Figure 1

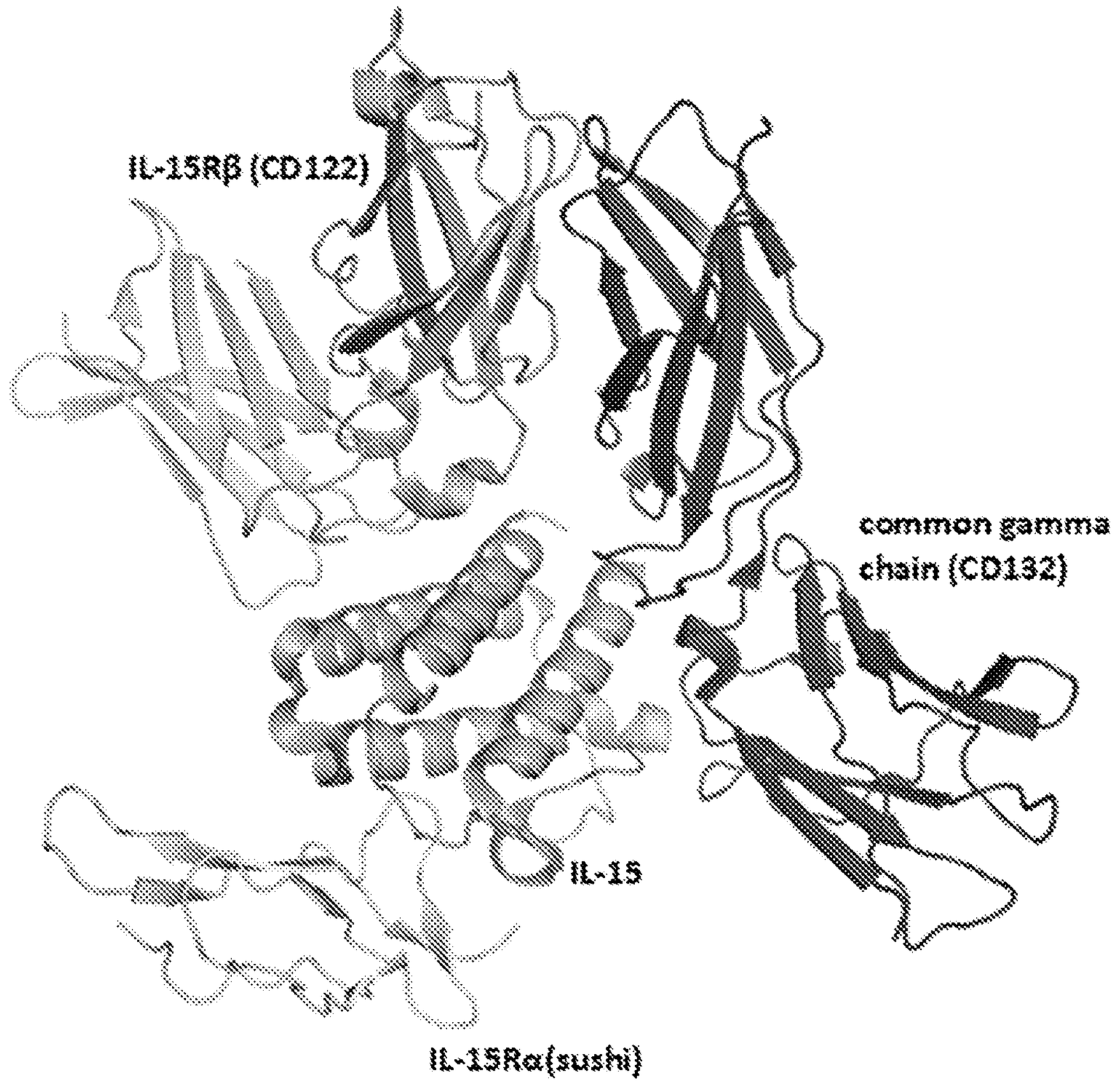


Figure 2A

Human IL-15 precursor sequence

>sp|P40933 (SEQ ID NO:1)
MRISKPHLRSISIQCYLCLLLNSHFLTEAGIHVFILGCFSAGLPKTEANWVNVISDLKKIEDLIQSMHIDATLYTES
DVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHI
VQMFINTS

Human IL-15 mature form sequence

>sp|P40933|49-162 (SEQ ID NO:2)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

Human IL-15Rα sequence

>sp|Q13261 (SEQ ID NO:3)
MAPRRARGCRTLGLPALLLLLLRPPATRGITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKAT
NVAHWTTPSLKCIRDPALVHQRPAPPSTVTTAGVTPQPESLSPSGKEPAASSPSSNNTAATTAAIVPGSQLMPSKSPST
GTTEISSHESSHGTPSQTTAKNWELTASASHQPPGVYPQGHSDTTVAISTSTVLLCGLSAVSLLACYLKSRQTPPLASVE
MEAMEALPVTWGTSSRDEDLENCSHHL

Human IL-15Rα, extracellular domain

>sp|Q13261|31-205 (SEQ ID NO:4)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPALVHQRPAPPSTV
TTAGVTPQPESLSPSGKEPAASSPSSNNTAATTAAIVPGSQLMPSKSPSTGTTEISSHESSHGTPSQTTAKNWELTASAS
HQPPGVYPQGHSDTT

Human IL-15Rα, sushi domain

>sp|Q13261|31-95 (SEQ ID NO:5)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR

Human IL-15Rß sequence

>sp|P14784 (SEQ ID NO:6)
MAAPALSWRLPLLILLLPLATSWASAAVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHAWPDRRRWNQTCELL
PVSQASWACNLILGAPDSQKLTTVDIVTLRVLCREGVRWRVMAIQDFKPFENLRLMAPISLQVVHVETHRCNISWEI
SQASHYFERHLEFEARTLSPGHTWEEAPLLTLKQKQEWICLETLTPDTQYEFQVRVKPLQGEFTTWSPWSQPLAFRT
KPAALGKDTIPWLGHLLVGLSGAFGFIILVYLLINCRNTGPWLKKVLKCNTPDPSKFFSQLSSEHGGDVQKWLSSPF
PSSSFSPGGLAPEISPLEVLERDKVTQLLLQQDKVPEPASLSSNHSLTSCFTNQGYFFFHLPDALEIEACQVYFTYD
PYSEEDPDEGVAGAPTGSSPQPLQPLSGEDDAYCTFPSRDDLLLFSPSLLGGPSPPSTAPGGSGAGEERMPPSLQER
VPRDWDPQPLGPPTPGVPDLVDFQPPPELVLREAGEEVPDAGPREGVSFPWSRPPGQGEFRALNARLPLNTDAYLSL
QELQGQDPTHLV

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Figure 2B

Human IL-15Rß, extracellular domain

>sp|P14784|27-240 (SEQ ID NO:7)
AVNGTSQFTCFYNSRANISCVWSQDGALQDTSCQVHAWPDRRRWNQTCELLPVSQASWACNLILGAPDSQKLTTVD
IVTLRVLCREGVRWRVMAIQDFKPFENLRLMAPISLQVVHVETHRCNISWEISQASHYFERHLEFEARTLSPGHTWEEA
PLLTLKQKQEWICLETLTPDTQYEFQVRVKPLQGEFTTWSPWSQPLAFRTKPAALGKDT

Human common gamma chain sequence

>sp|P31785 (SEQ ID NO:8)
MLKPSLPFTSLLFLQLPLLGVGLNTTILTPNGNEDTTADFFLTTMPTDSLSVSTLPLPEVQCFVFNVEYMNCTWNSSSEP
QPTNLTLHYWYKNSDNDKVQKCSHYLFSEEITSGCQLQKKEIHLYQTFVVQLQDPREPRRQATQMLKLQNLVIPWAPE
NLTLHKLSESQLELNWNNRFLNHCLEHLVQYRTDWDHSWTEQSVDYRHKFSLPSVDGQKRYTFRVRSRFNPLCGSAQ
HWSEWSHPIHWGSNTSKENPFLFALEAVVISVGSMGLIISLLCVYFWLERTMPRIPTLKNLEDLVTEYHGNFSAWSGVS
KGLAESLQPDYSERLCLVSEIPPKGGALGEGPGASPCNQHSPYWAPPCYTLKPET

Human common gamma chain, extracellular domain

>sp|P31785|23-262 (SEQ ID NO:9)
LNTTILTPNGNEDTTADFFLTTMPTDSLSVSTLPLPEVQCFVFNVEYMNCTWNSSSEPQPTNLTLHYWYKNSDNDKVQ
KCSHYLFSEEITSGCQLQKKEIHLYQTFVVQLQDPREPRRQATQMLKLQNLVIPWAPENLTLHKLSESQLELNWNNRFL
NHCLEHLVQYRTDWDHSWTEQSVDYRHKFSLPSVDGQKRYTFRVRSRFNPLCGSAQHWSEWSHPIHWGSNTSKENP
FLFALEA

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Figure 3A

Monomer 1	Monomer 2
F405A	T394F
S364D	Y349K
S364E	L368K
S364E	Y349K
S364F	K370G
S364H	Y349K
S364H	Y349T
S364Y	K370G
T411K	K370E
V397S/F405A	T394F
K370R/T411K	K370E/T411E
L351E/S364D	Y349K/L351K
L351E/S364E	Y349K/L351K
L351E/T366D	L351K/T366K
P395T/V397S/F405A	T394F
S364D/K370G	S364Y/K370R
S364D/T394F	Y349K/F405A
S364E/F405A	Y349K/T394F
S364E/F405S	Y349K/T394Y
S364E/T411E	Y349K/D401K
S364H/D401K	Y349T/T411E
S364H/F405A	Y349T/T394F
S364H/T394F	Y349T/F405A
Y349C/S364E	Y349K/S354C
L351E/S364D/F405A	Y349K/L351K/T394F
L351K/S364H/D401K	Y349T/L351E/T411E
S364E/T411E/F405A	Y349K/T394F/D401K
S364H/D401K/F405A	Y349T/T394F/T411E
S364H/F405A/T411E	Y349T/T394F/D401K

Figure 3B

Monomer 1	Monomer 2
K370E/T411D	T411K
L368E/K409E	L368K
Y349T/T394F/S354C	S364H/F405A/Y349C
T411E	D401K
T411E	D401R/T411R
Q347E/K360E	Q347R
L368E	S364K
L368E/K370S	S364K
L368E/K370T	S364K
L368E/D401R	S364K
L368E/D401N	S364K
L368E	E357S/S364K
L368E	S364K/K409E
L368E	S364K/K409V
L368D	S364K
L368D/K370S	S364K
L368D/K370S	S364K/E357L
L368D/K370S	S364K/E357Q
T411E/K360E/Q362E	D401K
K370S	S364K
L368E/K370S	S364K/E357Q
K370S	S364K/E357Q
T411E/K360D	D401K
T411E/K360E	D401K
T411E/Q362E	D401K
T411E/N390D	D401K
T411E	D401K/Q347K
T411E	D401K/Q347R
T411E/K360D/Q362E	D401K

Figure 3C

Monomer 1	Monomer 2
T411E/K360E/N390D	D401K
T411E/Q362E/N390D	D401K
T411E/Q347R	D401K/K360D
T411E/Q347R	D401K/K360E
T411E/K360	D401K/Q347K
T411E/K360D	D401K/Q347R
T411E/K360E	D401K/Q347K
T411E/K360E	D401K/Q347R
T411E/S364K	D401K/K370S
T411E/K370S	D401K/S364K
Q347E	E357Q
Q347E	E357Q/Q362K
K360D/Q362E	Q347R
K360D/Q362E	D401K
K360D/Q362E	Q347R/D401K
K360E/Q362E	Q347R
K360E/Q362E	D401K
K360E/Q362E	Q347R/D401K
Q362E/N390D	D401K
Q347E/K360D	D401N
K360D	Q347R/N390K
K360D	N390K/D401N
K360E	Y349H
K370S/Q347E	S364K
K370S/E357L	S364K
K370S/E357Q	S364K
K370S/Q347E/E357L	S364K
K370S/Q347E/E357Q	S364K

Figure 3D

Monomer 1	Monomer 2
L368D/K370S/Q347E	S364K
L368D/K370S/E357L	S364K
L368D/K370S/E357Q	S364K
L368D/K370S/Q347E/E357L	S364K
L368D/K370S/Q347E/E357Q	S364K
L368E/K370S/Q347E	S364K
L368E/K370S/E357L	S364K
L368E/K370S/E357Q	S364K
L368E/K370S/Q347E/E357L	S364K
L368E/K370S/Q347E/E357Q	S364K
L368D/K370T/Q347E	S364K
L368D/K370T/E357L	S364K
L368D/K370T/E357Q	S364K
L368D/K370T/Q347E/E357L	S364K
L368D/K370T/Q347E/E357Q	S364K
L368E/K370T/Q347E	S364K
L368E/K370T/E357L	S364K
L368E/K370T/E357Q	S364K
L368E/K370T/Q347E/E357L	S364K
L368E/K370T/Q347E/E357Q	S364K
T411E/Q362E	D401K/T411K
T411E/N390D	D401K/T411K
T411E/Q362E	D401R/T411R
T411E/N390D	D401R/T411R
Y407T	T366Y
F405A	T394W
T366Y/F405A	T394W/Y407T
Y407A	T366W
T366S/L368A/Y407V	T366W
T366S/L368A/Y407V/Y349C	T366W/S354C

Figure 3E

Monomer 1	Monomer 2
K392D/K409D	E356K/D399K
K370D/K392D/K409D	E356K/E357K/D399K
K247Q/R355Q/N384S/K392N/V397M/Q419E/K447_	P217R/P228R/N276K
K247Q/R355Q/N384S/K392N/V397M/Q419E/K447_	N276K
N384S/K392N/V397M/Q419E	N276K
D221E/P228E/L368E	D221R/P228R/K409R
C220E/P228E/L368E	C220R/E224R/P228R/K409R
F405L	K409R
T366I/K392M/T394W	F405A/Y407V
T366V/K409F	L351Y/Y407A
T366A/K392E/K409F/T411E	D399R/S400R/Y407A
L351K	L351E
K247Q/R355Q/Q419E/K447_	P217R/P228R/N276K
K247Q/R355Q/Q419E/K447_	N276K
K274Q/R355Q/N384S/K392N/V397M/Q419E/K447_	
Q295E/N384D/Q418E/N421D	
Q295E/Q418E/N421D	
P217R/P228R/N276K	
N276K	
E269Q/E272Q/E283Q/E357Q	
E269Q/E272Q/E283Q	
E269Q/E272Q	
E269Q/E283Q	
E272Q/E283Q	
E269Q	

Figure 4

Variant constant region	Substitutions
pI_ISO(-)-Fc only	K274Q/R355Q/N384S/K392N/V397M/Q419E/K447_
pI_(-)_isosteric A-Fc only	Q295E/N384D/Q418E/N421D
pI_(-)_isosteric_B-Fc only	Q295E/Q418E/N421D
pI_ISO(+RR)-Fc only	P217R/P228R/N276K
pI_ISO(+)-Fc only	N276K
pI_(+)_isosteric_A	E269Q/E272Q/E283Q/E357Q
pI_(+)_isosteric_B	E269Q/E272Q/E283Q
pI_(+)_isosteric_E269Q/E272Q	E269Q/E272Q
pI_(+)_isosteric_E269Q/E283Q	E269Q/E283Q
pI_(+)_isosteric_E272Q/E283Q	E272Q/E283Q
pI_(+)_isosteric_E269Q	E269Q

Figure 5

Ablation Variants
G236R
S239G
S239K
S239Q
S239R
V266D
S267K
S267R
H268K
E269R
299R
299K
K322A
A327G
A327L
A327N
A327Q
L328E
P329K
A330L
A330S/P331S
I332K
I332R
V266D/A327Q
V266D/P329K
S267R/A327Q
S267R/P329K
G236R/L328R
E233P/L234V/L235A/G236_/S239K
E233P/L234V/L235A/G236_/S267K
E233P/L234V/L235A/G236_/S239K/A327G
E233P/L234V/L235A/G236_/S267K/A327G
E233P/L234V/L235A/G236_
S239K/S267K
267K/P329K

Figure 6A

IL-15-Fc monomer (-)	IL-15Rα(sushi)-Fc monomer (+)
C220S	C220S
Heterodimer pI variants L368D/K370S	Heterodimer pI variants S364K/E357Q
Isosteric pI substitutions Q295E/N384D/Q418E/N421D	
FcKO E233P/L234V/L235A/G236_/S267K	FcKO E233P/L234V/L235A/G236_/S267K
±M428L/N434S	±M428L/N434S

Figure 6B

scIL-15/Rα-Fc monomer (-)	empty-Fc monomer (+)
C220S	C220S
Heterodimer pI variants L368D/K370S	Heterodimer pI variants S364K/E357Q
Isosteric pI substitutions Q295E/N384D/Q418E/N421D	
FcKO E233P/L234V/L235A/G236_/S267K	FcKO E233P/L234V/L235A/G236_/S267K
±M428L/N434S	±M428L/N434S

Figure 6C

empty-Fc monomer (-)	IL-15Rα(sushi)-Fc monomer (+)
C220S	C220S
Heterodimer pI variants L368D/K370S	Heterodimer pI variants S364K/E357Q
Isosteric pI substitutions Q295E/N384D/Q418E/N421D	
FcKO E233P/L234V/L235A/G236_/S267K	FcKO E233P/L234V/L235A/G236_/S267K
±M428L/N434S	±M428L/N434S

Figure 6D

IL-15Rα(sushi)-Fc Chain 1	IL-15Rα(sushi)-Fc Chain 2
C220S	C220S
FcKO E233P/L234V/L235A/G236_/S267K	FcKO E233P/L234V/L235A/G236_/S267K
±M428L/N434S	±M428L/N434S

Figure 6E

Fc-IL-15Rα(sushi) (-)	empty-Fc monomer (+)
C220S	C220S
Heterodimer pI variants L368D/K370S	Heterodimer pI variants S364K/E357Q
	Isosteric pI substitutions P217R/P228R/N276K
FcKO E233P/L234V/L235A/G236_/S267K	FcKO E233P/L234V/L235A/G236_/S267K
±M428L/N434S	±M428L/N434S

Figure 7

Name	Sequence	SEQ ID NO:
$(GGGGS)_1$ or GGGGS	GGGGS	27
$(GGGGS)_2$	GGGGSGGGGS	28
$(GGGGS)_3$	GGGGSGGGGSGGGGS	30
$(GGGGS)_4$	GGGGSGGGGSGGGGSGGGGS	29
$(GGGGS)_5$	GGGGSGGGGSGGGGSGGGGSGGGGS	32
$(GGGGS)_6$	GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS	31
$(GGGGS)_7$	GGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS	35
30AA-linker	DPALVHQRPAPPGGGGSGGGGSGGGGSGGG	36
$(GKPGS)_1$ or GKPGS	GKPGS	37
$(GKPGS)_5$	GKPGSGKPGSGKPGSGKPGSGKPGS	34
$(GKPGS)_6$	GKPGSGKPGSGKPGSGKPGSGKPGSGKPGS	33
$(GGGES)_1$ or GGGES	GGGES	38

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Figure 8A

IL-15/Rα-Fc Backbone 1

>IL-15/Rα-Fc monomer 1 (SEQ ID NO:39)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>IL-15/Rα-Fc monomer 2 (SEQ ID NO:40)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEE
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPS
DIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

IL-15/Rα-Fc Backbone 2

>IL-15/Rα-Fc monomer 1 (SEQ ID NO:41)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>IL-15/Rα-Fc monomer 2 (SEQ ID NO:42)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEE
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPS
DIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

IL-15/Rα-Fc Backbone 3

>IL-15/Rα-Fc monomer 1 (SEQ ID NO:43)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>IL-15/Rα-Fc monomer 2 (SEQ ID NO:44)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEE
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCEVSGFYPS
DIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

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Figure 8B

IL-15/Rα-Fc Backbone 4

>IL-15/Rα-Fc monomer 1 (SEQ ID NO:45)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSKGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>IL-15/Rα-Fc monomer 2 (SEQ ID NO:46)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEE
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTENEVSLTCLVKGFYPS
DIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLEVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

IL-15/Rα-Fc Backbone 5

>IL-15/Rα-Fc monomer 1 (SEQ ID NO:47)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDQLTKNQVKLTCLVKGFYP
SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>IL-15/Rα-Fc monomer 2 (SEQ ID NO:48)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEE
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCDVSGFYPS
DIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

IL-15/Rα-Fc Backbone 6

>IL-15/Rα-Fc monomer 1 (SEQ ID NO:49)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREE
QYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>IL-15/Rα-Fc monomer 2 (SEQ ID NO:50)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEE
YASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPS
DIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

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Figure 8C

IL-15/Rα-Fc Backbone 7

>IL-15/Rα-Fc monomer 1 (SEQ ID NO:51)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREE
QYSSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>IL-15/Rα-Fc monomer 2 (SEQ ID NO:52)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEE
YSSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPS
DIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

IL-15/Rα-Fc Backbone 8

>IL-15/Rα-Fc monomer 1 (SEQ ID NO:53)
ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQF
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEQMTKNQVKLTCLVKGFYPS
DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

>IL-15/Rα-Fc monomer 2 (SEQ ID NO:54)
ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEEFN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCDVSGFYPSDI
AVEWESDGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWEEGDVFSCSVMHEALHNHYTQKSLSLSLGK

IL-15/Rα-Fc Backbone 9

>IL-15/Rα-Fc monomer 1 (SEQ ID NO:55)
ERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFN
STFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>IL-15/Rα-Fc monomer 2 (SEQ ID NO:56)
ERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEEFN
STFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDI
AVEWESDGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

IL-15/Rα-Fc Backbone 10

>IL-15/Rα-Fc monomer 1 (SEQ ID NO:57)
ERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVQFNWYVDGVEVHNAKTKPREEQFN
STFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Figure 8D

>IL-15/Rα-Fc monomer 2 (SEQ ID NO:58)
ERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVQFNWYVDGVEVHNAKTKPREEEFN
STFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDI
AVEWESDGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

IL-15/Rα-Fc Backbone 11

>IL-15/Rα-Fc monomer 1 (SEQ ID NO:59)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

>IL-15/Rα-Fc monomer 2 (SEQ ID NO:60)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEE
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPS
DIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK

IL-15/Rα-Fc Backbone 12

>IL-15/Rα-Fc monomer 1 (SEQ ID NO:61)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>IL-15/Rα-Fc monomer 2 (SEQ ID NO:62)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

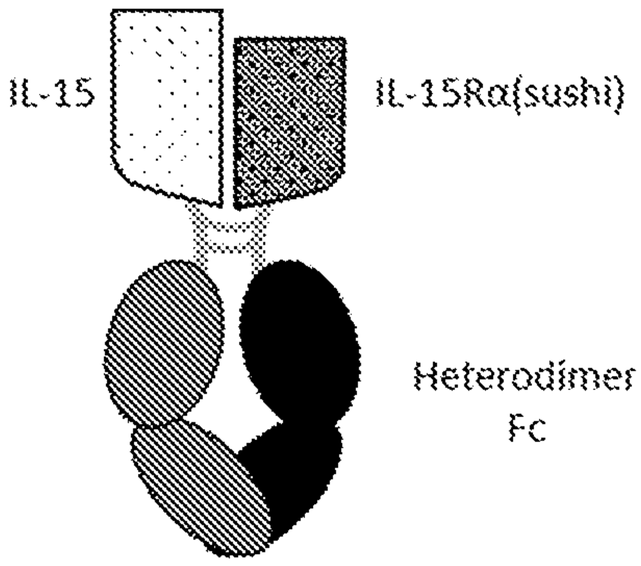
IL-15/Rα-Fc Backbone 13

>IL-15/Rα-Fc monomer 1 (SEQ ID NO:63)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEE
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPS
DIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

>IL-15/Rα-Fc monomer 2 (SEQ ID NO:64)
ERKSSDKTHTCPRCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFKWYVDGVEVHNAKTKPREEQ
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYP
SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

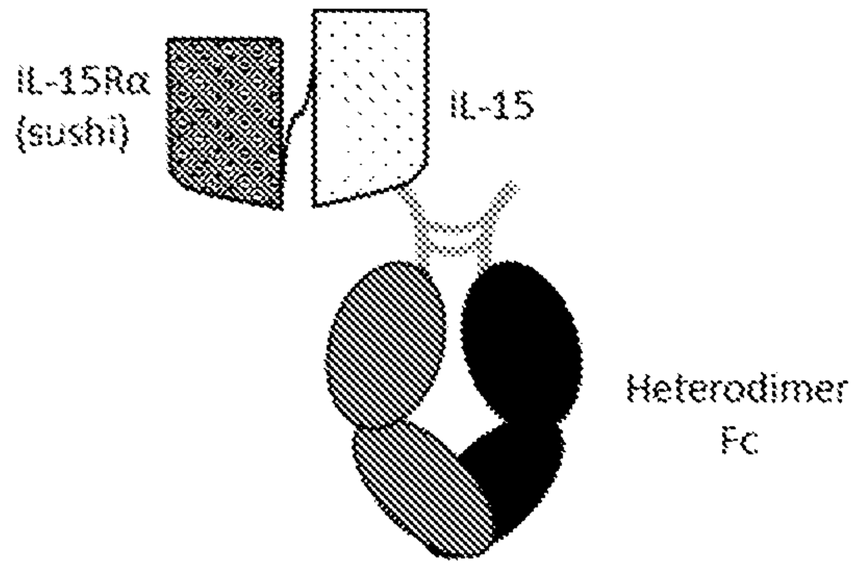
RECTIFIED SHEET (RULE 91) ISA/EP

Figure 9A



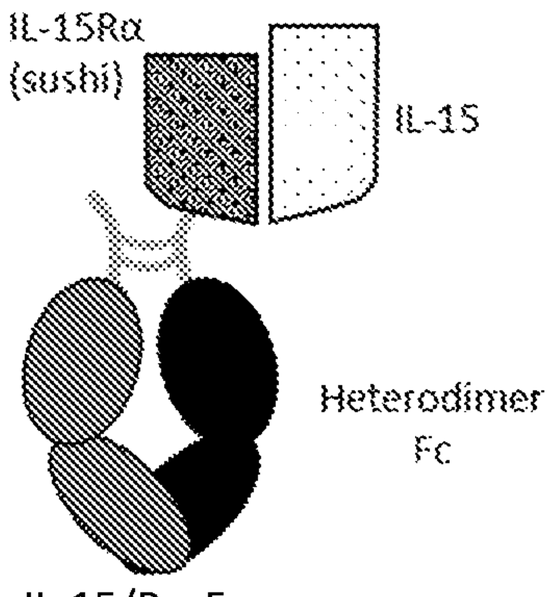
IL-15/Rα-heteroFc
Example: XENP20818

Figure 9B



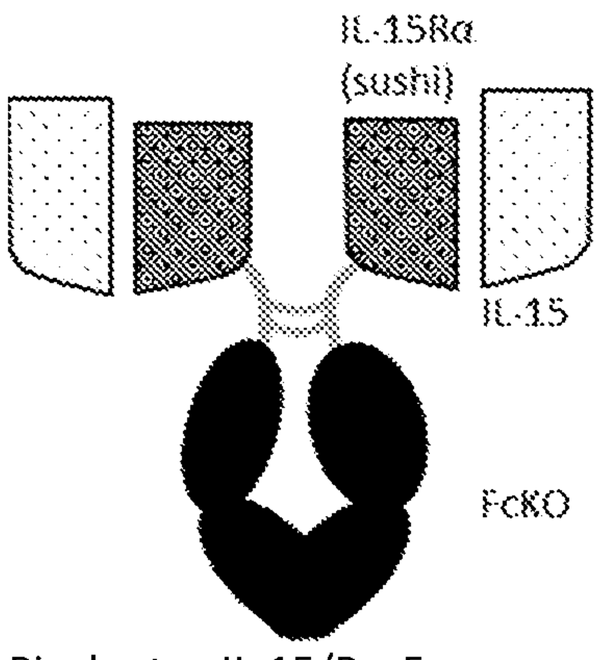
scIL-15/Rα-Fc
Example: XENP21478

Figure 9C



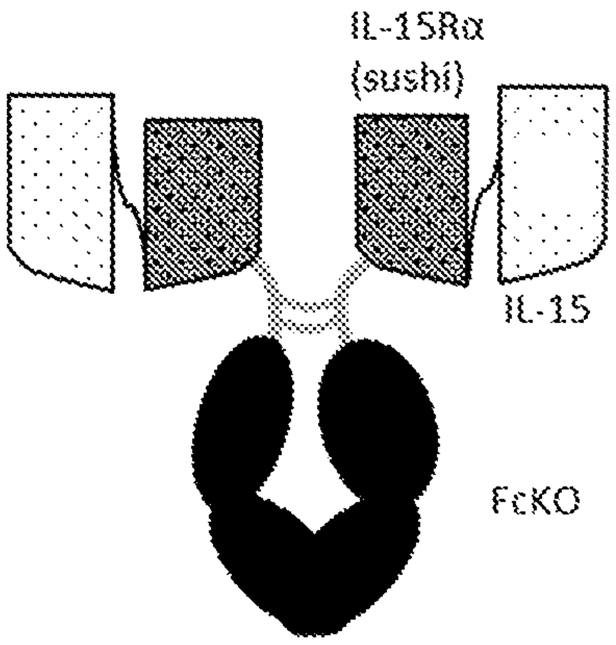
ncIL-15/Rα-Fc
Example: XENP21479

Figure 9D



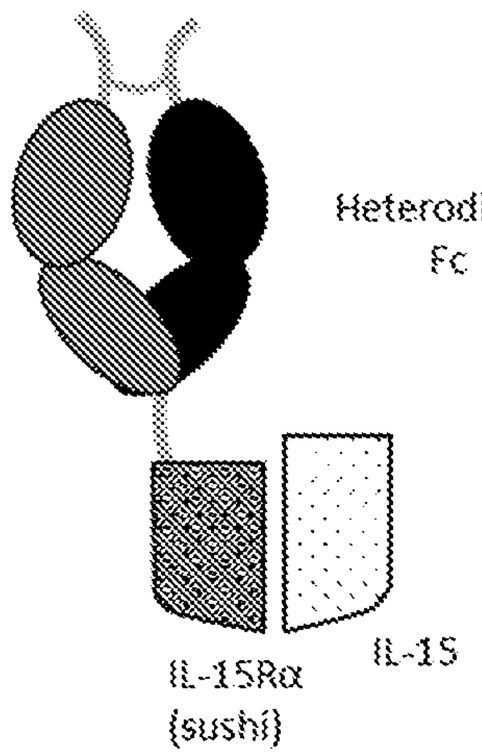
Bivalent ncIL-15/Rα-Fc
Example: XENP21978

Figure 9E



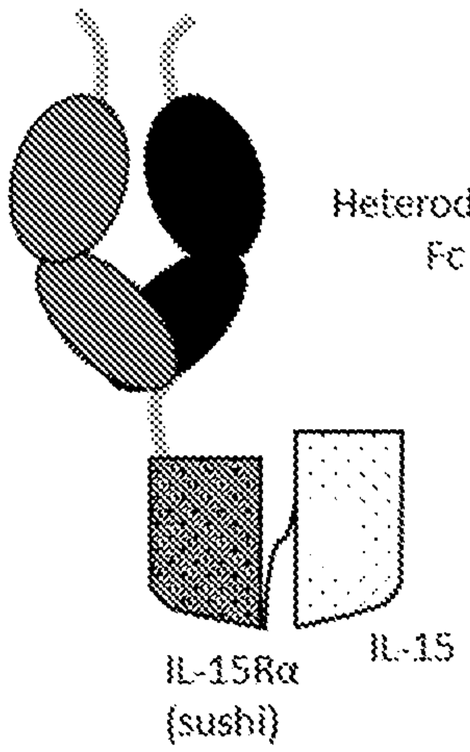
Bivalent scIL-15/Rα-Fc

Figure 9F



Fc-ncIL-15/Rα
Example: XENP22637

Figure 9G



Fc-scIL-15/Rα

Figure 10

>XENP20818 – human IL15-$(GGGGS)_1$ x human IL15Rα(Sushi)-$(GGGGS)_1$ Fc heterodimer

Chain 1 - human_IL15_$(GGGGS)_1$_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (15902) (SEQ ID NO:65)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - human_IL15Rα(Sushi)_$(GGGGS)_1$_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (15908) (SEQ ID NO:66)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGS/EPKSSDKTH
TCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
>XENP21475 – human IL15 x human IL15Rα(Sushi) Fc heterodimer

Chain 1 - human_IL15-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (16479) (SEQ ID NO:67)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVD
VKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
REPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGD
VFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - human_IL15Rα(Sushi)-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (16481) (SEQ ID NO:68)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/EPKSSDKTHTCPPCP
APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Figure 11

>XENP21478 – human IL15Rα(Sushi)-$(GGGGS)_6$-human IL15(single-chain) Fc heterodimer

Chain 1 - human_IL15Rα(sushi)_$(GGGGS)_6$-human_IL15-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (16478) (SEQ ID NO:69)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS/NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - empty-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (8924) (SEQ ID NO:70)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 12A

>XENP21479 – empty-Fc-IL15(non-covalent)-human_IL15Rα(Sushi) Fc heterodimer

Chain 1 - human_IL15_no_tag (16484) (SEQ ID NO:71)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

Chain 2 - empty-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (8793) (SEQ ID NO:72)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEE
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPS
DIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 3 - human_IL15Rα(Sushi)-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (16481) (SEQ ID NO:73)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/EPKSSDKTHTCPPCP
APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
>XENP022366 – empty-Fc-IL15(non-covalent)-human_IL15Ra(sushi)_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15_no_tag (16484) (SEQ ID NO:74)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

Chain 2 - empty-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (8793) (SEQ ID NO:75)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEE
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPS
DIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 3 - human_IL15Ra(Sushi)_(GGGGS)1_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (15908) (SEQ ID NO:76)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGS/EPKSSDKTH
TCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 12B

>XENP024348 IL15(non-covalent)-human_IL15Ra(Sushi)_empty-Fc_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 – IL15 WT (SEQ ID NO:77)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

Chain 2 – human_IL15Ra(Sushi)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S
(SEQ ID NO:78)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/EPKSSDKTHTCPPCP
APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 3 – empty_ Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:79)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Figure 13

>XENP021978 – human_IL15(non-covalent)-human_IL15Ra(Sushi)_Fc(216)_IgG1_C220S/PVA_/S267K

Chain 1 - human_IL15Ra(Sushi)-Fc(216)_IgG1_C220S/PVA_/S267K (17023) (SEQ ID NO:80)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/EPKSSDKTHTCPPCP
APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - human_IL15_no_tag (16484) (SEQ ID NO:81)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 14

human_IL15Ra(sushi)(single-chain)-human_IL15_Fc(216)_IgG1_C220S/PVA_/S267K (SEQ ID NO:82)

ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGS/NWVNVISD
LKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEEL
EEKNIKEFLQSFVHIVQMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEV
KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL
PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPGK

Figure 15

>XENP022637 – empty-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S_(GGGGS)2_IL15Ra(Sushi)_IL15(non-covalent)_IgG1_ISO(+RR)_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - empty-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S_(GGGGS)2_IL15Ra(Sushi) (17603) (SEQ ID NO:83)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEE
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPS
DIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK/GGGGS
GGGGS/ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR

Chain 2 - empty-Fc(216)_IgG1_ISO(+RR)_C220S/PVA_/S267K/S364K/E357Q (8927) (SEQ ID NO:84)
ERKSSDKTHTCPRCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFKWYVDGVEVHNAKTKPREEQ
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYP
SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 3 - human_IL15_no_tag (16484) (SEQ ID NO:85)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

Figure 16

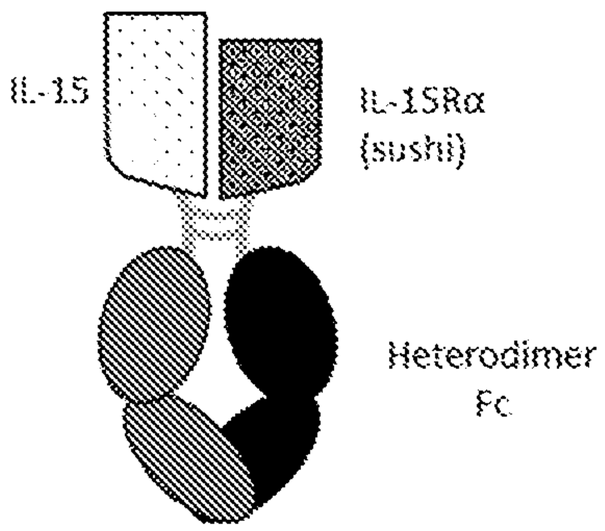
empty-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S_(GGGGS)2_IL15Ra(Sushi)_IL15(single-chain)_IgG1_ISO(+RR)_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - empty-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S_(GGGGS)2_IL15Ra(Sushi)_IL15(single-chain) (SEQ ID NO:86)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEE
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPS
DIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK/GGGGS
GGGGS/ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGS/N
WVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTES
GCKECEELEEKNIKEFLQSFVHIVQMFINTS

Chain 2 - empty-Fc(216)_IgG1_ISO(+RR)_C220S/PVA_/S267K/S364K/E357Q (8927) (SEQ ID NO:87)
ERKSSDKTHTCPRCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFKWYVDGVEVHNAKTKPREEQ
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYP
SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

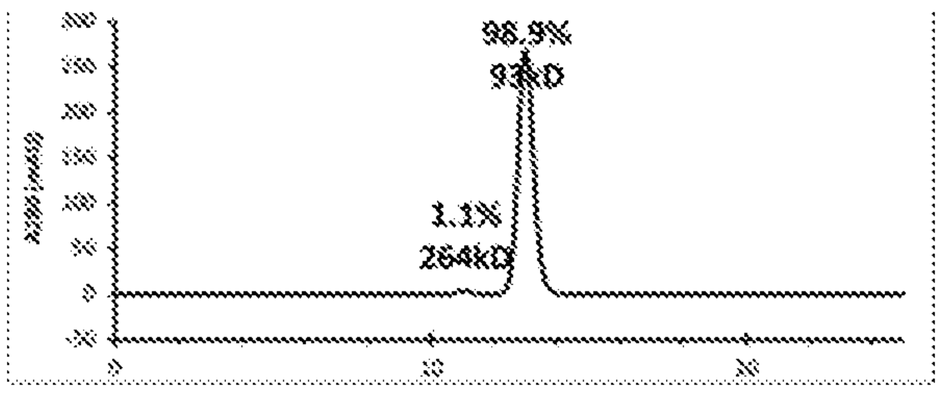
RECTIFIED SHEET (RULE 91) ISA/EP

Figure 17A



XENP20818

Figure 17B



pI(MW) = 6.41 (72.7 kDa)
Protein A yield = 25.7 mg/L

Figure 17C

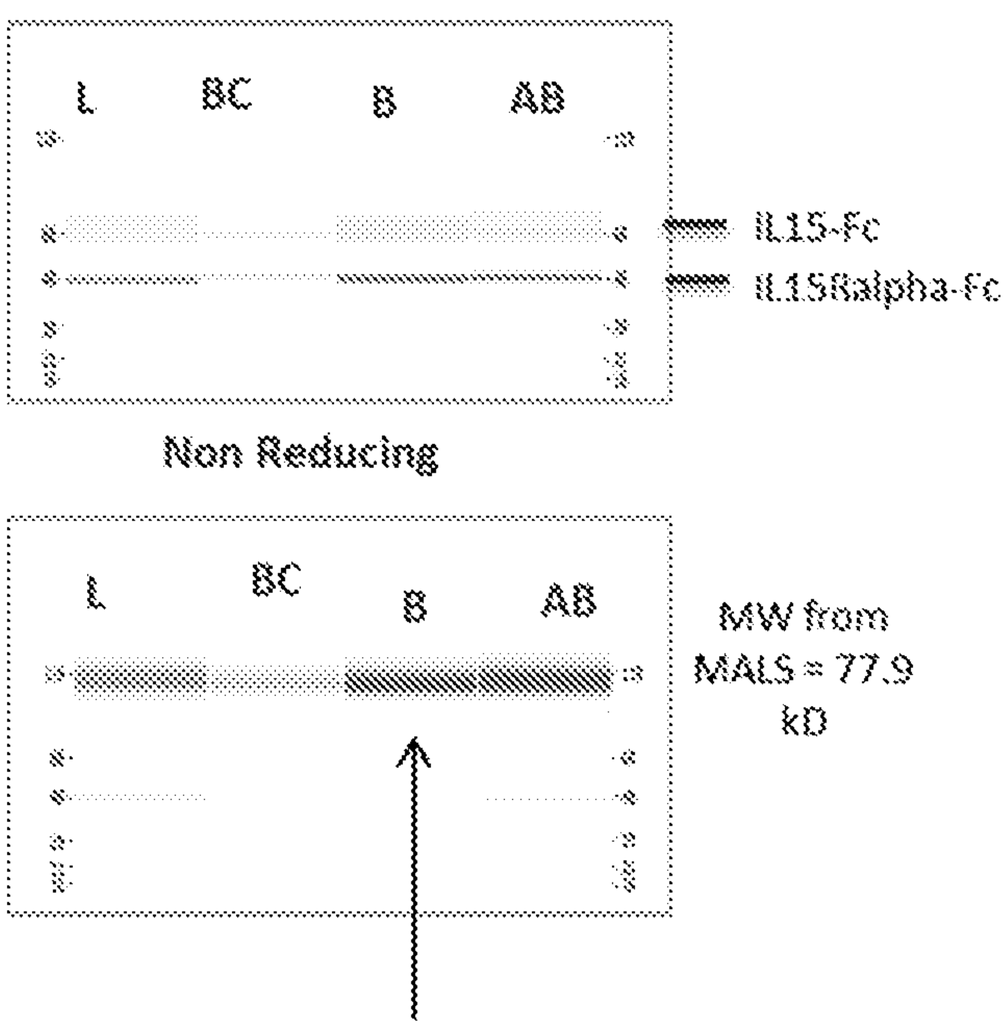
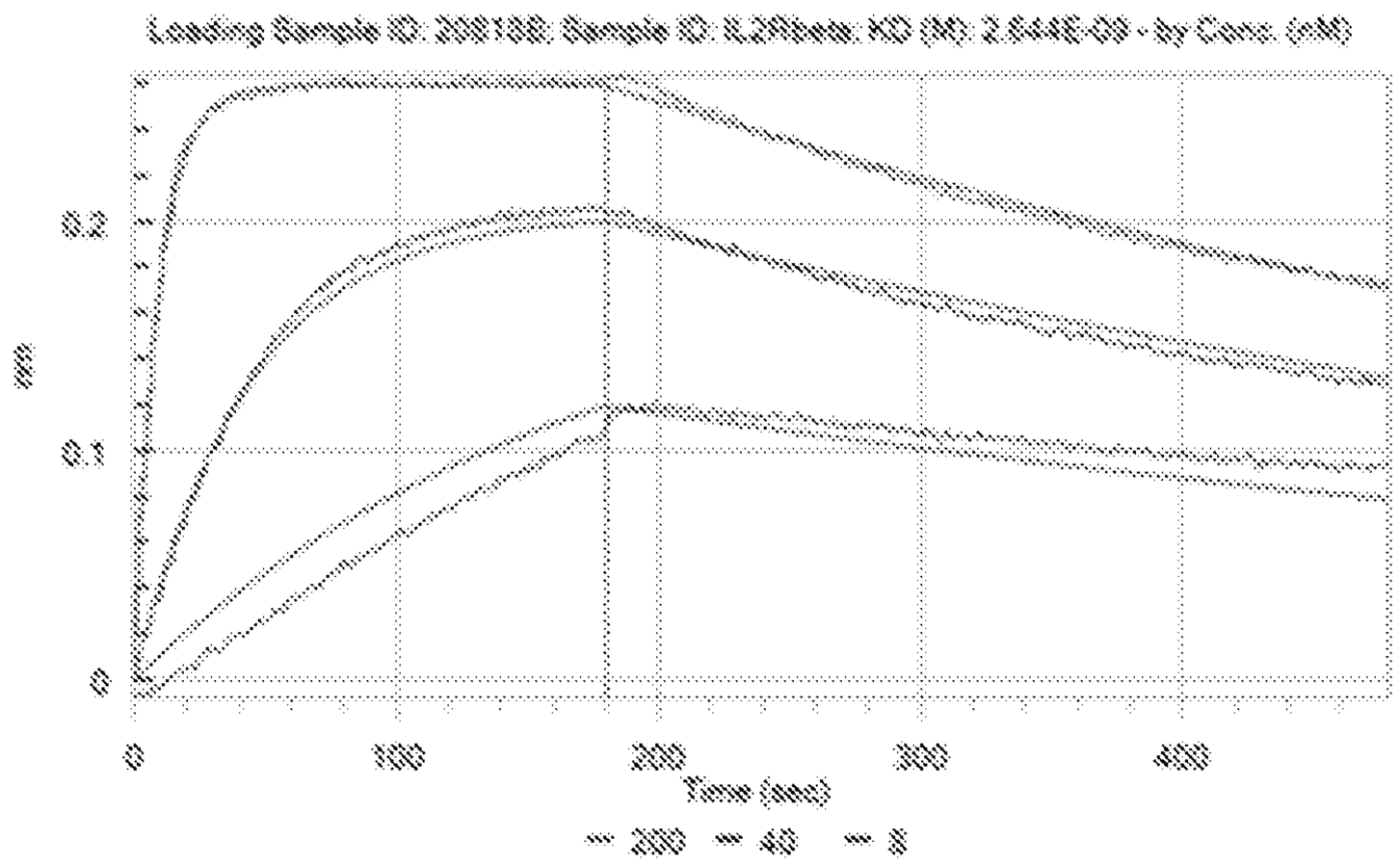


Figure 17D



Octet Red 96 – AHC capture of XENP20818; dip in 200 nM, 40 nM, or 8 nM IL2-Rβ (R&D systems); KD ~ 3 nM

Figure 17E

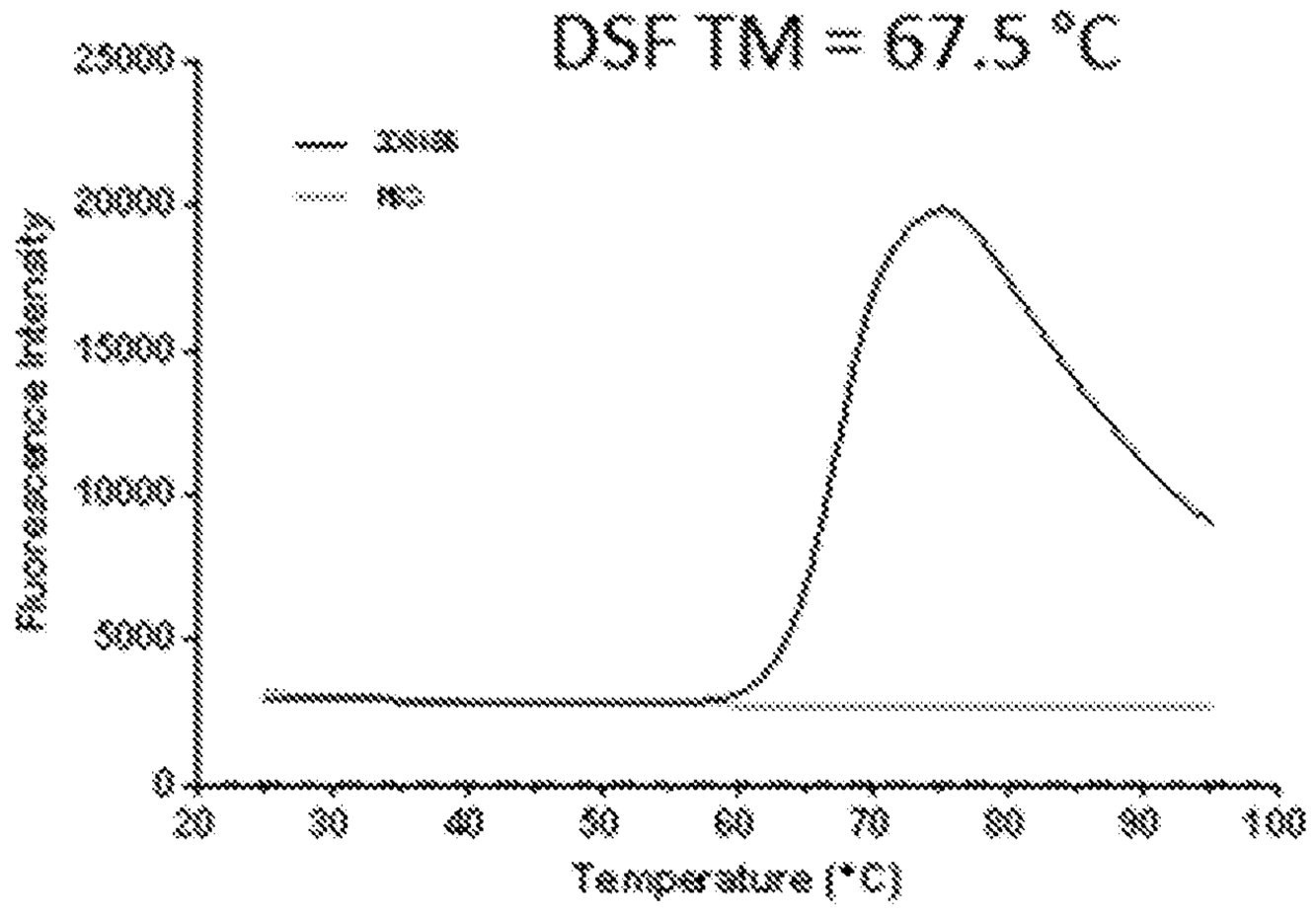


Figure 18A

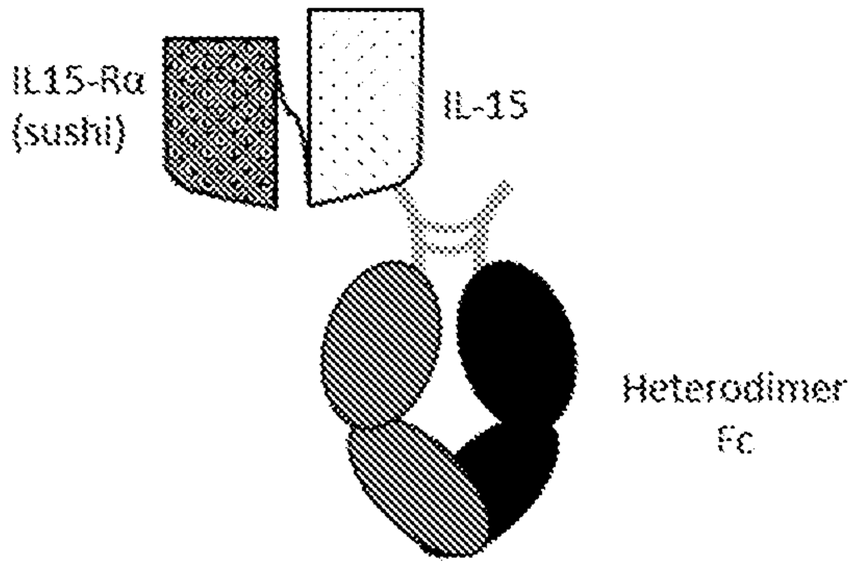
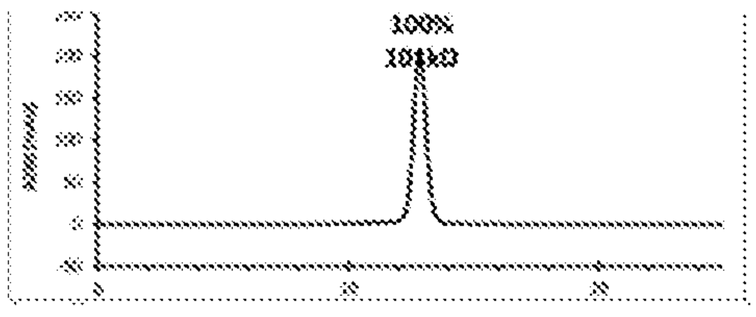
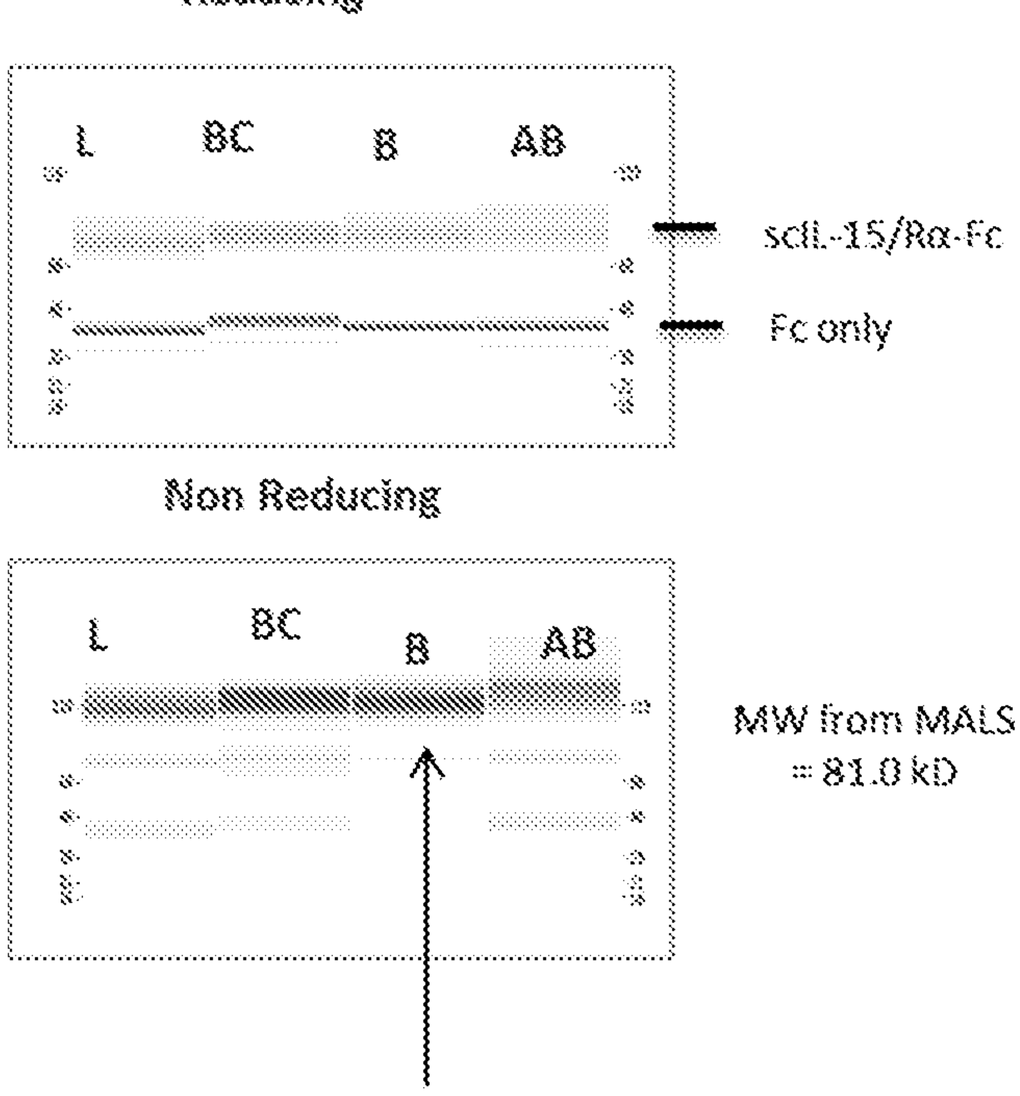


Figure 18B



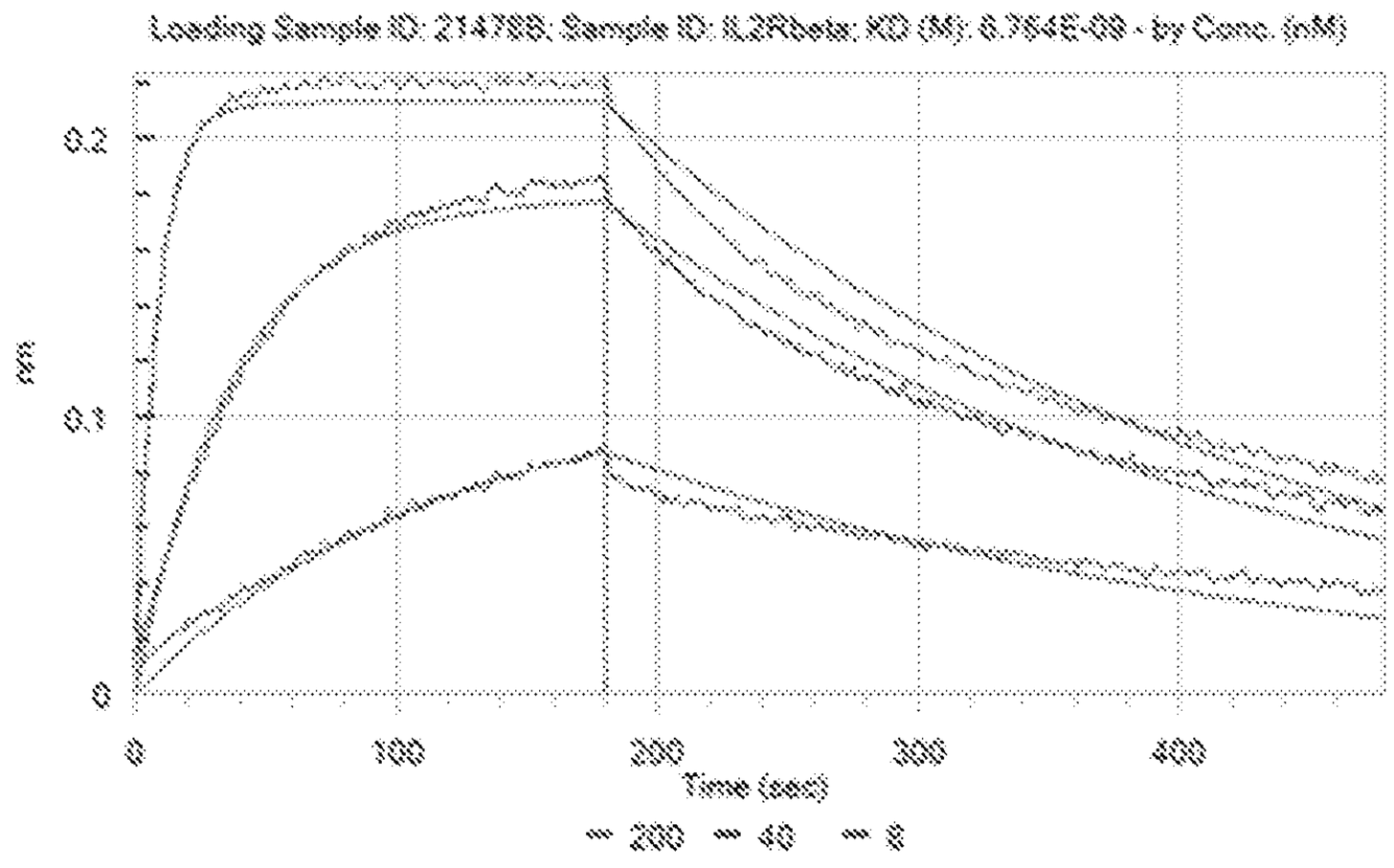
pI(MW) = 6.41 (74.0 kDa)
Protein A yield = 68.1 mg/L

Figure 18C



Purified
XENP21478

Figure 18D



Octet Red 96 – AHC capture of XENP21478; dip in 200 nM, 40 nM, or 8 nM IL2Rβ (R&D systems); KD ~ 3 nM

Figure 18E

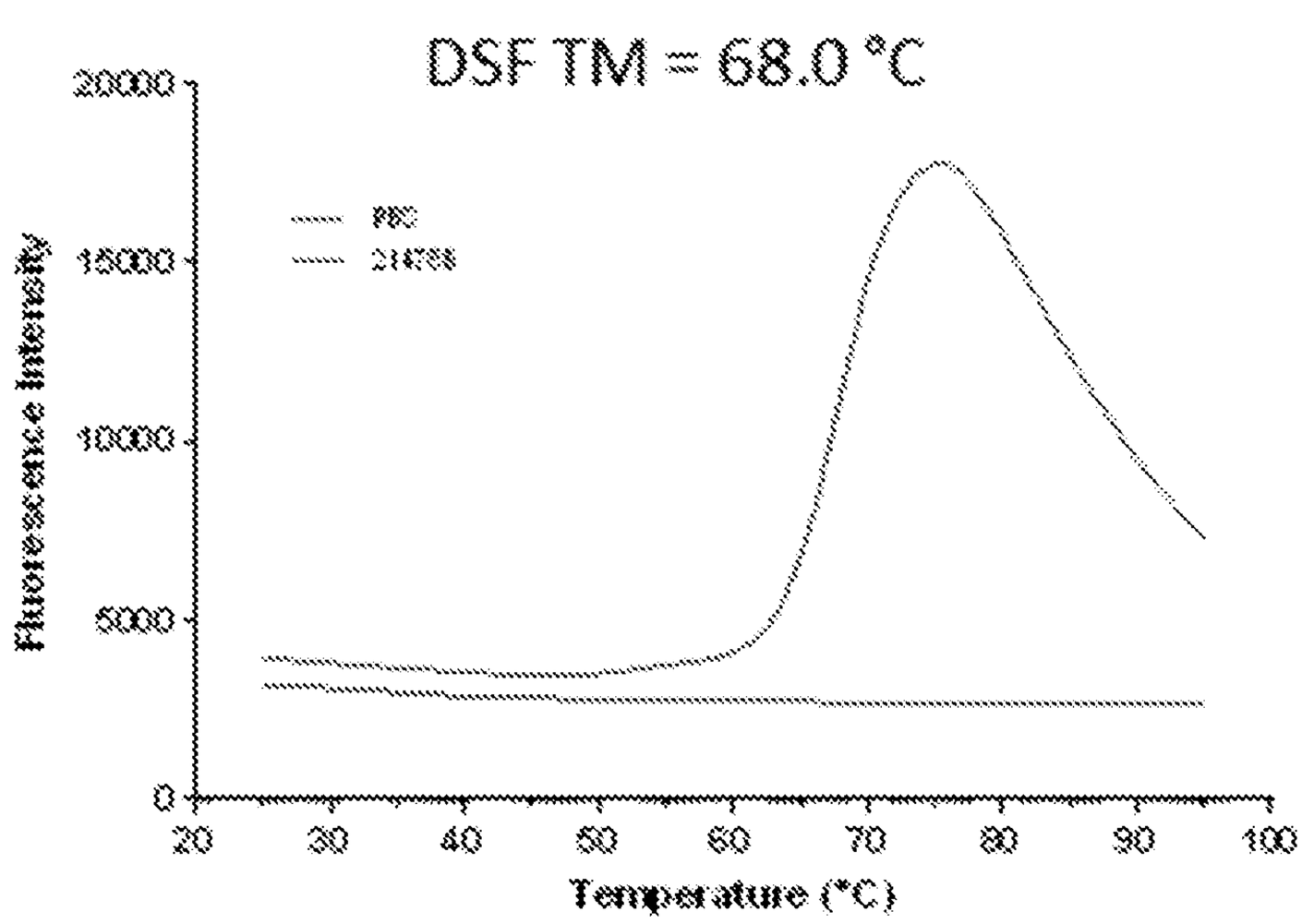


Figure 19A

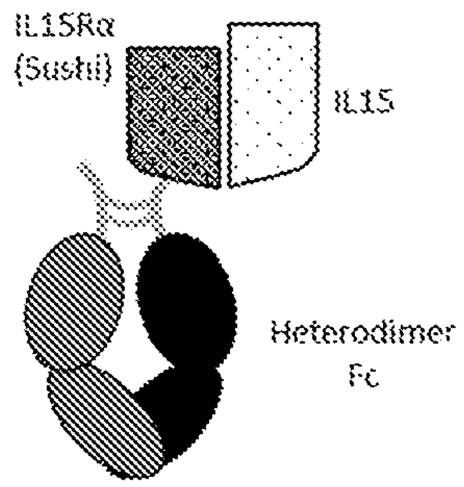
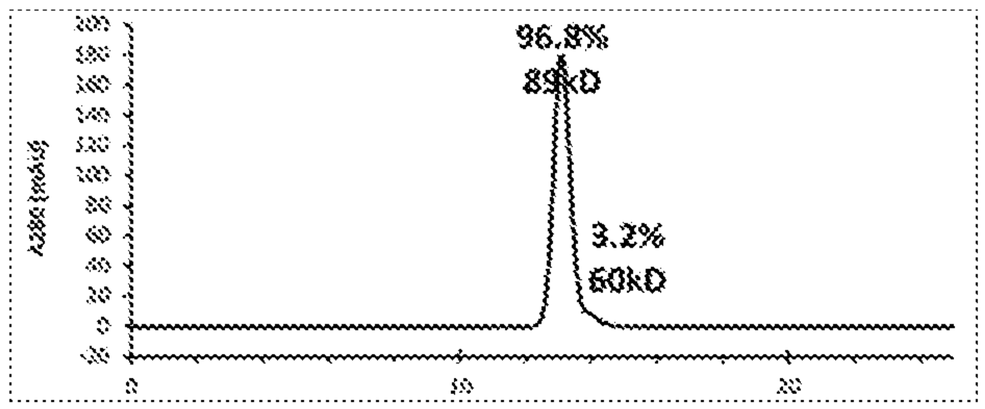


Figure 19B



pI(MW) = 6.41 (72.1 kDa)
Protein A yield = 57.1 mg/L

Figure 19C

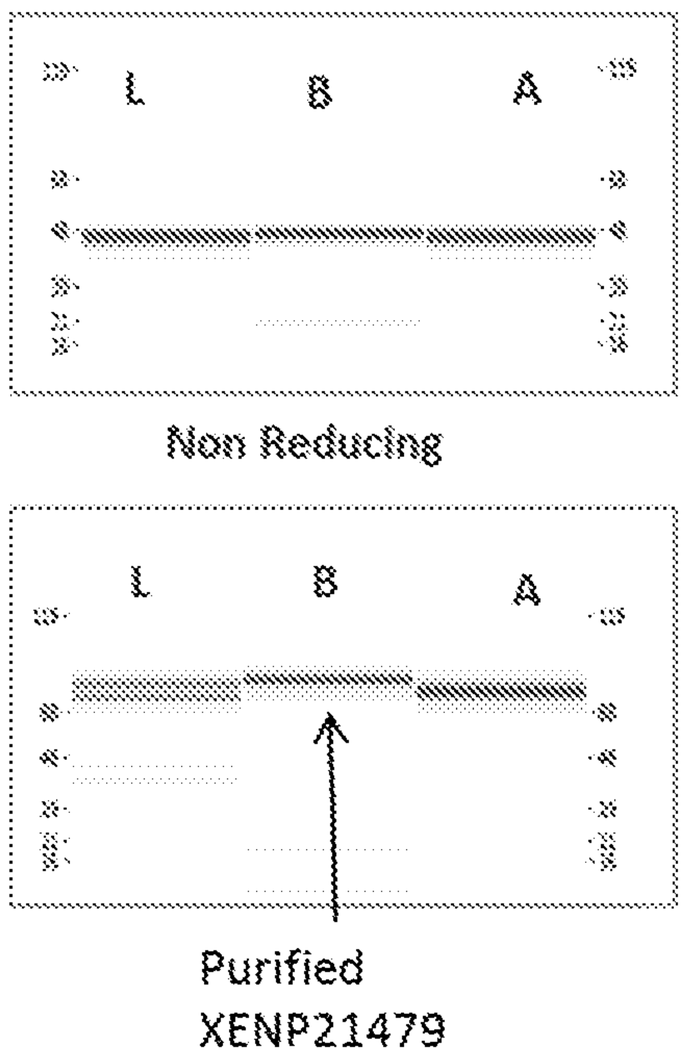
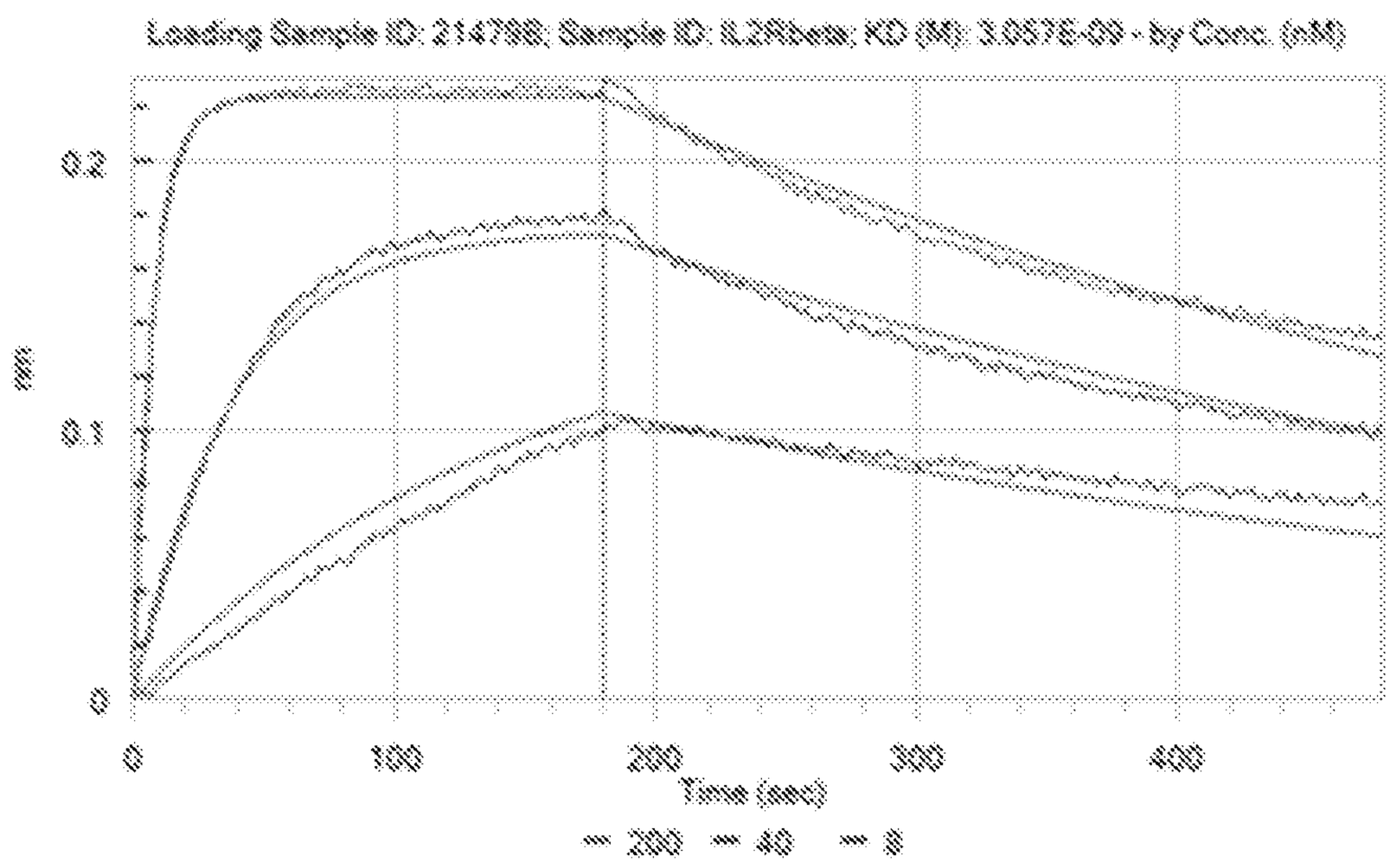


Figure 19D



Octet Red 96 – AHC capture of XENP21479; dip in 200 nM, 40 nM, or 8 nM IL2Rβ (R&D systems); KD ~ 3 nM

Figure 19E

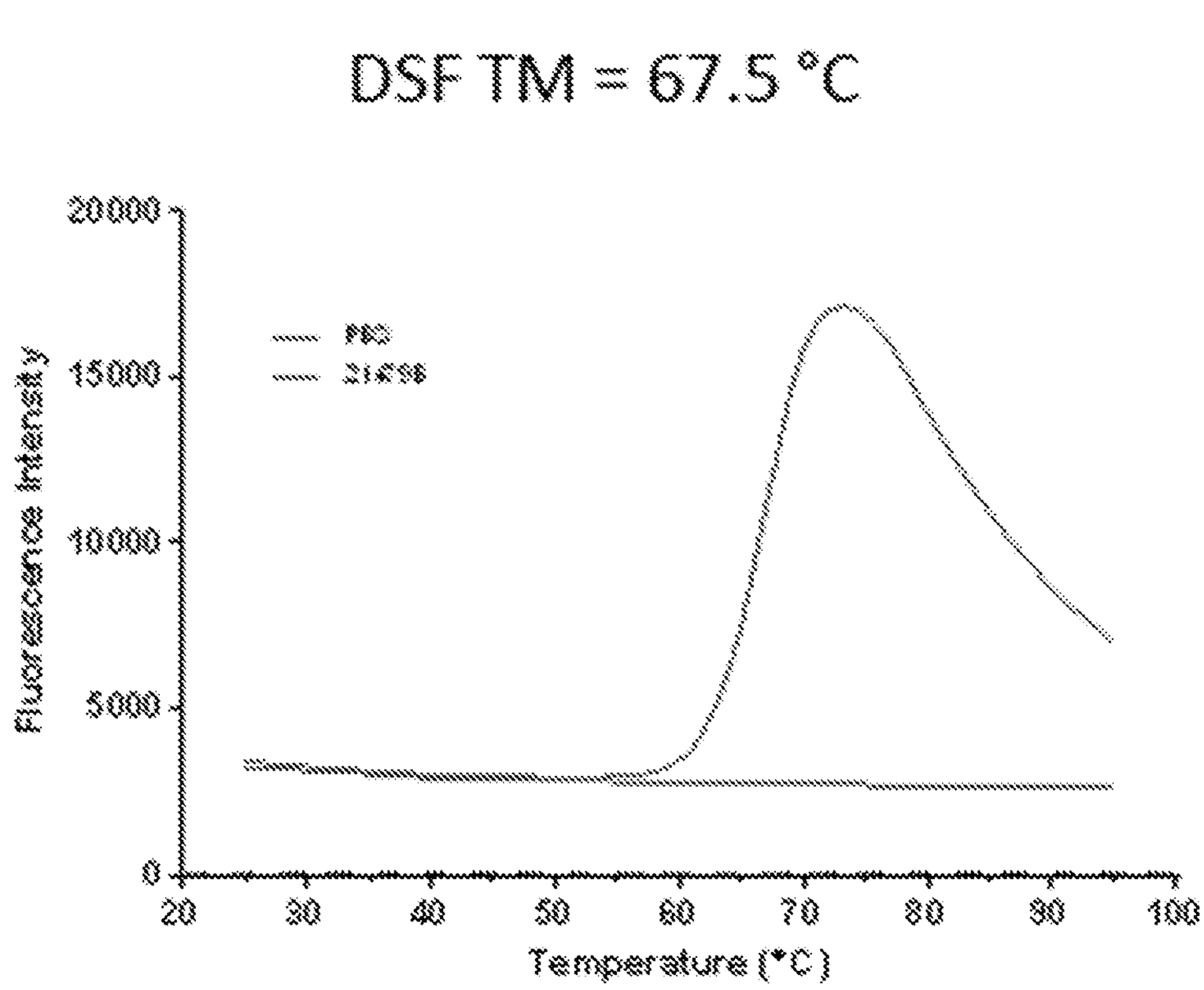


Figure 20A

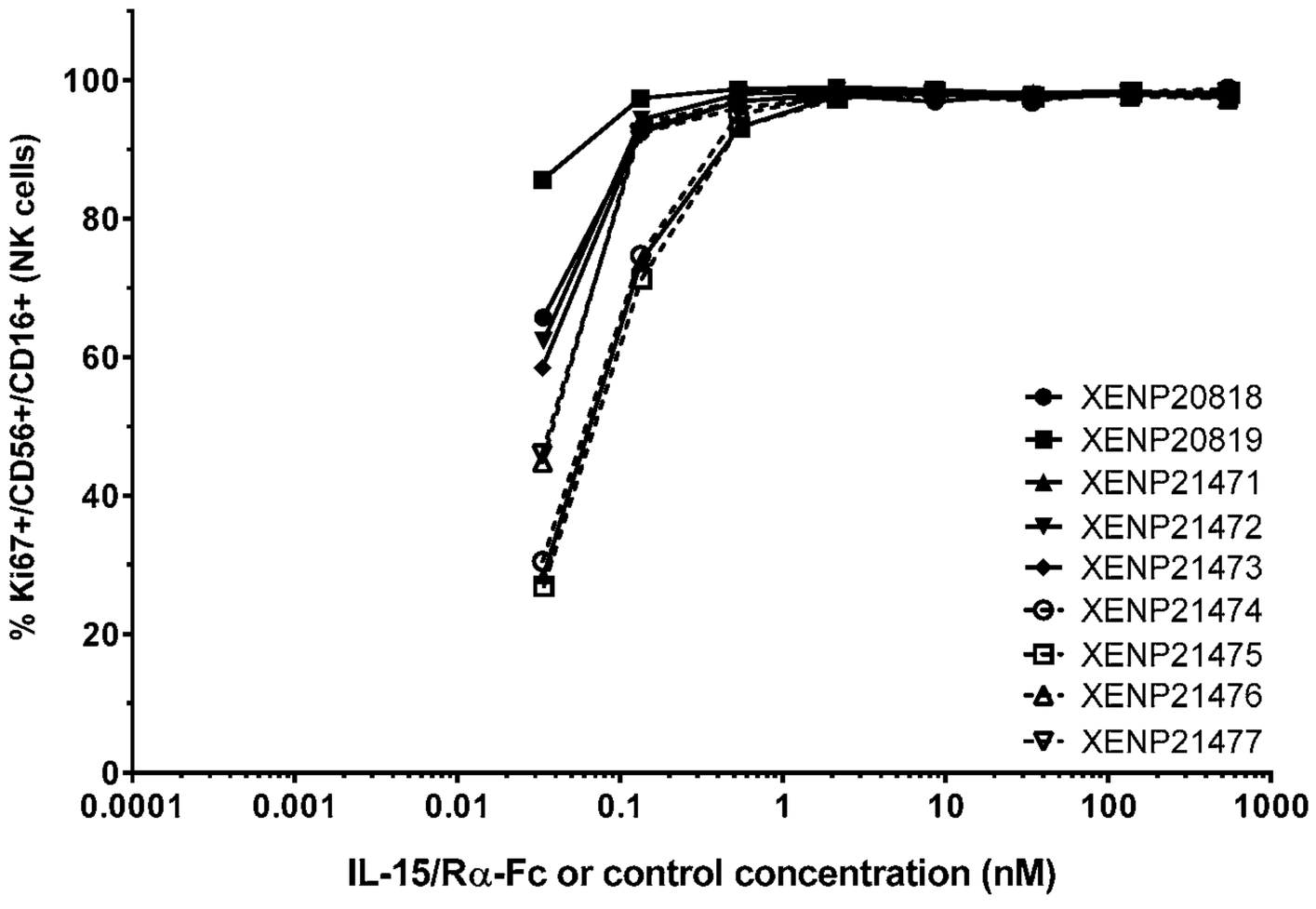


Figure 20B

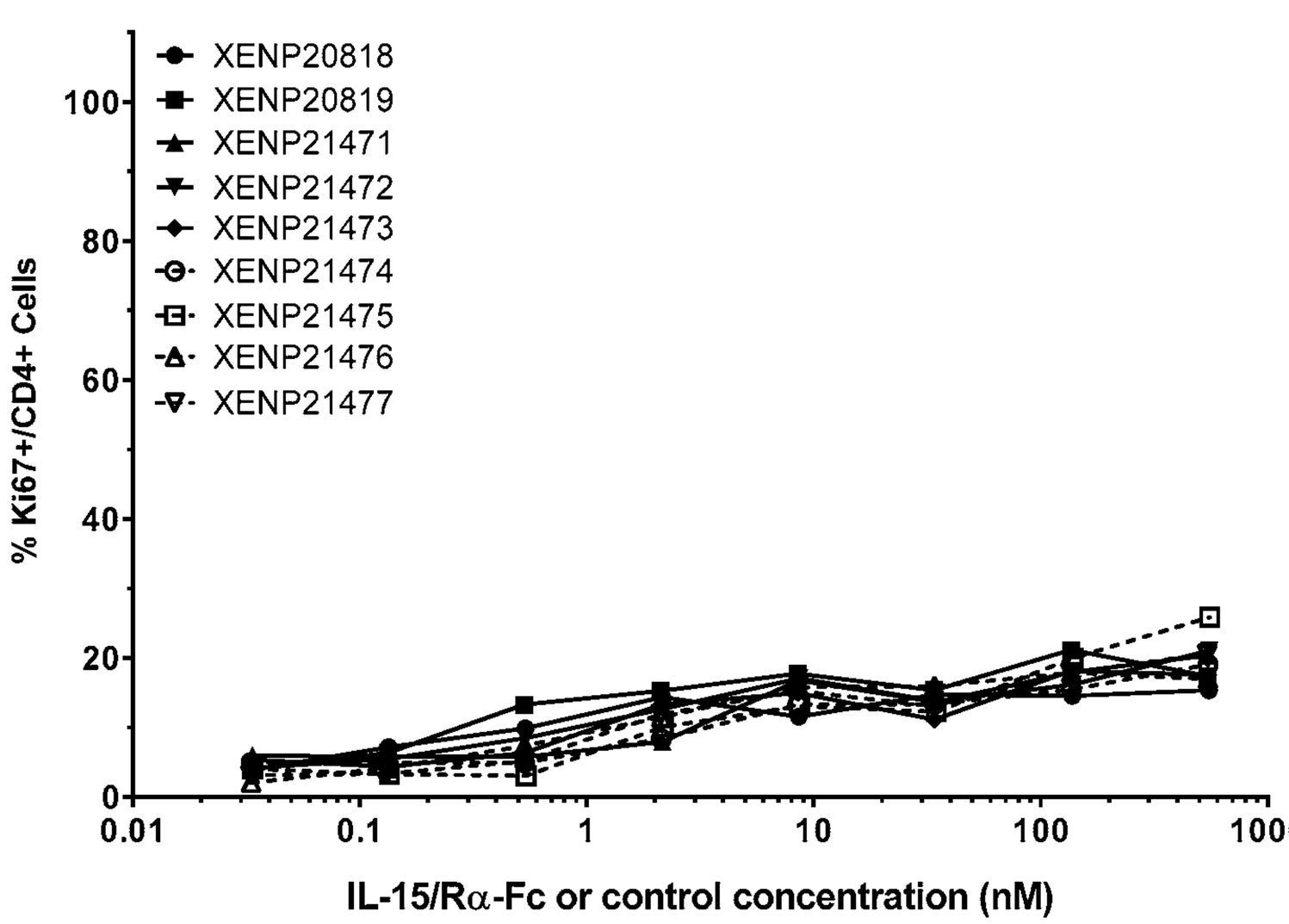


Figure 20C

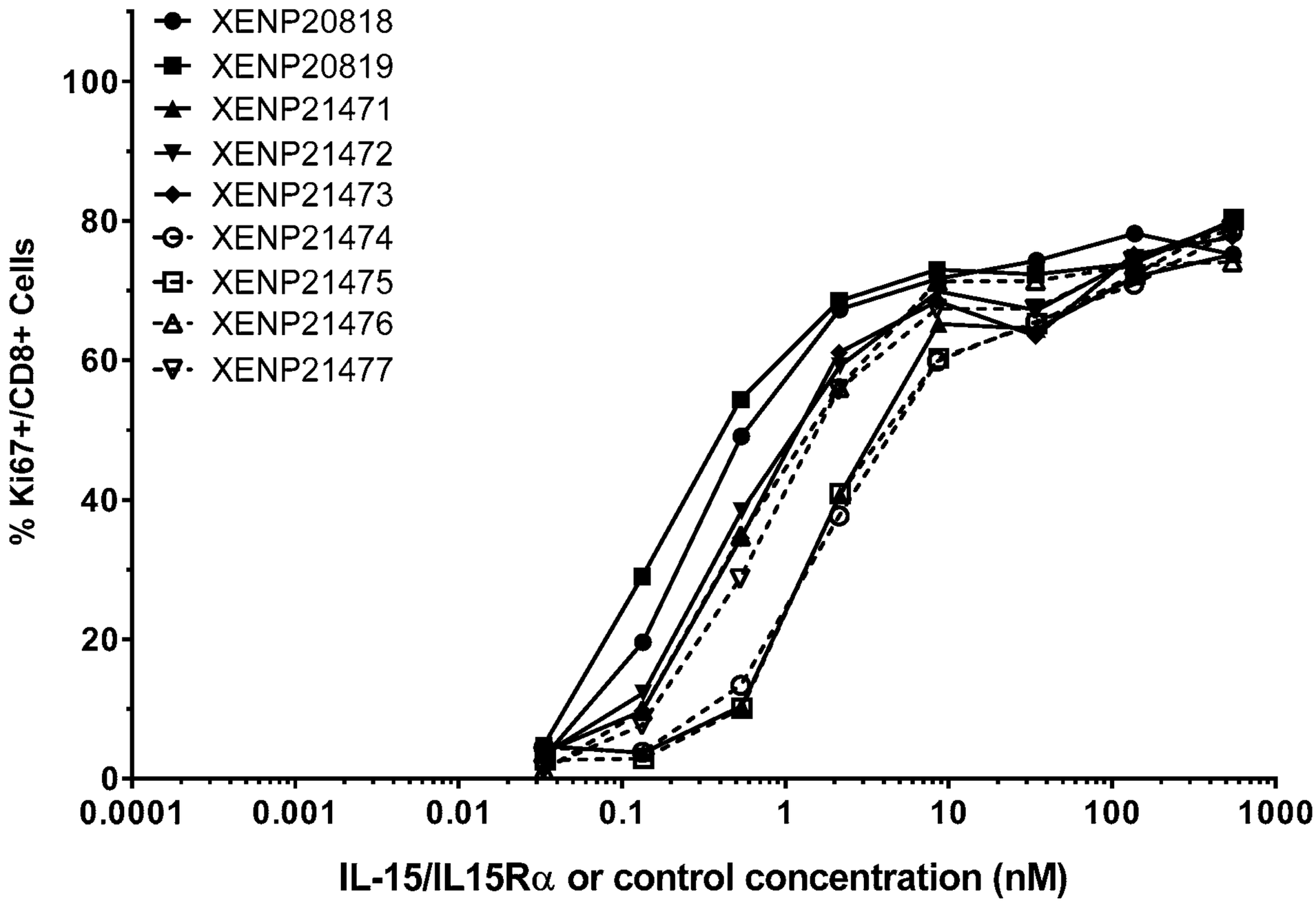

XENP20818
XENP20819
XENP21471
XENP21472
XENP21473
XENP21474
XENP21475
XENP21476
XENP21477
% Ki67+/CD8+ Cells
0
20
40
60
80
100
0.0001
0.001
0.01
0.1
1
10
100
1000
IL-15/IL15Rα or control concentration (nM)

Figure 21A

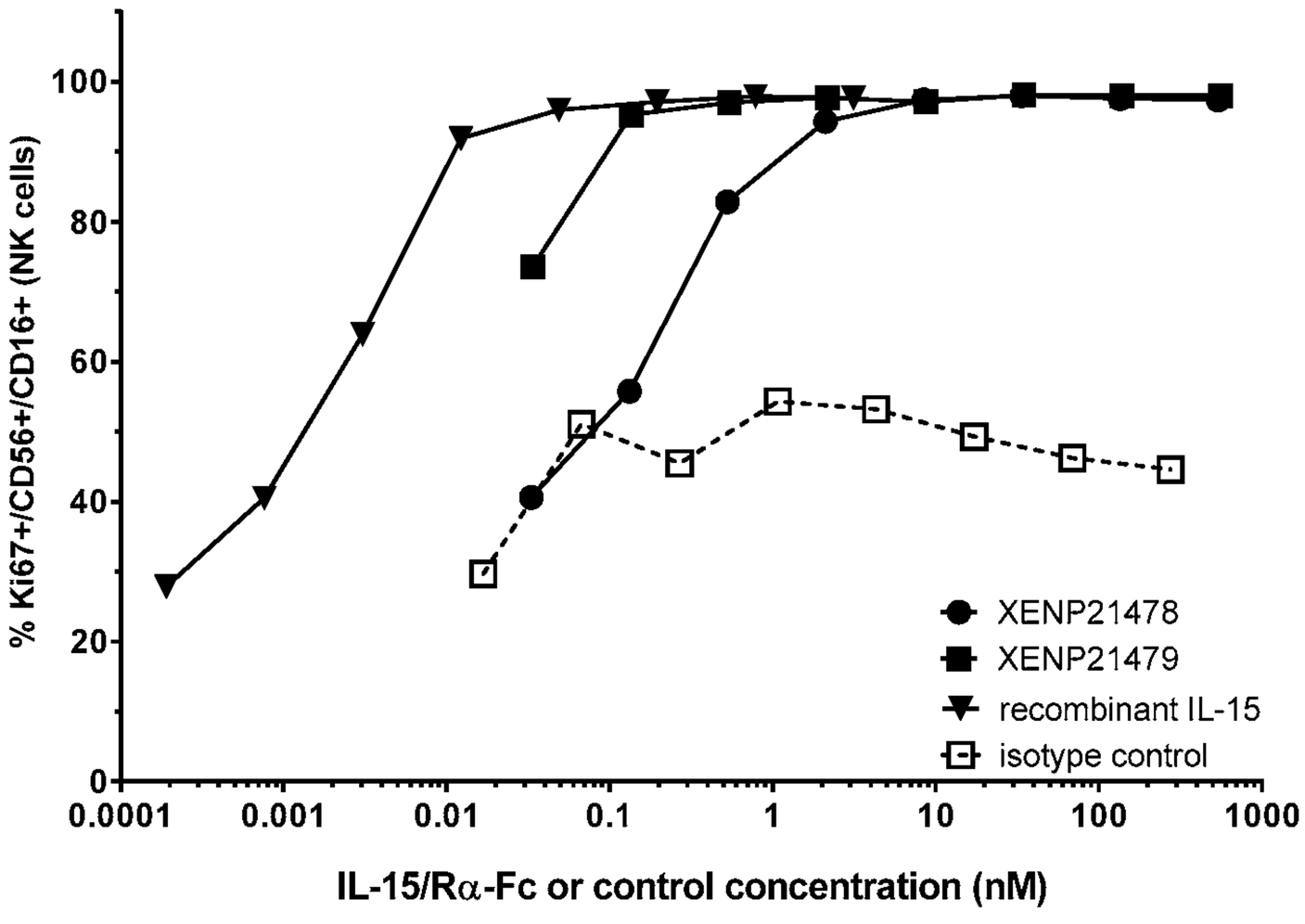


Figure 21B

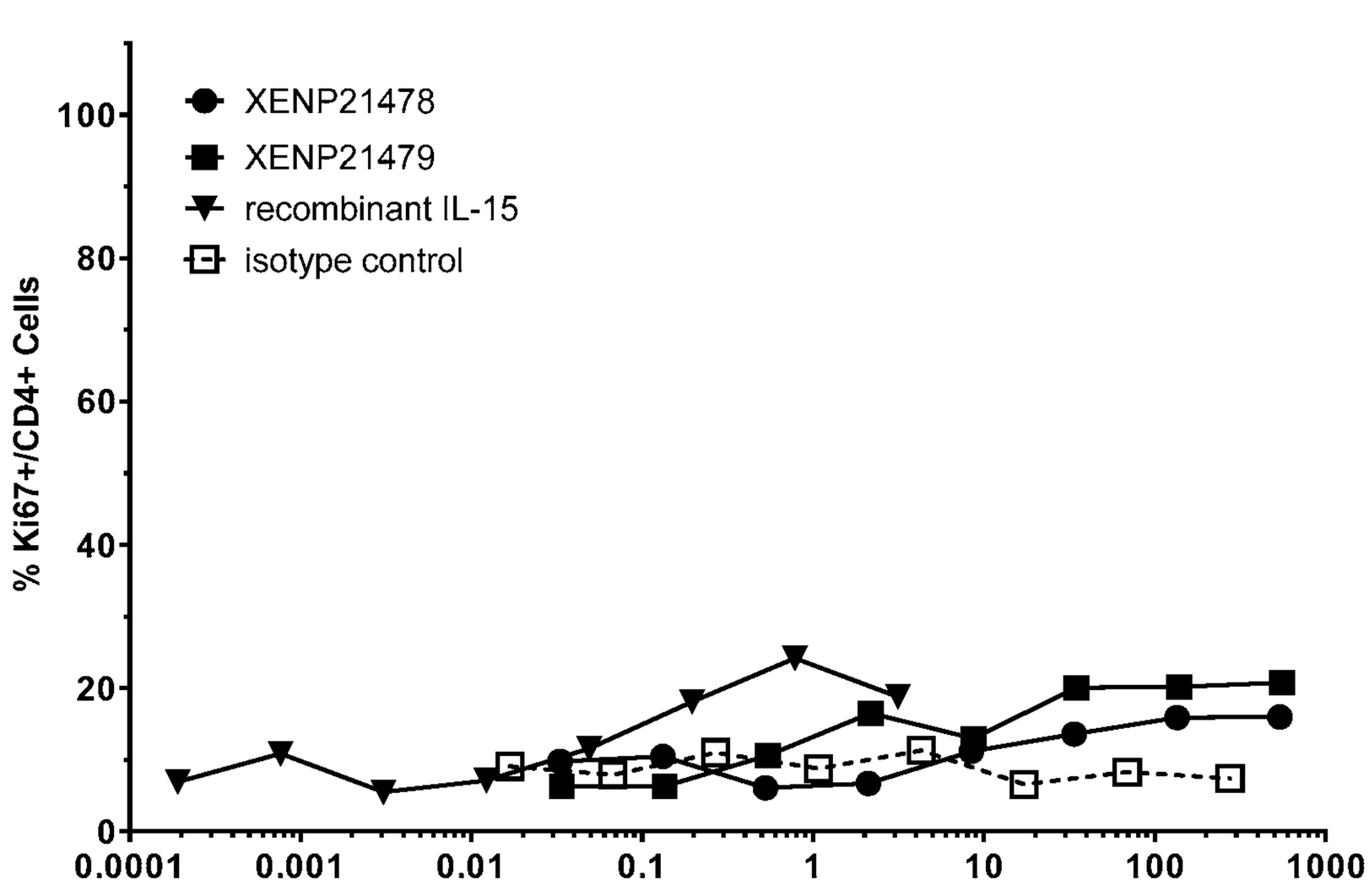


Figure 21C

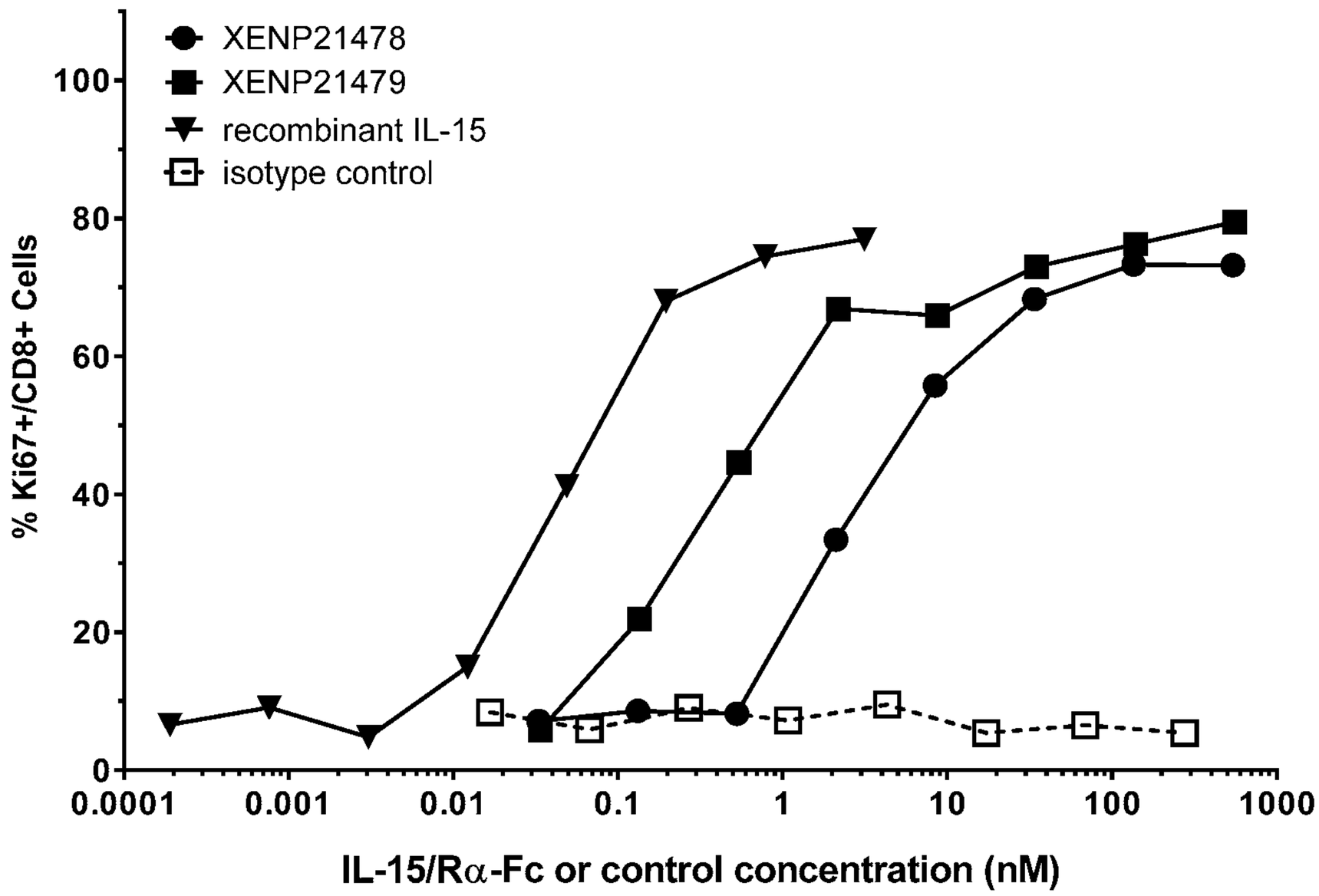

XENP21478
XENP21479
recombinant IL-15
isotype control
% Ki67+/CD8+ Cells
0
20
40
60
80
100
0.0001
0.001
0.01
0.1
1
10
100
1000
IL-15/Rα-Fc or control concentration (nM)

Figure 22

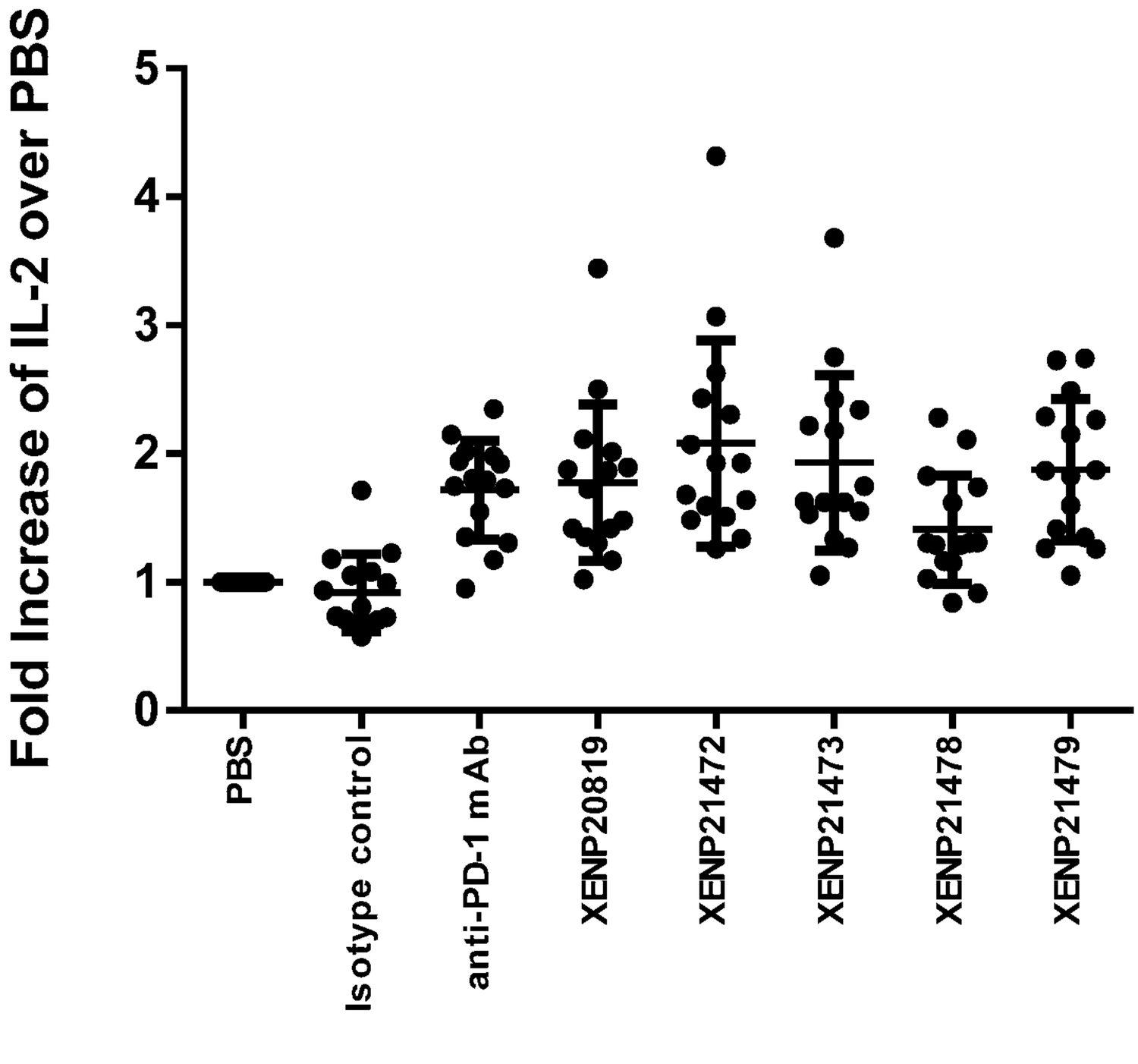

Fold Increase of IL-2 over PBS
0
1
2
3
4
5
PBS
Isotype control
anti-PD-1 mAb
XENP20819
XENP21472
XENP21473
XENP21478
XENP21479

