at 37 degrees
B
Internalization of S. minnesota LPS, Alexa 488 labeled
number of labeled vesicles per cell
50
40
30
20
10
0
0 (ice)
1 hour
3 hours
incubation time at 37 degrees

Figure 9

SEQUENCE LISTING

<110> Regeneron Pharmaceuticals, Inc.

<120> Multispecific Antigen-Binding Molecules and Uses Thereof

<130> 7650A-WO

<140> To be assigned
<141> Filed herewith

<150> 61/610,494
<151> 2012-03-14

<150> 61/721,831
<151> 2012-11-02

<150> 61/751,286
<151> 2013-01-11

<160> 4

<170> FastSEQ for Windows Version 4.0

<210> 1
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<212> PRT
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<220>
<223> Synthetic

<400> 1

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Leu Asn Ser Val Leu Asn Ser Asn Ala Ile Lys Asn Leu Pro Pro Pro
        35                  40                  45
Leu Gly Gly Ala Ala Gly His Pro Gly Ser Ala Val Ser Ala Ala Pro
    50                  55                  60
Gly Ile Leu Tyr Pro Gly Gly Asn Lys Tyr Gln Thr Ile Asp Asn Tyr
65                  70                  75                  80
Gln Pro Tyr Pro Cys Ala Glu Asp Glu Glu Cys Gly Thr Asp Glu Tyr
                85                  90                  95
Cys Ala Ser Pro Thr Arg Gly Gly Asp Ala Gly Val Gln Ile Cys Leu
            100                 105                 110
Ala Cys Arg Lys Arg Arg Lys Arg Cys Met Arg His Ala Met Cys Cys
        115                 120                 125
Pro Gly Asn Tyr Cys Lys Asn Gly Ile Cys Val Ser Ser Asp Gln Asn
    130                 135                 140
His Phe Arg Gly Glu Ile Glu Glu Thr Ile Thr Glu Ser Phe Gly Asn
145                 150                 155                 160
Asp His Ser Thr Leu Asp Gly Tyr Ser Arg Arg Thr Thr Leu Ser Ser
                165                 170                 175
Lys Met Tyr His Thr Lys Gly Gln Glu Gly Ser Val Cys Leu Arg Ser
            180                 185                 190
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Ser Asp Cys Ala Ser Gly Leu Cys Cys Ala Arg His Phe Trp Ser Lys
        195                 200                 205
Ile Cys Lys Pro Val Leu Lys Glu Gly Gln Val Cys Thr Lys His Arg
    210                 215                 220
Arg Lys Gly Ser His Gly Leu Glu Ile Phe Gln Arg Cys Tyr Cys Gly
225                 230                 235                 240
Glu Gly Leu Ser Cys Arg Ile Gln Lys Asp His His Gln Ala Ser Asn
                245                 250                 255
Ser Ser Arg Leu His Thr Cys Gln Arg His Gly Pro Gly Glu Pro Arg
            260                 265                 270
Gly Pro Thr Ile Lys Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn
        275                 280                 285
Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp
    290                 295                 300
Val Leu Met Ile Ser Leu Ser Pro Ile Val Thr Cys Val Val Val Asp
305                 310                 315                 320
Val Ser Glu Asp Asp Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn
                325                 330                 335
Val Glu Val His Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn
            340                 345                 350
Ser Thr Leu Arg Val Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp
        355                 360                 365
Met Ser Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Pro
    370                 375                 380
Ala Pro Ile Glu Arg Thr Ile Ser Lys Pro Lys Gly Ser Val Arg Ala
385                 390                 395                 400
Pro Gln Val Tyr Val Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys
                405                 410                 415
Gln Val Thr Leu Thr Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile
            420                 425                 430
Tyr Val Glu Trp Thr Asn Asn Gly Lys Thr Glu Leu Asn Tyr Lys Asn
        435                 440                 445
Thr Glu Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys
    450                 455                 460
Leu Arg Val Glu Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys
465                 470                 475                 480
Ser Val Val His Glu Gly Leu His Asn His His Thr Thr Lys Ser Phe
                485                 490                 495
Ser Arg Thr Pro Gly Lys
            500
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<210> 2
<211> 496
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 2

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            20                  25                  30
Leu Asn Ser Val Leu Asn Ser Asn Ala Ile Lys Asn Leu Pro Pro Pro
        35                  40                  45
Leu Gly Gly Ala Ala Gly His Pro Gly Ser Ala Val Ser Ala Ala Pro
```

```
    50                  55                  60
Gly Ile Leu Tyr Pro Gly Gly Asn Lys Tyr Gln Thr Ile Asp Asn Tyr
65                  70                  75                  80
Gln Pro Tyr Pro Cys Ala Glu Asp Glu Glu Cys Gly Thr Asp Glu Tyr
                85                  90                  95
Cys Ala Ser Pro Thr Arg Gly Gly Asp Ala Gly Val Gln Ile Cys Leu
            100                 105                 110
Ala Cys Arg Lys Arg Arg Lys Arg Cys Met Arg His Ala Met Cys Cys
        115                 120                 125
Pro Gly Asn Tyr Cys Lys Asn Gly Ile Cys Val Ser Ser Asp Gln Asn
    130                 135                 140
His Phe Arg Gly Glu Ile Glu Glu Thr Ile Thr Glu Ser Phe Gly Asn
145                 150                 155                 160
Asp His Ser Thr Leu Asp Gly Tyr Ser Arg Arg Thr Thr Leu Ser Ser
                165                 170                 175
Lys Met Tyr His Thr Lys Gly Gln Glu Gly Ser Val Cys Leu Arg Ser
            180                 185                 190
Ser Asp Cys Ala Ser Gly Leu Cys Cys Ala Arg His Phe Trp Ser Lys
        195                 200                 205
Ile Cys Lys Pro Val Leu Lys Glu Gly Gln Val Cys Thr Lys His Arg
    210                 215                 220
Arg Lys Gly Ser His Gly Leu Glu Ile Phe Gln Arg Cys Tyr Cys Gly
225                 230                 235                 240
Glu Gly Leu Ser Cys Arg Ile Gln Lys Asp His His Gln Ala Ser Asn
                245                 250                 255
Ser Ser Arg Leu His Thr Cys Gln Arg His Gly Pro Gly Asp Lys Thr
            260                 265                 270
His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
        275                 280                 285
Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
    290                 295                 300
Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
305                 310                 315                 320
Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
                325                 330                 335
Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
            340                 345                 350
Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
        355                 360                 365
Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
    370                 375                 380
Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
385                 390                 395                 400
Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
                405                 410                 415
Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
            420                 425                 430
Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
        435                 440                 445
Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
    450                 455                 460
Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
465                 470                 475                 480
Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                485                 490                 495
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<210> 3

<211> 122
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            20   25   30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ala Val Ile Trp Tyr Asp Gly Ser Ile Lys Tyr Phe Arg Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala His Tyr Tyr Cys
                85   90   95
Ala Lys Glu Ser Ser Ser Trp Tyr Phe Tyr His Gly Leu Asp Val Trp
            100   105   110
Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115   120

<210> 4
<211> 114
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 1   5   10   15
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            20   25   30
Asn Gly Asn Asn Tyr Leu Ala Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35   40   45
Pro His Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50   55   60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65   70   75   80
Ser Arg Val Glu Ala Gly Asp Val Gly Thr Tyr Phe Cys Met Gln Ser
                85   90   95
Leu Gln Ala Pro Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Glu Ile
            100   105   110
Lys Arg