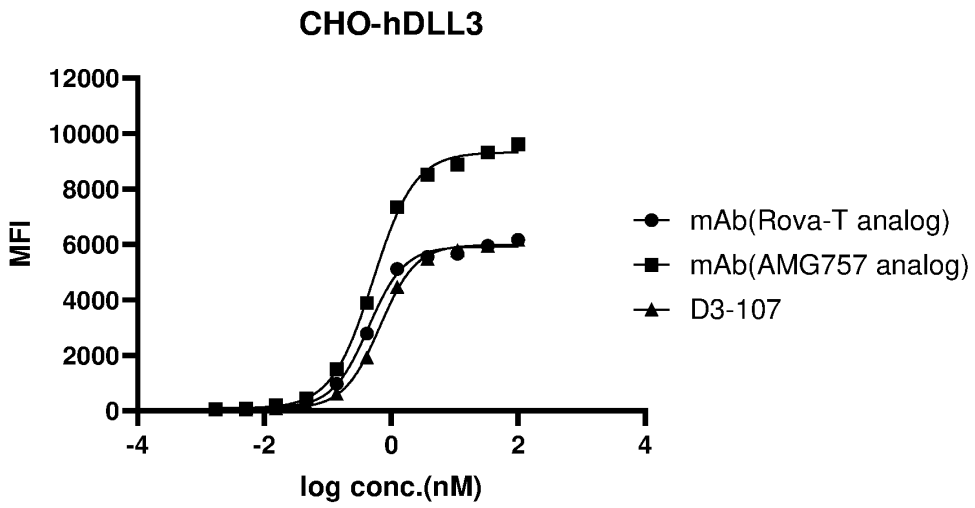

CHO-hDLL3
MFI
12000
10000
8000
6000
4000
2000
0
-4
-2
0
2
4
log conc.(nM)
mAb(Rova-T analog)
mAb(AMG757 analog)
D3-107

图 1

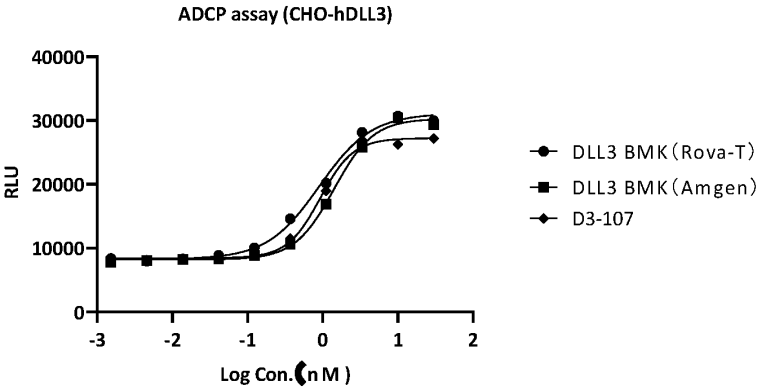
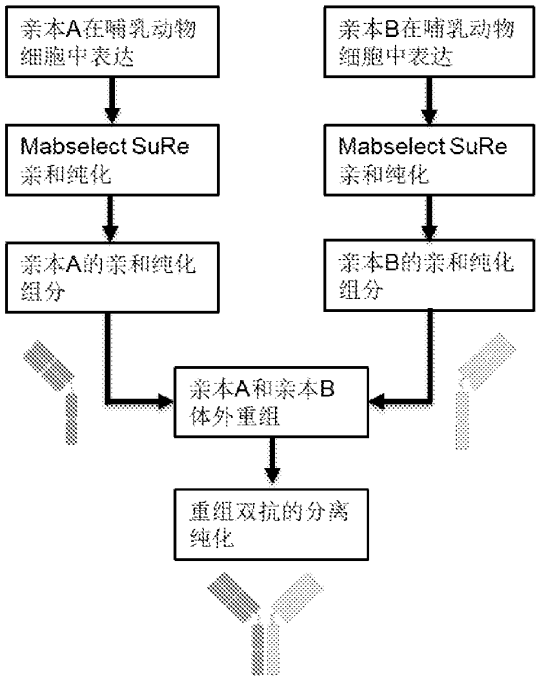

ADCP assay (CHO-hDLL3)
RLU
40000
30000
20000
10000
0
-3
-2
-1
0
1
2
Log Con.(nM)
DLL3 BMK(Rova-T)
DLL3 BMK(Amgen)
D3-107

图 2

A


亲本A在哺乳动物细胞中表达
亲本B在哺乳动物细胞中表达
Mabselect SuRe 亲和纯化
Mabselect SuRe 亲和纯化
亲本A的亲和纯化组分
亲本B的亲和纯化组分
亲本A和亲本B体外重组
重组双抗的分离纯化

B

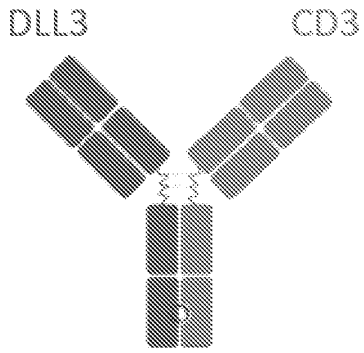
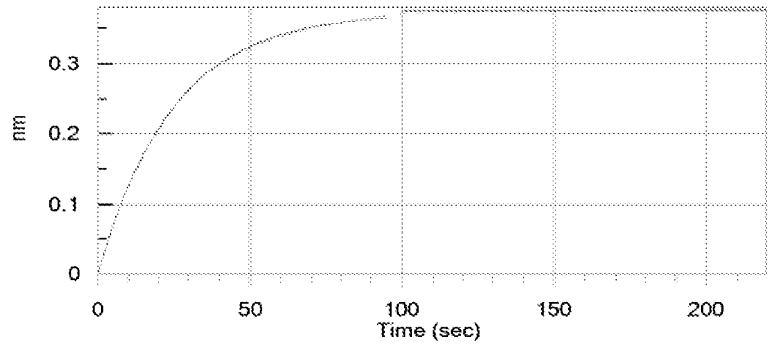

DLL3
CD3

图 3

A


nm
0.3
0.2
0.1
0
0
50
100
150
200
Time (sec)

B

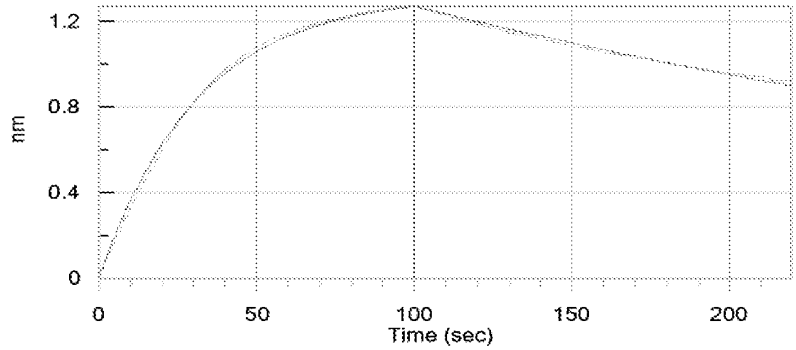

nm
1.2
0.8
0.4
0
0
50
100
150
200
Time (sec)

图 4

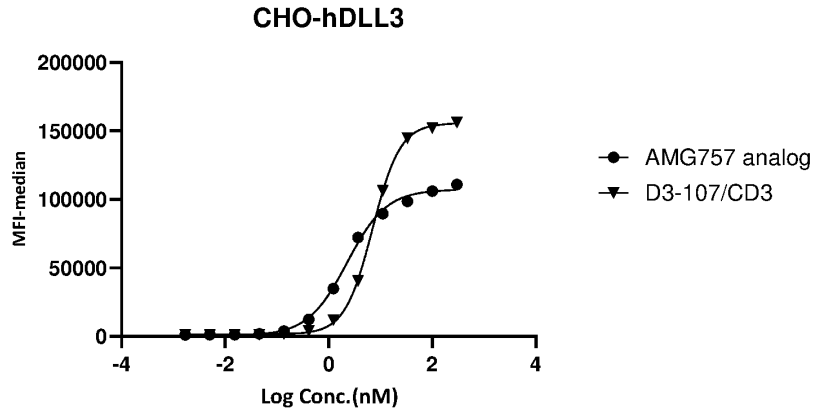
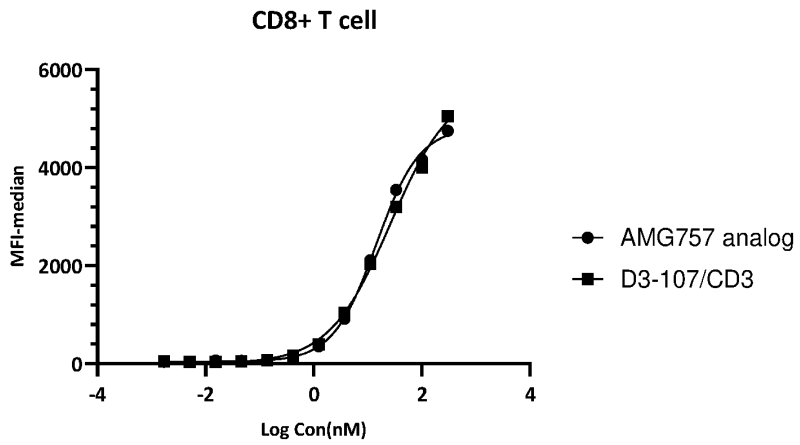

CHO-hDLL3
MFI-median
200000
150000
100000
50000
0
-4
-2
0
2
4
Log Conc.(nM)
AMG757 analog
D3-107/CD3