Figure 23

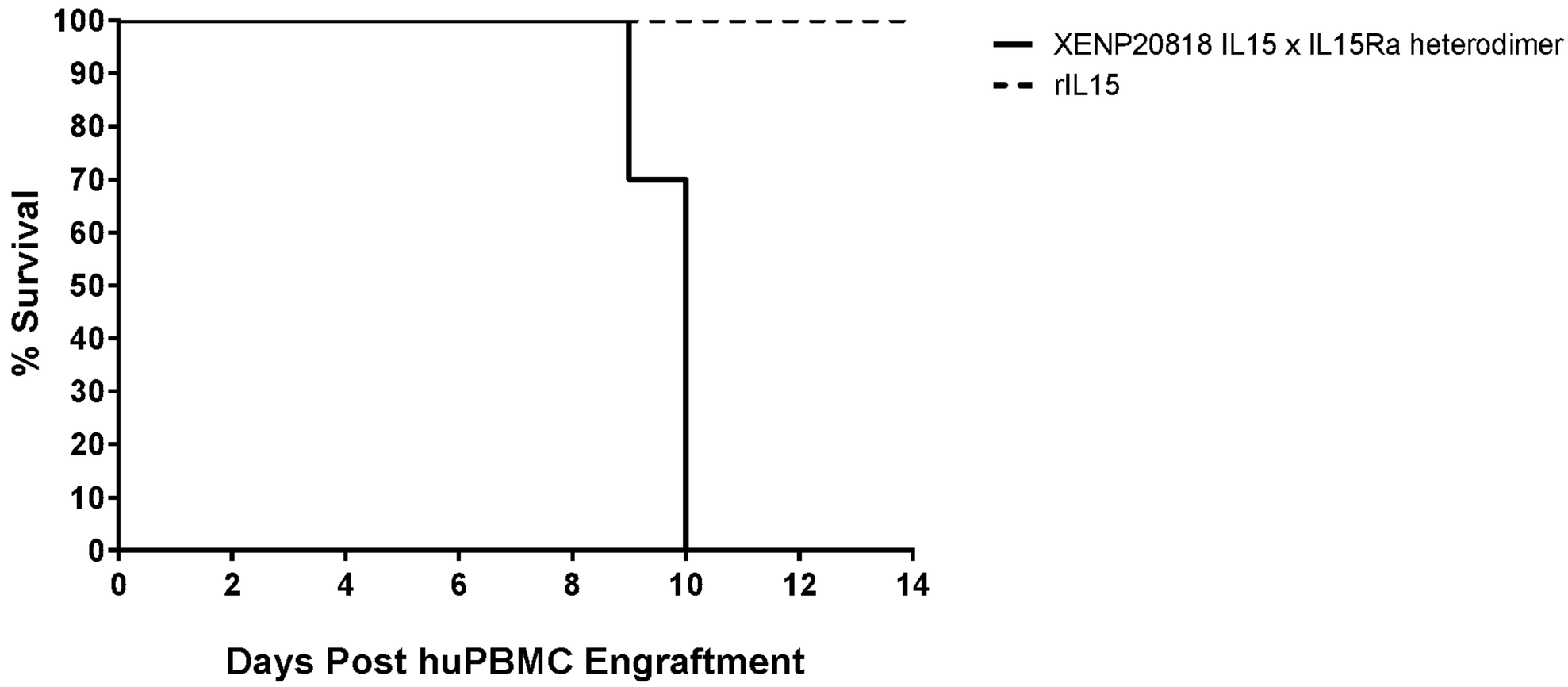

100
90
80
70
60
50
40
30
20
10
0
% Survival
0
2
4
6
8
10
12
14
Days Post huPBMC Engraftment
XENP20818 IL15 x IL15Ra heterodimer
rIL15

Figure 24

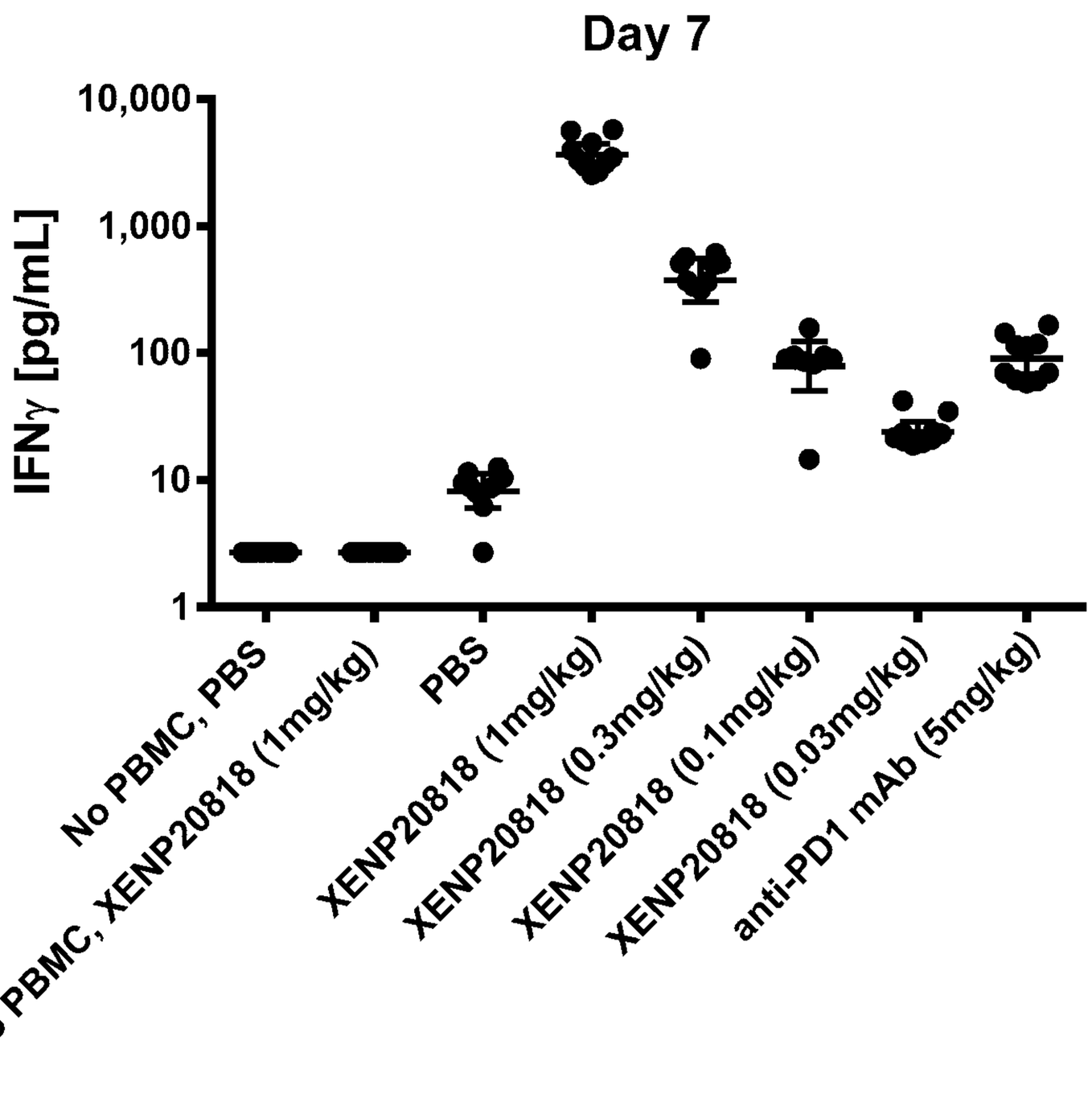

Day 7
IFNγ [pg/mL]
10,000
1,000
100
10
1
No PBMC, PBS
No PBMC, XENP20818 (1mg/kg)
PBS
XENP20818 (1mg/kg)
XENP20818 (0.3mg/kg)
XENP20818 (0.1mg/kg)
XENP20818 (0.03mg/kg)
anti-PD1 mAb (5mg/kg)

Figure 25A

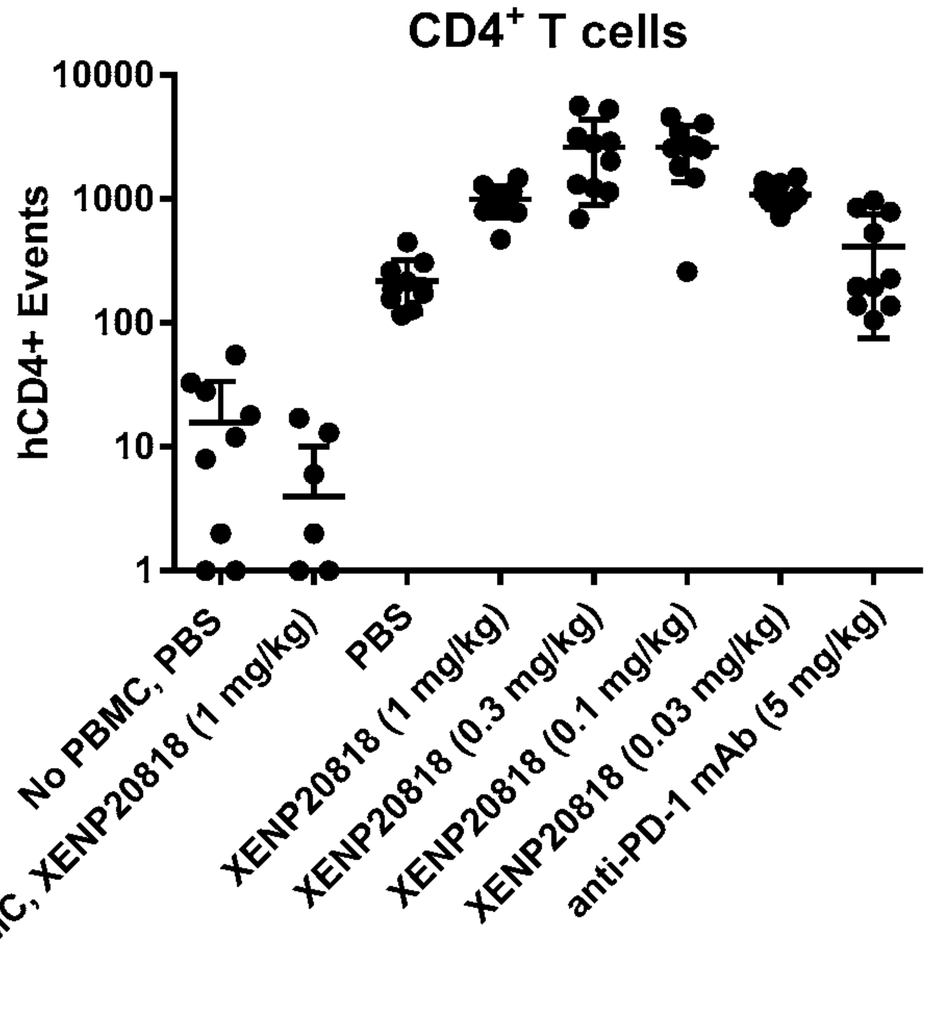


Figure 25B

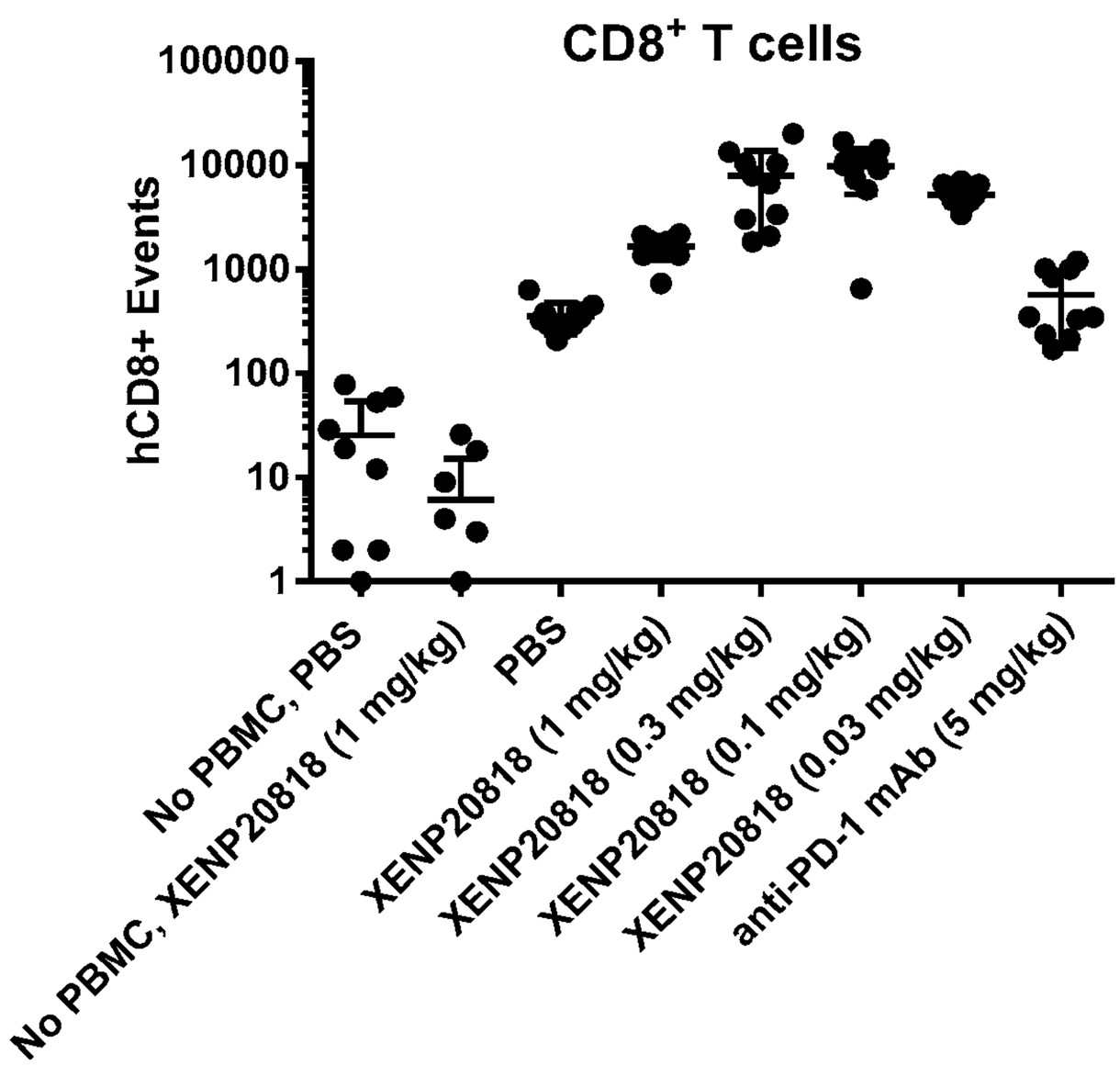


Figure 25C

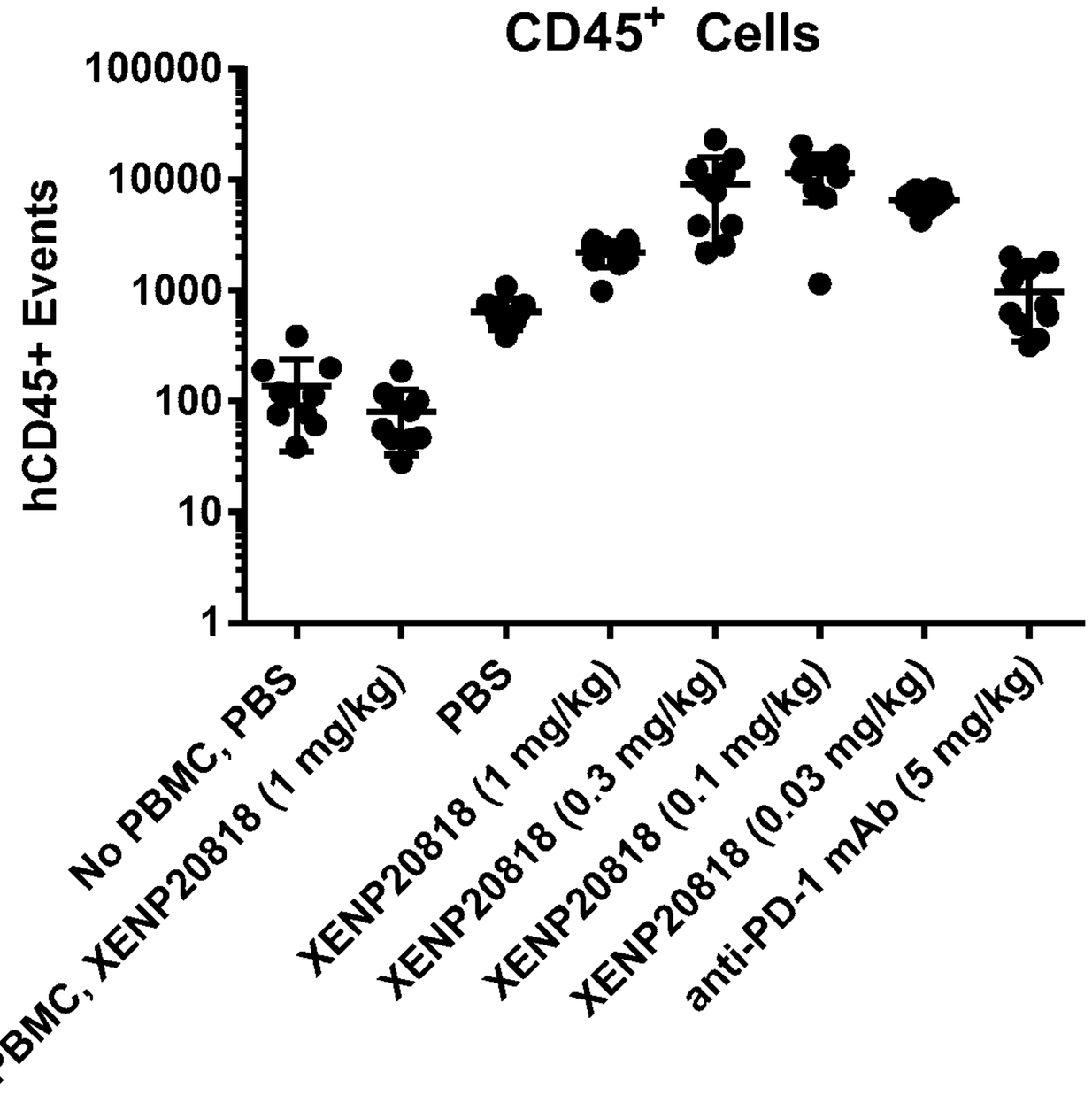

CD45+ Cells
hCD45+ Events
100000
10000
1000
100
10
1
No PBMC, PBS
No PBMC, XENP20818 (1 mg/kg)
PBS
XENP20818 (1 mg/kg)
XENP20818 (0.3 mg/kg)
XENP20818 (0.1 mg/kg)
XENP20818 (0.03 mg/kg)
anti-PD-1 mAb (5 mg/kg)

Figure 26

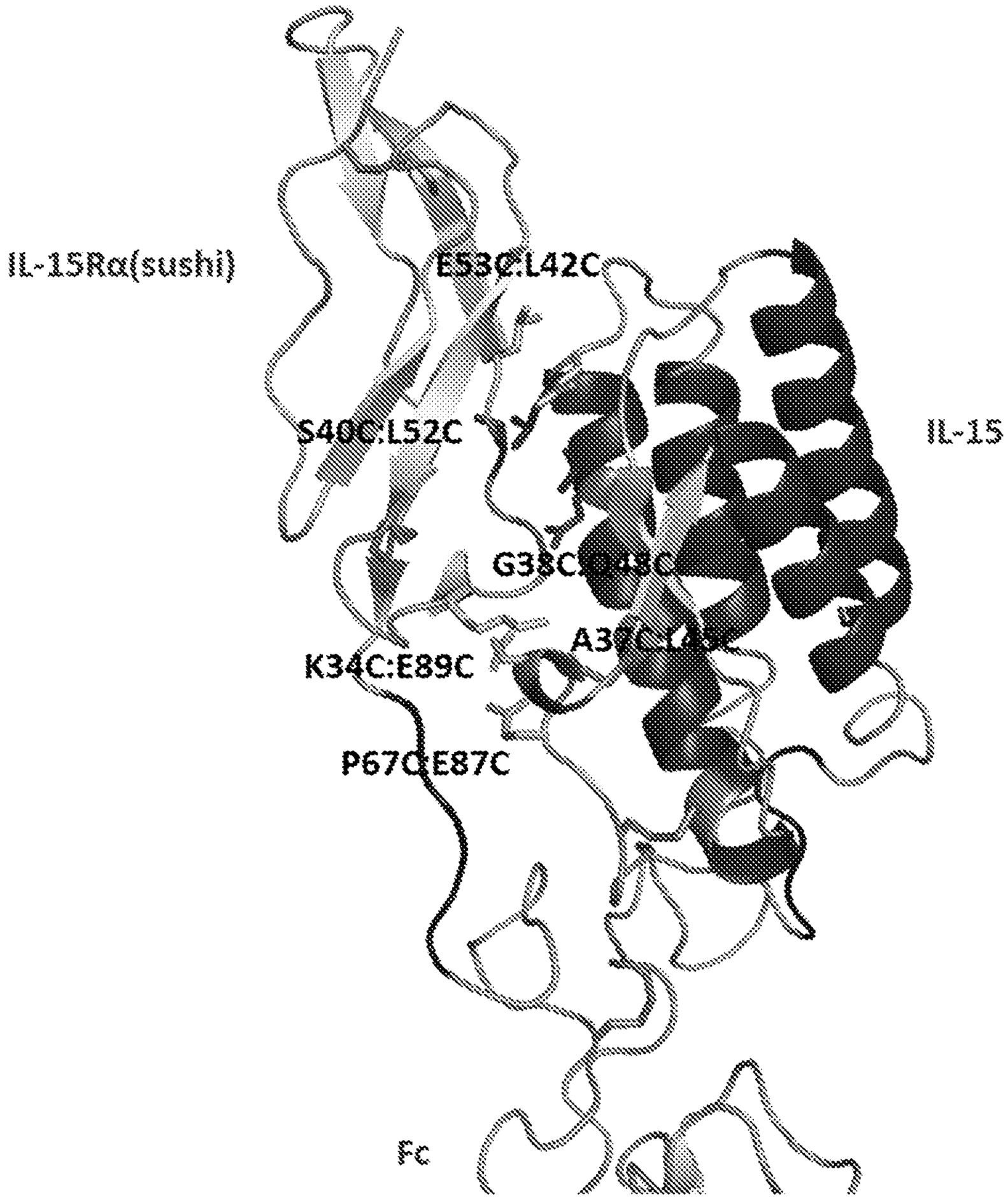

IL-15Rα(sushi)
E53C:L42C
S40C:L52C
IL-15
G38C
K34C:E89C
A37C
P67C:E87C

Figure 27

IL-15Rα(sushi-D96) (SEQ ID NO:88)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRD

IL-15Rα(sushi-D96/P97) (SEQ ID NO:89)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDP

IL-15Rα(sushi-D96/P97/A98) (SEQ ID NO:90)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPA

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 28

IL-15(E87C) (SEQ ID NO:91)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKCCEELEEKNIKEFLQSFVHIVQMFINTS

IL-15(V49C) (SEQ ID NO:92)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQCISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

IL-15(L52C) (SEQ ID NO:93)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISCESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

IL-15(E89C) (SEQ ID NO:94)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECCELEEKNIKEFLQSFVHIVQMFINTS

IL-15(Q48C) (SEQ ID NO:95)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELCVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

IL-15(E53C) (SEQ ID NO:96)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLCSGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

IL-15(C42S) (SEQ ID NO:97)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKSFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

IL-15(L45C) (SEQ ID NO:98)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLCELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 29

IL-15Rα(sushi-D96/C97) (SEQ ID NO:99)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDC

IL-15Rα(sushi-D96/P97/C98) (SEQ ID NO:100)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPC

IL-15Rα(sushi-D96/C97/A98) (SEQ ID NO:101)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDCA

IL-15Rα(sushi-S40C) (SEQ ID NO:102)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTCSLTECVLNKATNVAHWTTPSLKCIR

IL-15Rα(sushi-K34C) (SEQ ID NO:103)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFCRKAGTSSLTECVLNKATNVAHWTTPSLKCIR

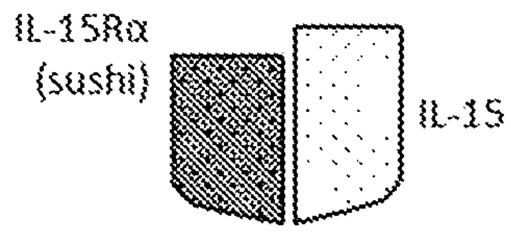
IL-15Rα(sushi-G38C) (SEQ ID NO:104)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKACTSSLTECVLNKATNVAHWTTPSLKCIR

IL-15Rα(sushi-L42C) (SEQ ID NO:105)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSCTECVLNKATNVAHWTTPSLKCIR

IL-15Rα(sushi-A37C) (SEQ ID NO:106)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKCGTSSLTECVLNKATNVAHWTTPSLKCIR

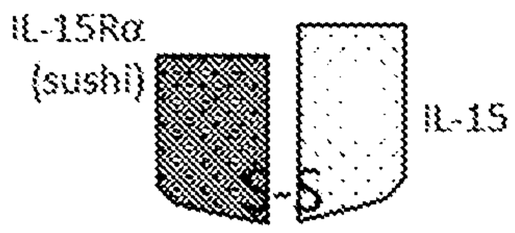
RECTIFIED SHEET (RULE 91) ISA/EP

Figure 30A



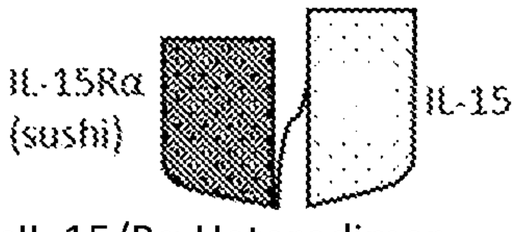
ncIL-15/Rα Heterodimer
Example: XENP21996

Figure 30B



dsIL-15/Rα Heterodimer
Example: XENP22004

Figure 30C



scIL-15/Rα Heterodimer
Example: XENP22049

Figure 31

>XENP021996 - human_IL15(non-covalent)-human_IL15Ra(Sushi)

Chain 1 - human_IL15_no_tag (16484) (SEQ ID NO:107)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

Chain 2 - human_IL15Ra(Sushi) (17033) (SEQ ID NO:108)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 32

>XENP022004 - human_IL15_E87C-human_IL15Ra(Sushi-D96/C97)

Chain 1 - human_IL15_E87C_no_tag (17074) (SEQ ID NO:109)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

Chain 2 - human_IL15Ra(Sushi-D96/C97) (17051) (SEQ ID NO:110)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDC

>XENP022005 - human_IL15_E87C-human_IL15Ra(Sushi-D96/P97/C98)

Chain 1 - human_IL15_E87C_no_tag (17074) (SEQ ID NO:111)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

Chain 2 - human_IL15Ra(Sushi-D96/P97/C98) (17052) (SEQ ID NO:112)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPC

>XENP022006 - human_IL15_E87C-human_IL15Ra(Sushi-D96/C97/A98)

Chain 1 - human_IL15_E87C_no_tag (17074) (SEQ ID NO:113)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

Chain 2 - human_IL15Ra(Sushi-D96/C97/A98) (17053) (SEQ ID NO:114)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDCA

>XENP022008 - human_IL15_L52C-human_IL15Ra(Sushi-S40C)

Chain 1 - human_IL15_L52C_no_tag (17072) (SEQ ID NO:115)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISCESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

Chain 2 - human_IL15Ra(Sushi-S40C) (17057) (SEQ ID NO:116)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTCSLTECVLNKATNVAHWTTPSLKCIR
>XENP022494 – human_IL15_L45C-human_IL15Ra(Sushi-A37C)

Chain 1 - human_IL15_L45C_no_tag (17069) (SEQ ID NO:117)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLCELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

Chain 2 - human_IL15Ra(Sushi-A37C) (17055) (SEQ ID NO:118)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKCGTSSLTECVLNKATNVAHWTTPSLKCIR

Figure 33

>XENP022049 - human_IL15Ra(sushi)_(GGGGS)6-human_IL15-sc (SEQ ID NO:119)

ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGSGGGGSGGG
GSGGGGSGGGGSGGGGS/NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHD
TVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS

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Figure 34

IL15Ra
(Sushi)
IL15

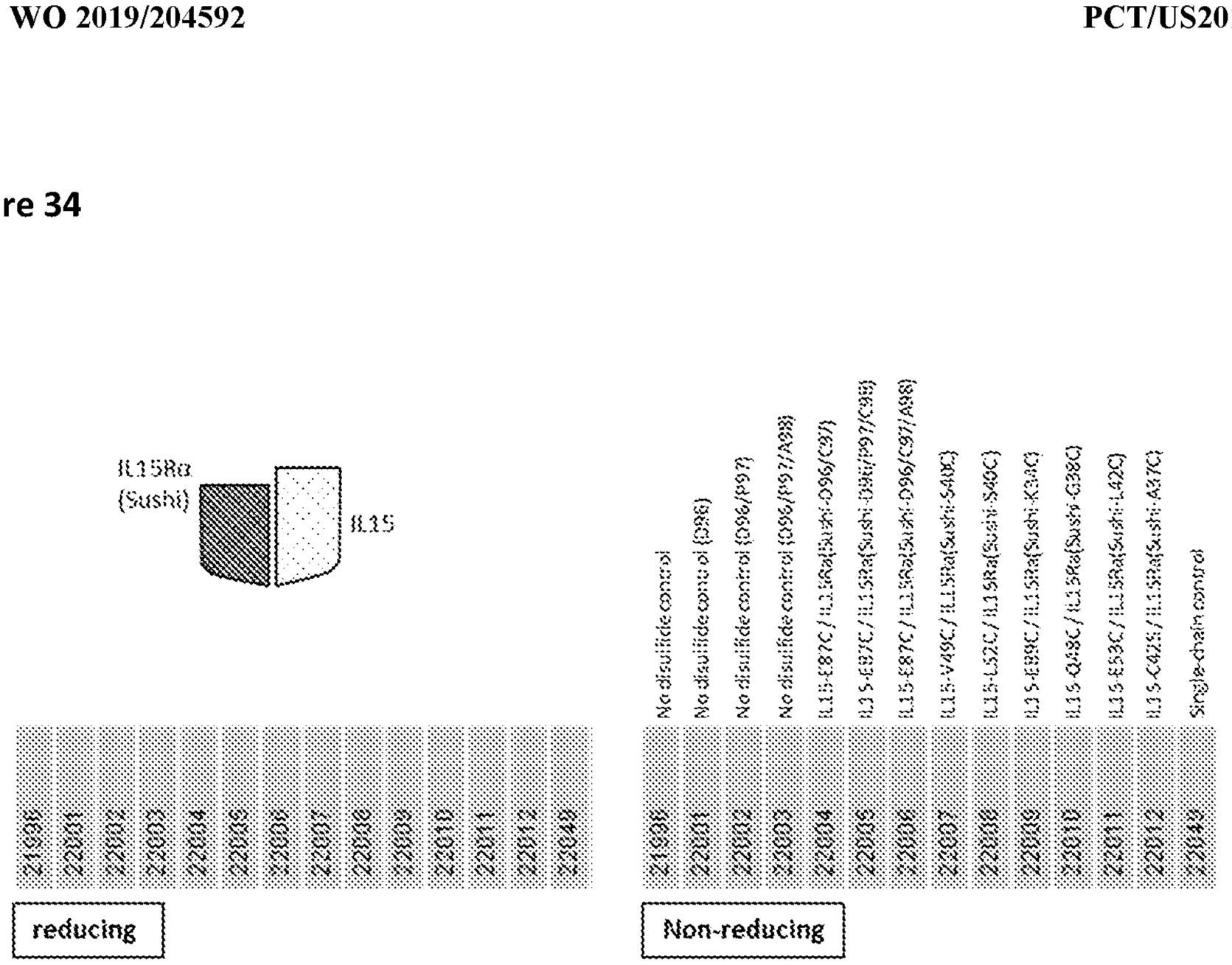

No disulfide control
No disulfide control (D96)
No disulfide control (D96/P97)
No disulfide control (D96/P97/A98)
IL15-E87C / IL15Ra(Sushi-D96/C97)
IL15-E87C / IL15Ra(Sushi-D96/P97/C98)
IL15-E87C / IL15Ra(Sushi-D96/C97/A98)
IL15-V49C / IL15Ra(Sushi-S40C)
IL15-L52C / IL15Ra(Sushi-S40C)
IL15-E89C / IL15Ra(Sushi-K38C)
IL15-Q48C / IL15Ra(Sushi-G38C)
IL15-E53C / IL15Ra(Sushi-L42C)
IL15-C42S / IL15Ra(Sushi-A37C)
Single-chain control
21908
22011
22012
22013
22014
22015
22016
22017
22018
22019
22810
22811
22812
22849
reducing
Non-reducing
IL-15 = 12.8 kD + glycosylation ~20 kD
IL-15Ra = 8.3 kD
kD
98
48
28
17
6
3
IL-15Ra(sushi)
IL-15
5-S Complex

Figure 35

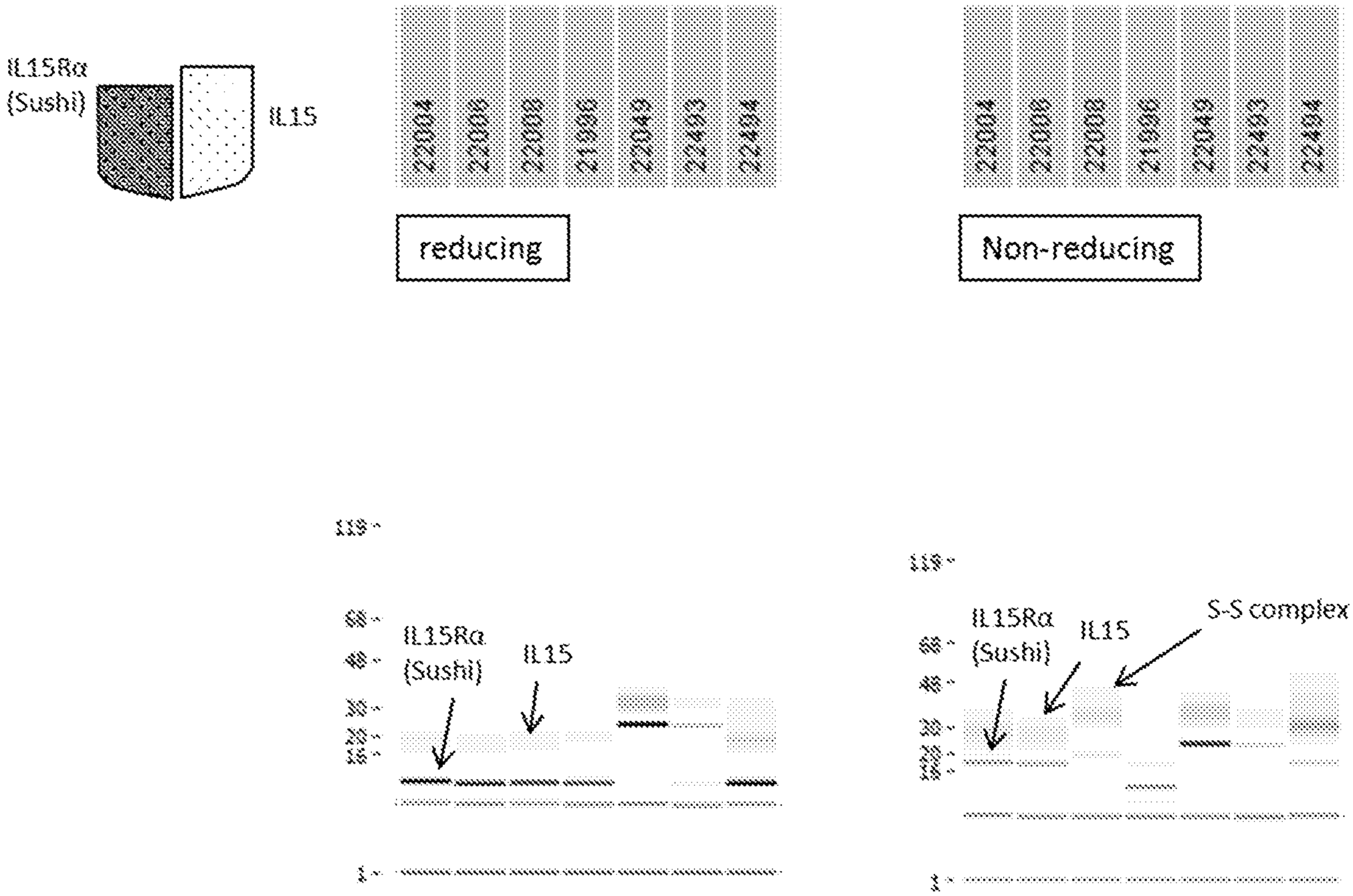

IL15Rα
(Sushi)
IL15
Z20034
Z20036
Z20038
Z19936
Z20043
Z24453
Z24454
reducing
Non-reducing
118
66
44
28
15
IL15Rα
(Sushi)
IL15
S-S complex

Figure 36

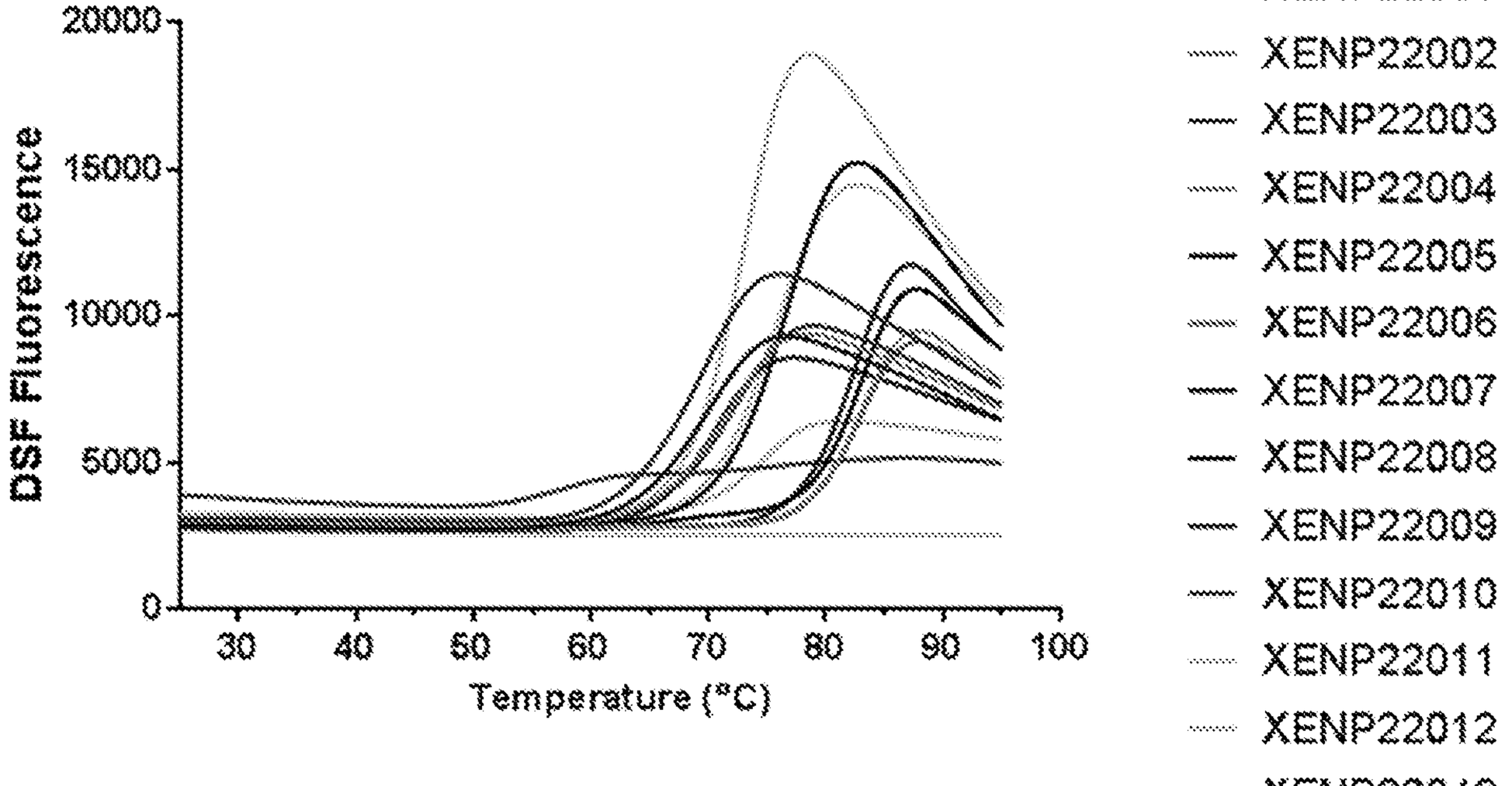

DSF Fluorescence
20000
15000
10000
5000
0
30
40
50
60
70
80
90
100
Temperature (°C)
XENP21996
XENP22001
XENP22002
XENP22003
XENP22004
XENP22005
XENP22006
XENP22007
XENP22008
XENP22009
XENP22010
XENP22011
XENP22012
XENP22049
PBS

Figure 37

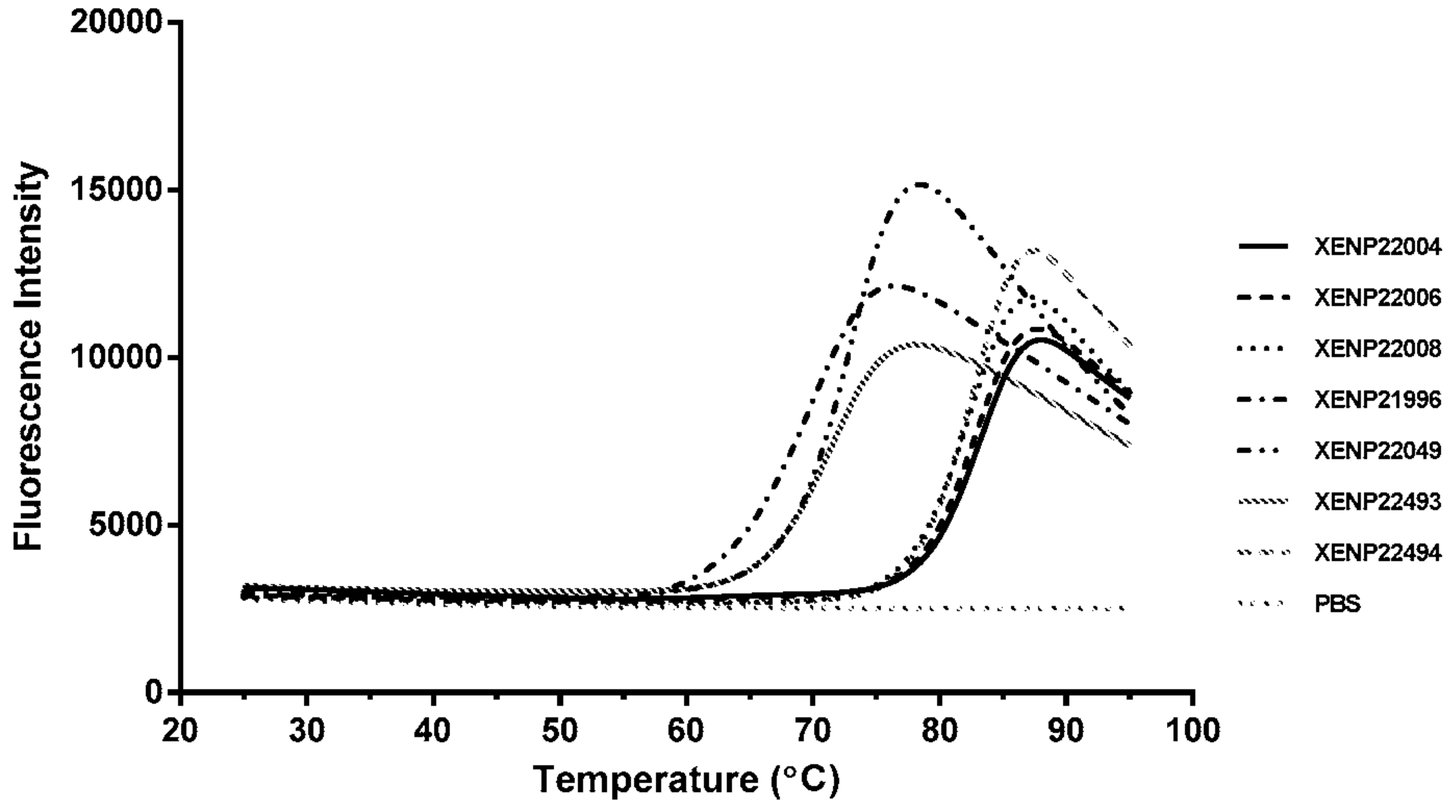
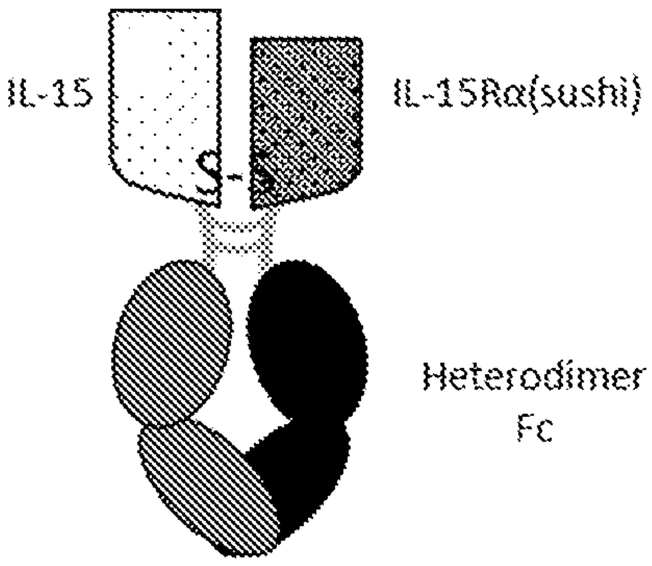

Fluorescence Intensity
20000
15000
10000
5000
0
20
30
40
50
60
70
80
90
100
Temperature (°C)
XENP22004
XENP22006
XENP22008
XENP21996
XENP22049
XENP22493
XENP22494
PBS

Figure 38

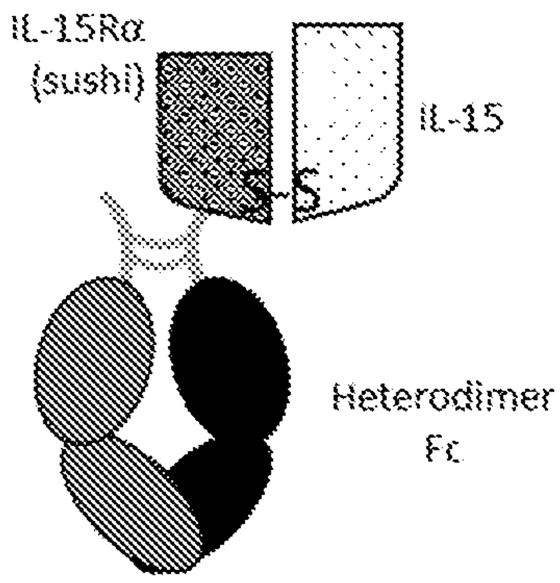
XENP	Variant	Yield (mg/ml)	MW (g/mol)	Calculated ΔAffinity	T_m (°C)	IL2Rß Affinity (~nM K_D)
21996	No Disulfide Control IL-15/Rα	8.04	21079.9	NA	70.0	6.3
22001	No Disulfide Control IL-15/Rα(D96)	2.45	21195.0	NA	70.0	5.2
22002	No Disulfide Control IL-15/Rα(D96/P97)	2.47	21292.1	NA	72.0	7.4
22003	No Disulfide Control IL-15/Rα(D96/P97/A98)	3.48	21363.2	NA	72.5	5.7
22004	IL-15(E87C)/Rα(D96/C97)	4.58	21272.2	-7.61	83.0	4.1
22005	IL-15(E87C)/Rα(D96/C97/A98)	8.4	21369.3	NA	83 (shoulder)	6.1
22006	IL-15(E87C)/Rα(D96/C97/A98)	3.19	21343.2	-7.61	83.0	5.1
22007	IL-15(V49C)/Rα(S40C)	1.58	21100.0	1.22	77.0	11
22008	IL-15(L52C)/Rα(S40C)	4.56	21085.9	-0.97	82.5	17
22009	IL-15(E89C)/Rα(K34C)	0.51	21028.9	-0.33	70.5	7.3
22010	IL-15(Q48C)/Rα(G38C)	0.42	21101.0	0.91	57.5	3.8
22011	IL-15(E53C)/Rα(L42C)	3.72	21043.9	3.73	76.0	17
22012	IL-15(C42S)/Rα(A37C)	0.44	21095.9	NA	75.0	5.3
22049	Single-chain control	5.77	22953.6	NA	73.0	22
22493	IL-15(L45C)/Rα(G38C)	0.40	21116.0	0.77	71.5	NA
22494	IL-15(L45C)/Rα(A37C)	3.63	21101.9	0.63	82.5	NA

Figure 39A



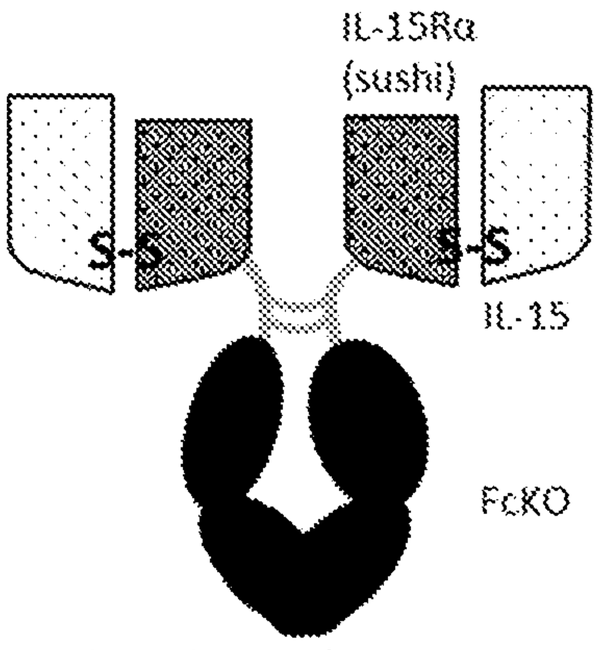
dsIL-15/Rα-heteroFc
Example: XENP22013

Figure 39B



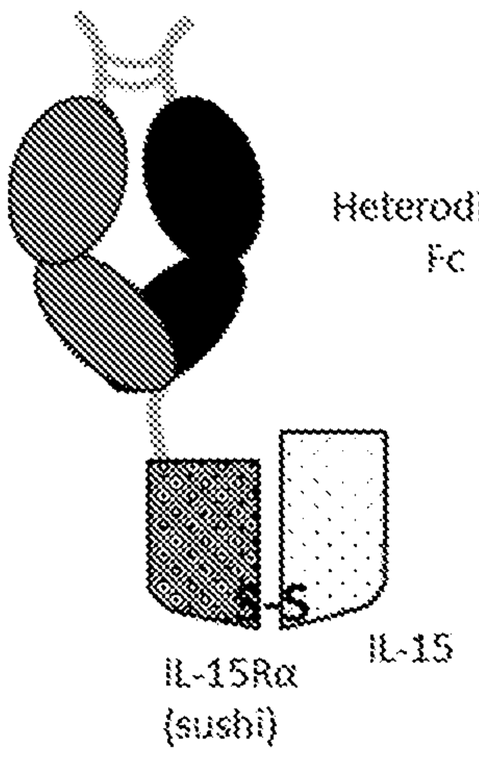
dsIL-15/Rα-Fc
Example: XENP22357

Figure 39C



Bivalent dsIL-15/Rα-Fc
Example: XENP22634

Figure 39D



Fc-dsIL-15/Rα
Example: XENP22639

Figure 40A

>XENP022013 human_IL15_E87C_(GGGGS)1-human_IL15Ra(Sushi-D96/C97)_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15_E87C_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:120)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKCCEELEEKNIKEFLQSFVHIVQMFINTS/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - human_IL15Ra(Sushi-D96/C97)_(GGGGS)1_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:121)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDC/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>XENP022014 human_IL15_E87C_(GGGGS)1-human_IL15Ra(Sushi-D96/P97/C98)_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15_E87C_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:122)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKCCEELEEKNIKEFLQSFVHIVQMFINTS/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - human_IL15Ra(Sushi-D96/P97/C98)_(GGGGS)1_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:123)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPC/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Figure 40B

>XENP022015 human_IL15_E87C_(GGGGS)1-human_IL15Ra(Sushi-D96/C97/A98)_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15_E87C_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:124)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKCCEELEEKNIKEFLQSFVHIVQMFINTS/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - human_IL15Ra(Sushi-D96/C97/A98)_(GGGGS)1_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:125)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDCA/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>XENP022017 human_IL15_L52C_(GGGGS)1-human_IL15Ra(Sushi-S40C)_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 – human_IL15_L52C_(GGGGS)1-_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:126)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISCESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 – human_IL15Ra(Sushi-S40C)_(GGGGS)1_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:127)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTCSLTECVLNKATNVAHWTTPSLKCIR/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

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Figure 41A

>XENP022358 – empty-Fc-IL15_E87C-human_IL15Ra(Sushi-D96/P97/C98)_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15_E87C_no_tag (17074) (SEQ ID NO:128)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKCCEELEEKNIKEFLQSFVHIVQMFINTS

Chain 2 - empty-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (8793)
(SEQ ID NO:129)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEE
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPS
DIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 3 - human_IL15Ra(Sushi-D96/P97/C98)_(GGGGS)1_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (17039)
(SEQ ID NO:130)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDPC/GGGGS/EPKSSD
KTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>XENP022359 – empty-Fc-IL15_E87C-human_IL15Ra(Sushi-D96/C97/A98)_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15_E87C_no_tag (17074) (SEQ ID NO:131)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKCCEELEEKNIKEFLQSFVHIVQMFINTS

Chain 2 - empty-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (8793)
(SEQ ID NO:132)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEE
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPS
DIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 3 - human_IL15Ra(Sushi-D96/C97/A98)_(GGGGS)1_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (17040)
(SEQ ID NO:133)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDCA/GGGGS/EPKSSD
KTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Figure 41B

>XENP022361 – empty-Fc-IL15_L52C-human_IL15Ra(Sushi-S40C)_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15_L52C_no_tag (17072) (SEQ ID NO:134)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISCESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

Chain 2 - empty-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (8793)
(SEQ ID NO:135)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEE
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPS
DIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 3 - human_IL15Ra(Sushi-S40C)_(GGGGS)1_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q
(17044) (SEQ ID NO:136)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTCSLTECVLNKATNVAHWTTPSLKCIR/GGGGS/EPKSSDKTH
TCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>XENP022684 empty-Fc-IL15_E87C-human_IL15Ra(Sushi-D96/C97/A98)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 – IL15_E87C (SEQ ID NO:137)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKCCEELEEKNIKEFLQSFVHIVQMFINTS

Chain 2 - IL15Ra(Sushi-D96/C97/A98)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S
(SEQ ID NO:138)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDCA/EPKSSDKTHTCP
PCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT
VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNG
QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Figure 42

>XENP022634 – human_IL15(E87C)-human_IL15Ra(Sushi-D96/C97)_Fc(216)_IgG1_C220S/PVA_/S267K

Chain 1 - human_IL15Ra(Sushi-D96/C97)-Fc(216)_IgG1_C220S/PVA_/S267K (17581) (SEQ ID NO:139)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDC/EPKSSDKTHTCPP
CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT
VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - human_IL15_E87C_no_tag (17074) (SEQ ID NO:140)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKCCEELEEKNIKEFLQSFVHIVQMFINTS

>XENP022635 – human_IL15(E87C)-human_IL15Ra(Sushi-D96/C97/A98)_Fc(216)_IgG1_C220S/PVA_/S267K

Chain 1 - human_IL15Ra(Sushi-D96/C97/A98)-Fc(216)_IgG1_C220S/PVA_/S267K (17582)
(SEQ ID NO:141)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDCA/EPKSSDKTHTCP
PCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT
VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - human_IL15_E87C_no_tag (17074) (SEQ ID NO:142)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKCCEELEEKNIKEFLQSFVHIVQMFINTS

>XENP022636 – human_IL15(L52C)-human_IL15Ra(Sushi-S40C)_Fc(216)_IgG1_C220S/PVA_/S267K

Chain 1 - human_IL15Ra(Sushi-S40C)-Fc(216)_IgG1_C220S/PVA_/S267K (17583) (SEQ ID NO:143)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTCSLTECVLNKATNVAHWTTPSLKCIR/EPKSSDKTHTCPPCP
APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - human_IL15_L52C_no_tag (17072) (SEQ ID NO:144)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISCESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 43

>XENP022639 – empty-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S_(GGGGS)2_IL15Ra(Sushi-D96/C97)_IL15(E87C)_IgG1_ISO(+RR)_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - empty-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S_(GGGGS)2_IL15Ra(Sushi-D96/C97) (17605)
(SEQ ID NO:145)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEE
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPS
DIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK/GGGGS
GGGGS/ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDC

Chain 2 - empty-Fc(216)_IgG1_ISO(+RR)_C220S/PVA_/S267K/S364K/E357Q (8927)
(SEQ ID NO:146)
ERKSSDKTHTCPRCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFKWYVDGVEVHNAKTKPREEQ
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYP
SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 3 - human_IL15_E87C_no_tag (17074) (SEQ ID NO:147)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKCCEELEEKNIKEFLQSFVHIVQMFINTS

>XENP022640 empty-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S_IgG1_ISO(+RR)_C220S/PVA_/S267K/S364K/E357Q_(GGGGS)2_IL15Ra(Sushi-D96/C97)_IL15(E87C)

Chain 1 – IL15 (SEQ ID NO:148)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKCCEELEEKNIKEFLQSFVHIVQMFINTS

Chain 2 – empty_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:149)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEE
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPS
DIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Figure 44

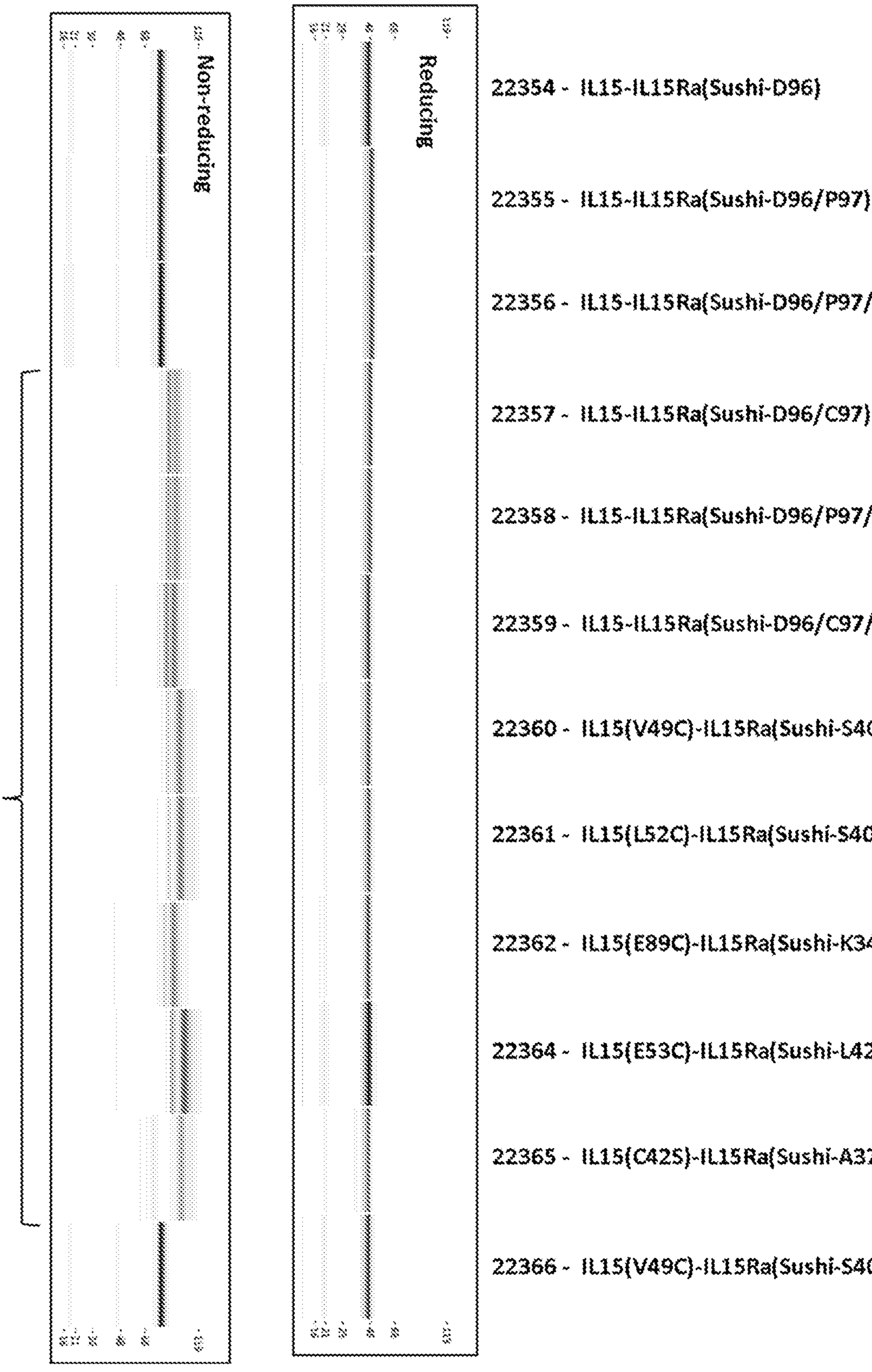

Non-reducing
Reducing
+ disulfide
22354 - IL15-IL15Ra(Sushi-D96)
22355 - IL15-IL15Ra(Sushi-D96/P97)
22356 - IL15-IL15Ra(Sushi-D96/P97/A98)
22357 - IL15-IL15Ra(Sushi-D96/C97)
22358 - IL15-IL15Ra(Sushi-D96/P97/C98)
22359 - IL15-IL15Ra(Sushi-D96/C97/A98)
22360 - IL15(V49C)-IL15Ra(Sushi-S40C)
22361 - IL15(L52C)-IL15Ra(Sushi-S40C)
22362 - IL15(E89C)-IL15Ra(Sushi-K34C)
22364 - IL15(E53C)-IL15Ra(Sushi-L42C)
22365 - IL15(C42S)-IL15Ra(Sushi-A37C)
22366 - IL15(V49C)-IL15Ra(Sushi-S40C)

Figure 45A

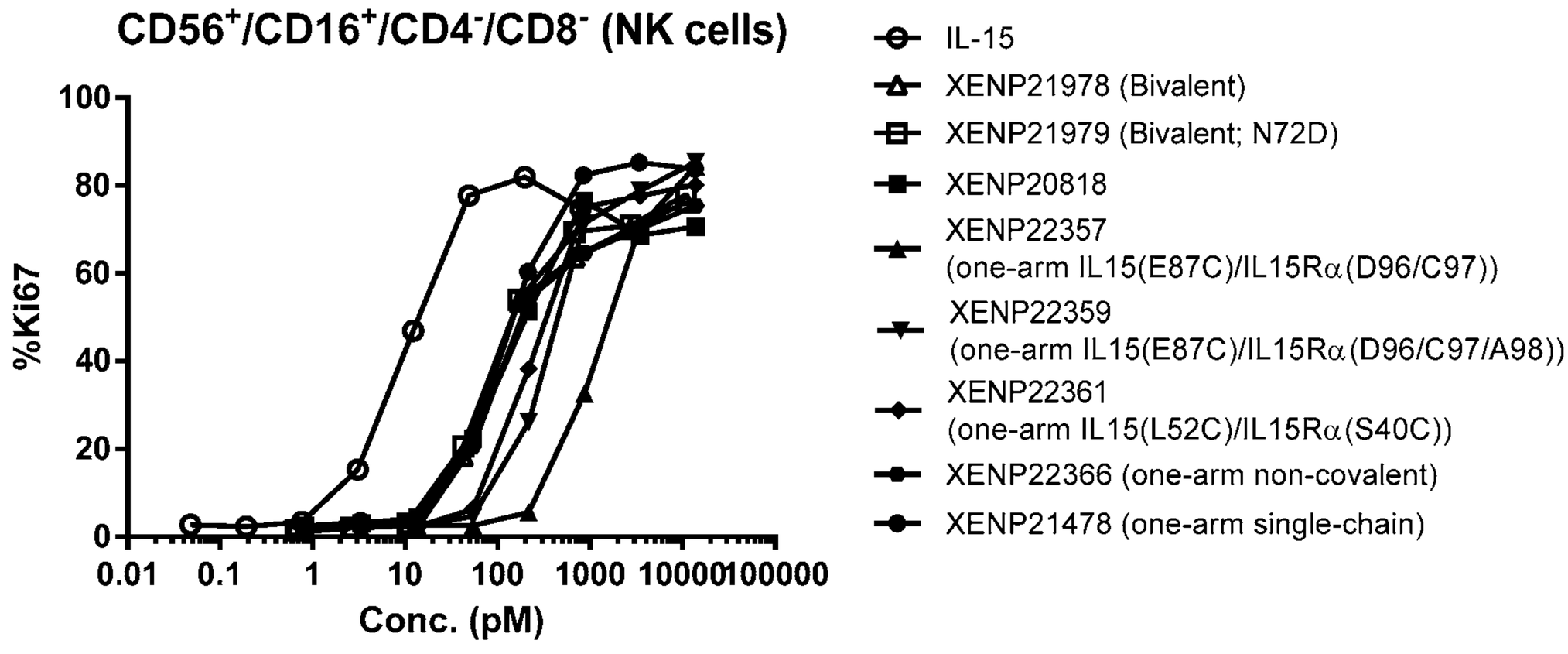


Figure 45B

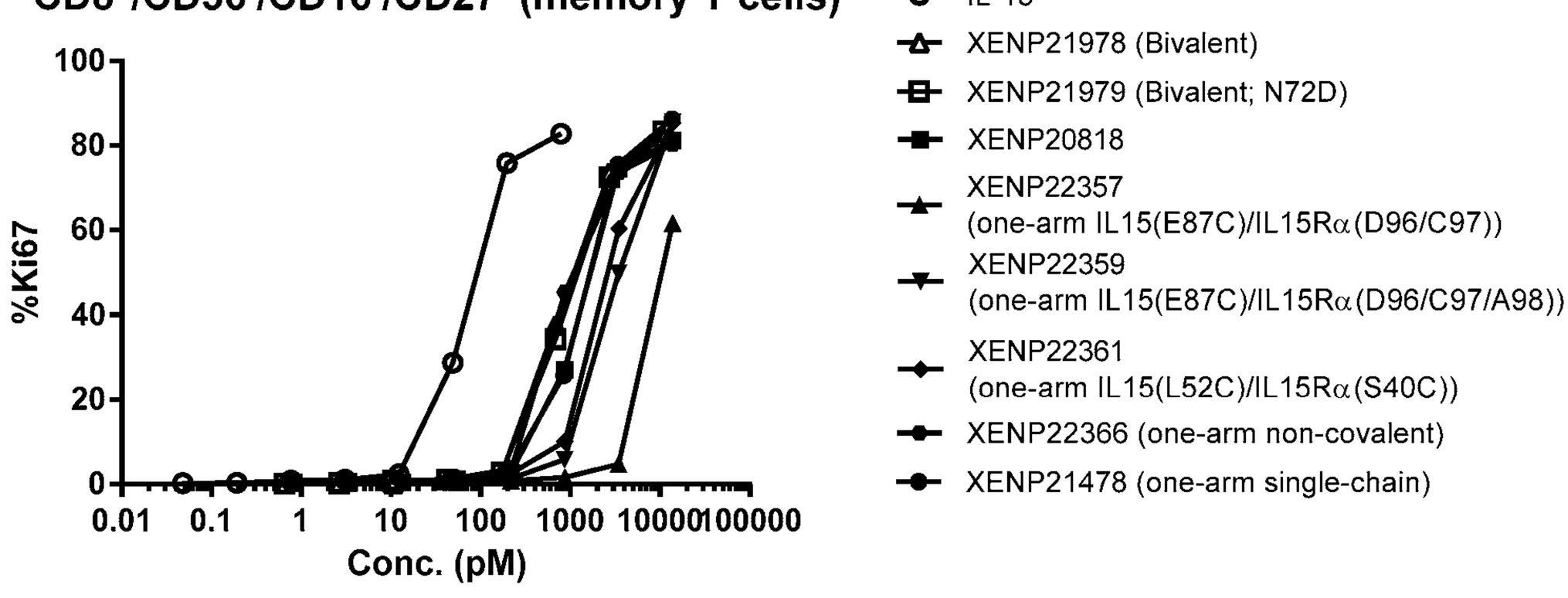


Figure 45C

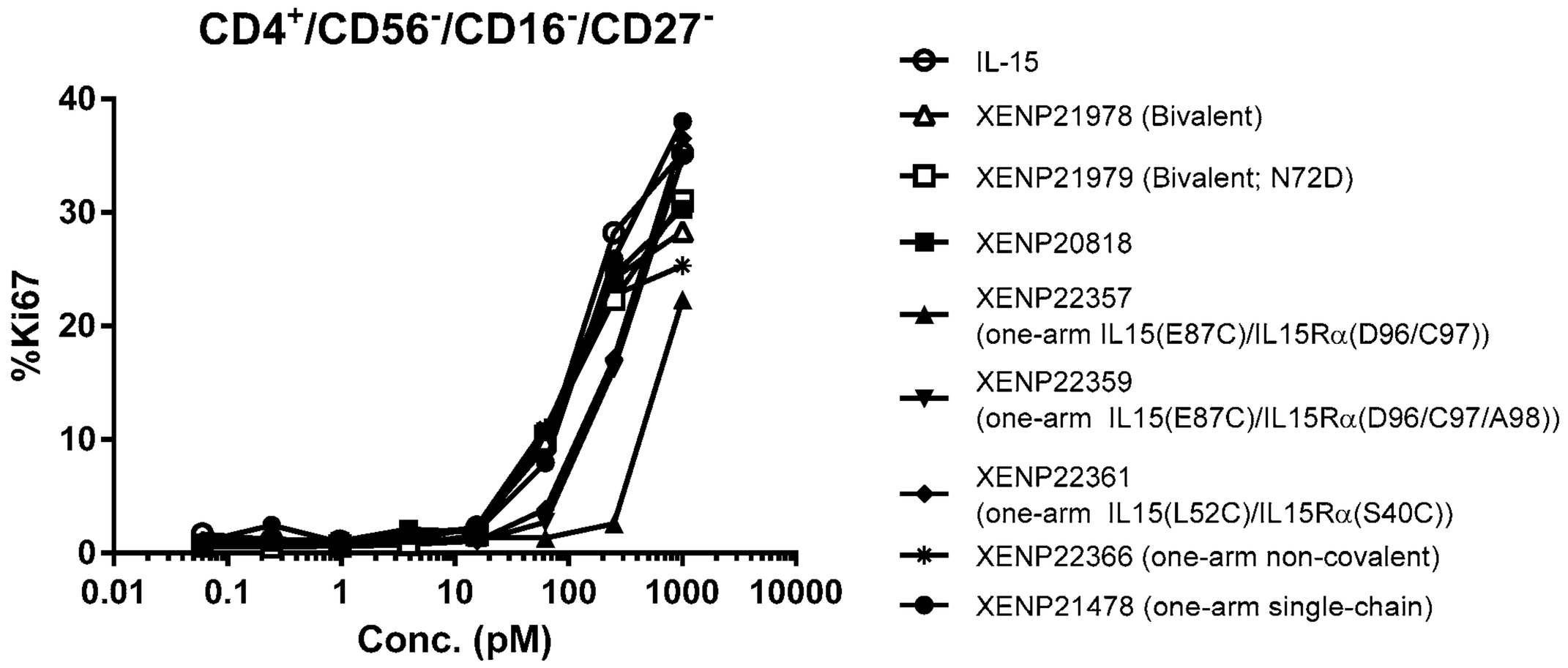

CD4+/CD56-/CD16-/CD27-
%Ki67
Conc. (pM)
0.01
0.1
1
10
100
1000
10000
0
10
20
30
40
IL-15
XENP21978 (Bivalent)
XENP21979 (Bivalent; N72D)
XENP20818
XENP22357
(one-arm IL15(E87C)/IL15Rα(D96/C97))
XENP22359
(one-arm IL15(E87C)/IL15Rα(D96/C97/A98))
XENP22361
(one-arm IL15(L52C)/IL15Rα(S40C))
XENP22366 (one-arm non-covalent)
XENP21478 (one-arm single-chain)

Figure 46

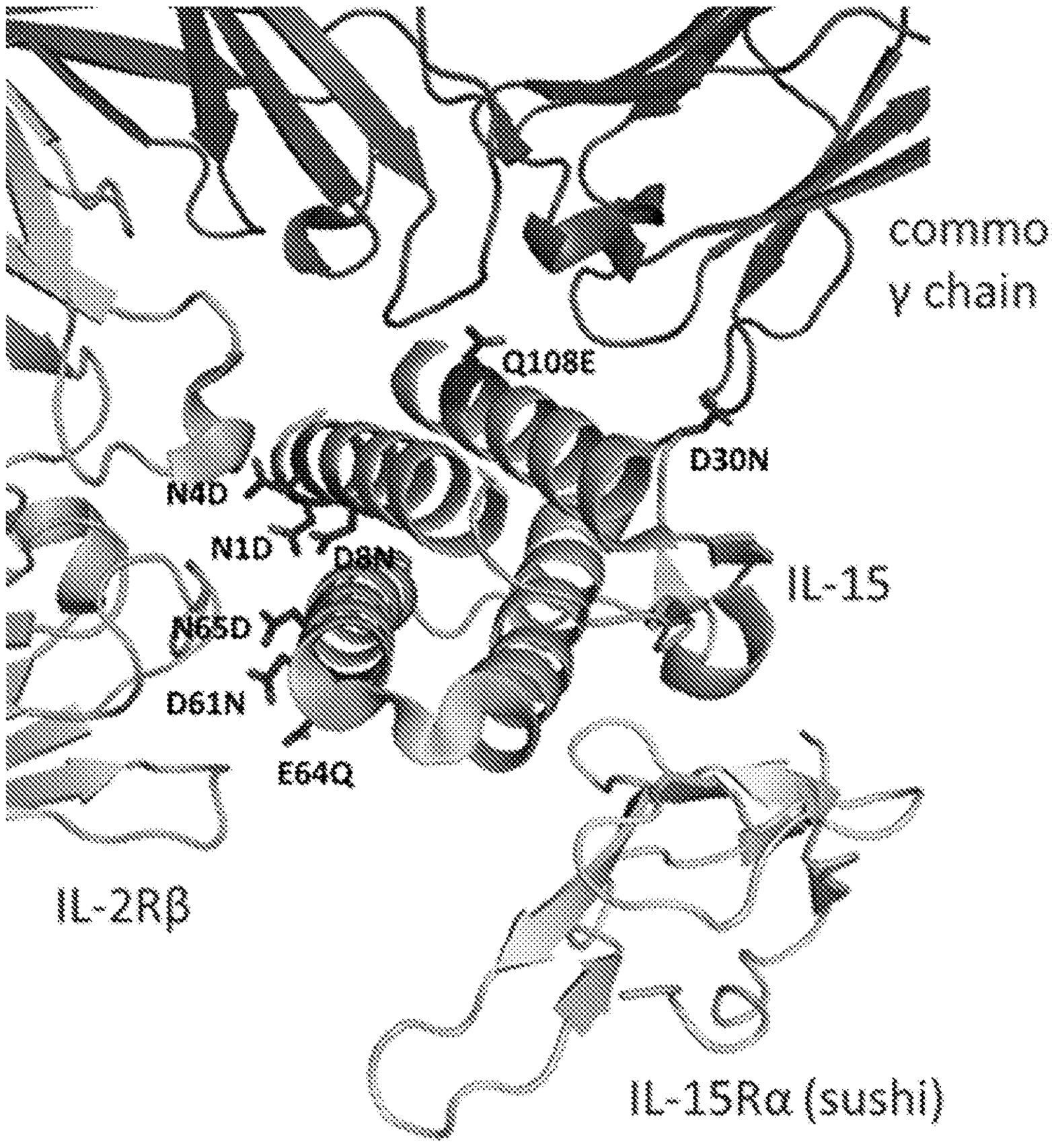

common
γ chain
Q108E
D30N
N4D
N1D
D8N
IL-15
N65D
D61N
E64Q
IL-2Rβ
IL-15Rα (sushi)

Figure 47A

N1D (SEQ ID NO:150)
DWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

N4D (SEQ ID NO:151)
NWVDVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

D8N (SEQ ID NO:152)
NWVNVISNLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

D30N (SEQ ID NO:153)
NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

D61N (SEQ ID NO:154)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHNTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

E64Q (SEQ ID NO:155)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVQNLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

N65D (SEQ ID NO:156)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

Q108E (SEQ ID NO:157)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVEMFINTS

N1D/D61N (SEQ ID NO:158)
DWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHNTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 47B

N1D/E64Q (SEQ ID NO:159)
DWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVQNLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

N4D/D61N (SEQ ID NO:160)
NWVDVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHNTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

N4D/E64Q (SEQ ID NO:161)
NWVDVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVQNLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

D8N/D61N (SEQ ID NO:162)
NWVNVISNLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHNTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

D8N/E64Q (SEQ ID NO:163)
NWVNVISNLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVQNLIILANNSLSSNGNVT
ESGCKECEELEEKNIKEFLQSFVHIVQMFINTS

D61N/E64Q (SEQ ID NO:164)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHNTVQNLIILANNSLSSNGNVT
ESGCKECEELEEKNIKEFLQSFVHIVQMFINTS

E64Q/Q108E (SEQ ID NO:165)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVQNLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVEMFINTS

N1D/N4D/D8N (SEQ ID NO:166)
DWVDVISNLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

D61N/E64Q/N65D (SEQ ID NO:167)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHNTVQDLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

N1D/D61N/E64Q/Q108E (SEQ ID NO:168)
DWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHNTVQNLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVEMFINTS

N4D/D61N/E64Q/Q108E (SEQ ID NO:169)
NWVDVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHNTVQNLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVEMFINTS

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 47C

N1D/N65D (SEQ ID NO:170)
DWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

N1D/Q108E (SEQ ID NO:171)
DWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVEMFINTS

N4D/N65D (SEQ ID NO:172)
NWVDVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

D30N/N65D (SEQ ID NO:173)
NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

D30N/Q108E (SEQ ID NO:174)
NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVEMFINTS

N65D/Q108E (SEQ ID NO:175)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVEMFINTS

E64Q/N65D (SEQ ID NO:176)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVQDLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

N1D/N4D/N65D (SEQ ID NO:177)
DWVDVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

D30N/E64Q/N65D (SEQ ID NO:178)
NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHDTVQDLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

N4D/D61N/N65D (SEQ ID NO:179)
NWVDVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHNTVEDLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 48A

>XENP022816 - human_IL15_N4D_$(GGGGS)_1$-human_IL15Rα(Sushi)_$(GGGGS)_1$_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15_N4D_$(GGGGS)_1$ (17687) (SEQ ID NO:180)
NWVDVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - human_IL15Rα(Sushi)_$(GGGGS)_1$_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (15908) (SEQ ID NO:181)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGS/EPKSSDKTH
TCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>XENP022819 - human_IL15_D61N_$(GGGGS)_1$-human_IL15Rα(Sushi)_$(GGGGS)_1$_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15_D61N_$(GGGGS)_1$ (17690) (SEQ ID NO:182)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHNTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - human_IL15Rα(Sushi)_$(GGGGS)_1$_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (15908) (SEQ ID NO:183)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGS/EPKSSDKTH
TCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Figure 48B

>XENP022820 - human_IL15_E64Q_(GGGGS)$_1$-human_IL15Rα(Sushi)_(GGGGS)$_1$_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15_E64Q_(GGGGS)$_1$ (17691) (SEQ ID NO:184)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVQNLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - human_IL15Rα(Sushi)_(GGGGS)$_1$_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (15908) (SEQ ID NO:185)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGS/EPKSSDKTH
TCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>XENP022821 - human_IL15_N65D_(GGGGS)$_1$-human_IL15Rα(Sushi)_(GGGGS)$_1$_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15_N65D_(GGGGS)$_1$ (17692) (SEQ ID NO:186)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - human_IL15Rα(Sushi)_(GGGGS)$_1$_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (15908) (SEQ ID NO:187)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGS/EPKSSDKTH
TCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

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Figure 48C

>XENP022822 - human_IL15_Q108E_(GGGGS)$_1$-human_IL15Rα(Sushi)_(GGGGS)$_1$_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15_Q108E_(GGGGS)$_1$ (17693) (SEQ ID NO:188)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVEMFINTS/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - human_IL15Rα(Sushi)_(GGGGS)$_1$_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (15908) (SEQ ID NO:189)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGS/EPKSSDKTH
TCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>XENP022829 - human_IL15_D61N/E64Q_(GGGGS)$_1$-human_IL15Rα(Sushi)_(GGGGS)$_1$_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15_D61N/E64Q_(GGGGS)$_1$ (17700) (SEQ ID NO:190)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHNTVQNLIILANNSLSSNGNVT
ESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS
RWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - human_IL15Rα(Sushi)_(GGGGS)$_1$_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (15908) (SEQ ID NO:191)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGS/EPKSSDKTH
TCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Figure 48D

>XENP022834 - human_IL15_N4D/D61N/E64Q/Q108E_$(GGGGS)_1$-human_IL15Rα(Sushi)_$(GGGGS)_1$_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15_N4D/D61N/E64Q/Q108E_$(GGGGS)_1$ (17705) (SEQ ID NO:192)
NWVDVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHNTVQNLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVEMFINTS/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - human_IL15Rα(Sushi)_$(GGGGS)_1$_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (15908) (SEQ ID NO:193)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGS/EPKSSDKTH
TCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>XENP023554 - human_IL15_N1D/N65D_(GGGGS)1-human_IL15Ra(Sushi)_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15_N1D/N65D_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (18783) (SEQ ID NO:194)
DWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - human_IL15Ra(Sushi)_(GGGGS)1_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (15908) (SEQ ID NO:195)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGS/EPKSSDKTH
TCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Figure 48E

>XENP023557 - human_IL15_N4D/N65D_(GGGGS)1-human_IL15Ra(Sushi)_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15_N4D/N65D_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (18786) (SEQ ID NO:196)
NWVDVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - human_IL15Ra(Sushi)_(GGGGS)1_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (15908) (SEQ ID NO:197)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>XENP023561 human_IL15_N65D/Q108E_(GGGGS)1-human_IL15Ra(Sushi)_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15_N65D/Q108E_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:198)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVEMFINTS/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - human_IL15Ra(Sushi)_(GGGGS)1_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:199)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

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Figure 48F

>XENP024018 human_IL15(N65D)-human_IL15Ra(Sushi)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15(N65D)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S
(SEQ ID NO:200)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - human_IL15Ra(Sushi)_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q
(SEQ ID NO:201)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>XENP024019 - human_IL15(Q108E)-human_IL15Ra(Sushi)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15(Q108E)-human_IL15Ra(Sushi)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (19242)
(SEQ ID NO:202)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVEMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - human_IL15Ra(Sushi)_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (16481)
(SEQ ID NO:203)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

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Figure 48G

>XENP024045 human_IL15_D30N/E64Q/N65D_(GGGGS)1-human_IL15Rα(Sushi)_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 – human_IL15_D30N/E64Q/N65D_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:204)
NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHDTVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 – human_IL15Rα(Sushi)_(GGGGS)1_ Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:205)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>XENP024051 human_IL15_N1D/N65D-human_IL15Rα(Sushi)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 – human_IL15_N1D/N65D-human_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:206)
DWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 – human_IL15Rα(Sushi)_ Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:207)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Figure 48H

>XENP024052 human_IL15_N4D/N65D-human_IL15Rα(Sushi)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 – human_IL15_N4D/N65D-human_ Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:208)
NWVDVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 – human_IL15Rα(Sushi)_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:209)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

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Figure 49A

>XENP024015 human_IL15Ra(sushi)_(GGGGS)5-human_IL15(Q108E;single-chain)-empty-Fc_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15Ra(sushi)_(GGGGS)5-human_IL15(Q108E;single-chain) _Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:210)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGSGGGGSGGGGSGGGGSGGGGS/NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLII
LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVEMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL
PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYS
KLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 – empty_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:211)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>XENP024050 human_IL15Ra(sushi)_(GGGGS)5-human_IL15_N4D/N65D_(single-chain)-empty-Fc_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15Ra(sushi)_(GGGGS)5-human_IL15_N4D/N65D_(single-chain)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:212)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGSGGGGSGGGGSGGGGSGGGGS/NWVDVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLII
LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL
PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYS
KLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 – empty_ Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:213)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

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Figure 49B

>XENP024475 human_IL15Ra(sushi)_(GGGGS)6-human_IL15(single-chain;Q108E)-empty-Fc_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15Ra(sushi)_(GGGGS)6-human_IL15(single-chain;Q108E)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:214)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS/NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVEMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 – empty_ Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:215)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>XENP024476 human_IL15Ra(sushi)_(GGGGS)6-human_IL15(single-chain;N4D/N65D)-empty-Fc_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15Ra(sushi)_(GGGGS)6-human_IL15(single-chain;N4D/N65D)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:216)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS/NWVDVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 – empty_ Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:217)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 49C

>XENP024478 human_IL15Ra(sushi)_(GGGGS)7-human_IL15(single-chain;Q108E)-empty-Fc_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15Ra(sushi)_(GGGGS)7-human_IL15(single-chain;Q108E)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:218)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS/NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVEMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 – empty_ Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:219)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>XENP024479 human_IL15Ra(sushi)_(GGGGS)7-human_IL15(single-chain;N4D/N65D)-empty-Fc_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15Ra(sushi)_(GGGGS)7-human_IL15(single-chain;N4D/N65D)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:220)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS/NWVDVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - empty-Fc_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:221)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

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Figure 49D

>XENP024481 human_IL15Ra(sushi)_(30AA_linker_variant)-human_IL15(single-chain;Q108E)-empty-Fc_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 - human_IL15Ra(sushi)_(30AA_linker_variant)-human_IL15(single-chain;Q108E)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:222)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/DPALVHQRPAPPGGGGSGGGGSGGGGSGGG/NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVEMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 – empty_ Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:223)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Figure 50A

>XENP024349 IL15_Q108E_(non-covalent)-human_IL15Rα(Sushi)_empty-Fc_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 – human_IL15Rα(Sushi)_ Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:224)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/EPKSSDKTHTCPPCP
APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 – empty- Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:225)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 3 – IL15_Q108E_(non-covalent) (SEQ ID NO:226)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVEMFINTS

>XENP024890 IL15_N4D/N65D_(non-covalent)-human_IL15Ra(Sushi)-empty-Fc_IgG1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-IgG1_PVA_/S267K/S364K/E357Q

Chain 1 – IL-15_N4D/N65D (SEQ ID NO:227)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/EPKSSDKTHTCPPCP
APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - human_IL15Ra(Sushi)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S
(SEQ ID NO:228)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/EPKSSDKTHTCPPCP
APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 3 – empty_Fc(216)_ IgG1_PVA_/S267K/S364K/E357Q
(SEQ ID NO:229)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

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Figure 50B

>XENP25138 IL15_D30N/E64Q/N65D_(non-covalent)-empty-Fc_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-IgG1_PVA_/S267K/S364K/E357Q

Chain 1 - IL15_D30N/E64Q/N65D (SEQ ID NO:230)
NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHDTVQDLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

Chain 2 - human_IL15Ra(Sushi)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S
(SEQ ID NO:231)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/EPKSSDKTHTCPPCP
APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 3 - empty_Fc(216)_ IgG1_PVA_/S267K/S364K/E357Q (SEQ ID NO:232)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

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Figure 51

>XENP022801 - human_IL15_N65D(non-covalent)-human_IL15Rα(Sushi)

Chain 1 - human_IL15_N65D(non-covalent) (17672) (SEQ ID NO:233)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

Chain 2 - human_IL15Rα(Sushi) (17033) (SEQ ID NO:234)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR

>XENP022802 - human_IL15_Q108E(non-covalent)-human_IL15Rα(Sushi)

Chain 1 - human_IL15_Q108E(non-covalent) (17673) (SEQ ID NO:235)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVEMFINTS

Chain 2 - human_IL15Rα(Sushi) (17033) (SEQ ID NO:236)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 52

>XENP024342 human_IL15(non-covalent; Q108E)-
human_IL15Rα(Sushi)_Fc(216)_IgG1_C220S/PVA_/S267K

Chain 1 – human_IL15Rα(Sushi) _Fc(216)_IgG1_C220S/PVA_/S267K (SEQ ID NO:237)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/EPKSSDKTHTCPPCP
APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 –human_IL15(non-covalent; Q108E) (SEQ ID NO:238)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVEMFINTS

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 53

>XENP023472 empty-Fc-IL15_N65D/E87C-human_IL15Ra(Sushi-D96/C97)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 – empty_ Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S
(SEQ ID NO:239)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEE
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPS
DIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - IL15_N65D/E87C (SEQ ID NO:240)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTE
SGCKCCEELEEKNIKEFLQSFVHIVQMFINTS

Chain 3 - IL15Ra(Sushi-D96/C97)_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q
(SEQ ID NO:241)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIRDC/EPKSSDKTHTCPP
CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT
VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNG
QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>XENP023473 empty-Fc-IL15_N65D/L52C-human_IL15Ra(Sushi-S40C)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

Chain 1 – empty_ Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:242)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEE
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPS
DIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

Chain 2 - IL15_N65D/L52C (SEQ ID NO:243)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISCESGDASIHDTVEDLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

Chain 3 - IL15Ra(Sushi-S40C)_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:244)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTCSLTECVLNKATNVAHWTTPSLKCIR/EPKSSDKTHTCPPCP
APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

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Figure 54A

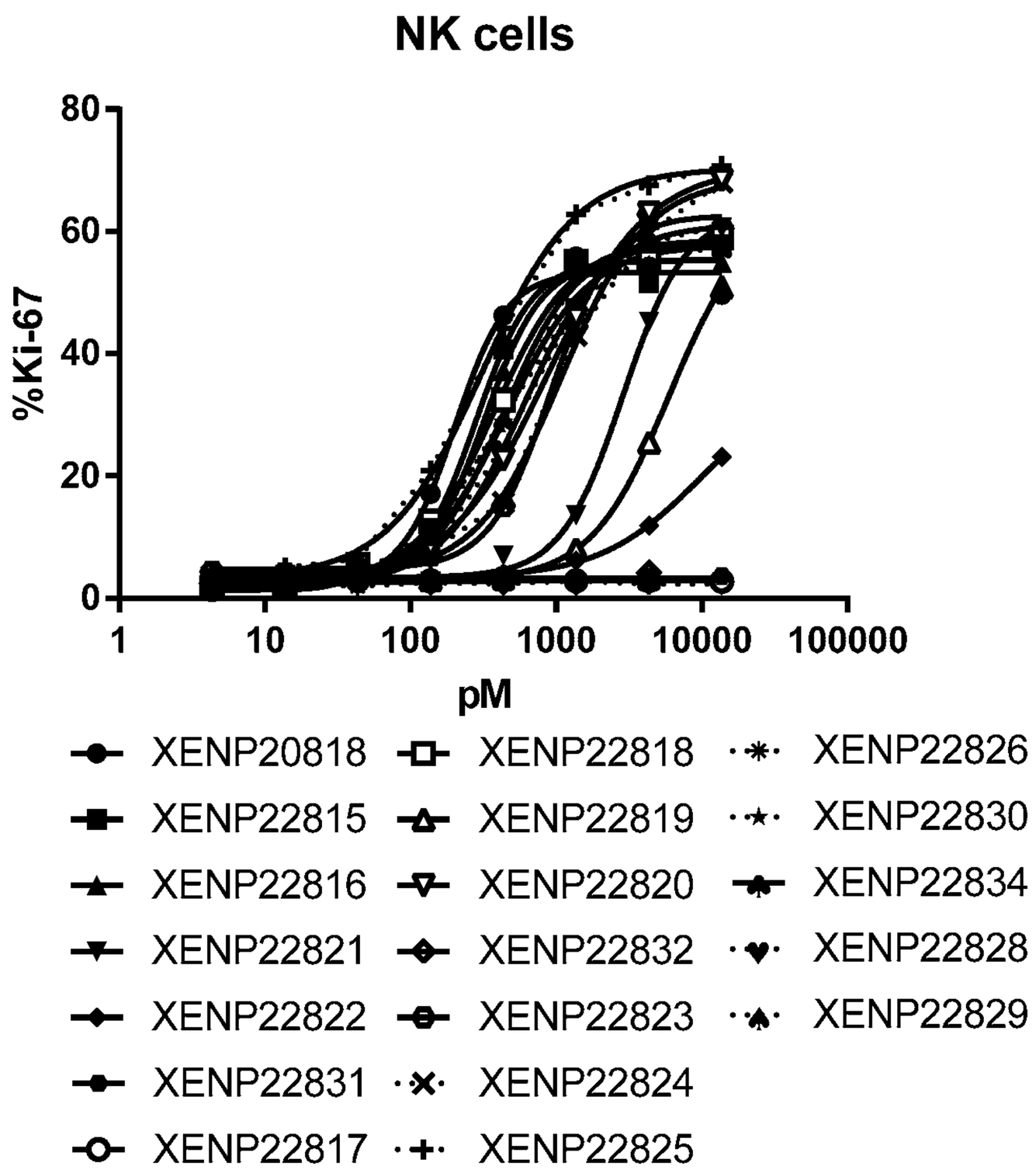

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XENP22819
XENP22830
XENP22816
XENP22820
XENP22834
XENP22821
XENP22832
XENP22828
XENP22822
XENP22823
XENP22829
XENP22831
XENP22824
XENP22817
XENP22825

Figure 54B

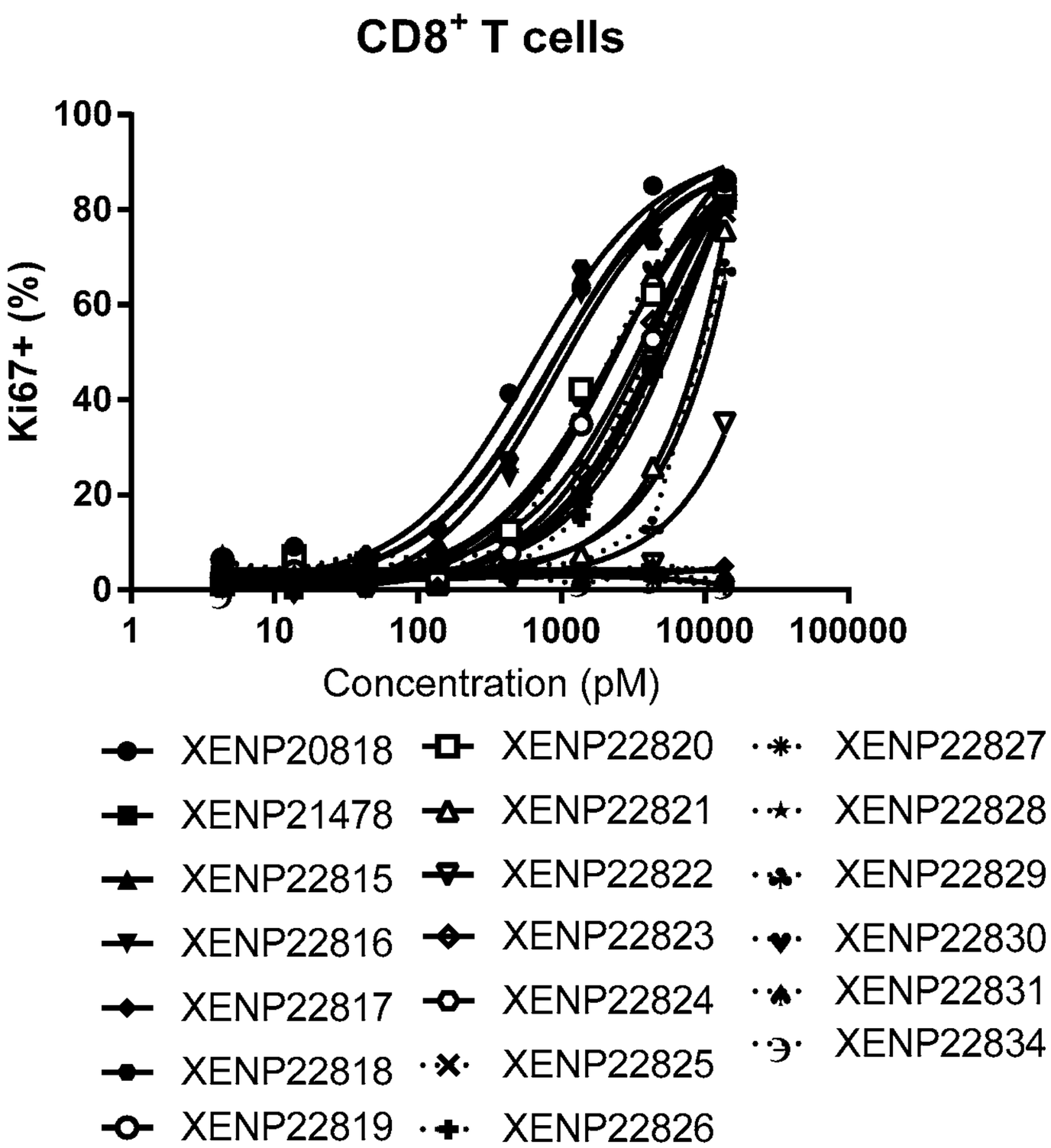

CD8+ T cells
Ki67+ (%)
0
20
40
60
80
100
1
10
100
1000
10000
100000
Concentration (pM)
XENP20818
XENP21478
XENP22815
XENP22816
XENP22817
XENP22818
XENP22819
XENP22820
XENP22821
XENP22822
XENP22823
XENP22824
XENP22825
XENP22826
XENP22827
XENP22828
XENP22829
XENP22830
XENP22831
XENP22834

Figure 54C

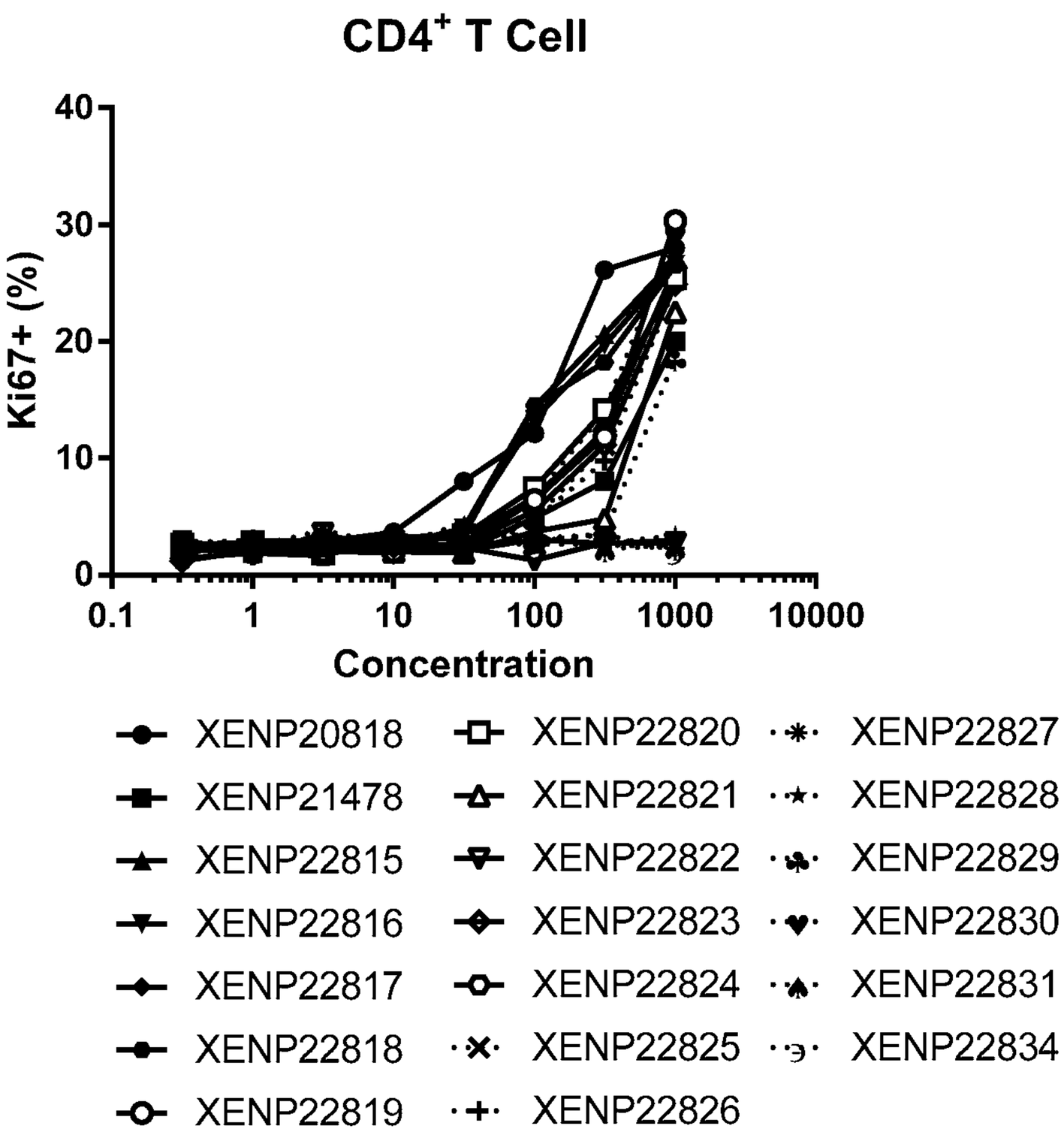

CD4+ T Cell
Ki67+ (%)
0
10
20
30
0.1
1
10
100
1000
10000
Concentration
XENP20818
XENP21478
XENP22815
XENP22816
XENP22817
XENP22818
XENP22819
XENP22820
XENP22821
XENP22822
XENP22823
XENP22824
XENP22825
XENP22826
XENP22827
XENP22828
XENP22829
XENP22830
XENP22831
XENP22834

Figure 55

XENP	Variant	EC50 pM (NK cells)	Fold reduced (NK cells)	EC50 pM (CD8 T cells)	Fold reduced (CD8 T cells)
20818	WT	200.6		637.1	
21478	single-chain	848.5	4.2	4982.0	7.8
22815	N1D	281.3	1.4	1051.0	1.6
22816	N4D	321.9	1.6	1190.0	1.9
22817	D8N	very weak	very weak	very weak	very weak
22818	D30N	376.3	1.9	1366.0	2.1
22819	D61N	5934.0	29.6	161937.0	>100
22820	E64Q	877.0	4.4	2858.0	4.5
22821	N65D	2883.0	14.4	6928.0	10.9
22822	Q108E	9777.0	48.7	very weak	>100
22823	N1D/D61N	918.0	4.6	4225.0	6.6
22824	N1D/E64Q	1091.0	5.4	4228.0	6.6
22825	N4D/D61N	309.0	1.5	1070.0	1.7
22826	N4D/E64Q	very weak	very weak	very weak	very weak
22827	D8N/D61N	ND	ND	ND	ND
22828	D8N/E64Q	597.7	3.0	1658.0	2.6
22829	D61N/E64Q	458.2	2.3	2115.0	3.3
22830	E64Q/Q108E	436.6	2.2	1815.0	2.8
22831	N1D/N4D/D8N	very weak	very weak	very weak	very weak
22832	D61N/E64Q/N65D	ND	ND	ND	ND
22833	N1D/D61N/E64Q/Q108E	ND	ND	ND	ND
22834	N4D/D61N/E64Q/Q108E	very weak	very weak	very weak	very weak