图 5

A


CD8+ T cell
MFI-median
6000
4000
2000
0
-4
-2
0
2
4
Log Con(nM)
AMG757 analog
D3-107/CD3

B

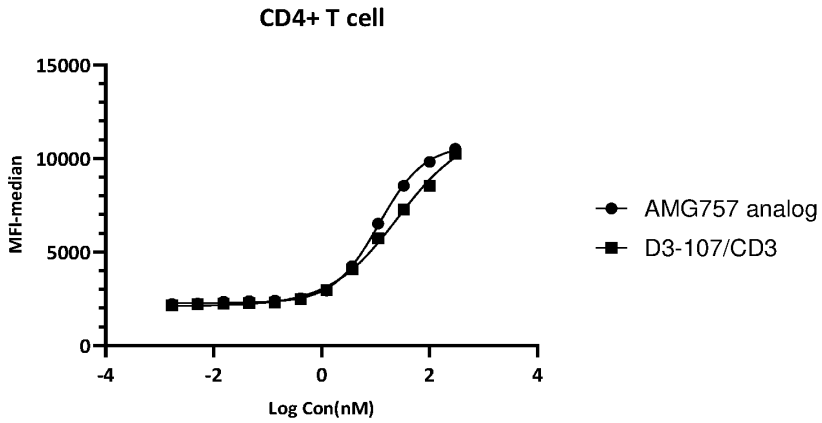
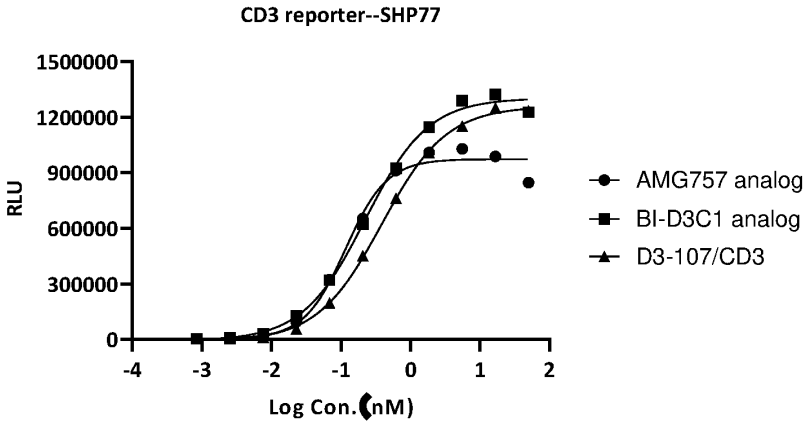

CD4+ T cell
MFI-median
15000
10000
5000
0
-4
-2
0
2
4
Log Con(nM)
AMG757 analog
D3-107/CD3

图 6

A


CD3 reporter--SHP77
RLU
1500000
1200000
900000
600000
300000
0
-4
-3
-2
-1
0
1
2
Log Con.(nM)
AMG757 analog
BI-D3C1 analog
D3-107/CD3

B

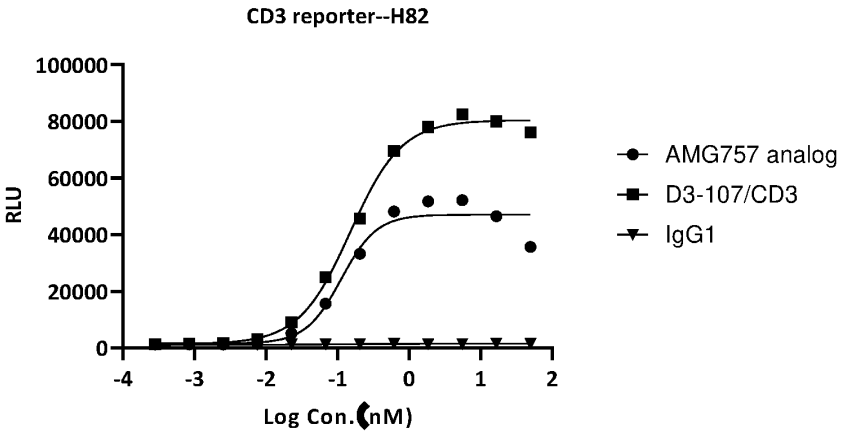
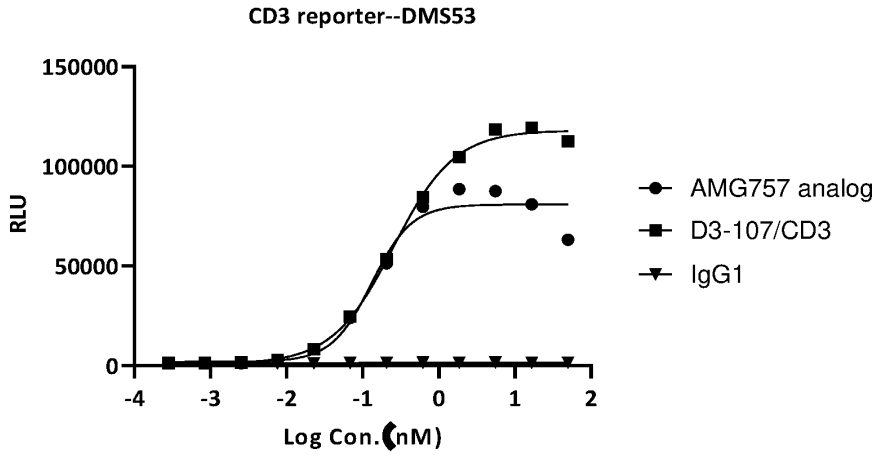

CD3 reporter--H82
RLU
100000
80000
60000
40000
20000
0
-4
-3
-2
-1
0
1
2
Log Con.(nM)
AMG757 analog
D3-107/CD3
IgG1

图 7

C


CD3 reporter--DMS53
150000
100000
50000
0
RLU
-4
-3
-2
-1
0
1
2
Log Con.(nM)
AMG757 analog
D3-107/CD3
IgG1

D

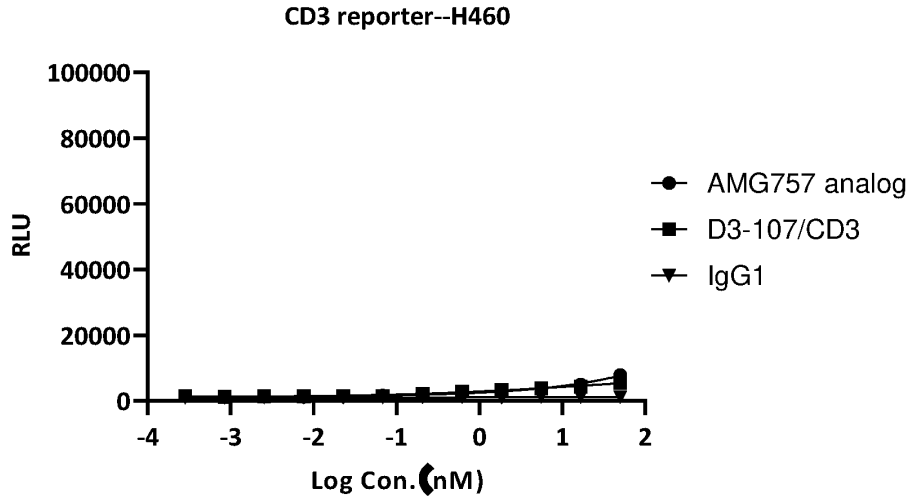
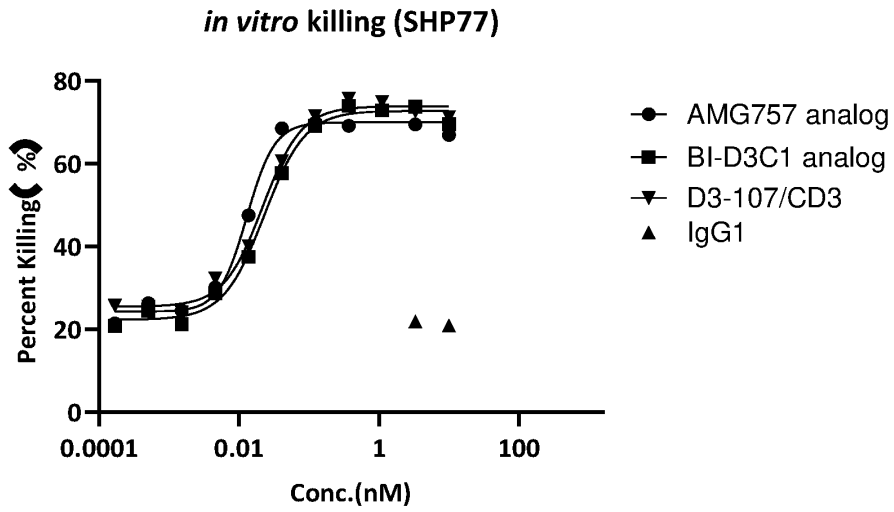

CD3 reporter--H460
100000
80000
60000
40000
20000
0
RLU
-4
-3
-2
-1
0
1
2
Log Con.(nM)
AMG757 analog
D3-107/CD3
IgG1

图 7（续）

A


in vitro killing (SHP77)
Percent Killing (%)
80
60
40
20
0
0.0001
0.01
1
100
Conc.(nM)
AMG757 analog
BI-D3C1 analog
D3-107/CD3
IgG1

B

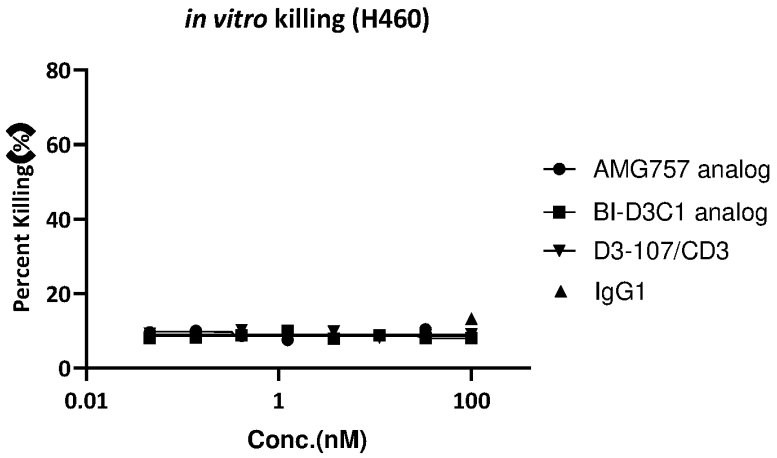
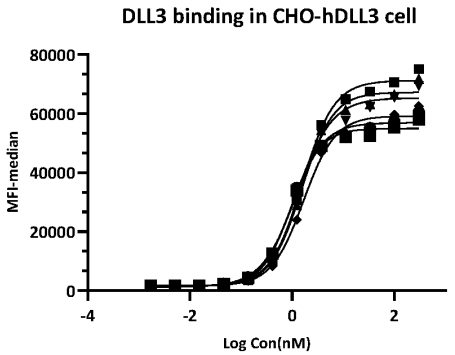

in vitro killing (H460)
Percent Killing (%)
80
60
40
20
0
0.01
1
100
Conc.(nM)
AMG757 analog
BI-D3C1 analog
D3-107/CD3
IgG1

图 8



	EC50
D3-107	1.575
D3-107-P1	1.541
D3-107-P2	1.252
D3-107-P3	1.664
D3-107-P4	1.010
D3-107-P5	0.9556

图 9

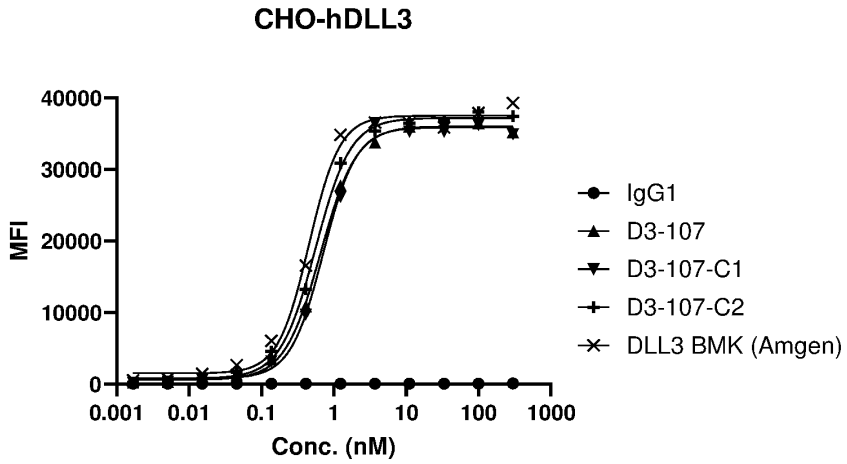
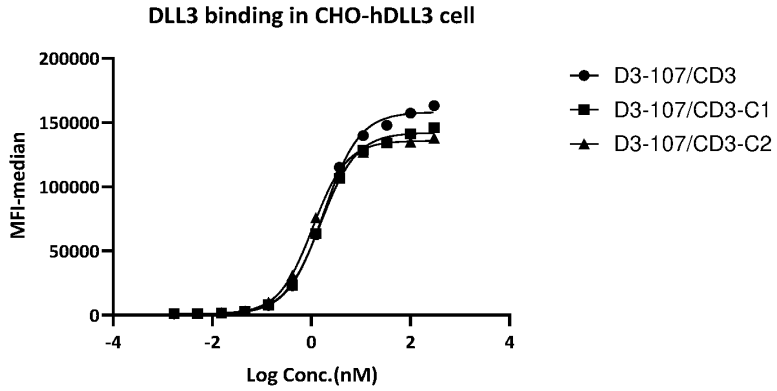
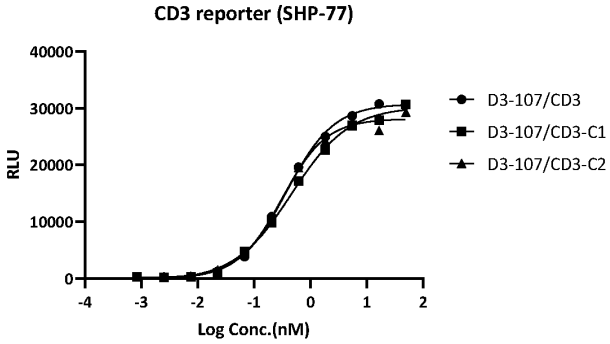


图 10



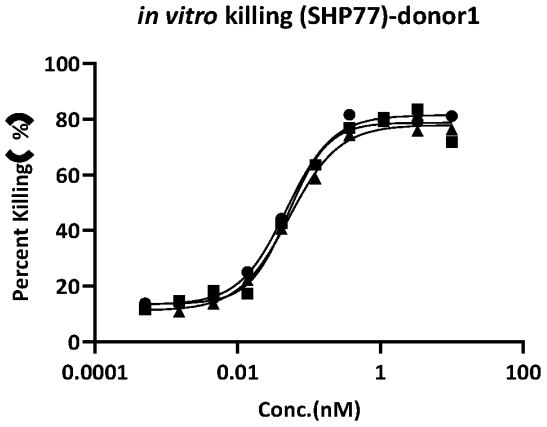
	D3-107/CD3	D3-107/CD3-C1	D3-107/CD3-C2
EC50	1.767	1.537	1.071

图 11



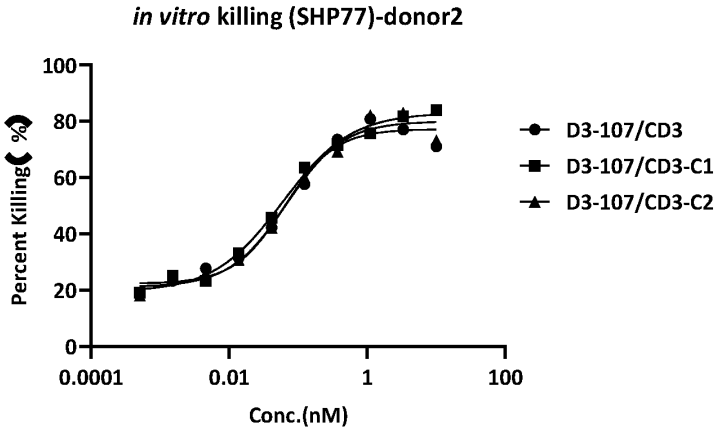
	D3-107/CD3	D3-107/CD3-C1	D3-107/CD3-C2
EC50	0.3798	0.4682	0.3172

图 12



	D3-107/CD3	D3-107/CD3-C1	D3-107/CD3-C2
EC50	0.04815	0.05160	0.05252

图 13



	D3-107/CD3	D3-107/CD3-C1	D3-107/CD3-C2
EC50	0.06329	0.05900	0.06743

图 14

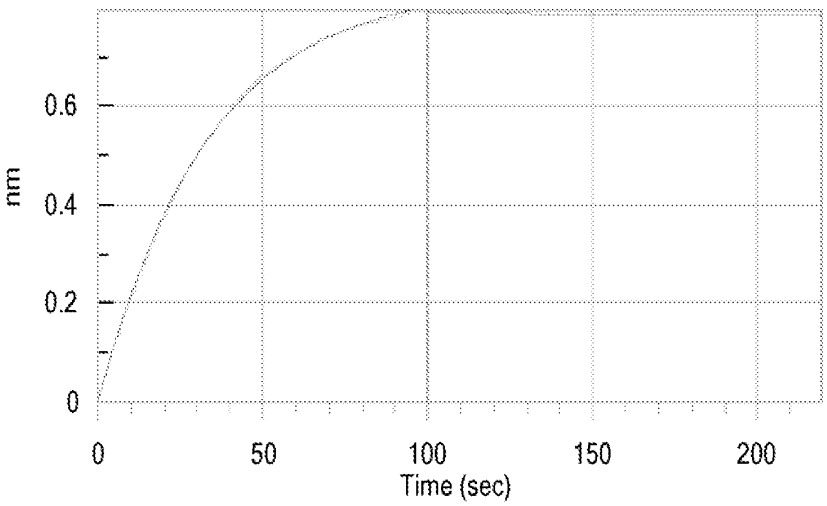

0.6
0.4
0.2
0
nm
0
50
100
150
200
Time (sec)

图 15A

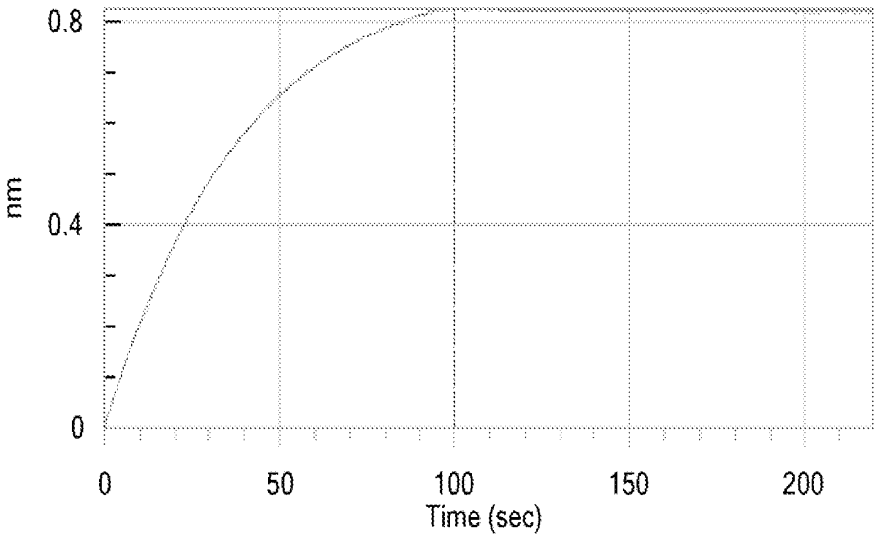

0.8
0.4
0
nm
0
50
100
150
200
Time (sec)