Figures 56A-56C

Figure 56A

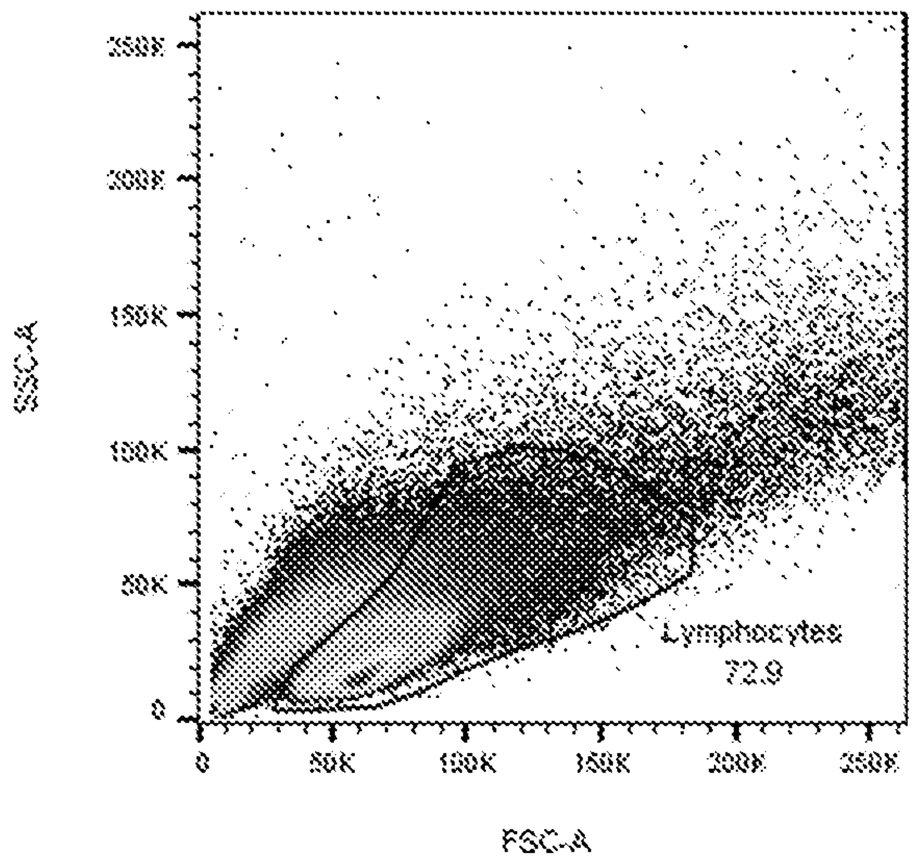


Figure 56B

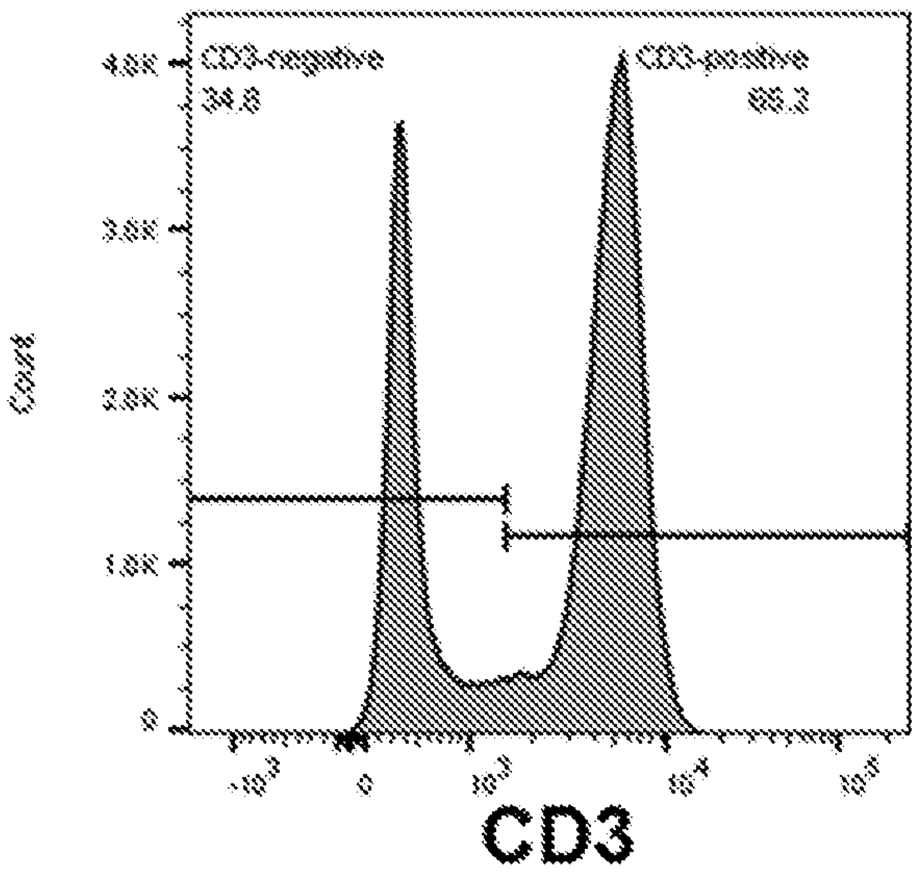


Figure 56C

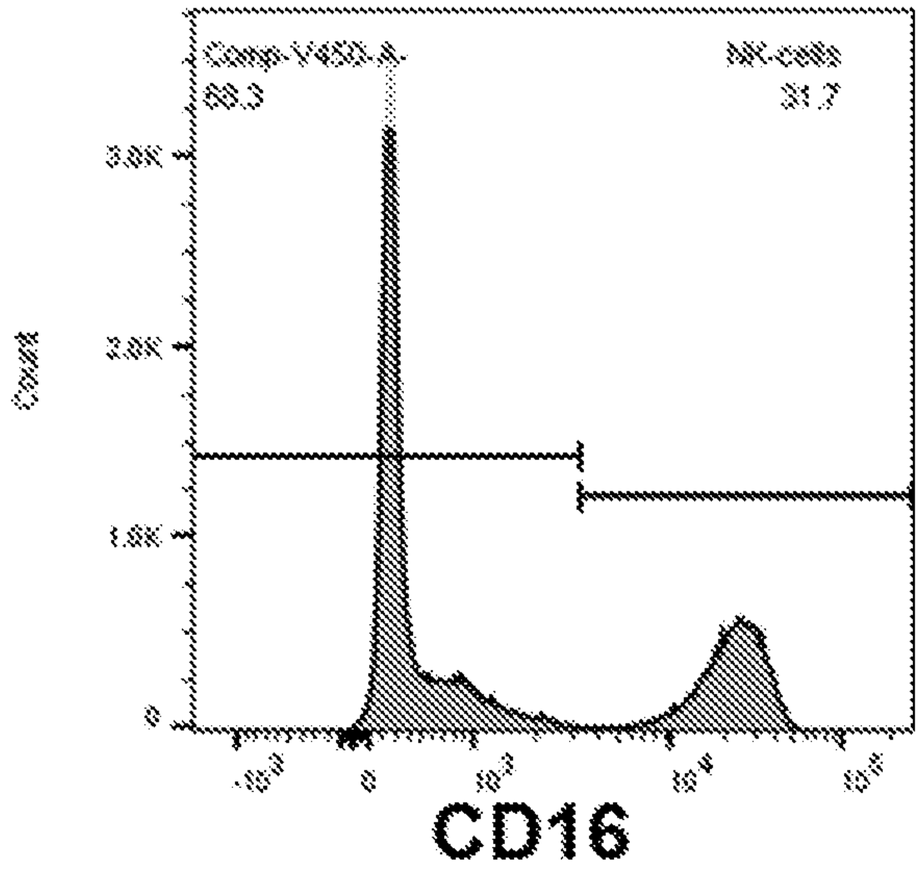


Figure 57A

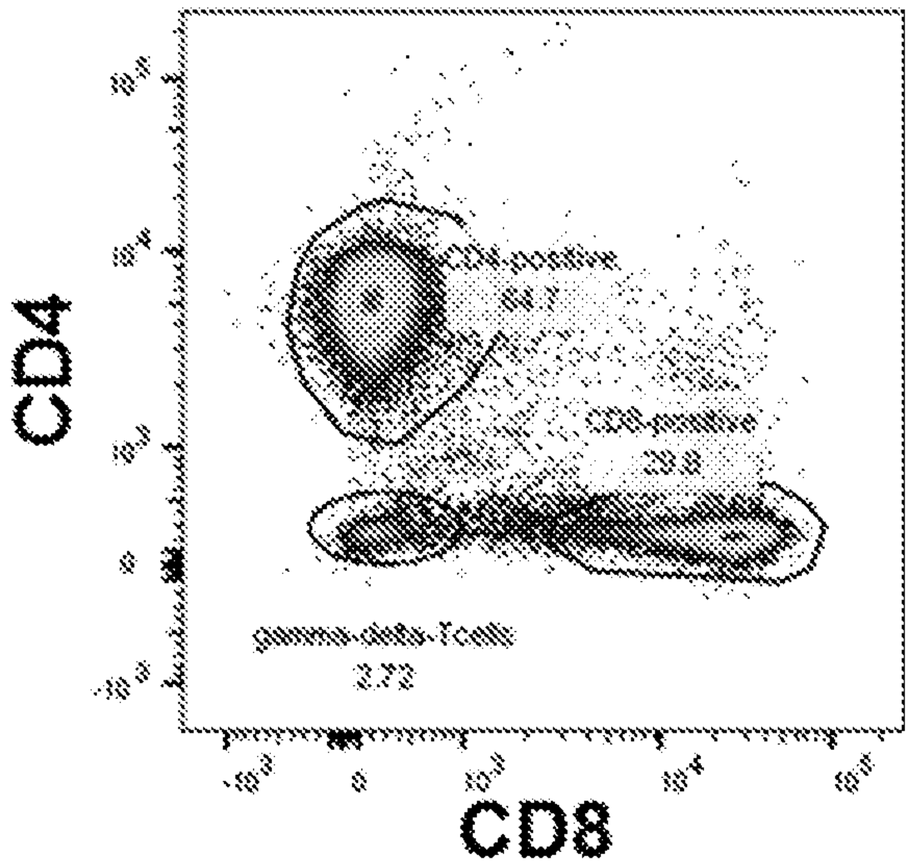


Figure 57B

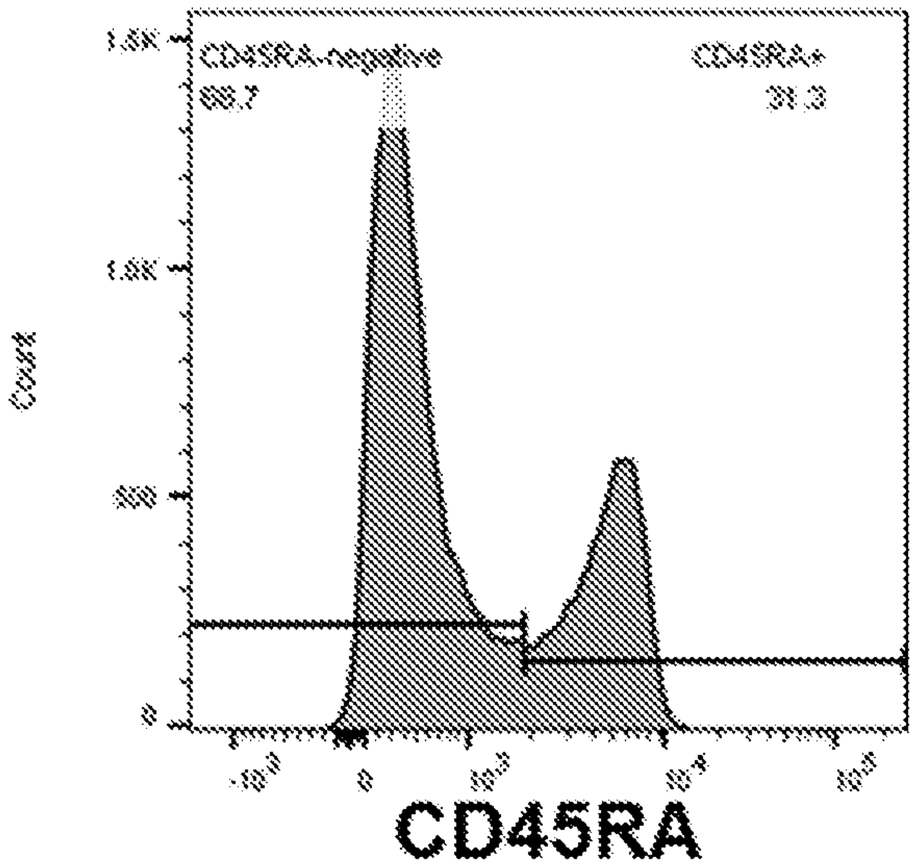


Figure 57C

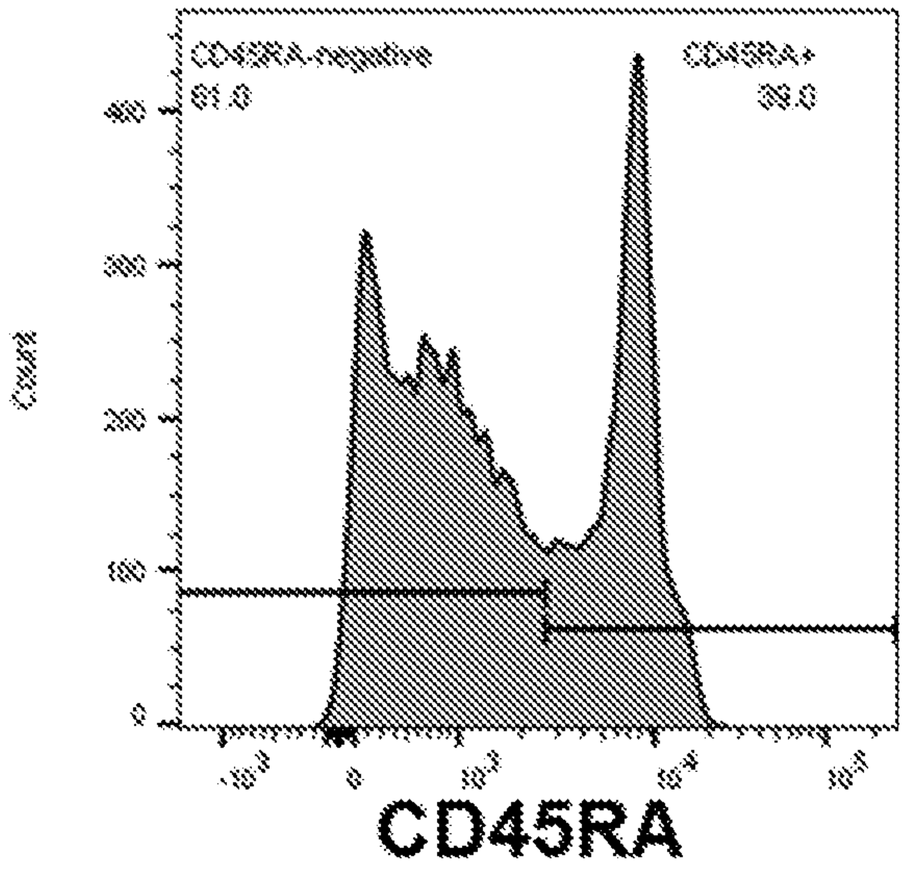


Figure 58A

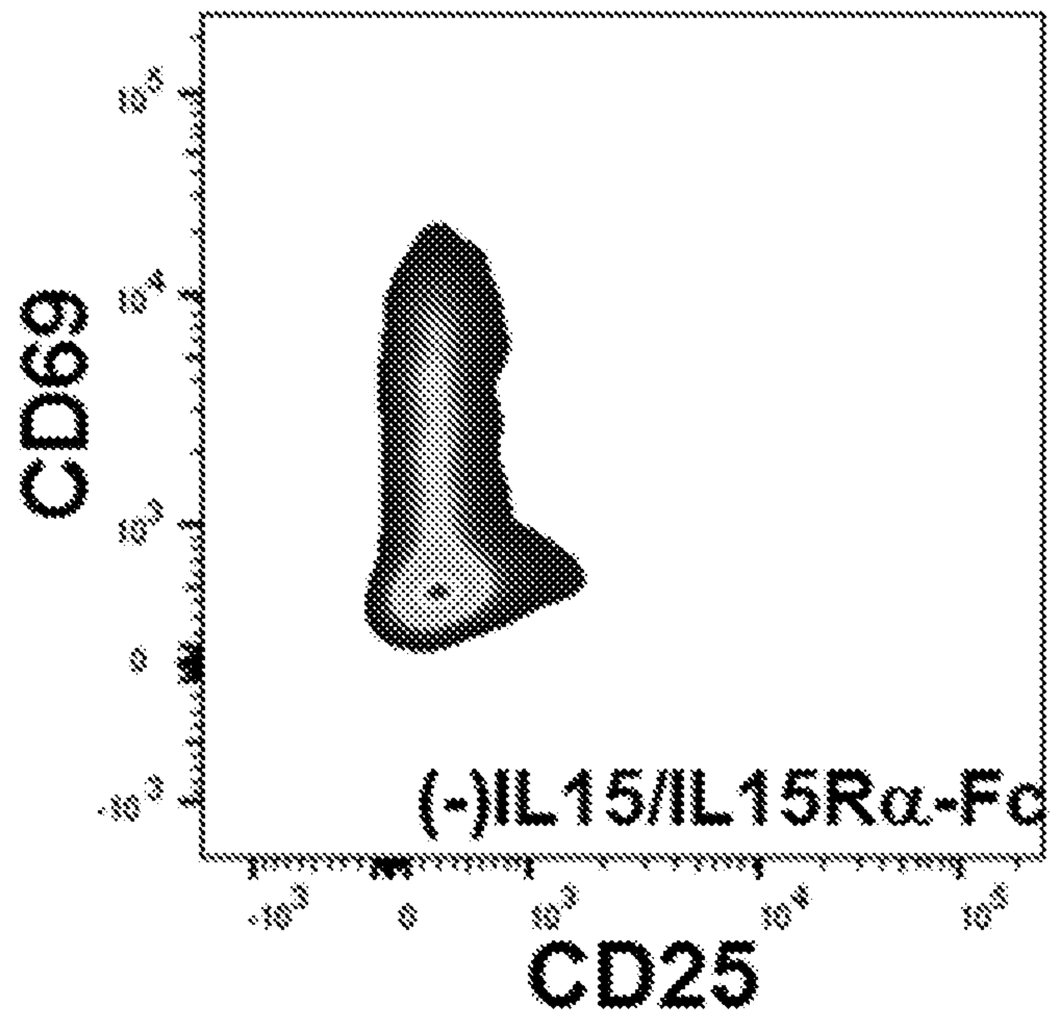


Figure 58B

Figure 59A

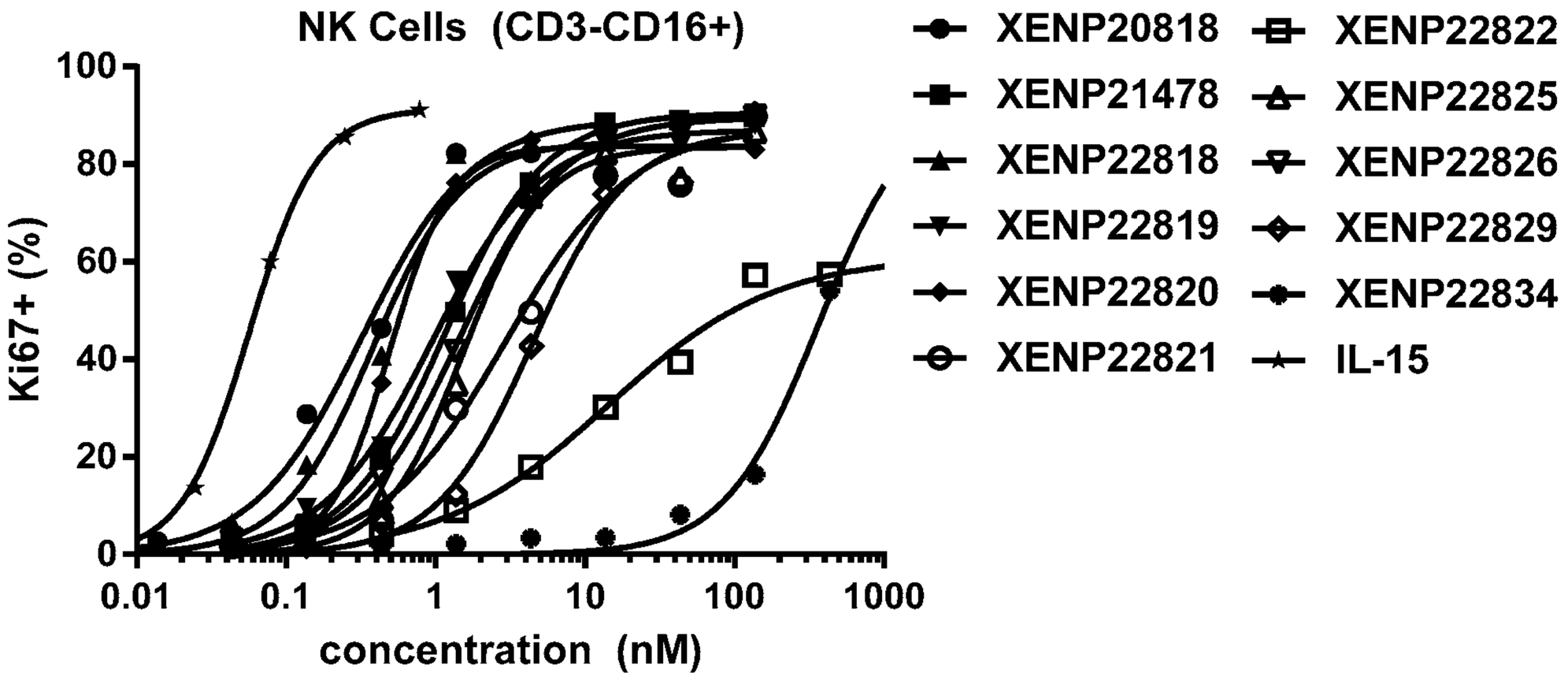


Figure 59B

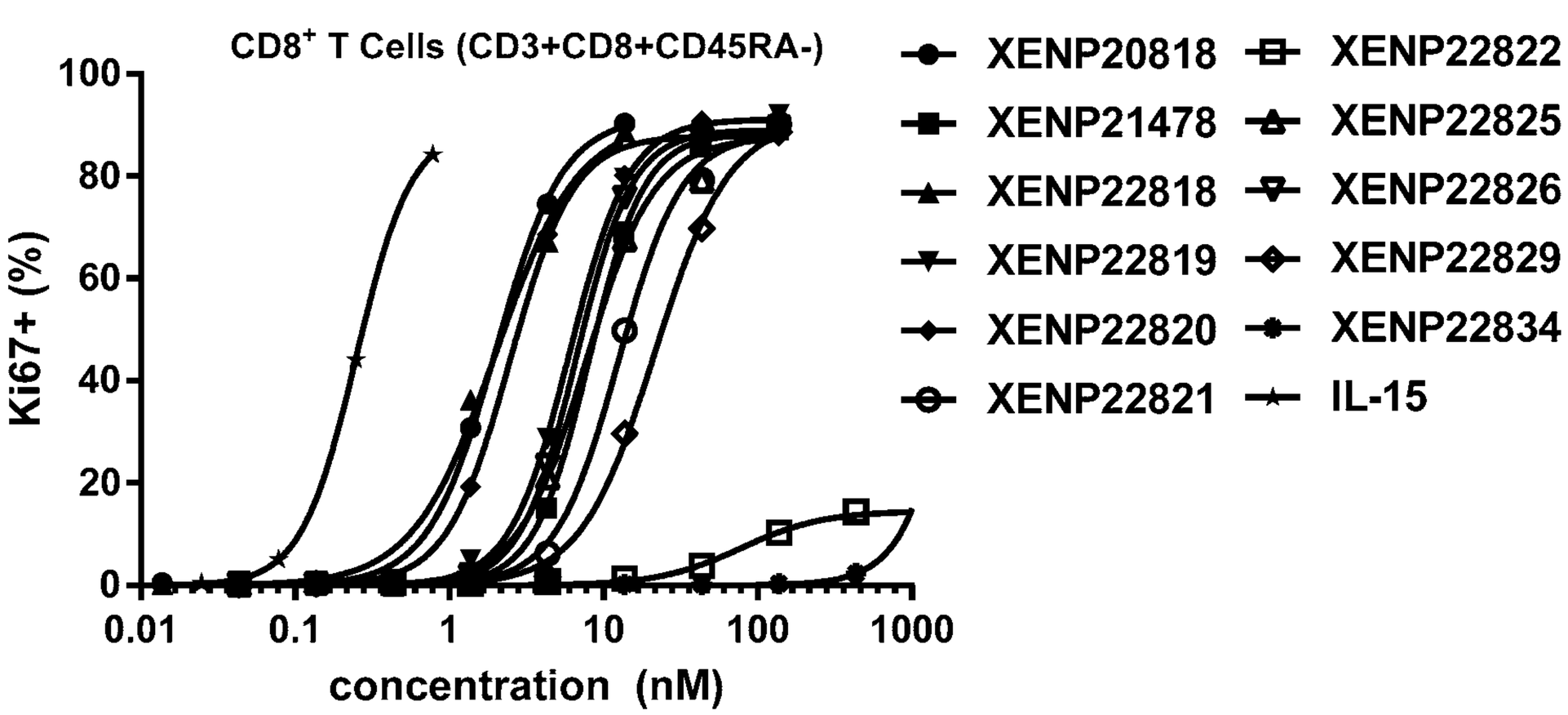


Figure 59C

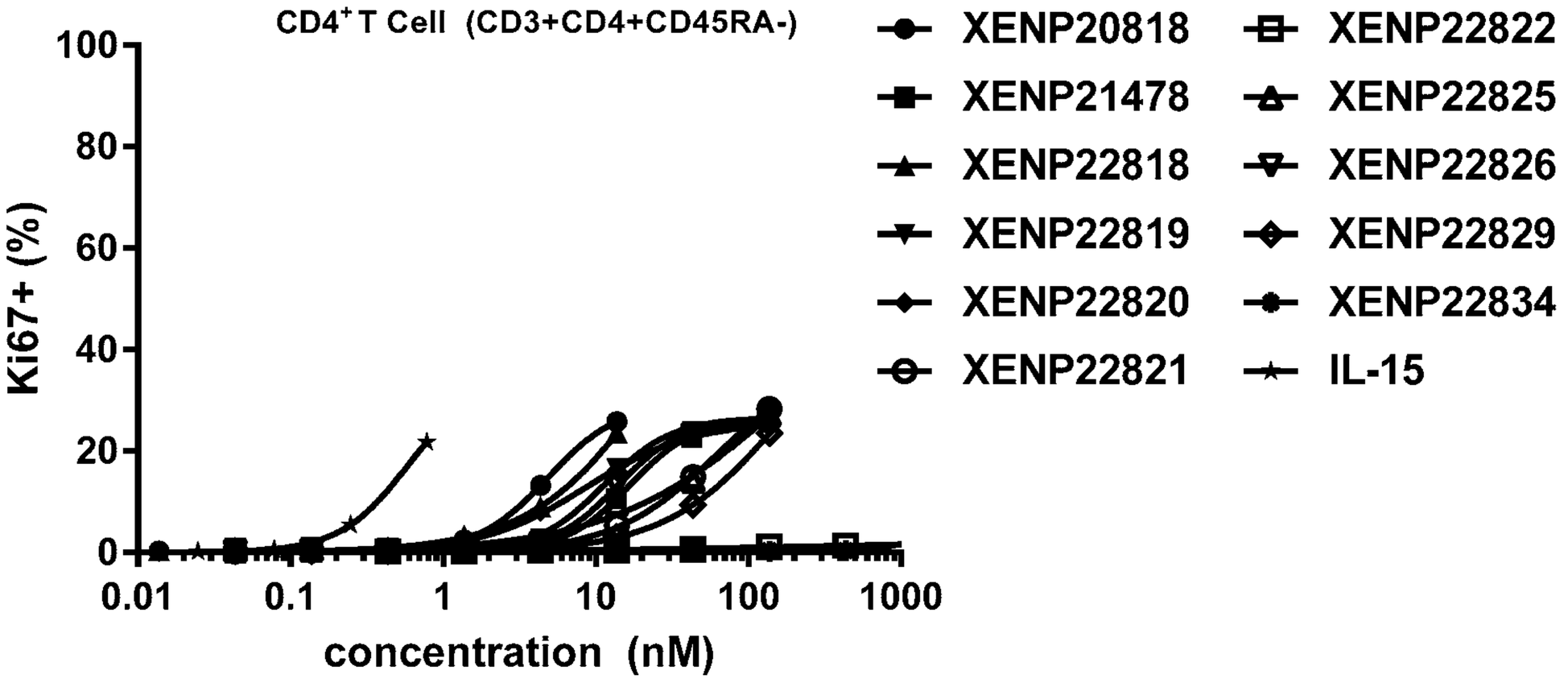

CD4+ T Cell (CD3+CD4+CD45RA-)
XENP20818
XENP21478
XENP22818
XENP22819
XENP22820
XENP22821
XENP22822
XENP22825
XENP22826
XENP22829
XENP22834
IL-15
Ki67+ (%)
100
80
60
40
20
0
0.01
0.1
1
10
100
1000
concentration (nM)

Figure 59D

XENP	EC50 nM (NK cells)	Fold reduced (NK cells)	EC50 nM (CD8 T cells)	Fold reduced (CD8 T cells)	EC50 nM (CD4 T cells)	Fold reduced (CD4 T cells)
20818	0.3223	1.0	2.701	1.0	16.467	1.0
21478	1.116	3.5	11.728	4.3	28.349	1.7
22818	0.4205	1.3	2.829	1.0	40.676	2.5
22819	1.016	3.2	8.254	3.1	18.101	1.1
22820	0.562	1.7	3.918	1.5	10.362	0.6
22821	3.14	9.7	18.706	6.9	112.823	6.9
22822	68.866	213.7	6439.69	2384.2	48.738	3.0
22825	1.769	5.5	12.09	4.5	60.081	3.6
22826	1.448	4.5	9.678	3.6	22.41	1.4
22829	4.839	15.0	29.638	11.0	337.571	20.5
22834	331.293	1027.9	4107.897	1520.9	ND	ND
IL-15	0.05322	0.2	0.3452	0.1	ND	ND

Figure 60A

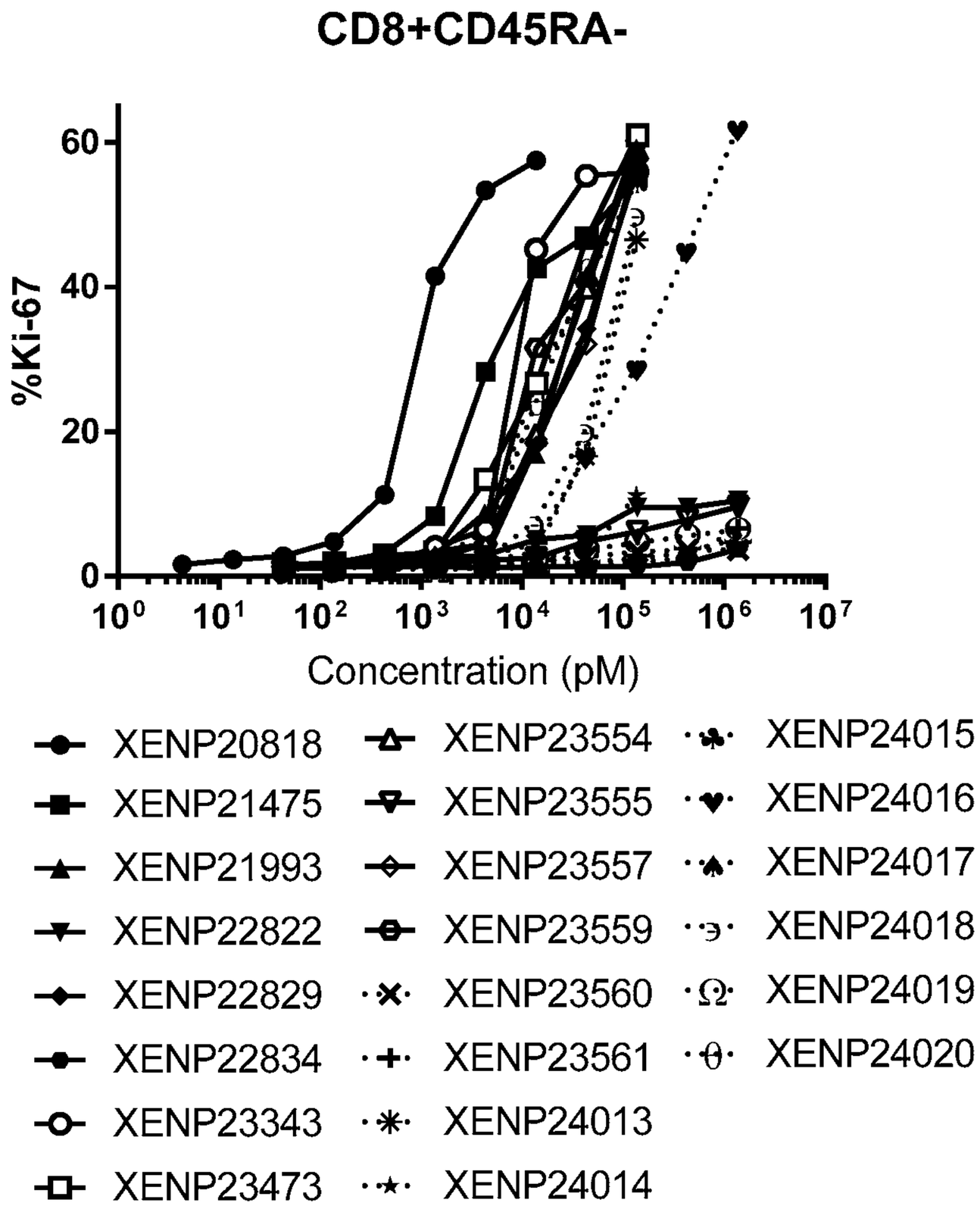

CD8+CD45RA-
%Ki-67
0
20
40
60
10^0
10^1
10^2
10^3
10^4
10^5
10^6
10^7
Concentration (pM)
XENP20818
XENP21475
XENP21993
XENP22822
XENP22829
XENP22834
XENP23343
XENP23473
XENP23554
XENP23555
XENP23557
XENP23559
XENP23560
XENP23561
XENP24013
XENP24014
XENP24015
XENP24016
XENP24017
XENP24018
XENP24019
XENP24020

Figure 60B

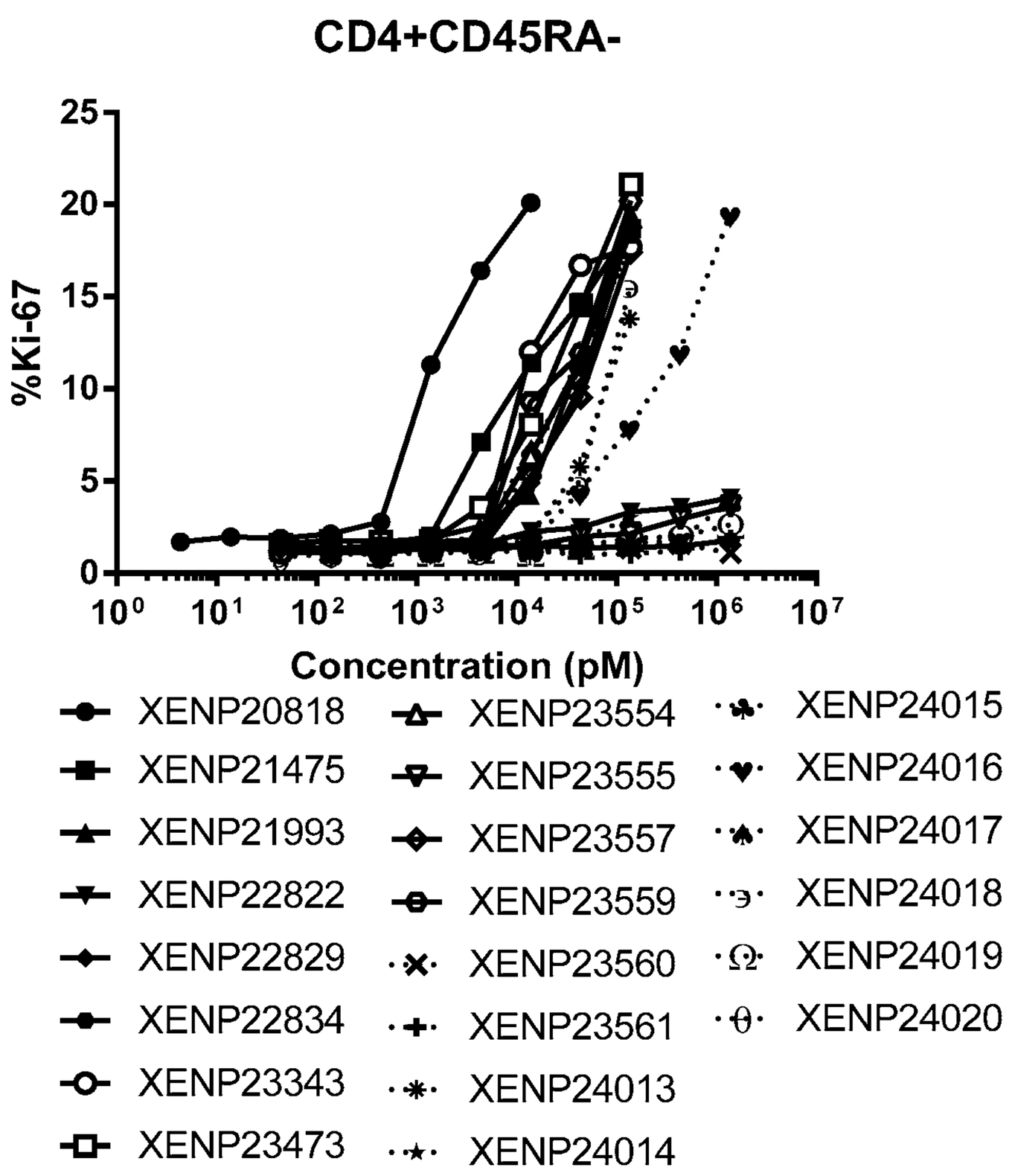

CD4+CD45RA-
%Ki-67
Concentration (pM)
XENP20818
XENP21475
XENP21993
XENP22822
XENP22829
XENP22834
XENP23343
XENP23473
XENP23554
XENP23555
XENP23557
XENP23559
XENP23560
XENP23561
XENP24013
XENP24014
XENP24015
XENP24016
XENP24017
XENP24018
XENP24019
XENP24020

Figure 60C

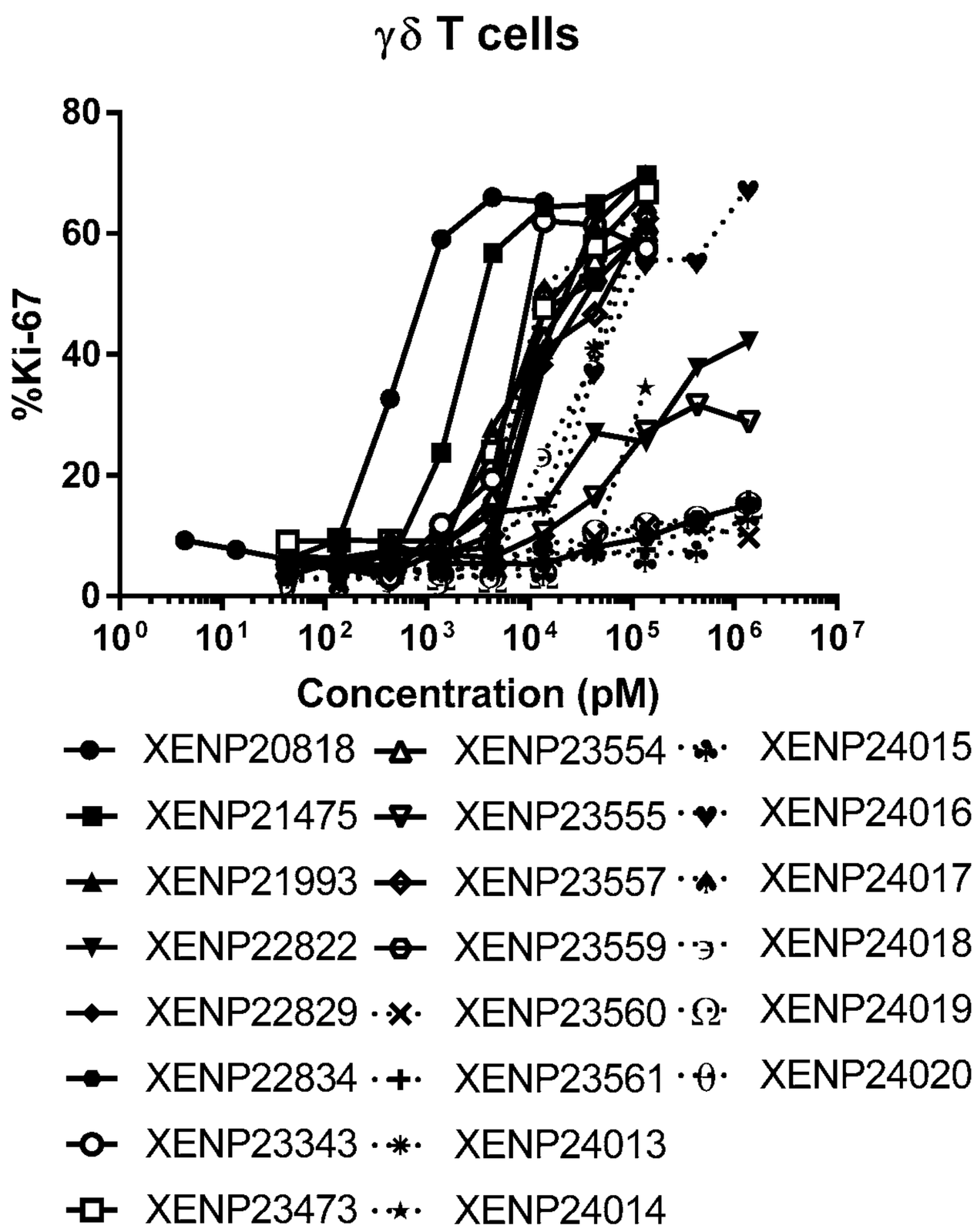

γδ T cells
%Ki-67
Concentration (pM)
XENP20818
XENP21475
XENP21993
XENP22822
XENP22829
XENP22834
XENP23343
XENP23473
XENP23554
XENP23555
XENP23557
XENP23559
XENP23560
XENP23561
XENP24013
XENP24014
XENP24015
XENP24016
XENP24017
XENP24018
XENP24019
XENP24020

Figure 60D

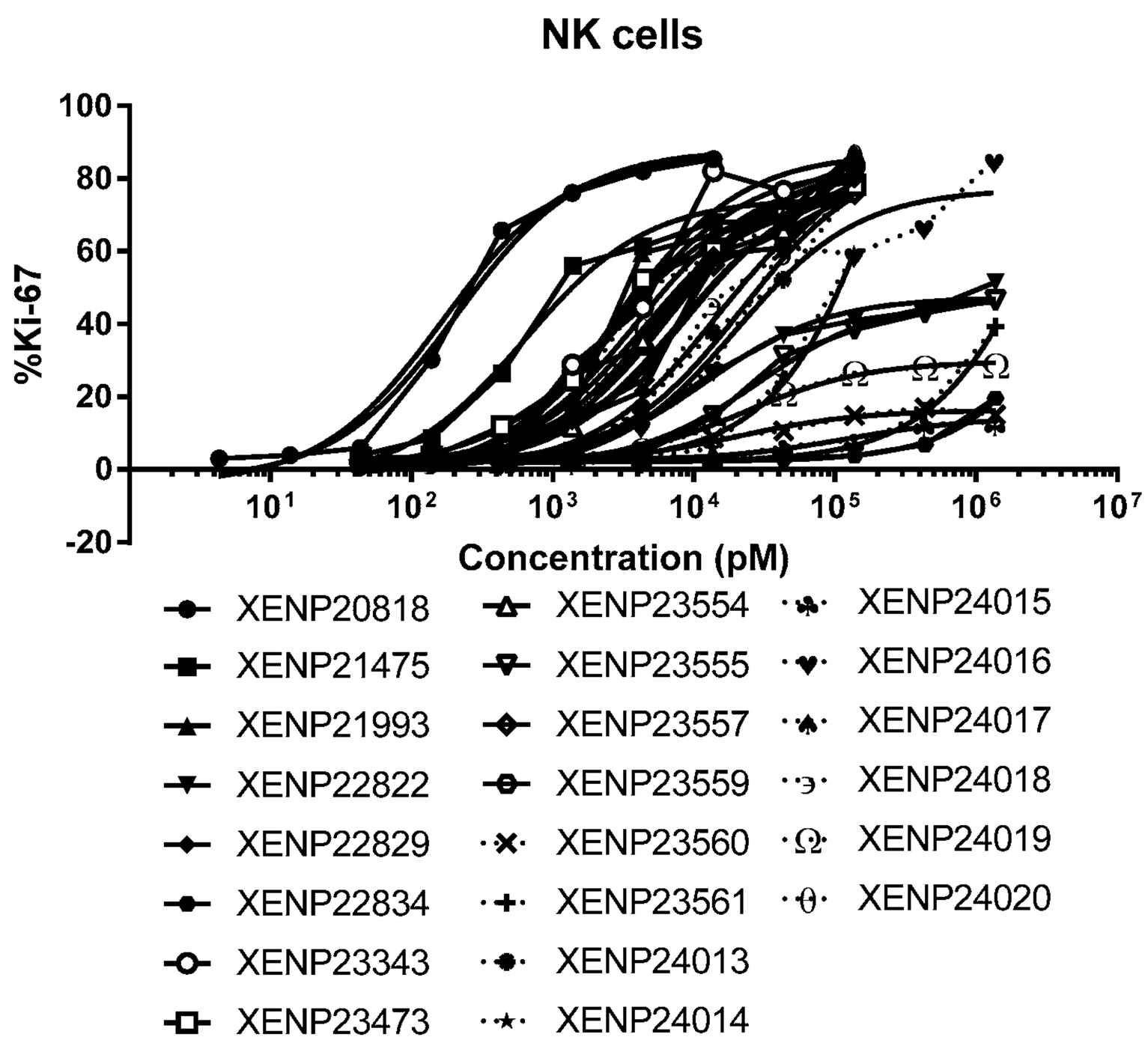

NK cells
%Ki-67
100
80
60
40
20
0
-20
10^1
10^2
10^3
10^4
10^5
10^6
10^7
Concentration (pM)
XENP20818
XENP21475
XENP21993
XENP22822
XENP22829
XENP22834
XENP23343
XENP23473
XENP23554
XENP23555
XENP23557
XENP23559
XENP23560
XENP23561
XENP24015
XENP24016
XENP24017
XENP24018
XENP24019
XENP24020
XENP24013
XENP24014

Figure 61A

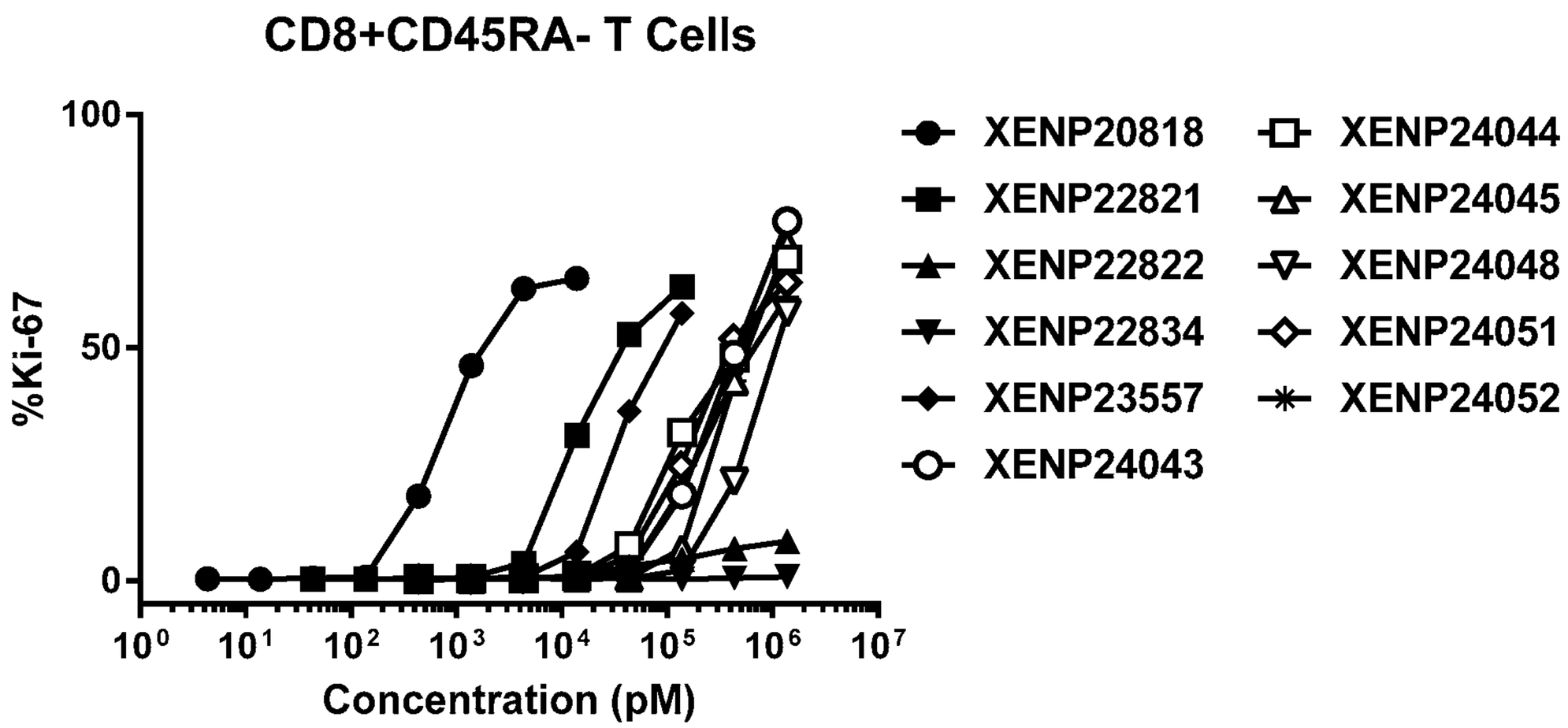


Figure 61B

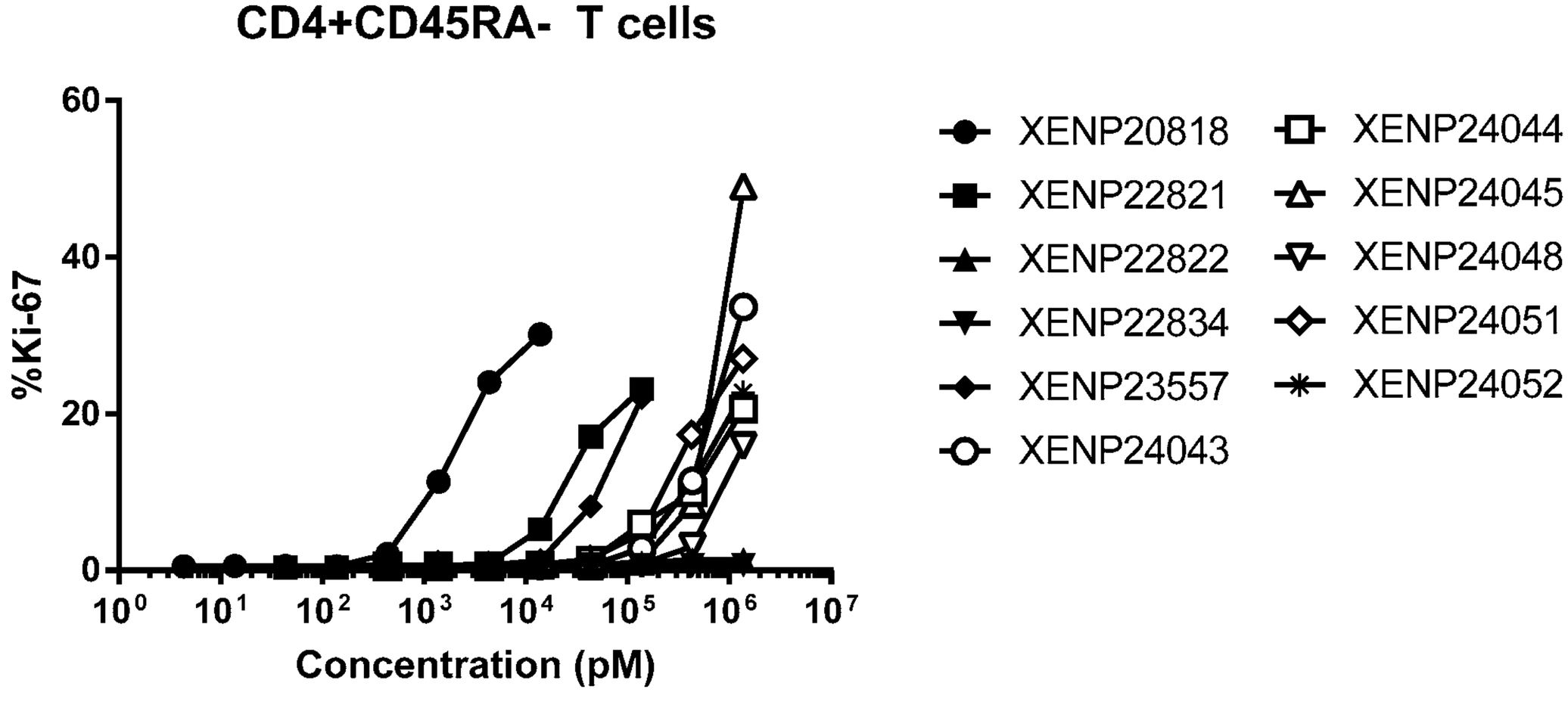


Figure 61C

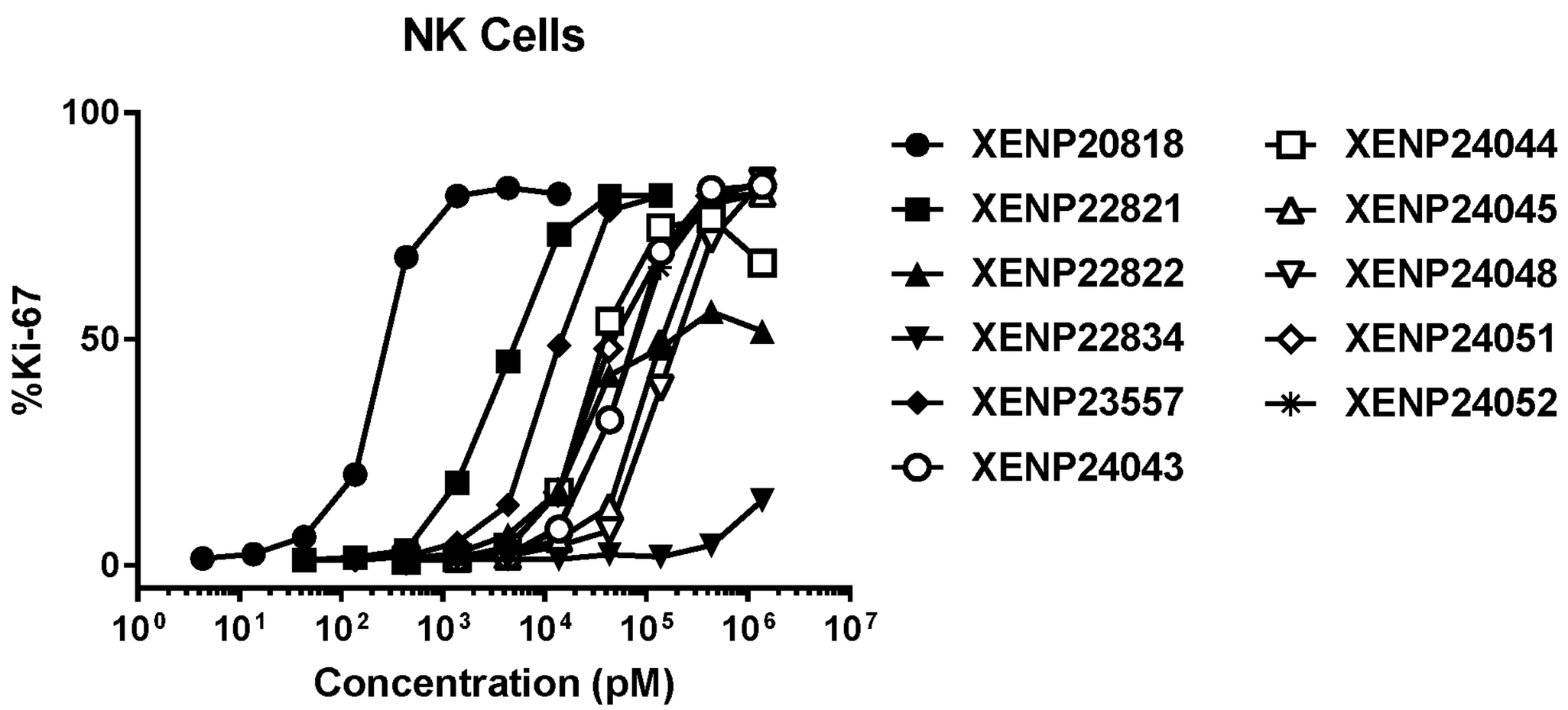

NK Cells
100
50
0
%Ki-67
10^0 10^1 10^2 10^3 10^4 10^5 10^6 10^7
Concentration (pM)
XENP20818
XENP22821
XENP22822
XENP22834
XENP23557
XENP24043
XENP24044
XENP24045
XENP24048
XENP24051
XENP24052

Figure 62A

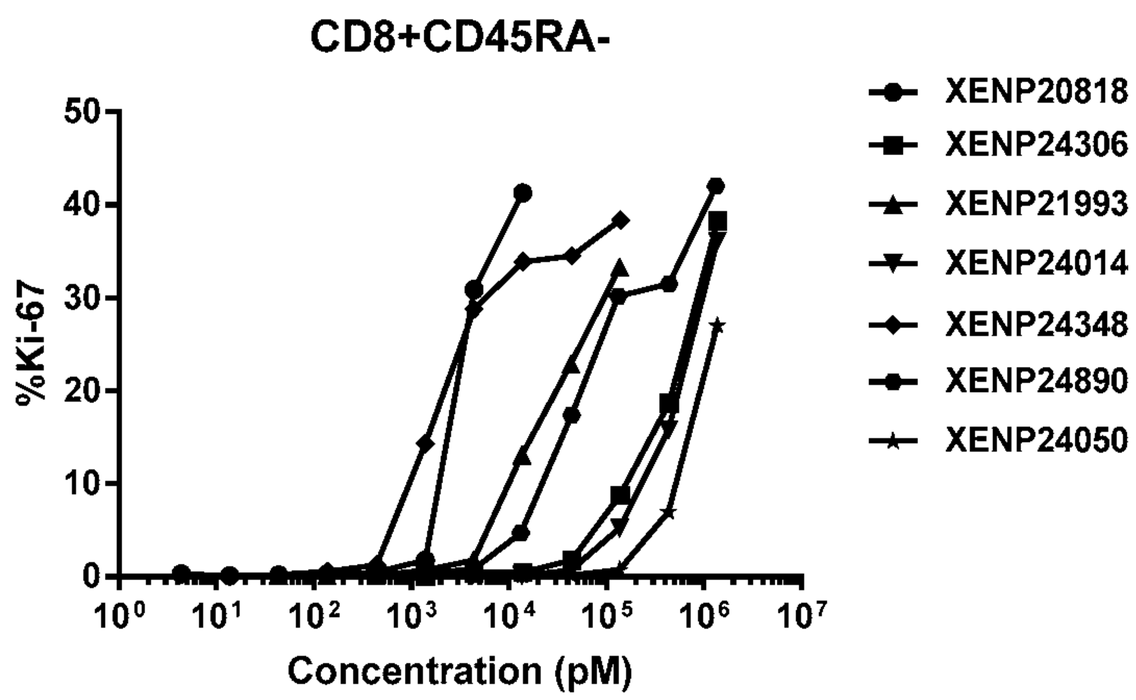


Figure 62B

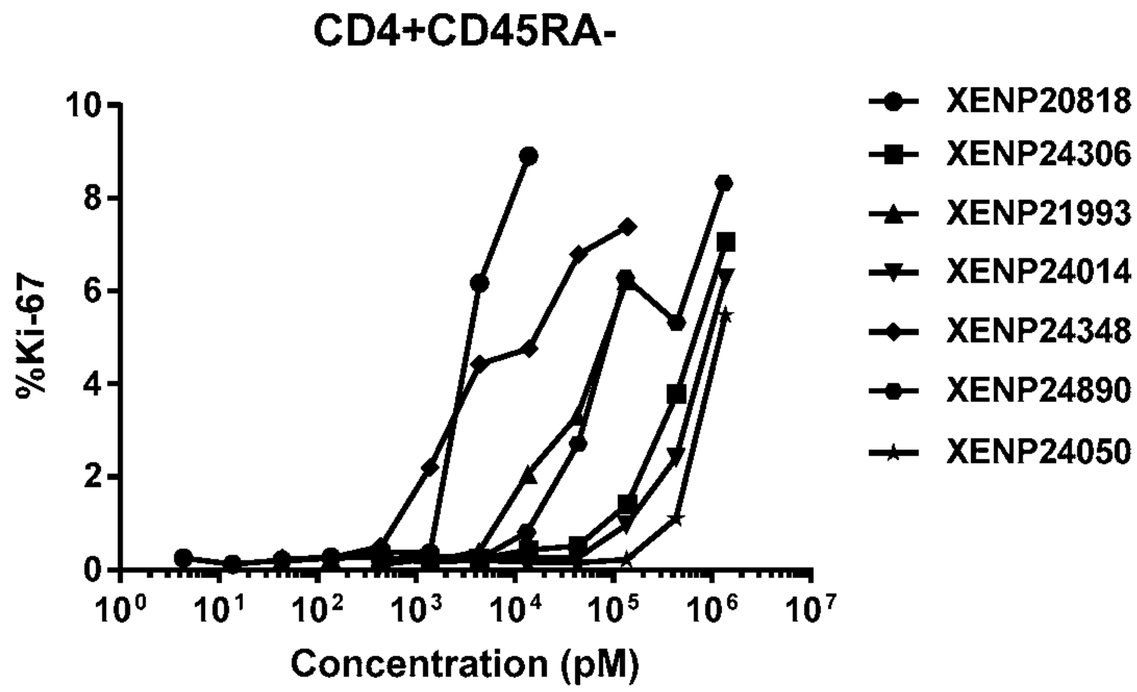


Figure 62C

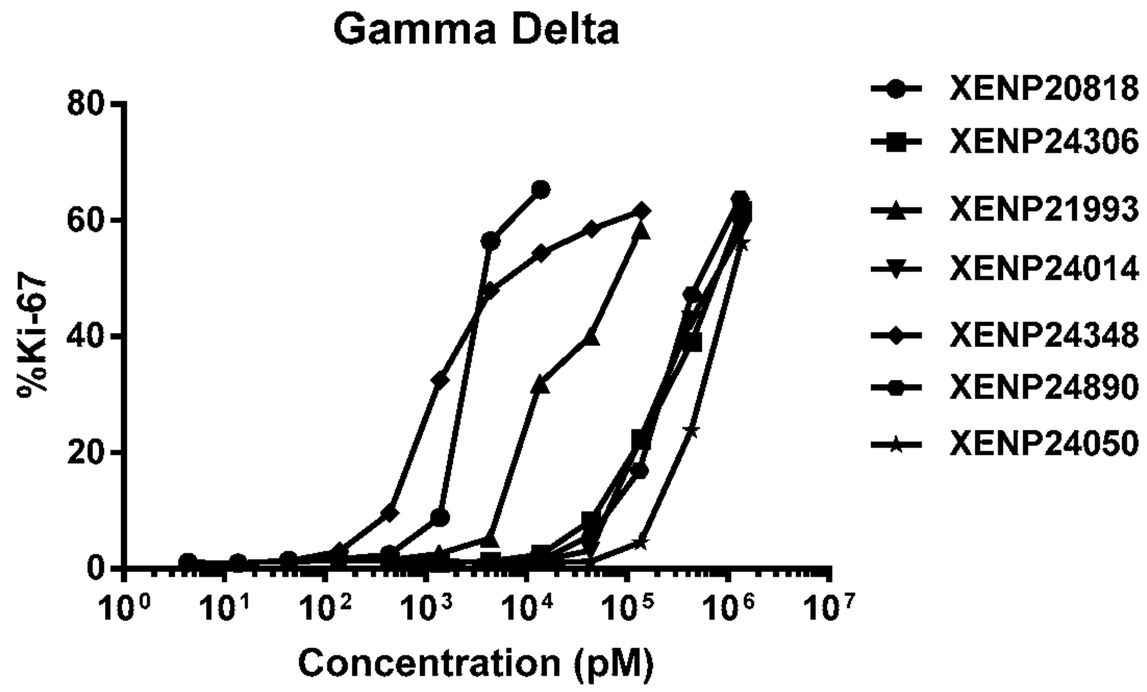


Figure 62D

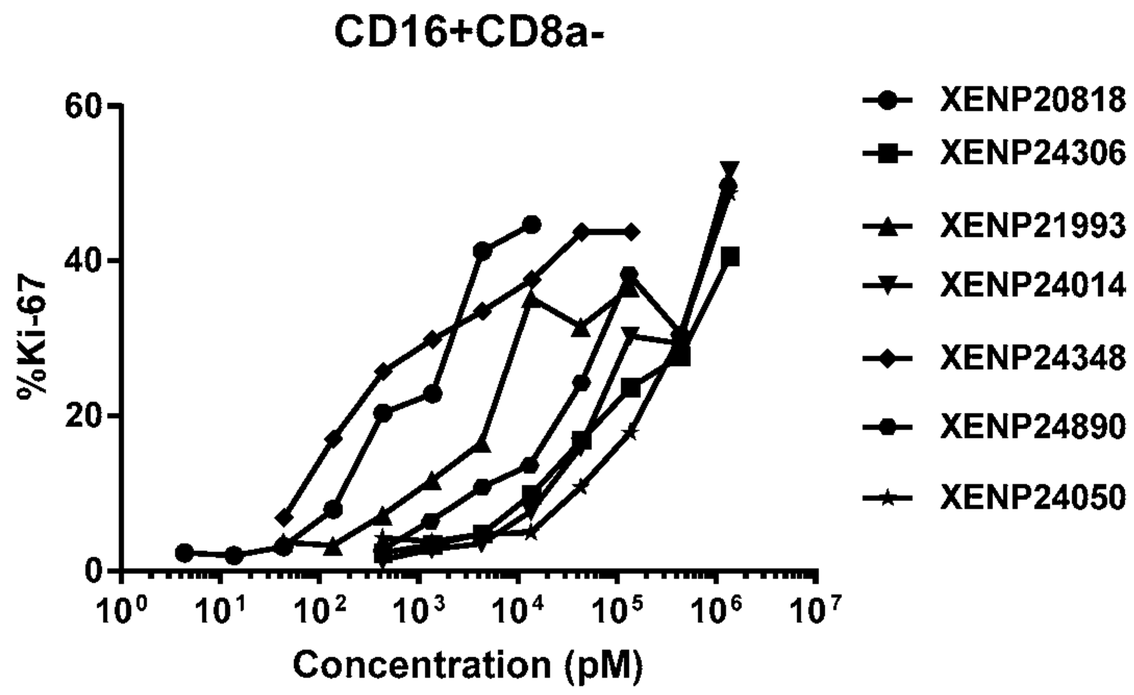


Figure 62E

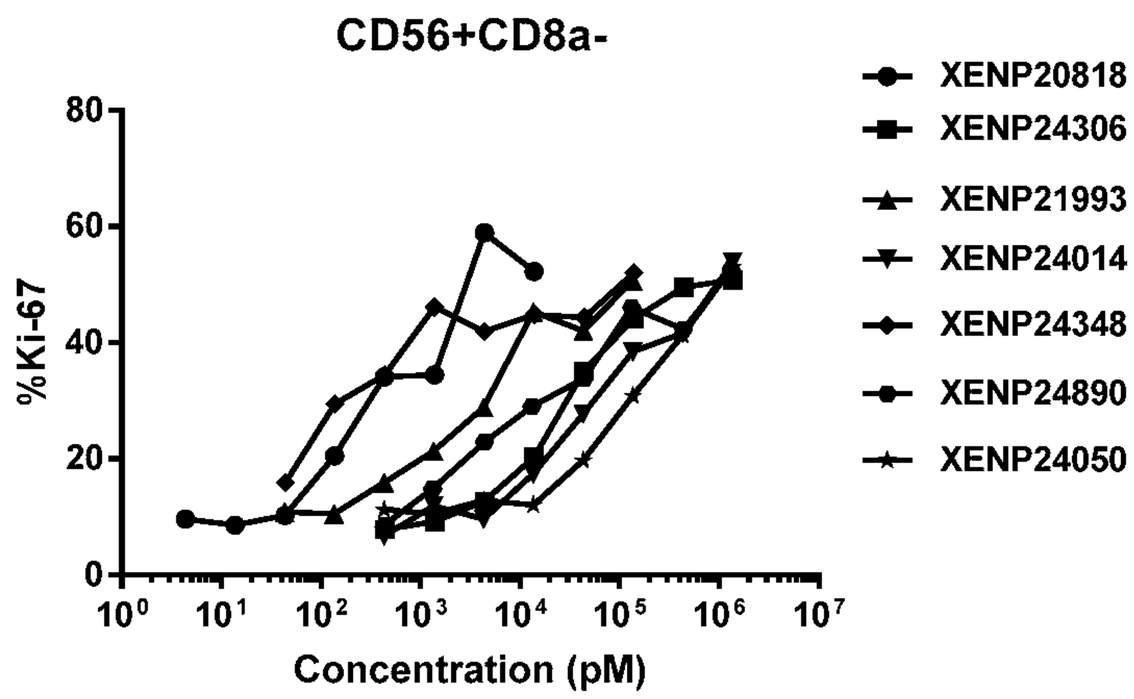


Figure 63A

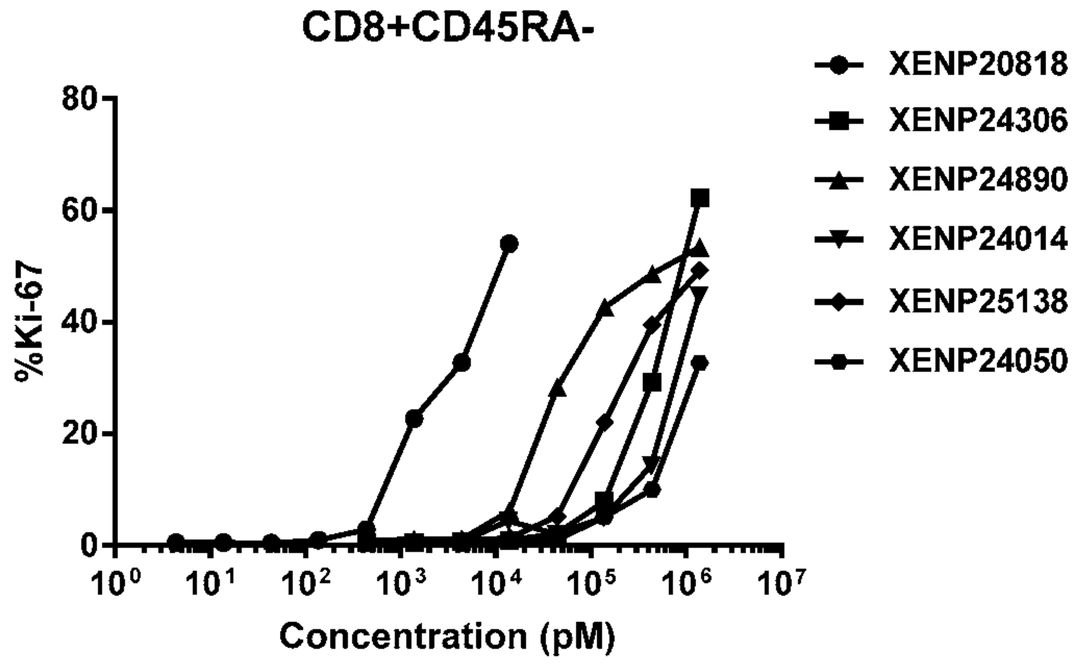


Figure 63B

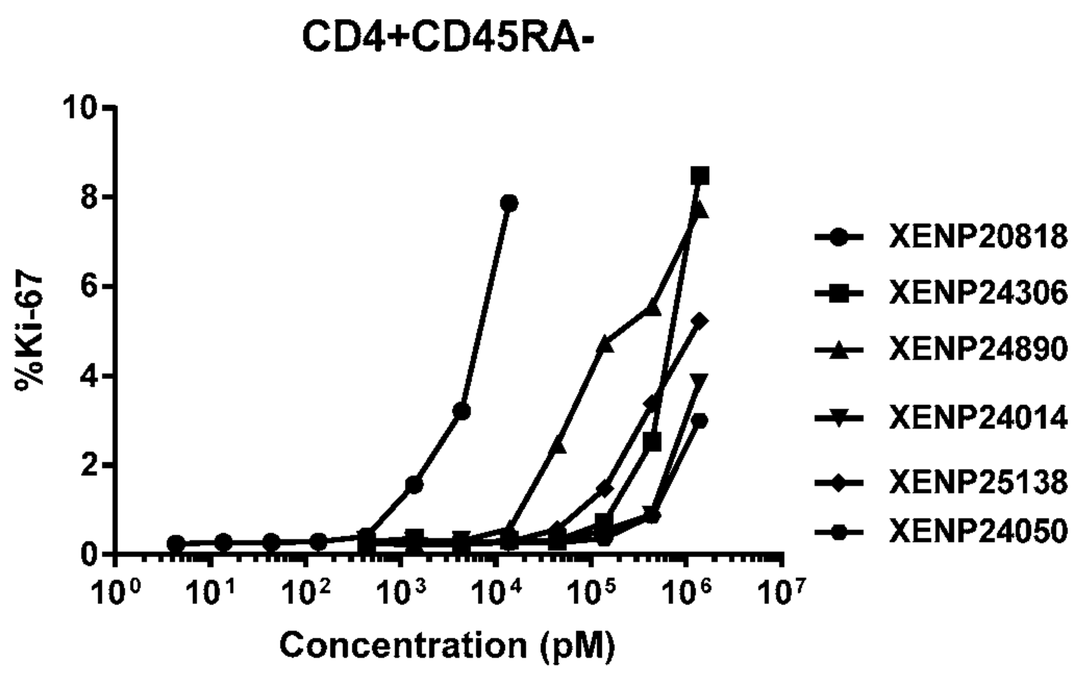


Figure 63C

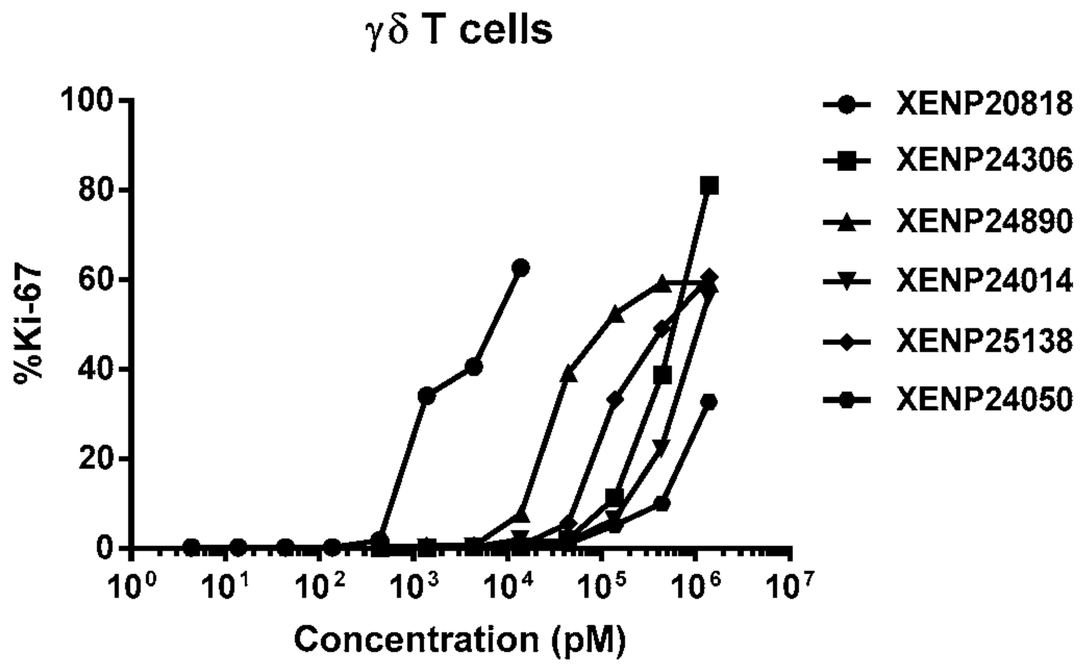


Figure 63D

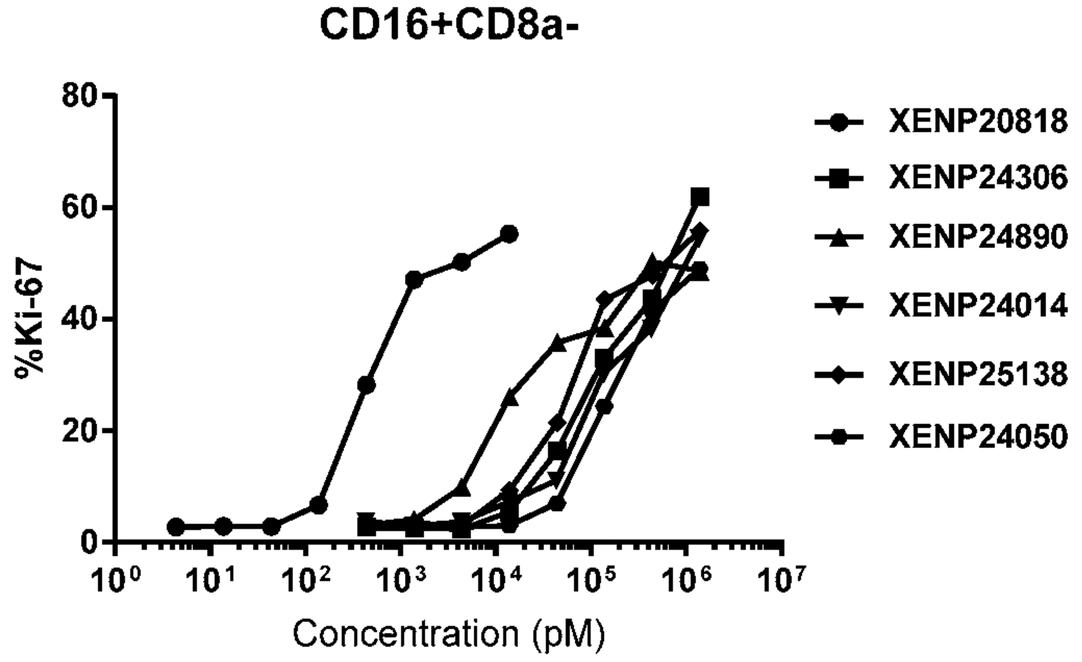


Figure 63E

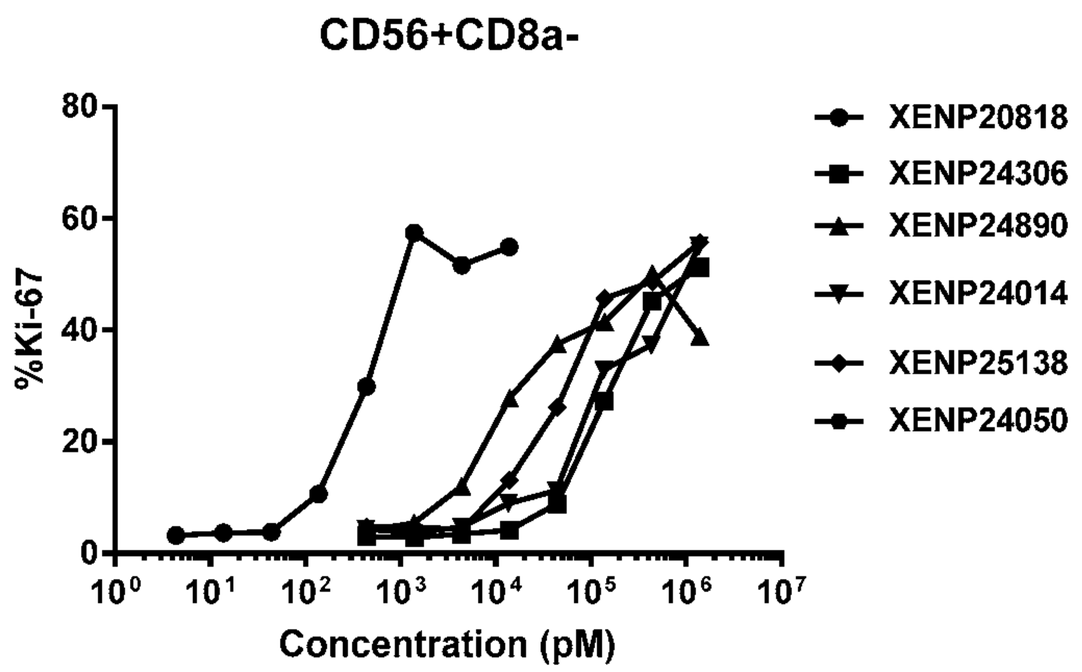


Figure 64A

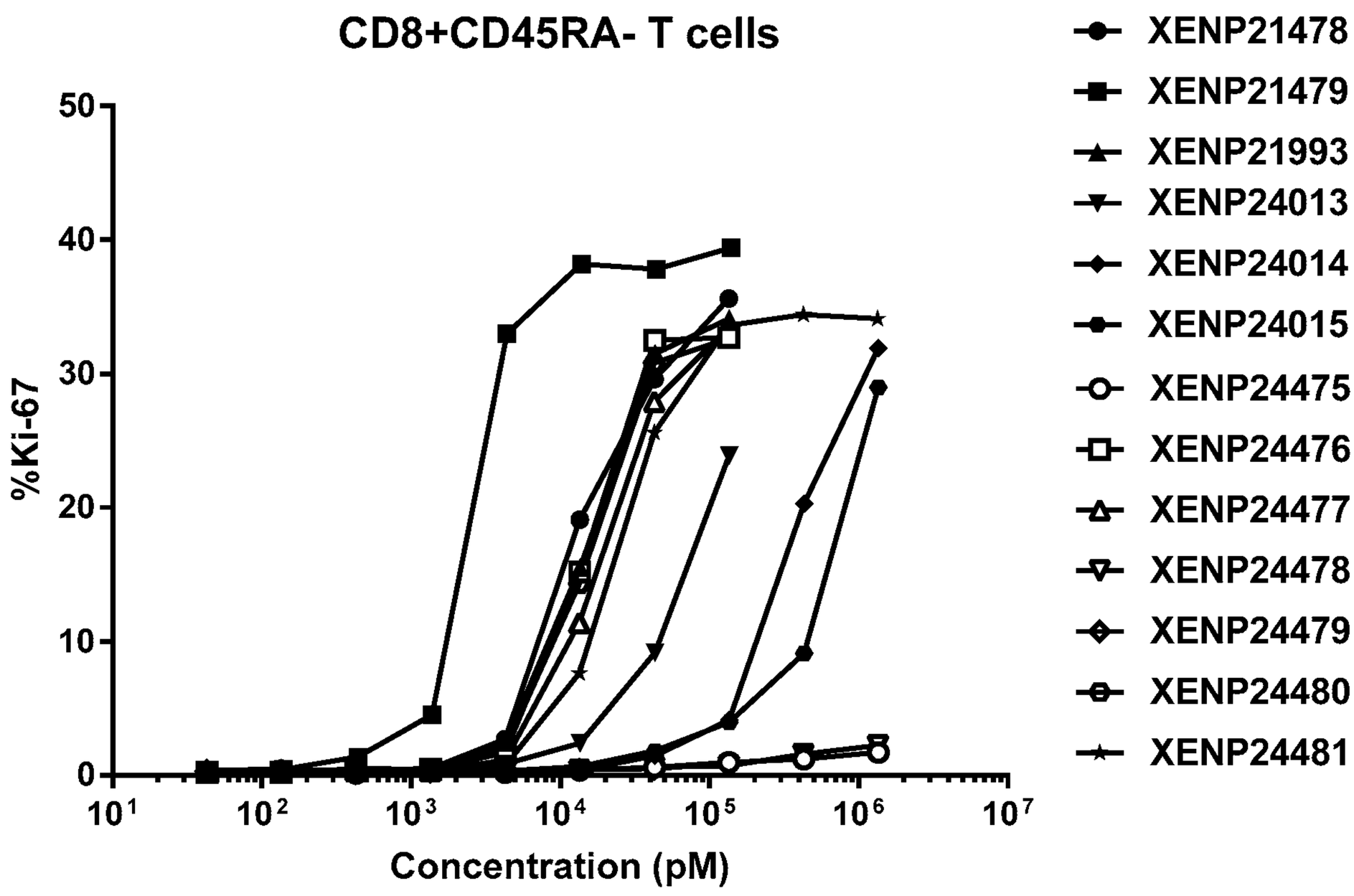

CD8+CD45RA- T cells
%Ki-67
Concentration (pM)
XENP21478
XENP21479
XENP21993
XENP24013
XENP24014
XENP24015
XENP24475
XENP24476
XENP24477
XENP24478
XENP24479
XENP24480
XENP24481

Figure 64B

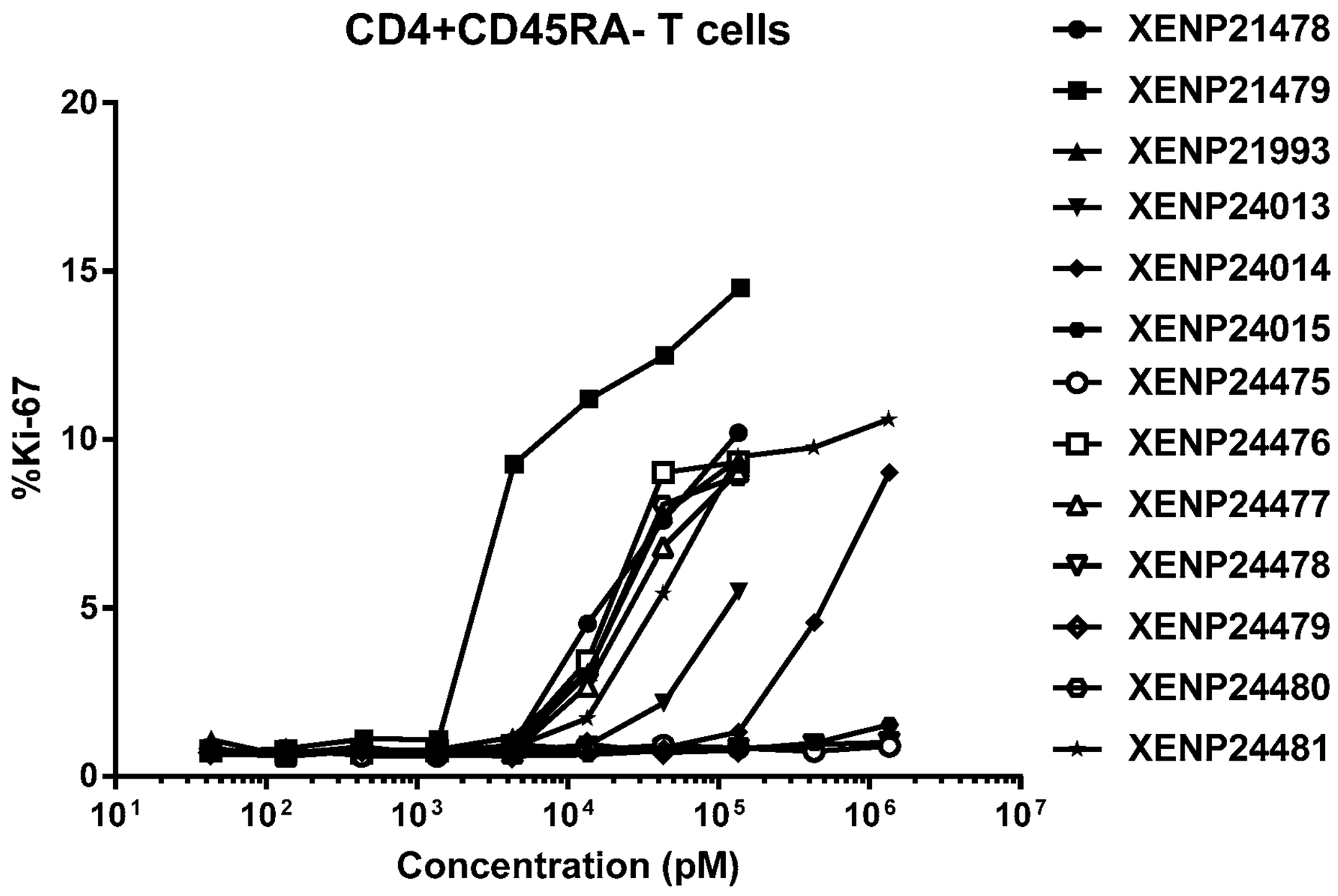

CD4+CD45RA- T cells
%Ki-67
Concentration (pM)
XENP21478
XENP21479
XENP21993
XENP24013
XENP24014
XENP24015
XENP24475
XENP24476
XENP24477
XENP24478
XENP24479
XENP24480
XENP24481

Figure 64C

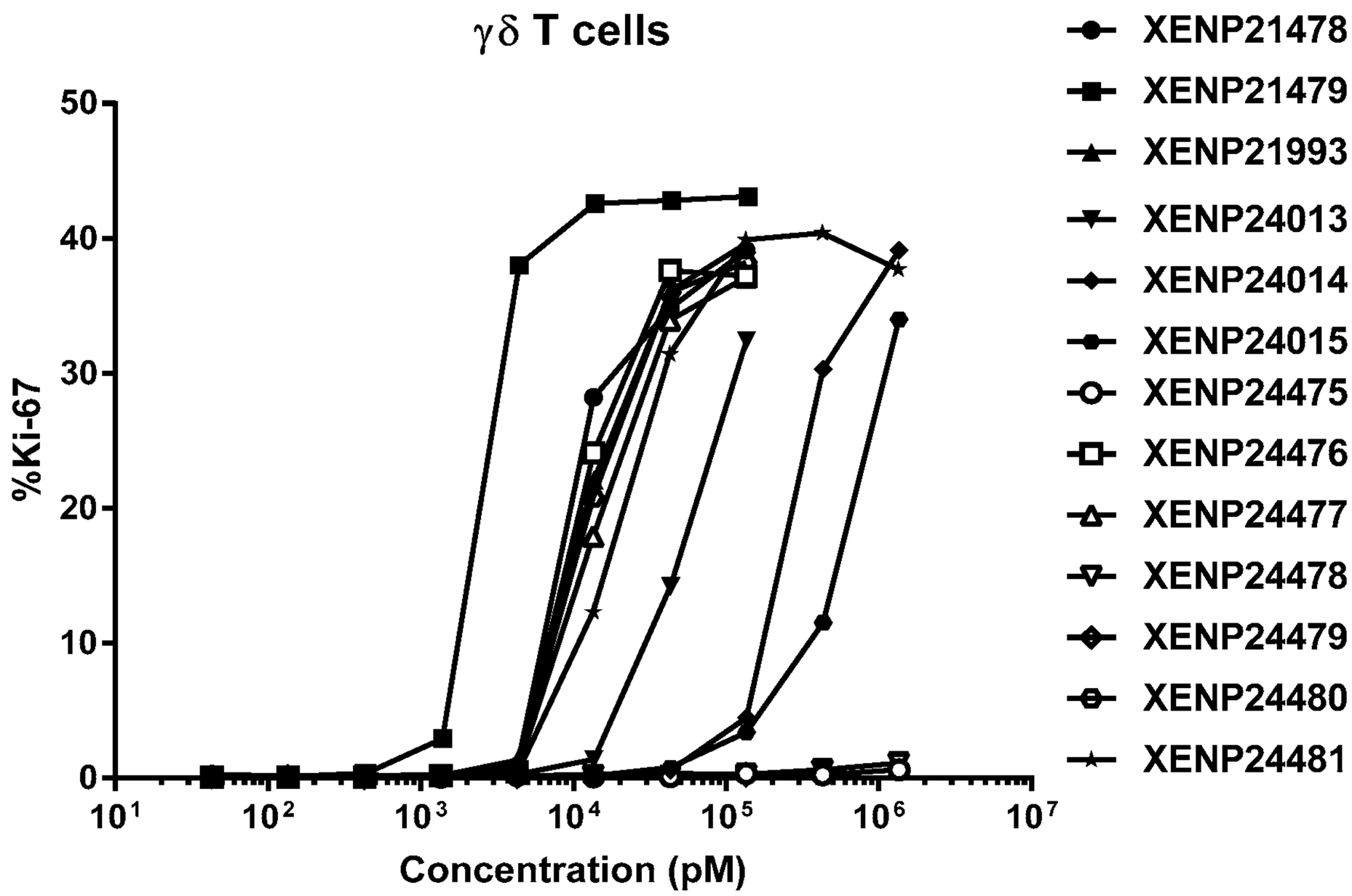

γδ T cells
%Ki-67
Concentration (pM)
0
10
20
30
40
50
10¹
10²
10³
10⁴
10⁵
10⁶
10⁷
XENP21478
XENP21479
XENP21993
XENP24013
XENP24014
XENP24015
XENP24475
XENP24476
XENP24477
XENP24478
XENP24479
XENP24480
XENP24481

Figure 64D

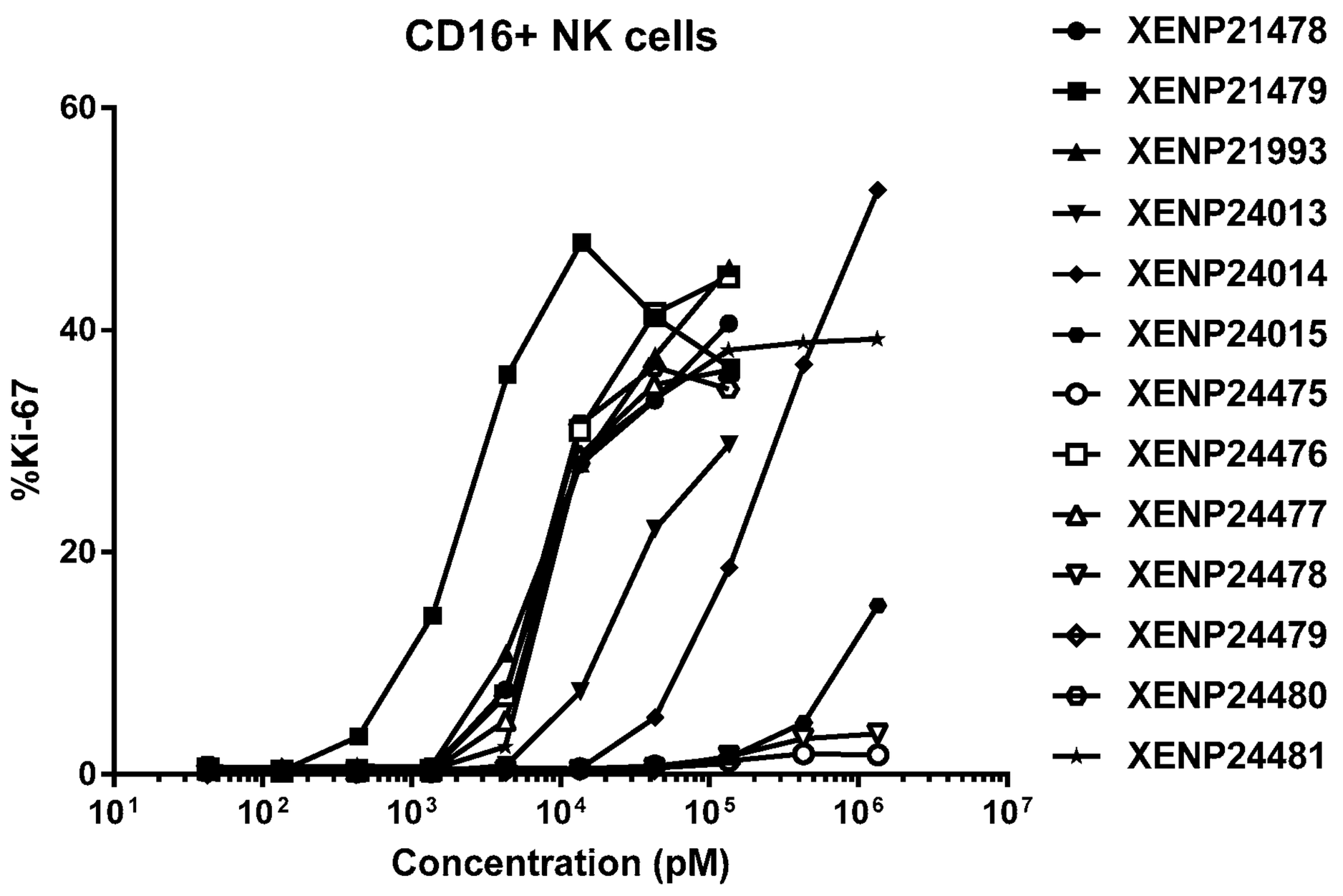

CD16+ NK cells
%Ki-67
Concentration (pM)
0
20
40
60
10^1
10^2
10^3
10^4
10^5
10^6
10^7
XENP21478
XENP21479
XENP21993
XENP24013
XENP24014
XENP24015
XENP24475
XENP24476
XENP24477
XENP24478
XENP24479
XENP24480
XENP24481