图 15B

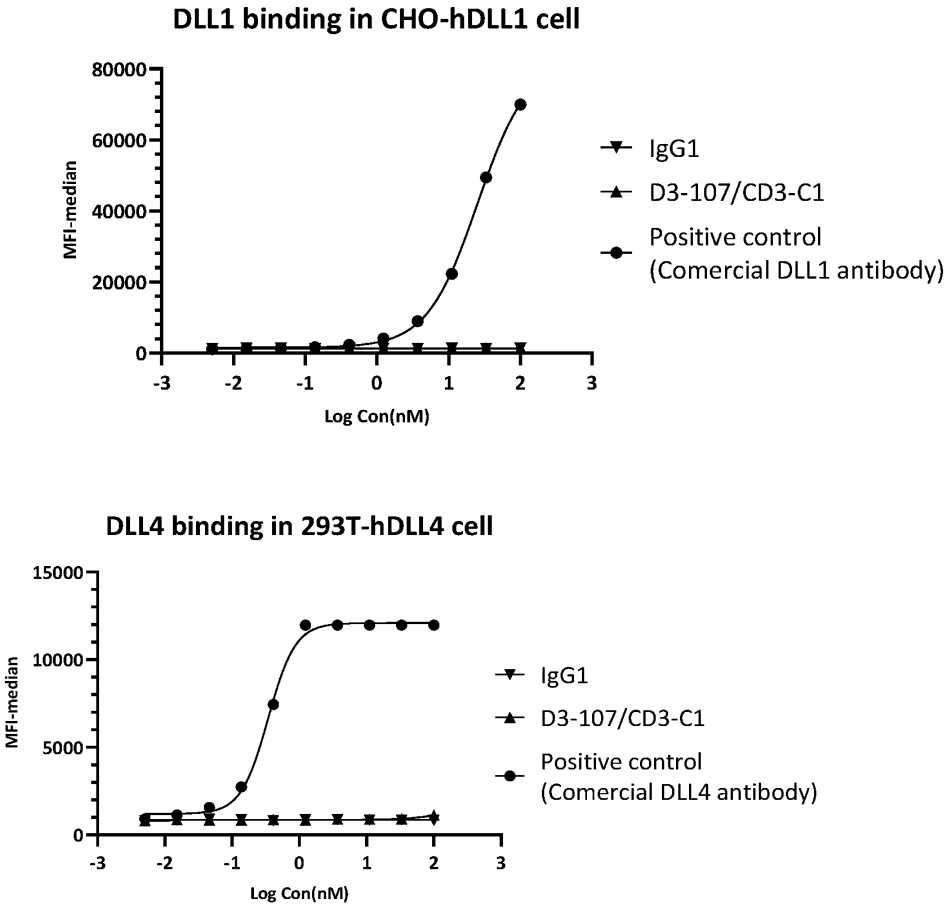

DLL1 binding in CHO-hDLL1 cell
MFI-median
80000
60000
40000
20000
0
-3
-2
-1
0
1
2
3
Log Con(nM)
IgG1
D3-107/CD3-C1
Positive control
(Comercial DLL1 antibody)
DLL4 binding in 293T-hDLL4 cell
MFI-median
15000
10000
5000
0
-3
-2
-1
0
1
2
3
Log Con(nM)
IgG1
D3-107/CD3-C1
Positive control
(Comercial DLL4 antibody)

图 16

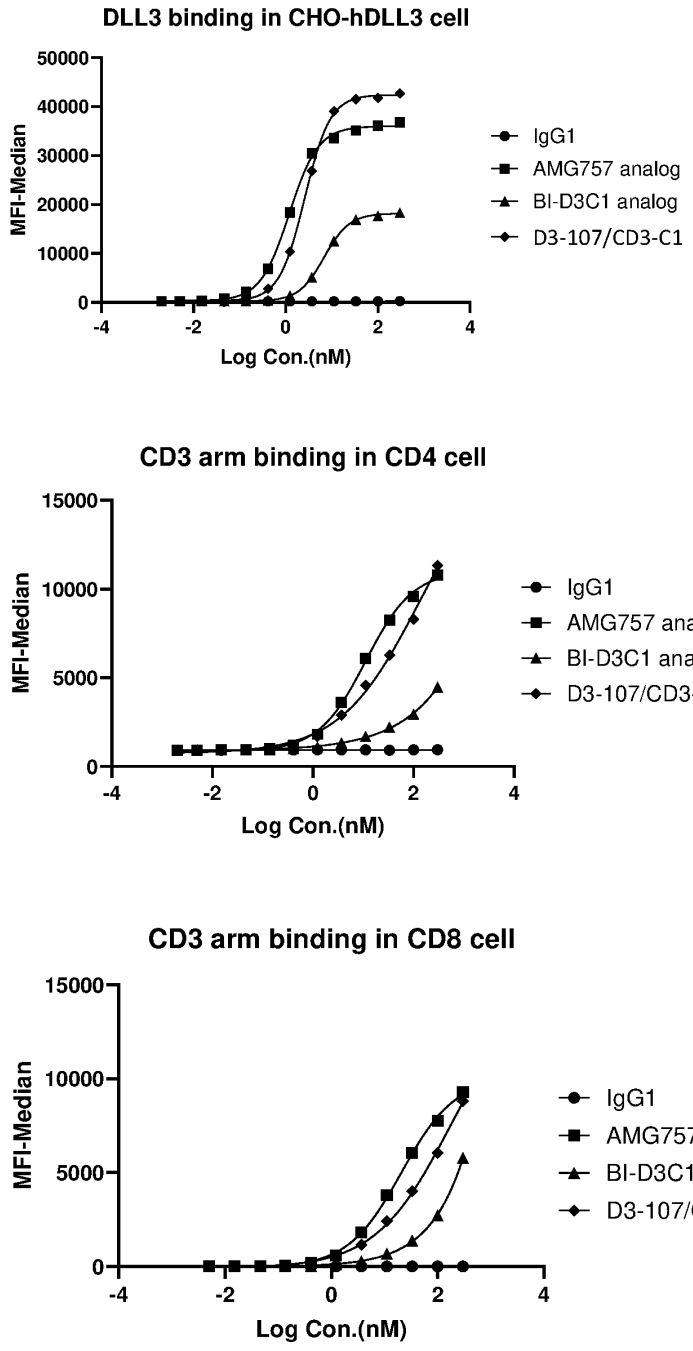

DLL3 binding in CHO-hDLL3 cell
MFI-Median
50000
40000
30000
20000
10000
0
-4
-2
0
2
4
Log Con.(nM)
IgG1
AMG757 analog
BI-D3C1 analog
D3-107/CD3-C1
CD3 arm binding in CD4 cell
MFI-Median
15000
10000
5000
0
-4
-2
0
2
4
Log Con.(nM)
IgG1
AMG757 analog
BI-D3C1 analog
D3-107/CD3-C1
CD3 arm binding in CD8 cell
MFI-Median
15000
10000
5000
0
-4
-2
0
2
4
Log Con.(nM)
IgG1
AMG757 analog
BI-D3C1 analog
D3-107/CD3-C1

图 17

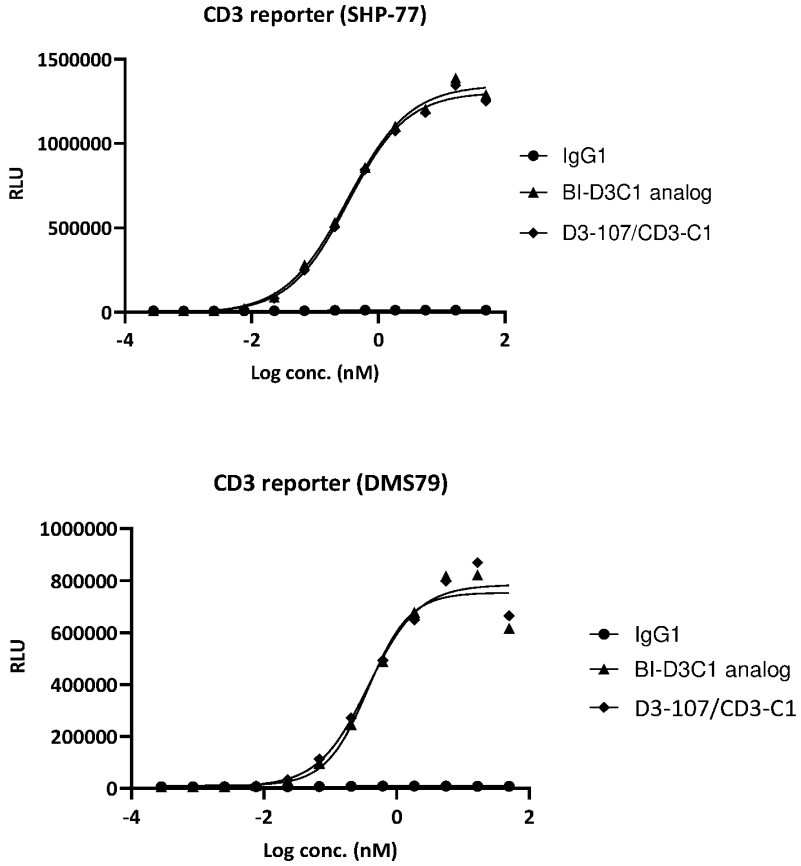

CD3 reporter (SHP-77)
1500000
1000000
500000
0
RLU
-4
-2
0
2
Log conc. (nM)
IgG1
BI-D3C1 analog
D3-107/CD3-C1
CD3 reporter (DMS79)
1000000
800000
600000
400000
200000
0
RLU
-4
-2
0
2
Log conc. (nM)
IgG1
BI-D3C1 analog
D3-107/CD3-C1

图 18

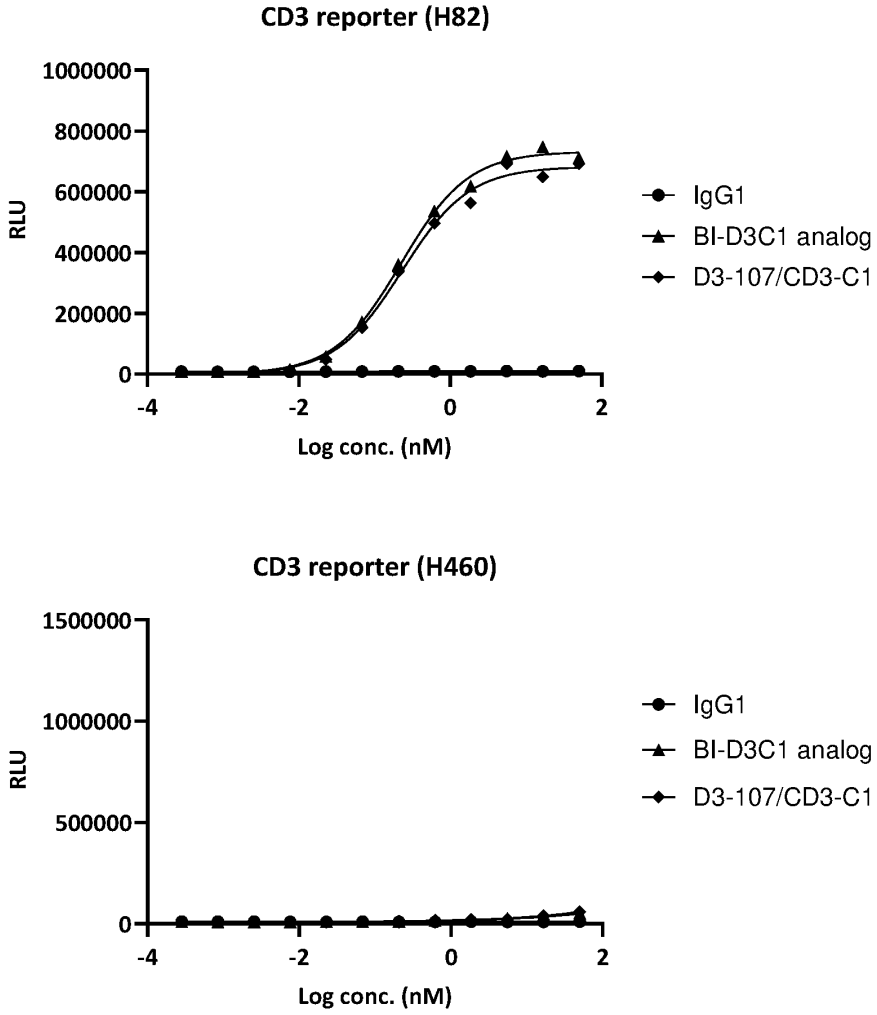

CD3 reporter (H82)
1000000
800000
600000
400000
200000
0
RLU
-4
-2
0
2
Log conc. (nM)
IgG1
BI-D3C1 analog
D3-107/CD3-C1
CD3 reporter (H460)
1500000
1000000
500000
0
RLU
-4
-2
0
2
Log conc. (nM)
IgG1
BI-D3C1 analog
D3-107/CD3-C1

图 18（续）

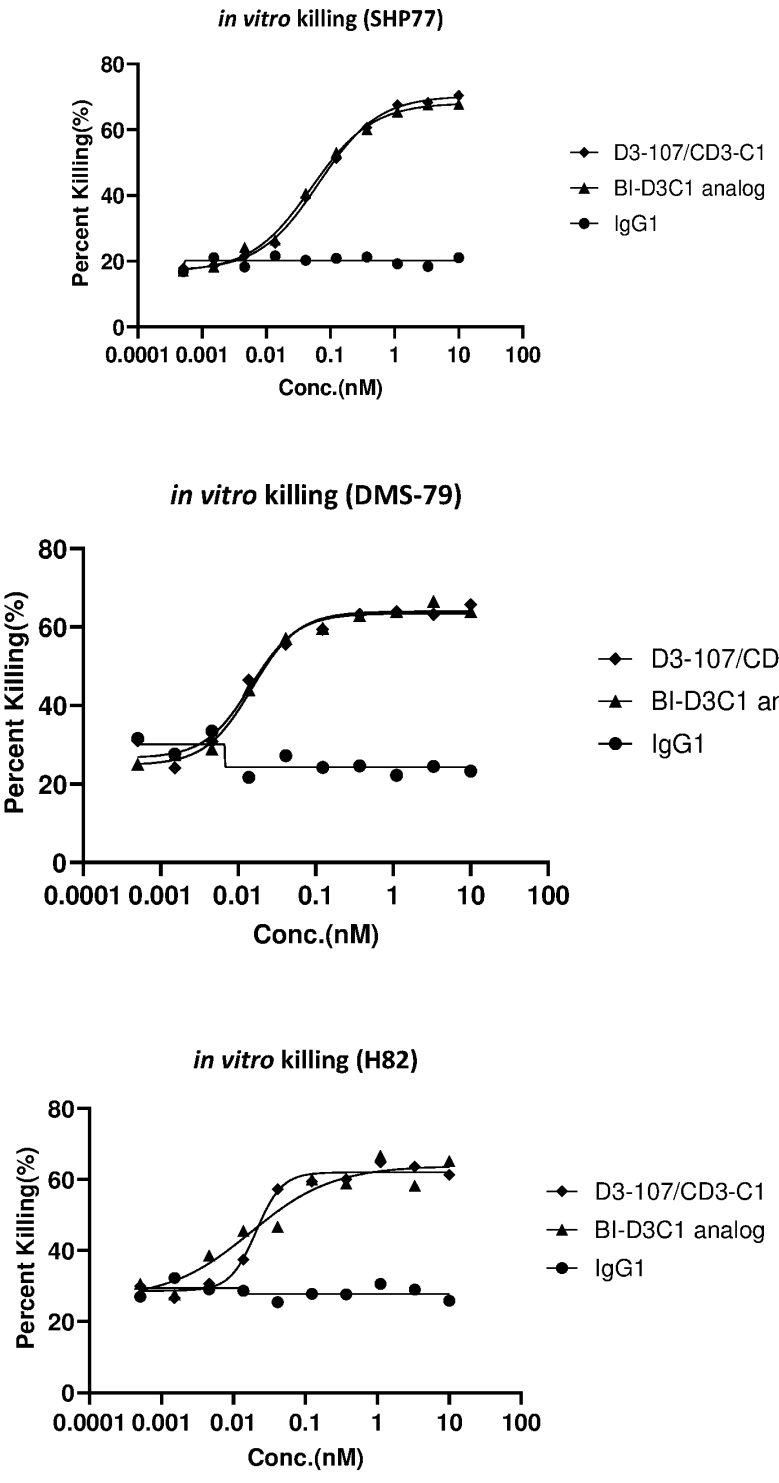

in vitro killing (SHP77)
Percent Killing(%)
80
60
40
20
0
0.0001 0.001 0.01 0.1 1 10 100
Conc.(nM)
D3-107/CD3-C1
BI-D3C1 analog
IgG1
in vitro killing (DMS-79)
Percent Killing(%)
80
60
40
20
0
0.0001 0.001 0.01 0.1 1 10 100
Conc.(nM)
D3-107/CD3-C1
BI-D3C1 analog
IgG1
in vitro killing (H82)
Percent Killing(%)
80
60
40
20
0
0.0001 0.001 0.01 0.1 1 10 100
Conc.(nM)
D3-107/CD3-C1
BI-D3C1 analog
IgG1