Figure 65A

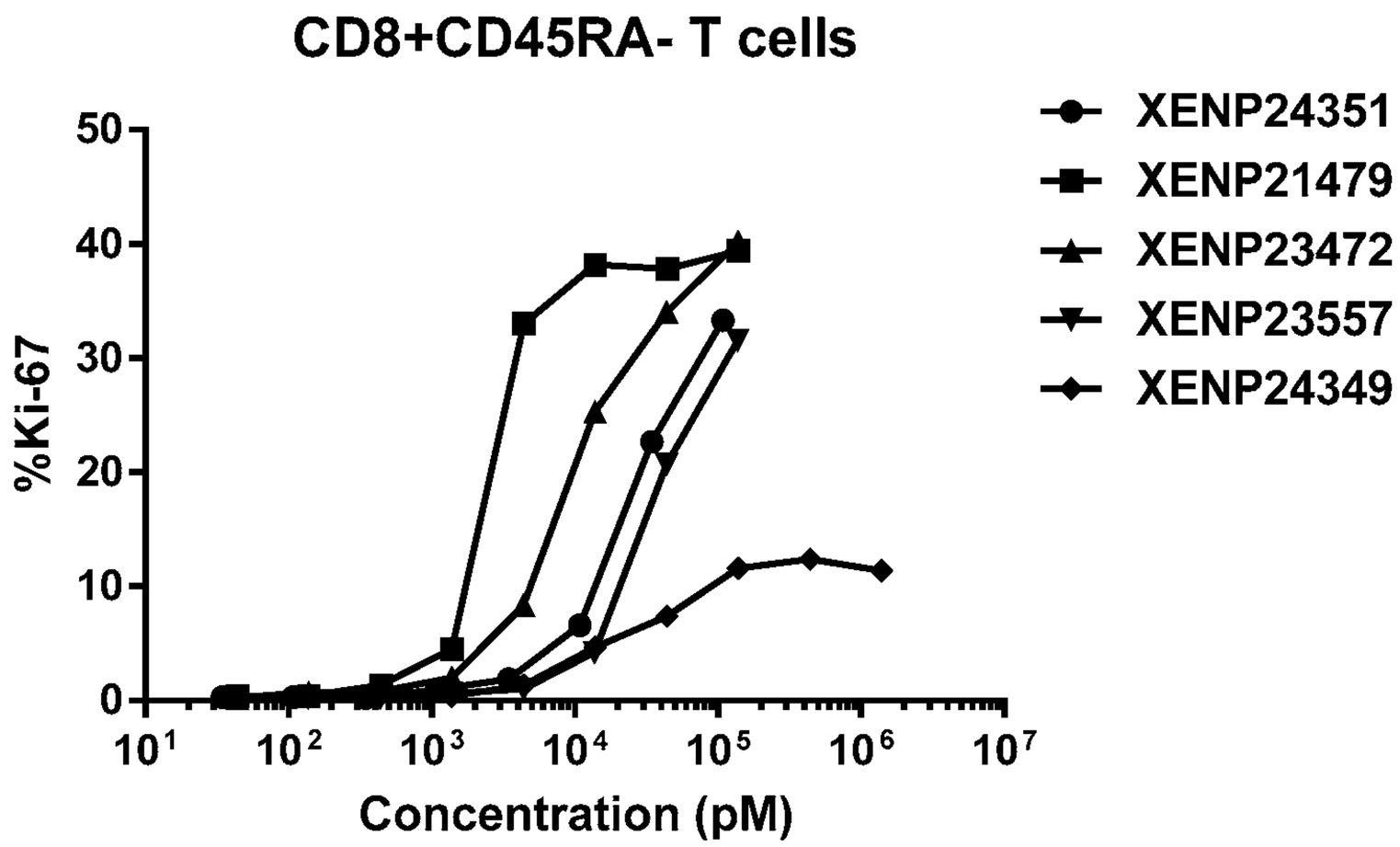


Figure 65B

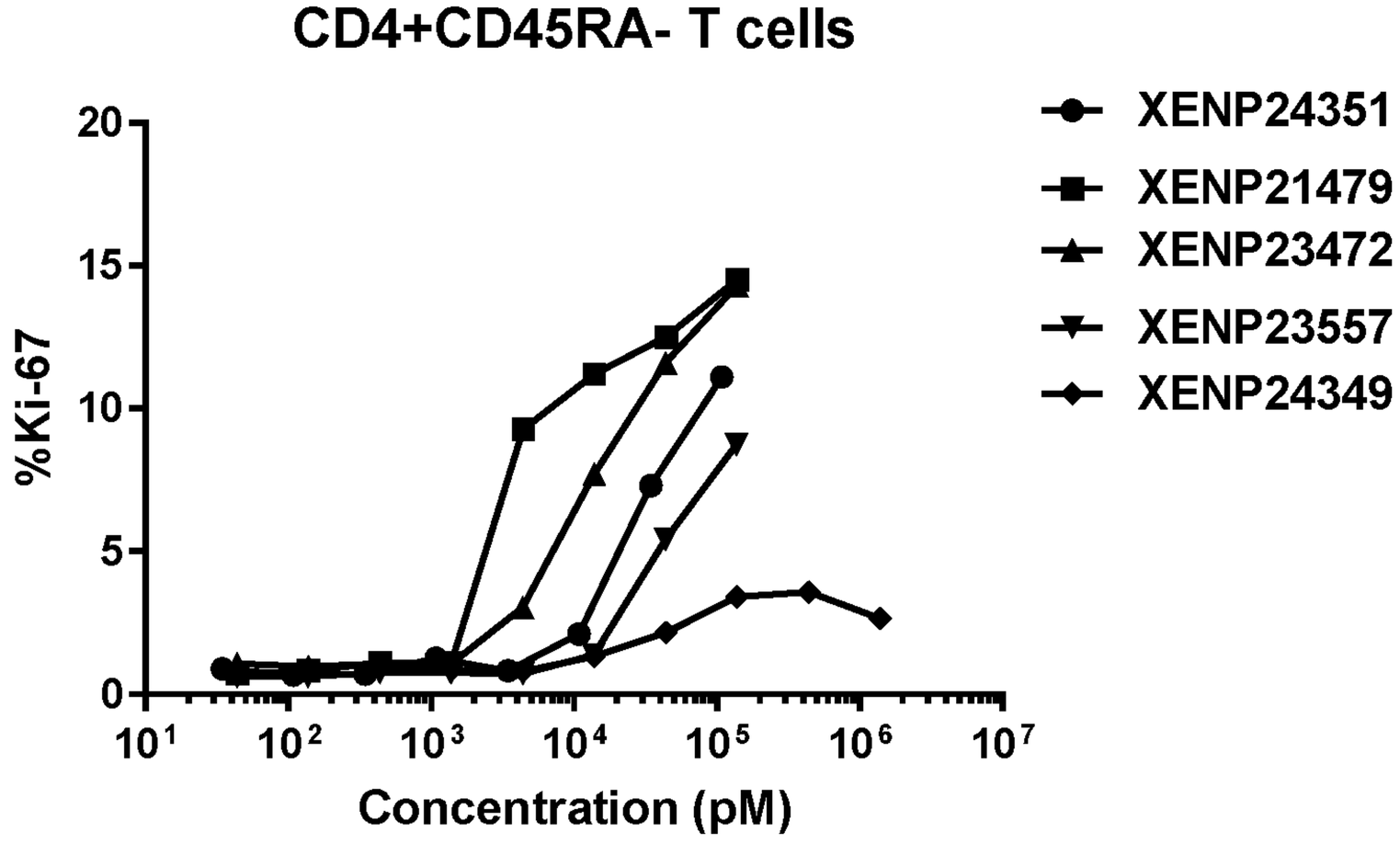


Figure 65C

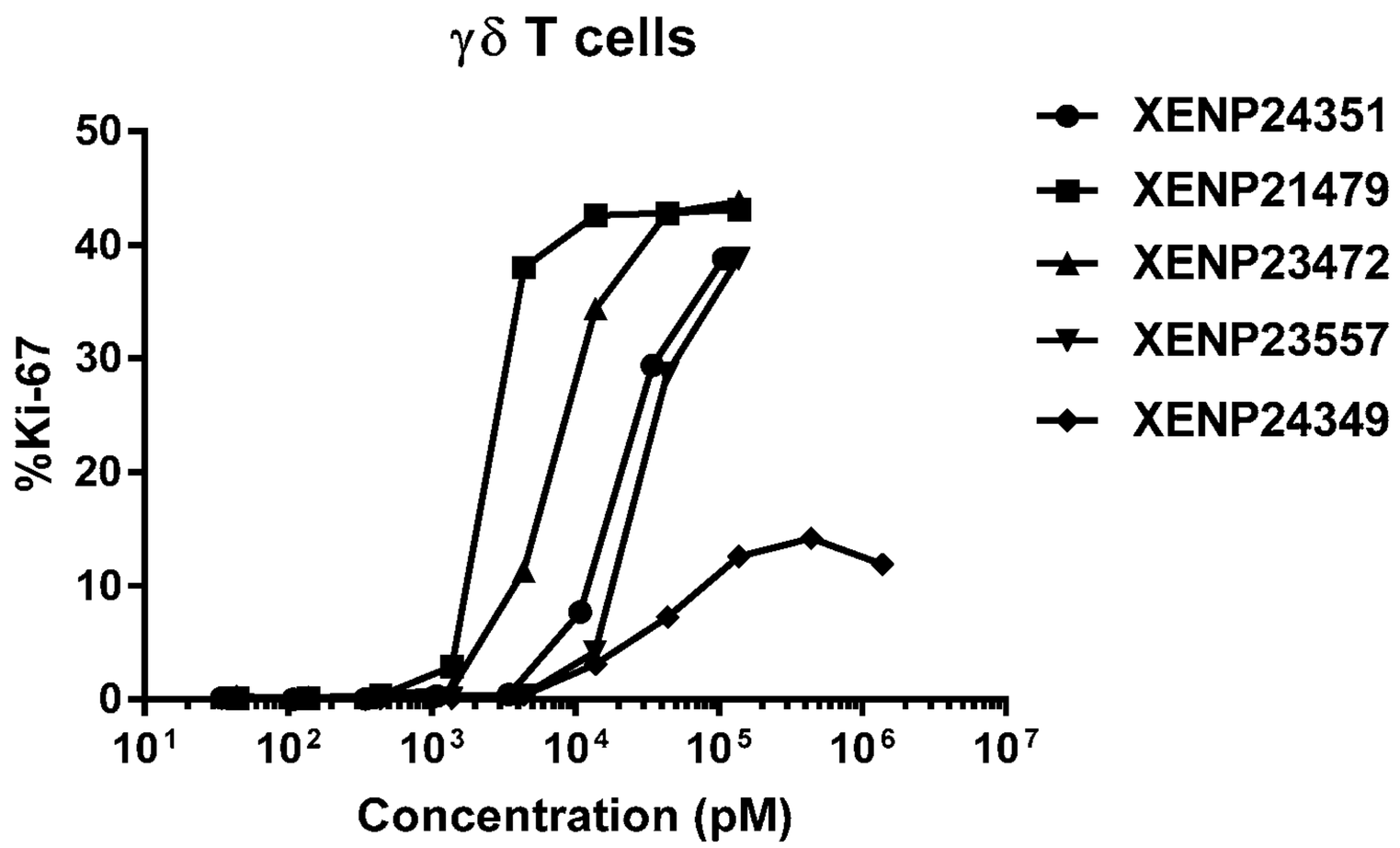


Figure 65D

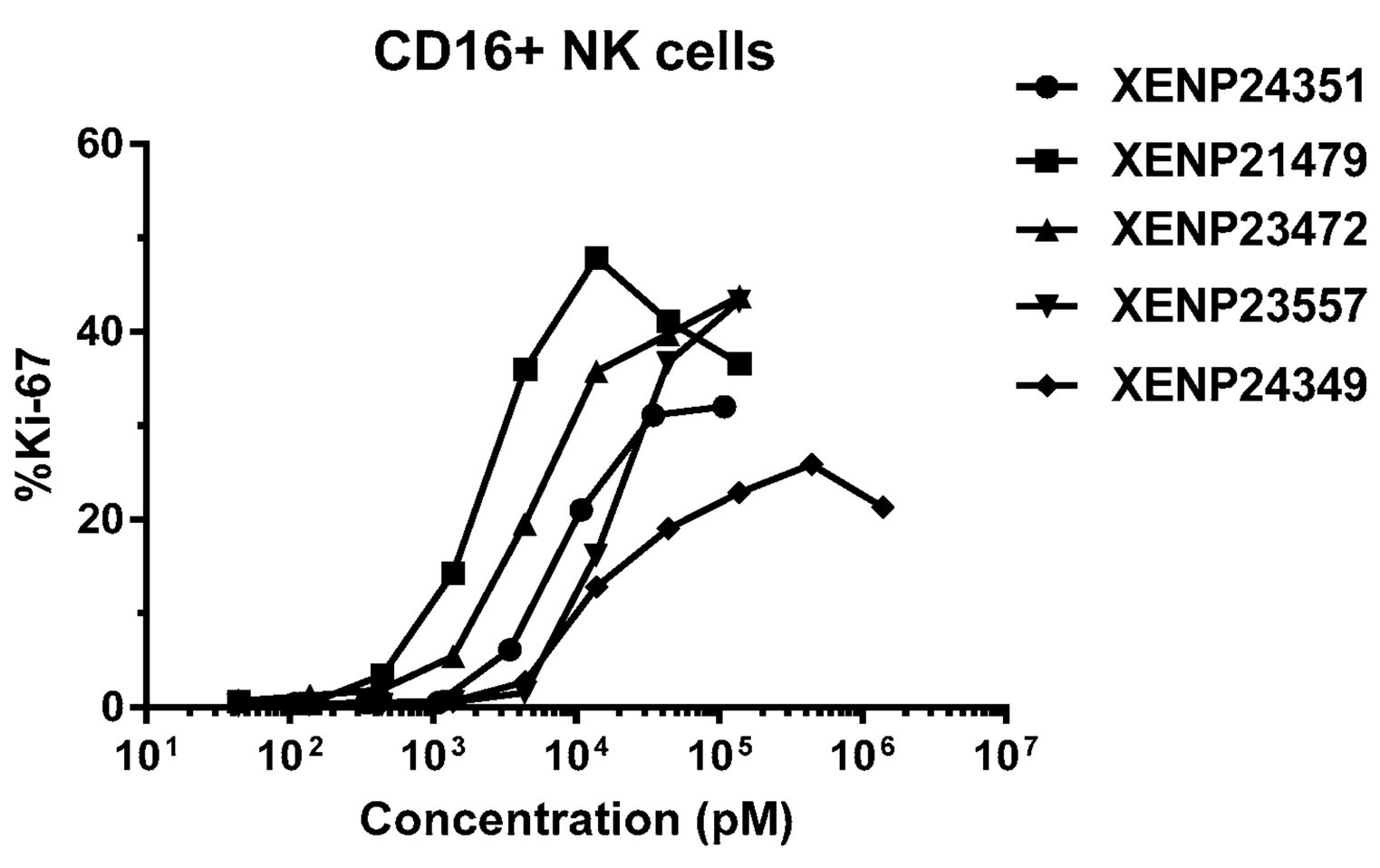


Figure 66A

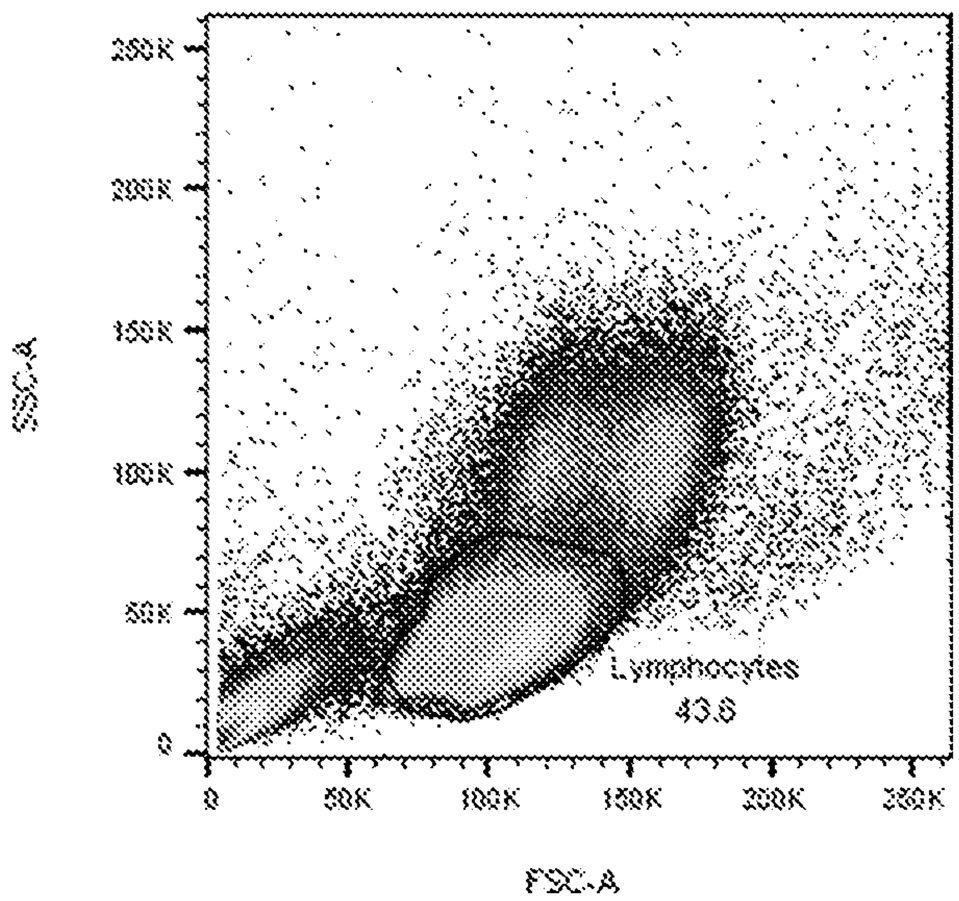


Figure 66B

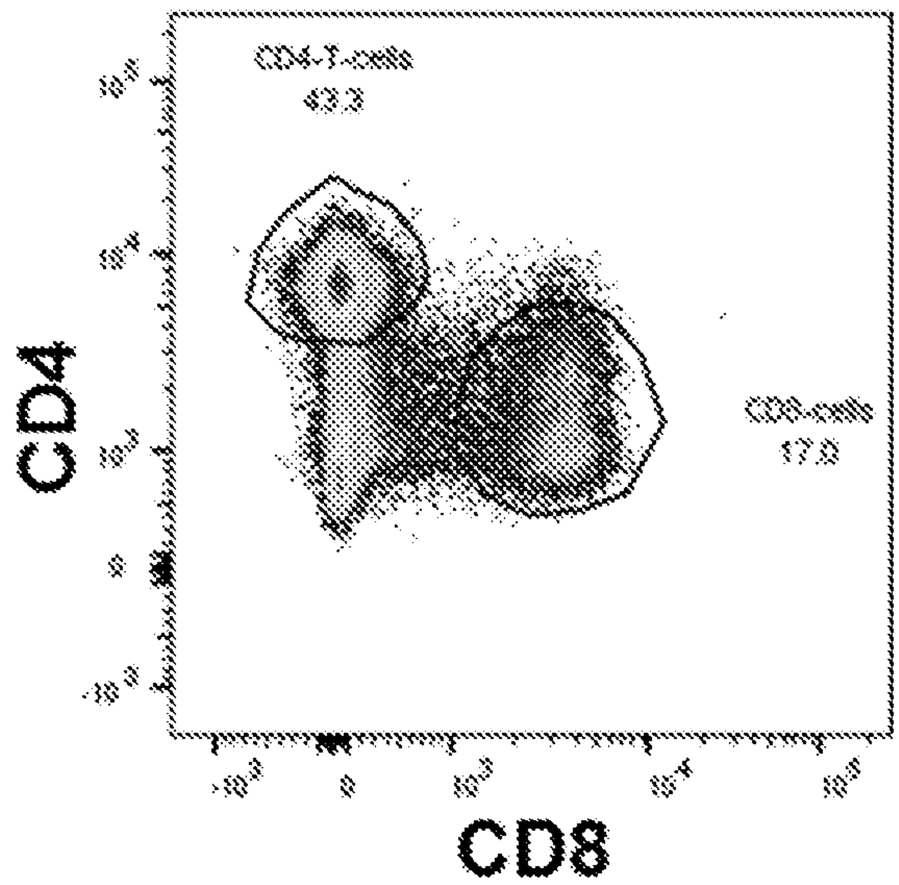


Figure 66C

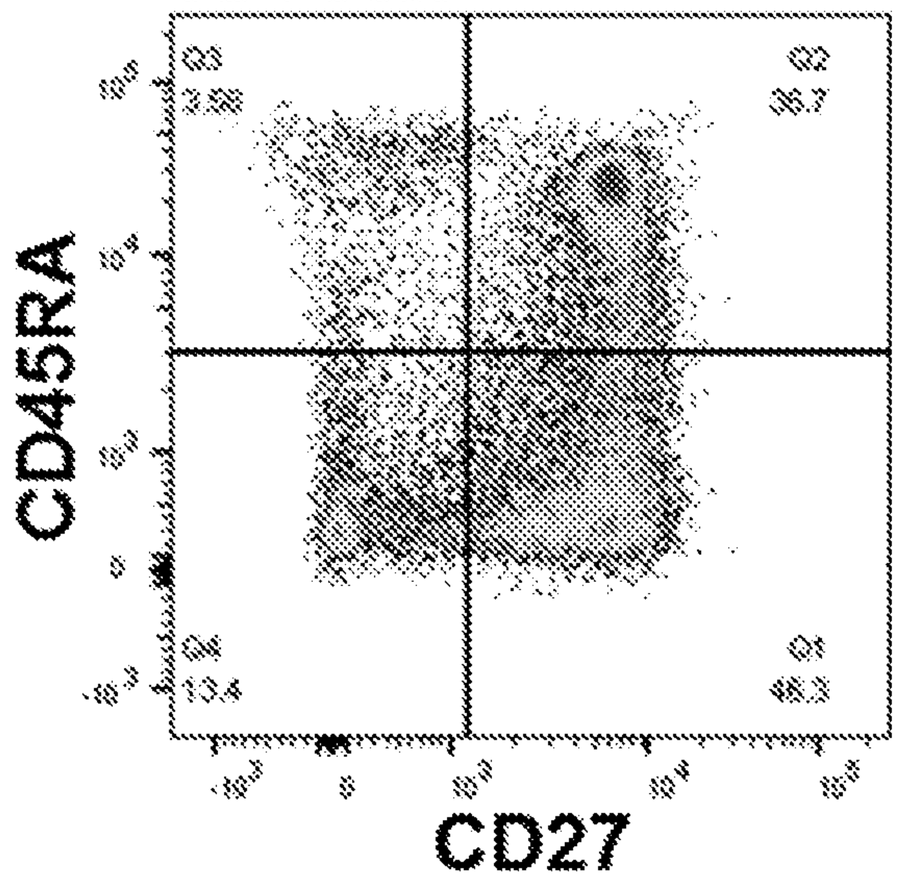


Figure 66D

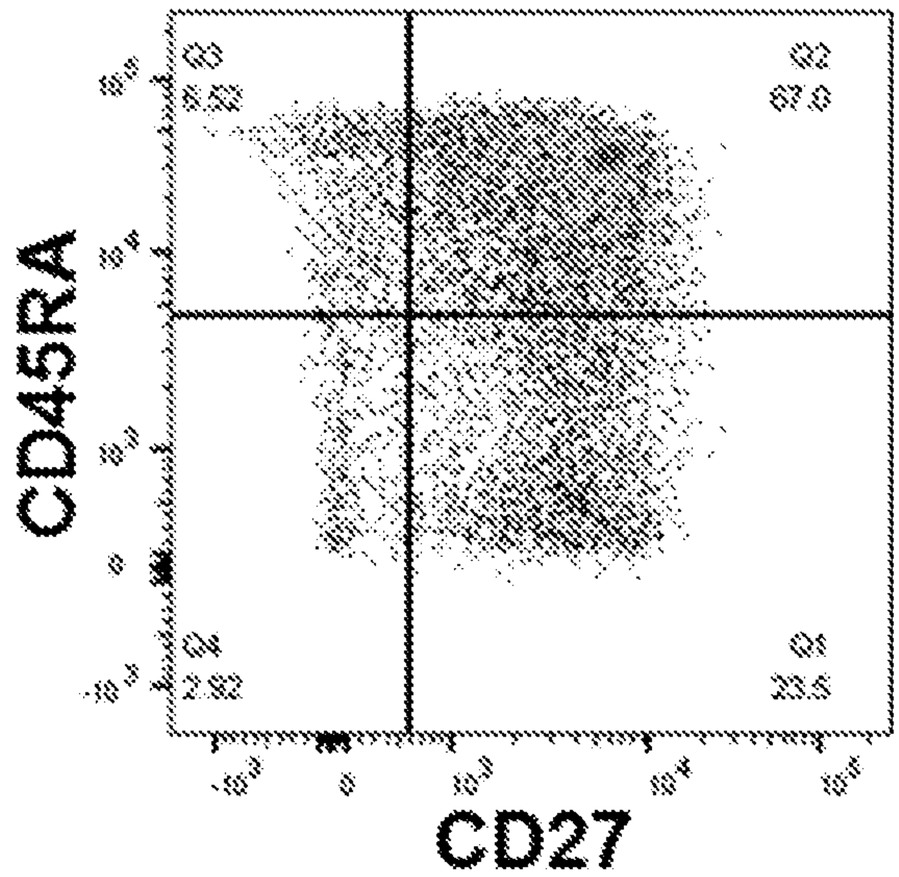


Figure 67A

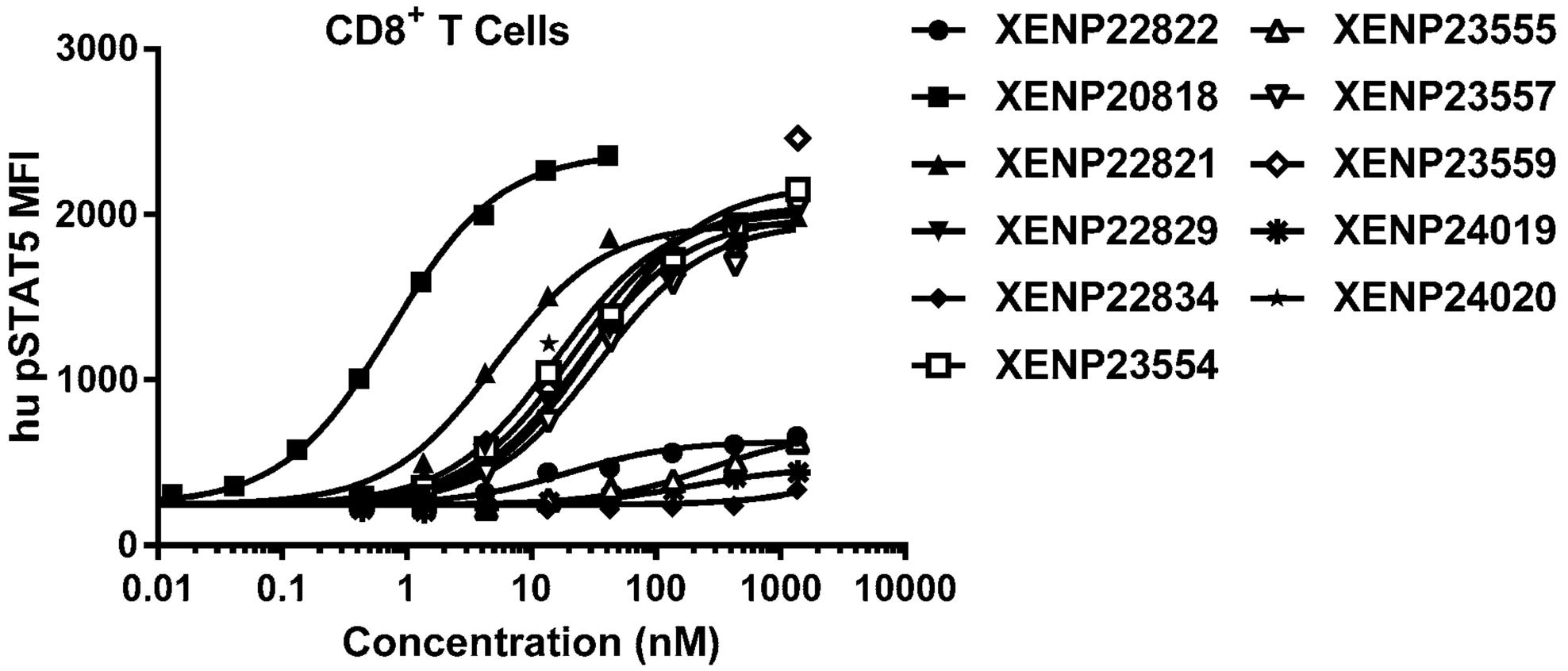


Figure 67B

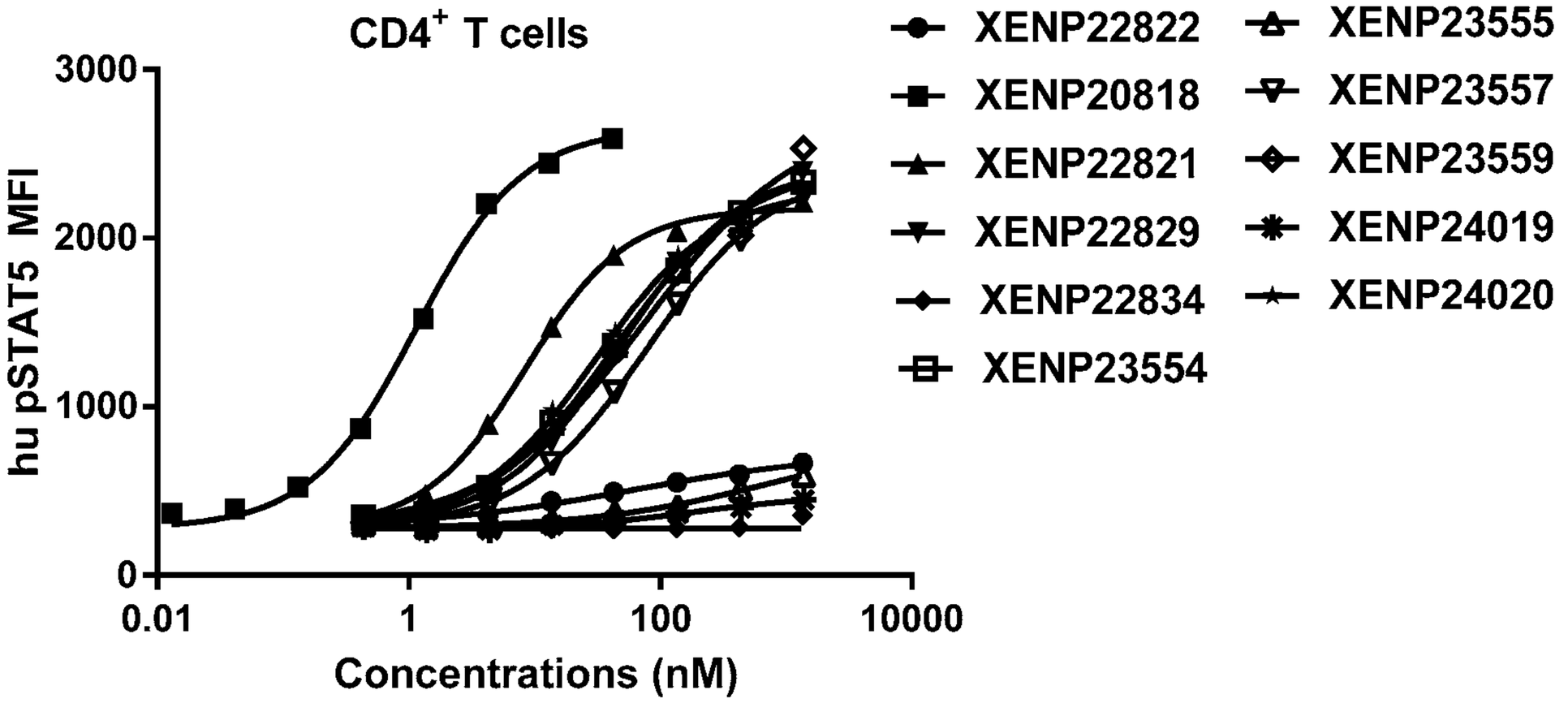


Figure 67C

XENP	EC50 nM (CD8 T cells)	Fold reduced (CD8 T cells)	EC50 nM (CD4 T cells)	Fold reduced (CD4 T cells)
22822	19.34	25.6	61.46	53.8
20818	0.7543	1.0	1.142	1.0
22821	5.196	6.9	8.485	7.4
22829	25.27	33.5	47.11	41.3
22834	ND	ND	ND	ND
23554	21.56	28.6	44.18	38.7
23555	270	357.9	818.2	716.5
23557	34.27	45.4	78.62	68.8
23559	32.91	43.6	76.03	66.6
24019	198.1	262.6	176.7	154.7
24020	15.92	21.1	30.98	27.1

Figure 68A

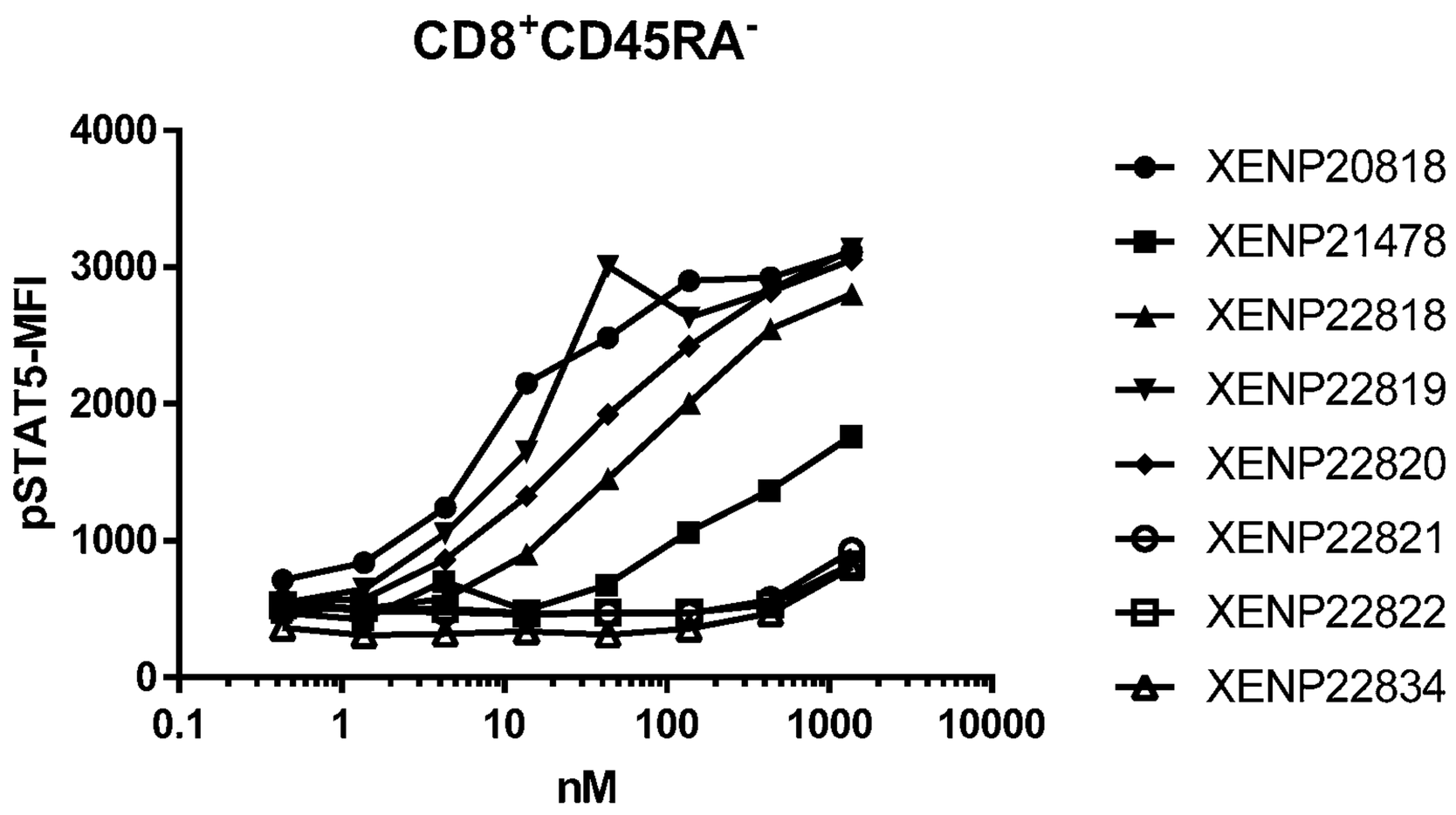


Figure 68B

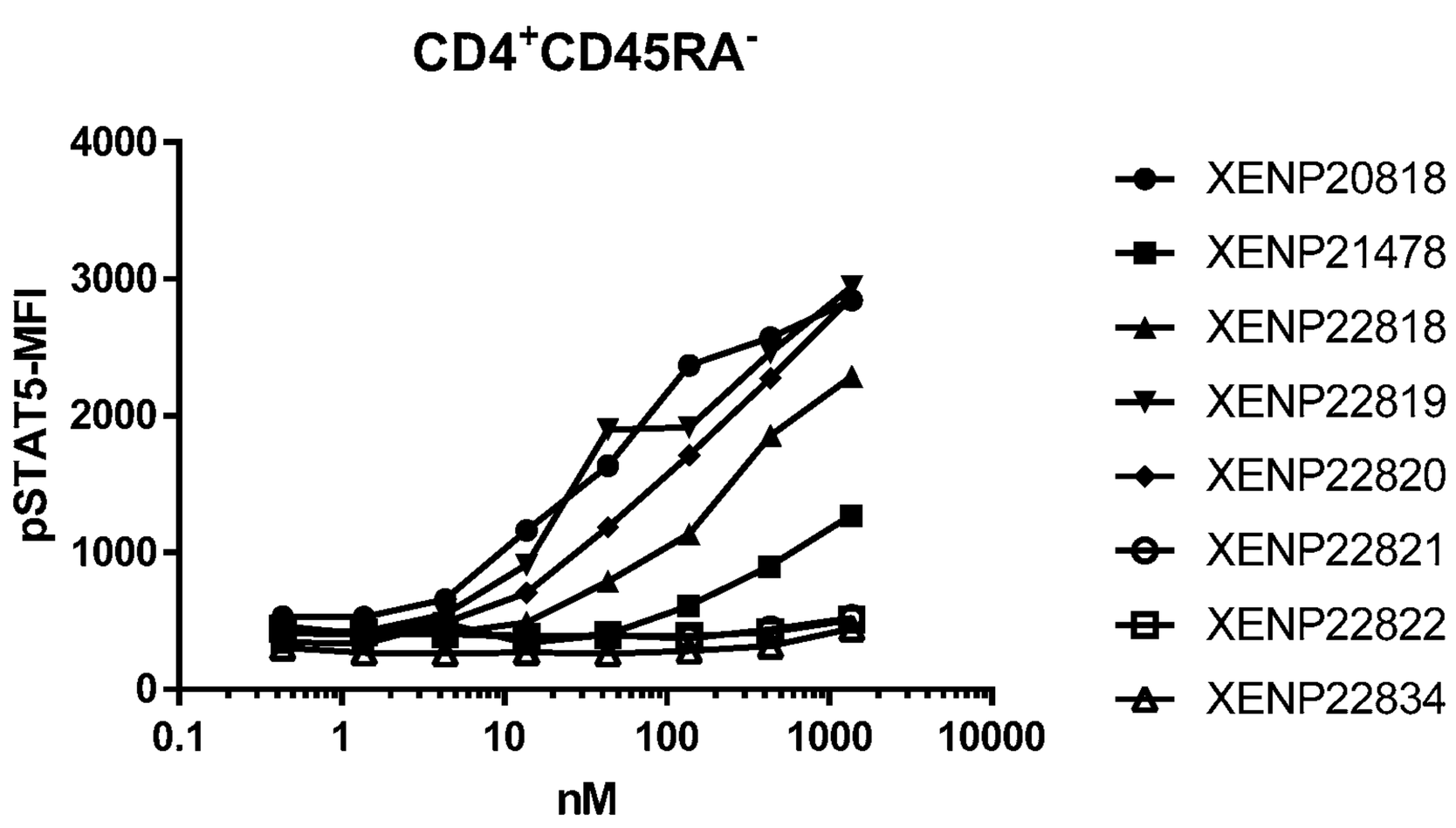
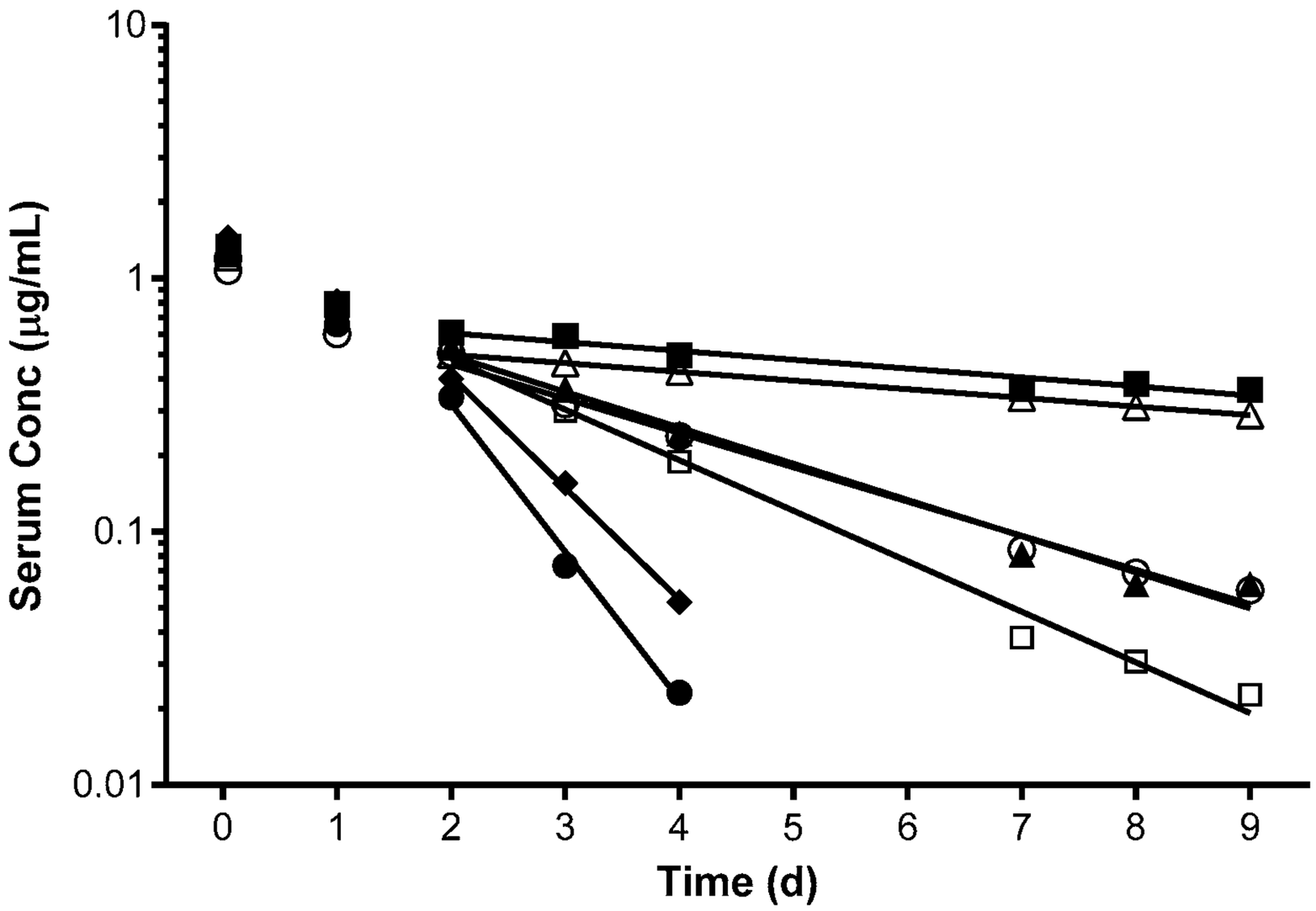


Figure 69



●	XENP20818 IL15/IL15Ra-Fc	$t_{1/2}$ ~ 0.5 d
■	XENP22821 IL15/IL15Ra-Fc N65D	$t_{1/2}$ ~ 8.6 d
▲	XENP22818 IL15/IL15Ra-Fc D30N	$t_{1/2}$ ~ 2.1 d
◆	XENP22820 IL15/IL15Ra-Fc E64Q	$t_{1/2}$ ~ 0.7 d
○	XENP21478 IL15/IL15Ra-Fc single-chain	$t_{1/2}$ ~ 2.2 d
□	XENP22819 IL15/IL15Ra-Fc D61N	$t_{1/2}$ ~ 1.5 d
△	XENP22822 IL15/IL15Ra-Fc Q108E	$t_{1/2}$ ~ 8.8 d

Figure 70

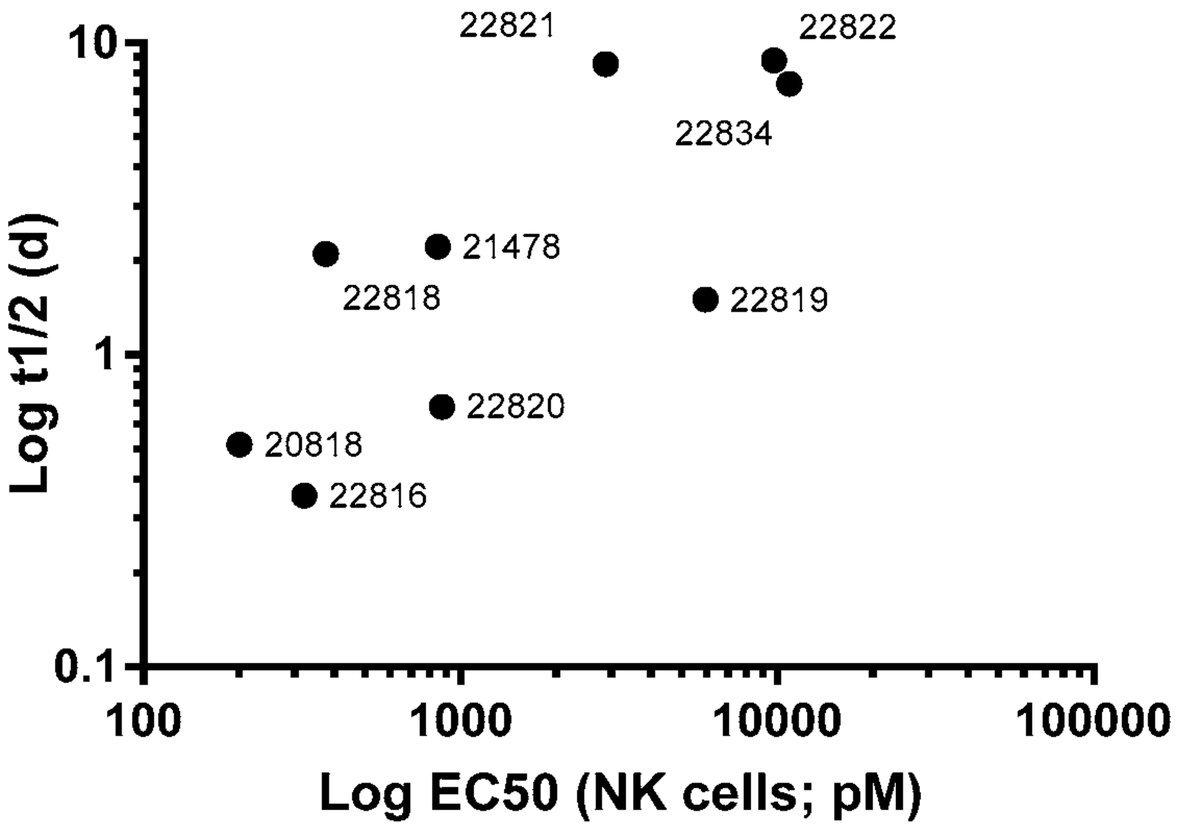

22821
22822
22834
21478
22818
22819
22820
20818
22816
10
1
0.1
100
1000
10000
100000
Log t1/2 (d)
Log EC50 (NK cells; pM)

Figure 71

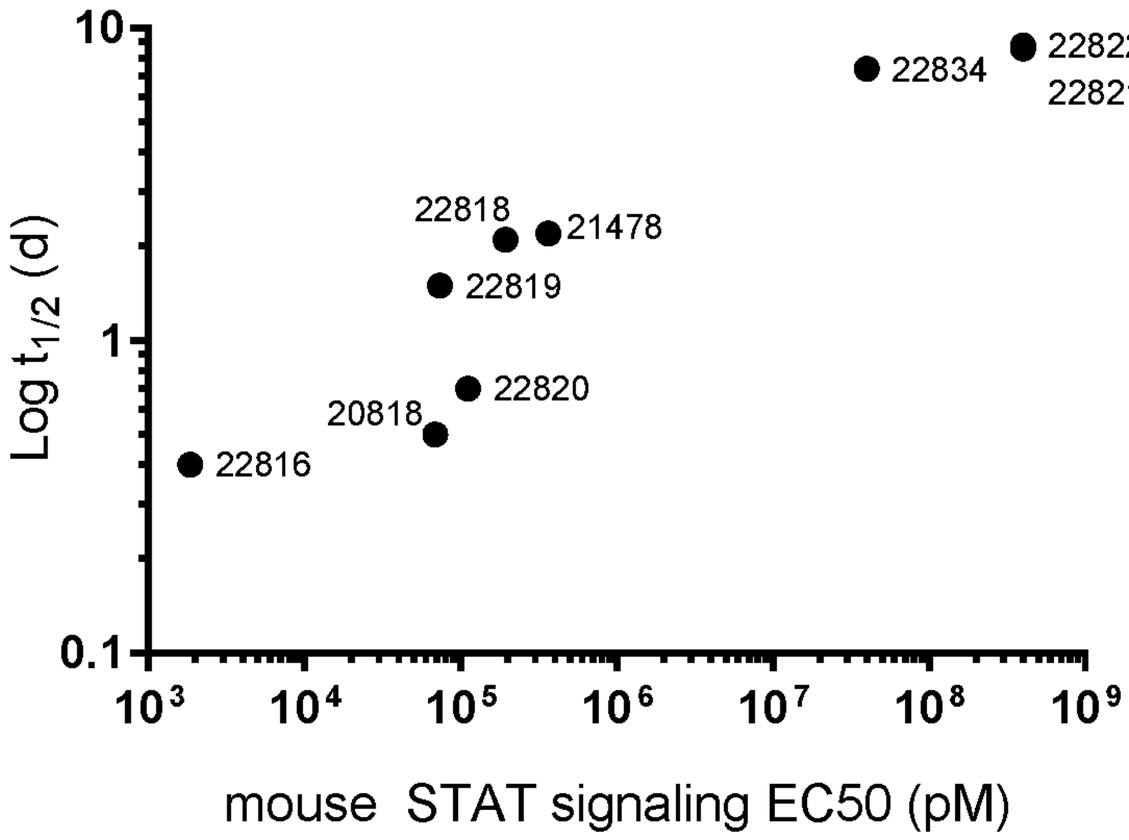

10
1
0.1
Log $t_{1/2}$ (d)
22834
22822
22821
22818
21478
22819
22820
20818
22816
10^3
10^4
10^5
10^6
10^7
10^8
10^9
mouse STAT signaling EC50 (pM)

Figure 72

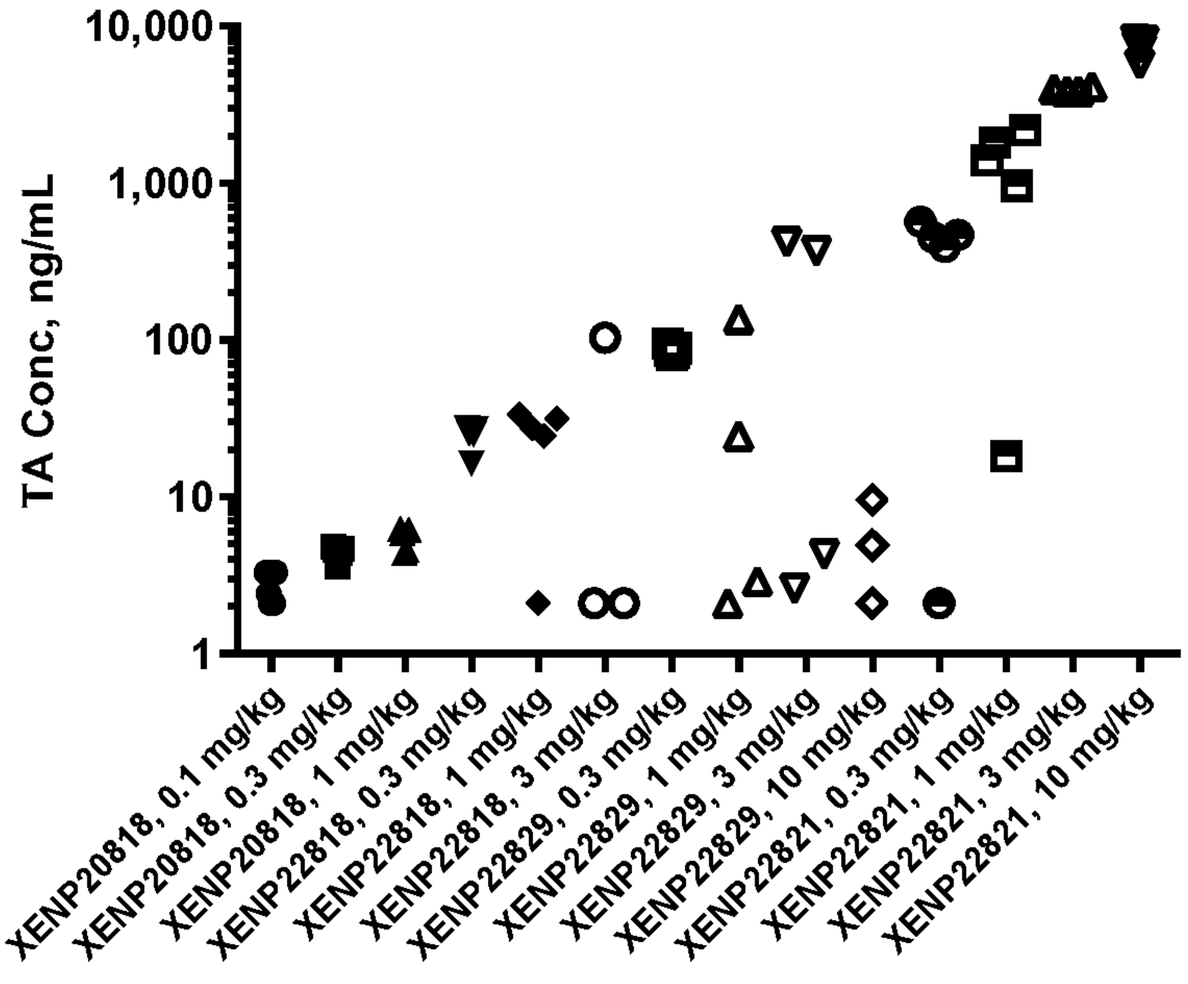

Day 8
TA Conc, ng/mL
10,000
1,000
100
10
1
XENP20818, 0.1 mg/kg
XENP20818, 0.3 mg/kg
XENP20818, 1 mg/kg
XENP22818, 0.3 mg/kg
XENP22818, 1 mg/kg
XENP22818, 3 mg/kg
XENP22829, 0.3 mg/kg
XENP22829, 1 mg/kg
XENP22829, 3 mg/kg
XENP22829, 10 mg/kg
XENP22821, 0.3 mg/kg
XENP22821, 1 mg/kg
XENP22821, 3 mg/kg
XENP22821, 10 mg/kg

Figure 73

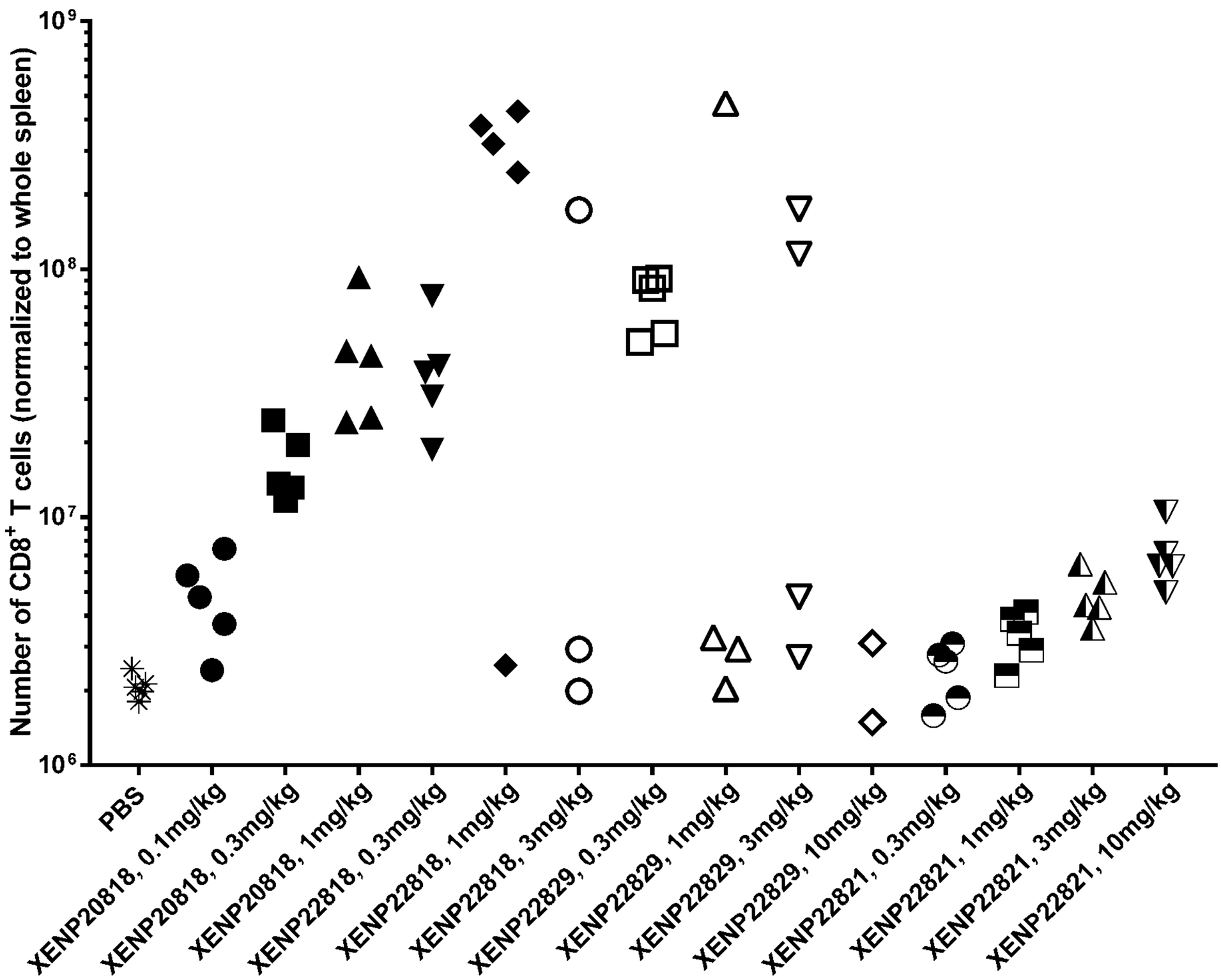

Number of CD8+ T cells (normalized to whole spleen)
10^9
10^8
10^7
10^6
PBS
XENP20818, 0.1mg/kg
XENP20818, 0.3mg/kg
XENP20818, 1mg/kg
XENP22818, 0.3mg/kg
XENP22818, 1mg/kg
XENP22818, 3mg/kg
XENP22829, 0.3mg/kg
XENP22829, 1mg/kg
XENP22829, 3mg/kg
XENP22829, 10mg/kg
XENP22821, 0.3mg/kg
XENP22821, 1mg/kg
XENP22821, 3mg/kg
XENP22821, 10mg/kg

Figure 74

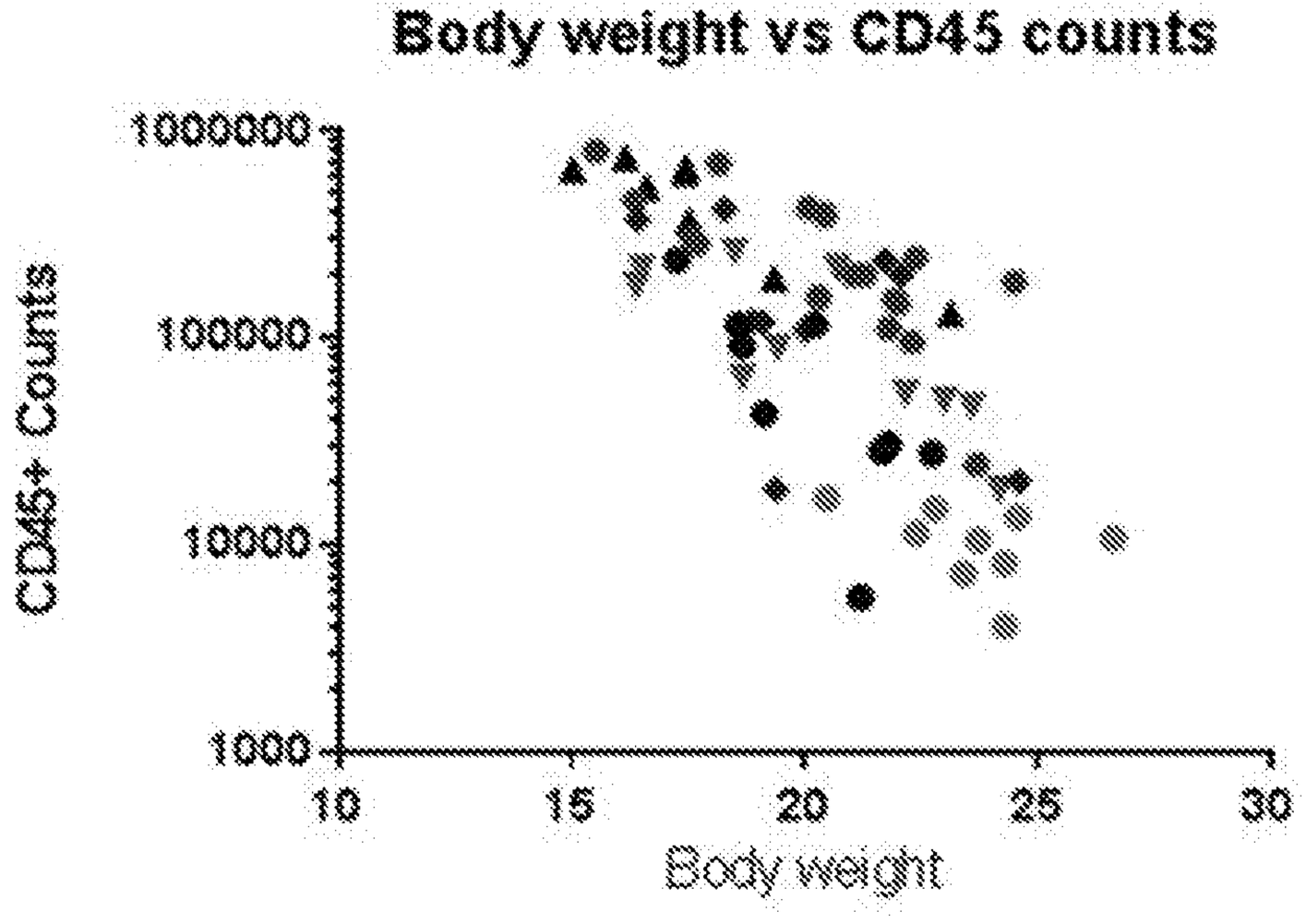

Body weight vs CD45 counts
CD45+ Counts
1000000
100000
10000
1000
10
15
20
25
30
Body weight

Figure 75A

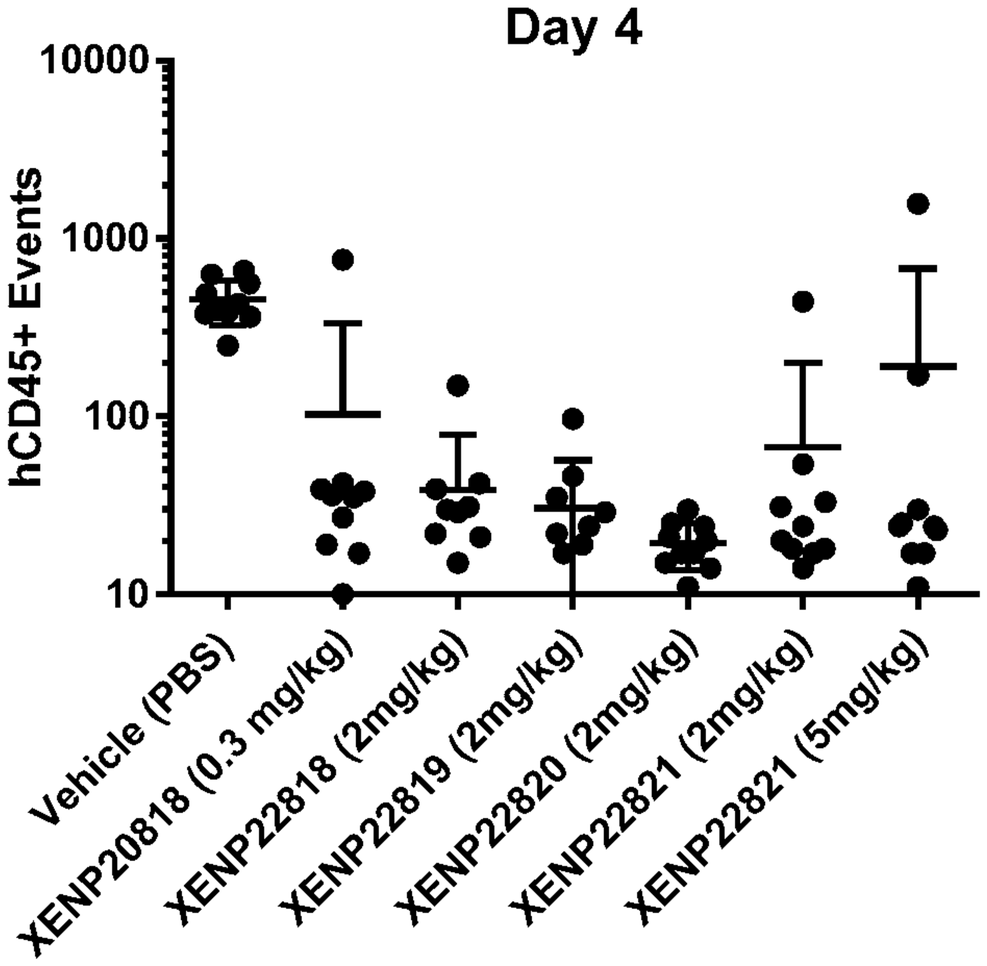


Figure 75B

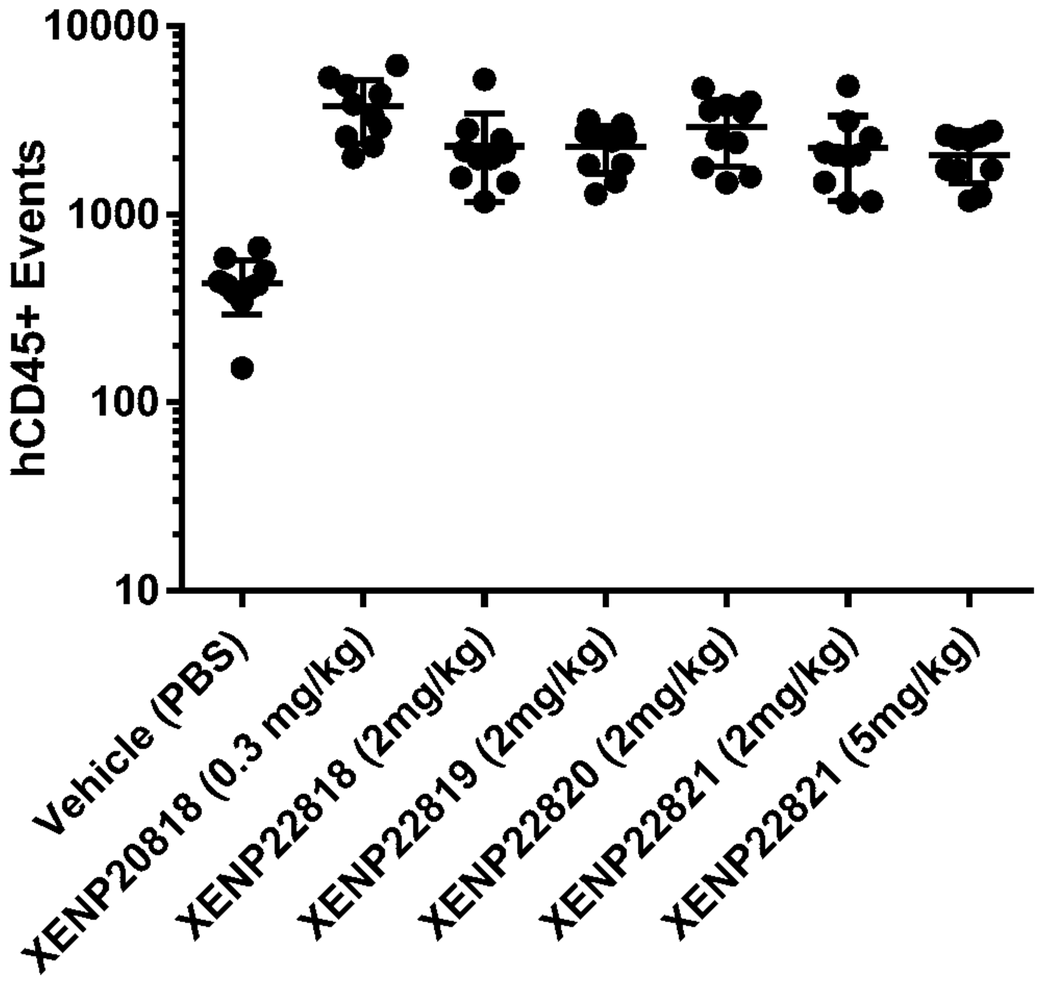


Figure 76A

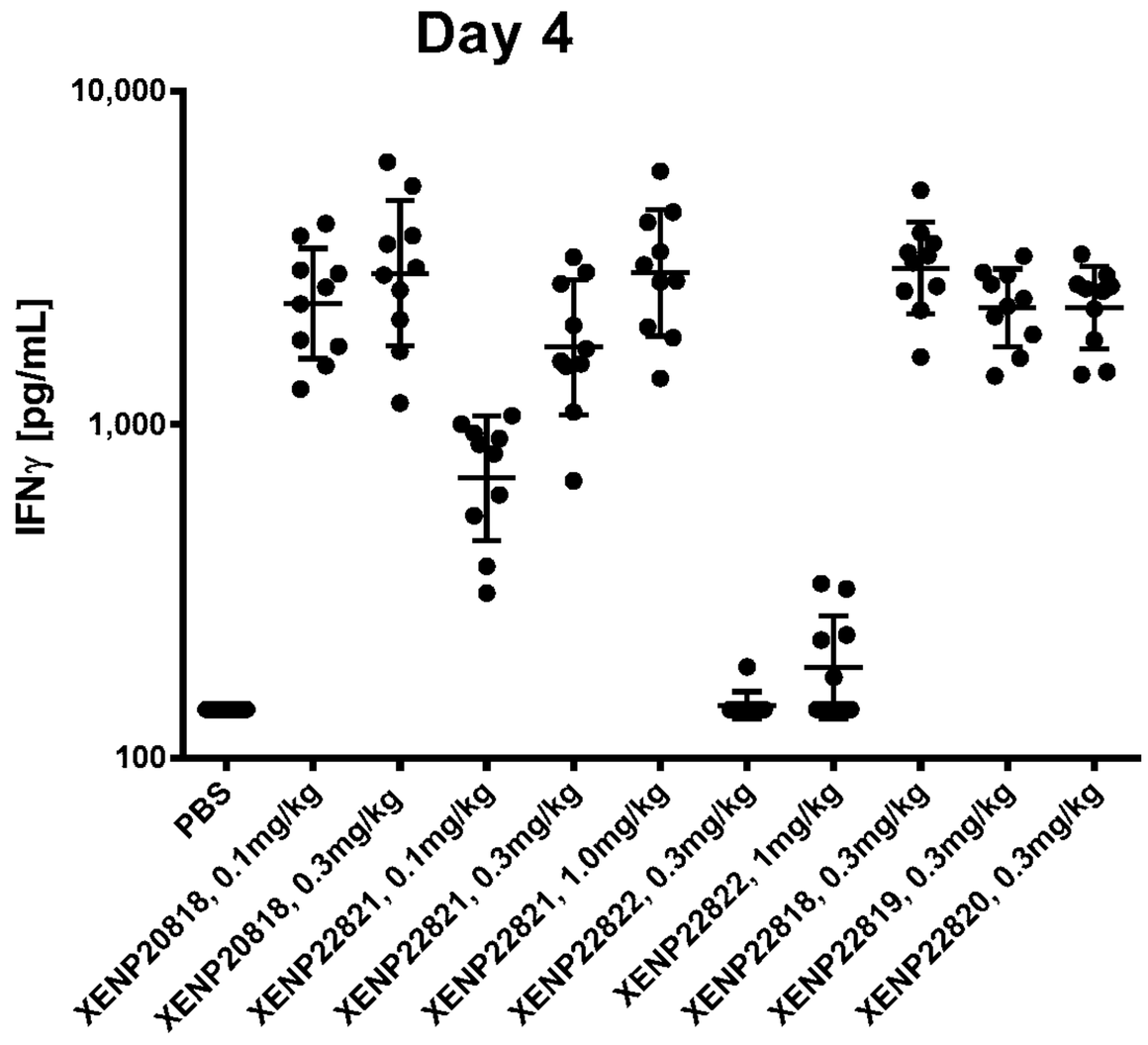


Figure 76B

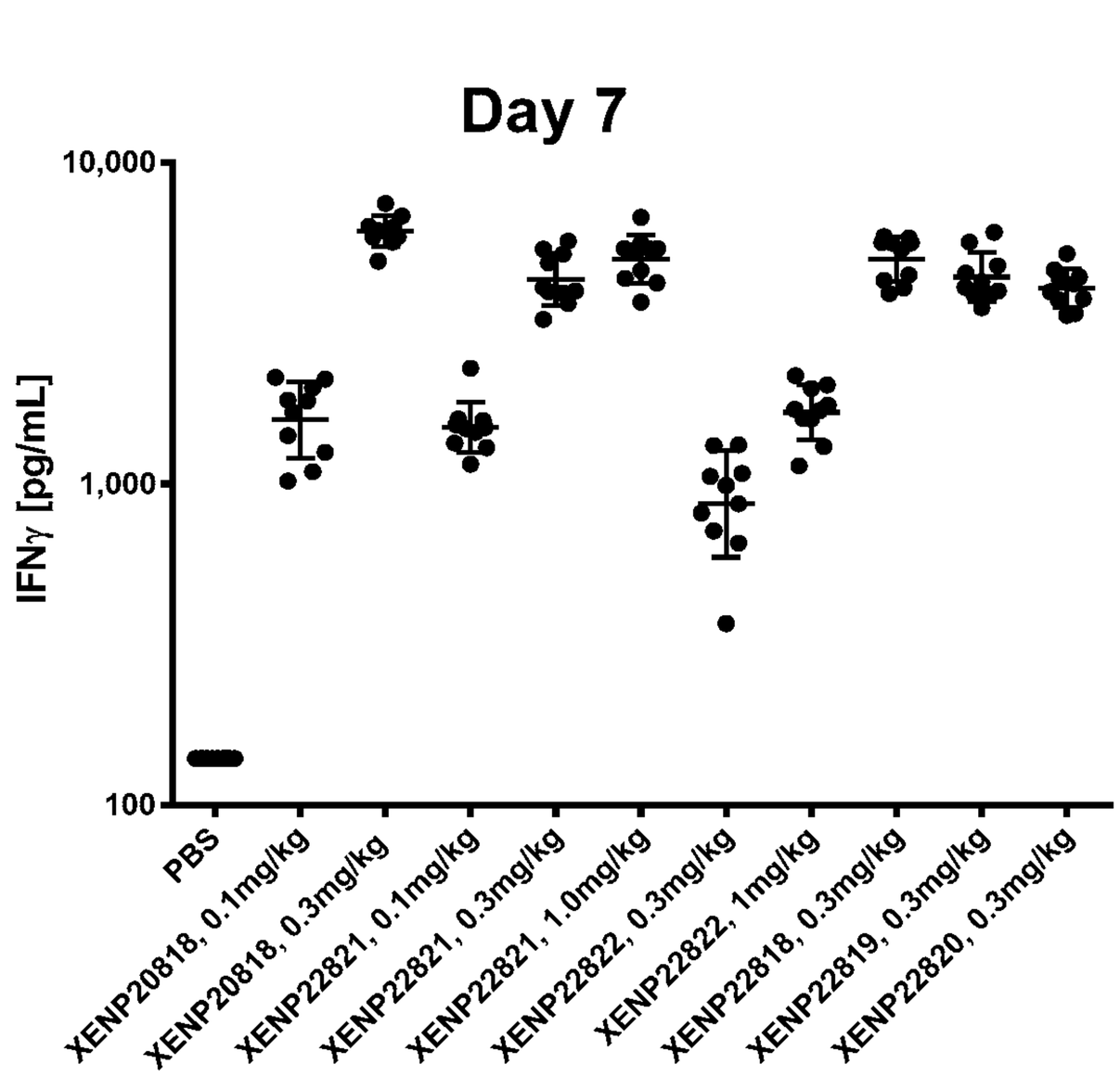


Figure 76C

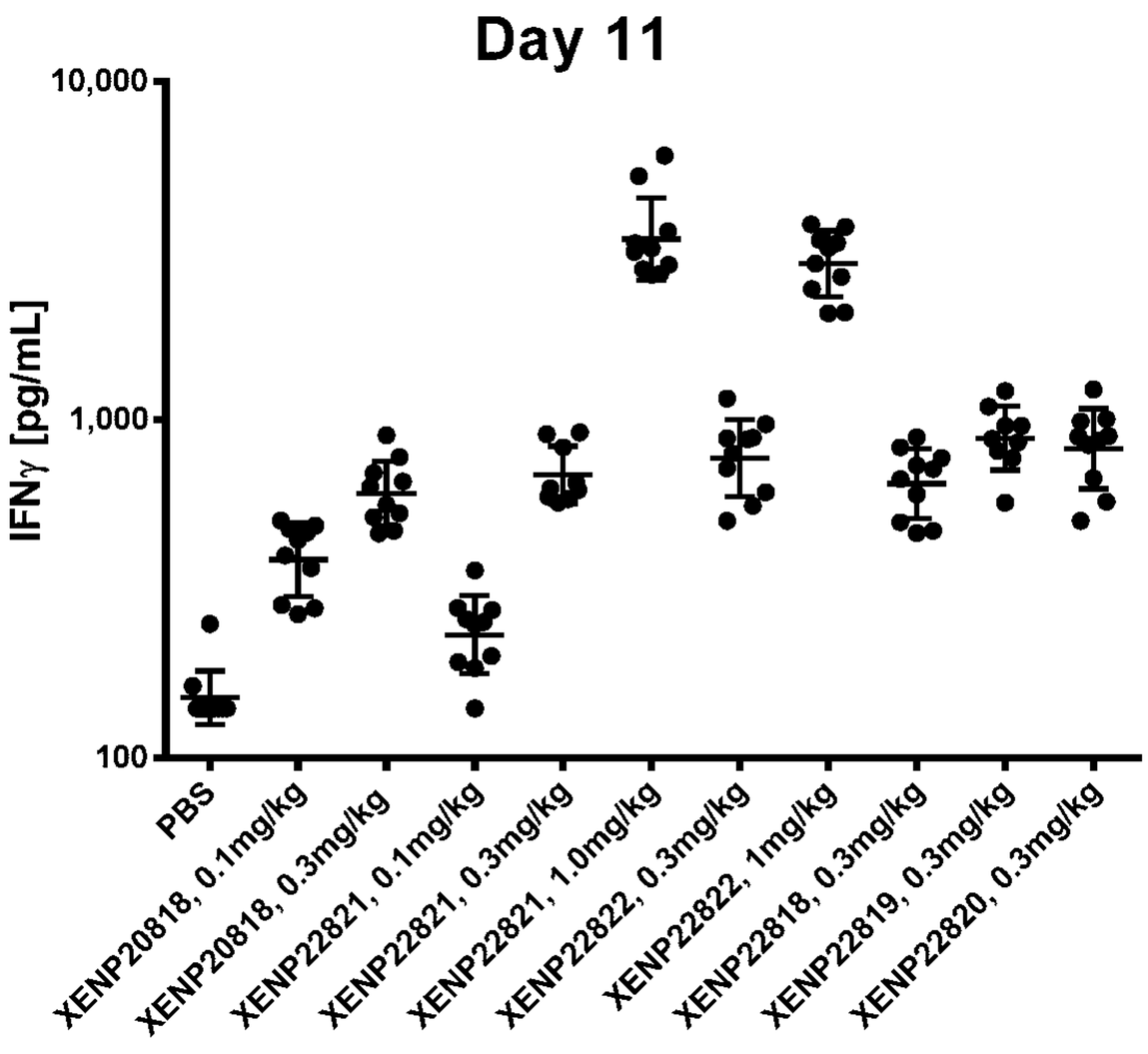

Day 11
IFNγ [pg/mL]
10,000
1,000
100
PBS
XENP20818, 0.1mg/kg
XENP20818, 0.3mg/kg
XENP22821, 0.1mg/kg
XENP22821, 0.3mg/kg
XENP22821, 1.0mg/kg
XENP22822, 0.3mg/kg
XENP22822, 1mg/kg
XENP22818, 0.3mg/kg
XENP22819, 0.3mg/kg
XENP22820, 0.3mg/kg

Figure 77A

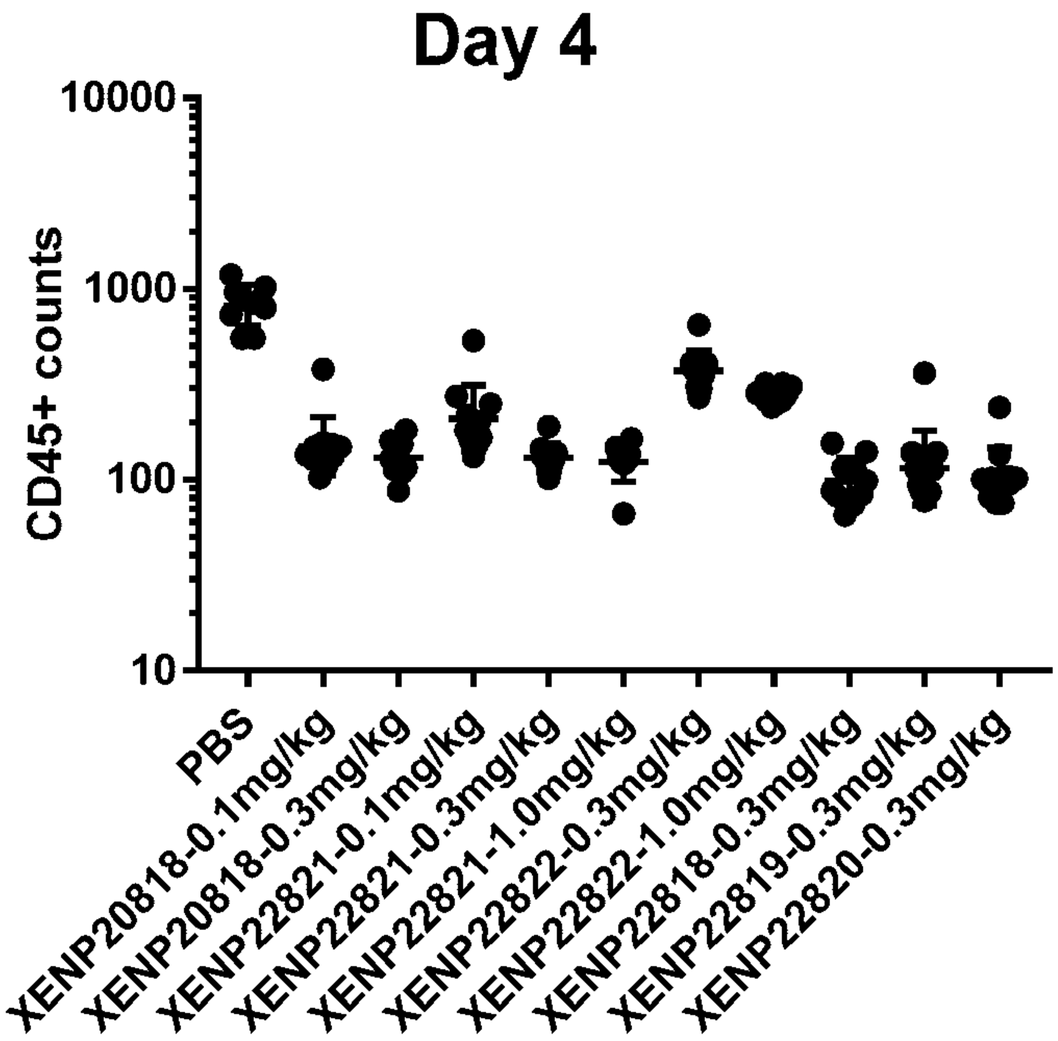


Figure 77B

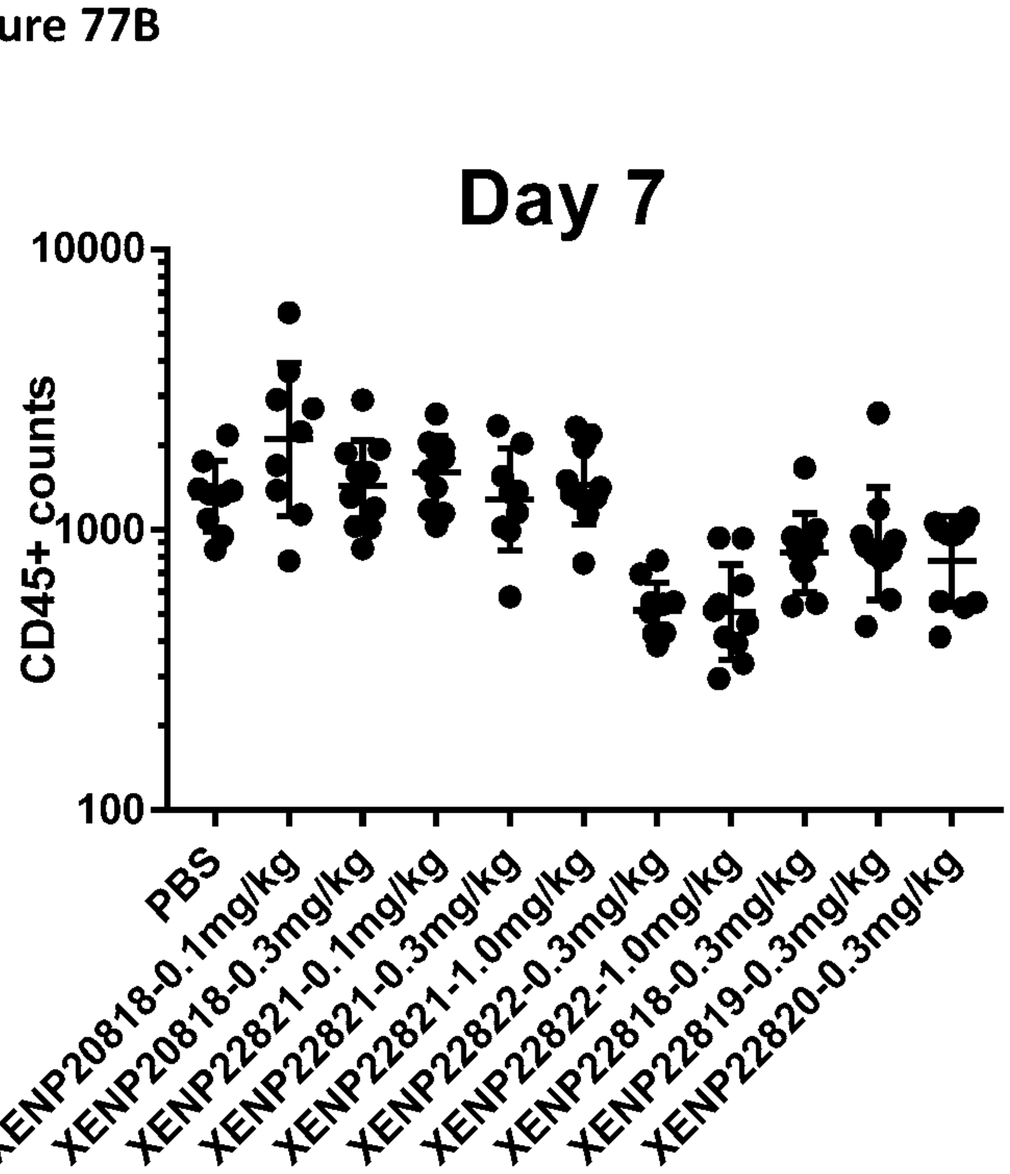


Figure 77C

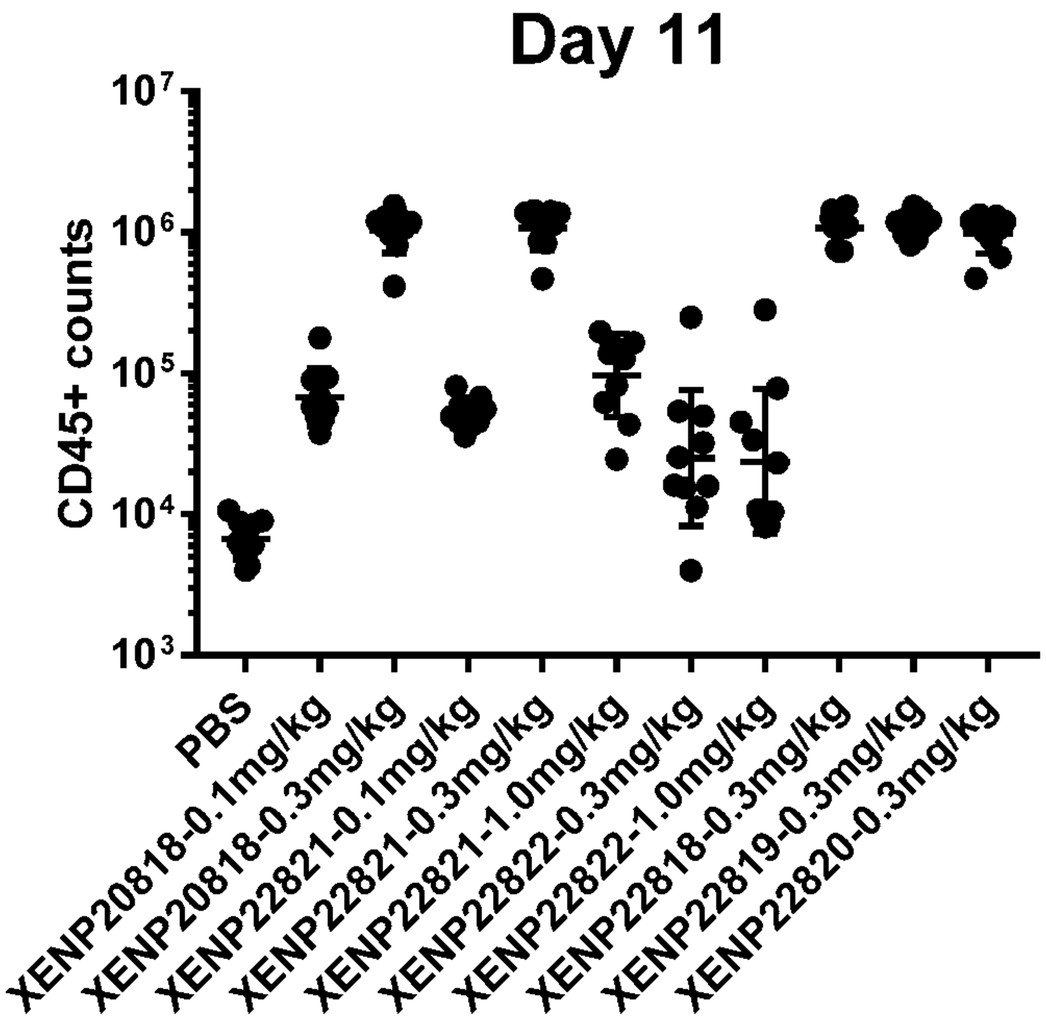

Day 11
CD45+ counts
10^7
10^6
10^5
10^4
10^3
PBS
XENP20818-0.1mg/kg
XENP20818-0.3mg/kg
XENP22821-0.1mg/kg
XENP22821-0.3mg/kg
XENP22821-1.0mg/kg
XENP22822-0.3mg/kg
XENP22822-1.0mg/kg
XENP22818-0.3mg/kg
XENP22819-0.3mg/kg
XENP22820-0.3mg/kg

Figure 78A

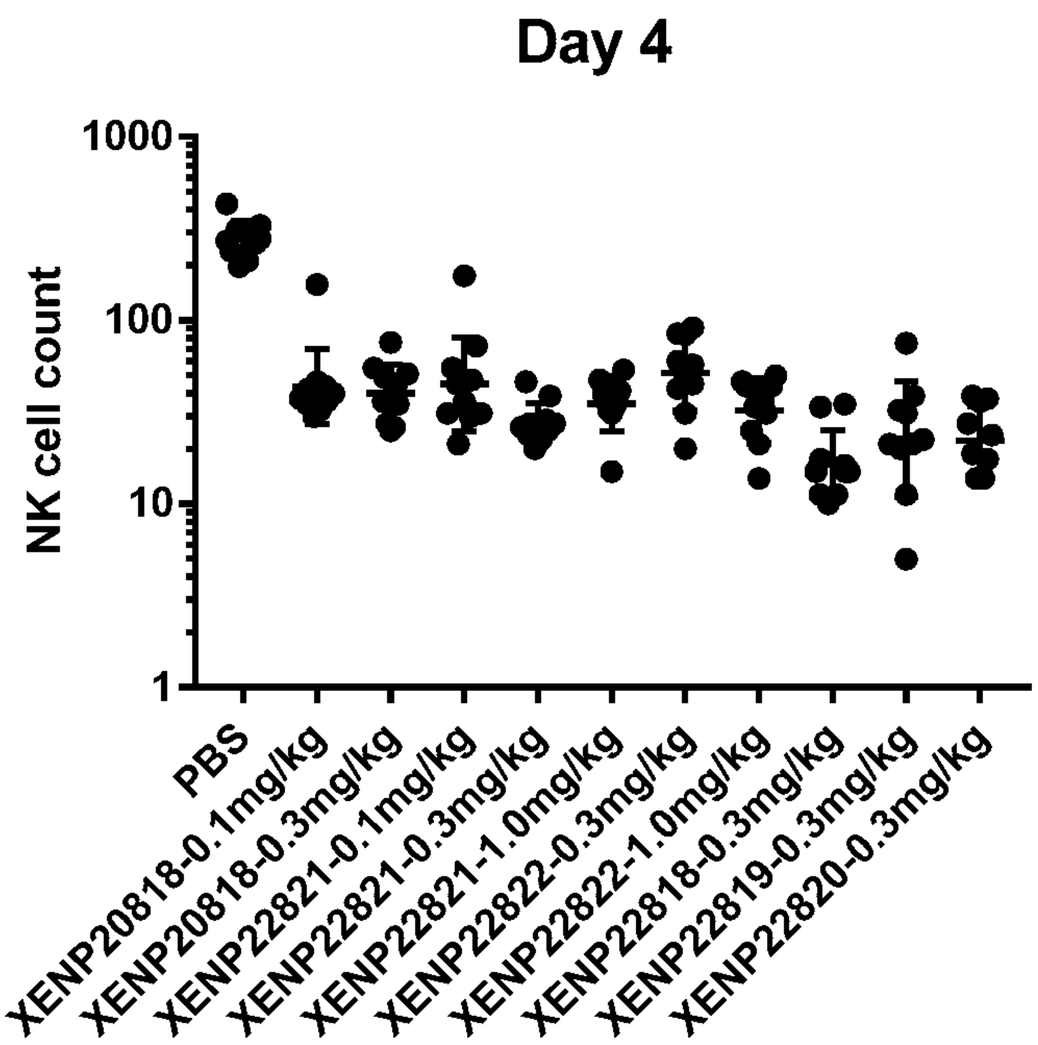


Figure 78B

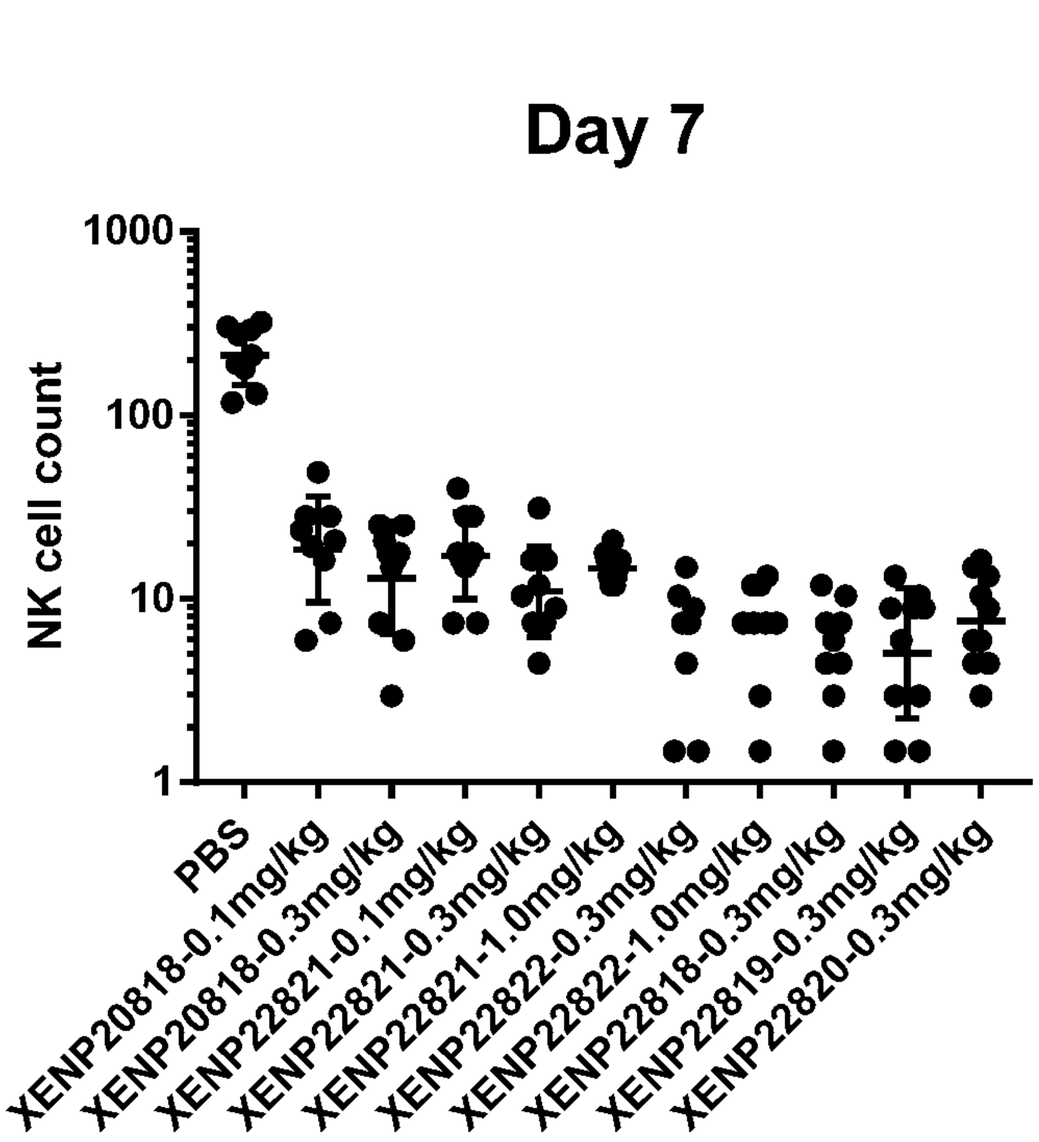


Figure 78C

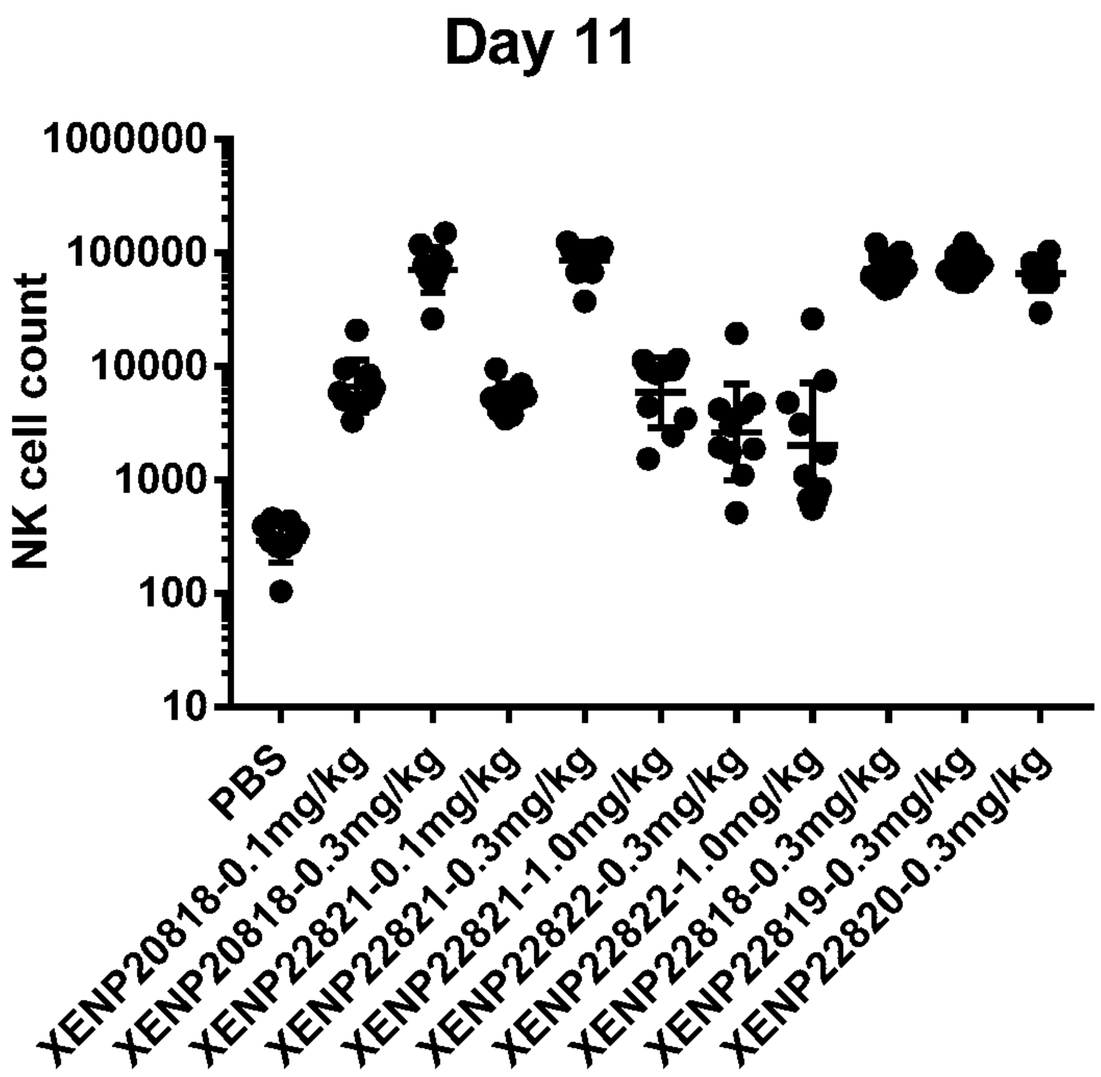

Day 11
NK cell count
1000000
100000
10000
1000
100
10
PBS
XENP20818-0.1mg/kg
XENP20818-0.3mg/kg
XENP22821-0.1mg/kg
XENP22821-0.3mg/kg
XENP22821-1.0mg/kg
XENP22822-0.3mg/kg
XENP22822-1.0mg/kg
XENP22818-0.3mg/kg
XENP22819-0.3mg/kg
XENP22820-0.3mg/kg

Figure 79A

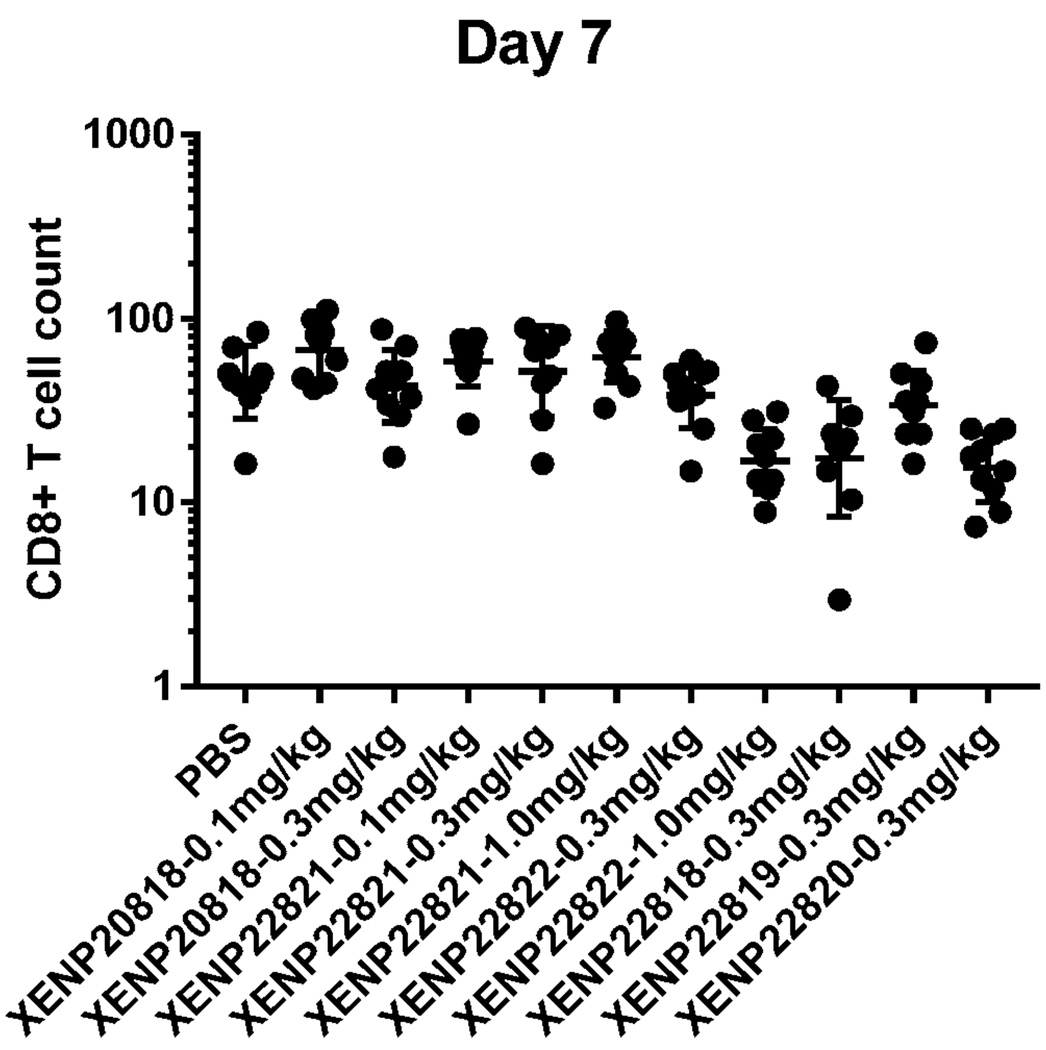
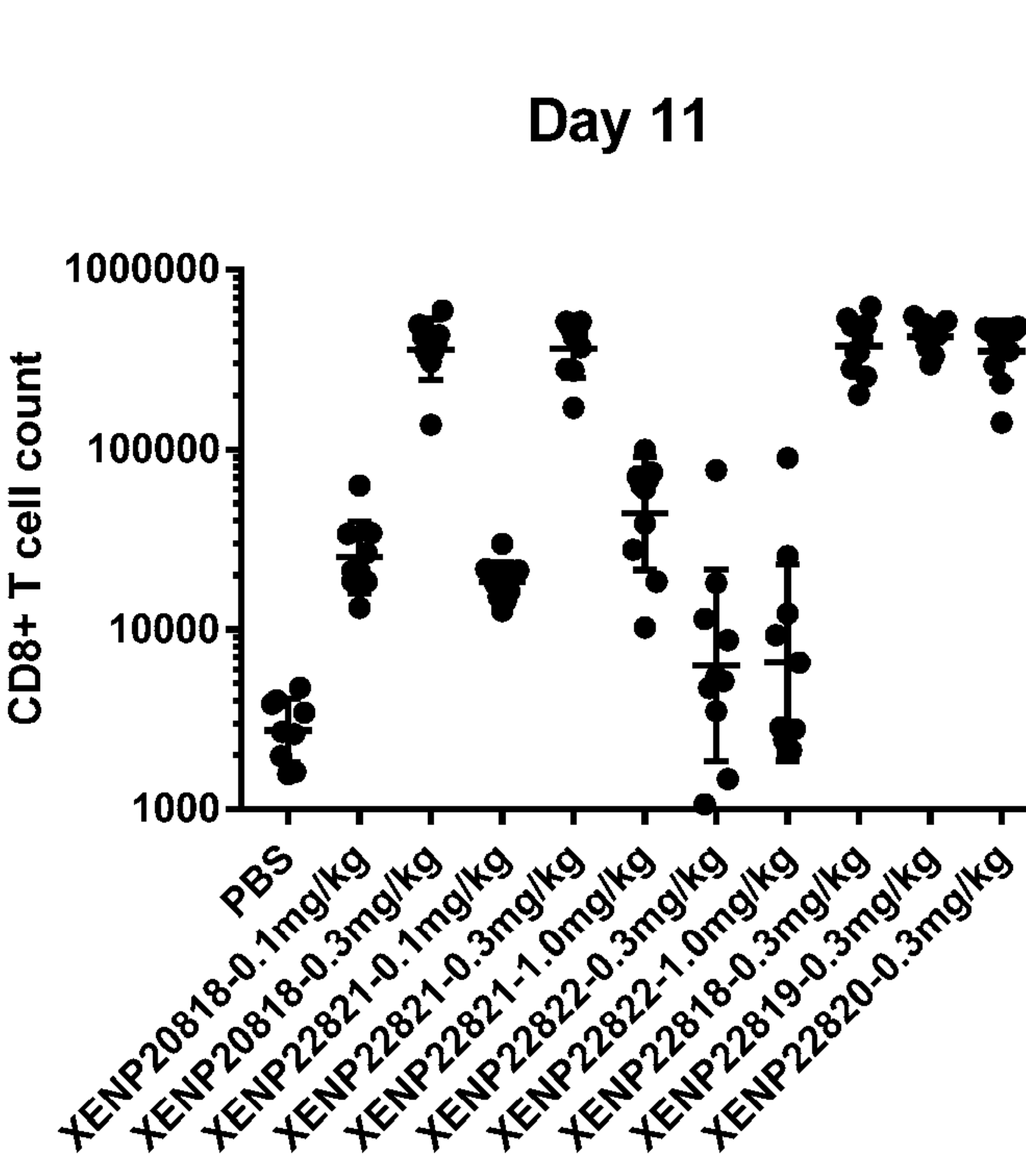


Figure 79B



Figures 80A-80B respectively depict $CD4^+$ T cell (CD4+CD45RA+) counts on Day 7 (Figure 80A) and Day 11 (Figure 80B) after treatment of NSG mice engrafted with human PBMCs with the indicated IL15/Rα-Fc fusion proteins or control.