图 19

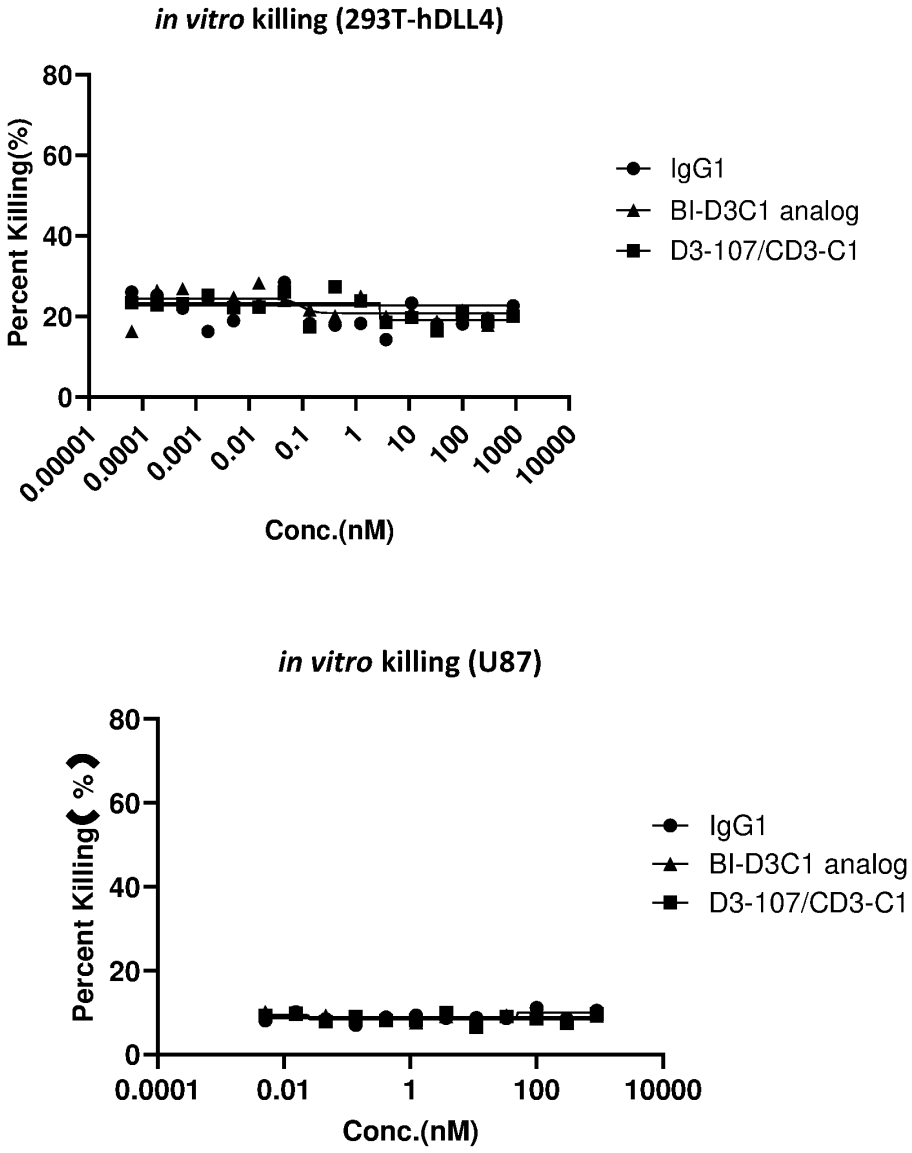

in vitro killing (293T-hDLL4)
Percent Killing(%)
80
60
40
20
0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1000
10000
Conc.(nM)
IgG1
BI-D3C1 analog
D3-107/CD3-C1
in vitro killing (U87)
Percent Killing(%)
80
60
40
20
0
0.0001
0.01
1
100
10000
Conc.(nM)
IgG1
BI-D3C1 analog
D3-107/CD3-C1

图 19（续）

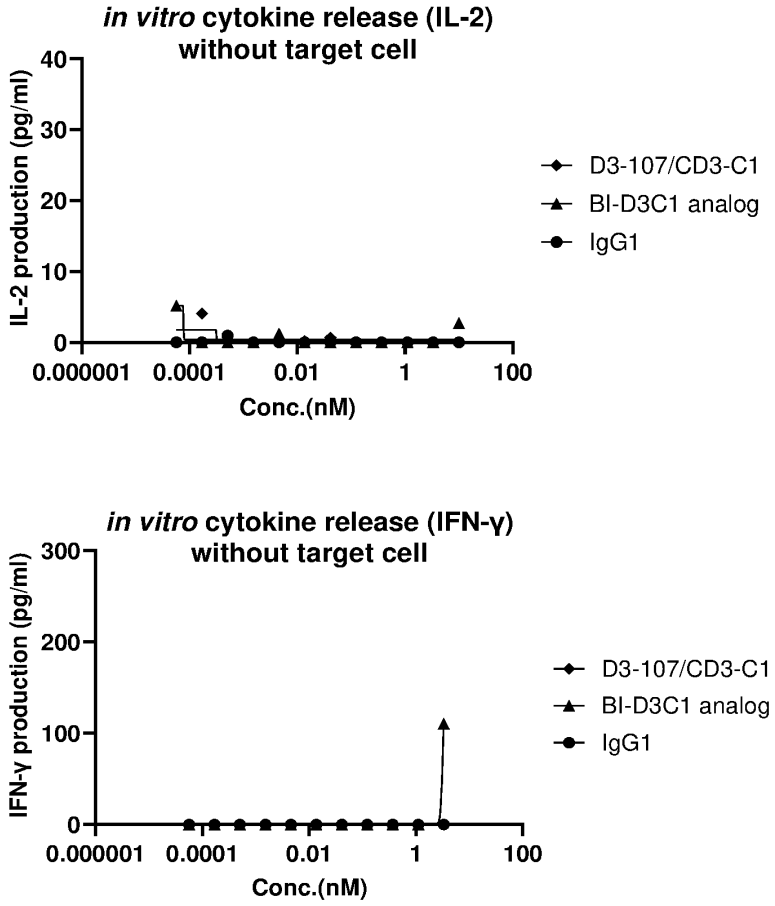
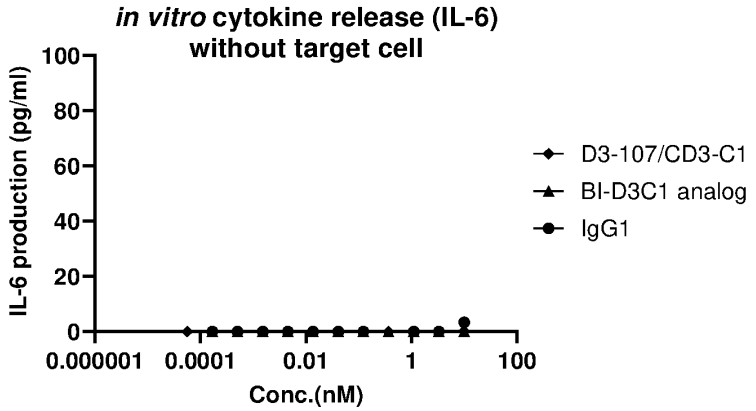

in vitro cytokine release (IL-2)
without target cell
IL-2 production (pg/ml)
40
30
20
10
0
0.000001
0.0001
0.01
1
100
Conc.(nM)
D3-107/CD3-C1
BI-D3C1 analog
IgG1
in vitro cytokine release (IFN-γ)
without target cell
IFN-γ production (pg/ml)
300
200
100
0
0.000001
0.0001
0.01
1
100
Conc.(nM)
D3-107/CD3-C1
BI-D3C1 analog
IgG1

图 20


in vitro cytokine release (IL-6)
without target cell
IL-6 production (pg/ml)
100
80
60
40
20
0
0.000001
0.0001
0.01
1
100
Conc.(nM)
D3-107/CD3-C1
BI-D3C1 analog
IgG1

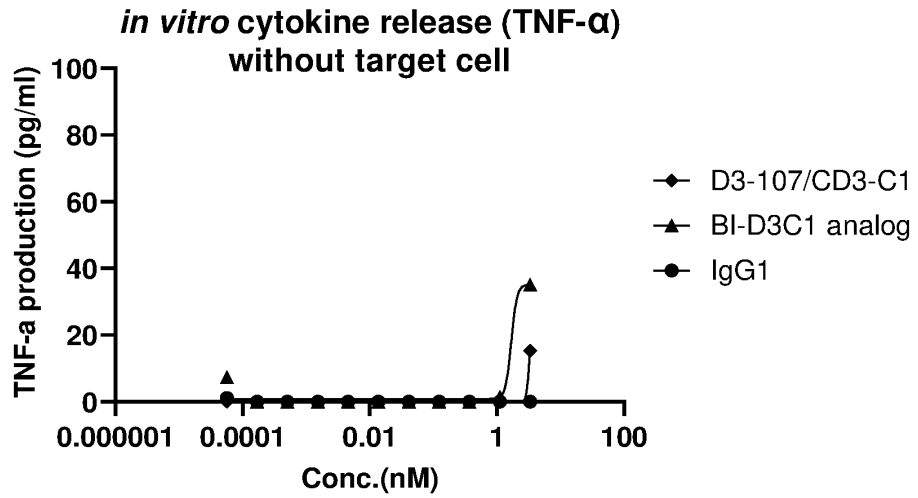

in vitro cytokine release (TNF-α)
without target cell
TNF-a production (pg/ml)
100
80
60
40
20
0
0.000001
0.0001
0.01
1
100
Conc.(nM)
D3-107/CD3-C1
BI-D3C1 analog
IgG1