Figure 80A

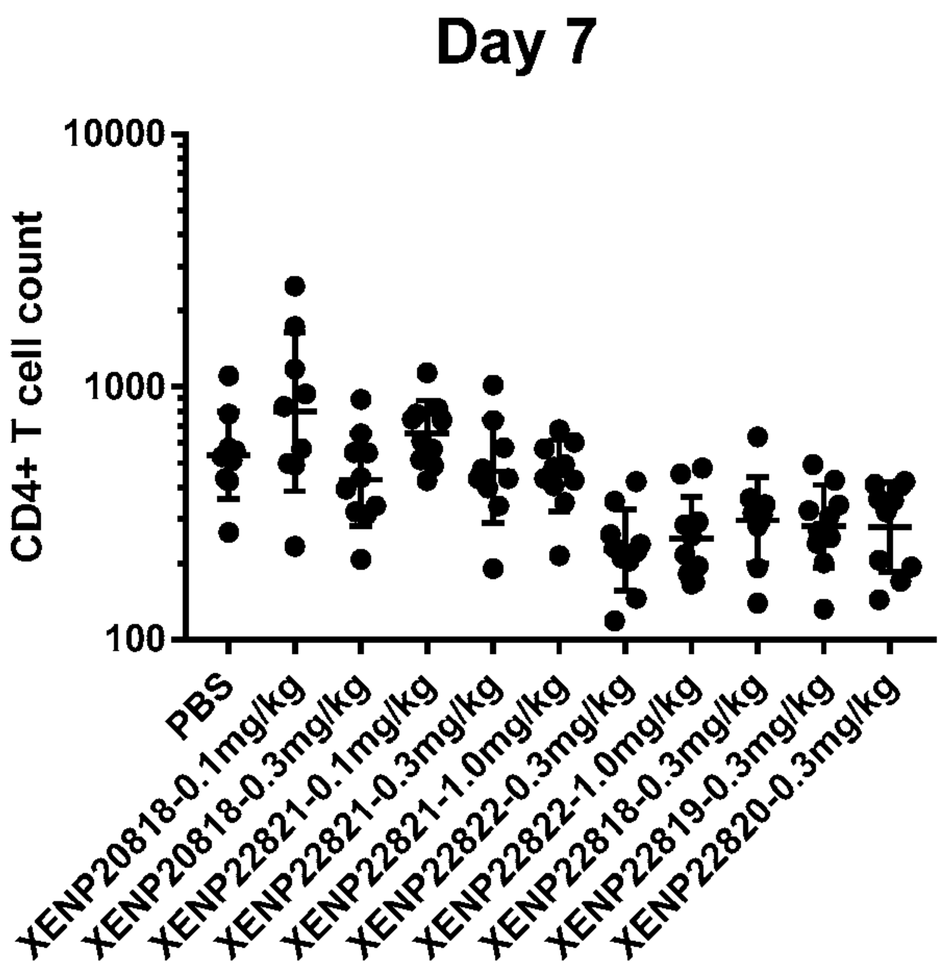


Figure 80B

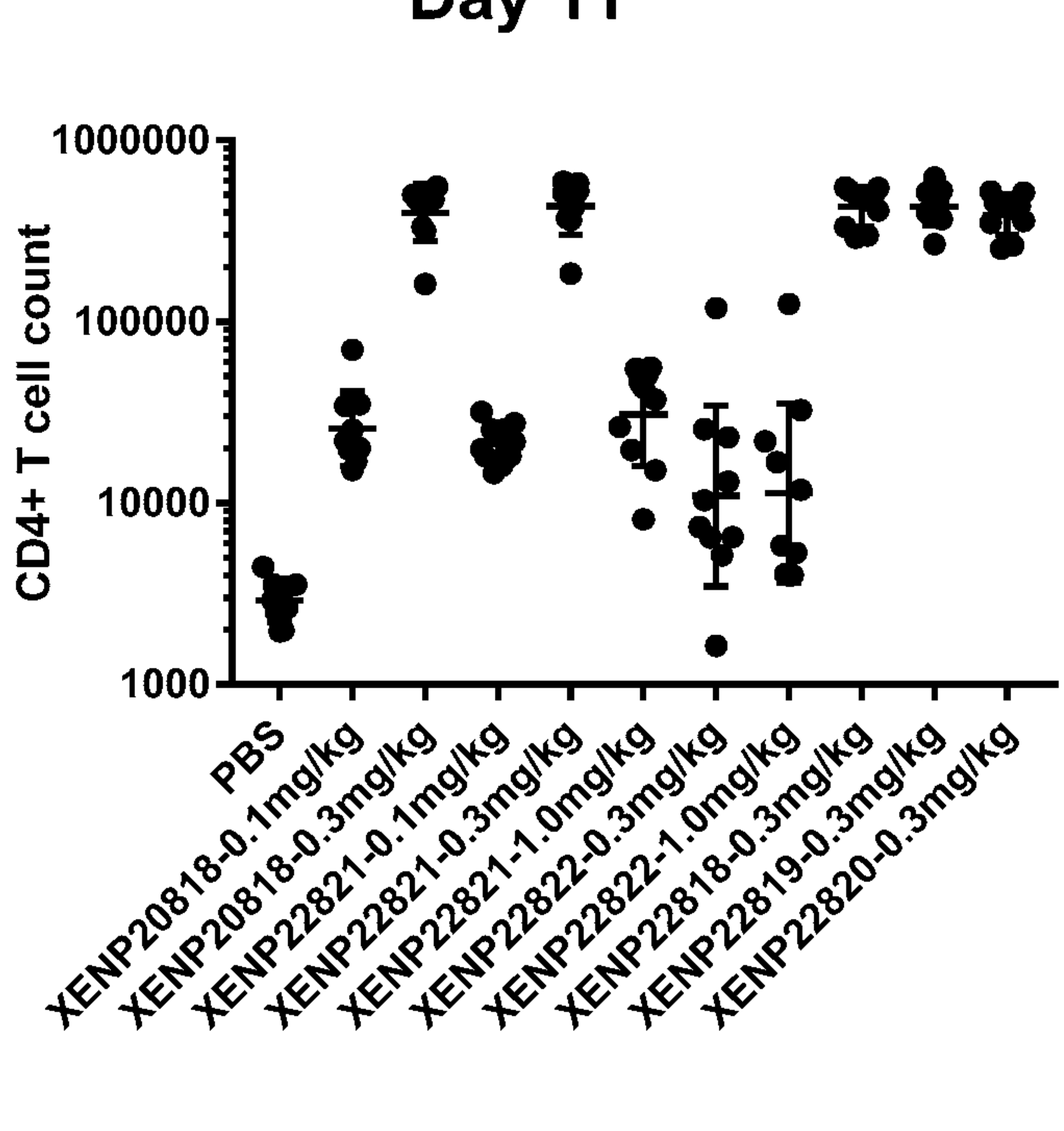


Figure 81

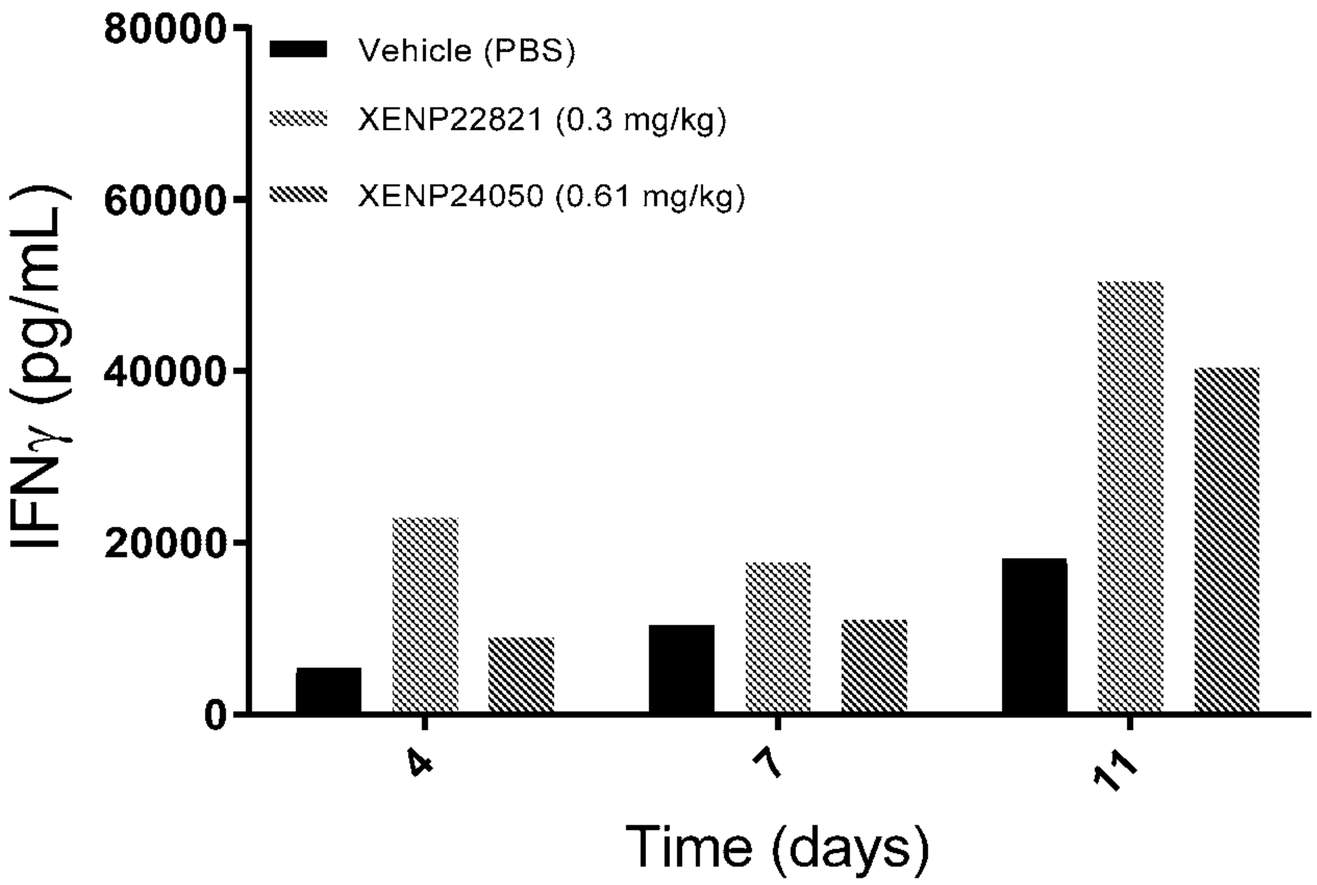

80000
60000
40000
20000
0
IFNγ (pg/mL)
Vehicle (PBS)
XENP22821 (0.3 mg/kg)
XENP24050 (0.61 mg/kg)
4
7
11
Time (days)

Figure 82A

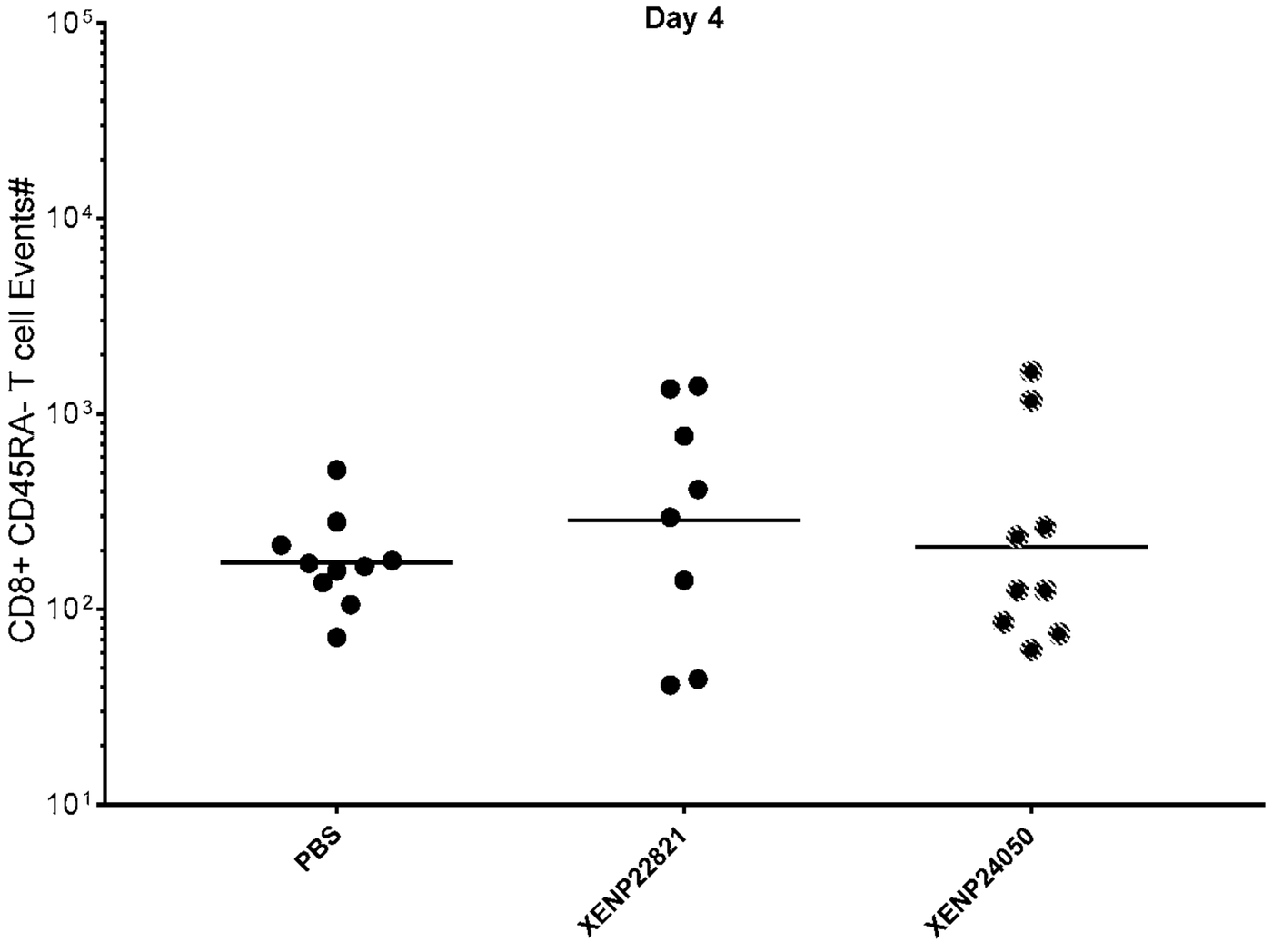


Figure 82B

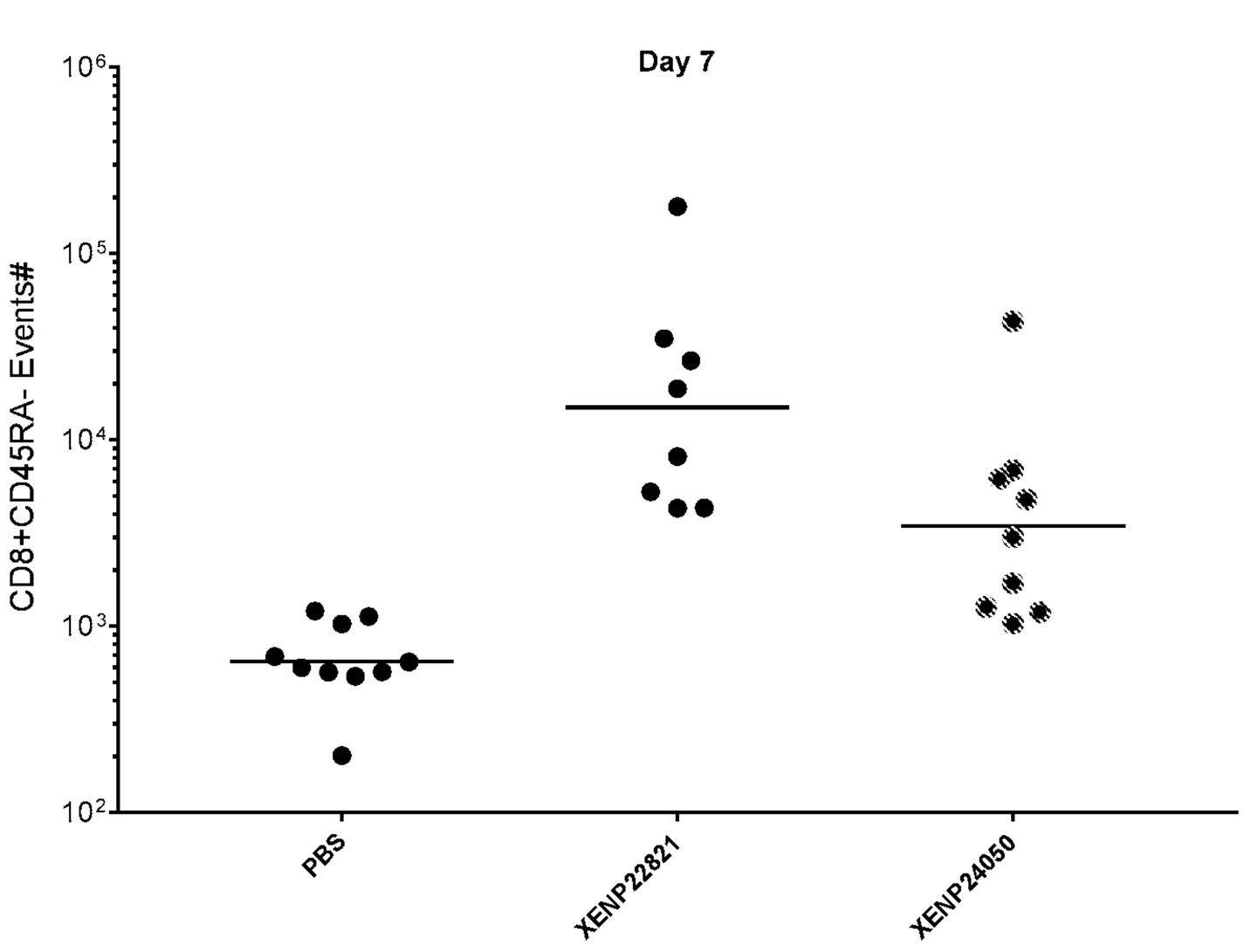


Figure 82C

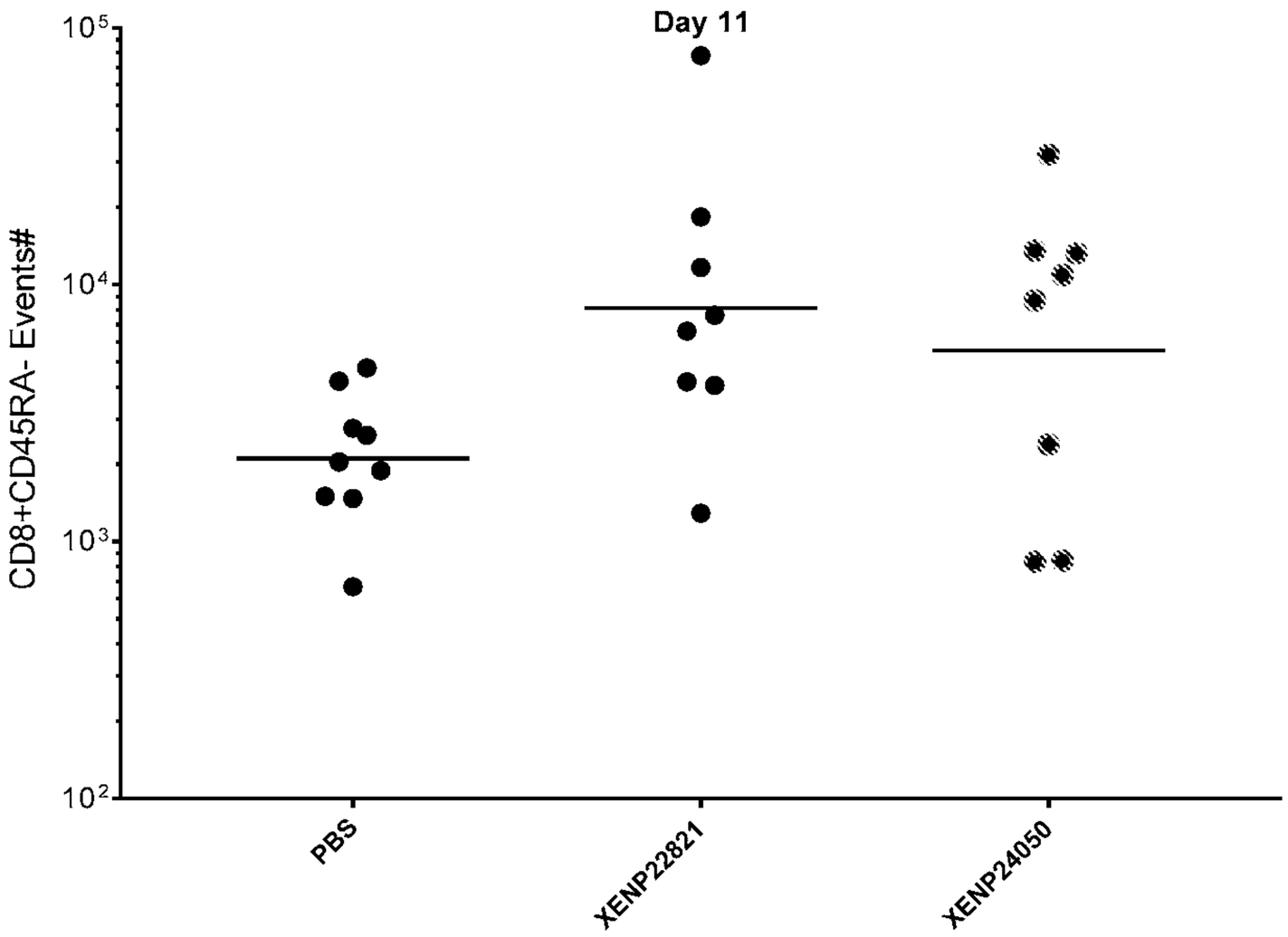

Day 11
10^5
10^4
10^3
10^2
CD8+CD45RA- Events#
PBS
XENP22821
XENP24050

Figure 83A

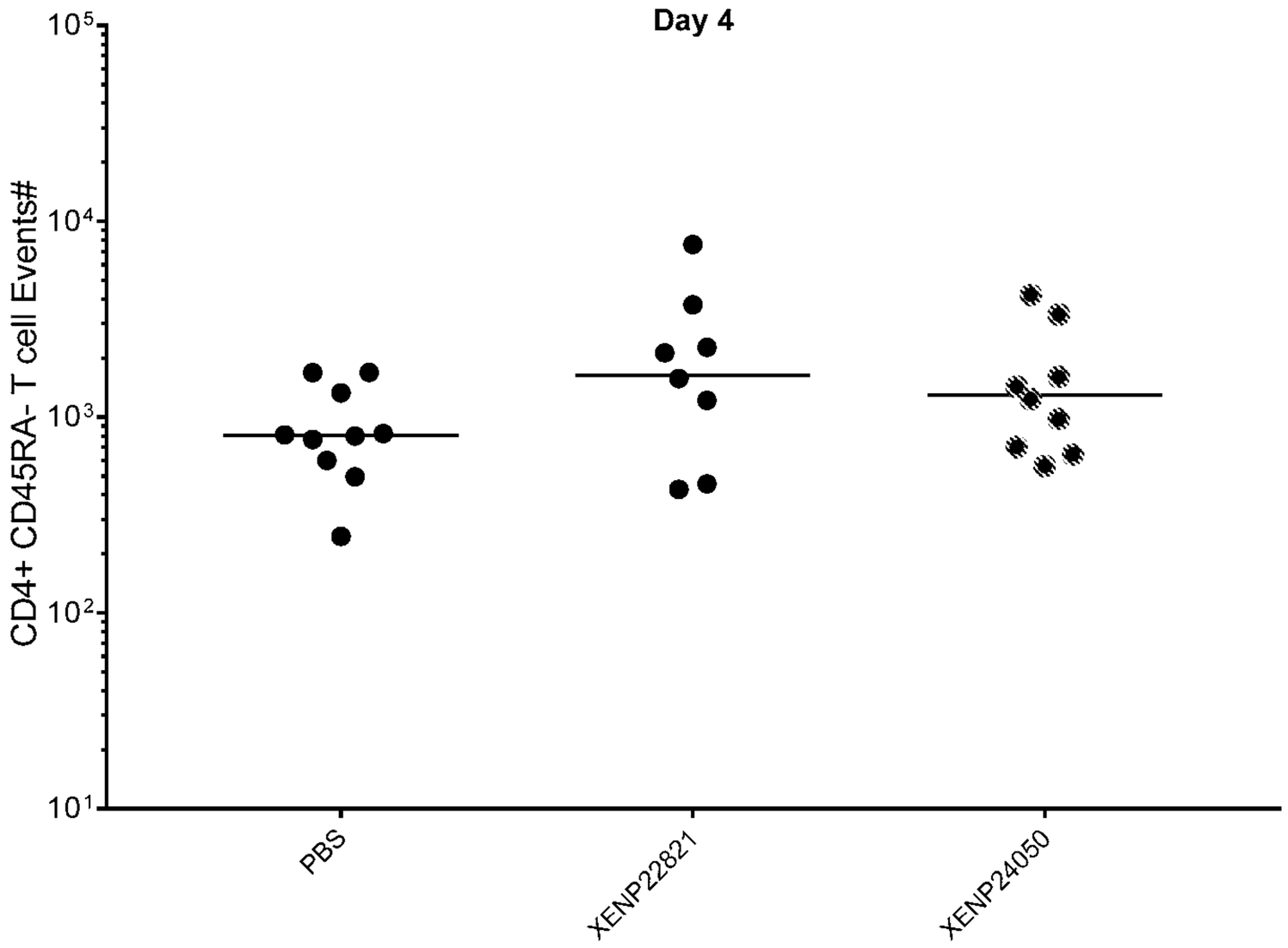


Figure 83B

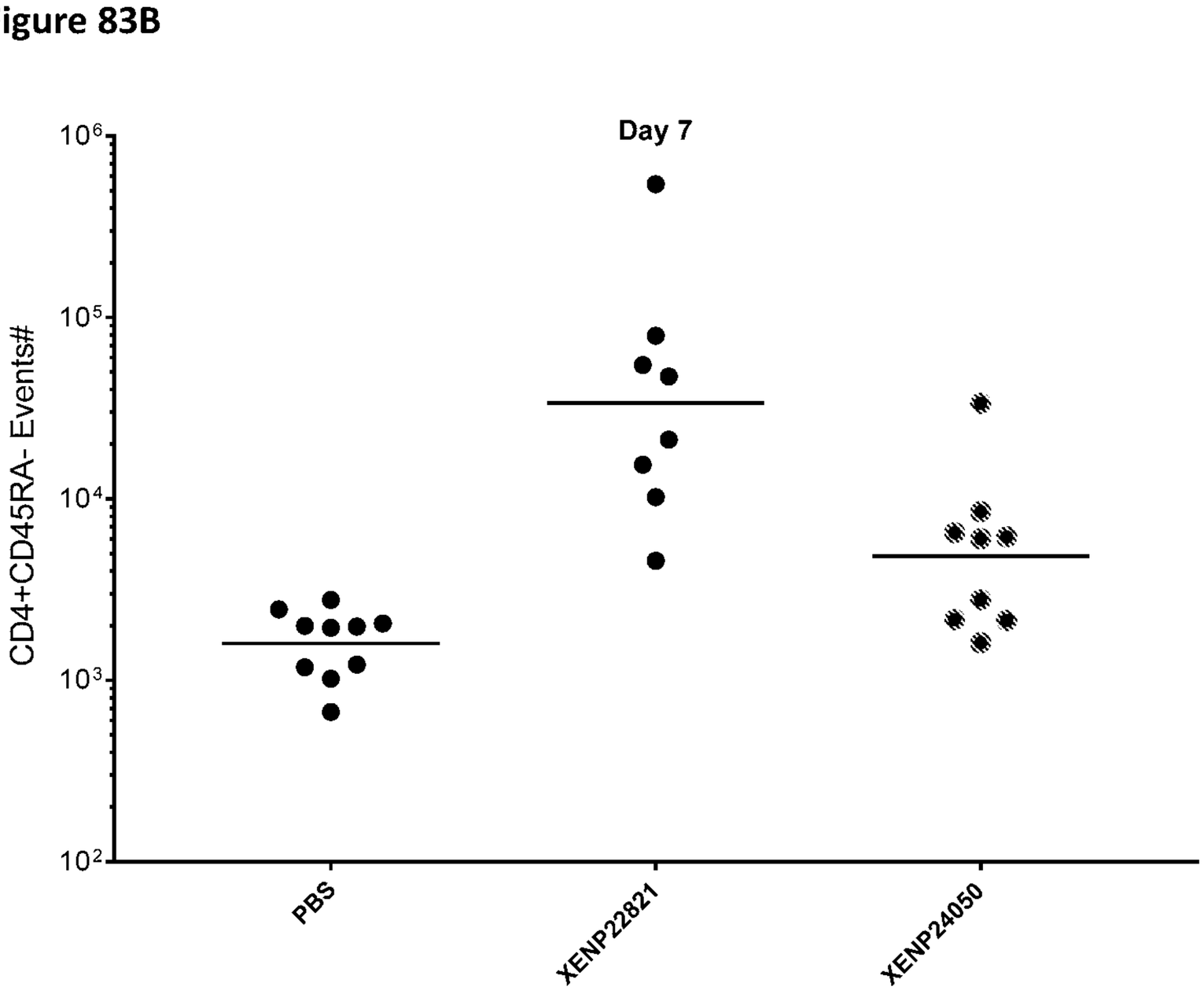


Figure 83C

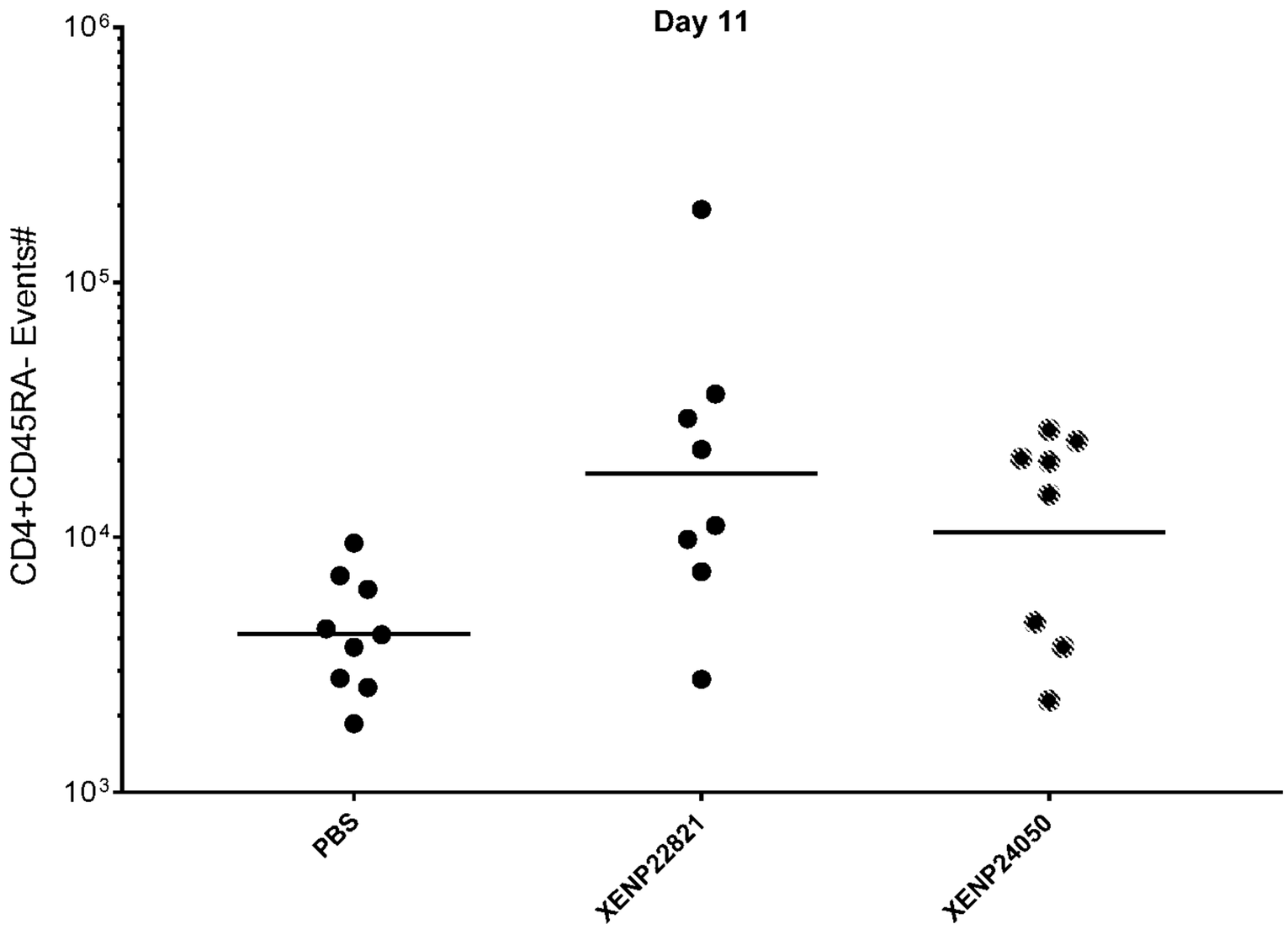

Day 11
CD4+CD45RA- Events#
10^6
10^5
10^4
10^3
PBS
XENP22821
XENP24050

Figure 84A

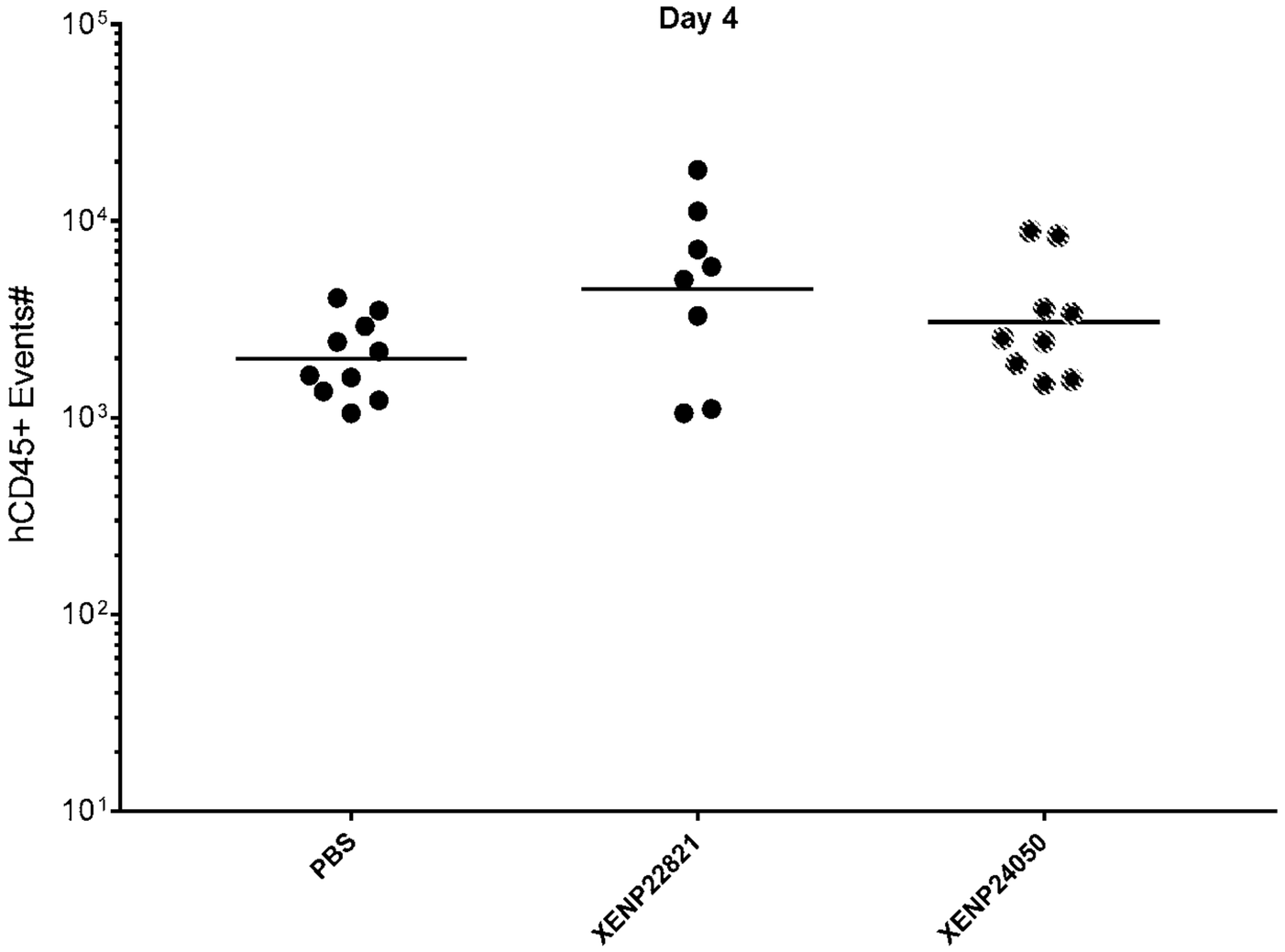


Figure 84B

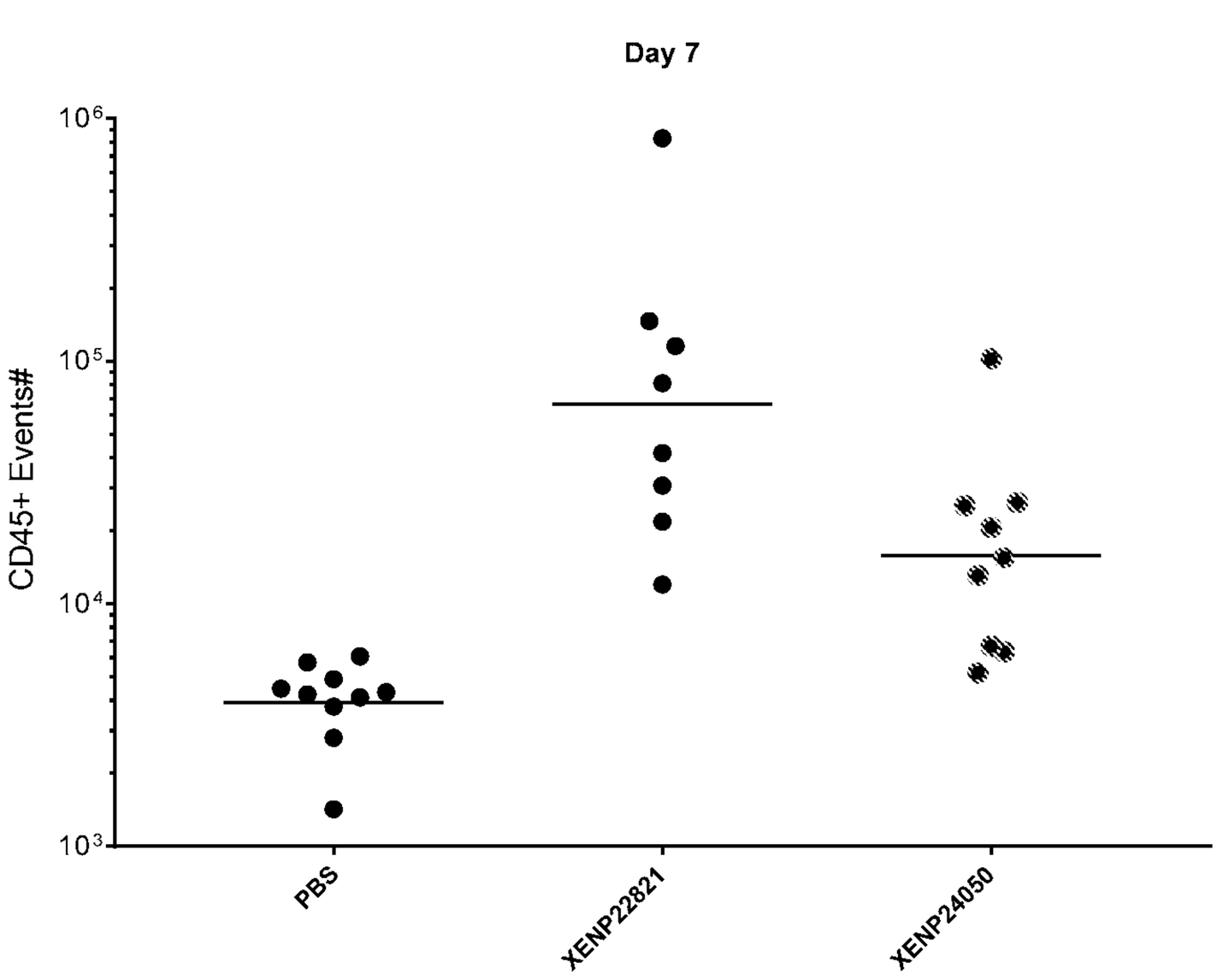


Figure 84C

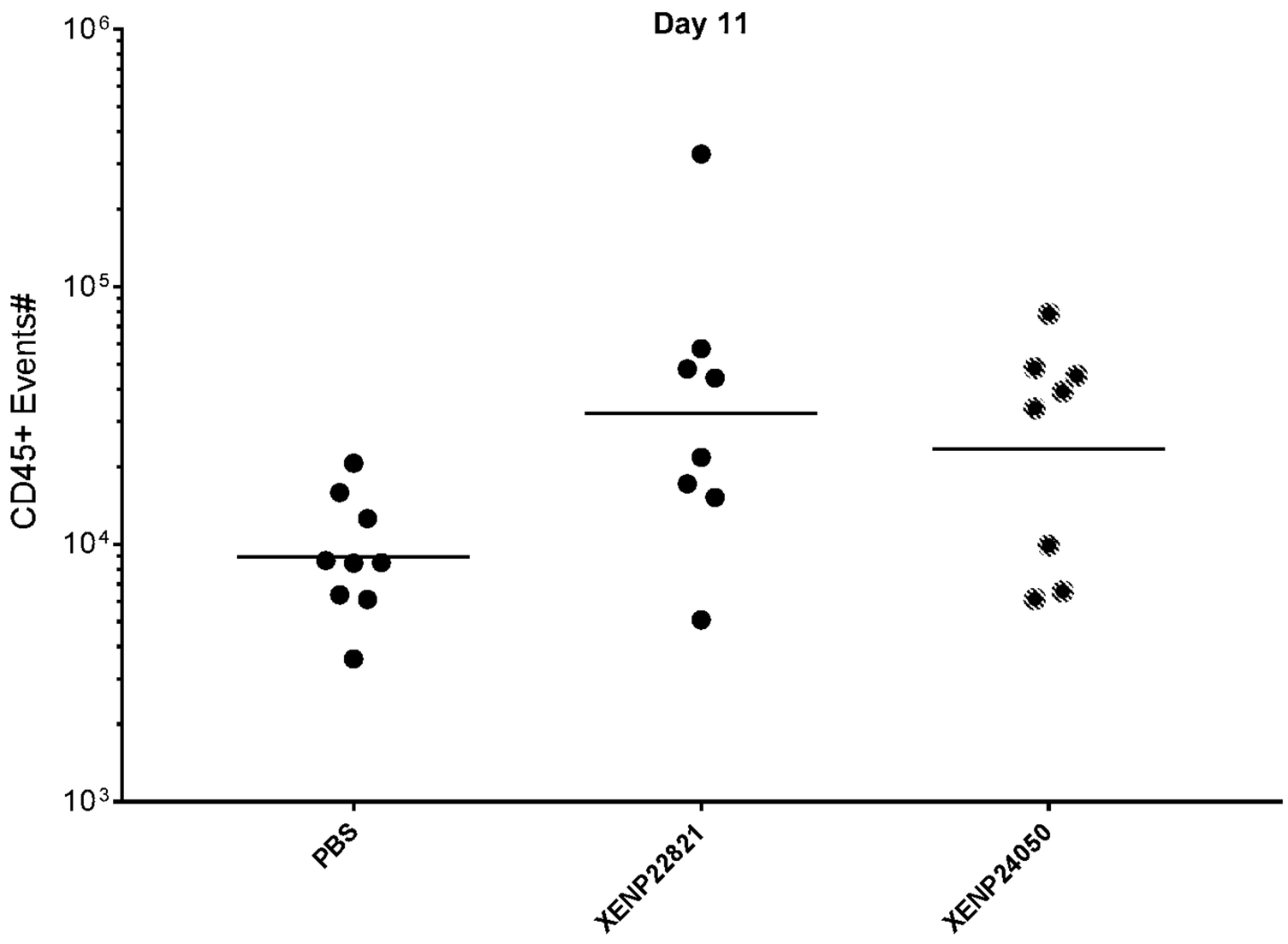


Figure 85A

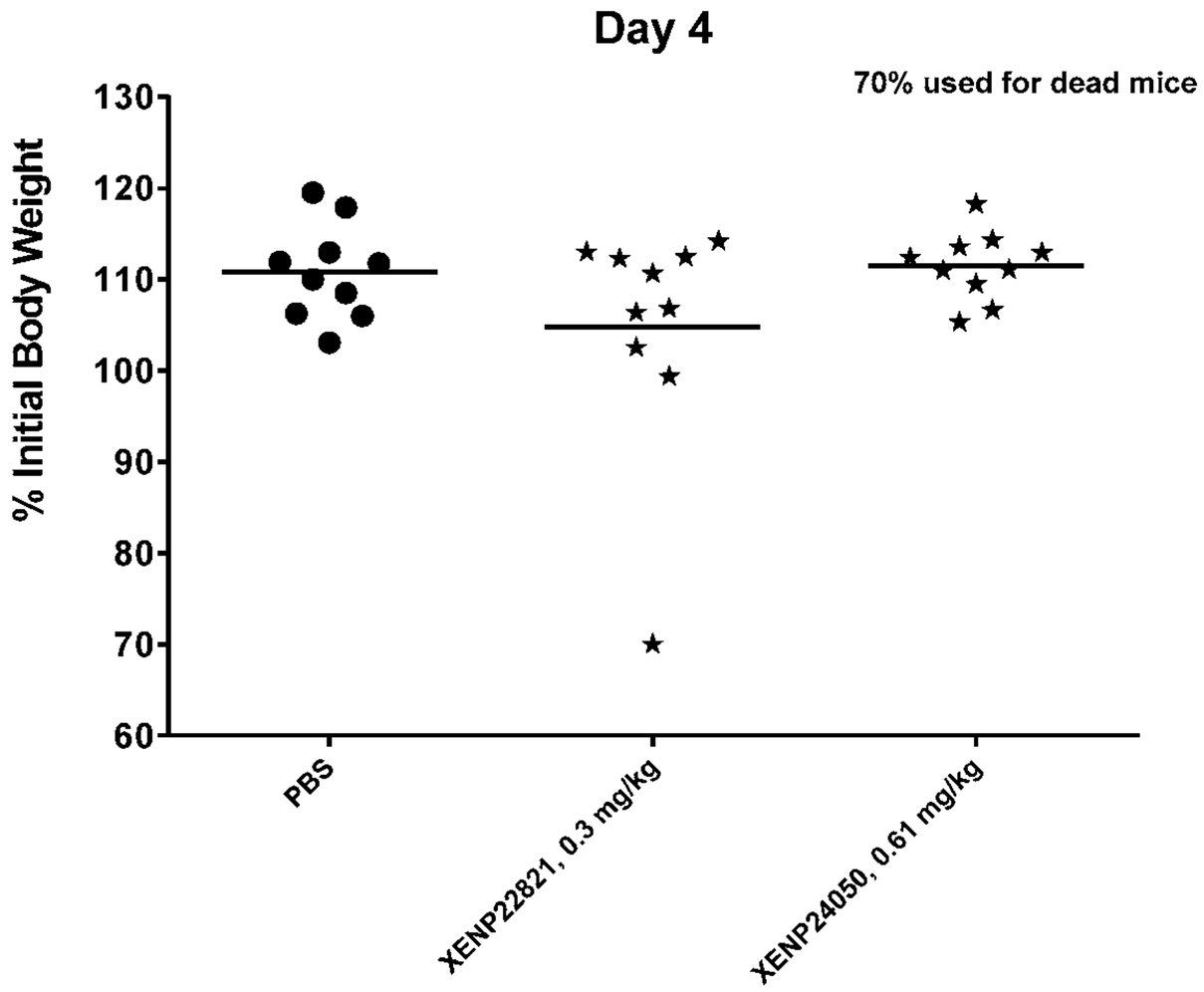


Figure 85B

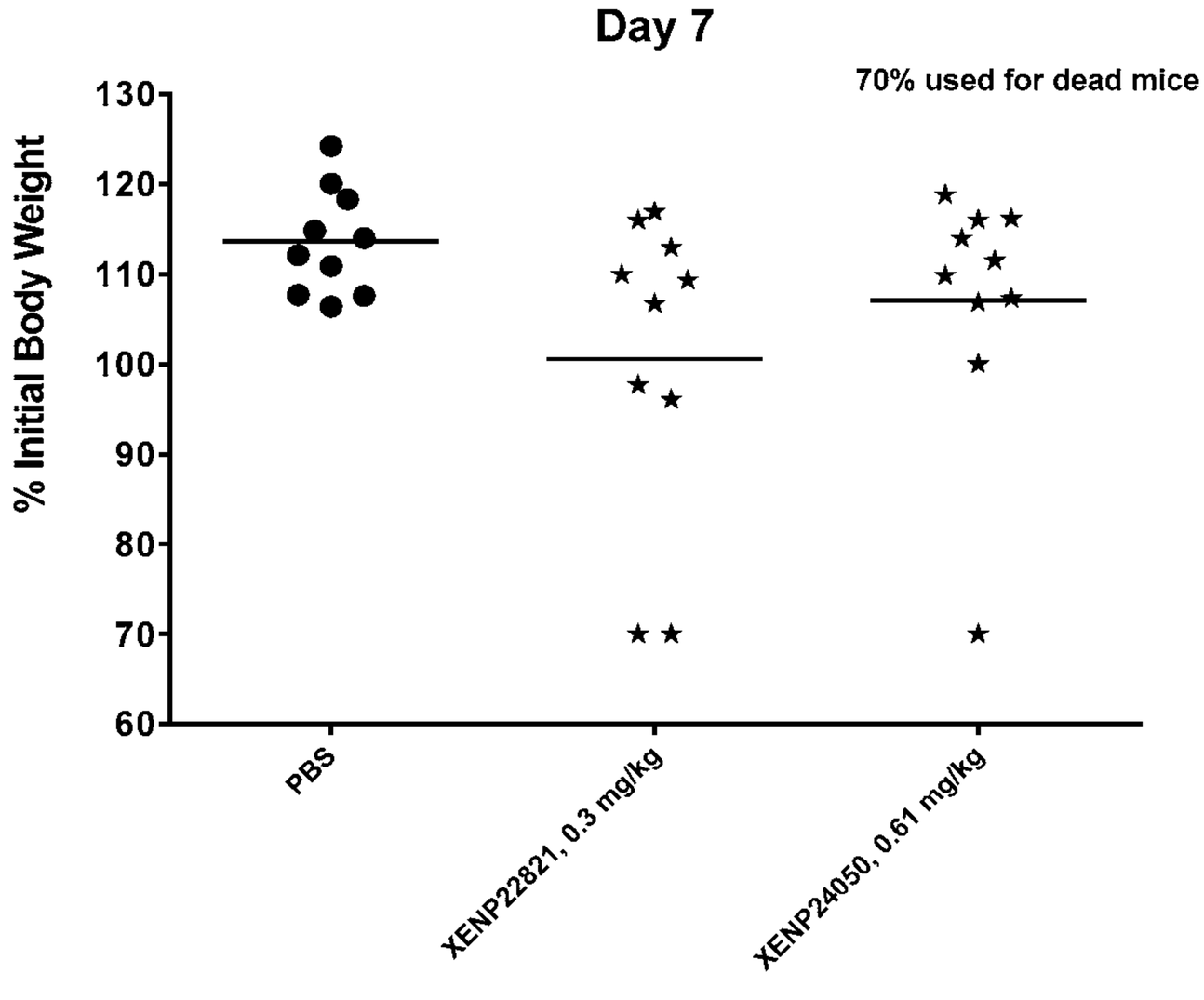


Figure 85C

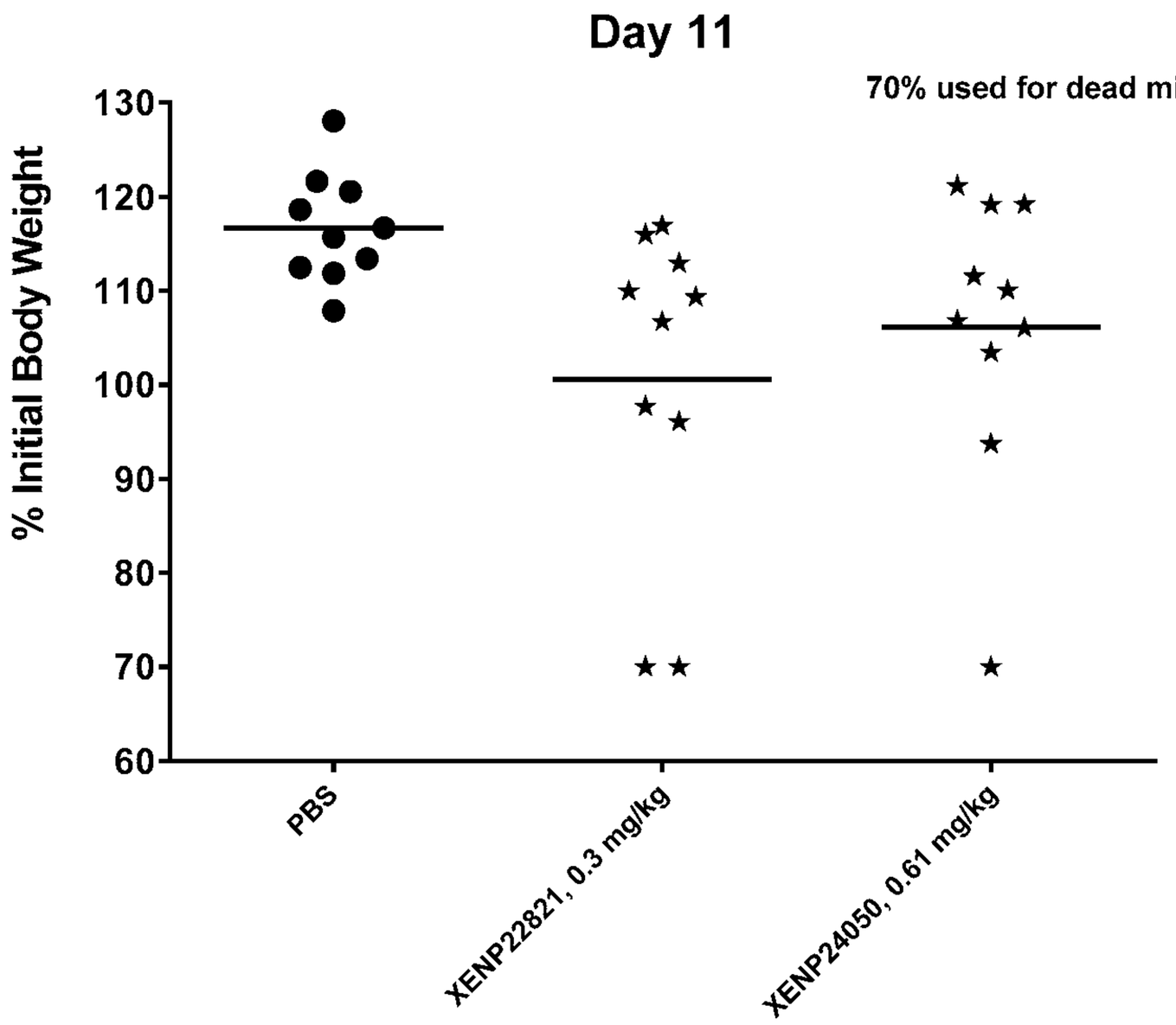

Day 11
70% used for dead mice
% Initial Body Weight
130
120
110
100
90
80
70
60
PBS
XENP22821, 0.3 mg/kg
XENP24050, 0.61 mg/kg

Figure 86A

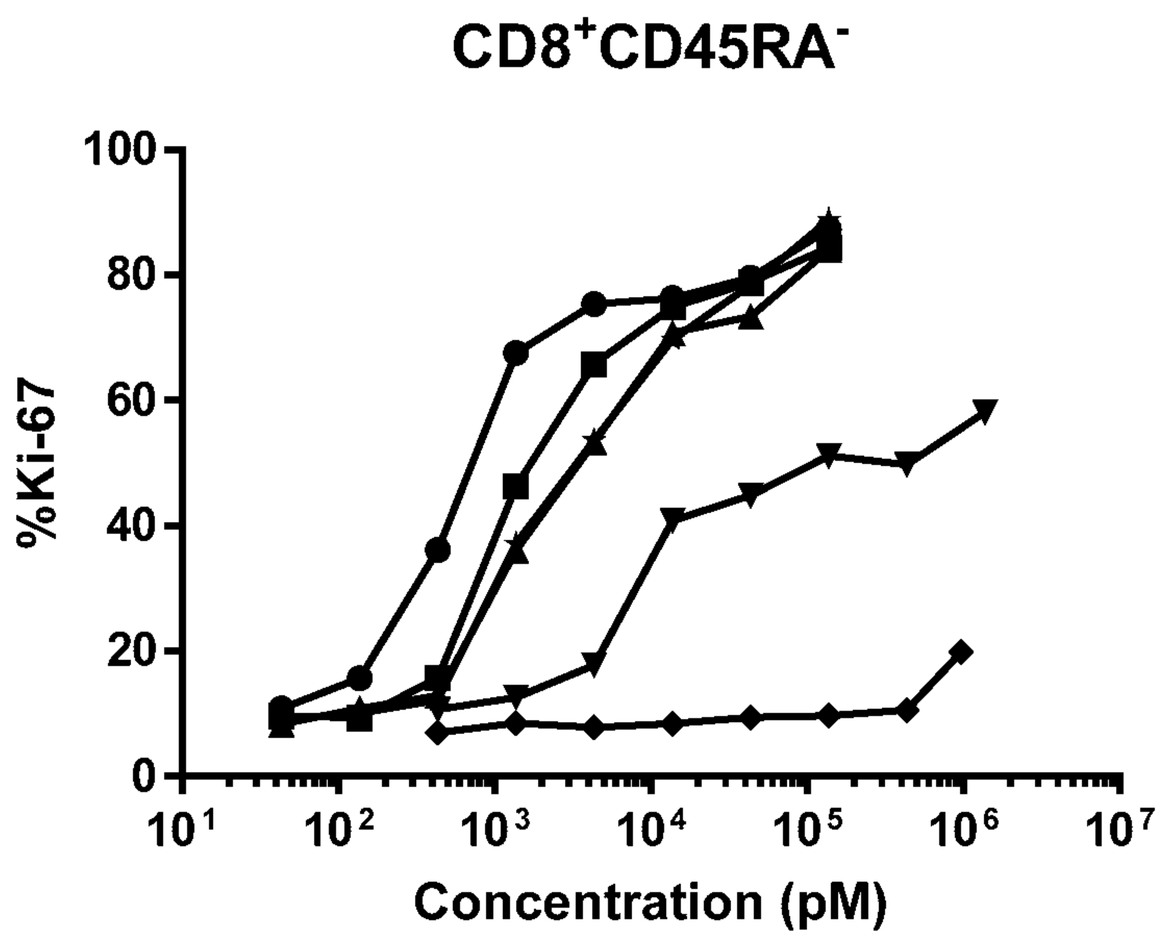


Figure 86B

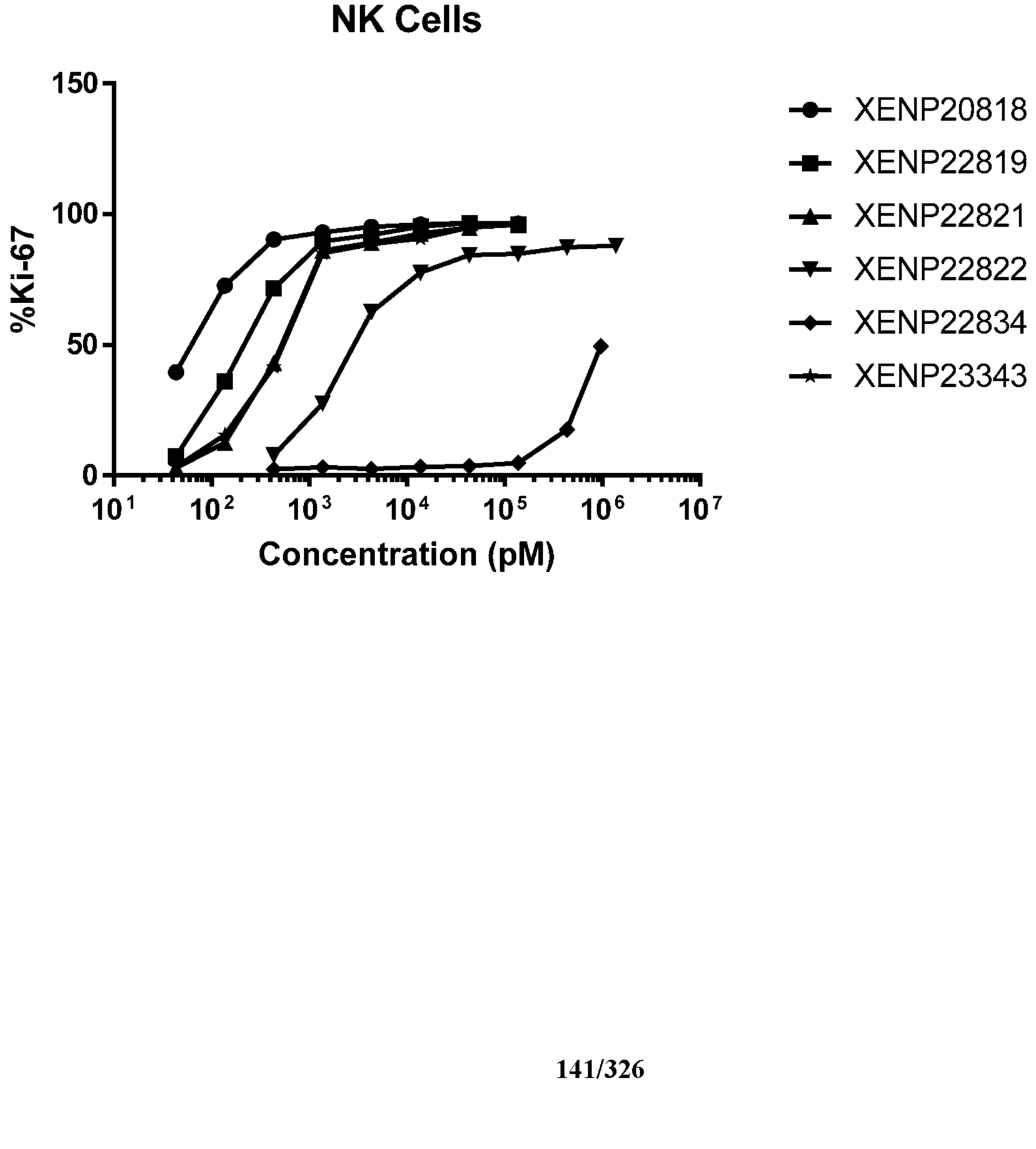


Figure 87A

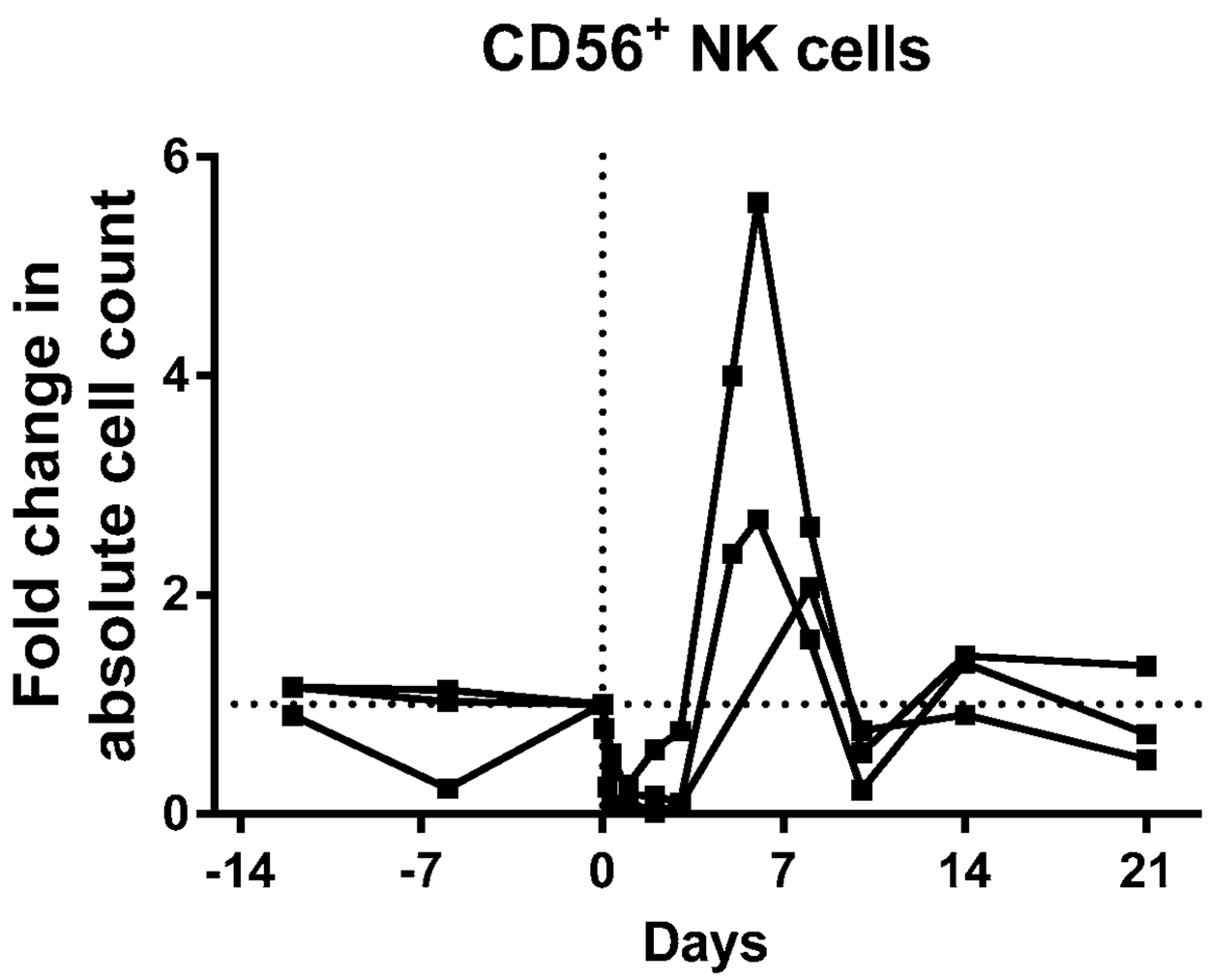


Figure 87B

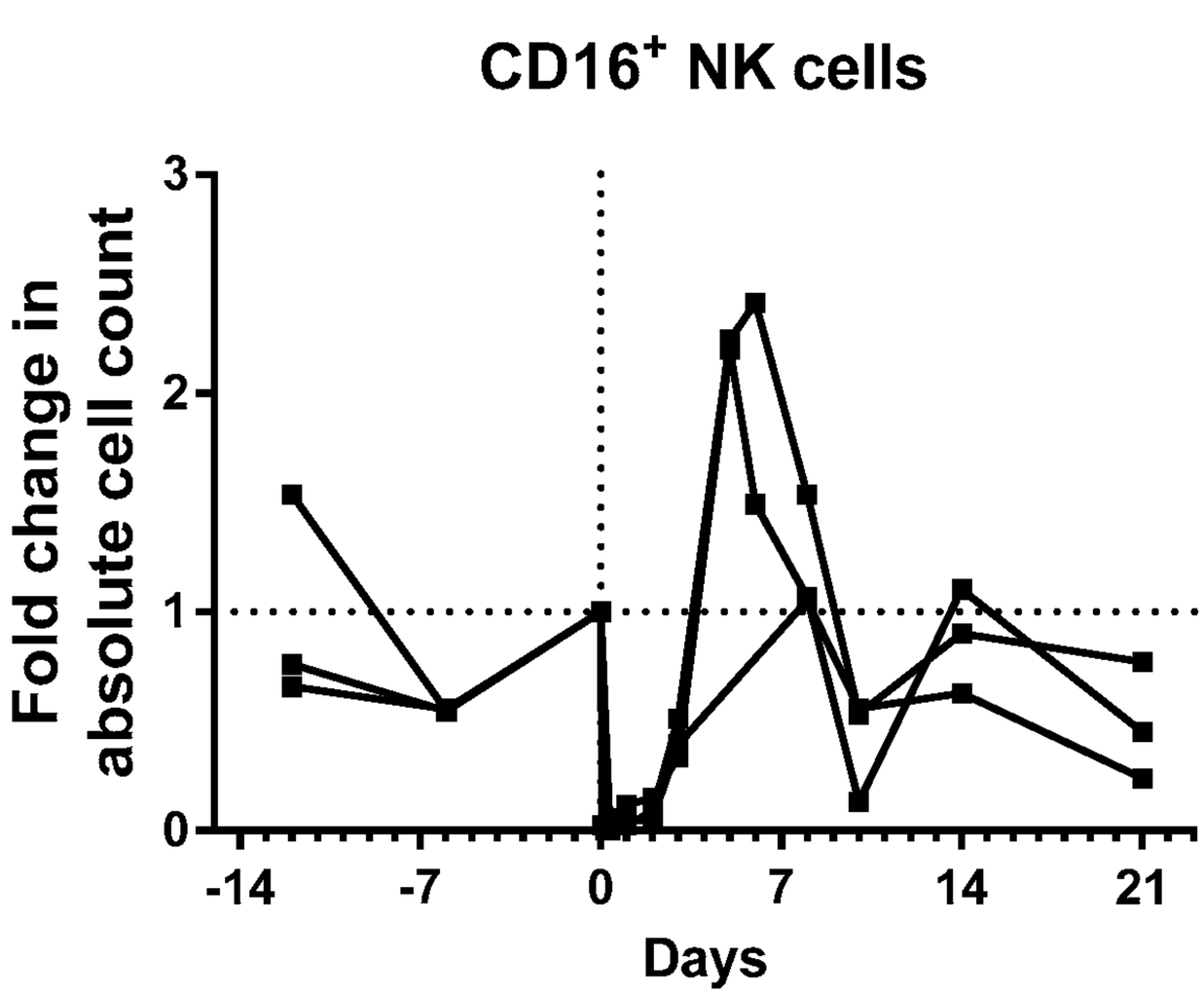


Figure 87C

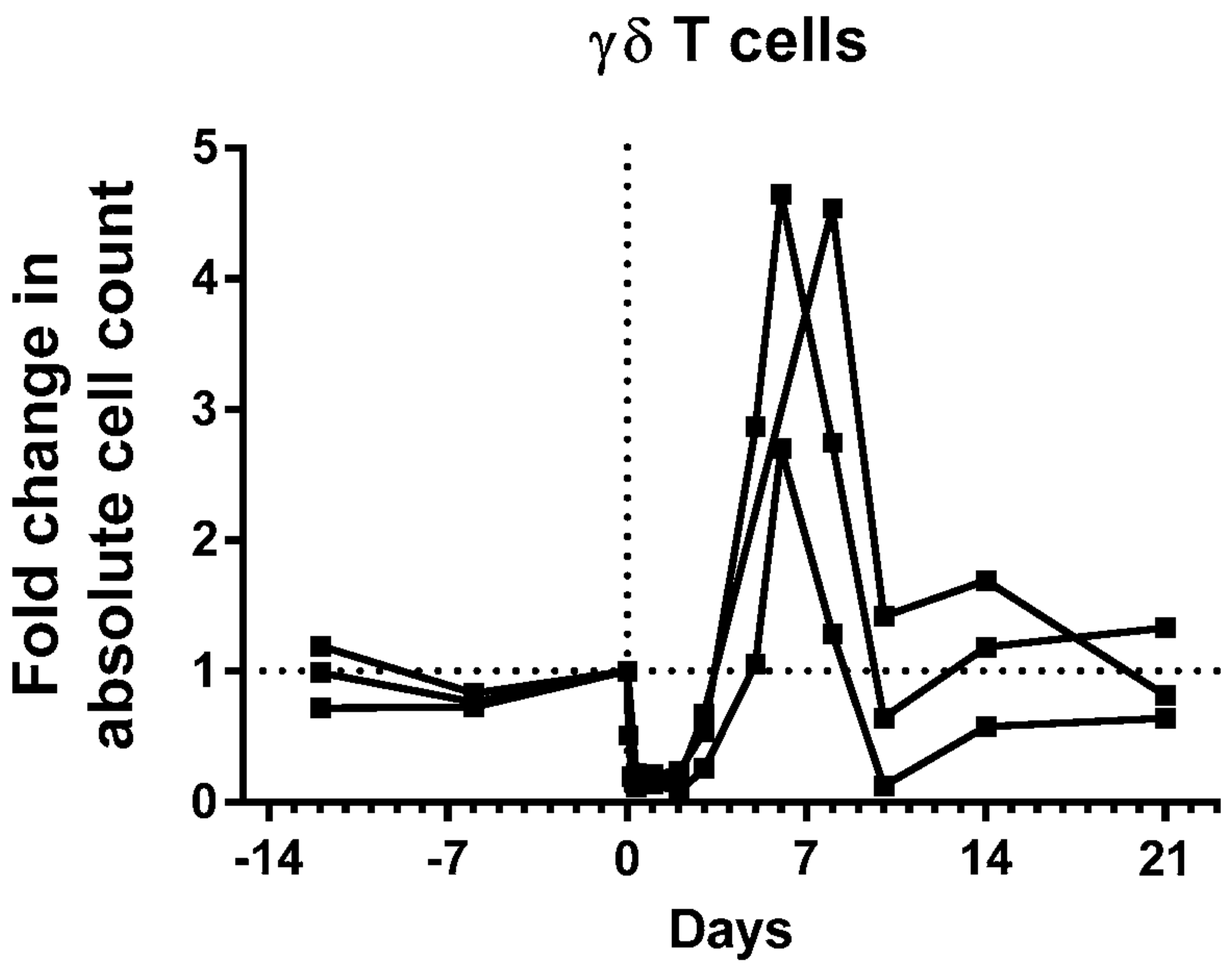


Figure 87D

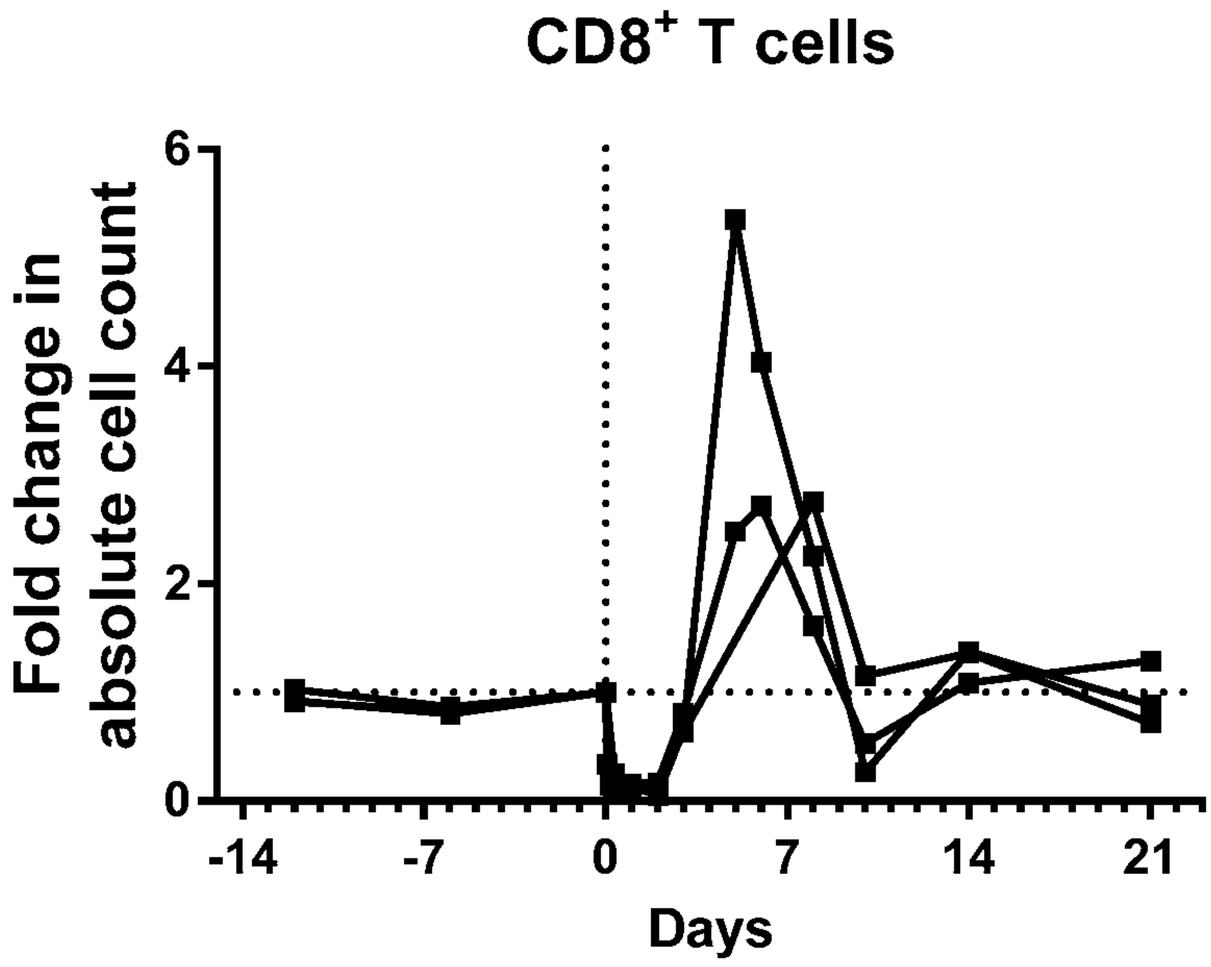


Figure 87E

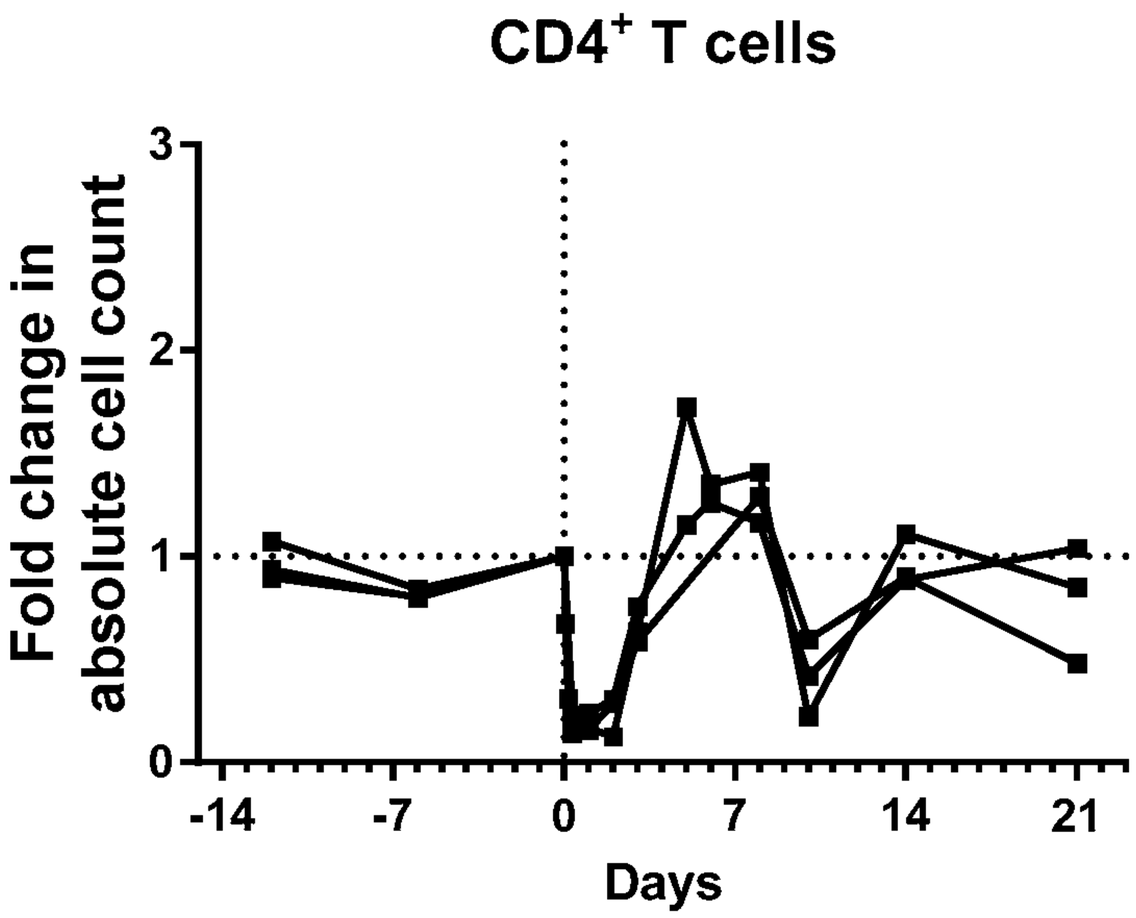

CD4+ T cells
Fold change in absolute cell count
3
2
1
0
-14
-7
0
7
14
21
Days

Figure 88A

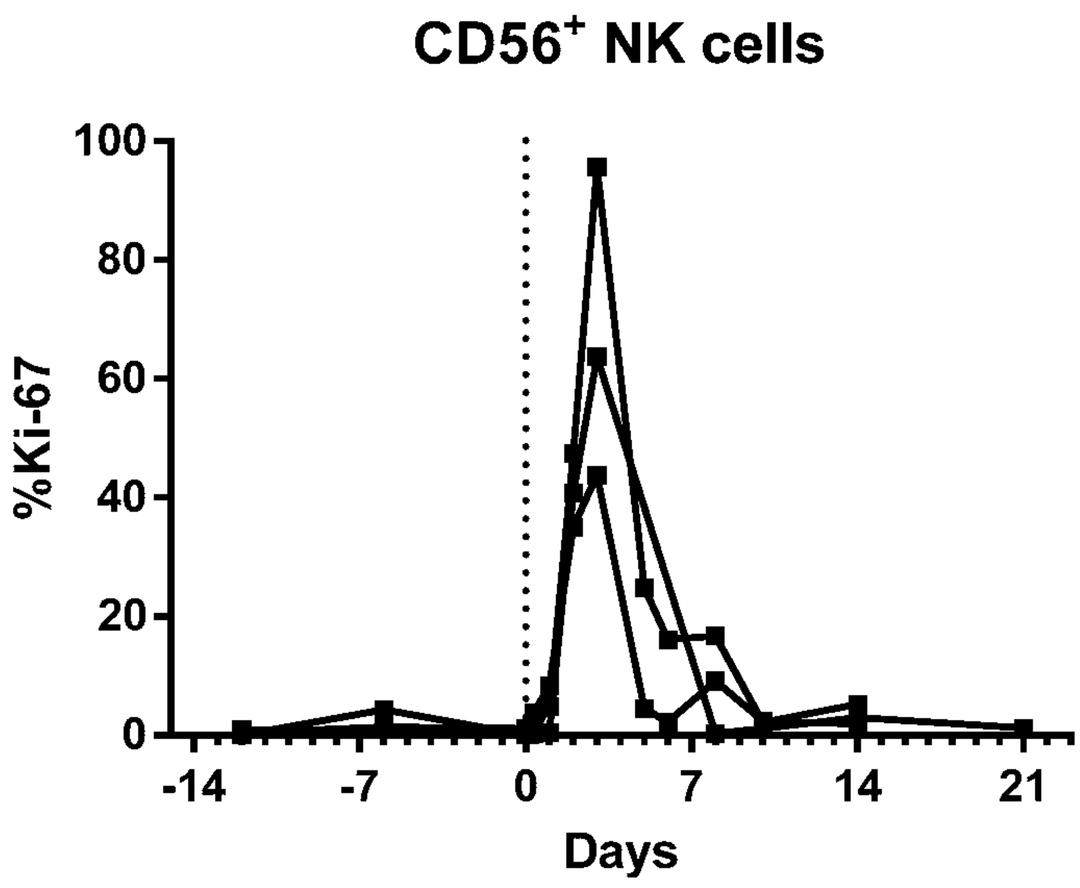


Figure 88B

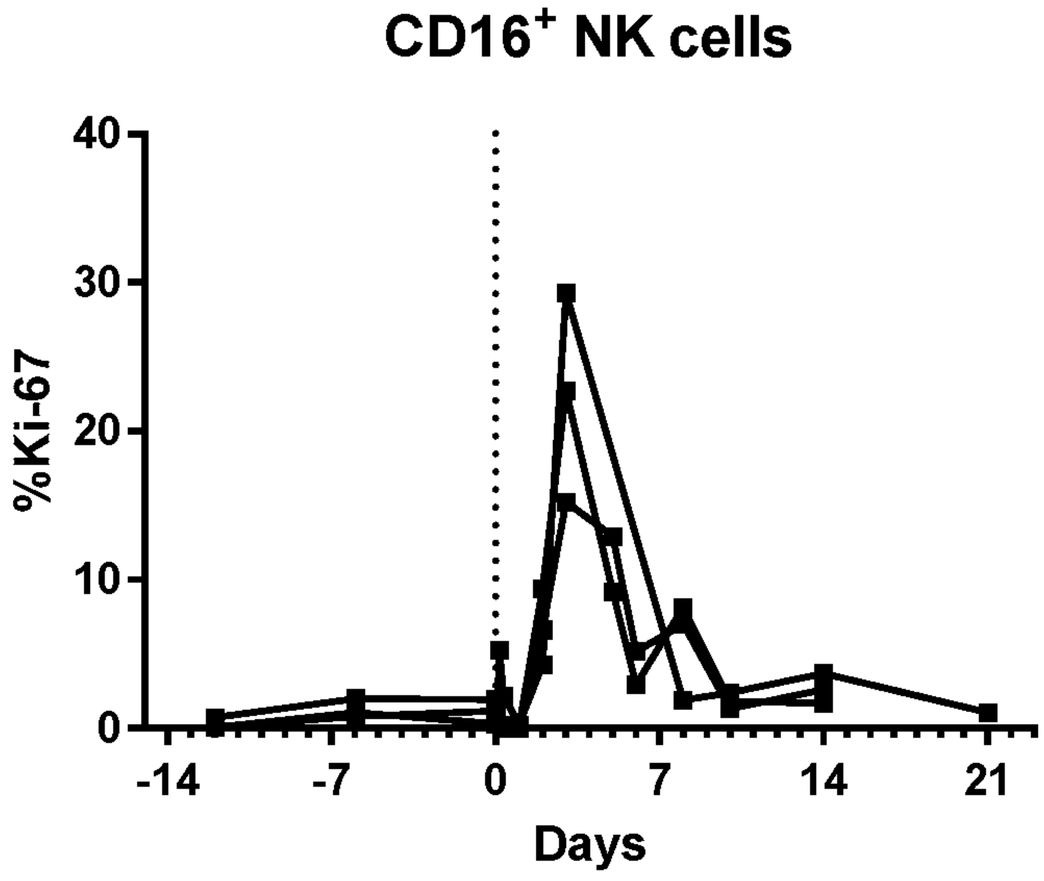


Figure 88C

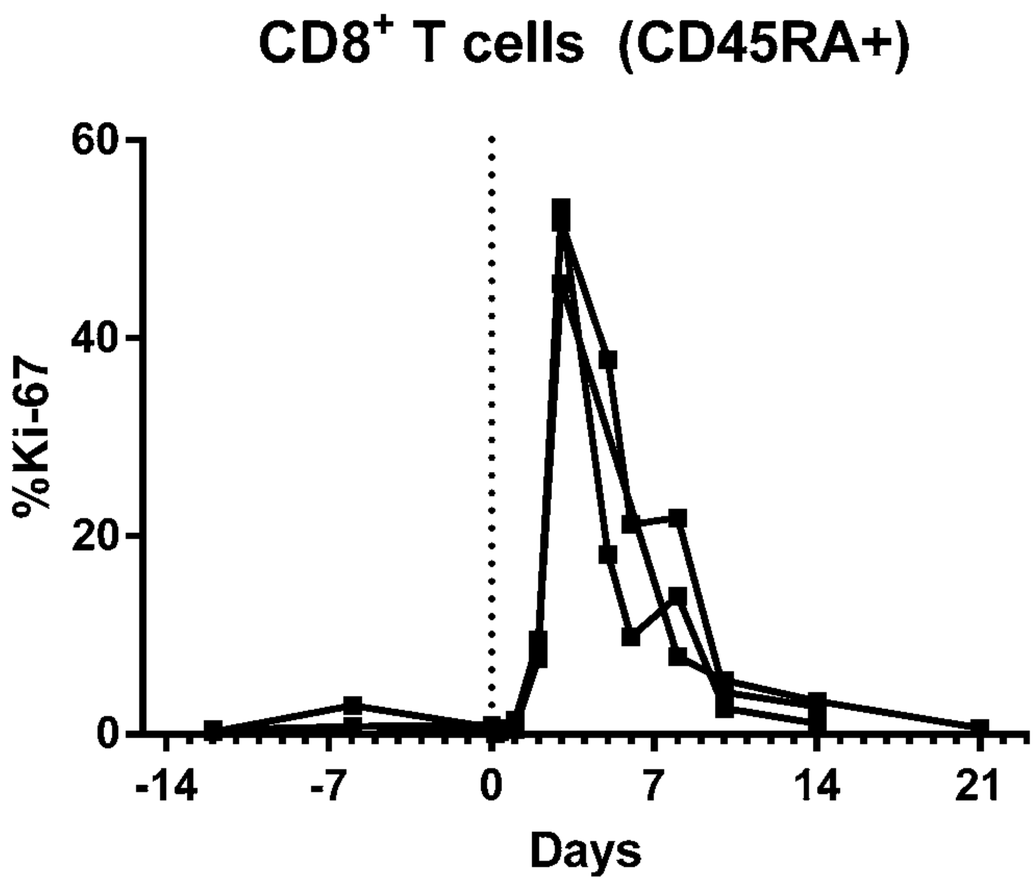


Figure 88D

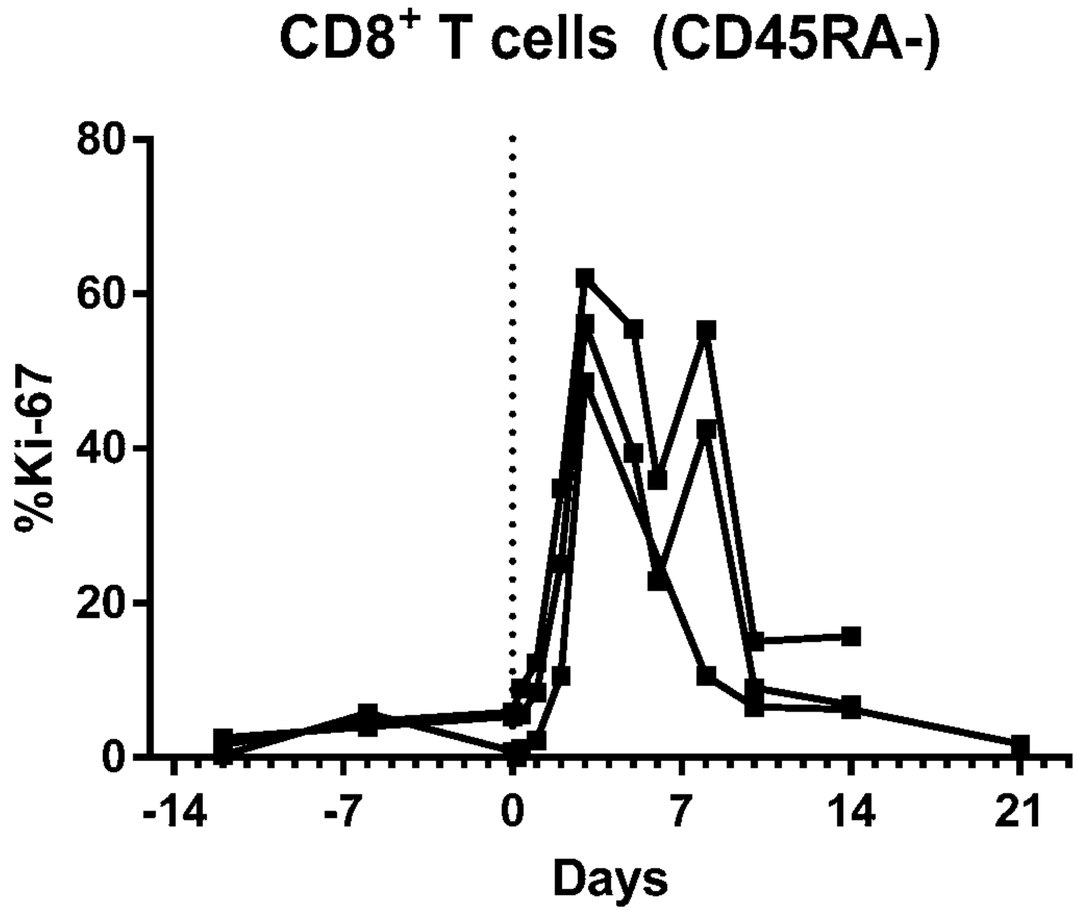


Figure 88E

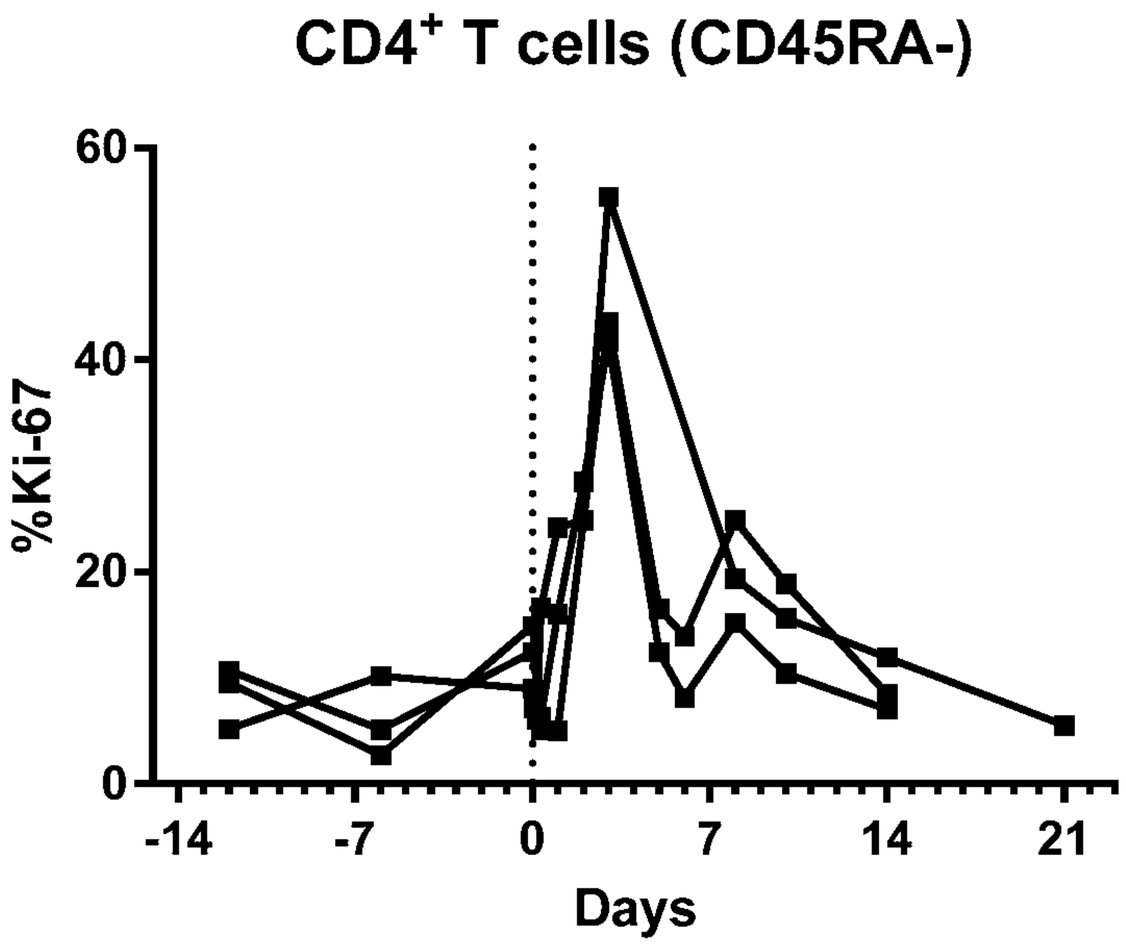


Figure 89A

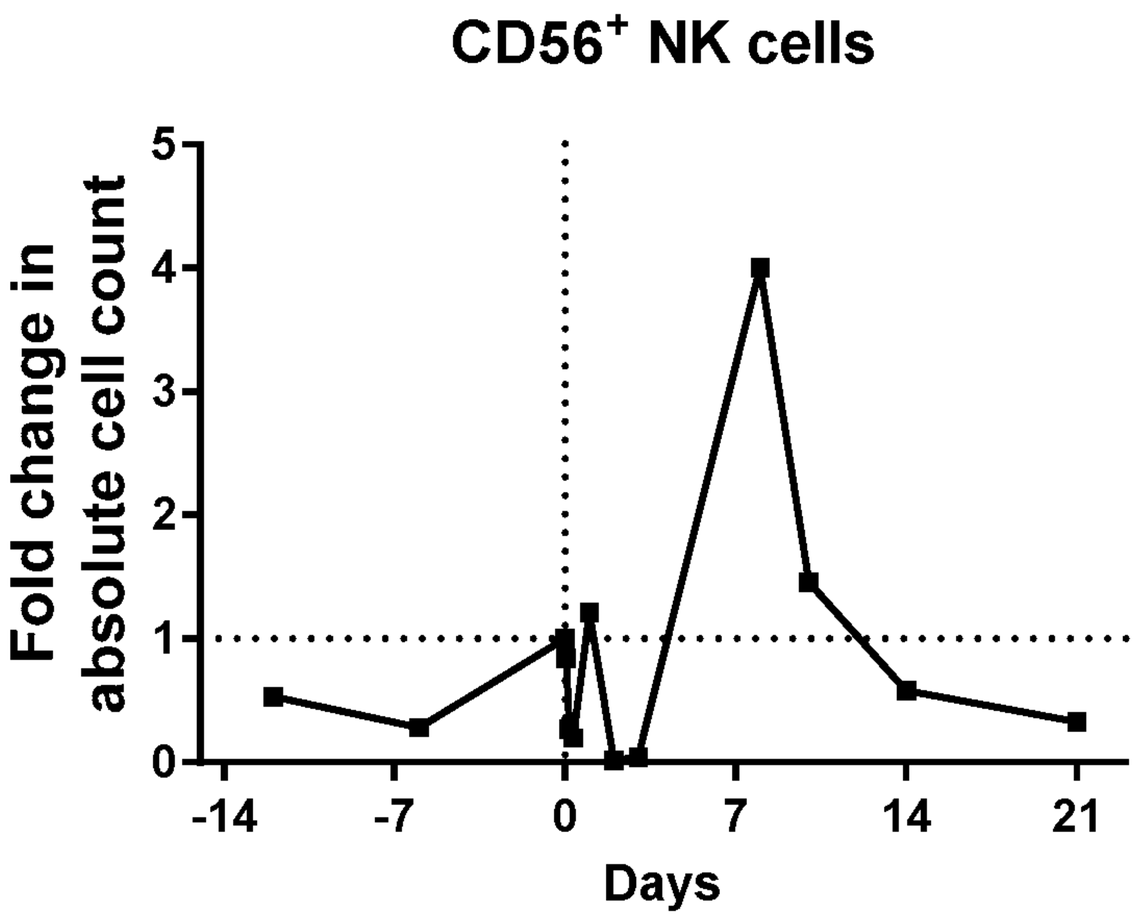


Figure 89B

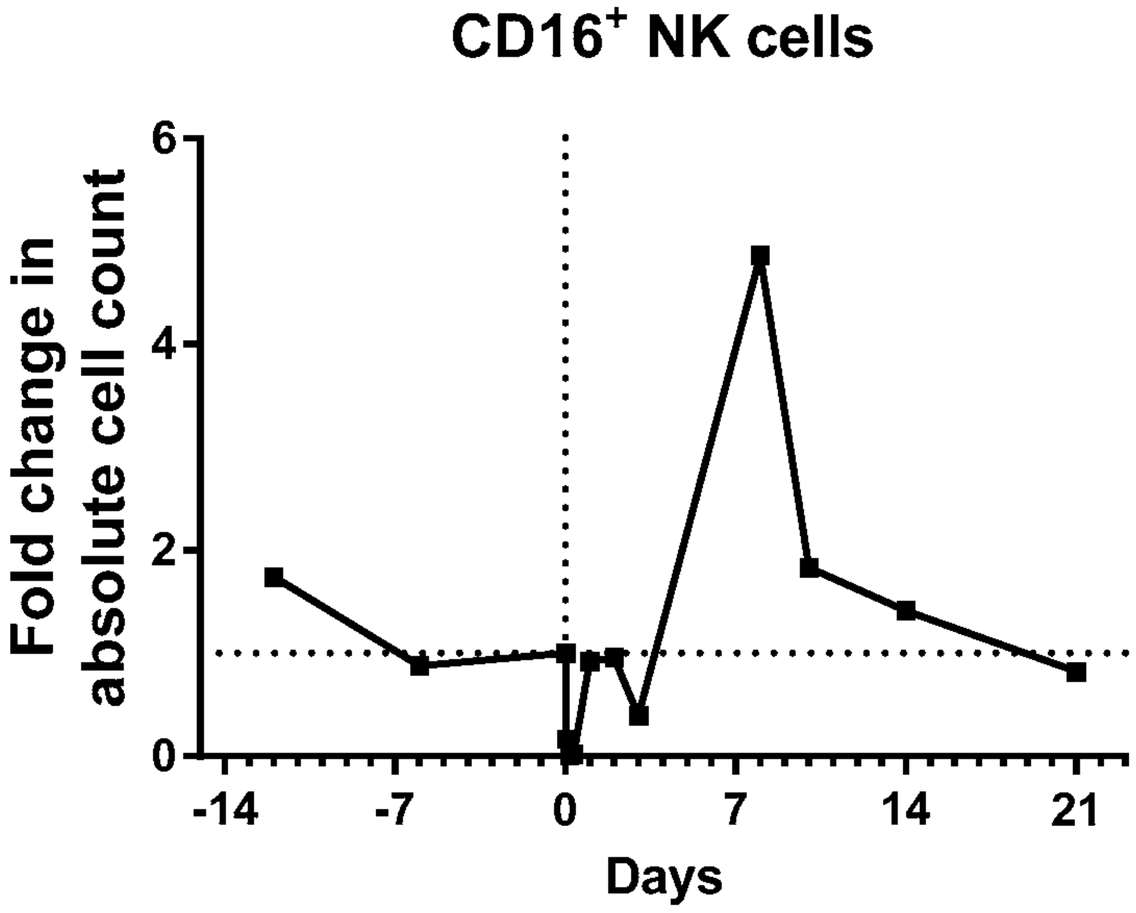


Figure 89C

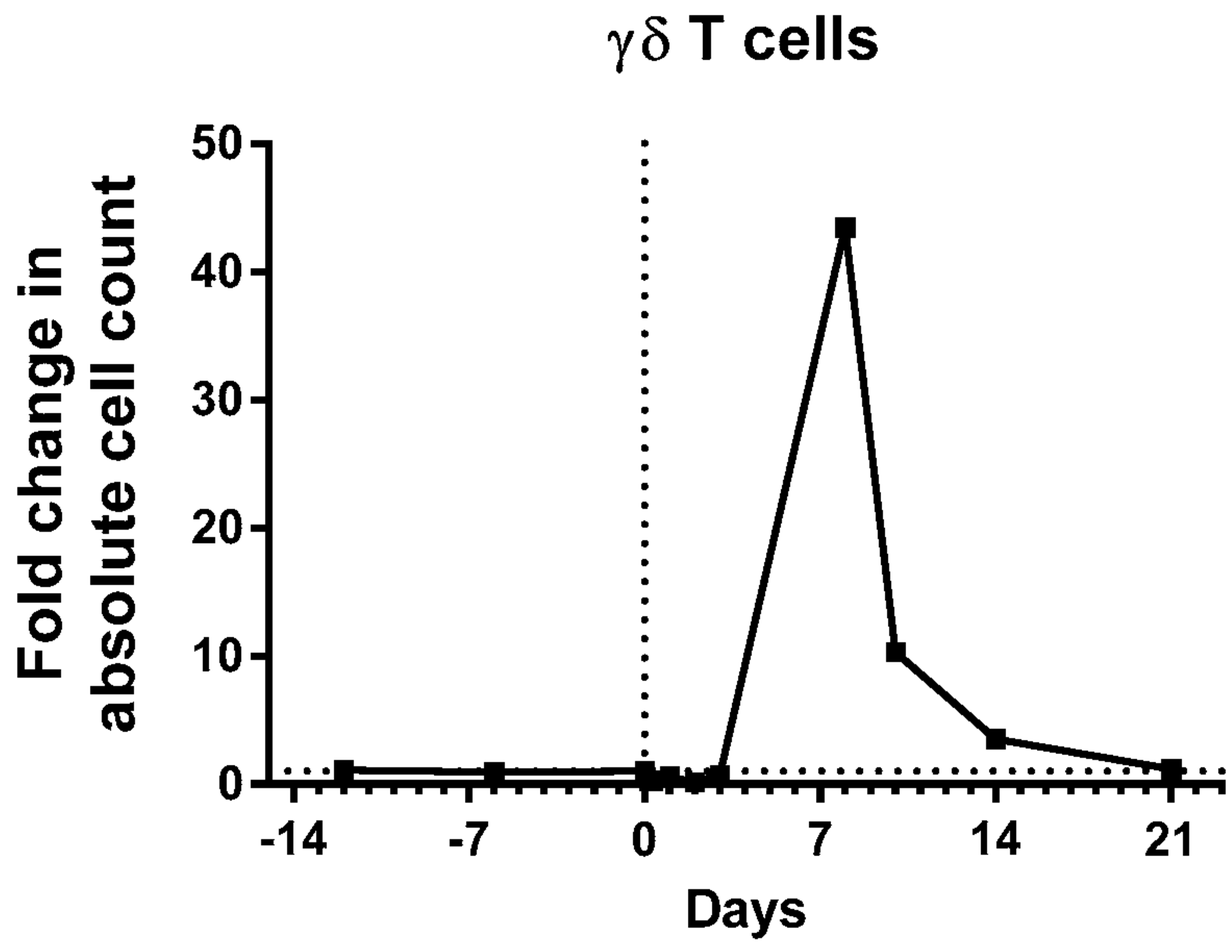


Figure 89D

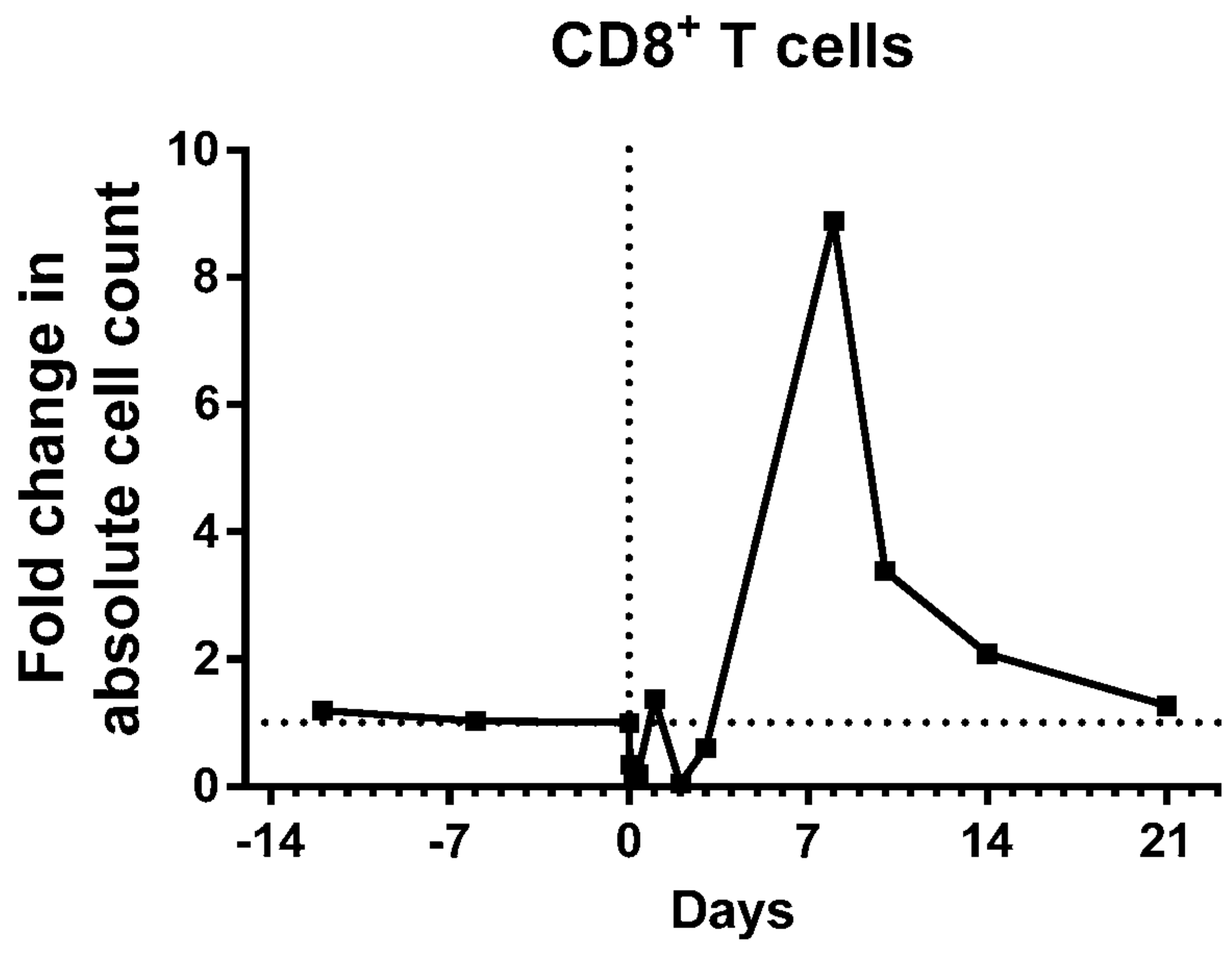


Figure 89E

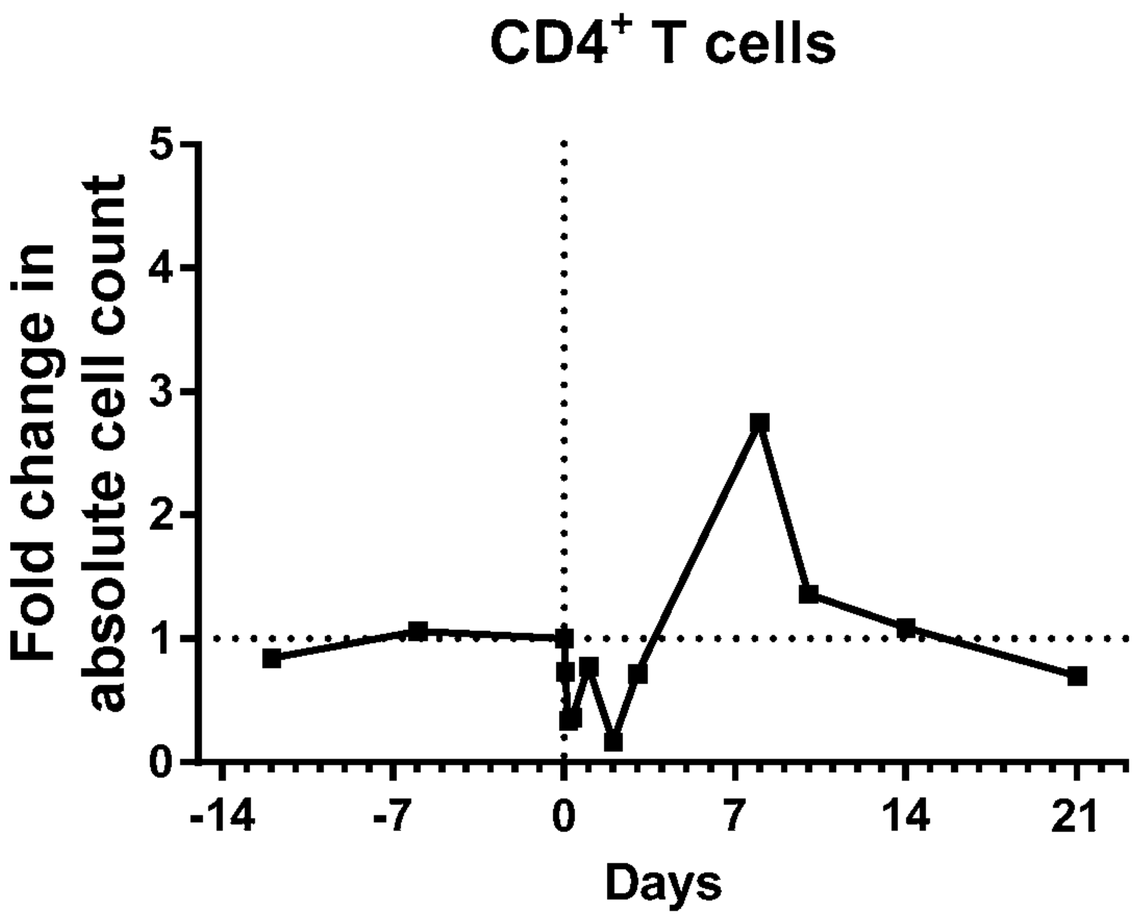

CD4+ T cells
Fold change in absolute cell count
0
1
2
3
4
5
-14
-7
0
7
14
21
Days

Figure 90A

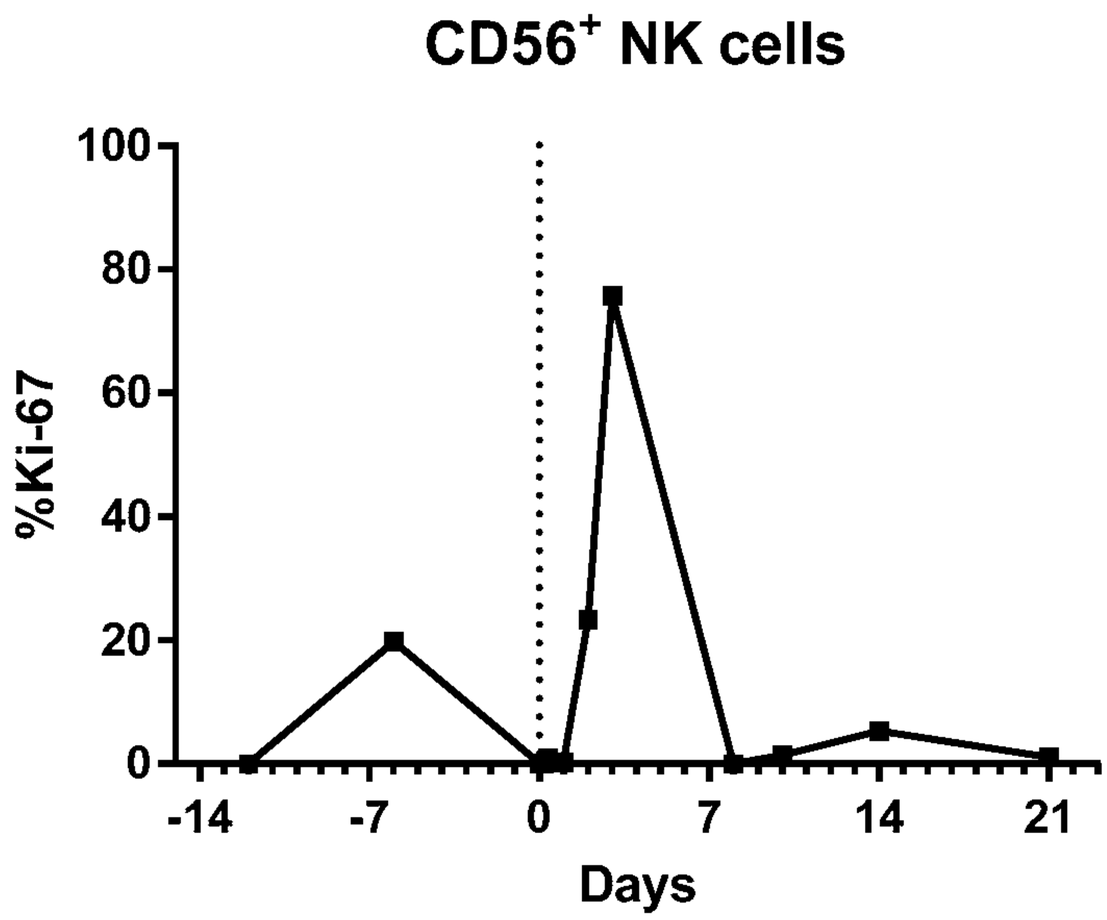


Figure 90B

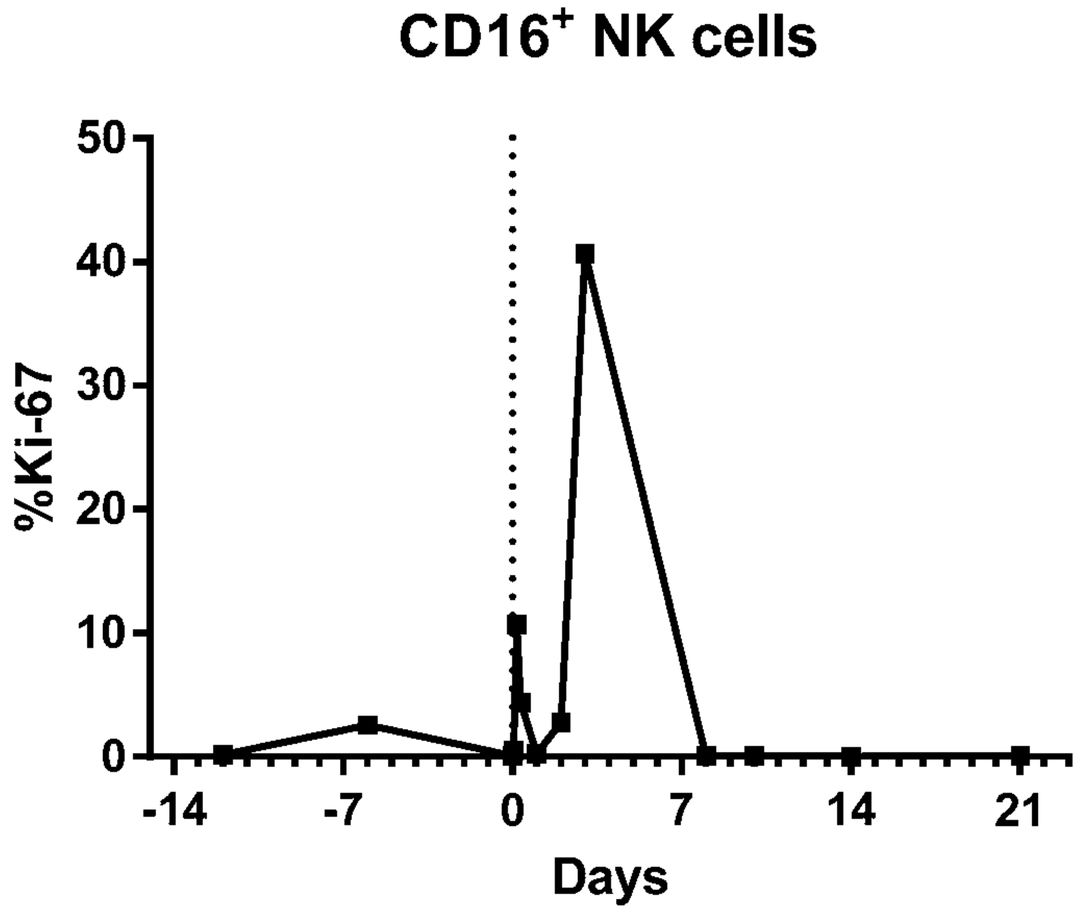


Figure 90C

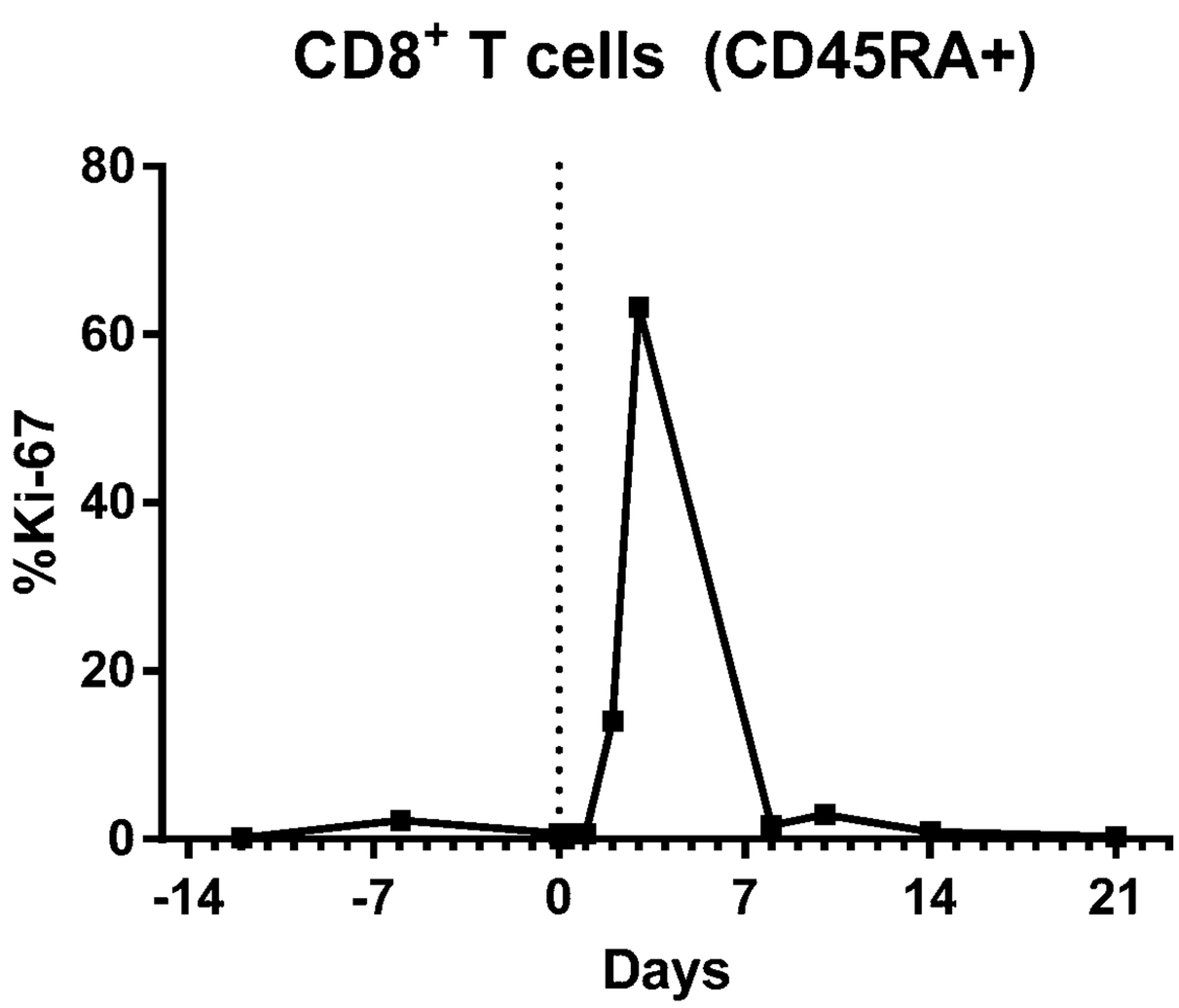


Figure 90D

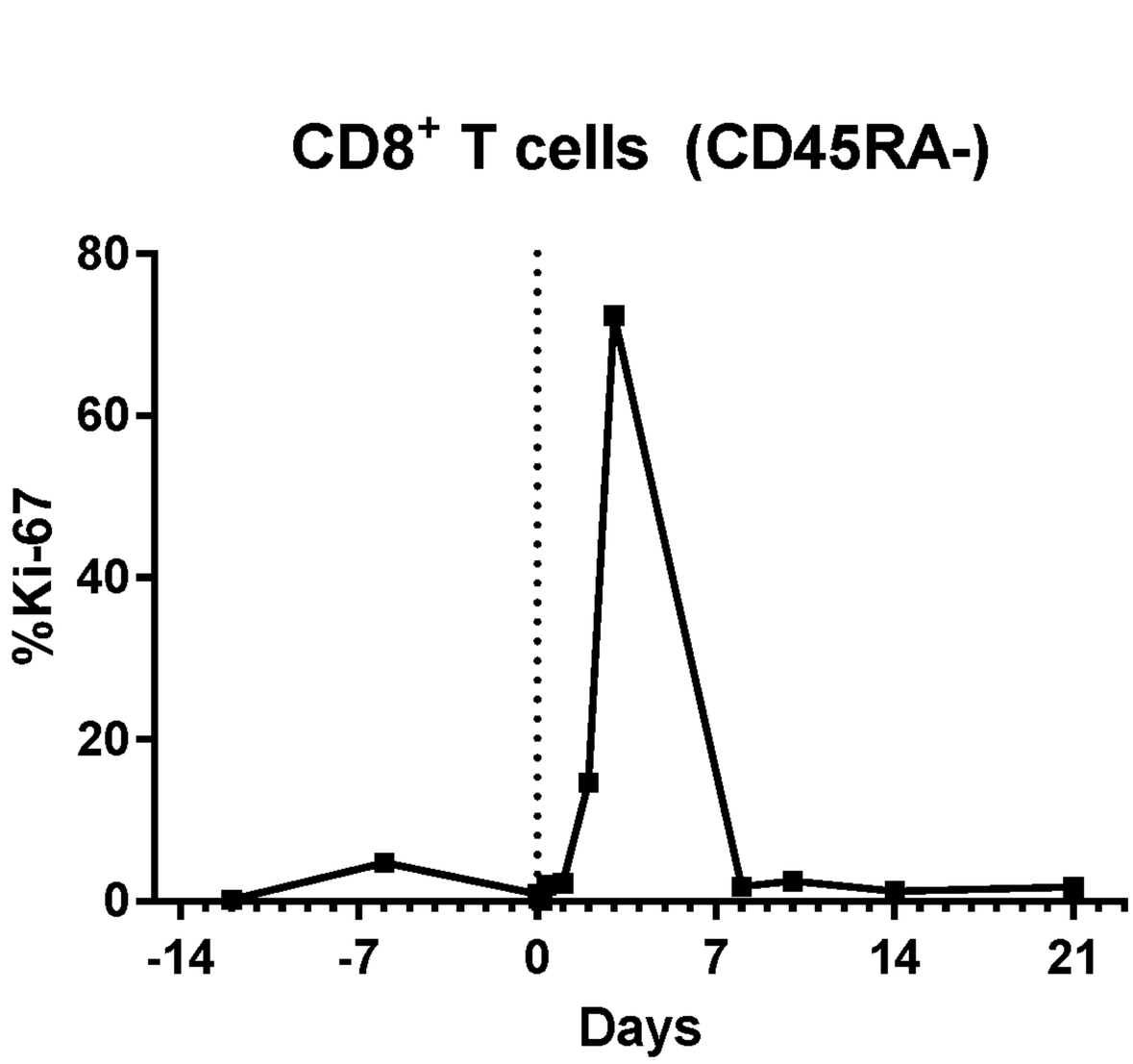


Figure 90E

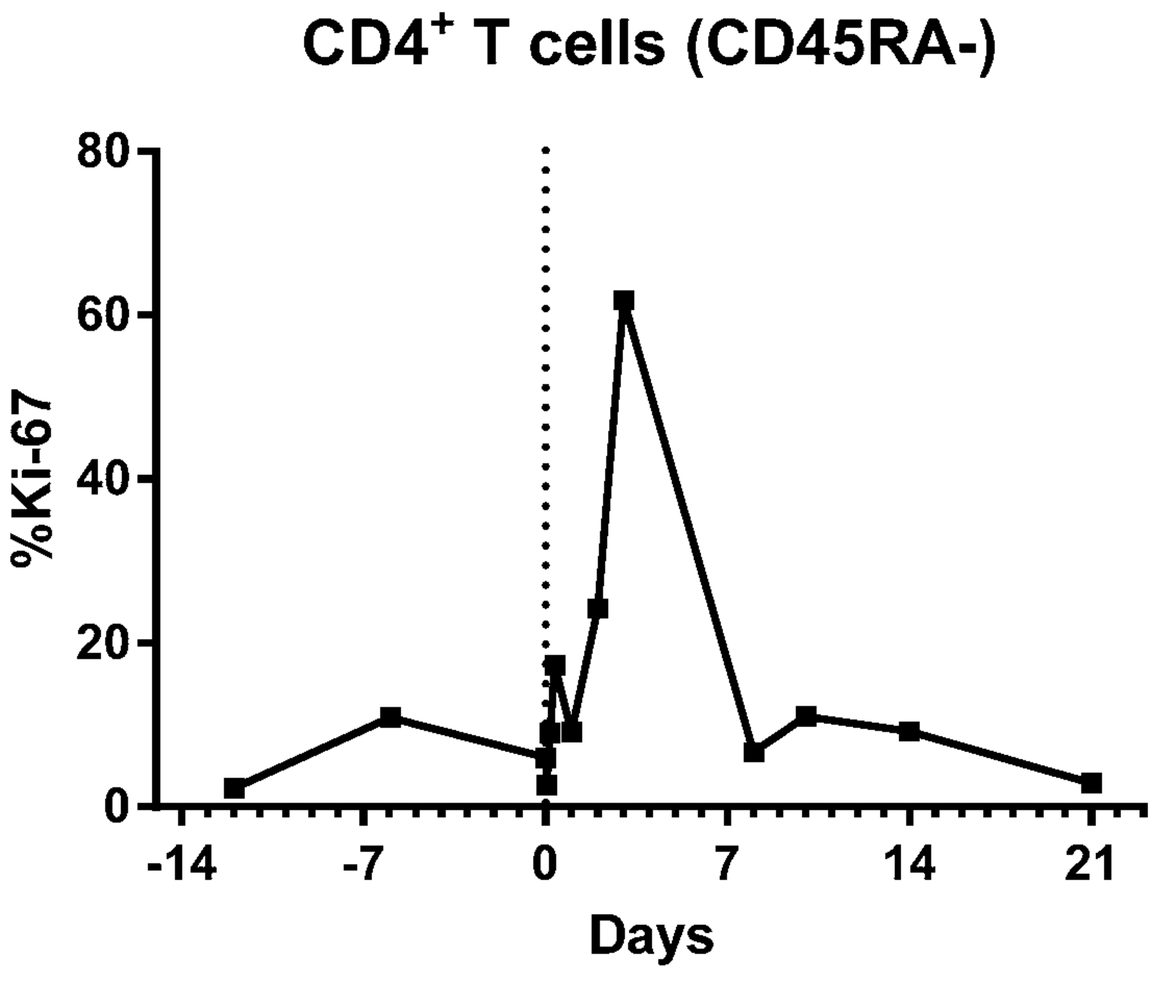


Figure 91A

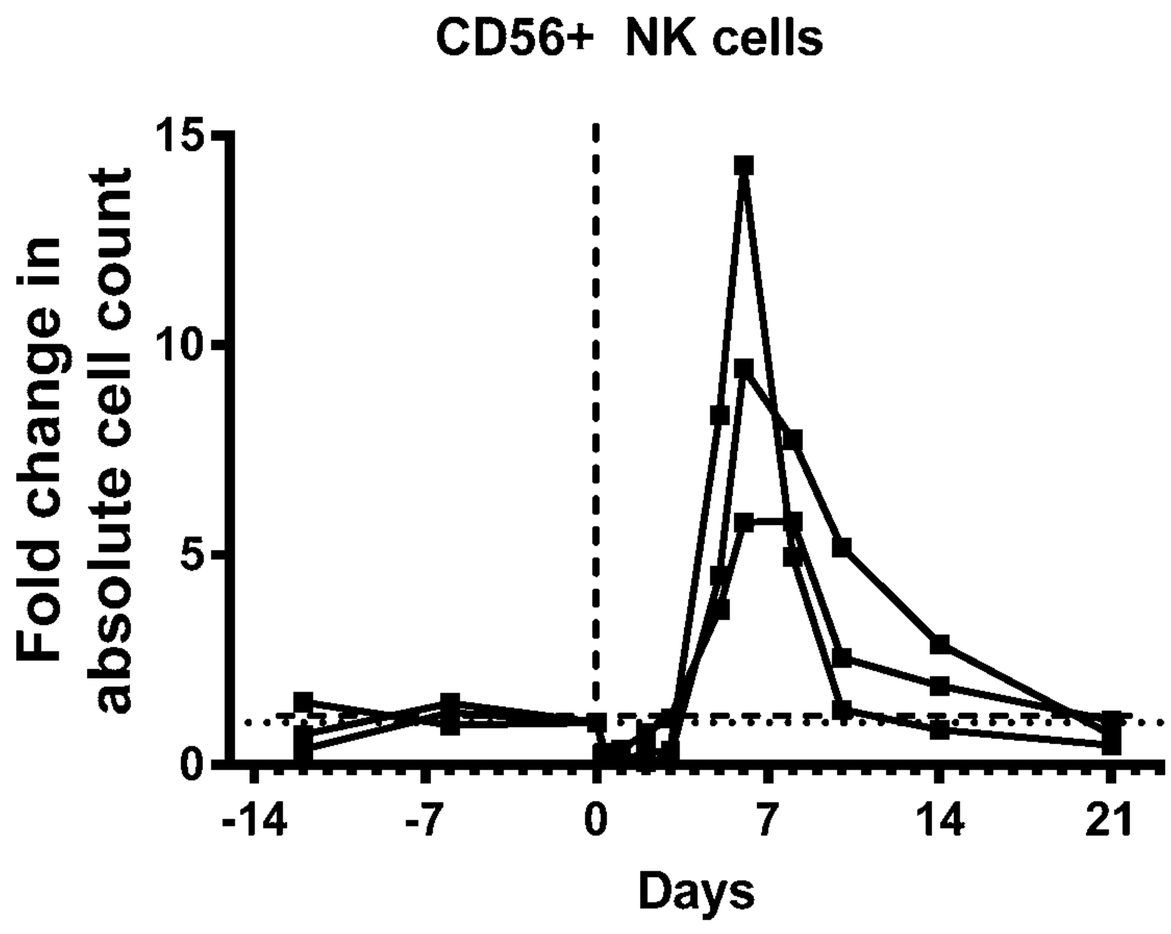


Figure 91B

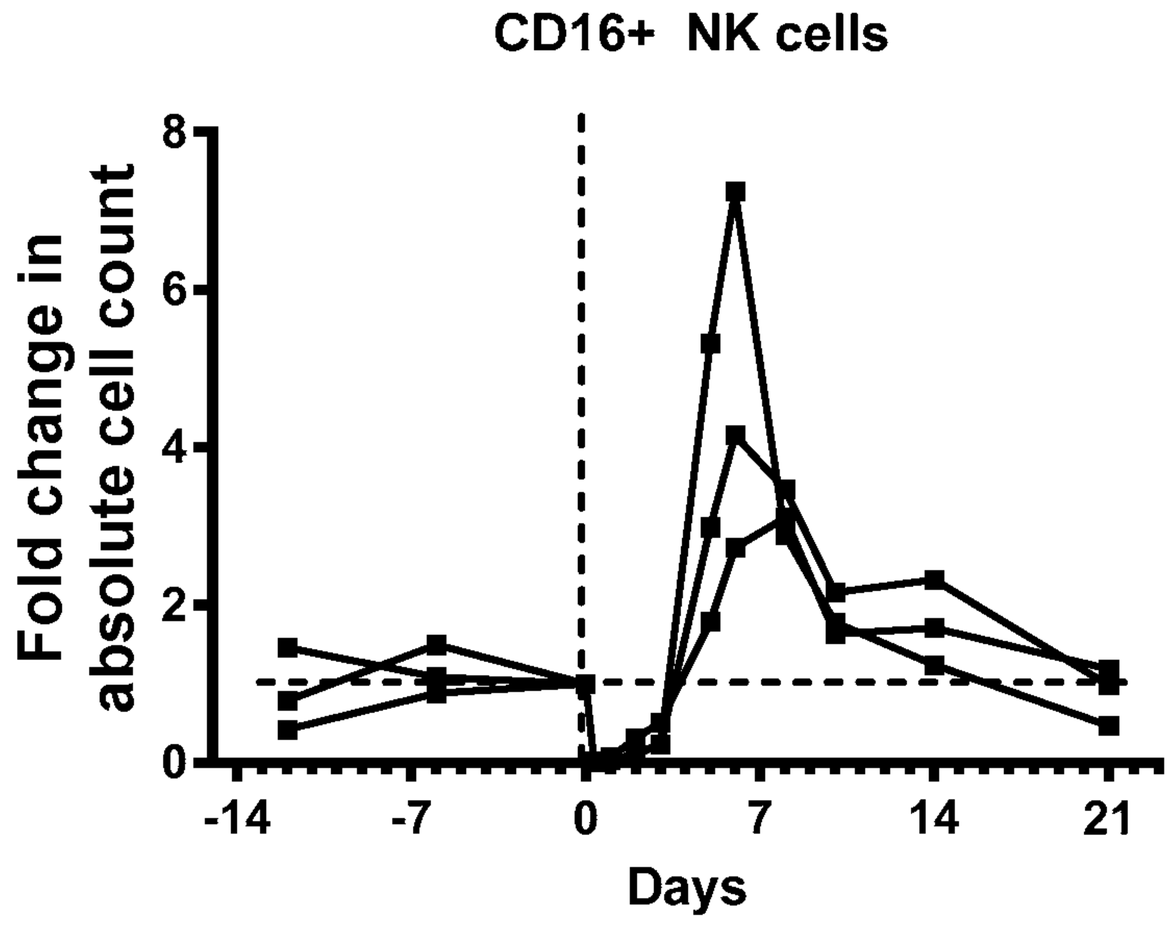


Figure 91C

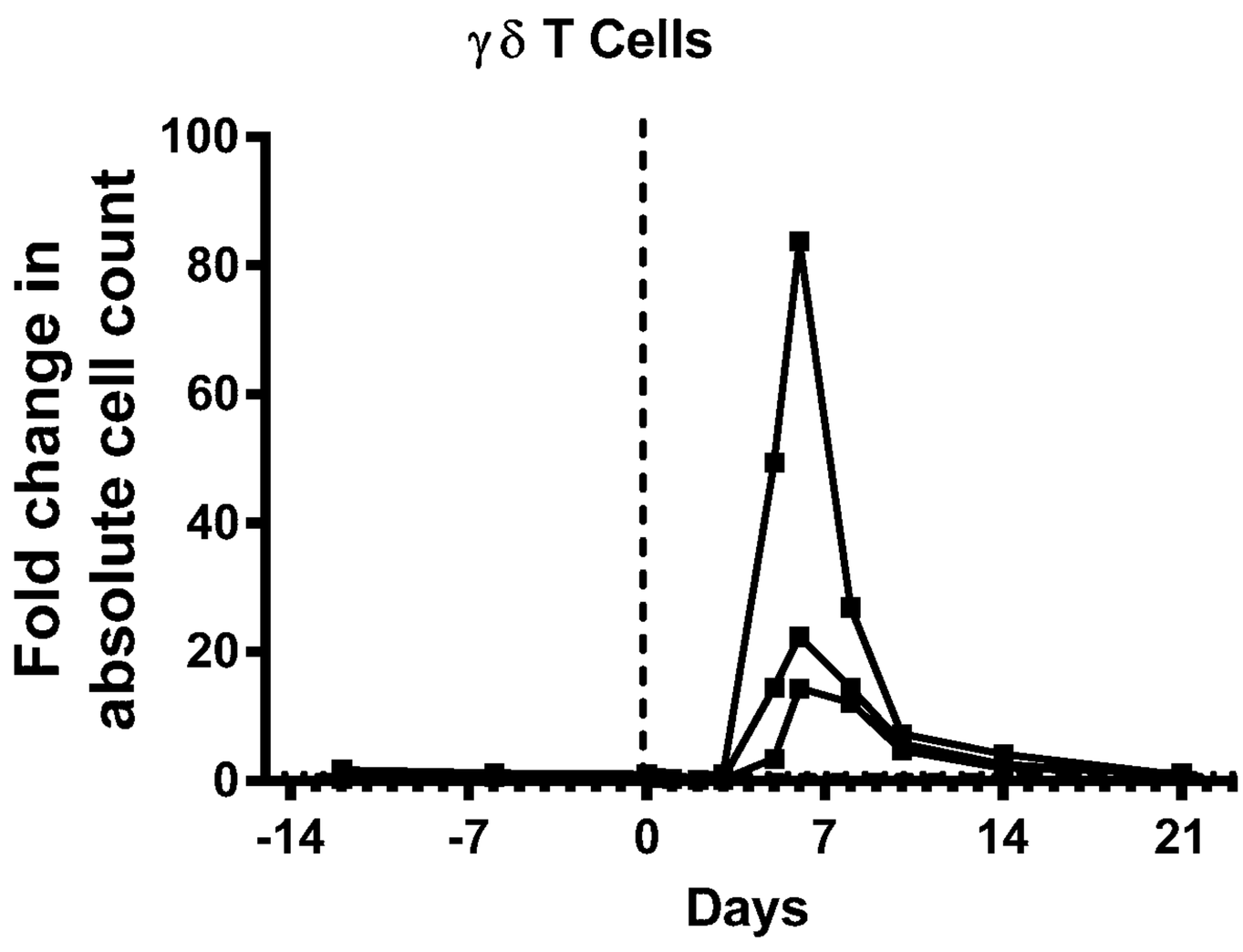


Figure 91D

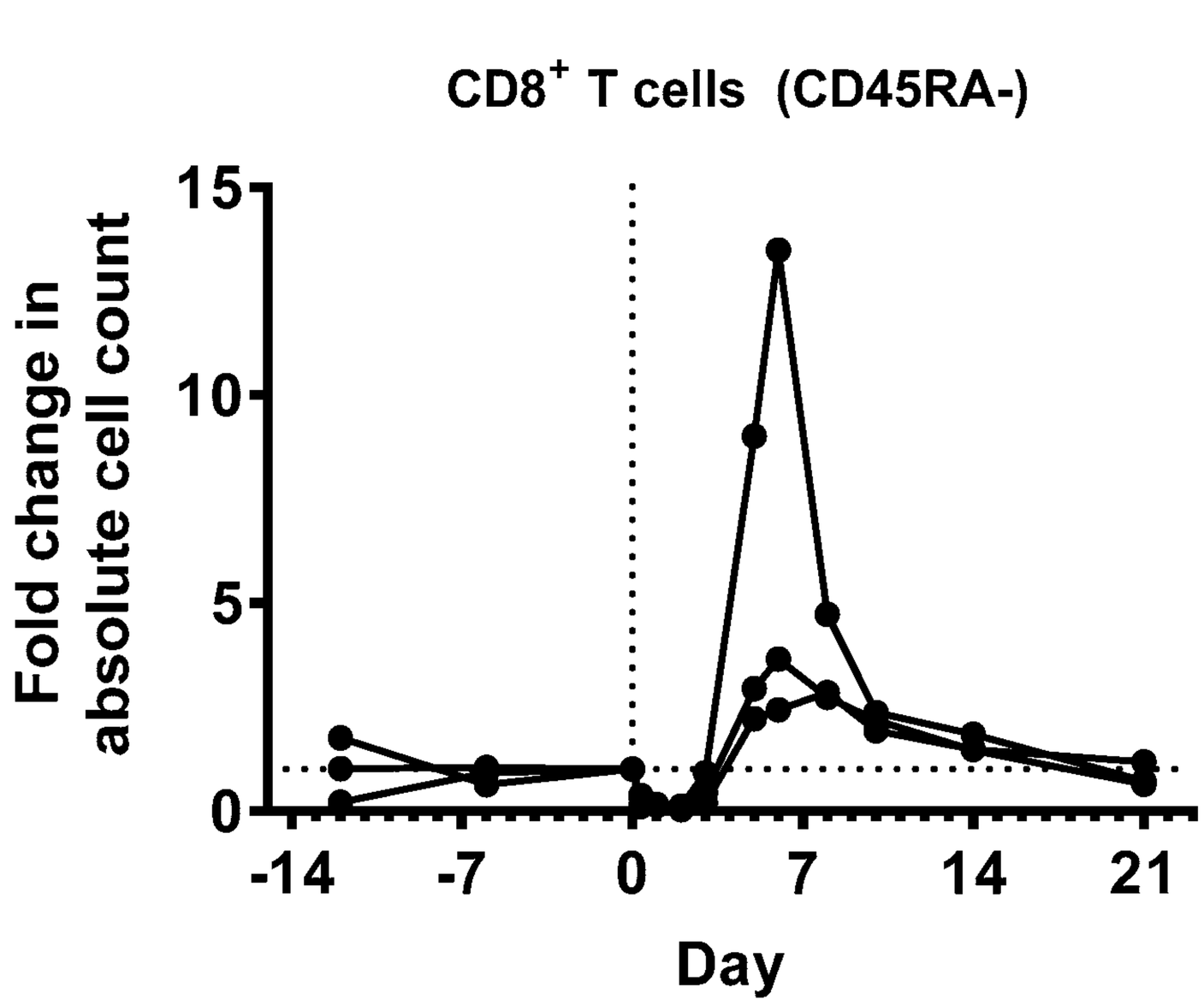


Figure 91E

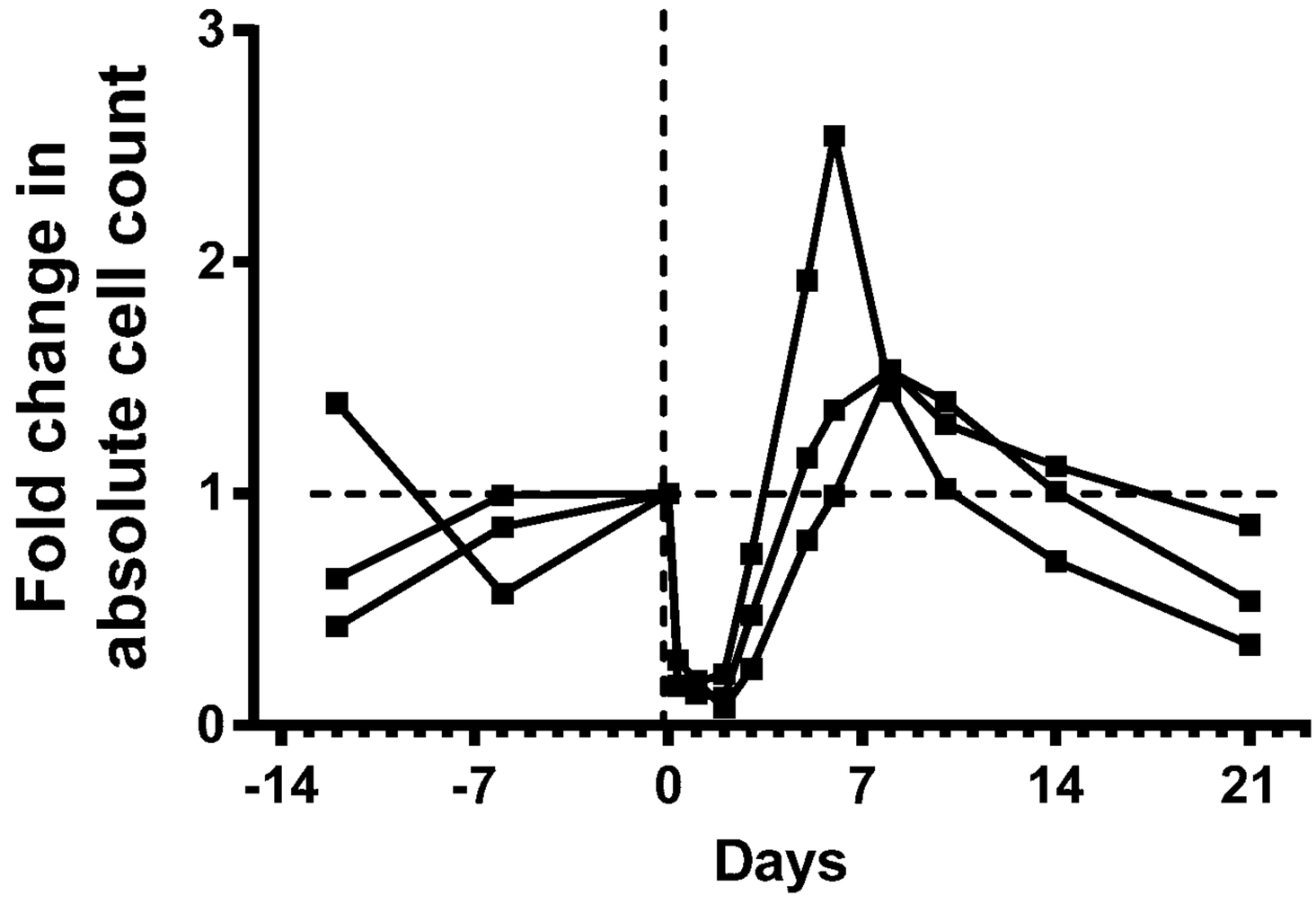


Figure 92A

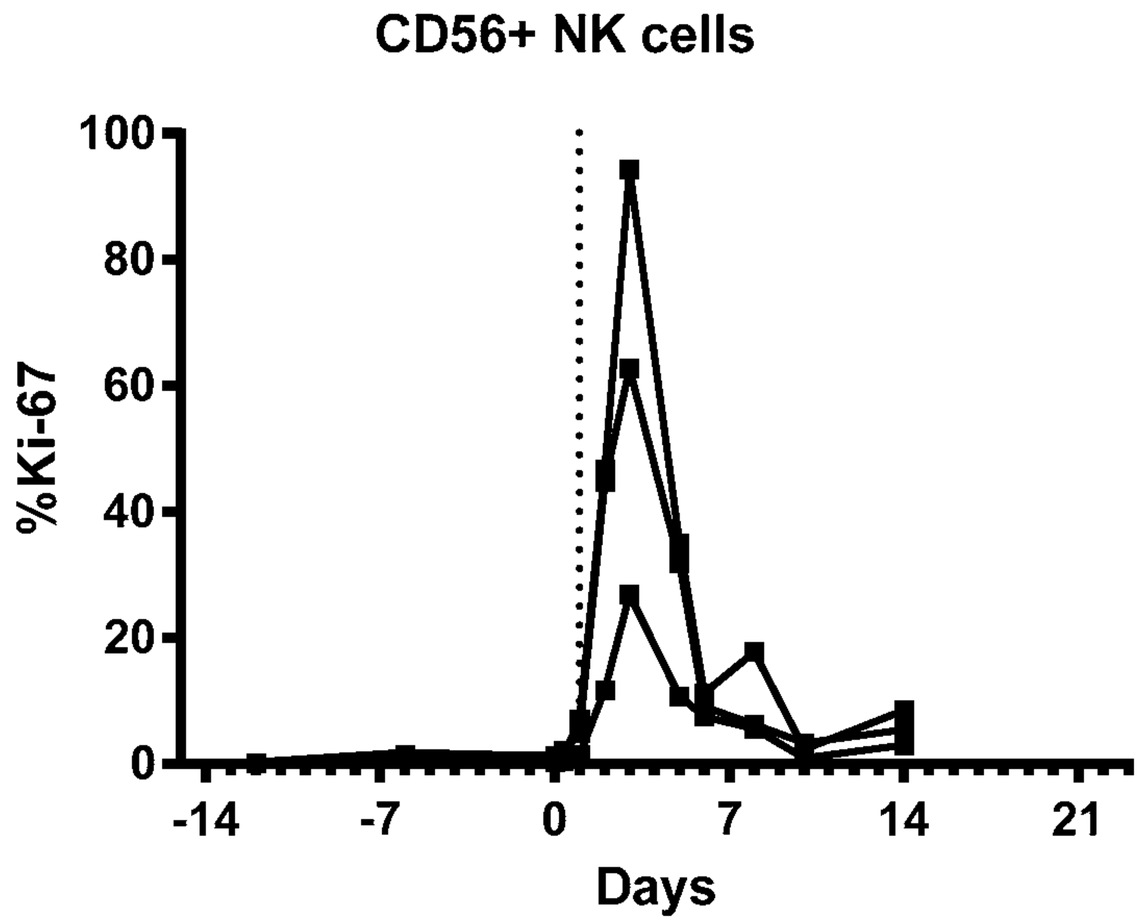


Figure 92B

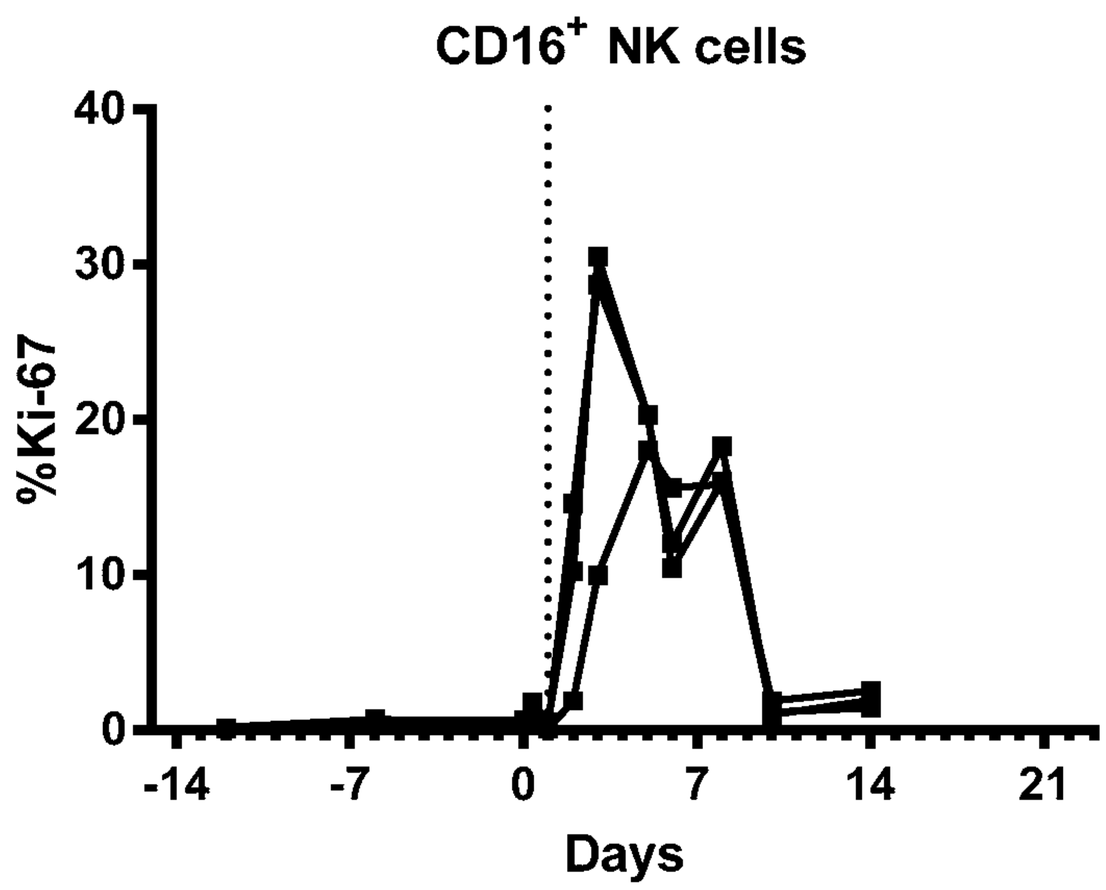


Figure 92C

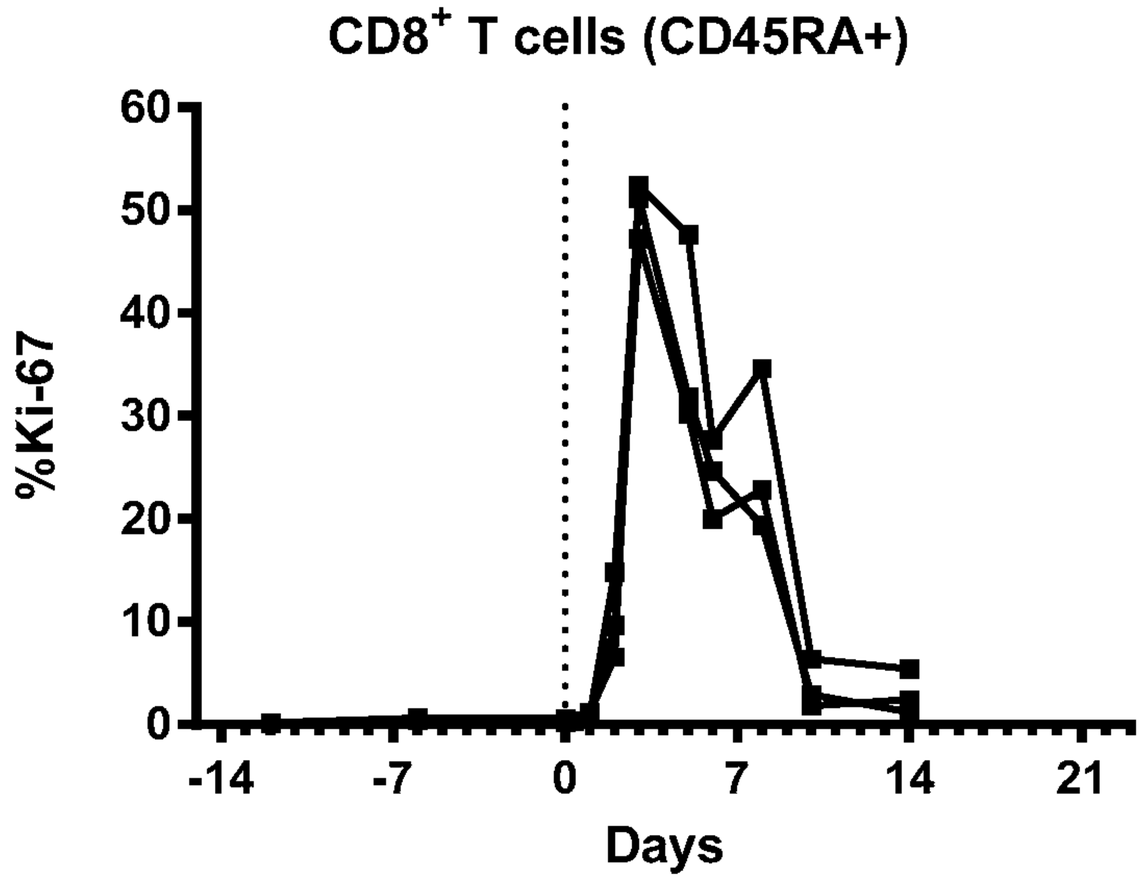


Figure 92D

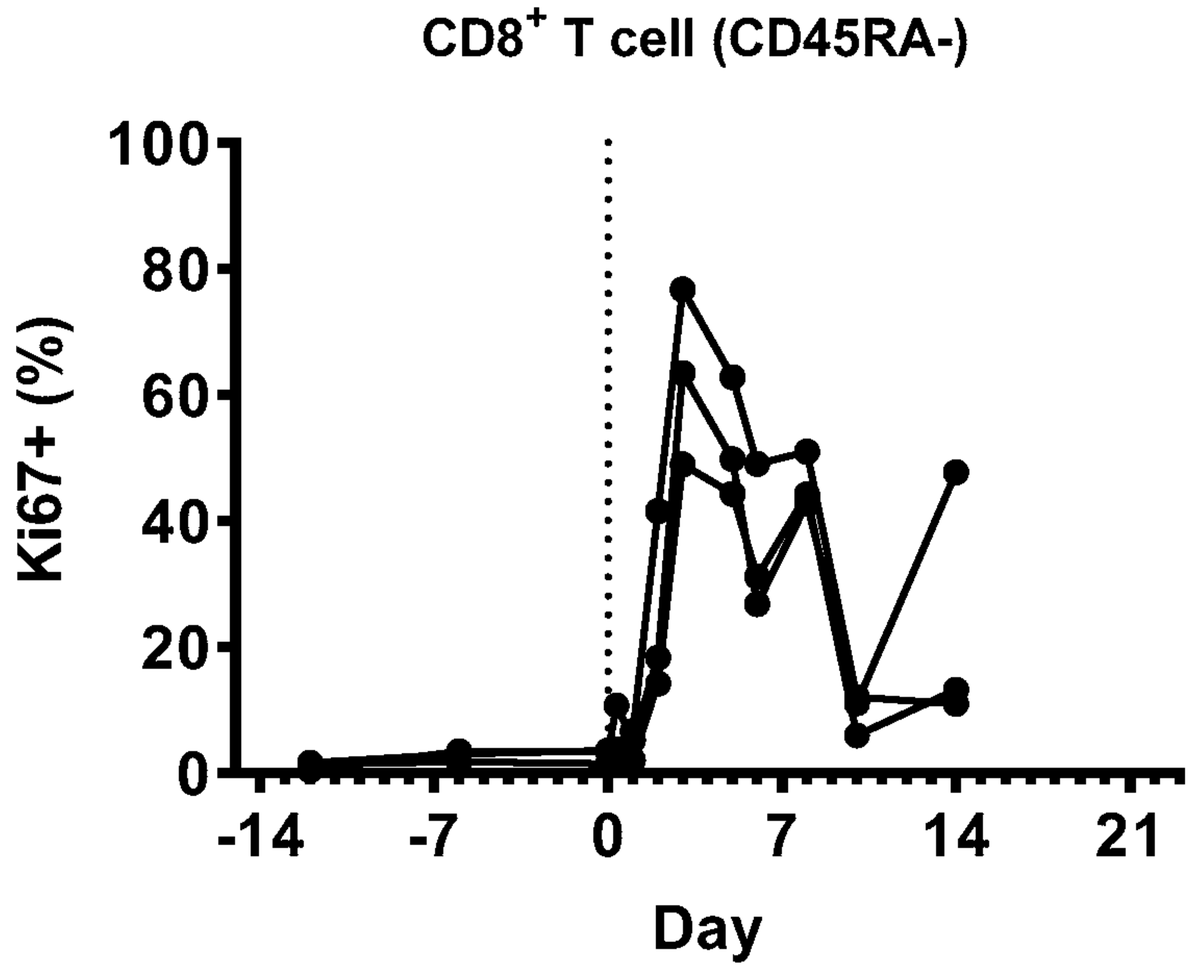


Figure 92E

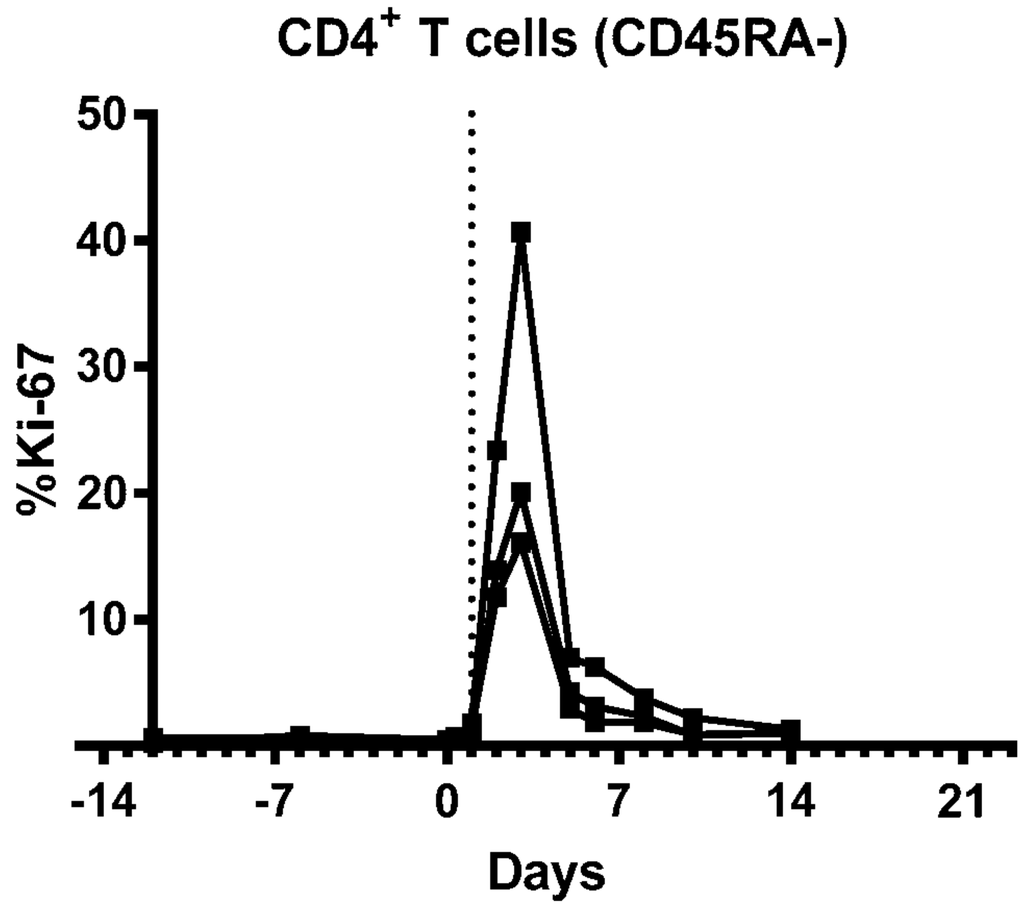


Figure 93A

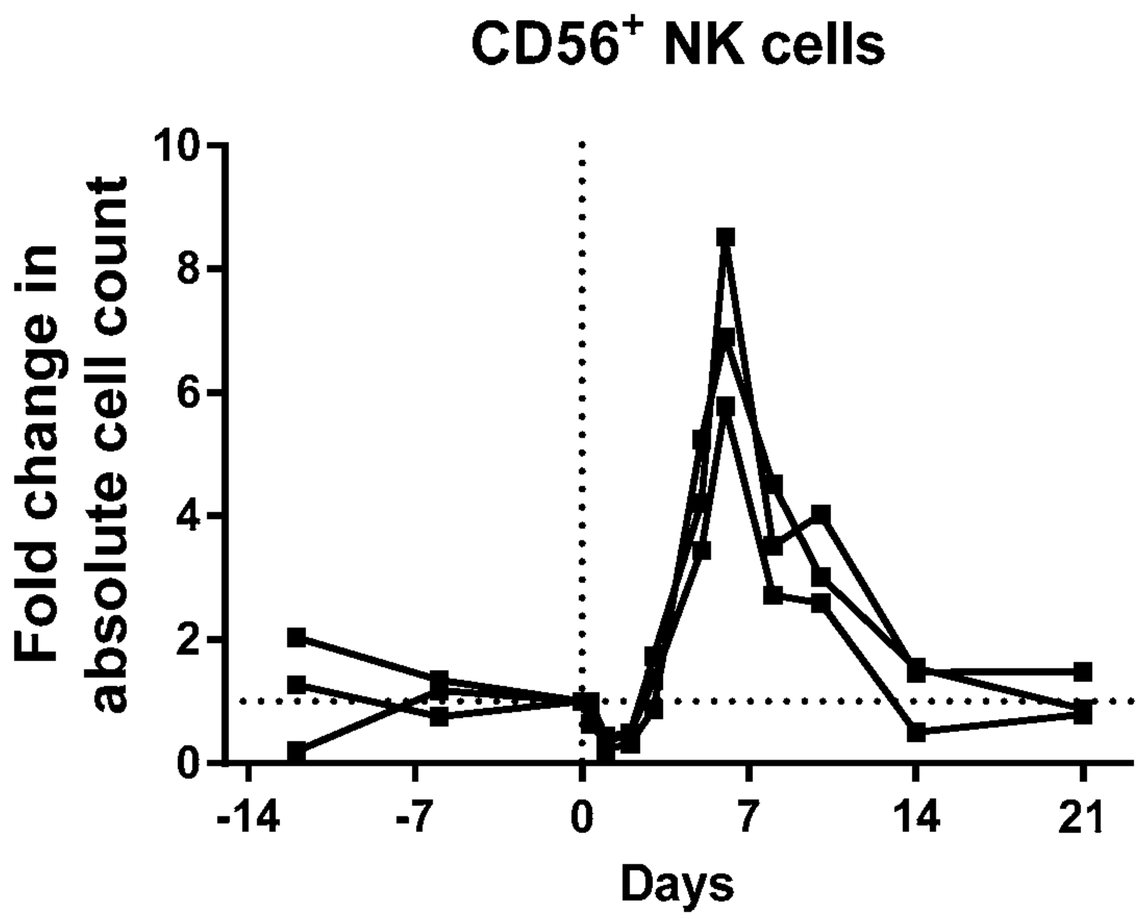


Figure 93B

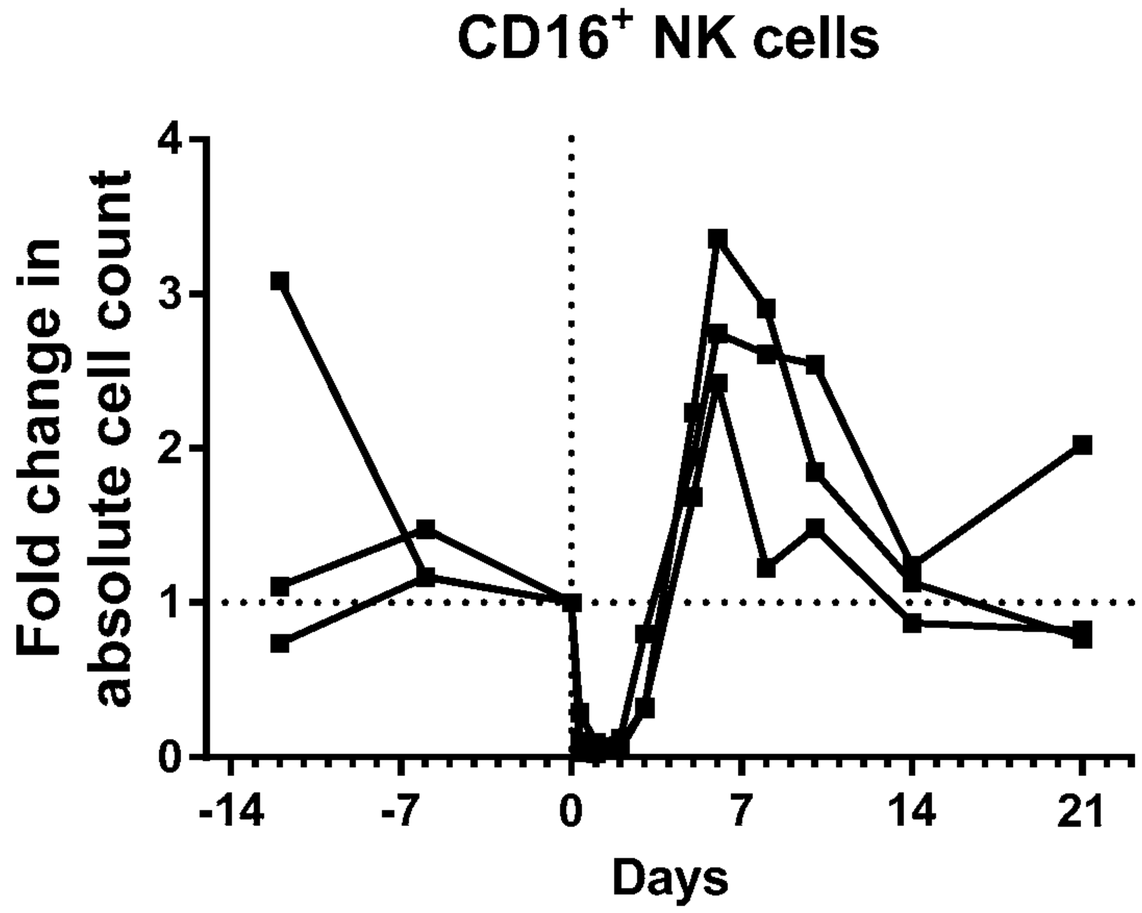


Figure 93C

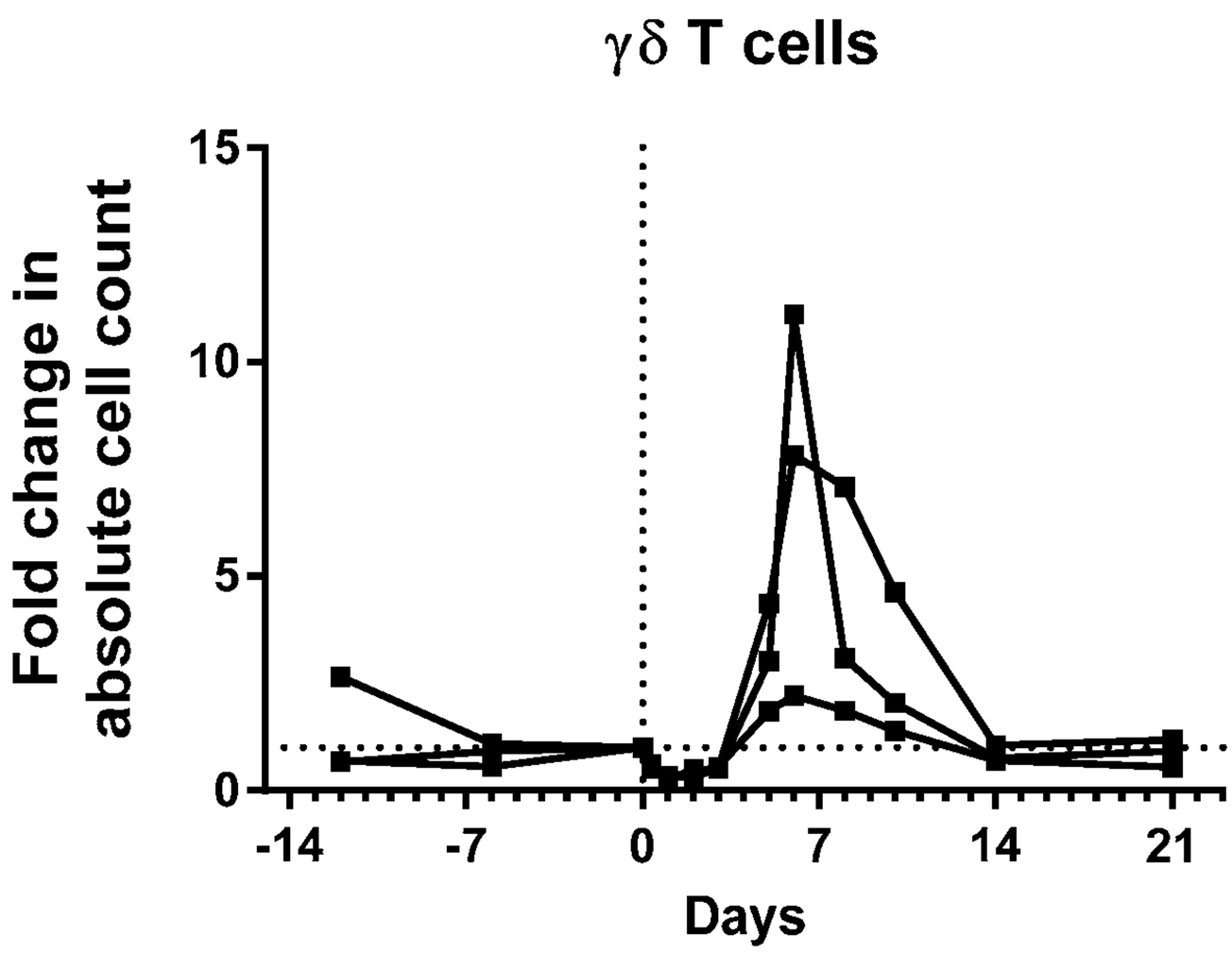


Figure 93D

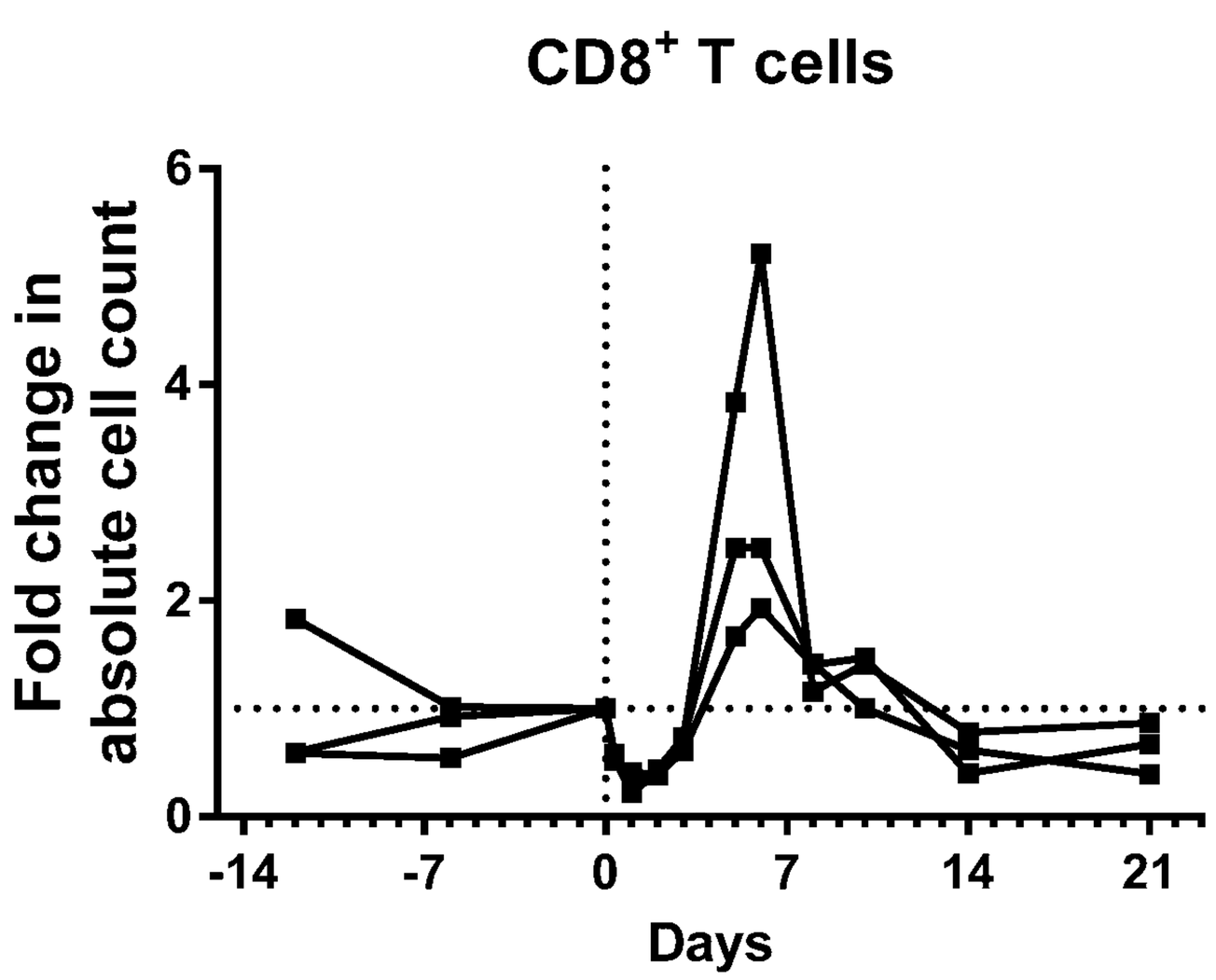


Figure 93E

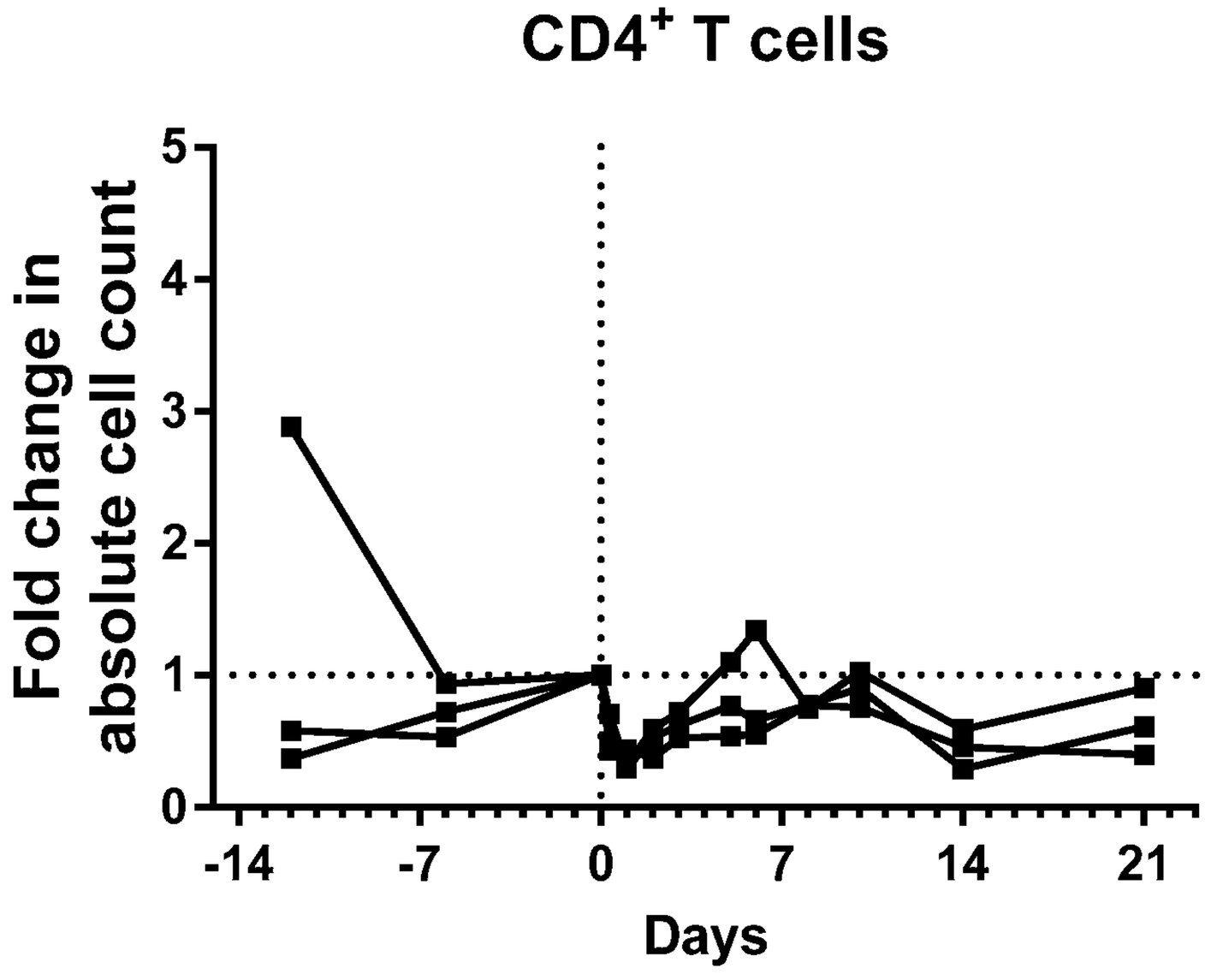

CD4+ T cells
Fold change in absolute cell count
5
4
3
2
1
0
-14
-7
0
7
14
21
Days

Figure 94A

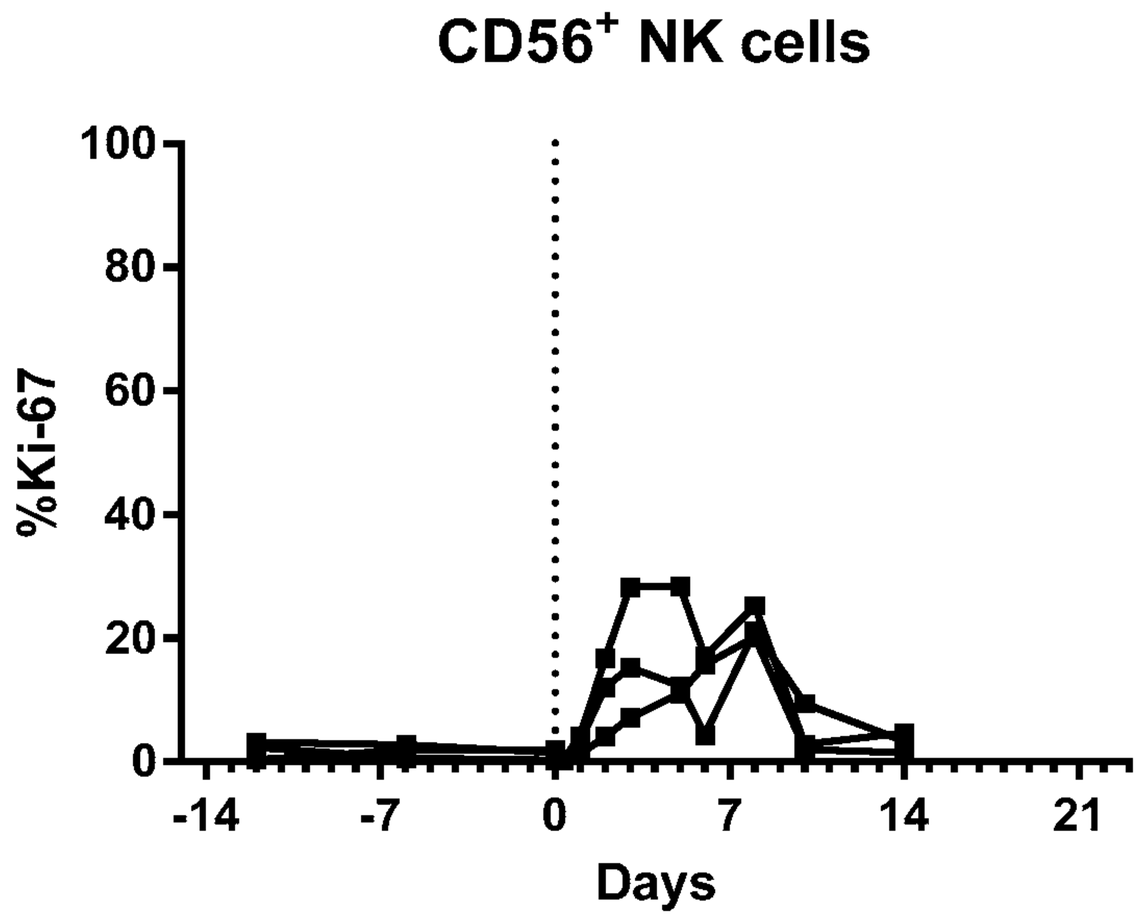


Figure 94B

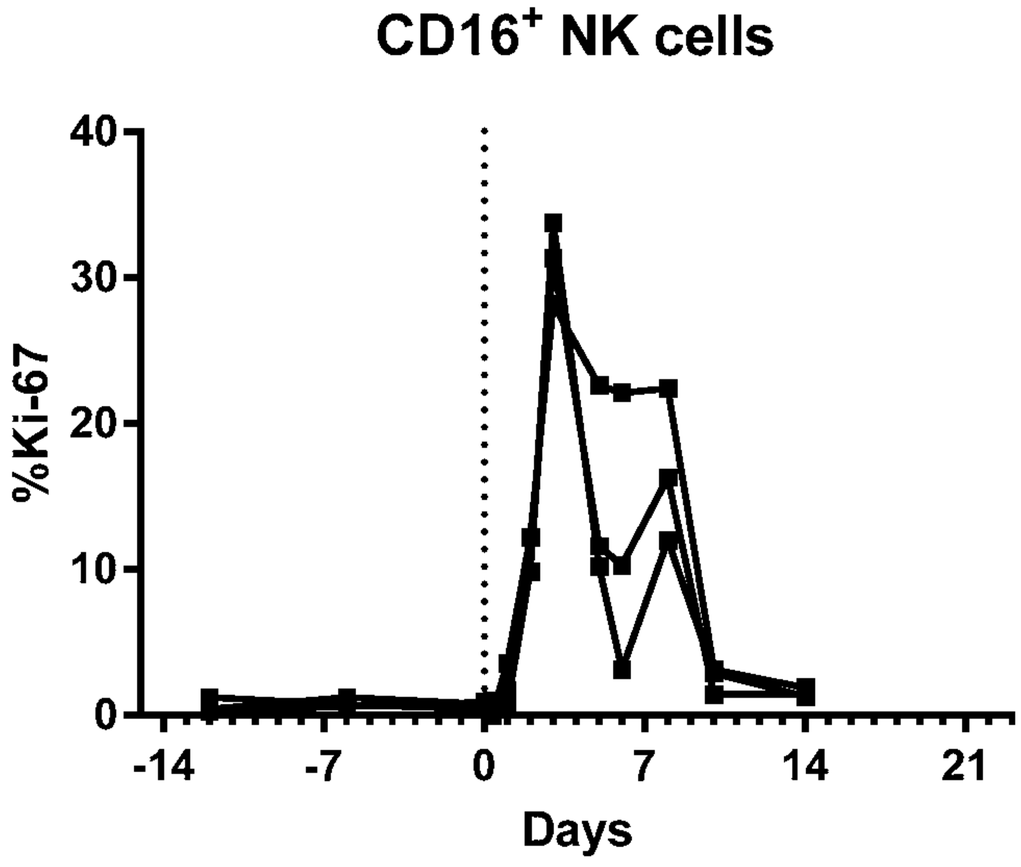


Figure 94C

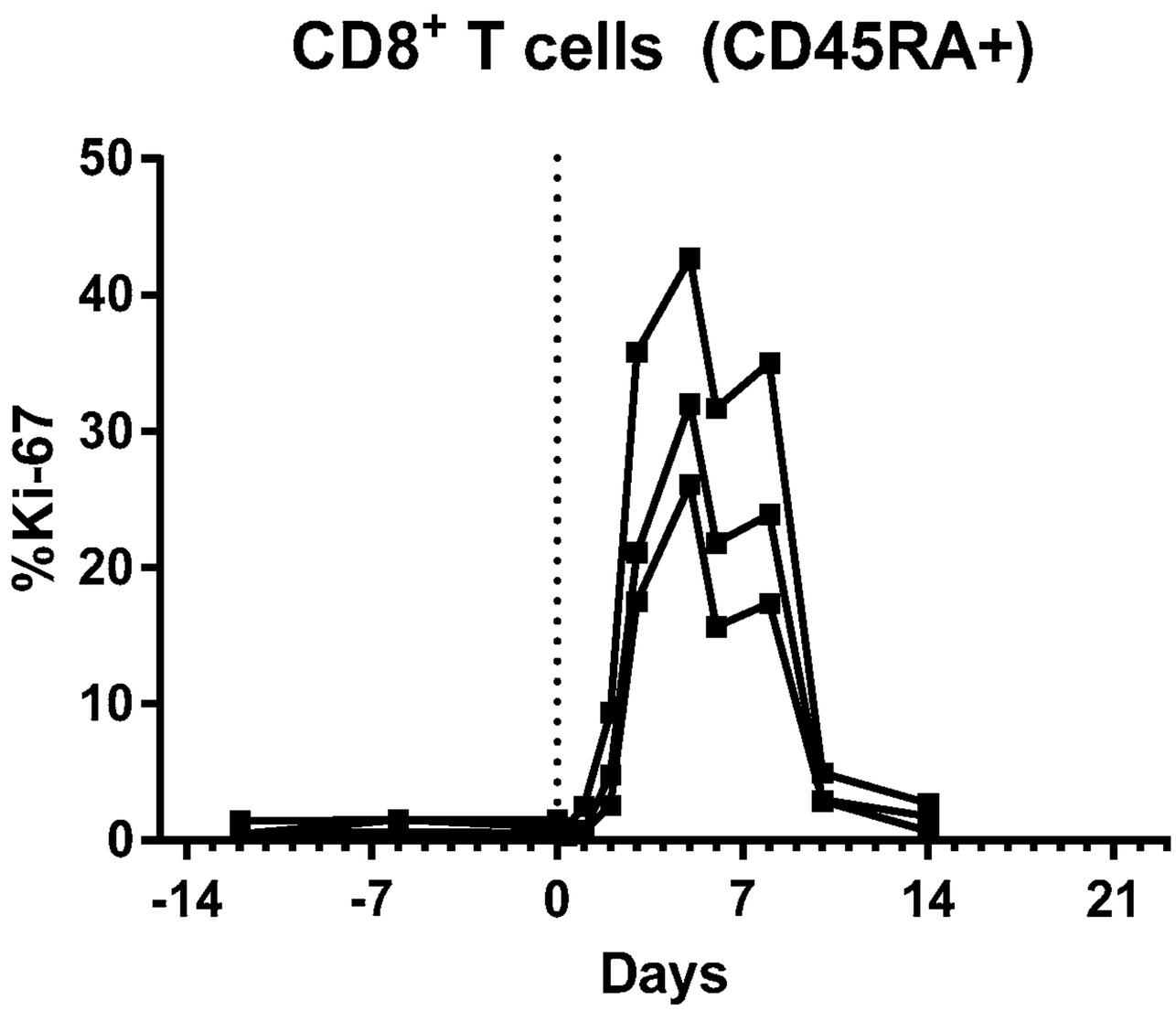


Figure 94D

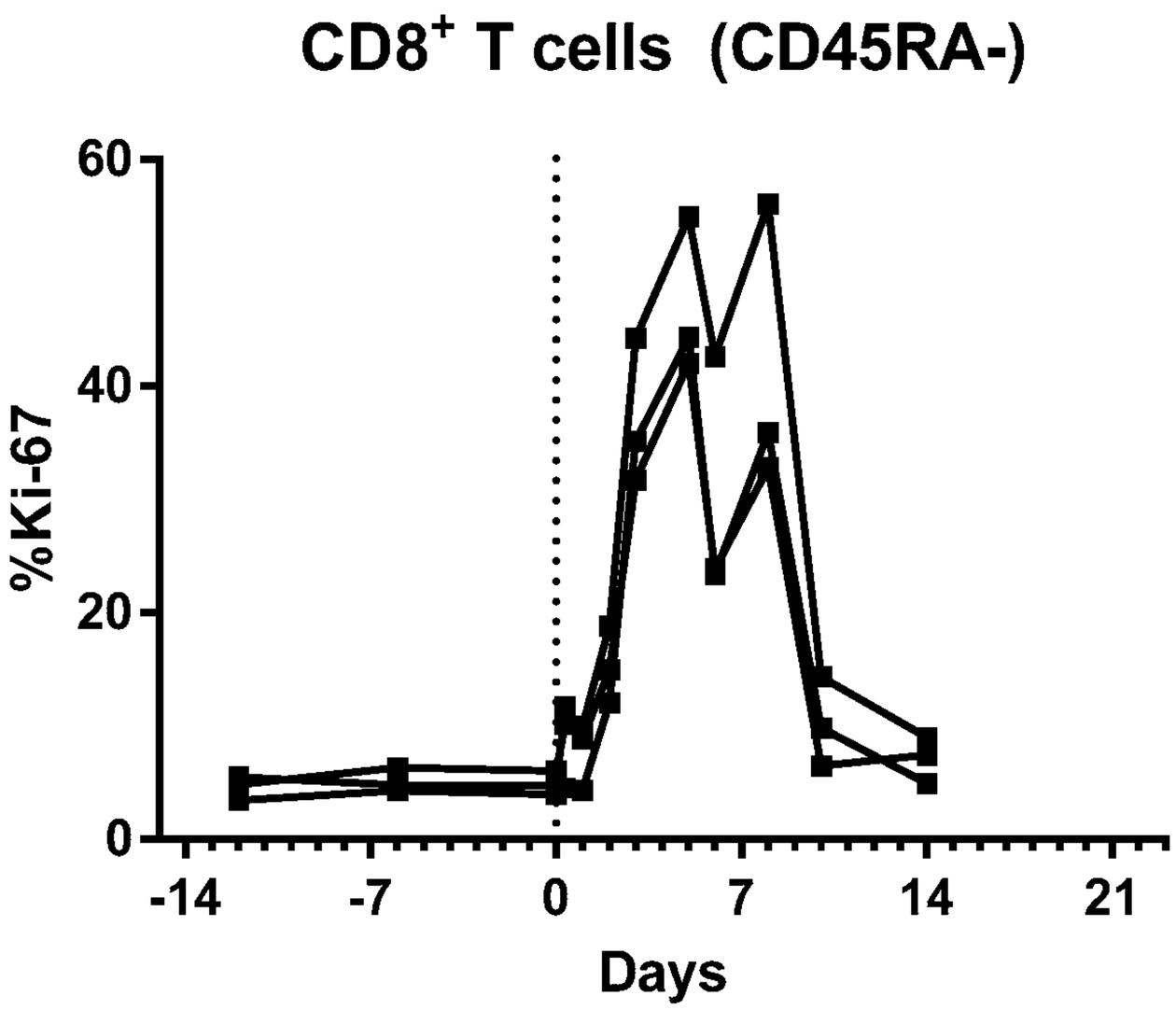


Figure 94E

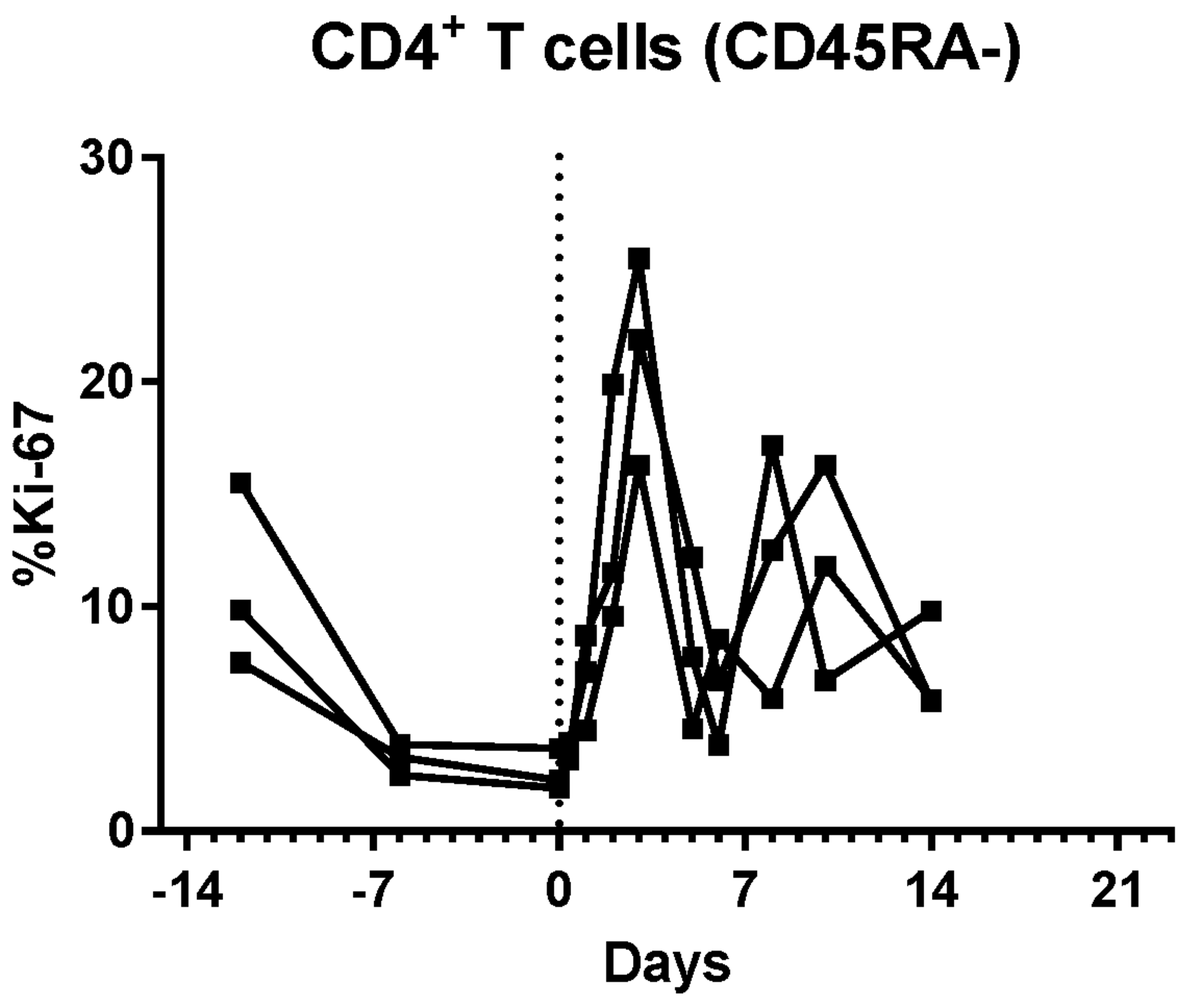


Figure 95A

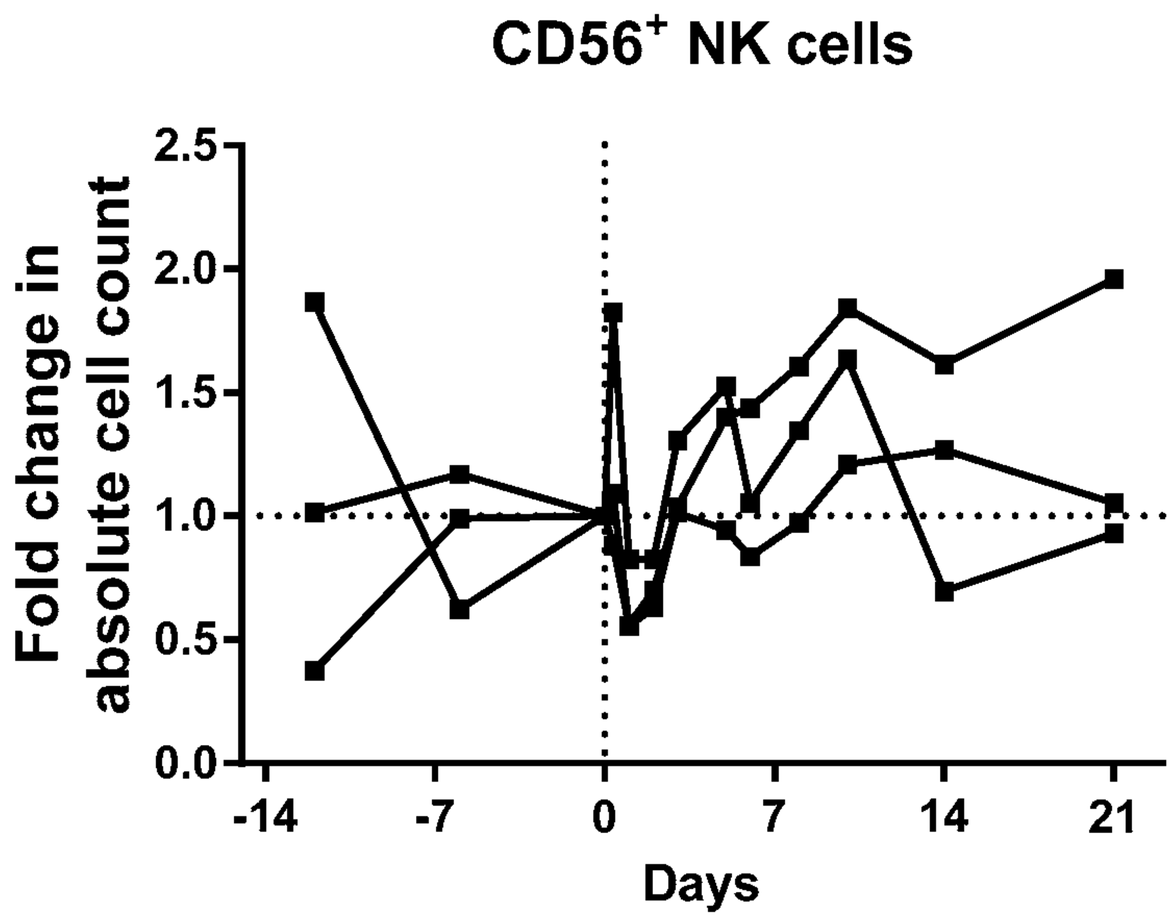


Figure 95B

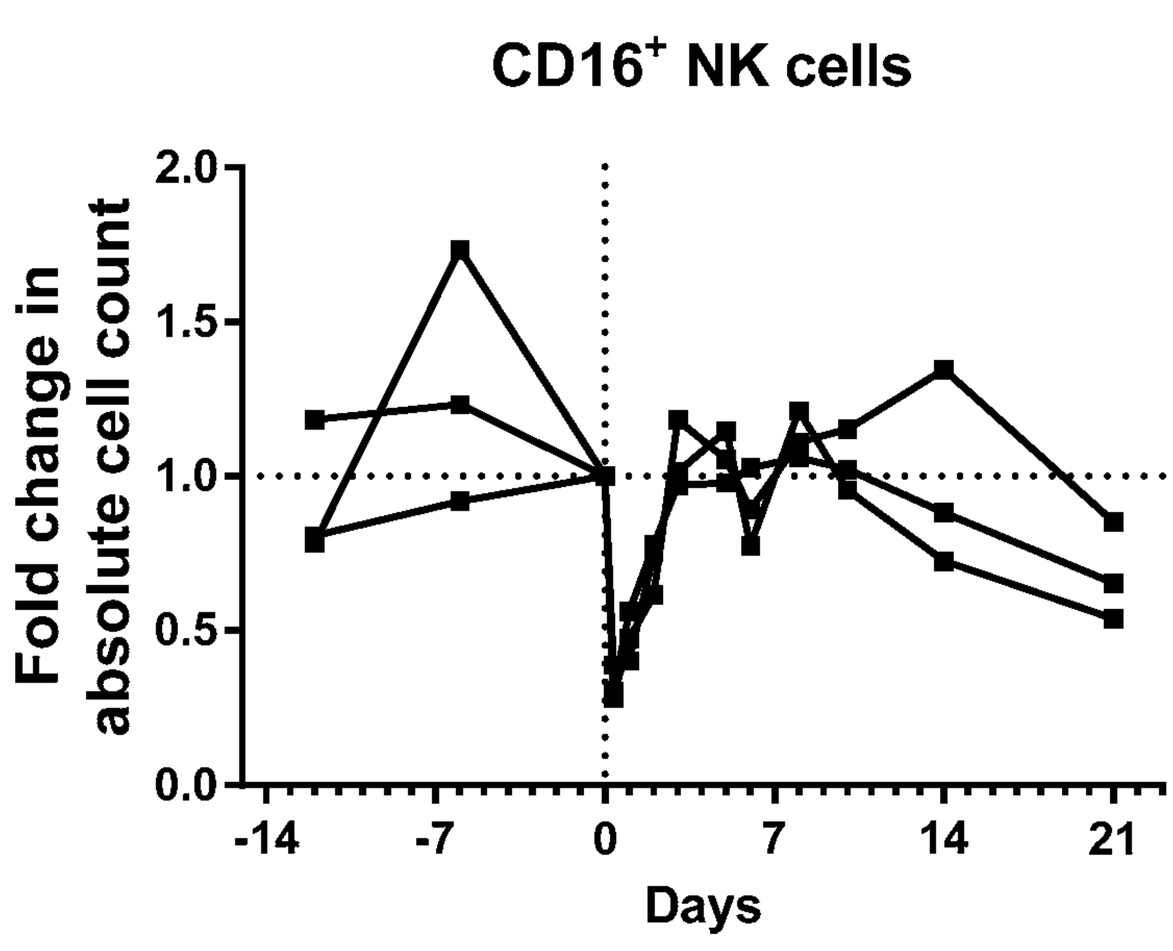


Figure 95C

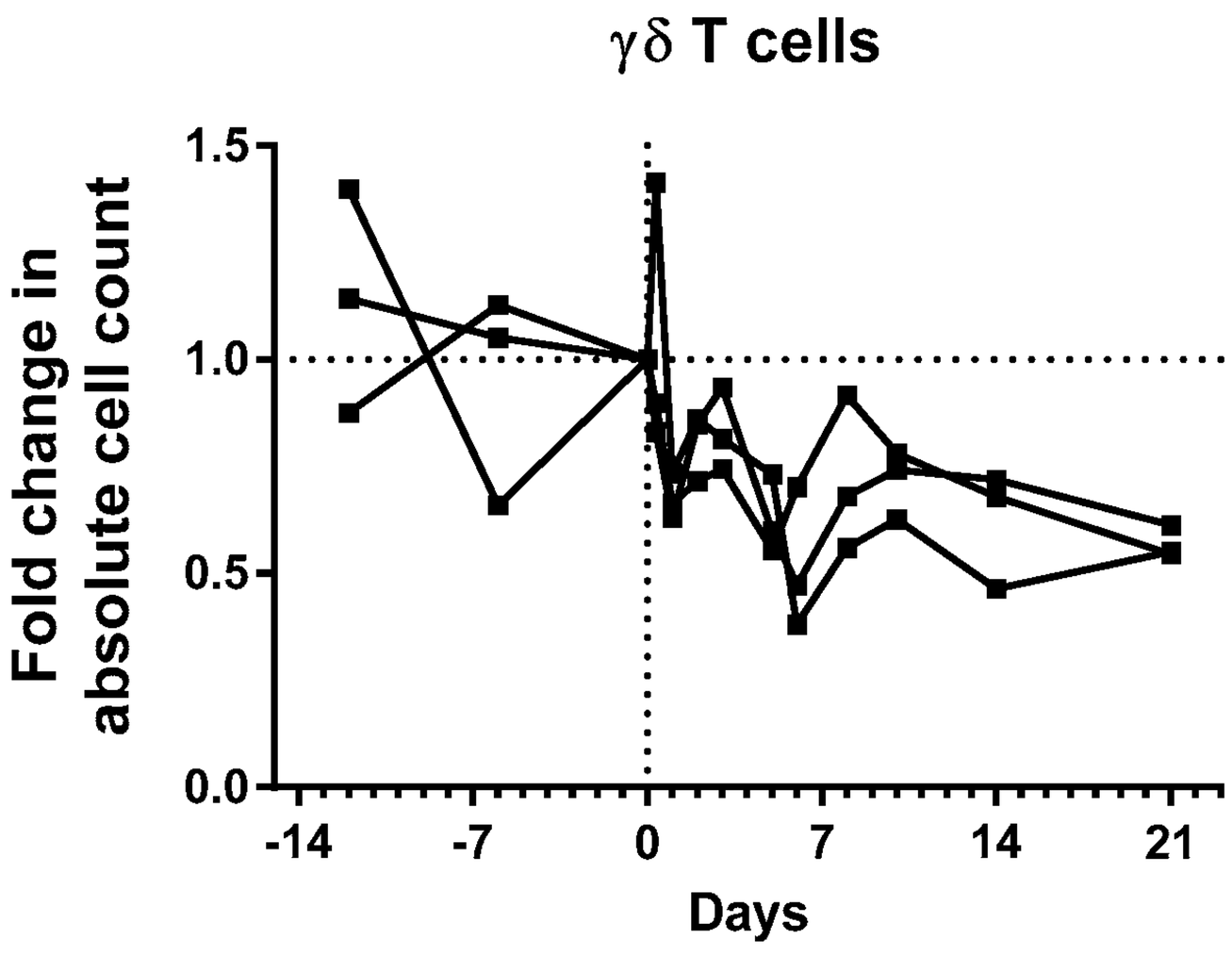
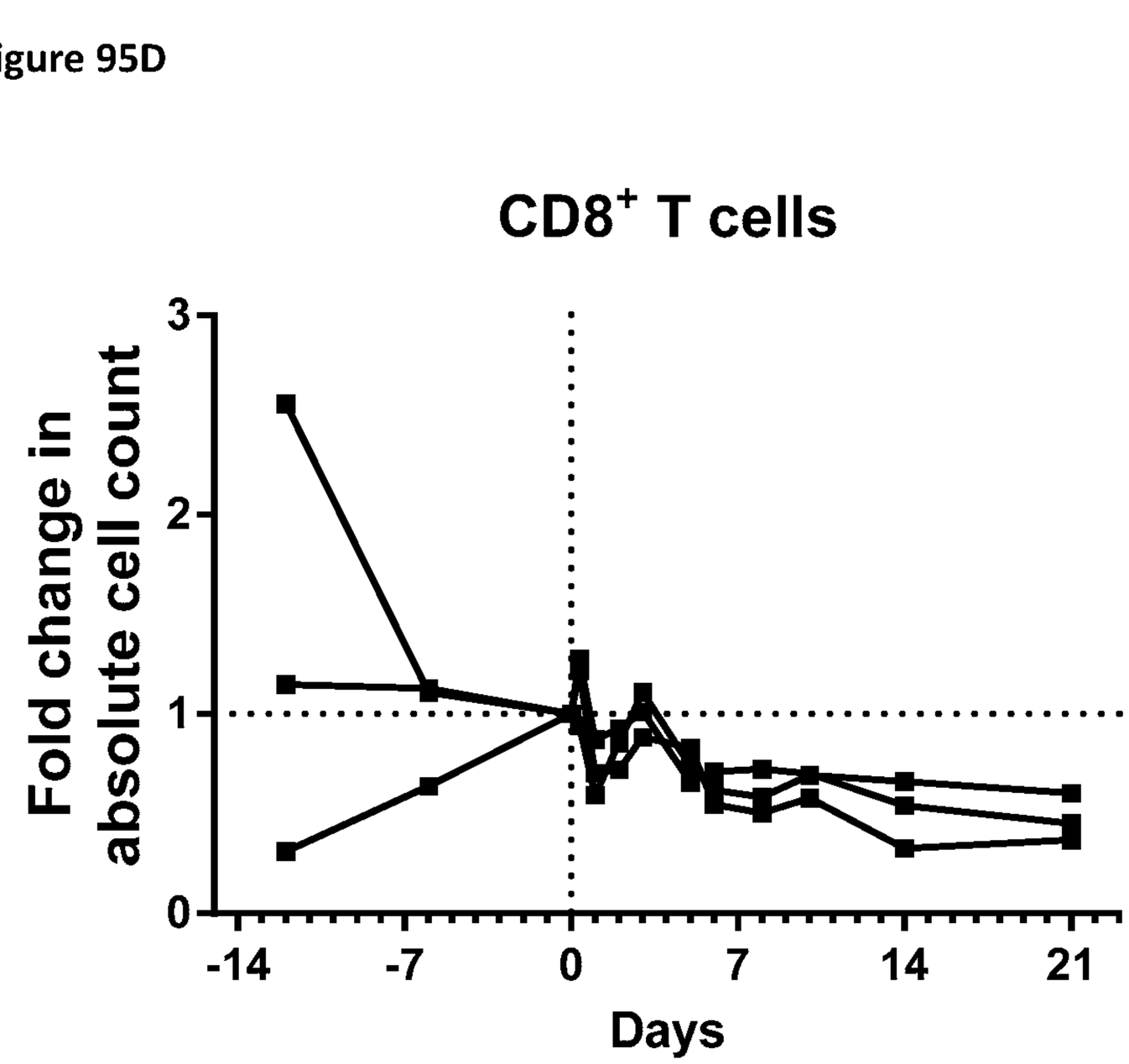