图 20（续）

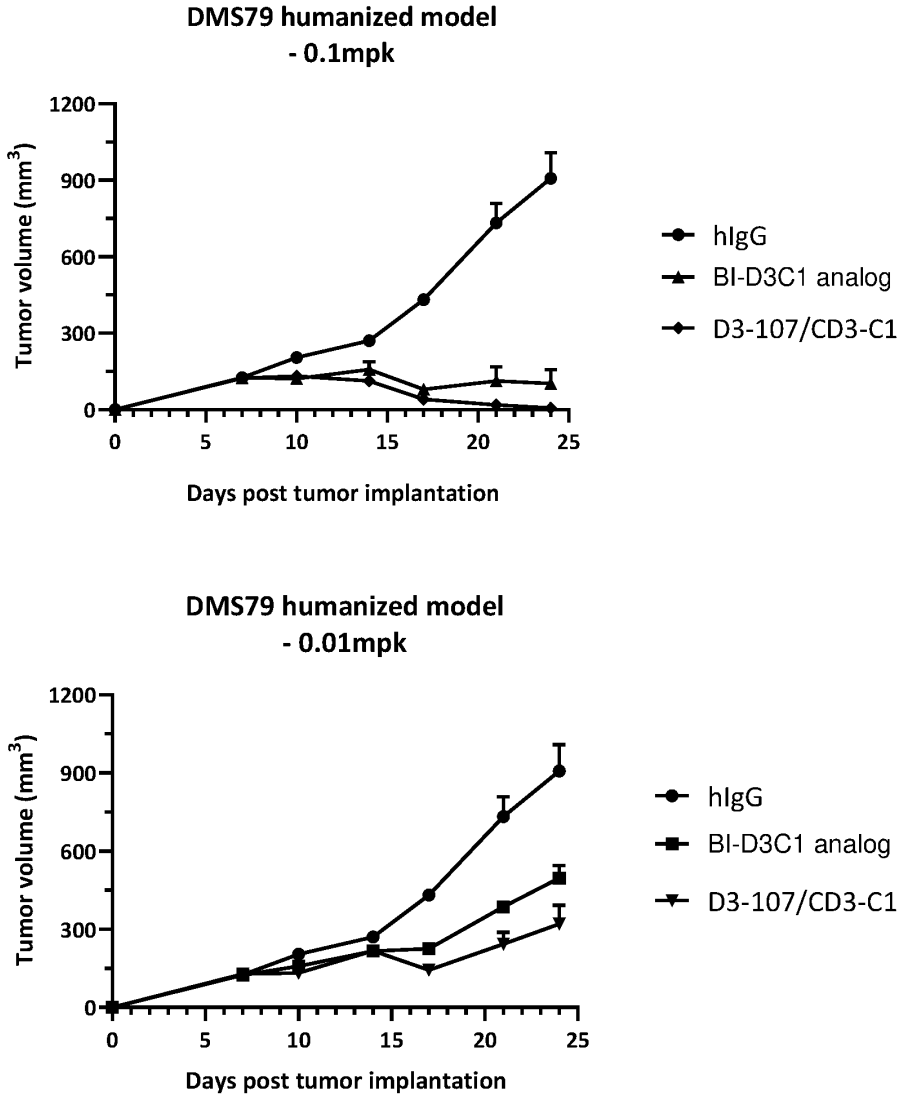
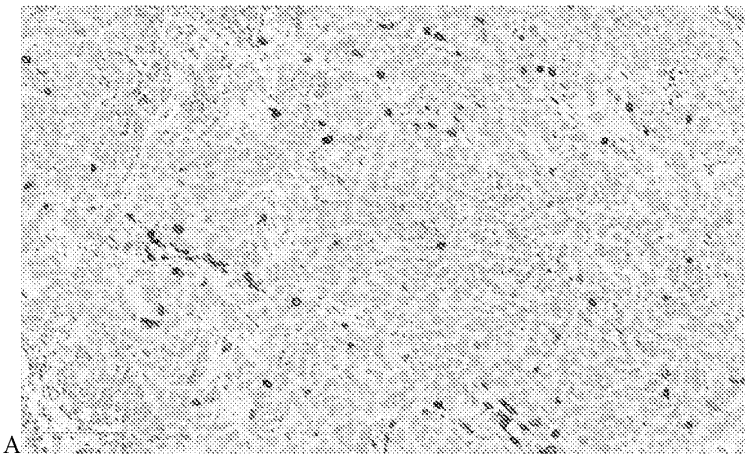
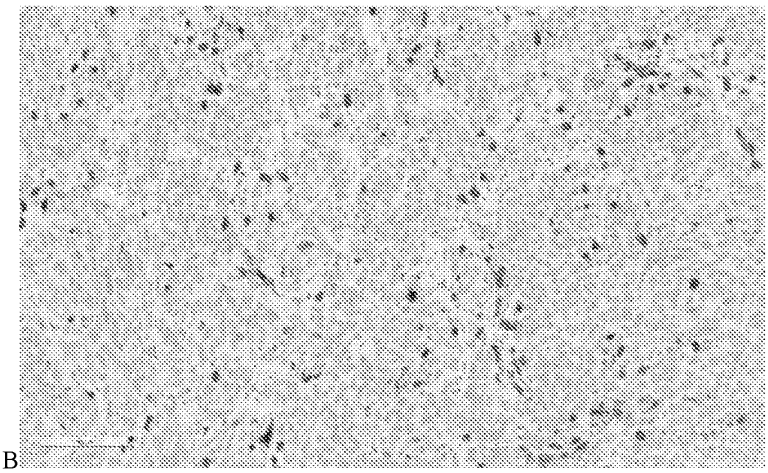

DMS79 humanized model
- 0.1mpk
Tumor volume (mm3)
1200
900
600
300
0
0
5
10
15
20
25
Days post tumor implantation
hIgG
BI-D3C1 analog
D3-107/CD3-C1
DMS79 humanized model
- 0.01mpk
Tumor volume (mm3)
1200
900
600
300
0
0
5
10
15
20
25
Days post tumor implantation
hIgG
BI-D3C1 analog
D3-107/CD3-C1

图 21

A



B



C

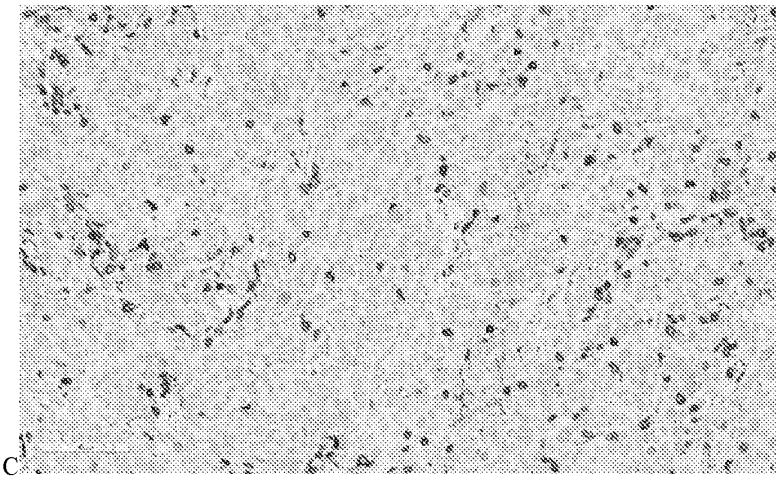


图 22

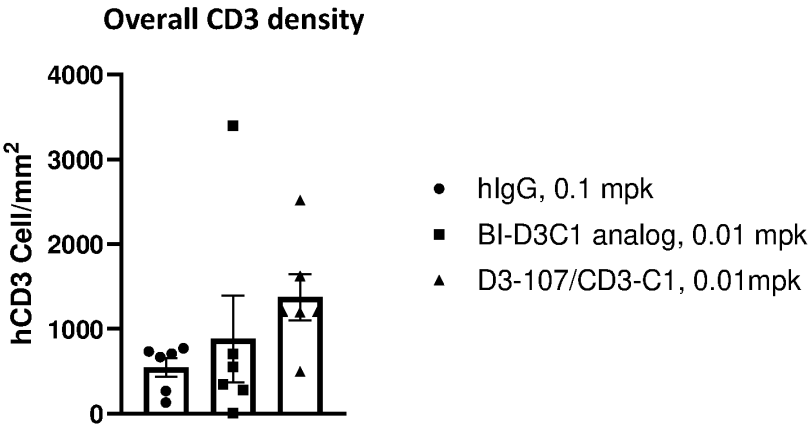
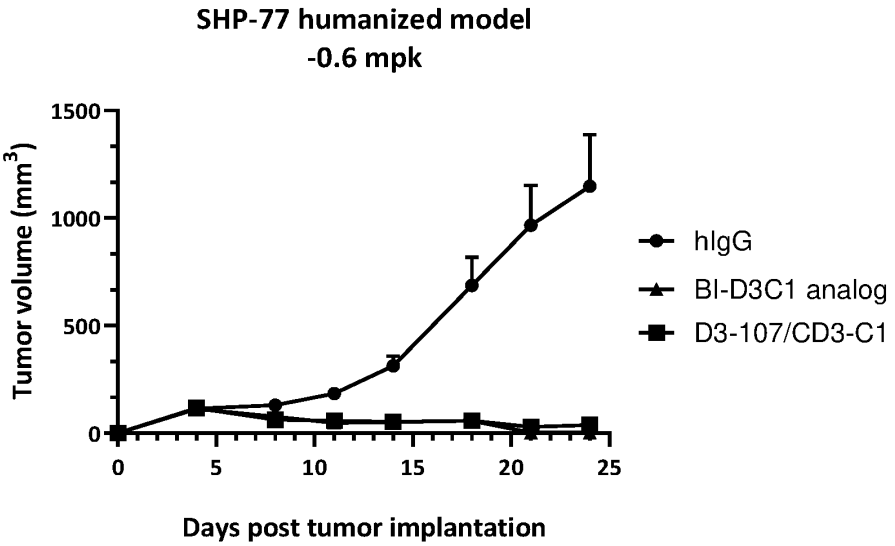

Overall CD3 density
hCD3 Cell/mm2
4000
3000
2000
1000
0
hIgG, 0.1 mpk
BI-D3C1 analog, 0.01 mpk
D3-107/CD3-C1, 0.01mpk

图 23


SHP-77 humanized model
-0.6 mpk
Tumor volume (mm3)
1500
1000
500
0
0
5
10
15
20
25
Days post tumor implantation
hIgG
BI-D3C1 analog
D3-107/CD3-C1