Figure 95D



igure 95E

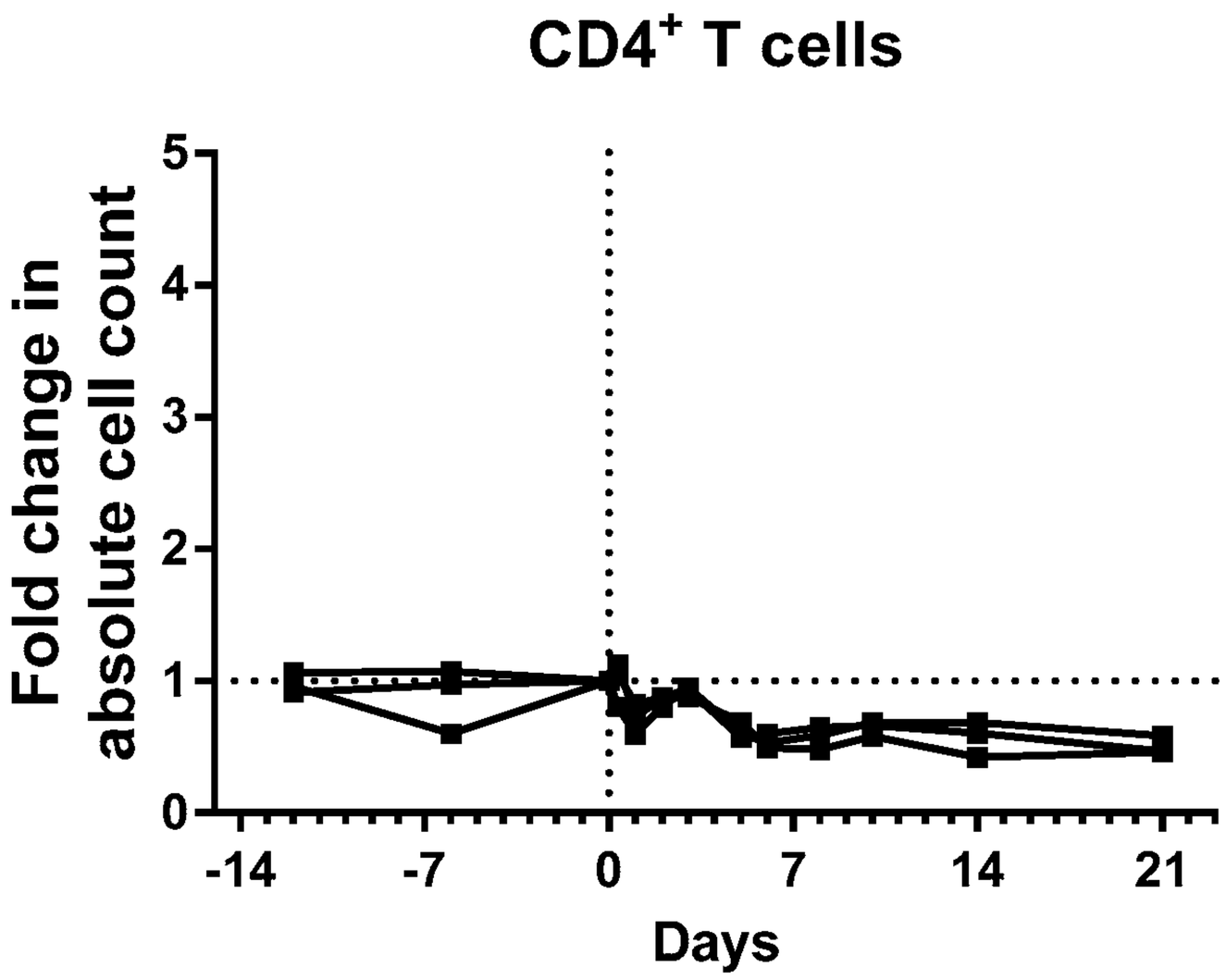

CD4+ T cells
Fold change in absolute cell count
0
1
2
3
4
5
-14
-7
0
7
14
21
Days

Figure 96A

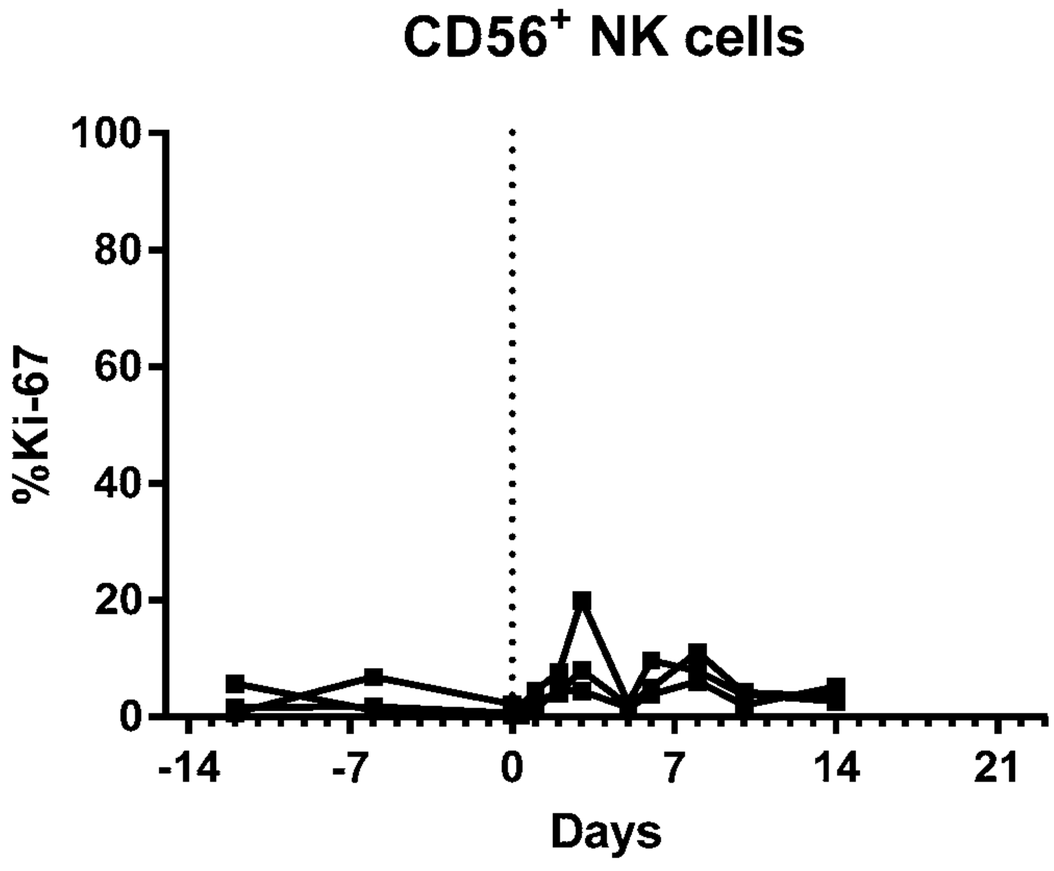


Figure 96B

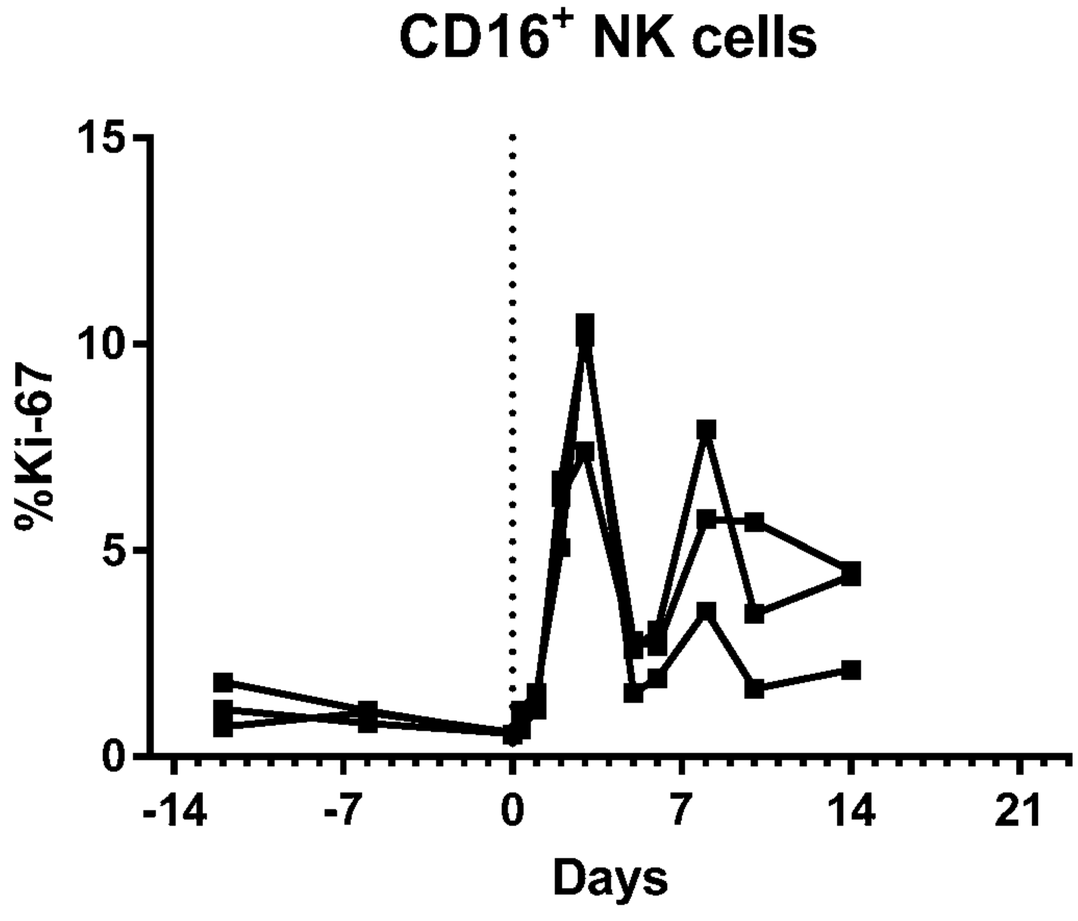


Figure 96C

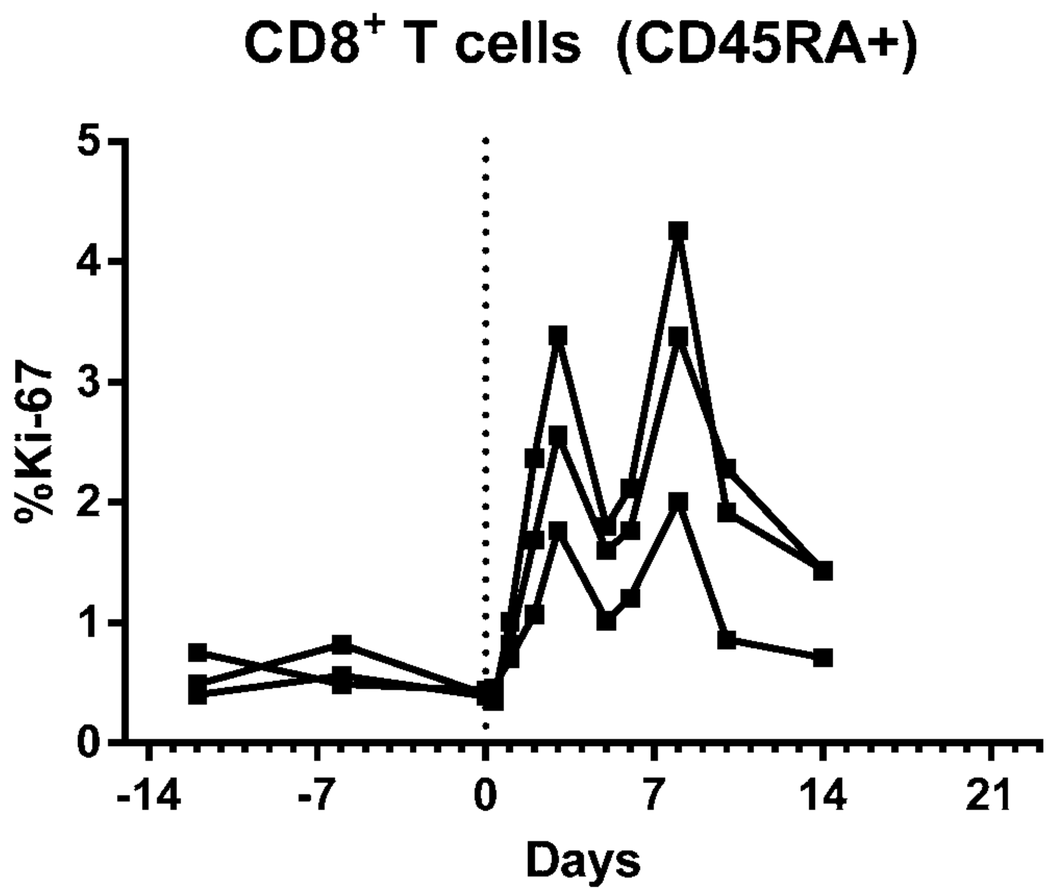


Figure 96D

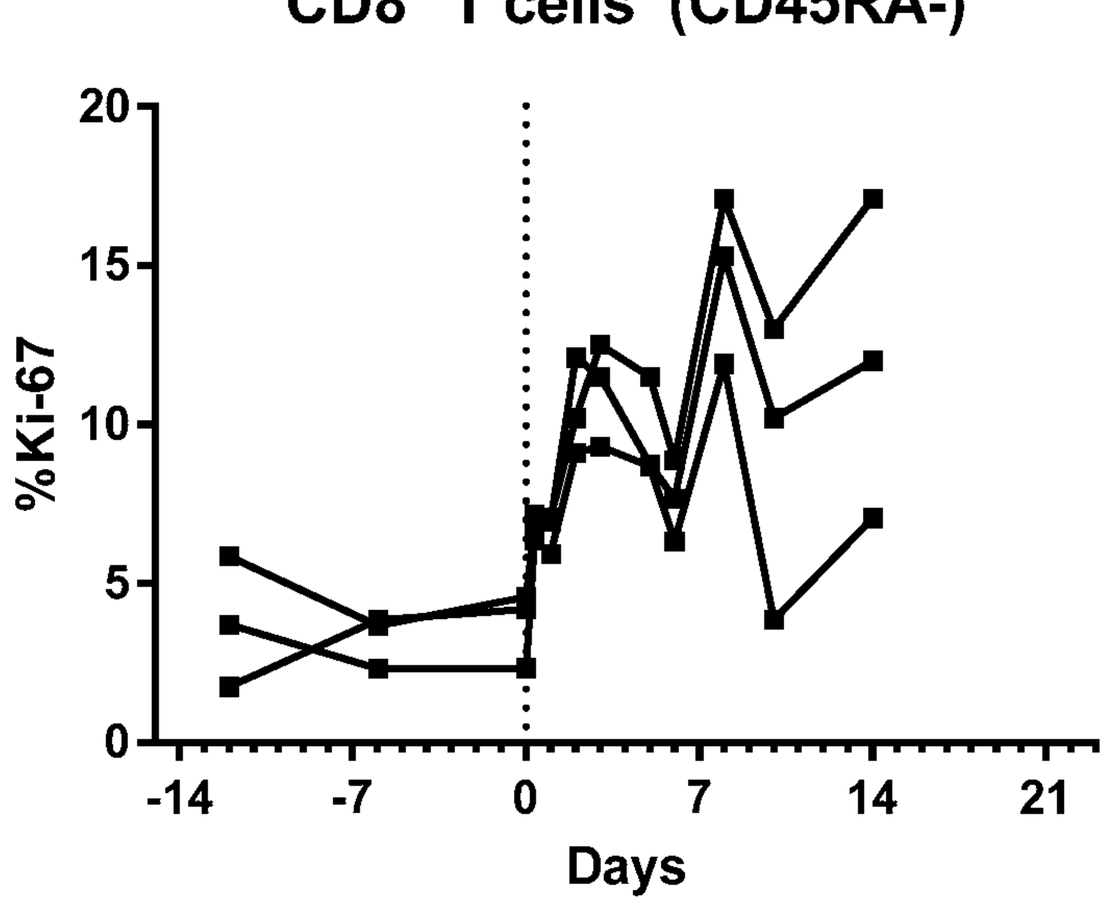


Figure 96E

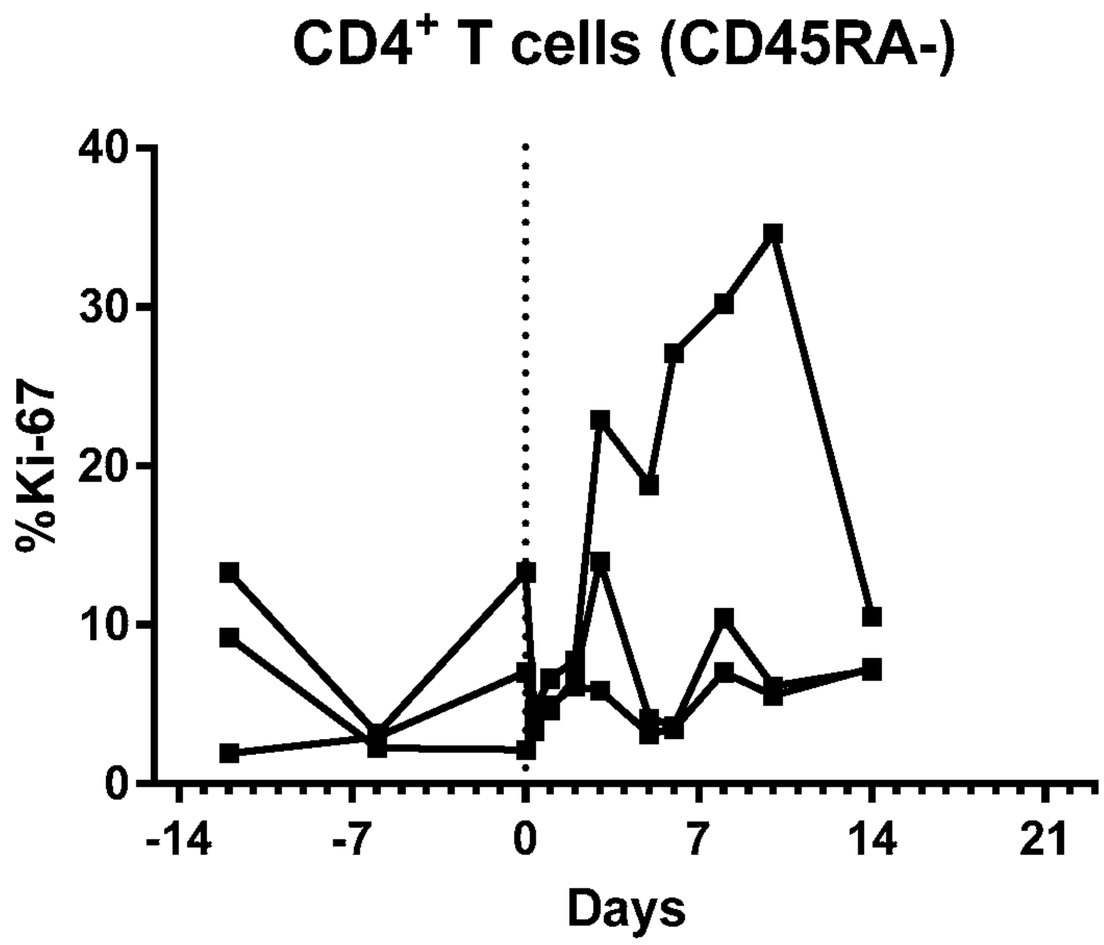


Figure 97A

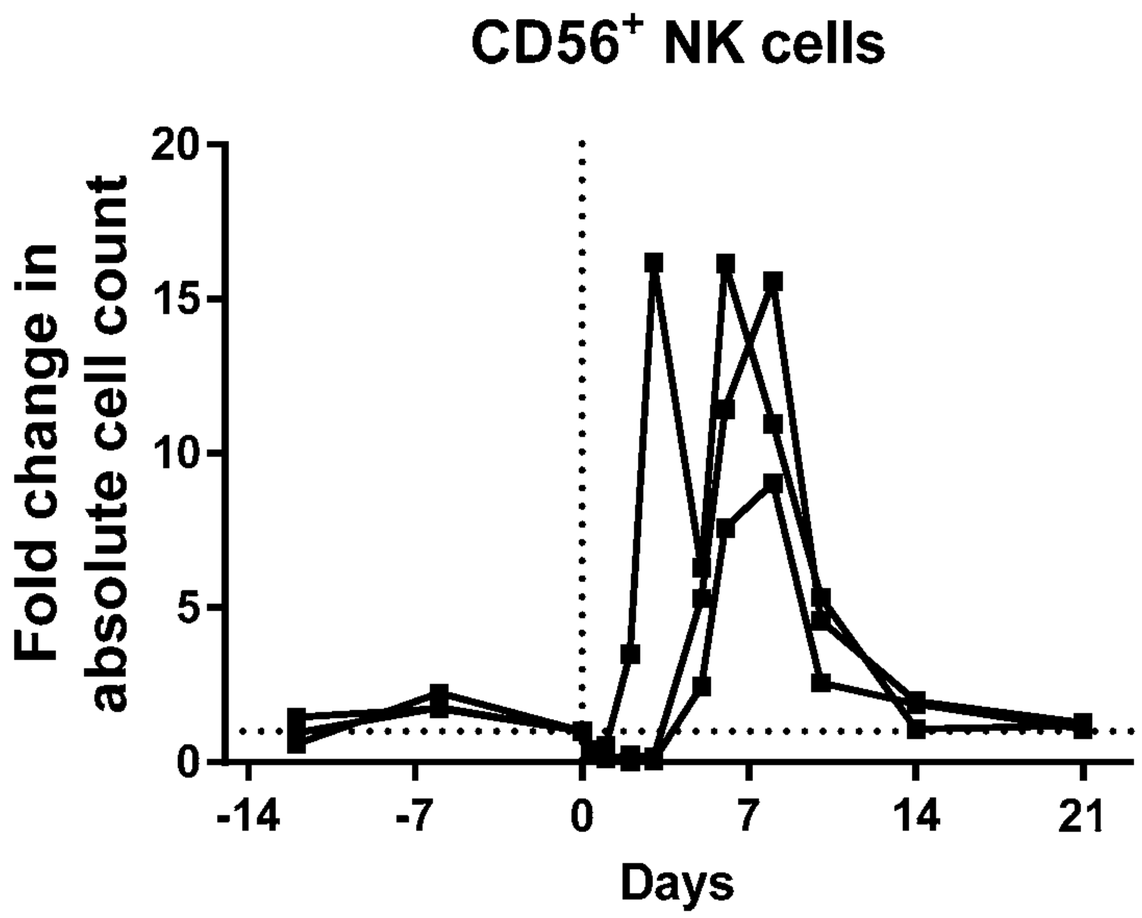


Figure 97B

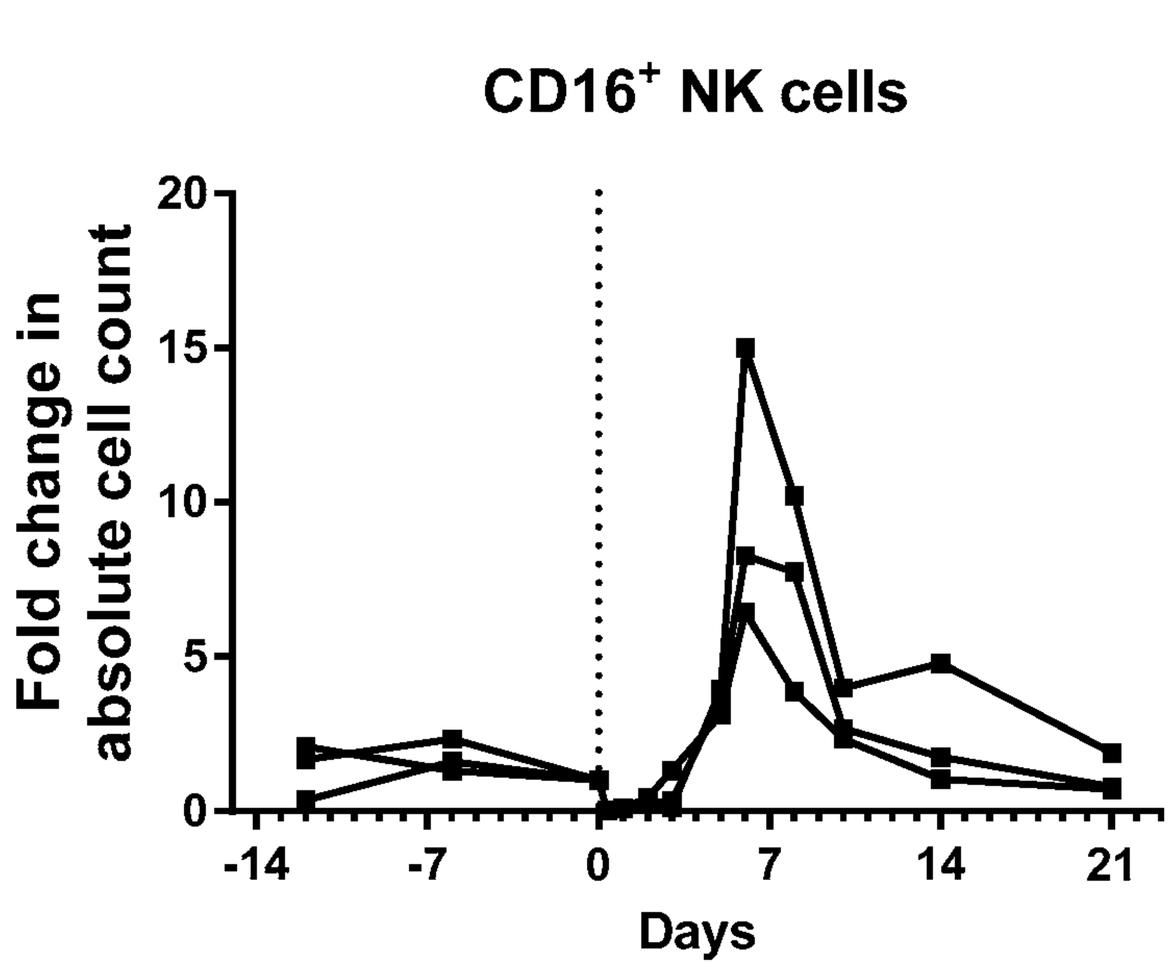


Figure 97C

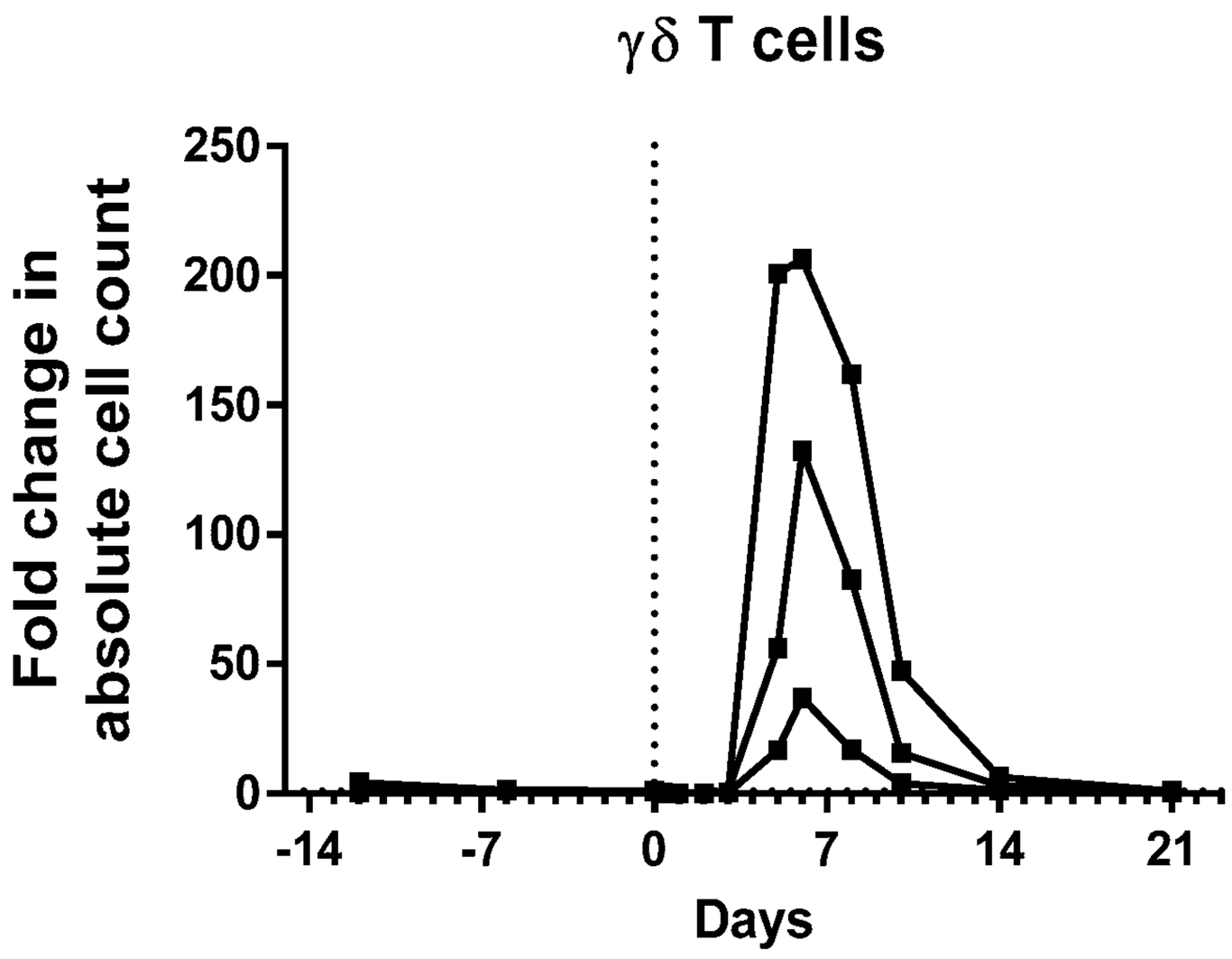


Figure 97D

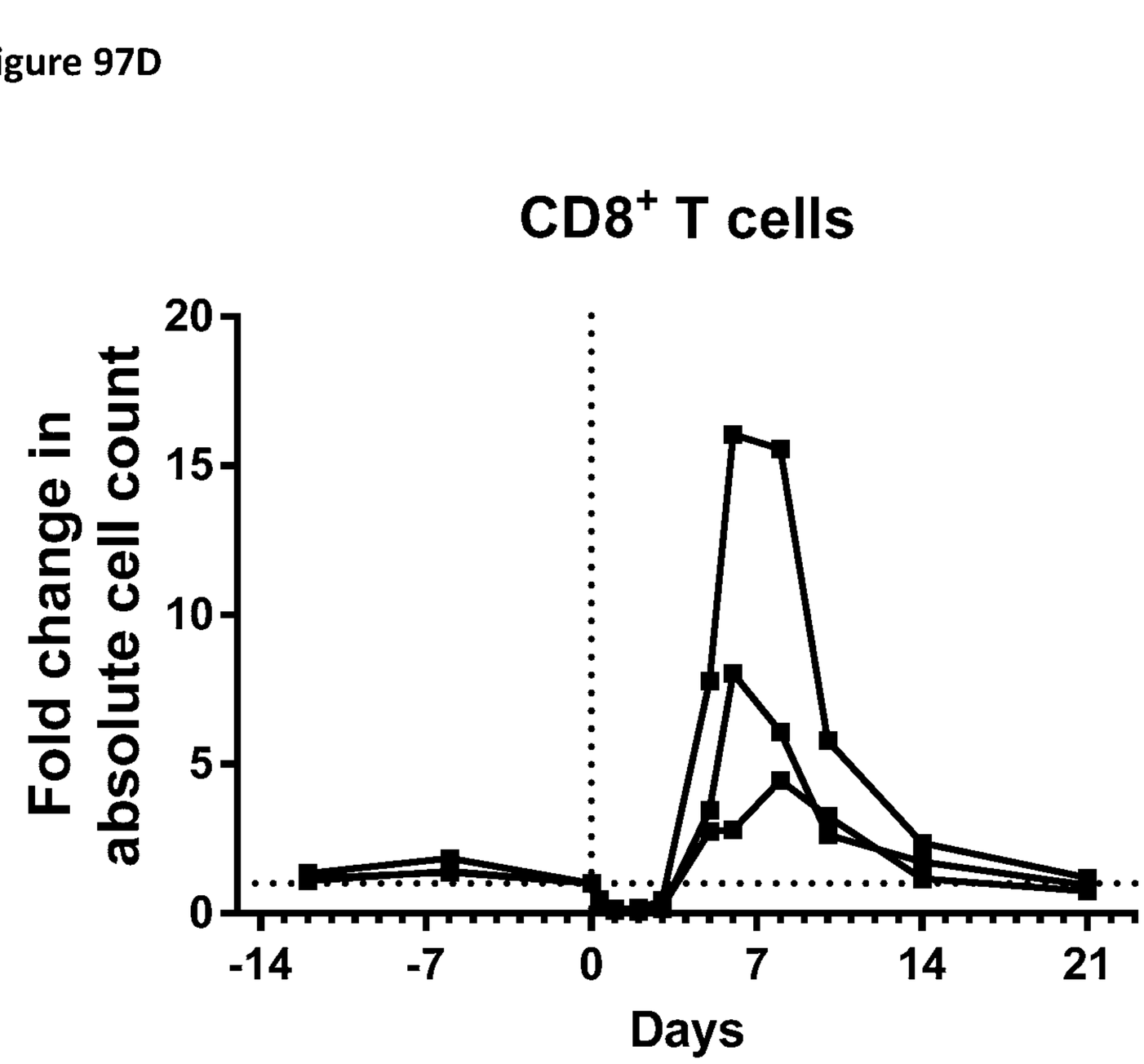


Figure 97E

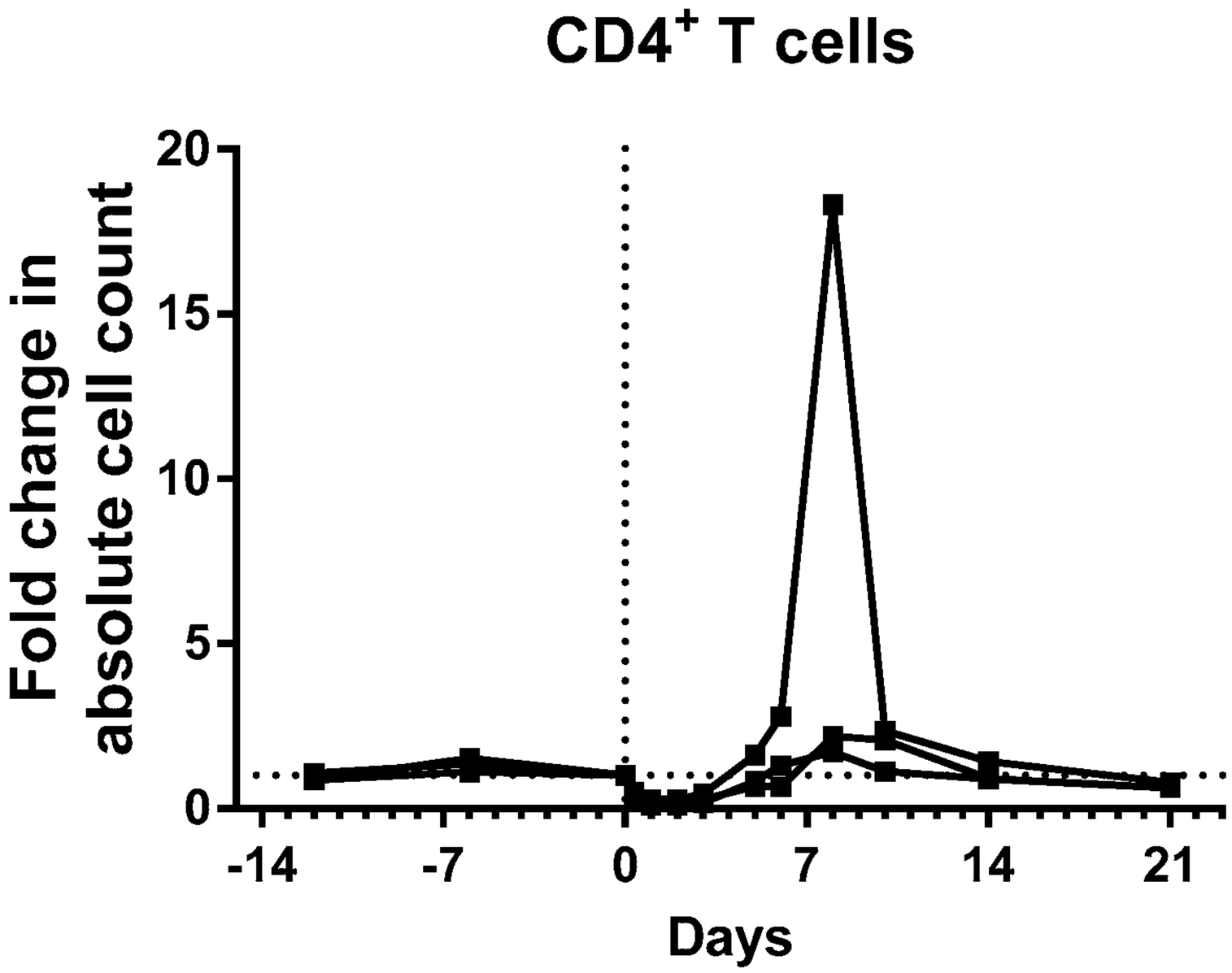

CD4+ T cells
Fold change in absolute cell count
20
15
10
5
0
-14
-7
0
7
14
21
Days

Figure 98A

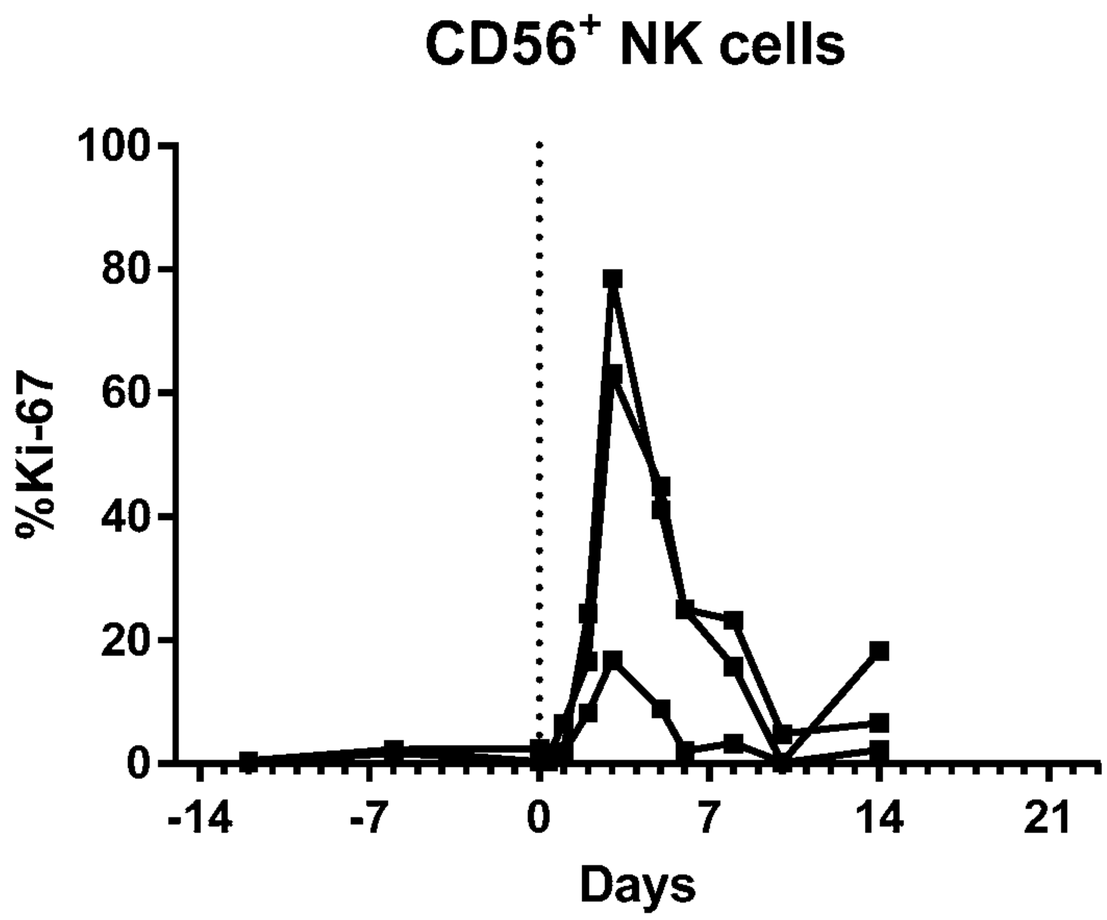


Figure 98B

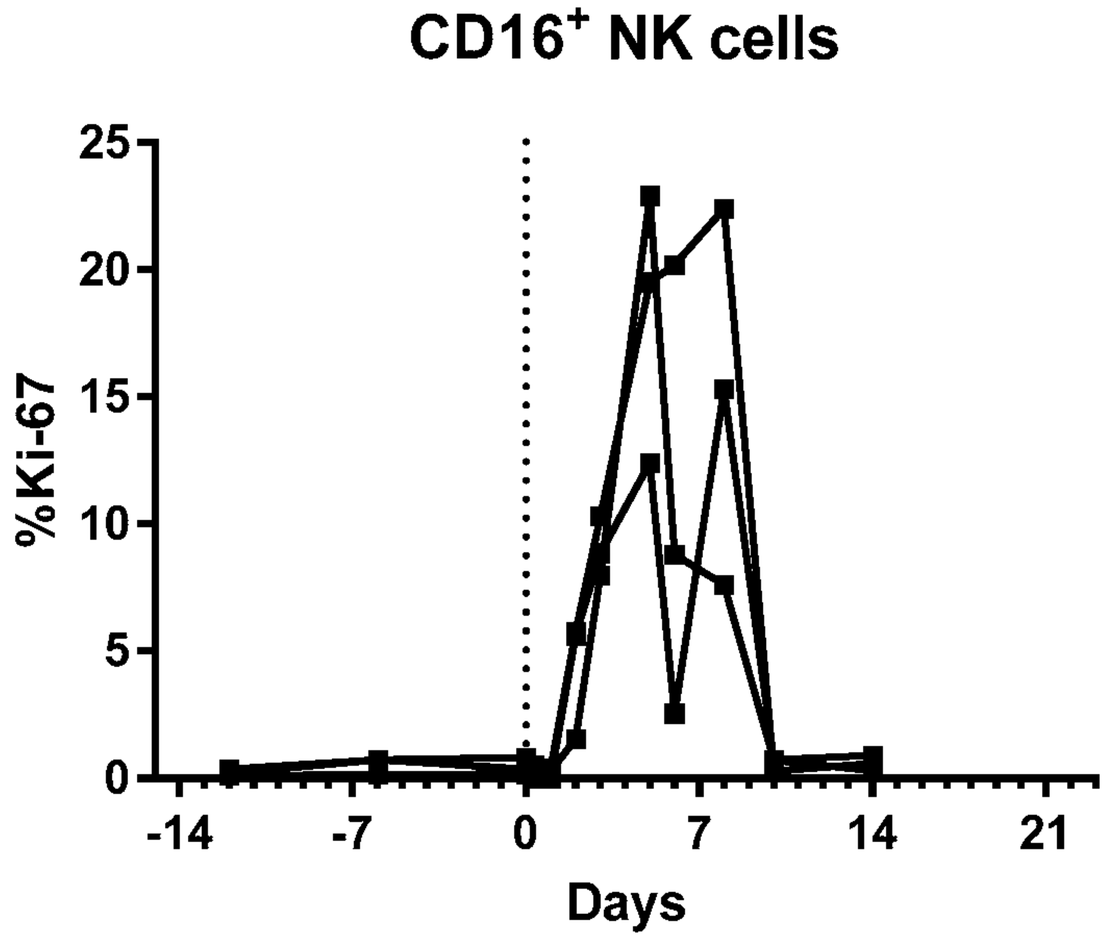


Figure 98C

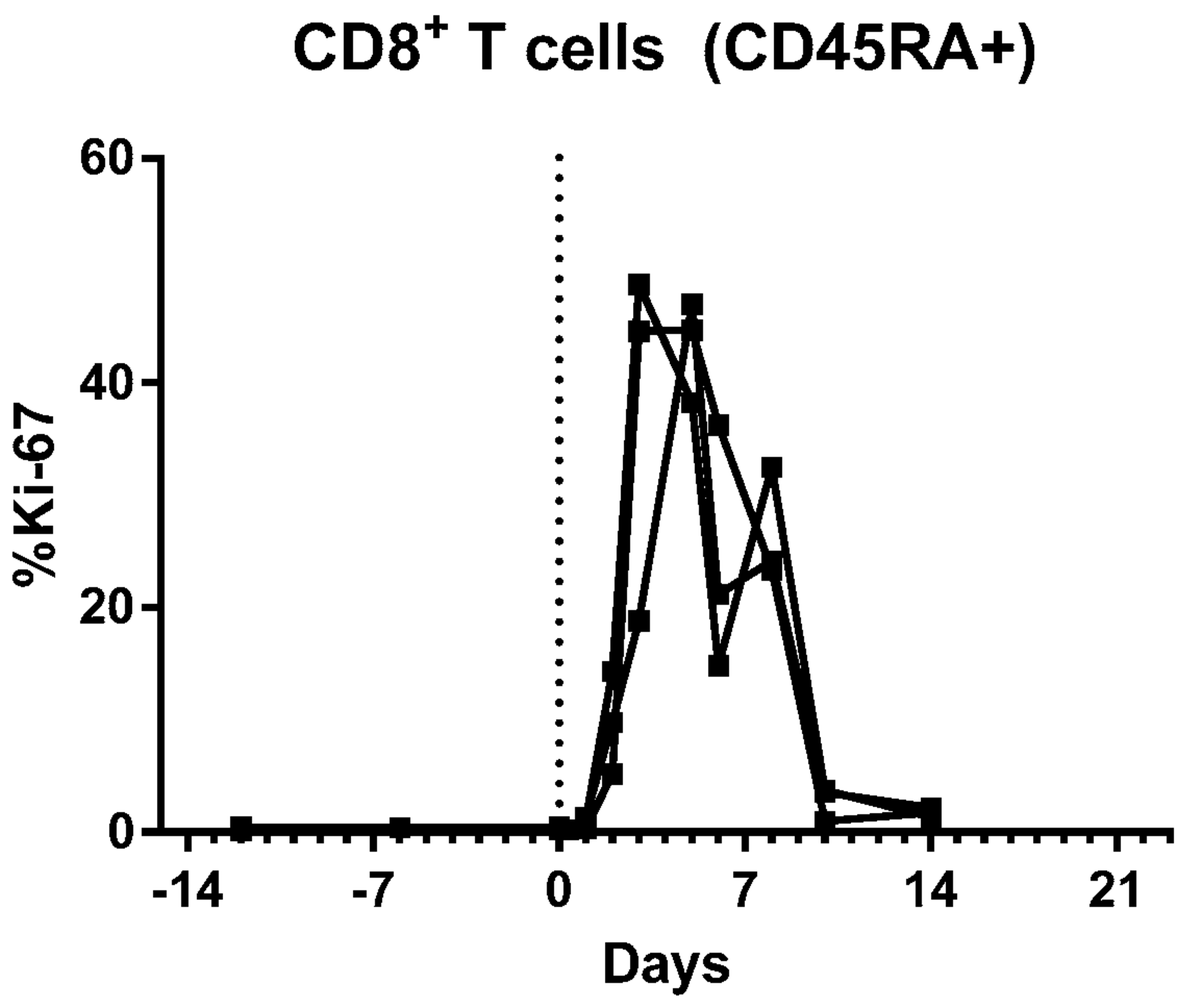


Figure 98D

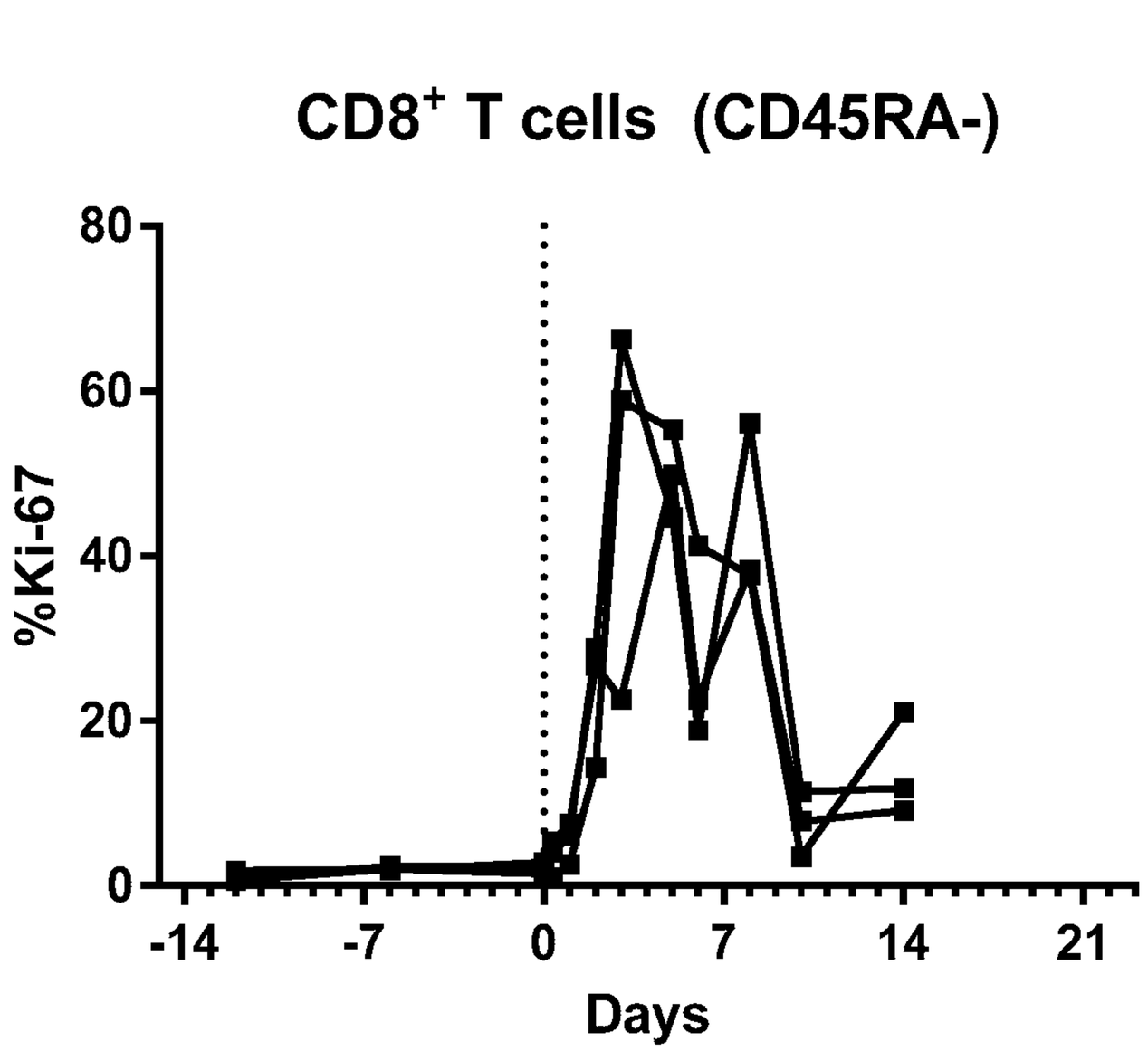


Figure 98E

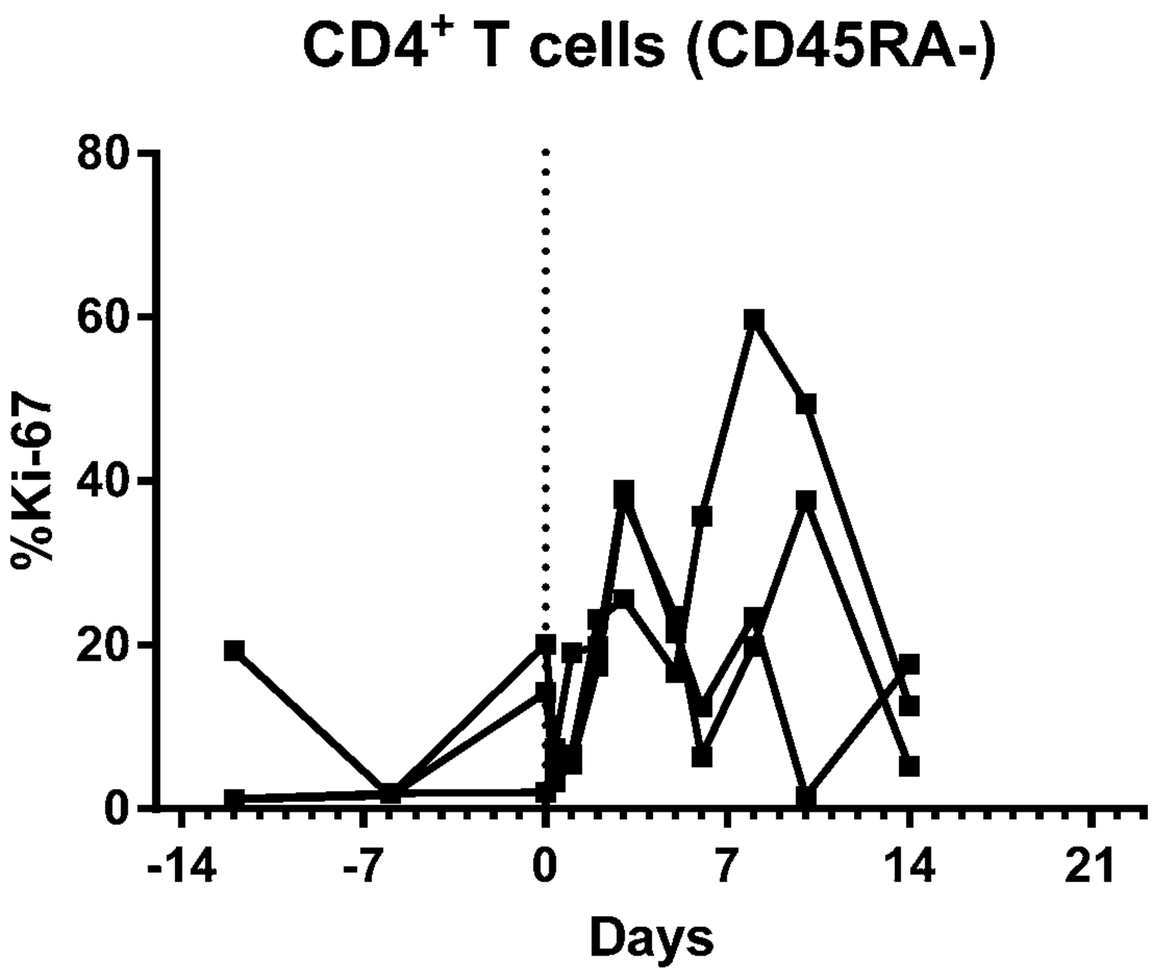


Figure 99A

>XENP023343 - human_IL15_N65D_(GGGGS)1-human_IL15Ra(Sushi)_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S/M428L/N434S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q/M428L/N434S

Chain 1 - human_IL15_N65D_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S/M428L/N434S (18295) (SEQ ID NO:245)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK

Chain 2 - human_IL15Ra(Sushi)_(GGGGS)1_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q/M428L/N434S (17761) (SEQ ID NO:246)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

>XENP023504 human_IL15_Q108E_(GGGGS)1-human_IL15Rα(Sushi)_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S/M428L/N434S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q/M428L/N434S

Chain 1 – human_IL15_Q108E_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S/M428L/N434S (SEQ ID NO:247)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVEMFINTS/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK

Chain 2 – human_IL15Rα(Sushi)_(GGGGS)1_
Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q/M428L/N434S (SEQ ID NO:248)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 99B

>XENP024113 human_IL15_N4D/N65D_(GGGGS)1-human_IL15Rα(Sushi)_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S/M428L/N434S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q/M428L/N434S

Chain 1 – human_IL15_N4D/N65D_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S/M428L/N434S (SEQ ID NO:249)
NWVDVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK

Chain 2 – human_IL15Rα(Sushi)_(GGGGS)1_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q/M428L/N434S (SEQ ID NO:250)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

>XENP024301 human_IL15_N4D/N65D-human_IL15Rα(Sushi)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S/M428L/N434S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q/M428L/N434S

Chain 1 – human_IL15_N4D/N65D_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S/M428L/N434S (SEQ ID NO:251)
NWVDVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK

Chain 2 – human_IL15Rα(Sushi)_ Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q/M428L/N434S (SEQ ID NO:252)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 99C

>XENP024306 human_IL15_D30N/E64Q/N65D_(GGGGS)1-human_IL15Rα(Sushi)_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S/M428L/N434S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q/M428L/N434S

Chain 1 – human_IL15_D30N/E64Q/N65D_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S/M428L/N434S (SEQ ID NO:253)
NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHDTVQDLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WEQGDVFSCSVLHEALHSHYTQKSLSLSPGK

Chain 2 –
human_IL15Rα(Sushi)_(GGGGS)1_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q/M428L/N434S
(SEQ ID NO:254)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGS/EPKSSDKTH
TCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

>XENP024341 human_IL15_N1D/N65D-human_IL15Rα(Sushi)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S/M428L/N434S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q/M428L/N434S

Chain 1 – human_IL15_N1D/N65D-human_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S/M428L/N434S (SEQ ID NO:255)
DWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVD
VKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
REPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGD
VFSCSVLHEALHSHYTQKSLSLSPGK

Chain 2 – human_IL15Rα(Sushi)_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q/M428L/N434S
(SEQ ID NO:256)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/EPKSSDKTHTCPPCP
APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

Figure 100

>XENP025938 human_IL15Ra(sushi)_(GGGGS)5-human_IL15_N4D/N65D_(single-chain)-empty-Fc_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S/M428L/N434S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q/M428L/N434S

Chain 1 – human_IL15Ra(sushi)_(GGGGS)5-human_IL15_N4D/N65D_(single-chain)-_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S/M428L/N434S (SEQ ID NO:257)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGSGGGGSGGGGSGGGGSGGGGS/NWVDVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLII
LANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL
PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYS
KLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK

Chain 2 – empty_Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q/M428L/N434S (SEQ ID NO:258)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 101

>XENP024383 IL15_Q108E_(non-covalent)-human_IL15Ra(Sushi)_empty-Fc_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S/M428L/N434S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q/M428L/N434S

Chain 1 - IL15_Q108E (SEQ ID NO: 259)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVEMFINTS

Chain 2 - human_IL15Ra(Sushi)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S/M428L/N434S (SEQ ID NO:260)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK

Chain 3 – empty_ Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q/M428L/N434S (SEQ ID NO:261)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 102

>XENP024346 human_IL15(non-covalent; Q108E)-
human_IL15Rα(Sushi)_Fc(216)_IgG1_C220S/PVA_/S267K/M428L/N434S

Chain 1 – human_IL15Rα(Sushi)_Fc(216)_IgG1_C220S/PVA_/S267K/M428L/N434S
(SEQ ID NO:262)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/EPKSSDKTHTCPPCP
APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

Chain 2 – human_IL15(non-covalent; Q108E) (SEQ ID NO:263)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVEMFINTS

>XENP024351 human_IL15(non-covalent; N4D/N65D)-
human_IL15Ra(Sushi)_Fc(216)_IgG1_C220S/PVA_/S267K/M428L/N434S

Chain 1 – IL15(N4D/N65D) (SEQ ID NO:264)
NWVDVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTE
SGCKECEELEEKNIKEFLQSFVHIVQMFINTS

Chain 2 - human_IL15Ra(Sushi)_Fc(216)_IgG1_C220S/PVA_/S267K/M428L/N434S (SEQ ID NO:265)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/EPKSSDKTHTCPPCP
APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL
HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 103A

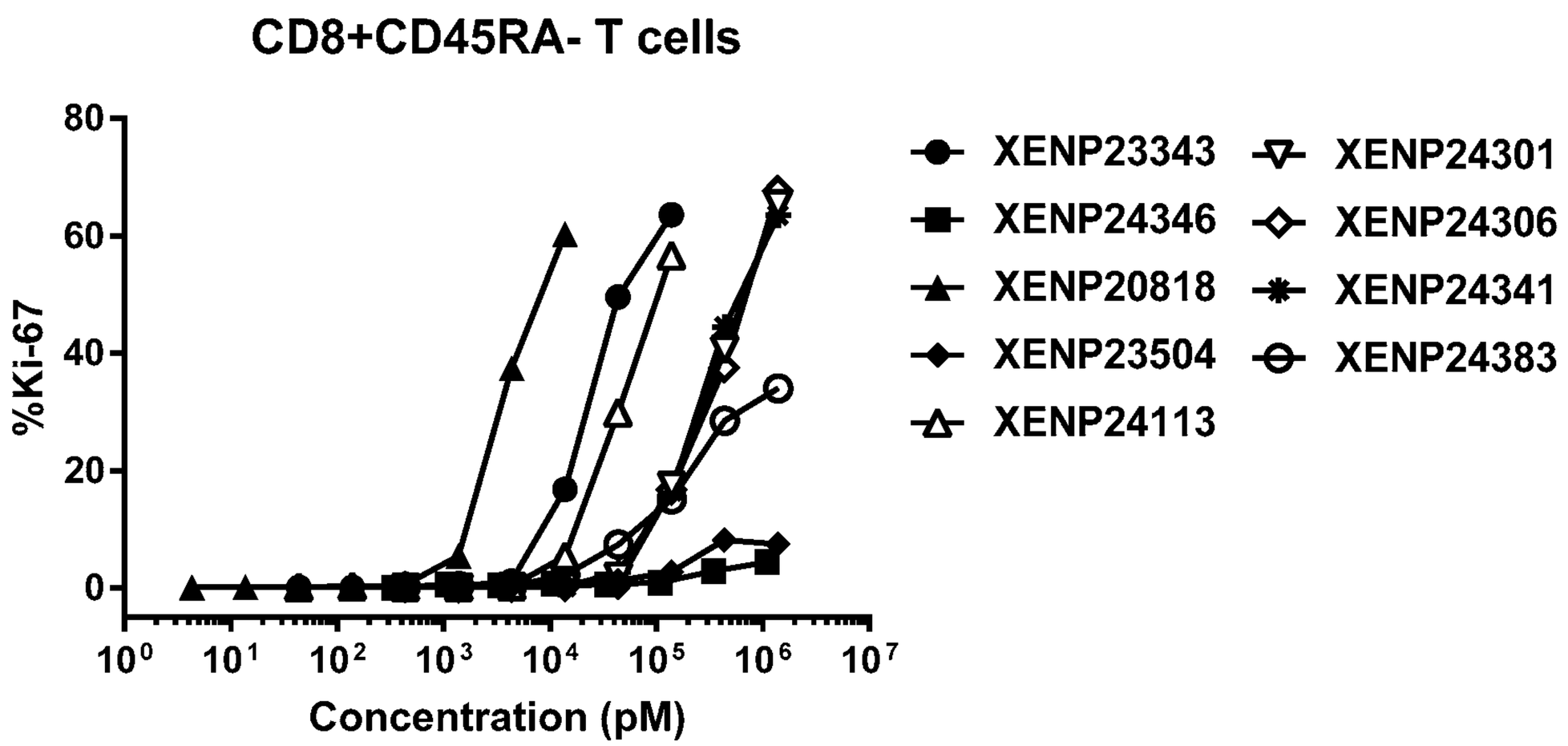


Figure 103B

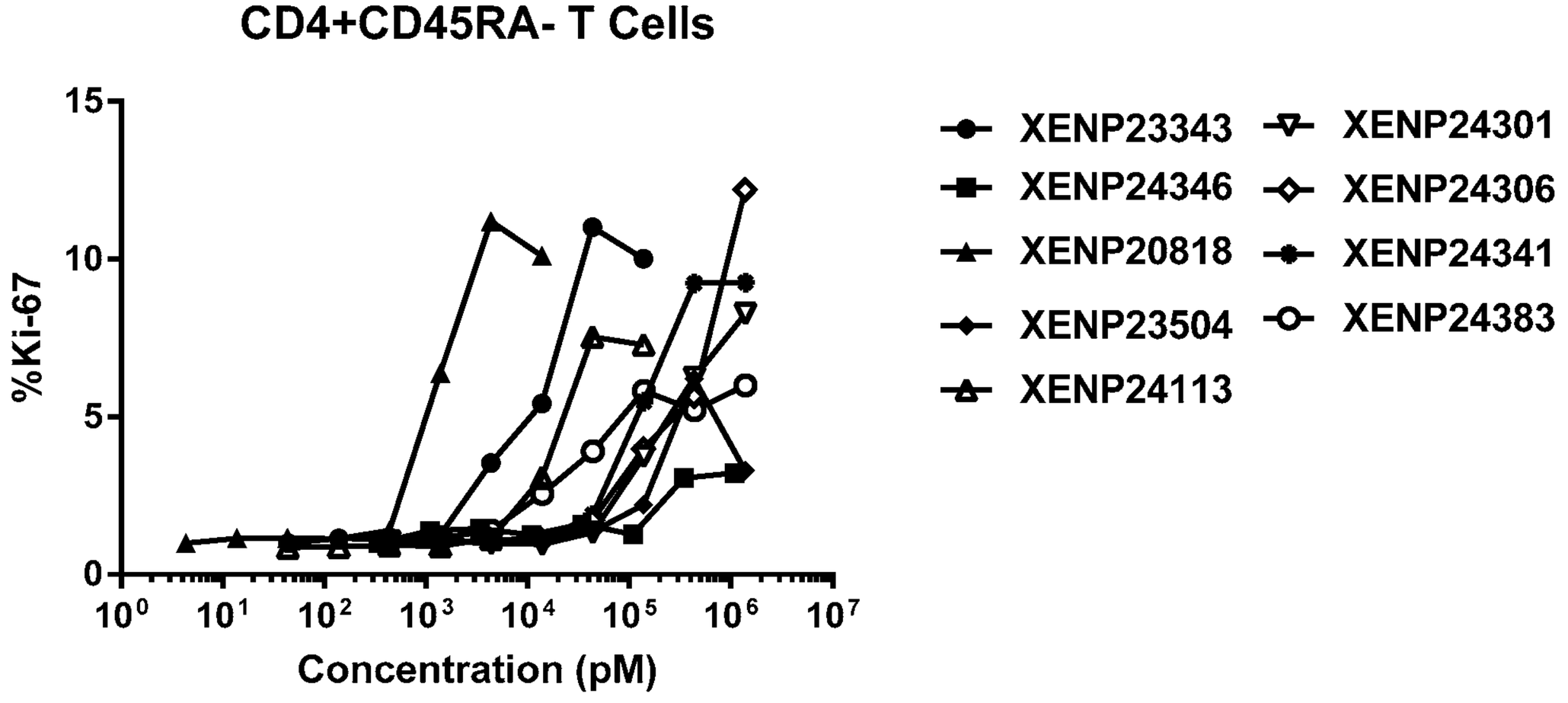


Figure 103C

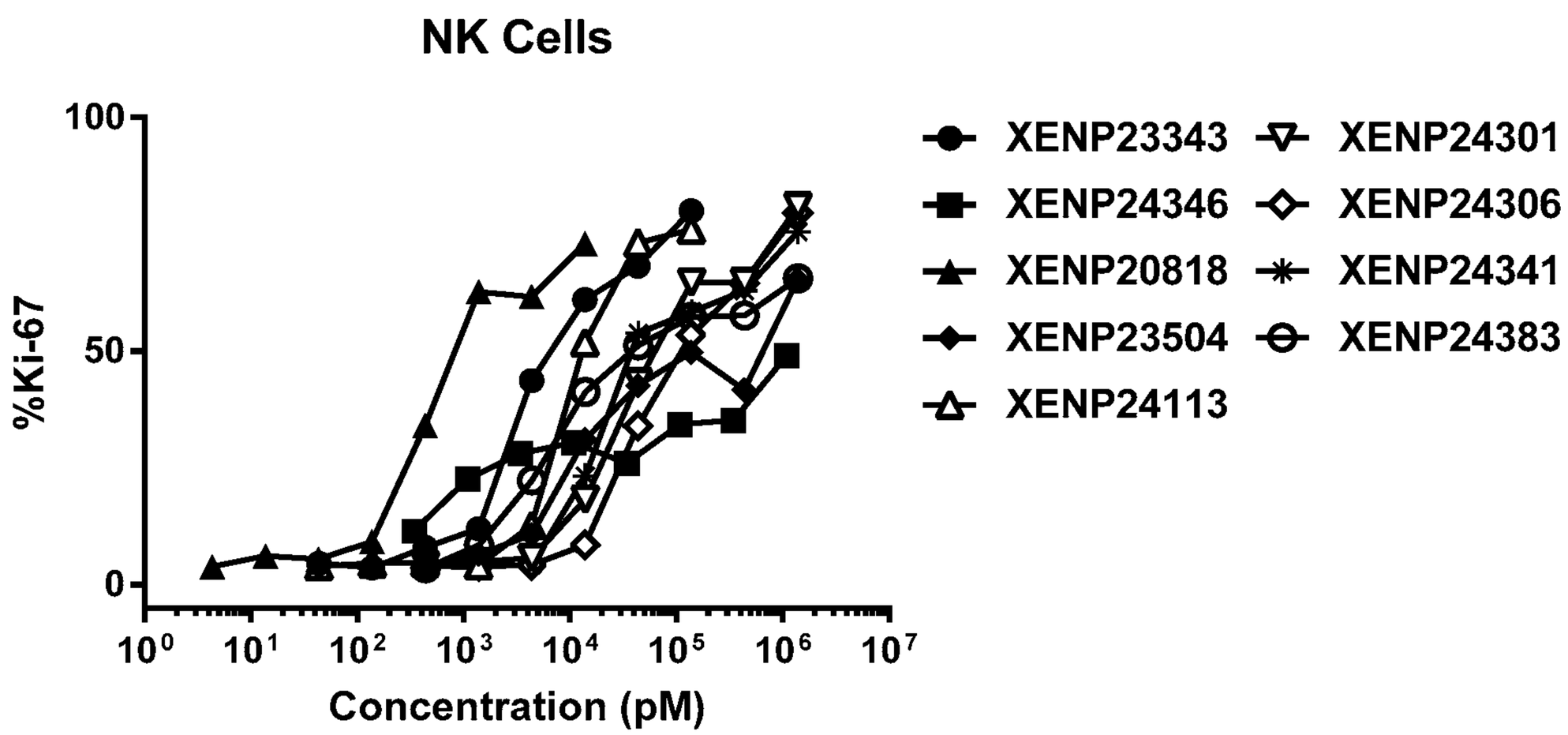

NK Cells
100
50
0
%Ki-67
10^0 10^1 10^2 10^3 10^4 10^5 10^6 10^7
Concentration (pM)
XENP23343
XENP24301
XENP24346
XENP24306
XENP20818
XENP24341
XENP23504
XENP24383
XENP24113

Figure 104A

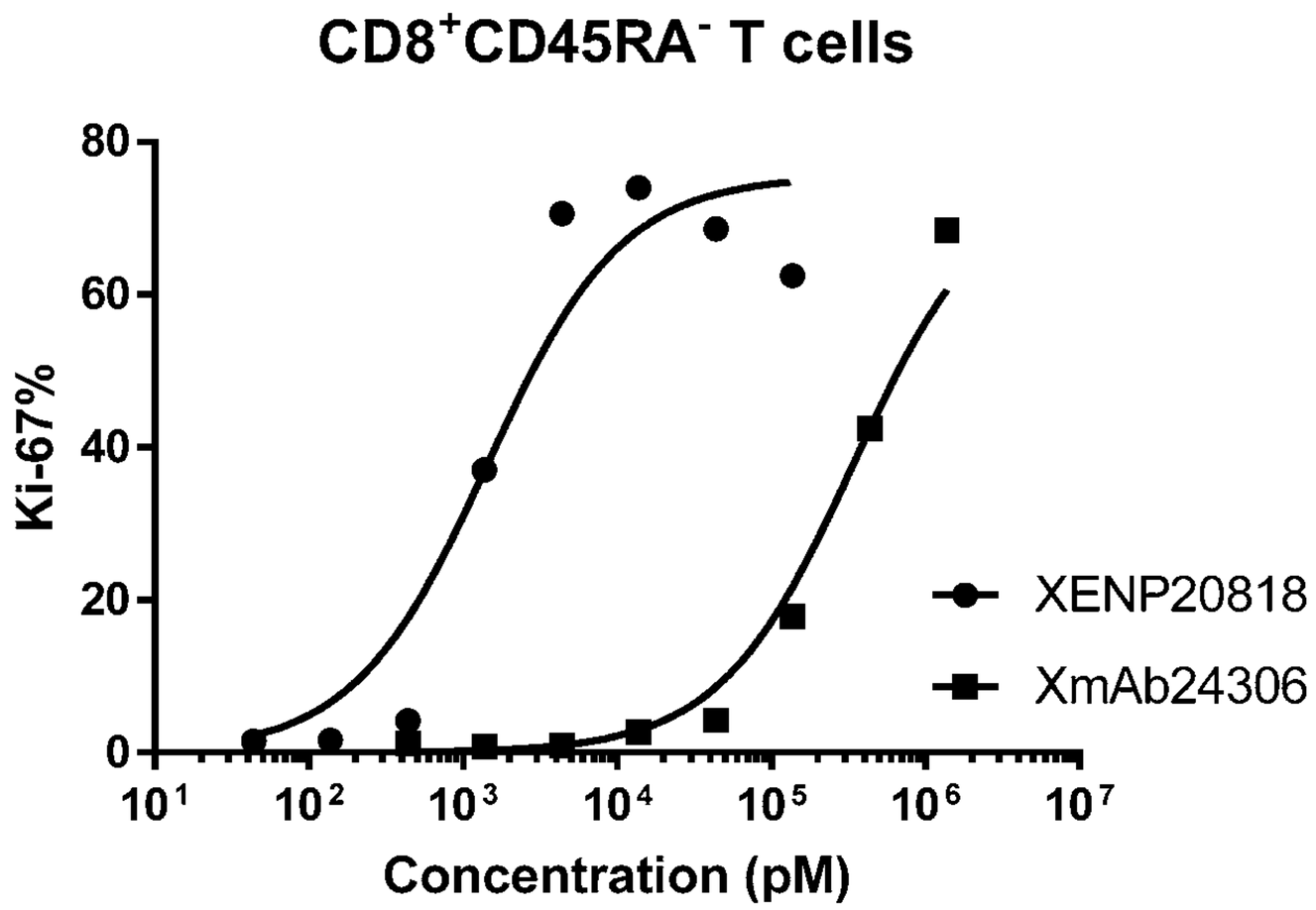


Figure 104B

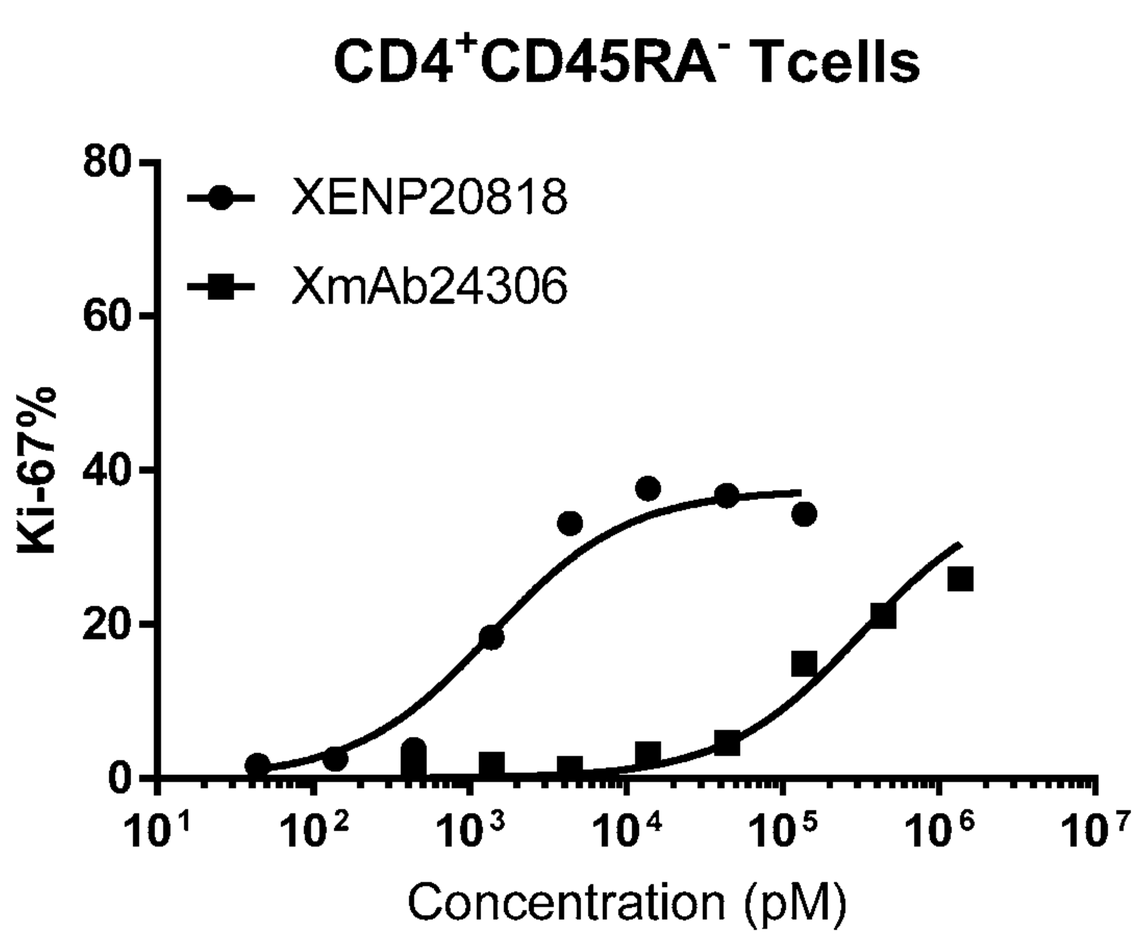


Figure 104C

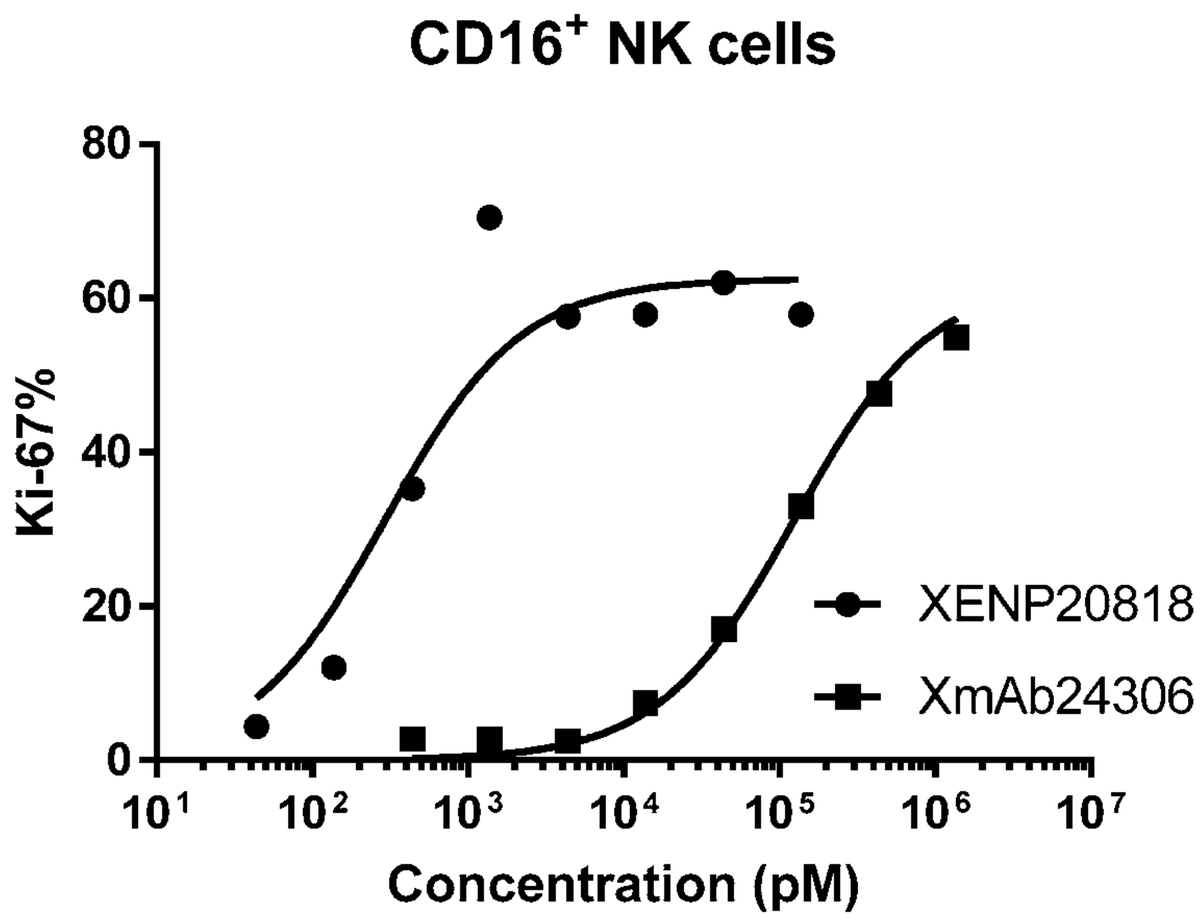


Figure 104D

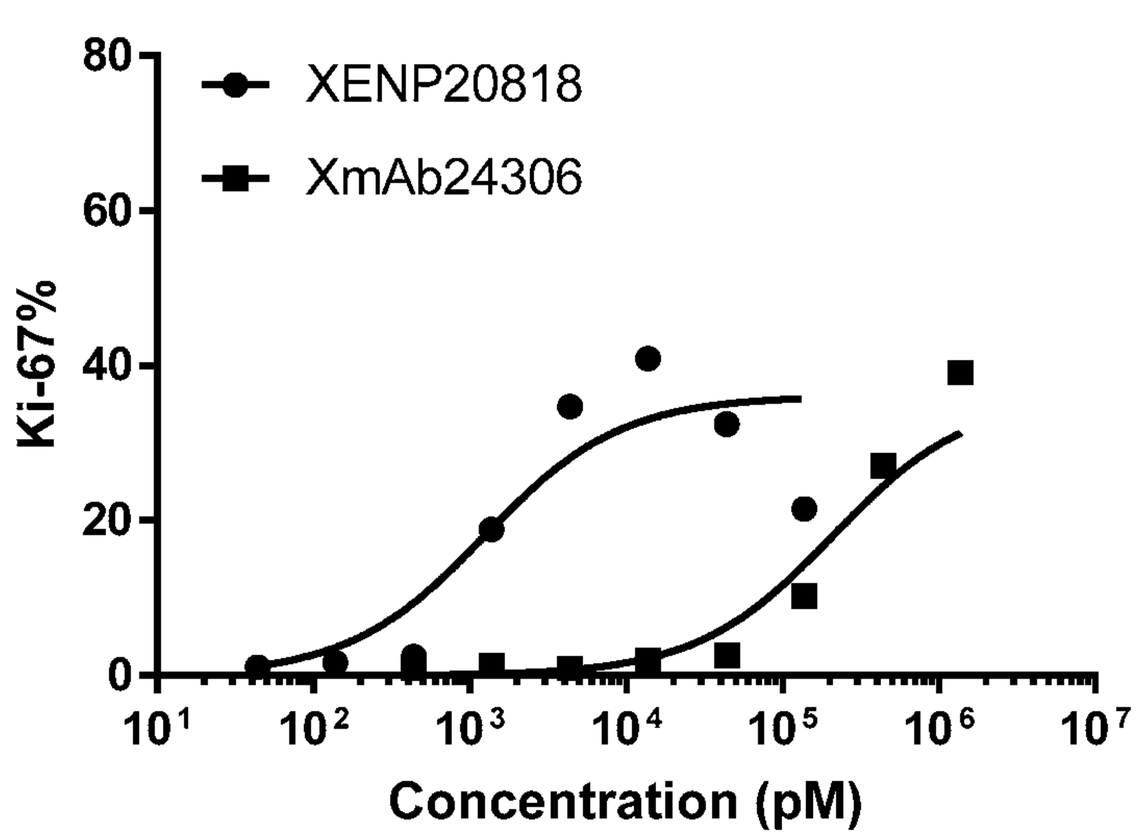


Figure 105A

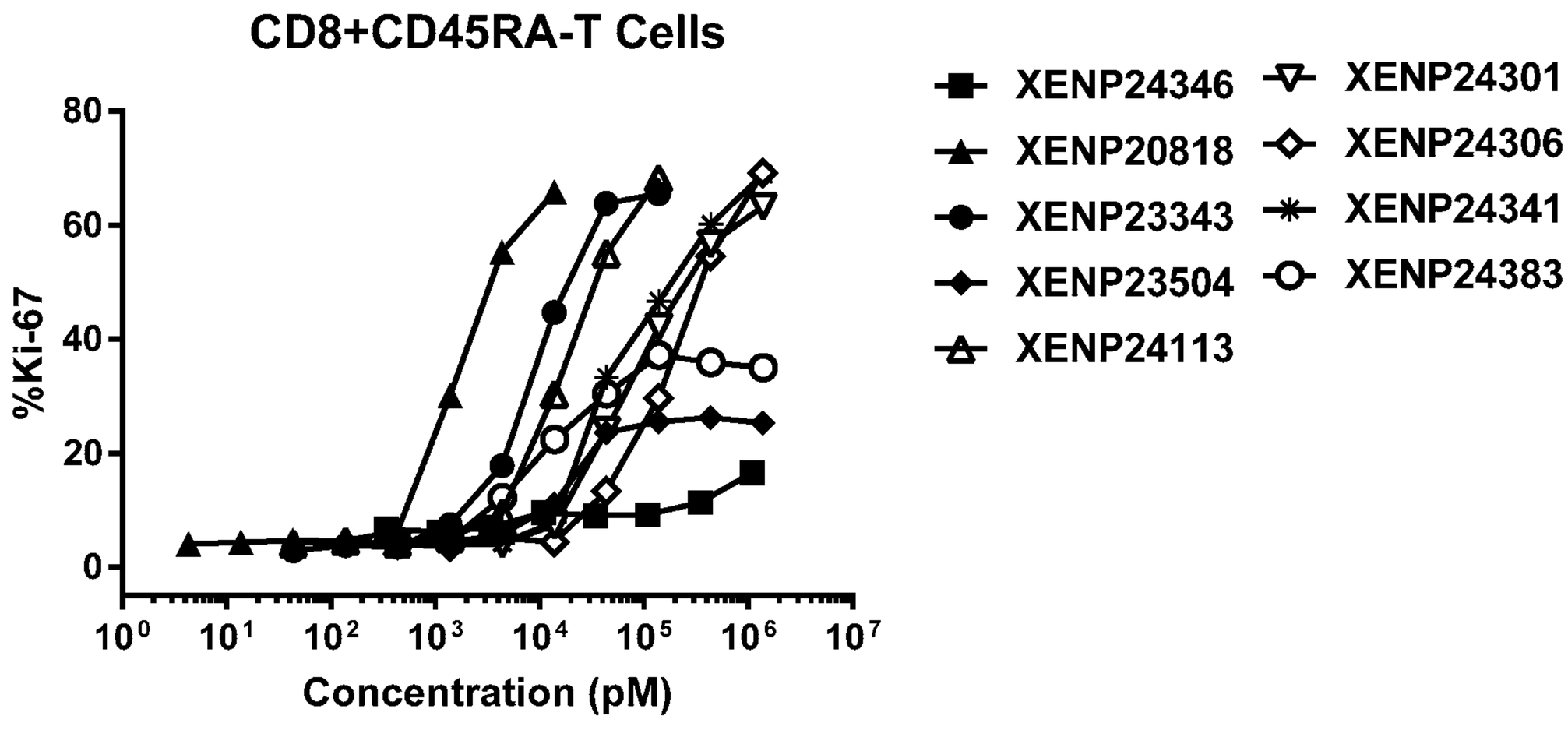


Figure 105B

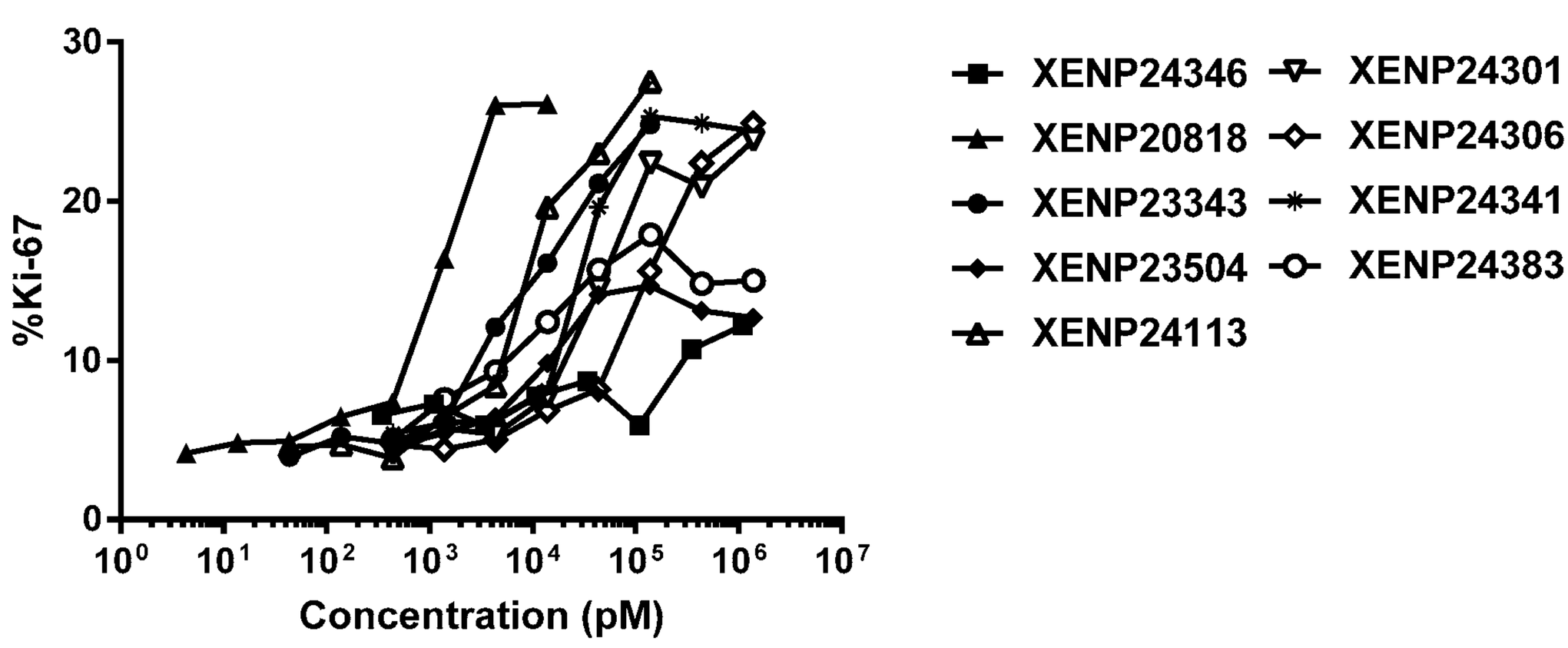


Figure 105C

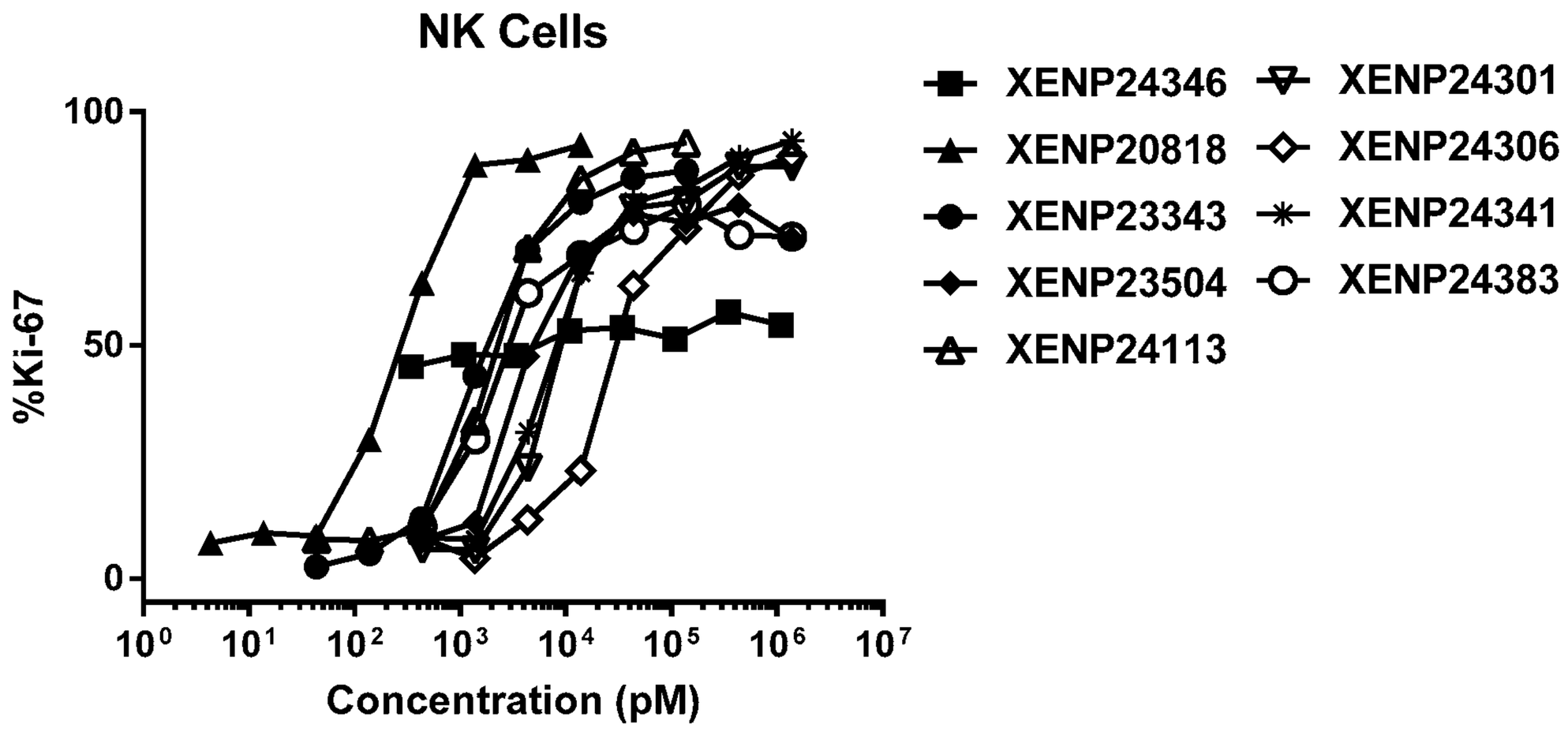

NK Cells
XENP24346
XENP24301
XENP20818
XENP24306
XENP23343
XENP24341
XENP23504
XENP24383
XENP24113
%Ki-67
100
50
0
10^0 10^1 10^2 10^3 10^4 10^5 10^6 10^7
Concentration (pM)