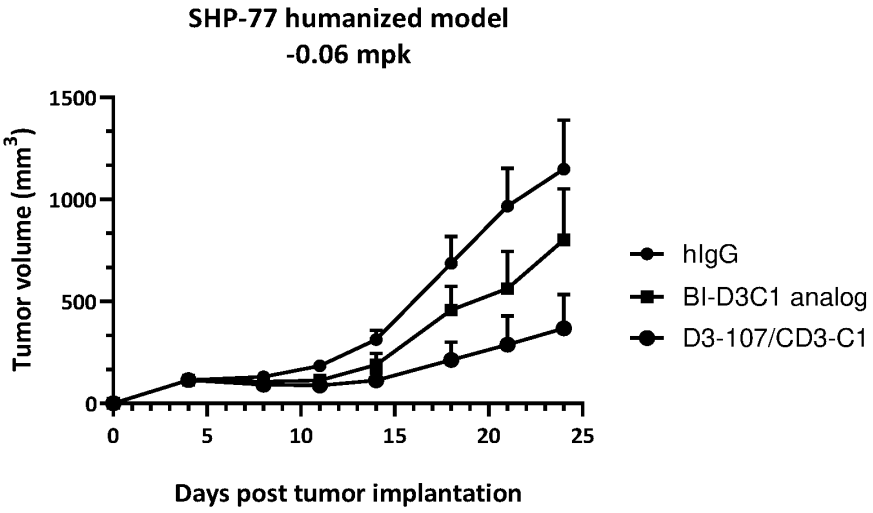

SHP-77 humanized model
-0.06 mpk
Tumor volume (mm3)
1500
1000
500
0
0
5
10
15
20
25
Days post tumor implantation
hIgG
BI-D3C1 analog
D3-107/CD3-C1

图 24

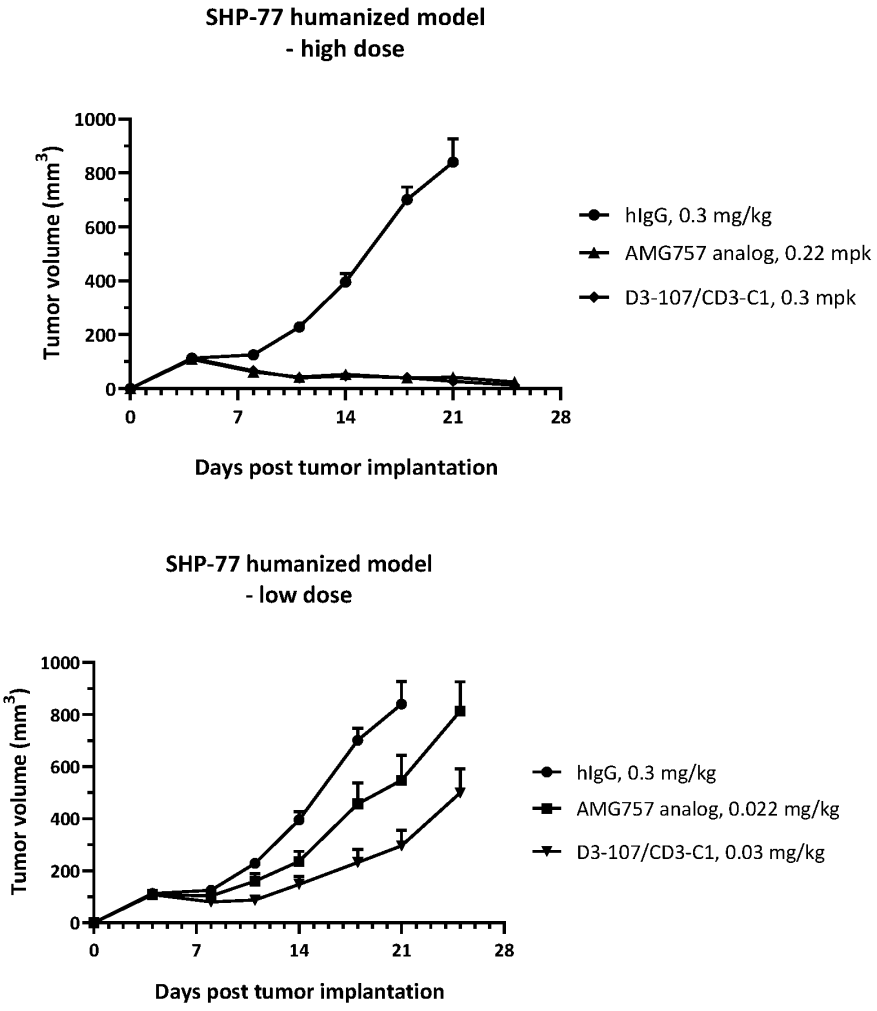

SHP-77 humanized model
- high dose
Tumor volume (mm3)
1000
800
600
400
200
0
0
7
14
21
28
Days post tumor implantation
hIgG, 0.3 mg/kg
AMG757 analog, 0.22 mpk
D3-107/CD3-C1, 0.3 mpk
SHP-77 humanized model
- low dose
Tumor volume (mm3)
1000
800
600
400
200
0
0
7
14
21
28
Days post tumor implantation
hIgG, 0.3 mg/kg
AMG757 analog, 0.022 mg/kg
D3-107/CD3-C1, 0.03 mg/kg

图 25

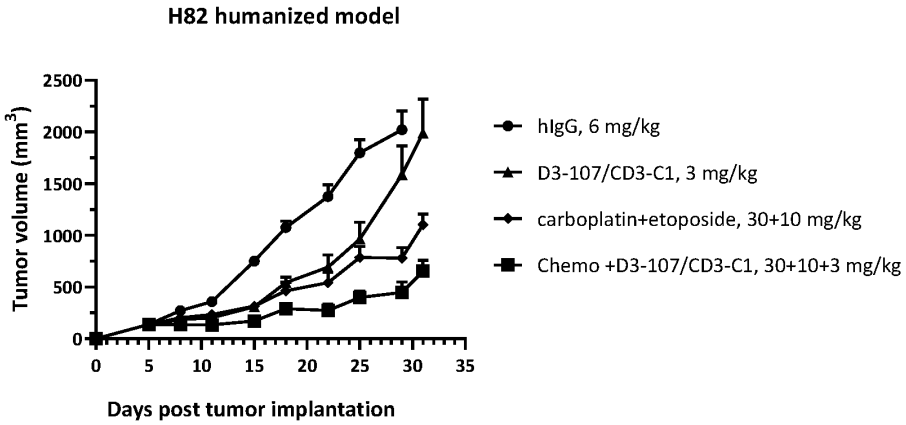

H82 humanized model
Tumor volume (mm3)
2500
2000
1500
1000
500
0
0
5
10
15
20
25
30
35
Days post tumor implantation
hIgG, 6 mg/kg
D3-107/CD3-C1, 3 mg/kg
carboplatin+etoposide, 30+10 mg/kg
Chemo +D3-107/CD3-C1, 30+10+3 mg/kg

图 26

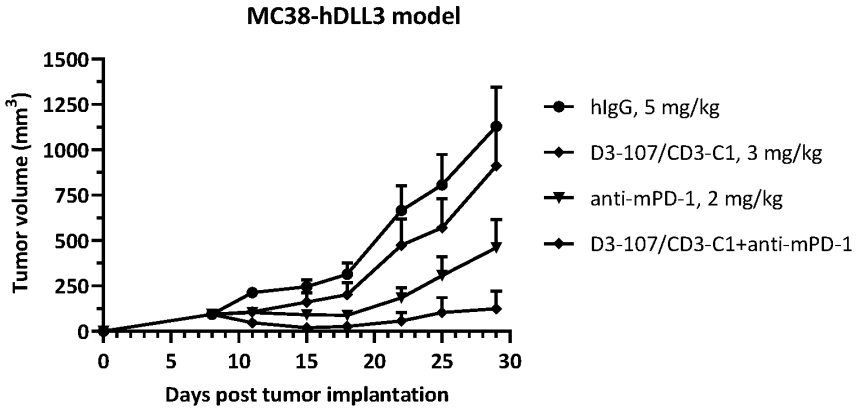

MC38-hDLL3 model
Tumor volume (mm3)
1500
1250
1000
750
500
250
0
0
5
10
15
20
25
30
Days post tumor implantation
hIgG, 5 mg/kg
D3-107/CD3-C1, 3 mg/kg
anti-mPD-1, 2 mg/kg
D3-107/CD3-C1+anti-mPD-1

图 27

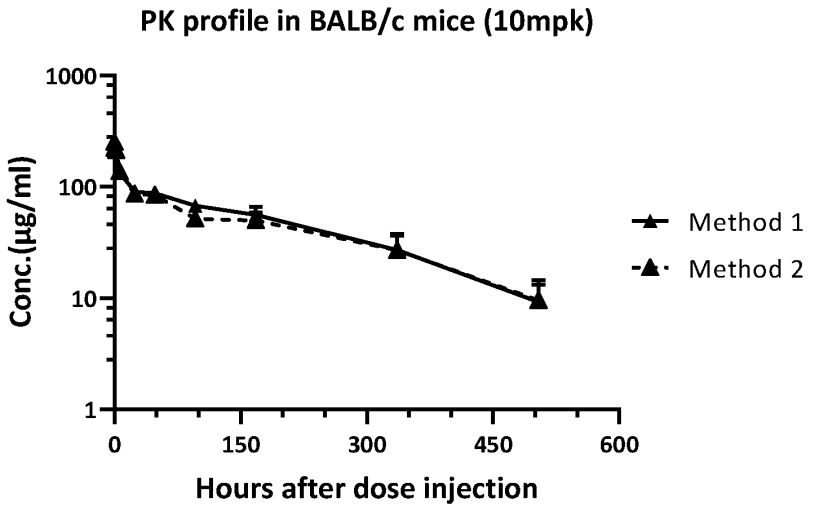

PK profile in BALB/c mice (10mpk)
Conc.(μg/ml)
1000
100
10
1
0
150
300
450
600
Hours after dose injection
Method 1
Method 2

图 28