Figure 106

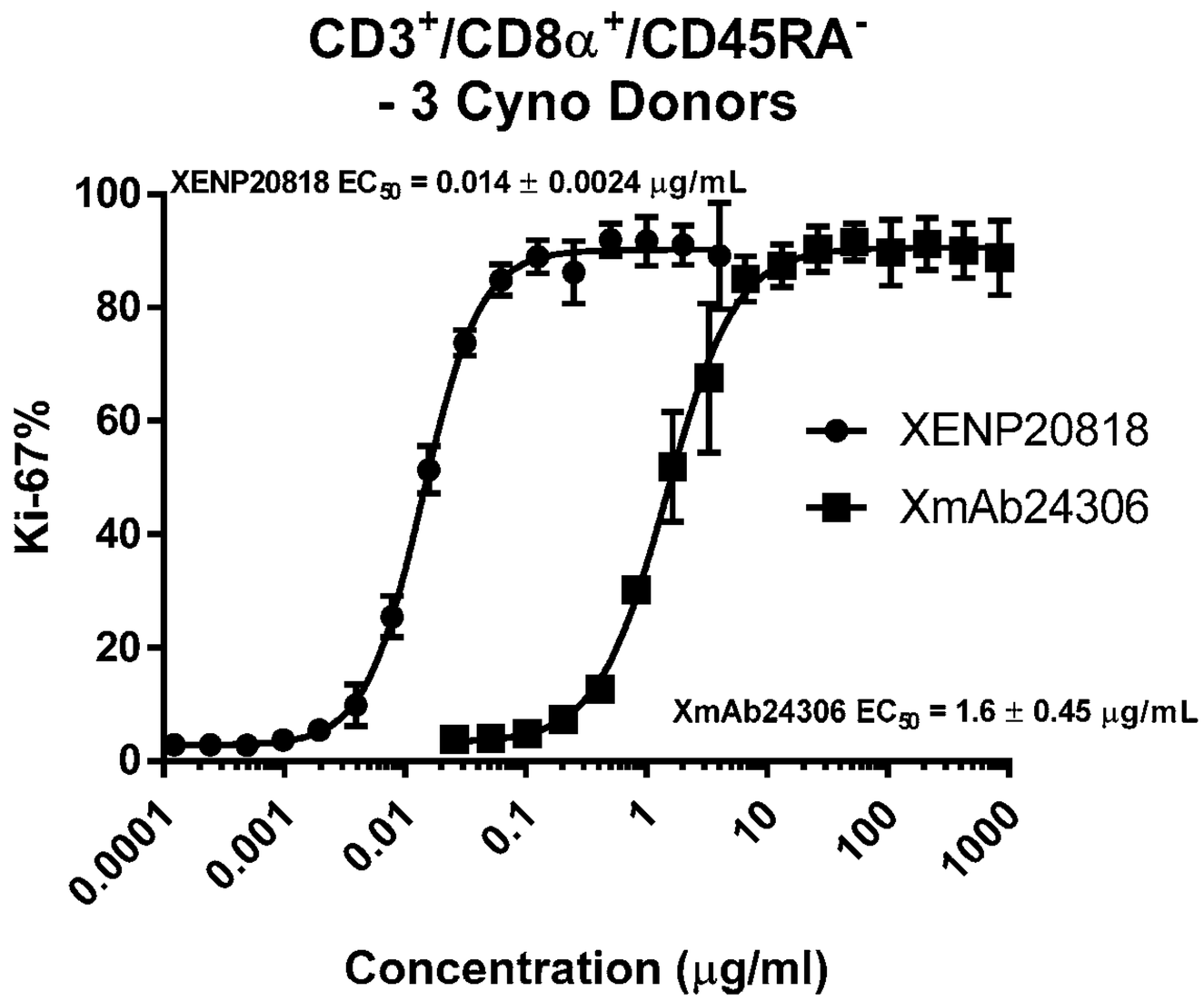

CD3+/CD8α+/CD45RA-
- 3 Cyno Donors
XENP20818 EC50 = 0.014 ± 0.0024 μg/mL
XmAb24306 EC50 = 1.6 ± 0.45 μg/mL
XENP20818
XmAb24306
Ki-67%
100
80
60
40
20
0
0.0001
0.001
0.01
0.1
1
10
100
1000
Concentration (μg/ml)

Figure 107A

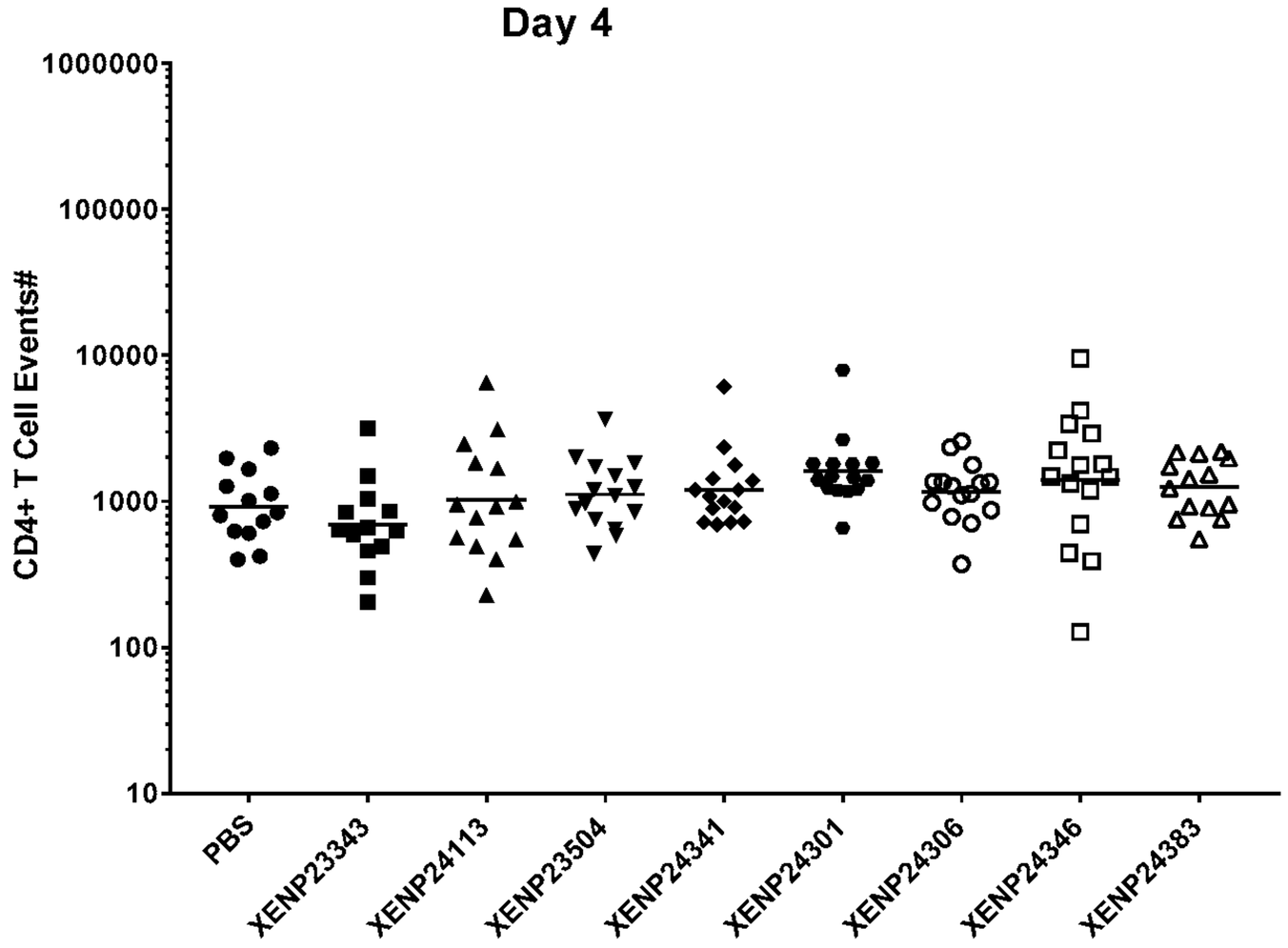


Figure 107B

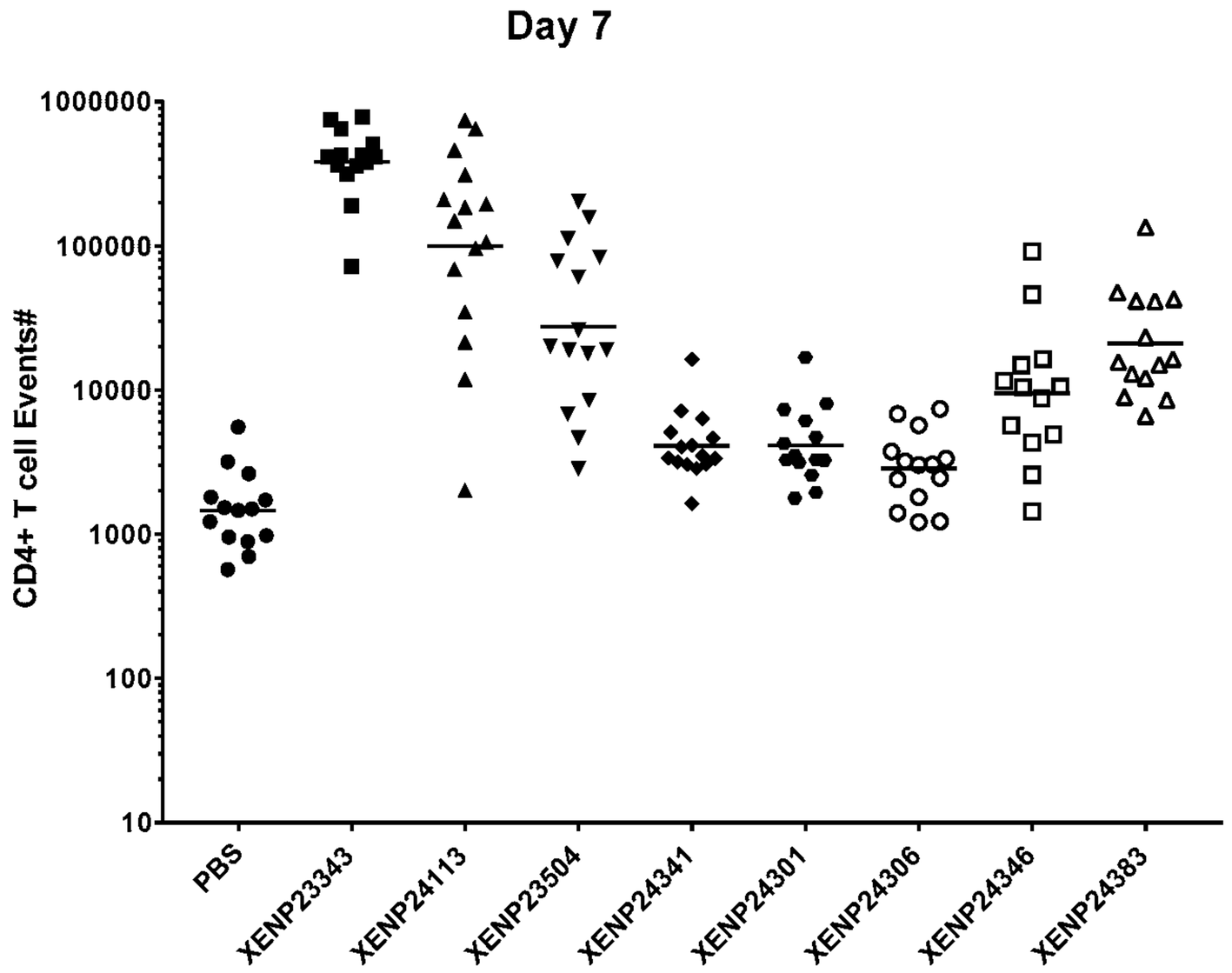


Figure 107C

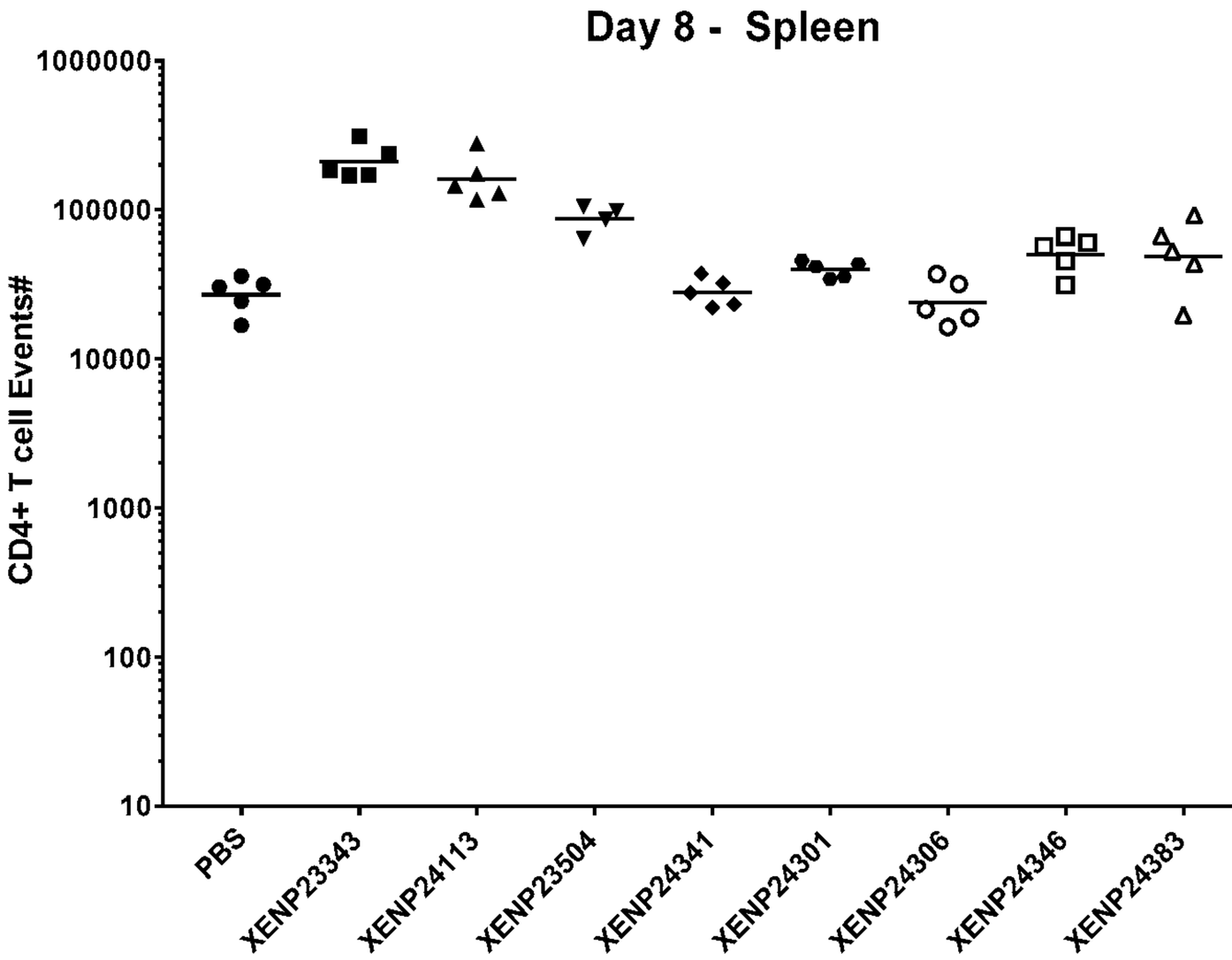

Day 8 - Spleen
CD4+ T cell Events#
1000000
100000
10000
1000
100
10
PBS
XENP23343
XENP24113
XENP23504
XENP24341
XENP24301
XENP24306
XENP24346
XENP24383

Figure 108A

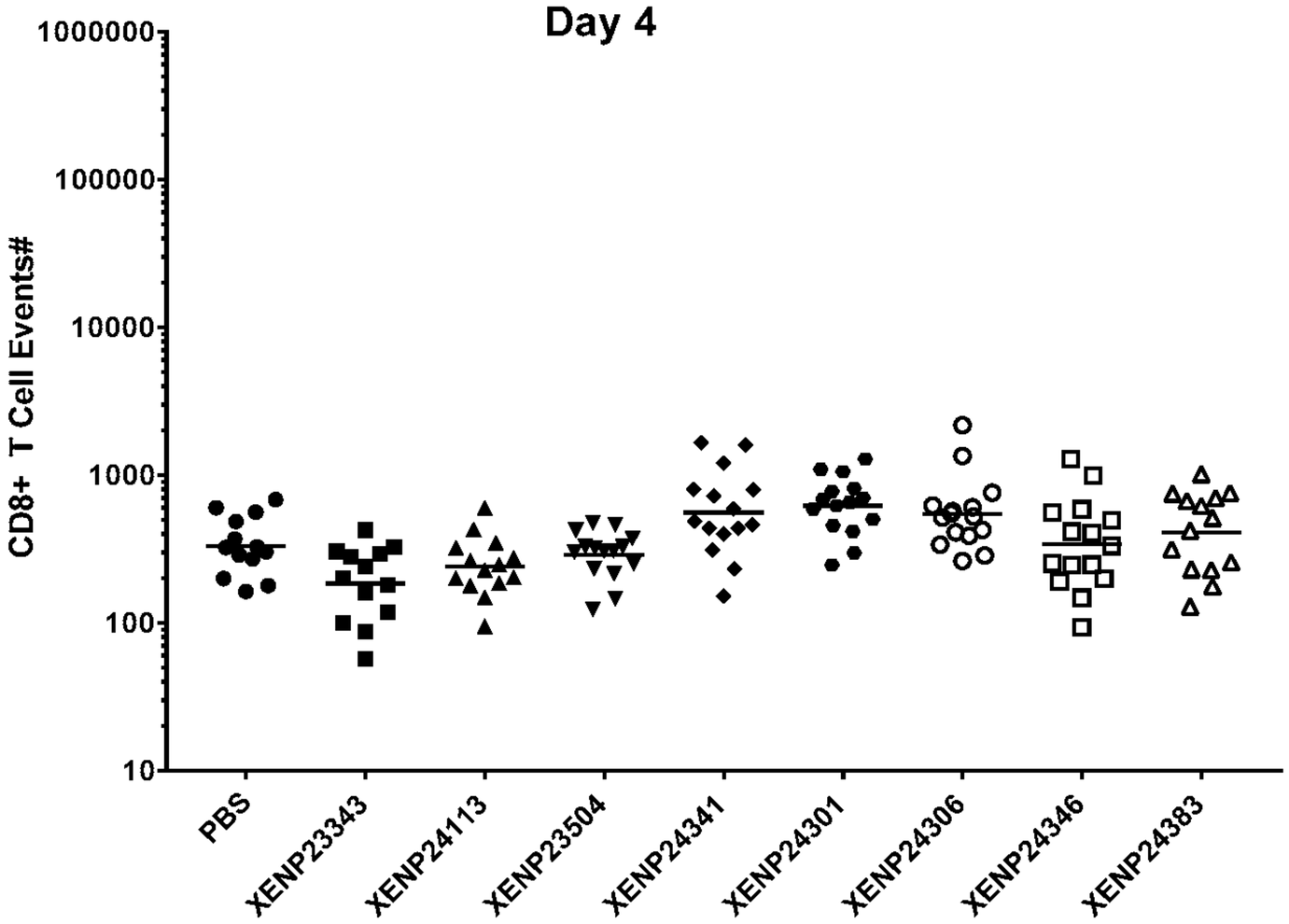


Figure 108B

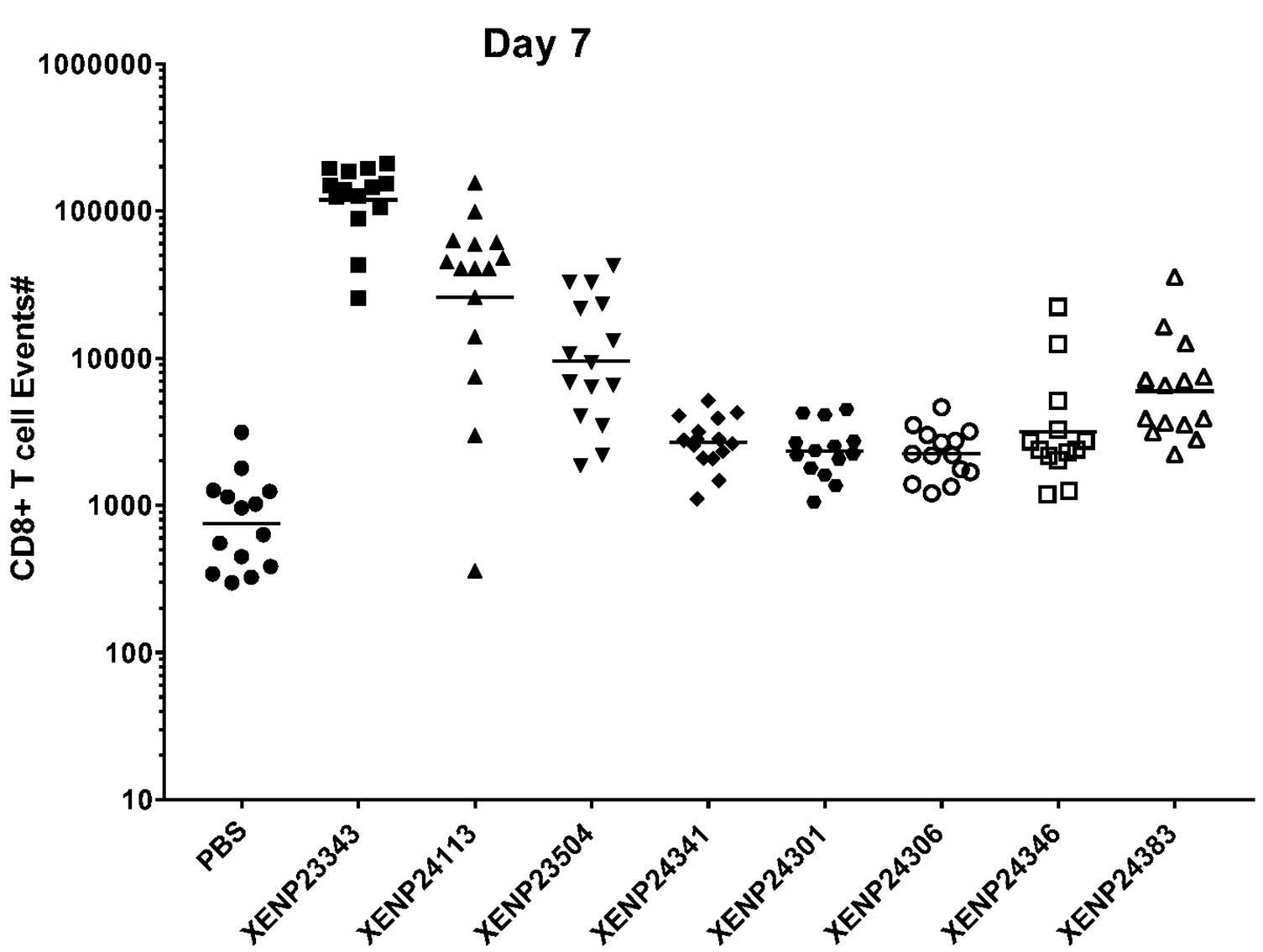


Figure 108C

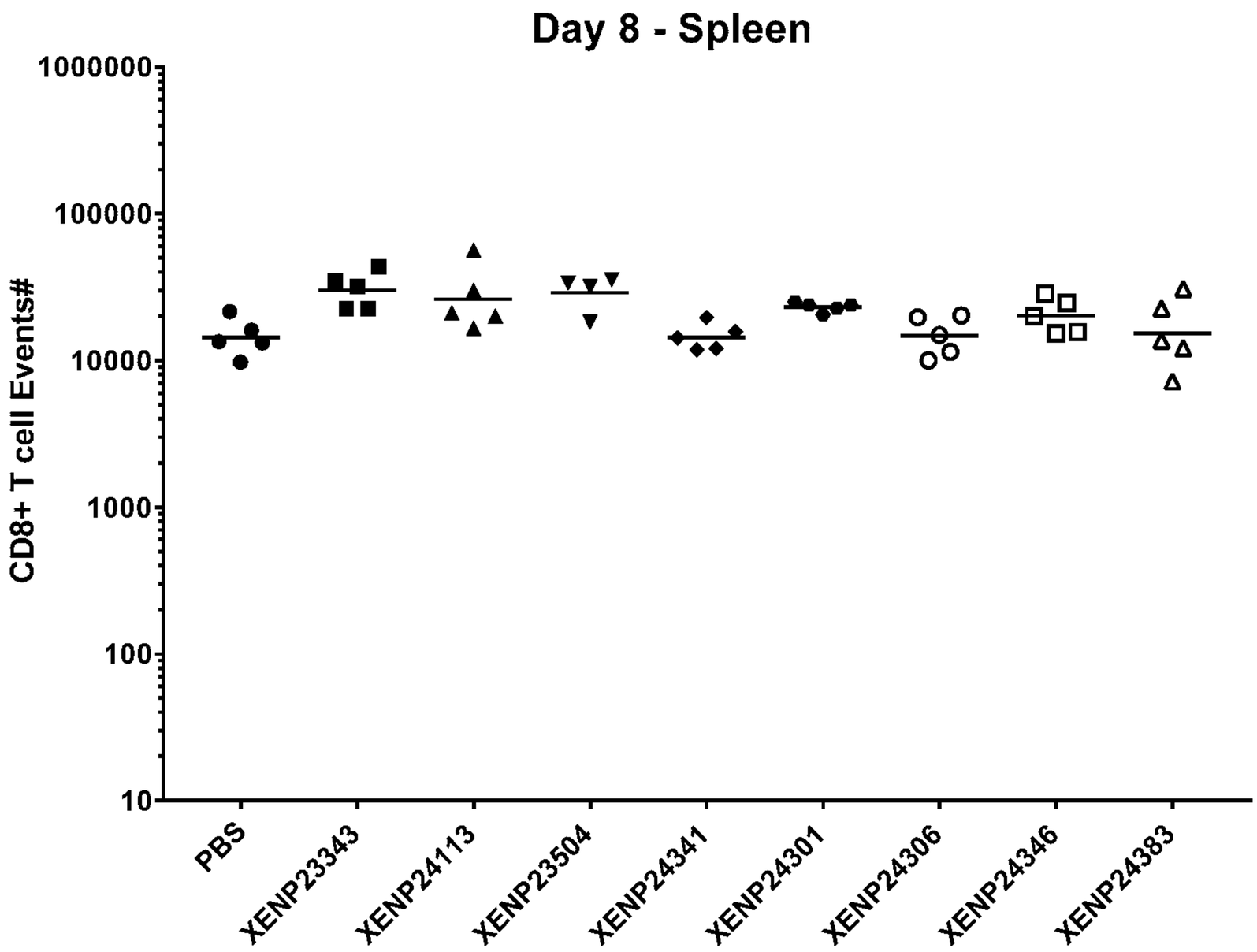

Day 8 - Spleen
CD8+ T cell Events#
1000000
100000
10000
1000
100
10
PBS
XENP23343
XENP24113
XENP23504
XENP24341
XENP24301
XENP24306
XENP24346
XENP24383

Figure 109A

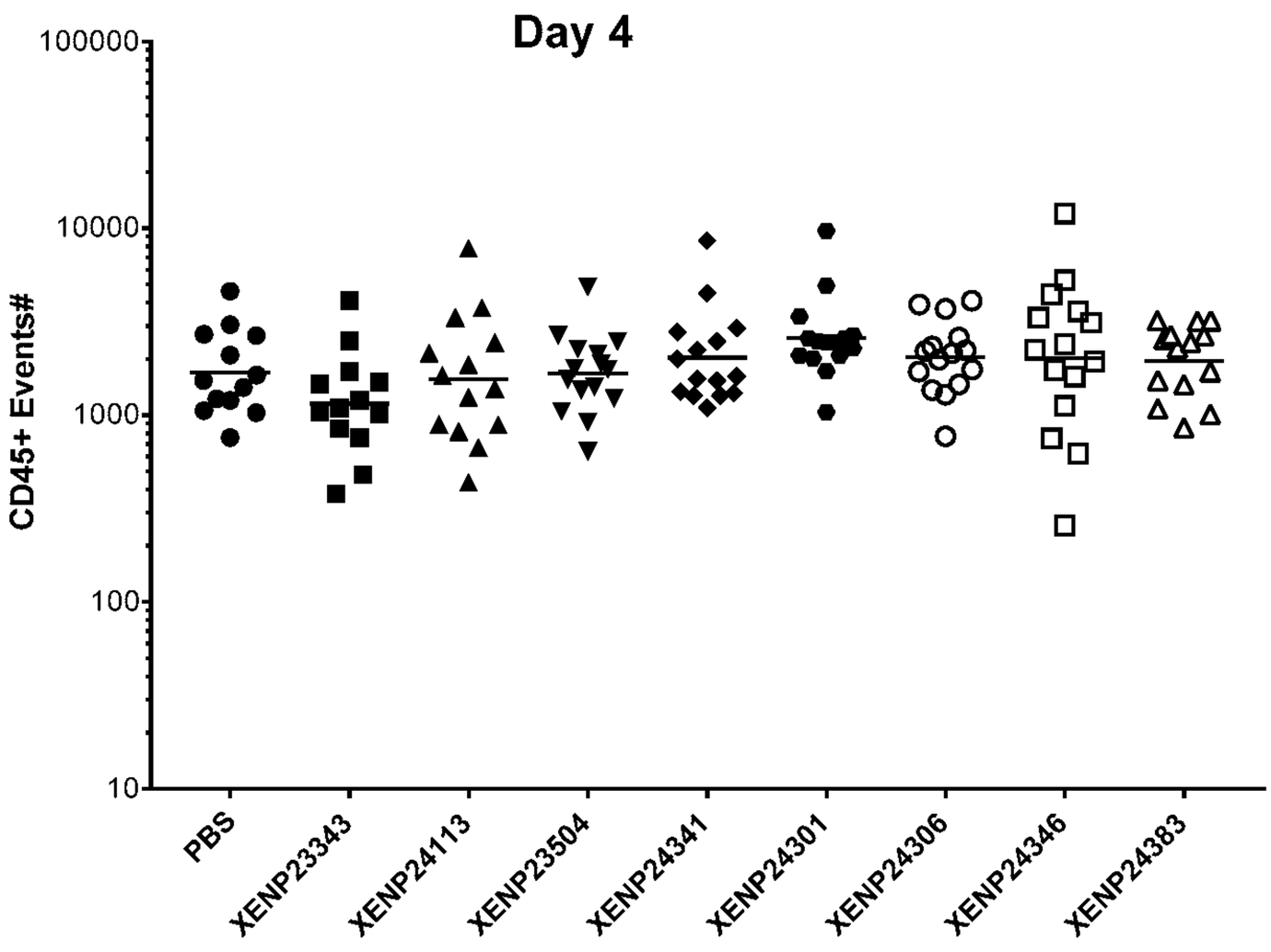


Figure 109B

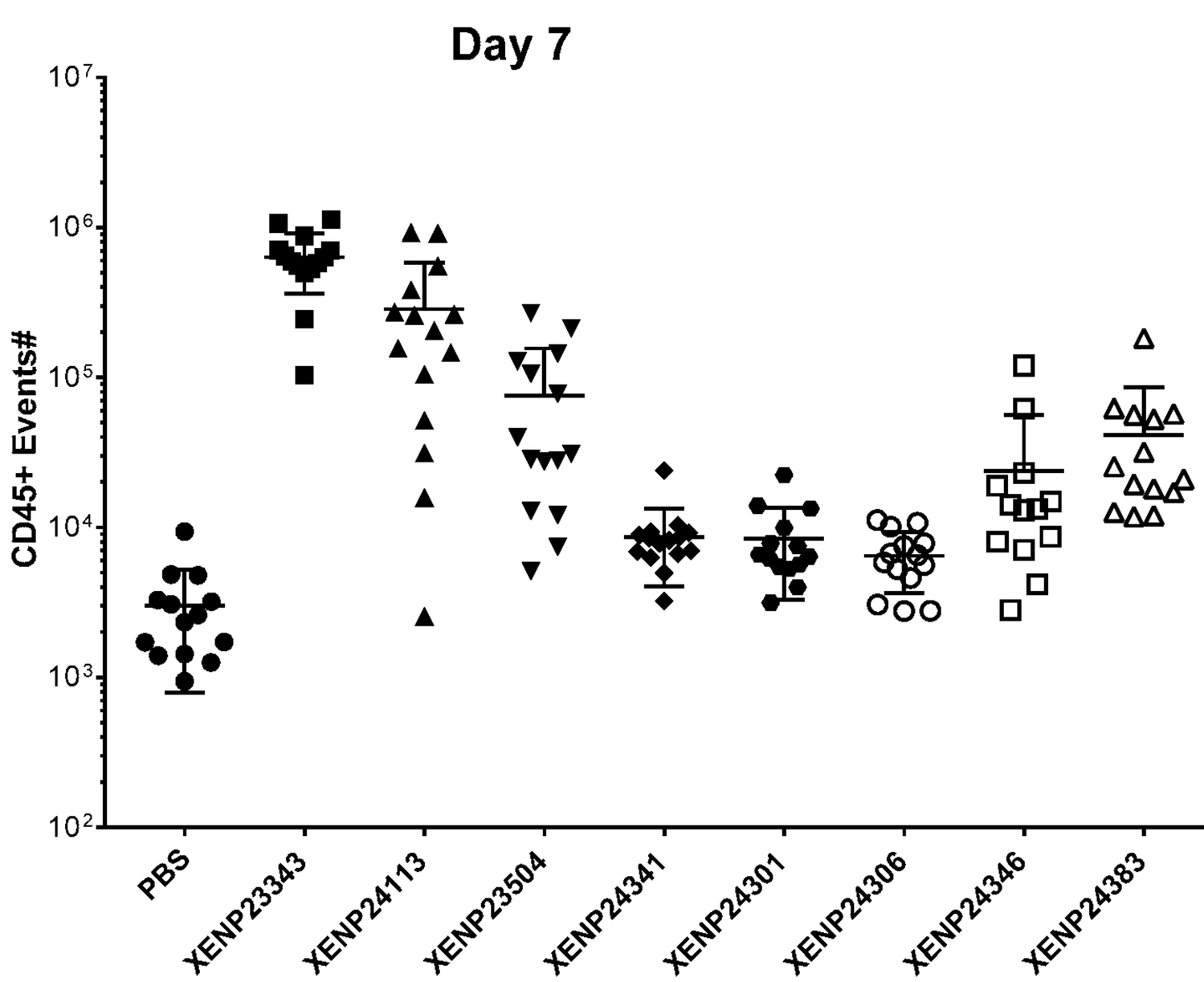


Figure 109C

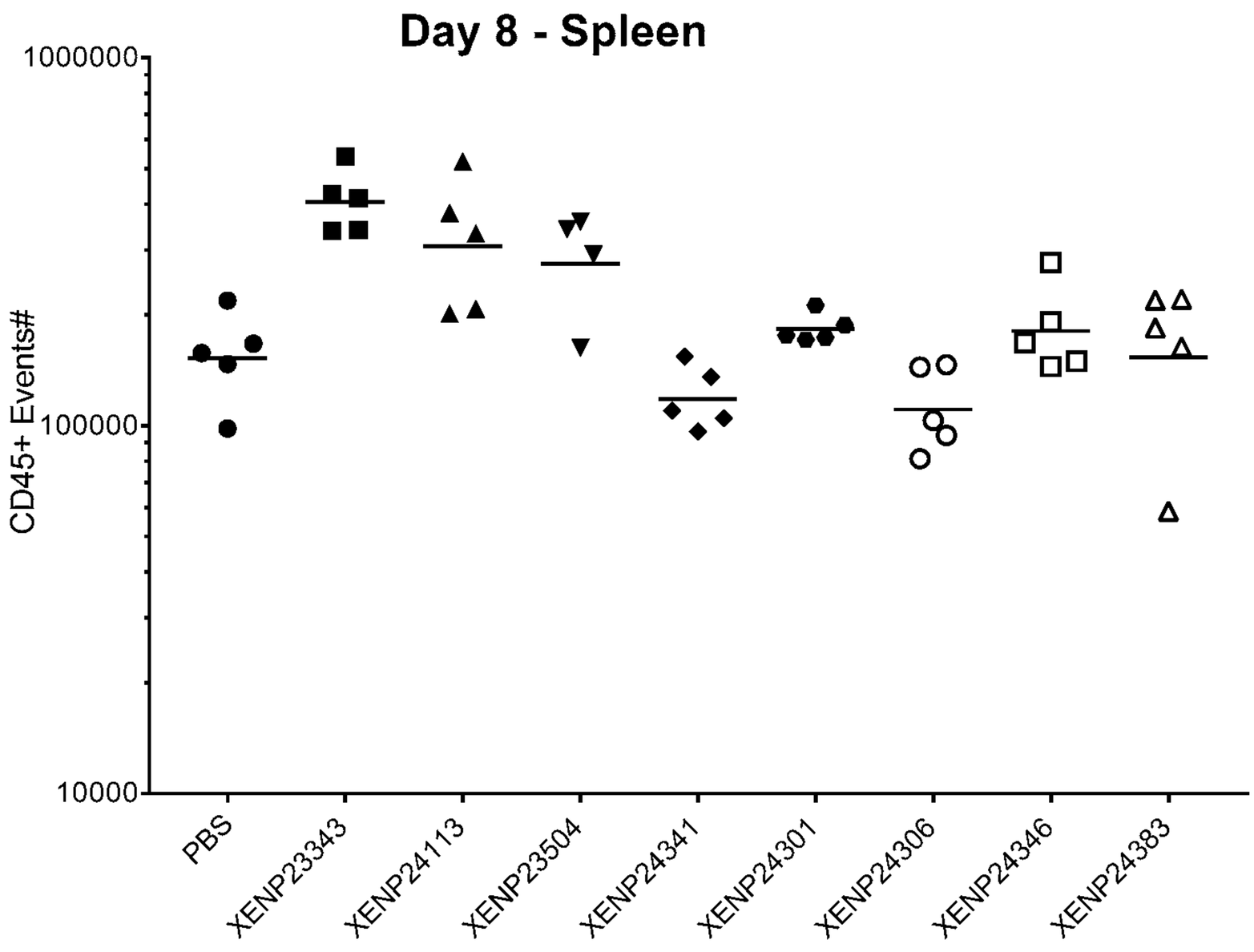

Day 8 - Spleen
CD45+ Events#
1000000
100000
10000
PBS
XENP23343
XENP24113
XENP23504
XENP24341
XENP24301
XENP24306
XENP24346
XENP24383

Figure 110A

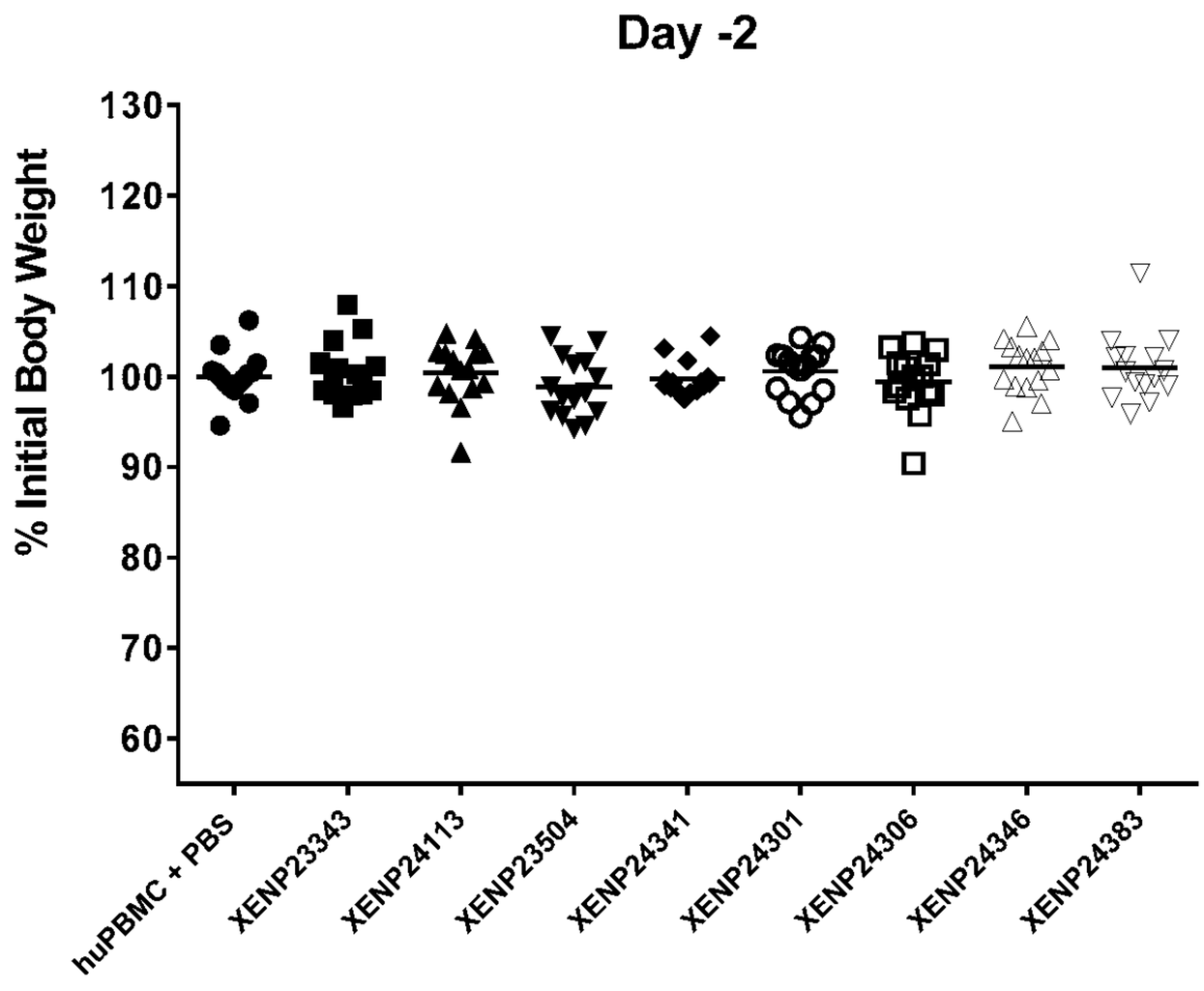


Figure 110B

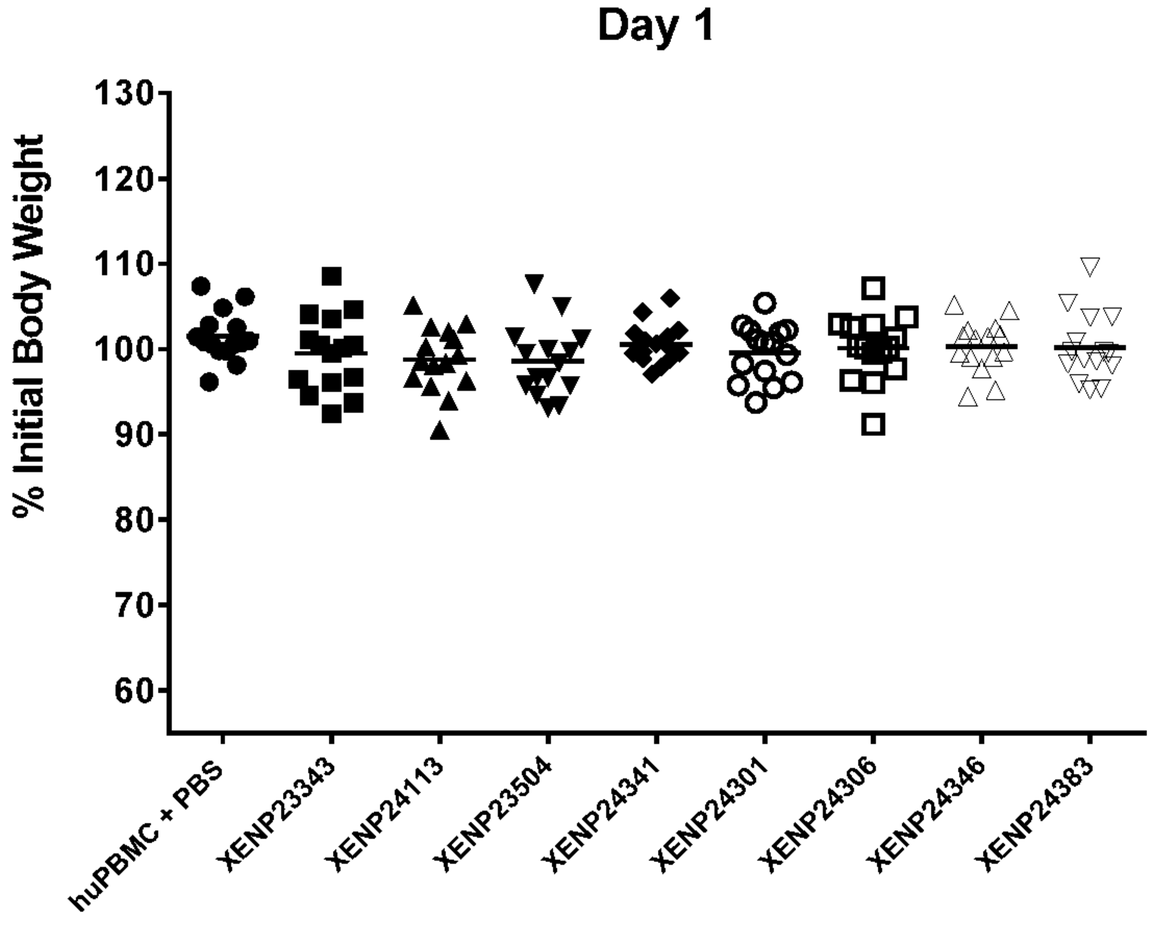


Figure 110C

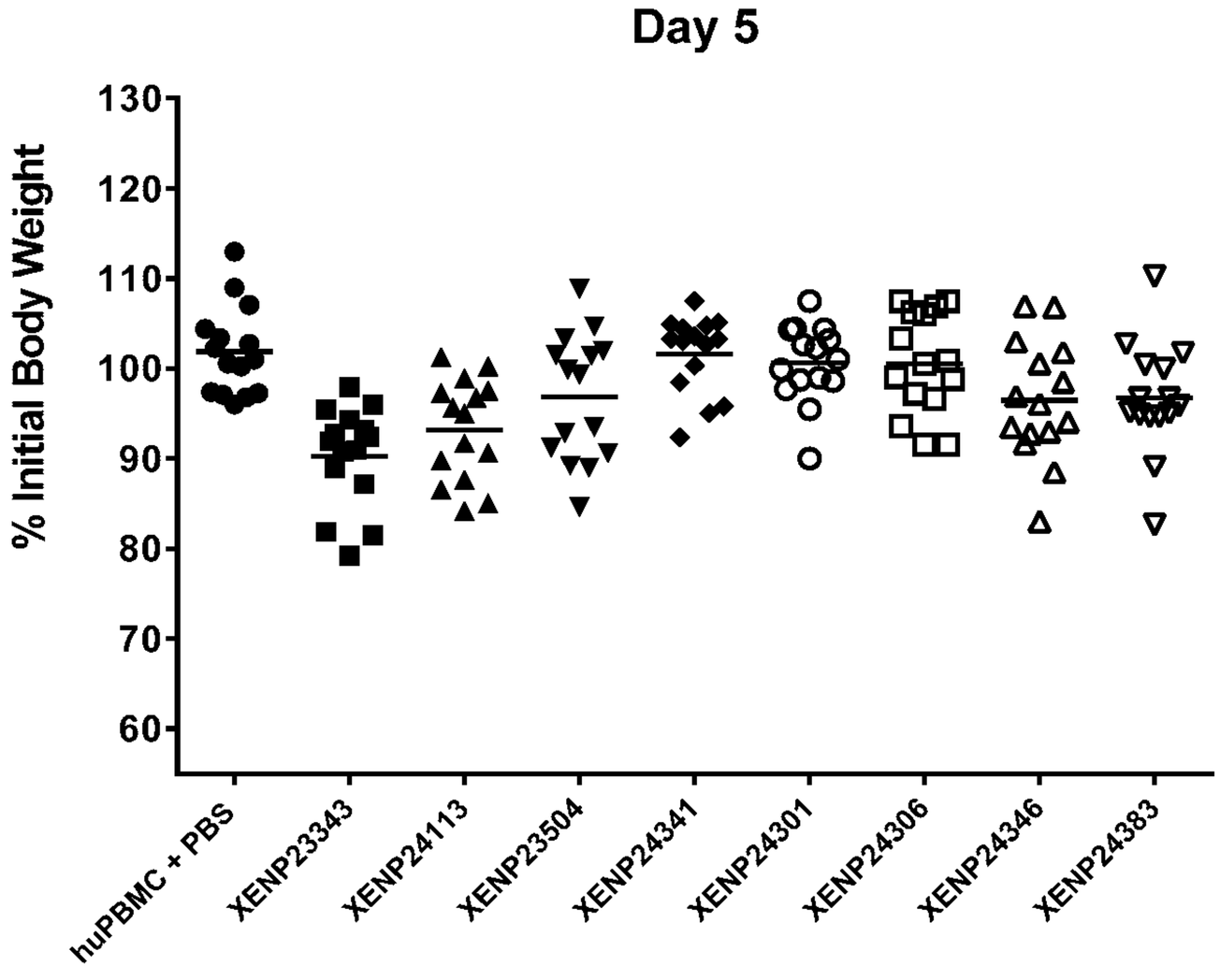


Figure 110D

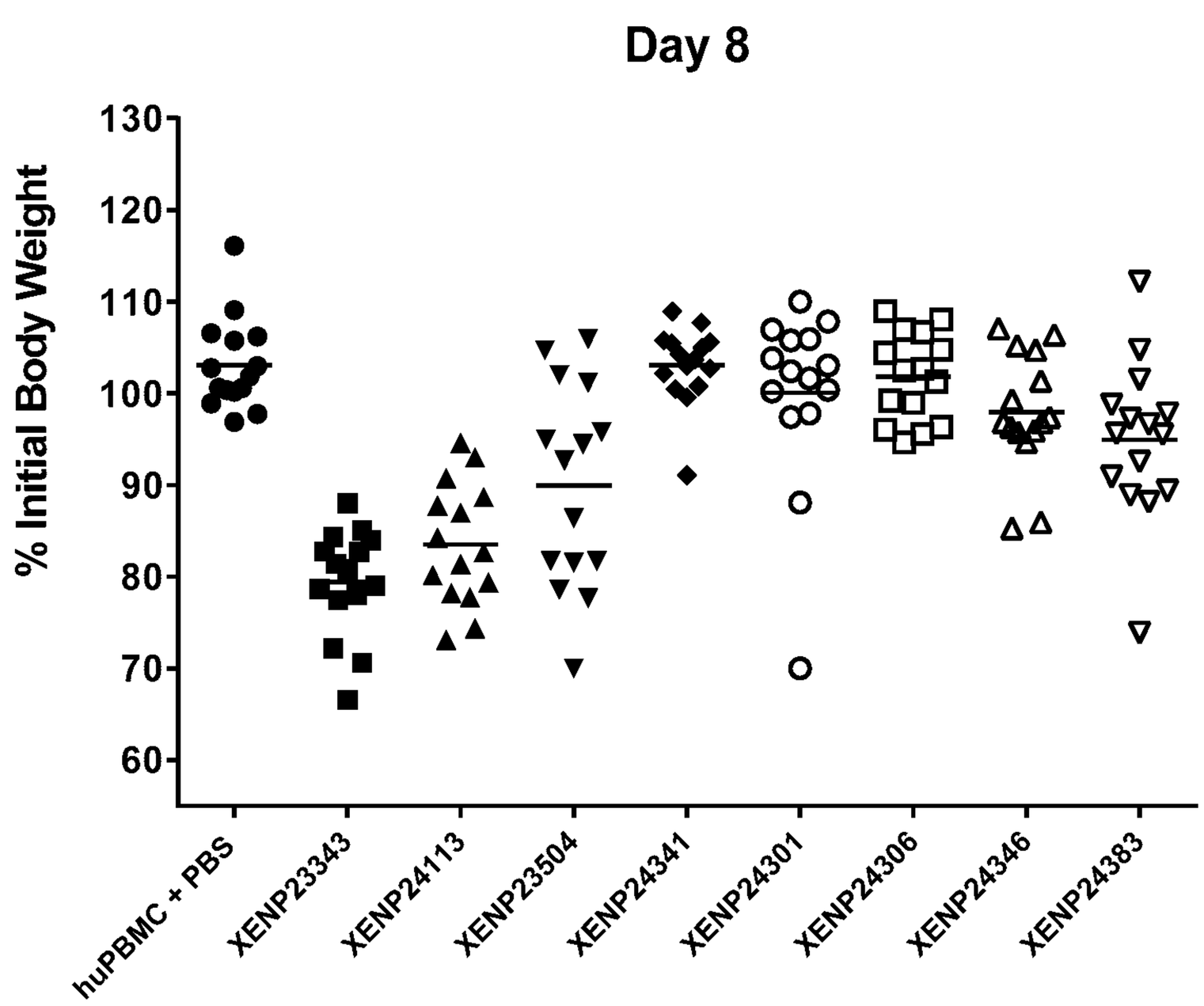


Figure 110E

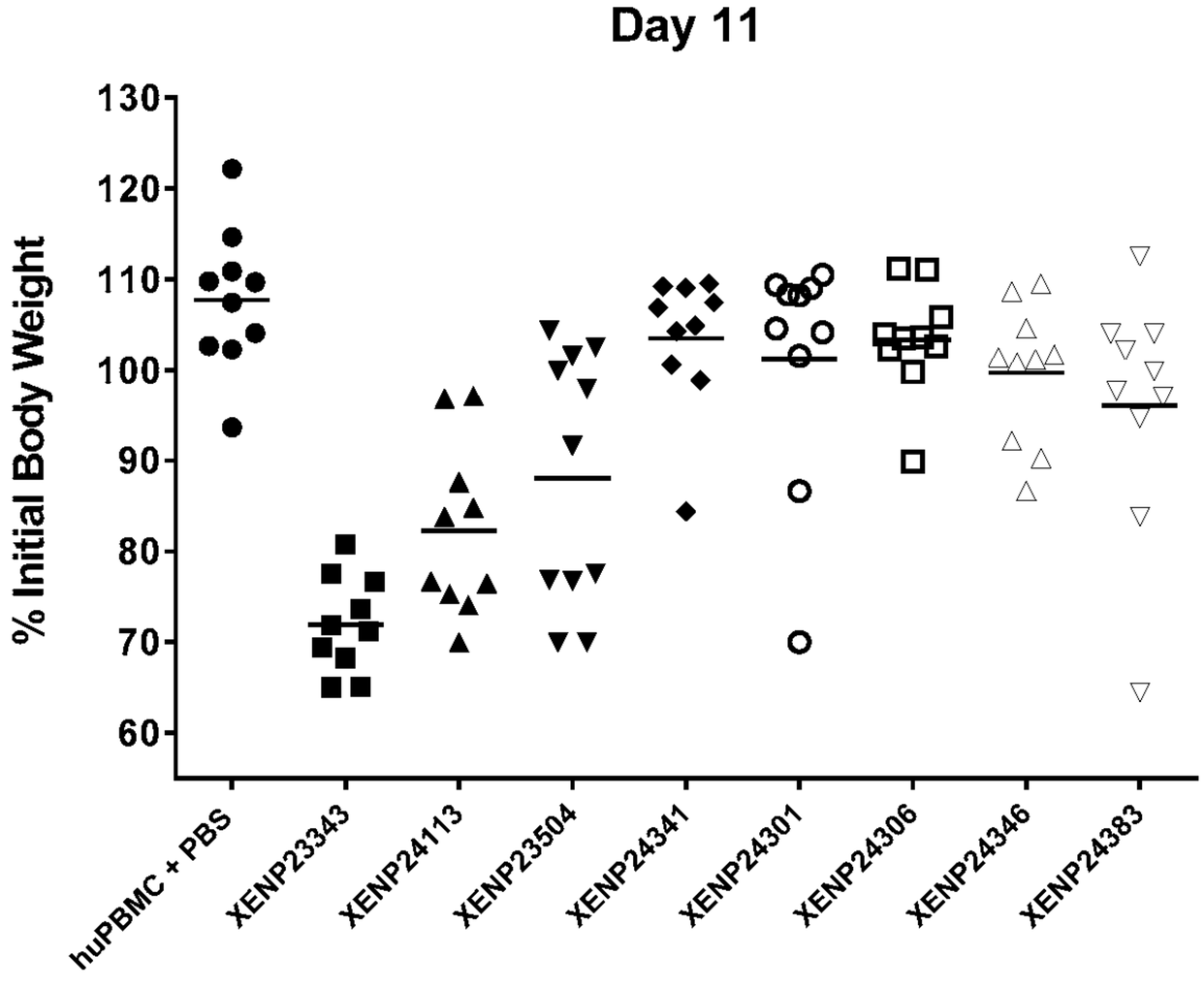


Figure 110F

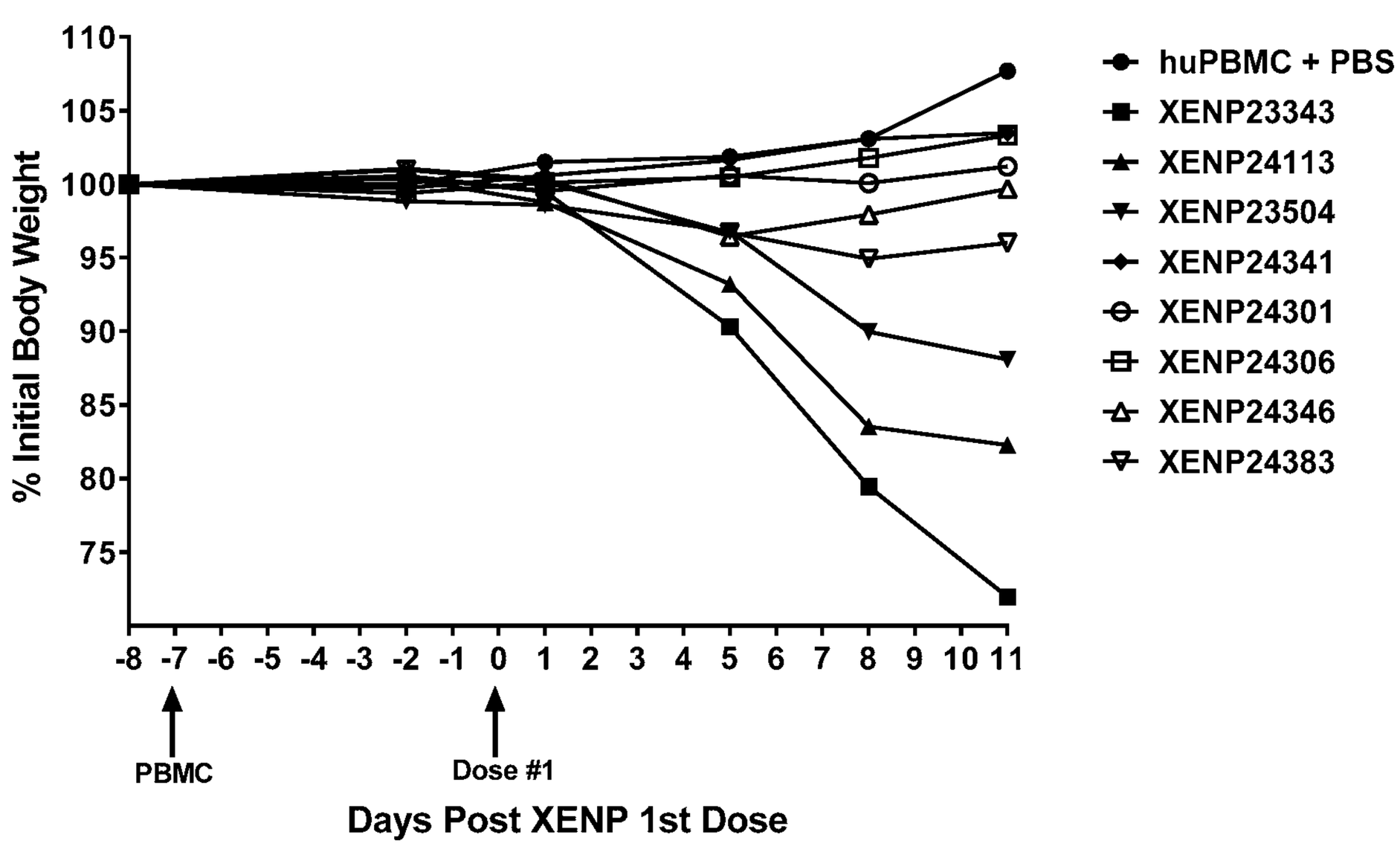


Figure 111A

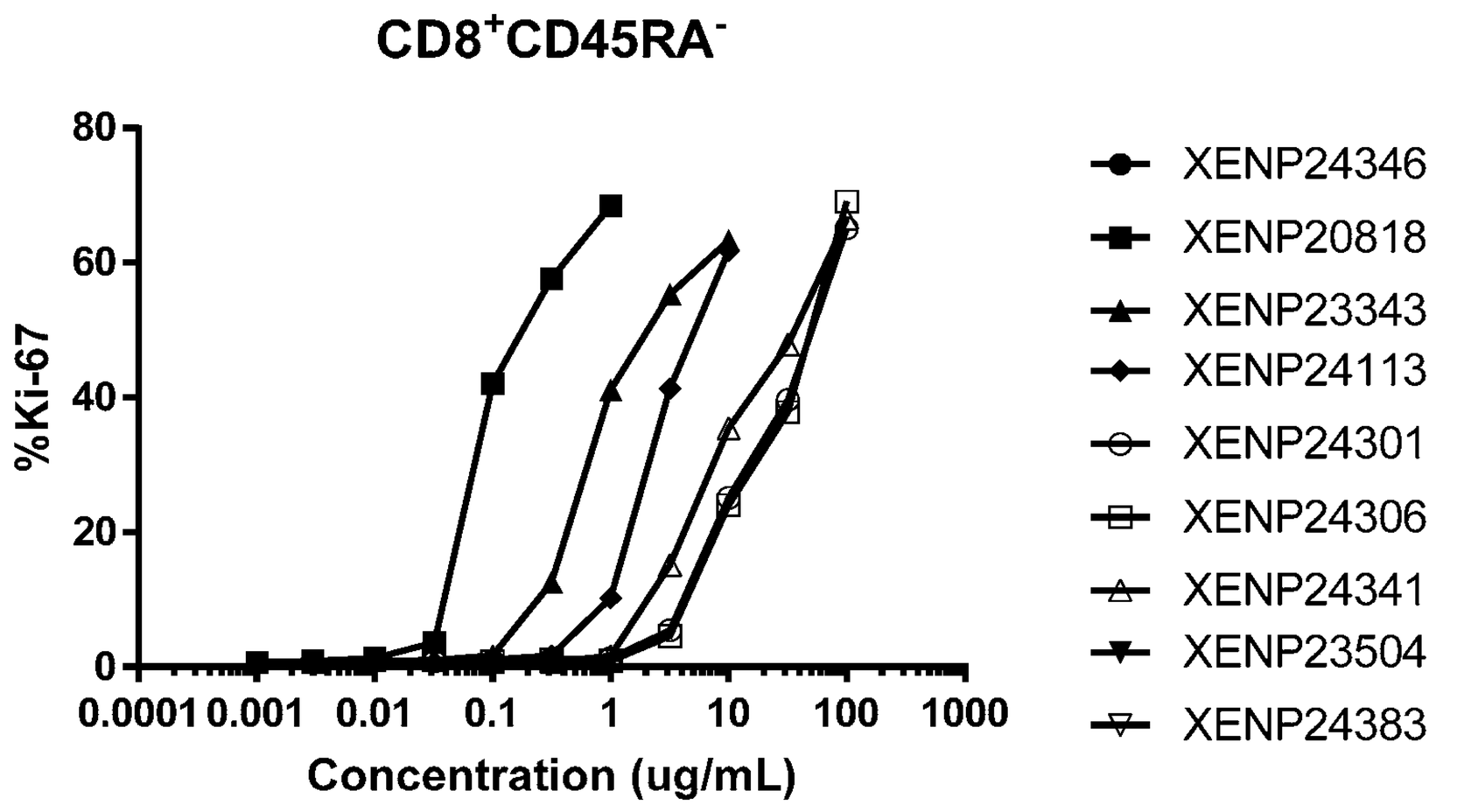


Figure 111B

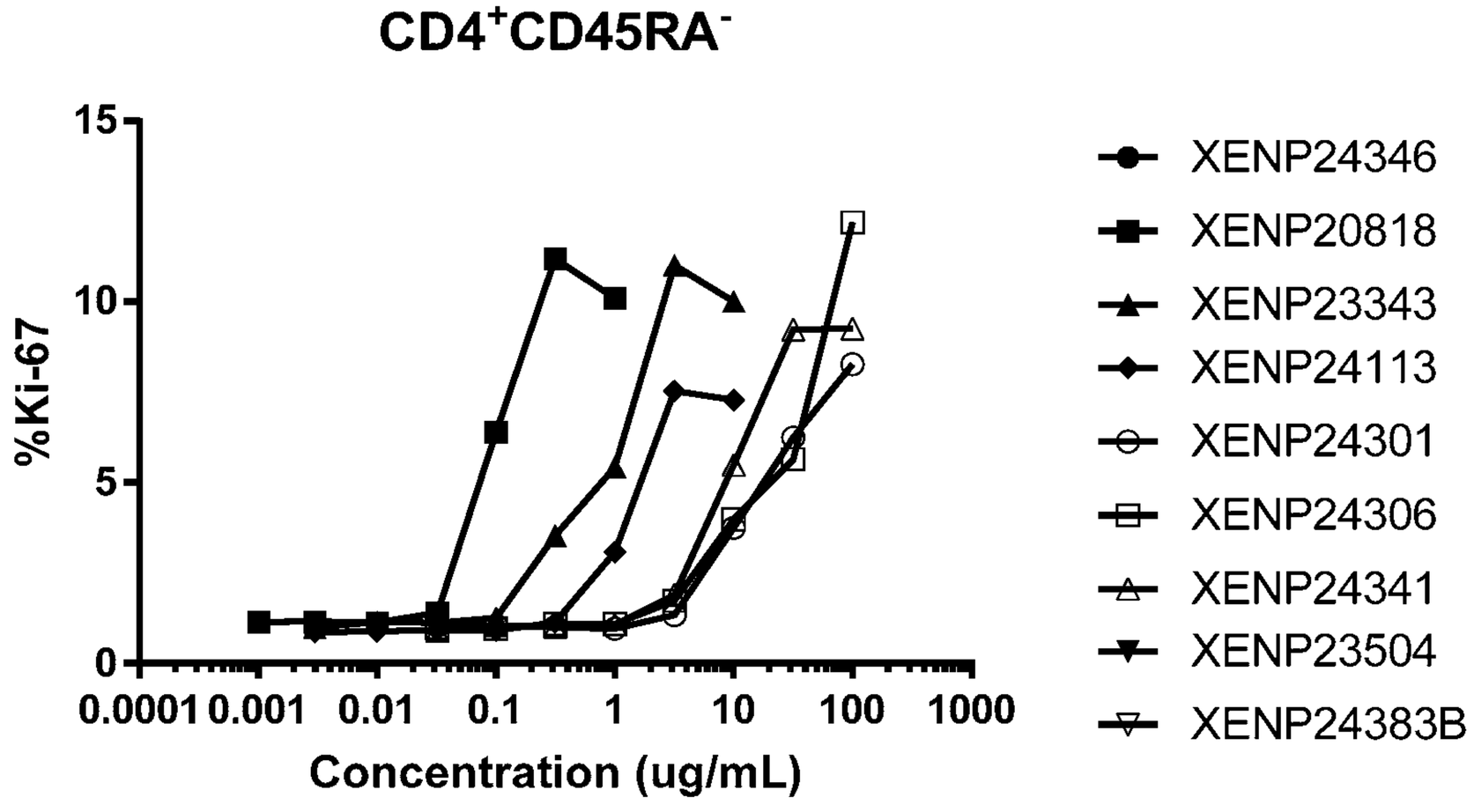


Figure 111C

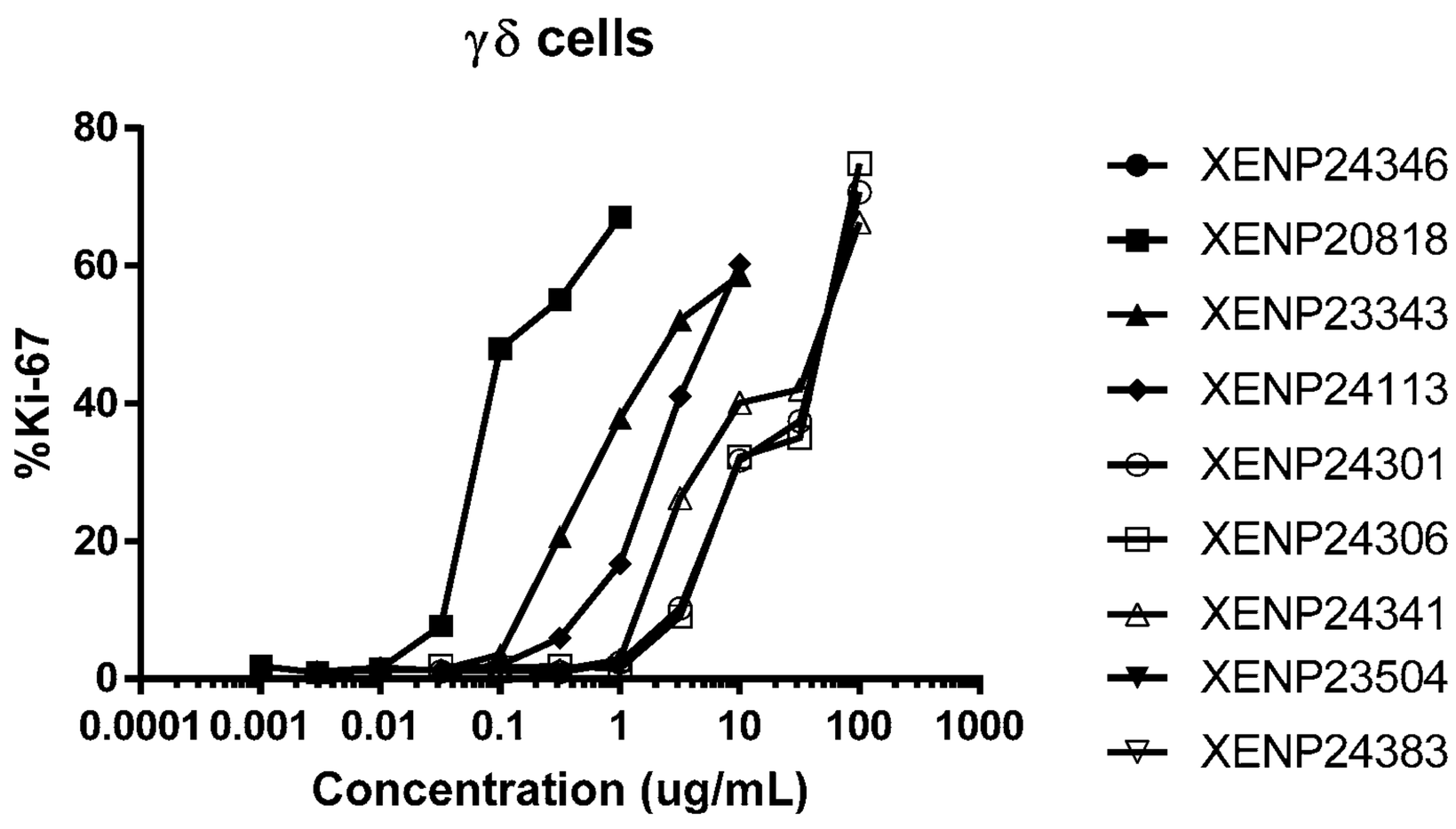


Figure 111D

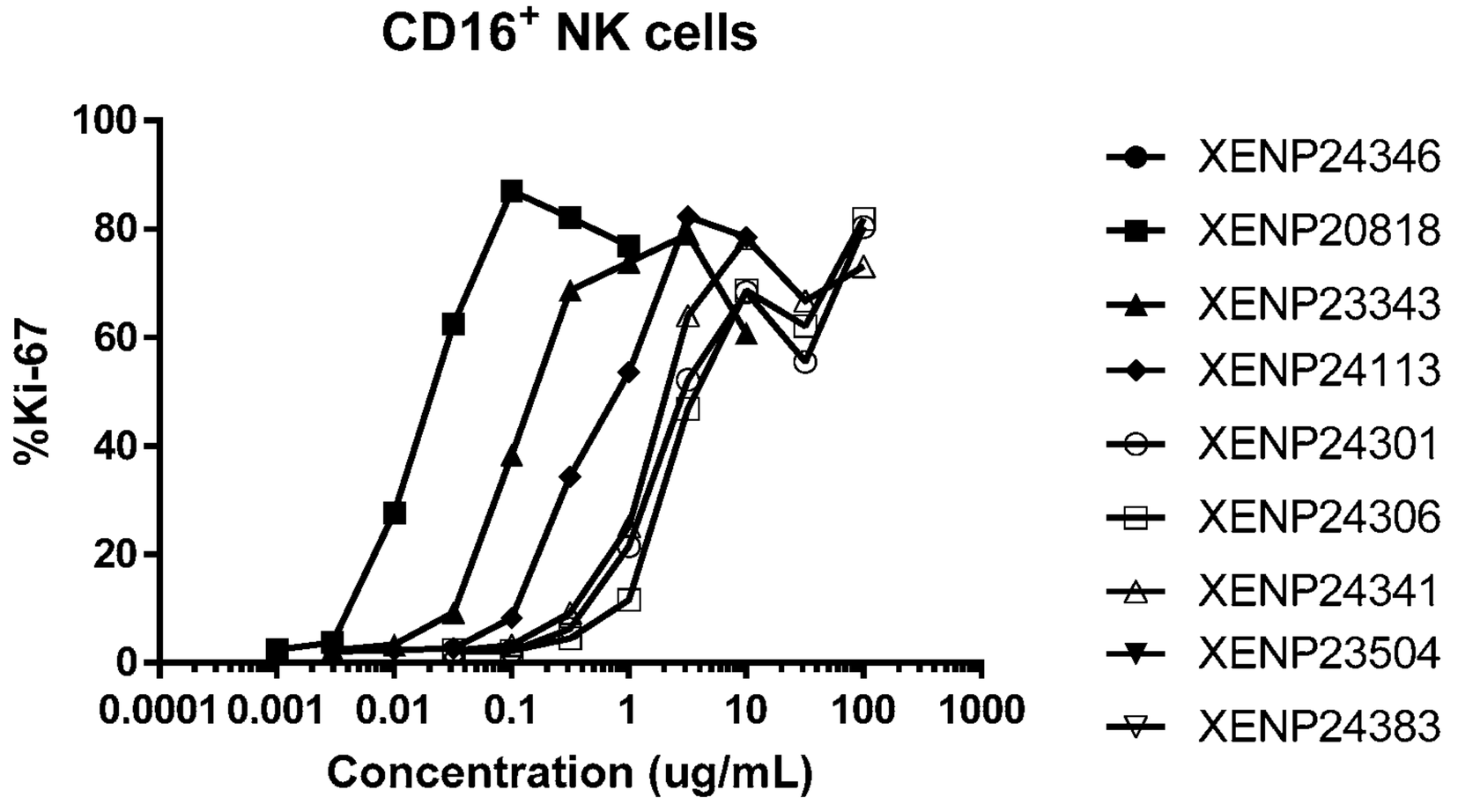


Figure 112A

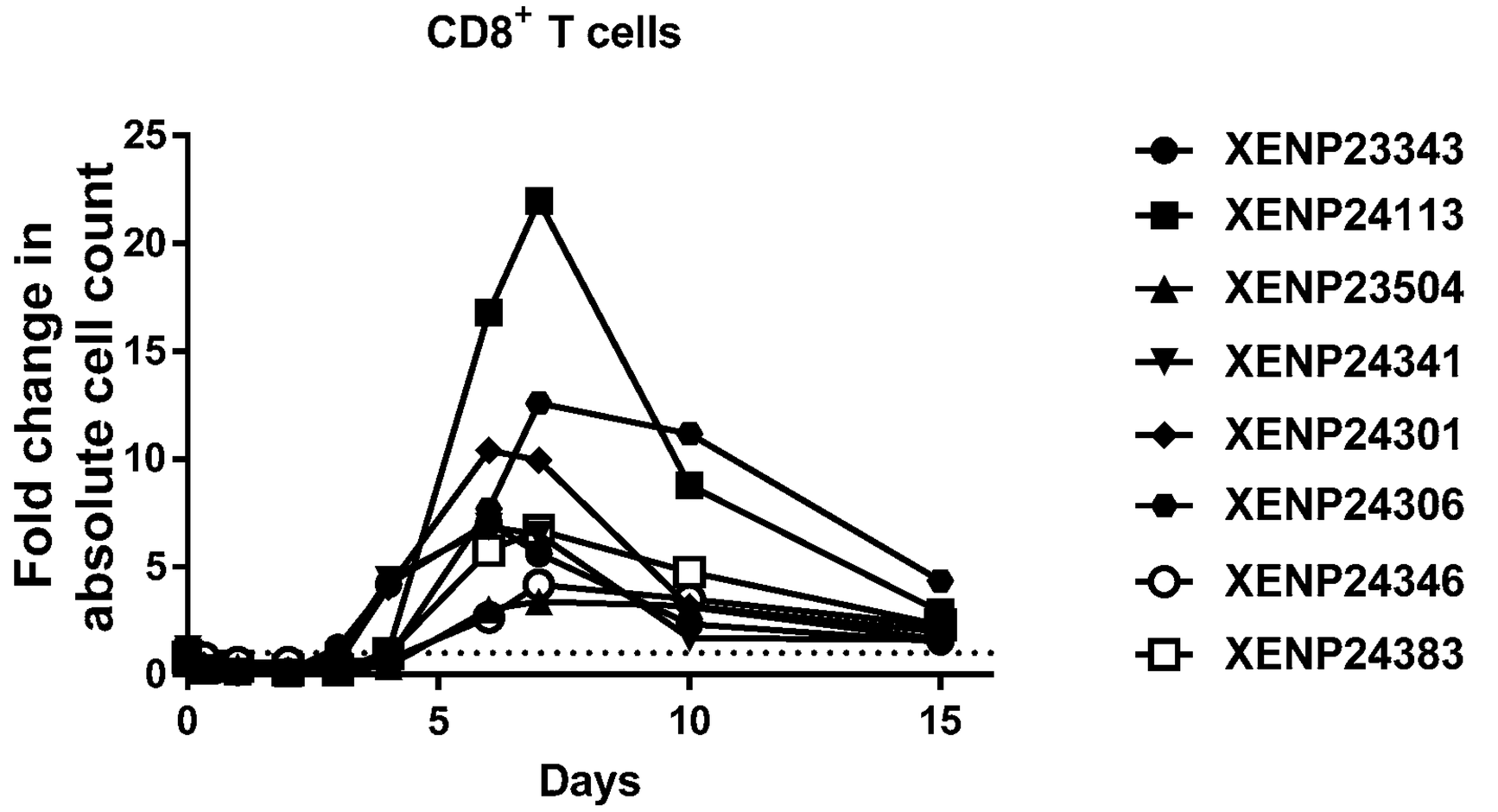


Figure 112B

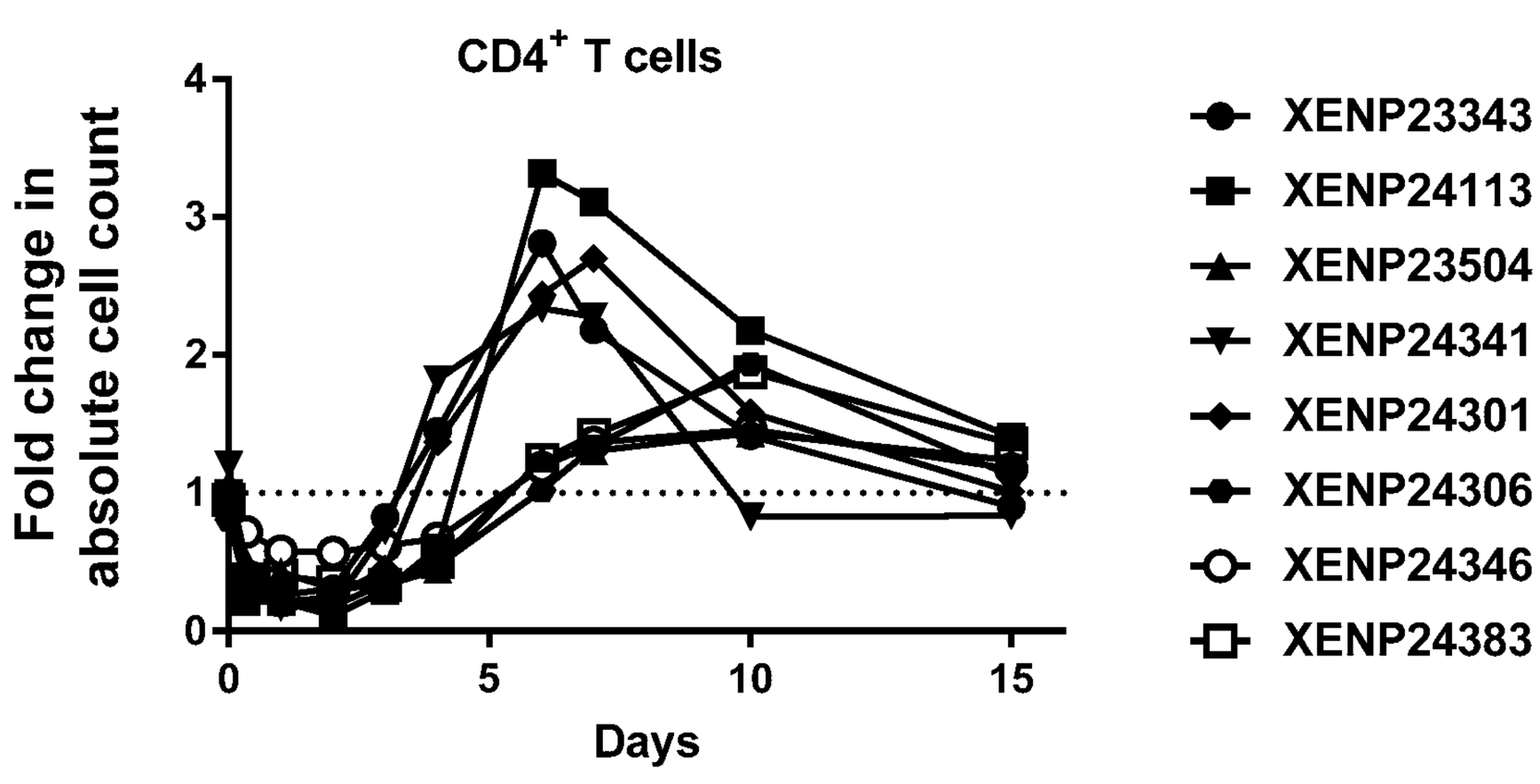


Figure 112C

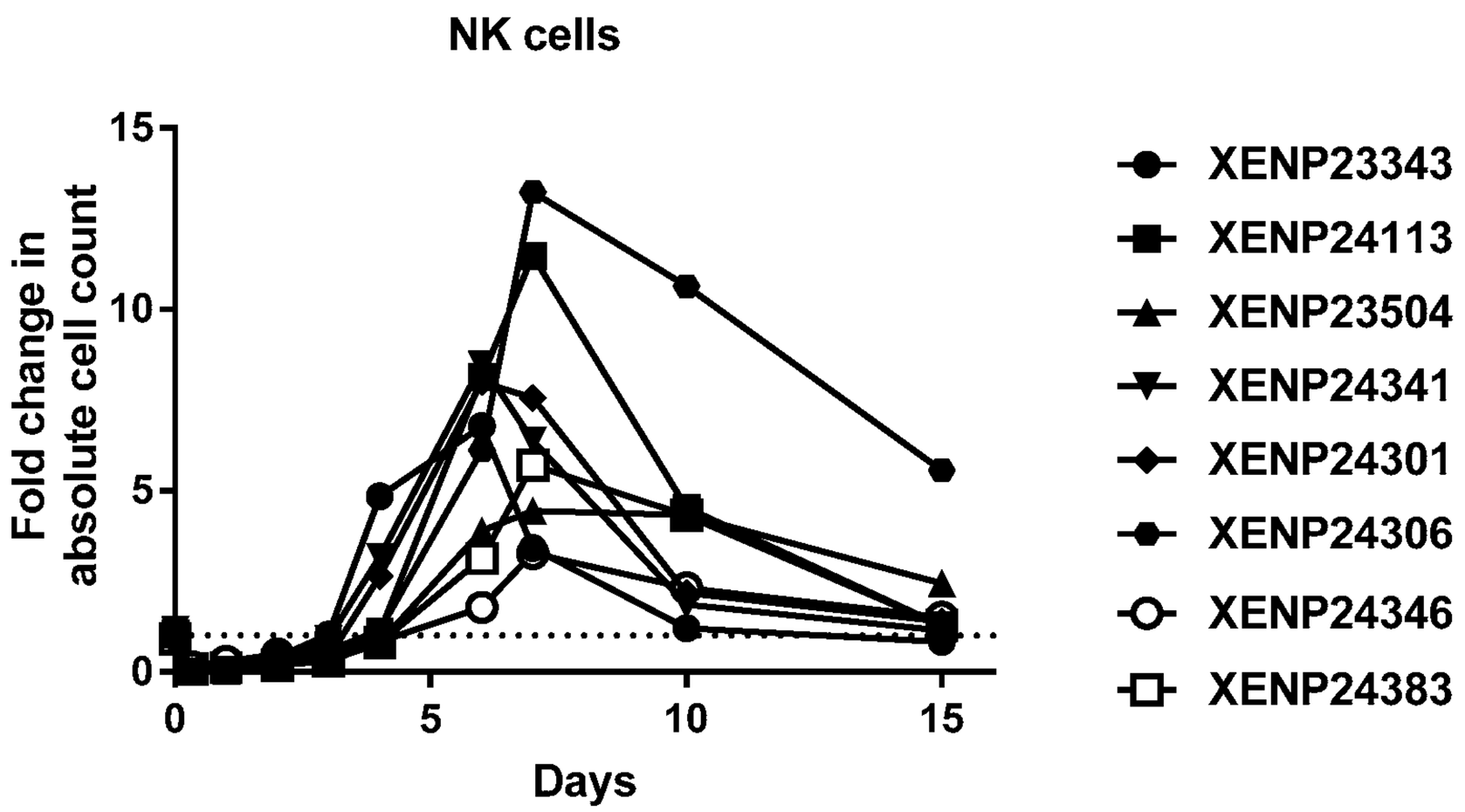


Figure 112D

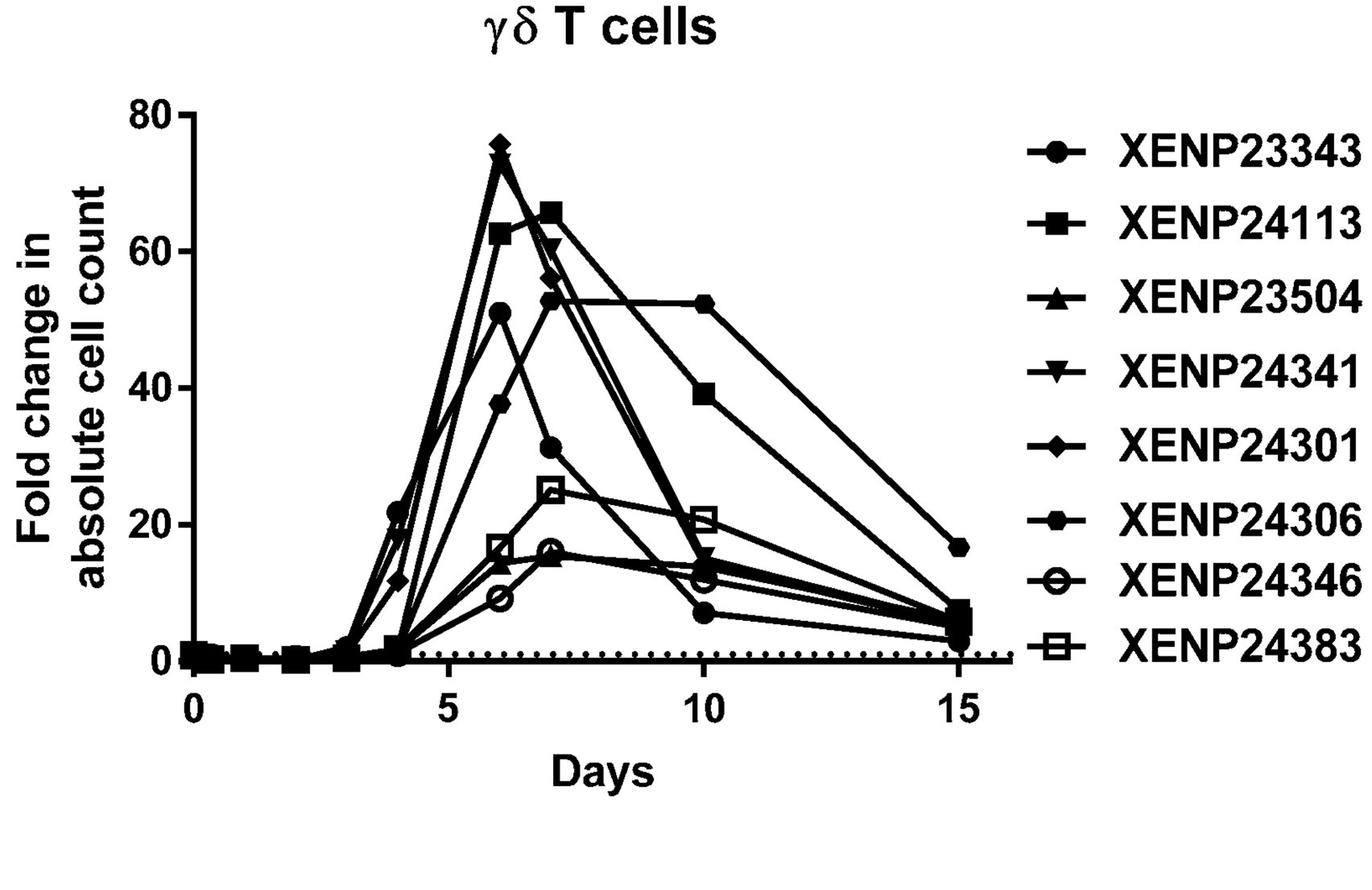


Figure 113

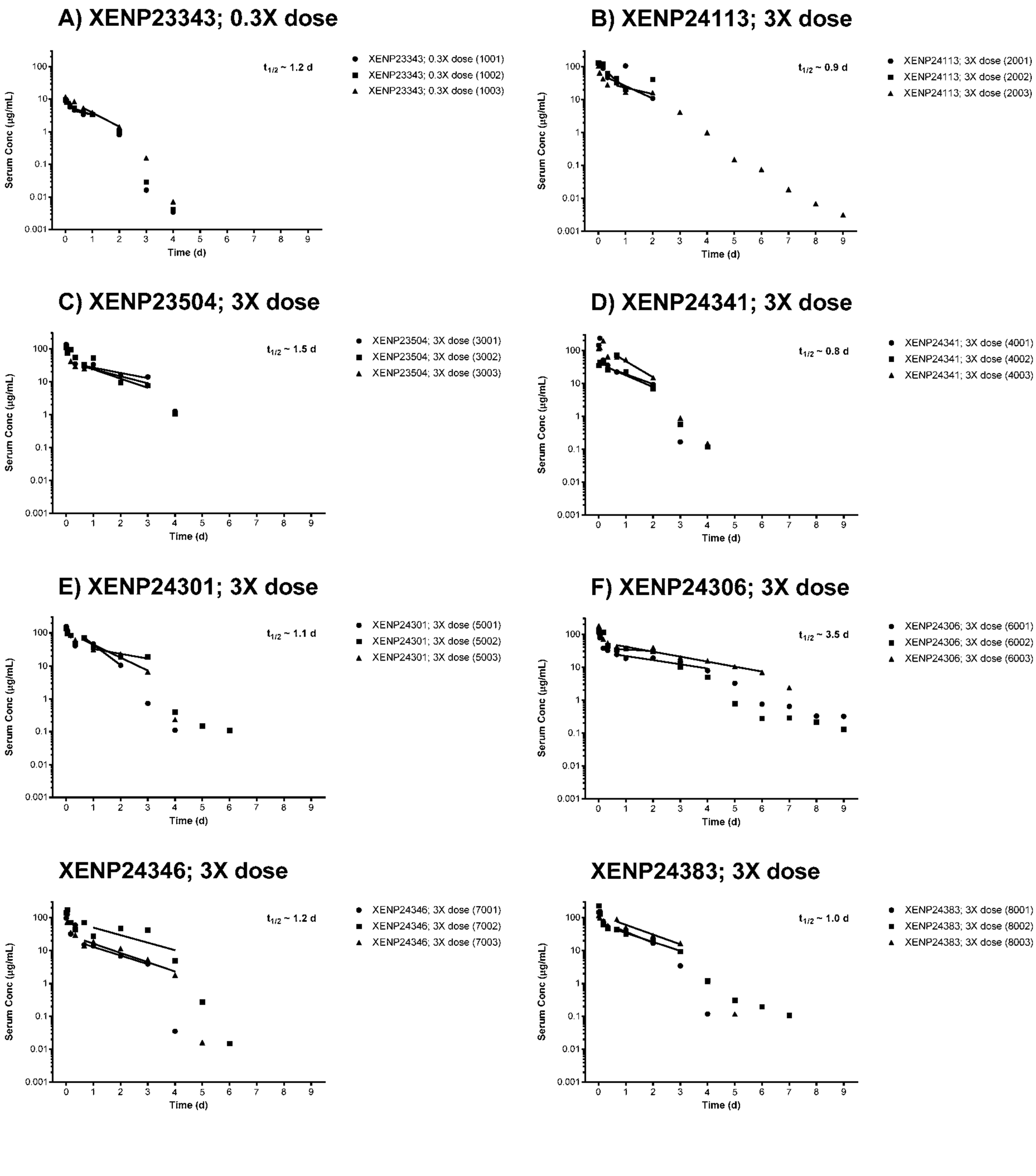

A) XENP23343; 0.3X dose
$t_{1/2}$ ~ 1.2 d
XENP23343; 0.3X dose (1001)
XENP23343; 0.3X dose (1002)
XENP23343; 0.3X dose (1003)
B) XENP24113; 3X dose
$t_{1/2}$ ~ 0.9 d
XENP24113; 3X dose (2001)
XENP24113; 3X dose (2002)
XENP24113; 3X dose (2003)
C) XENP23504; 3X dose
$t_{1/2}$ ~ 1.5 d
XENP23504; 3X dose (3001)
XENP23504; 3X dose (3002)
XENP23504; 3X dose (3003)
D) XENP24341; 3X dose
$t_{1/2}$ ~ 0.8 d
XENP24341; 3X dose (4001)
XENP24341; 3X dose (4002)
XENP24341; 3X dose (4003)
E) XENP24301; 3X dose
$t_{1/2}$ ~ 1.1 d
XENP24301; 3X dose (5001)
XENP24301; 3X dose (5002)
XENP24301; 3X dose (5003)
F) XENP24306; 3X dose
$t_{1/2}$ ~ 3.5 d
XENP24306; 3X dose (6001)
XENP24306; 3X dose (6002)
XENP24306; 3X dose (6003)
XENP24346; 3X dose
$t_{1/2}$ ~ 1.2 d
XENP24346; 3X dose (7001)
XENP24346; 3X dose (7002)
XENP24346; 3X dose (7003)
XENP24383; 3X dose
$t_{1/2}$ ~ 1.0 d
XENP24383; 3X dose (8001)
XENP24383; 3X dose (8002)
XENP24383; 3X dose (8003)
Serum Conc (µg/mL)
Time (d)

Figure 114A

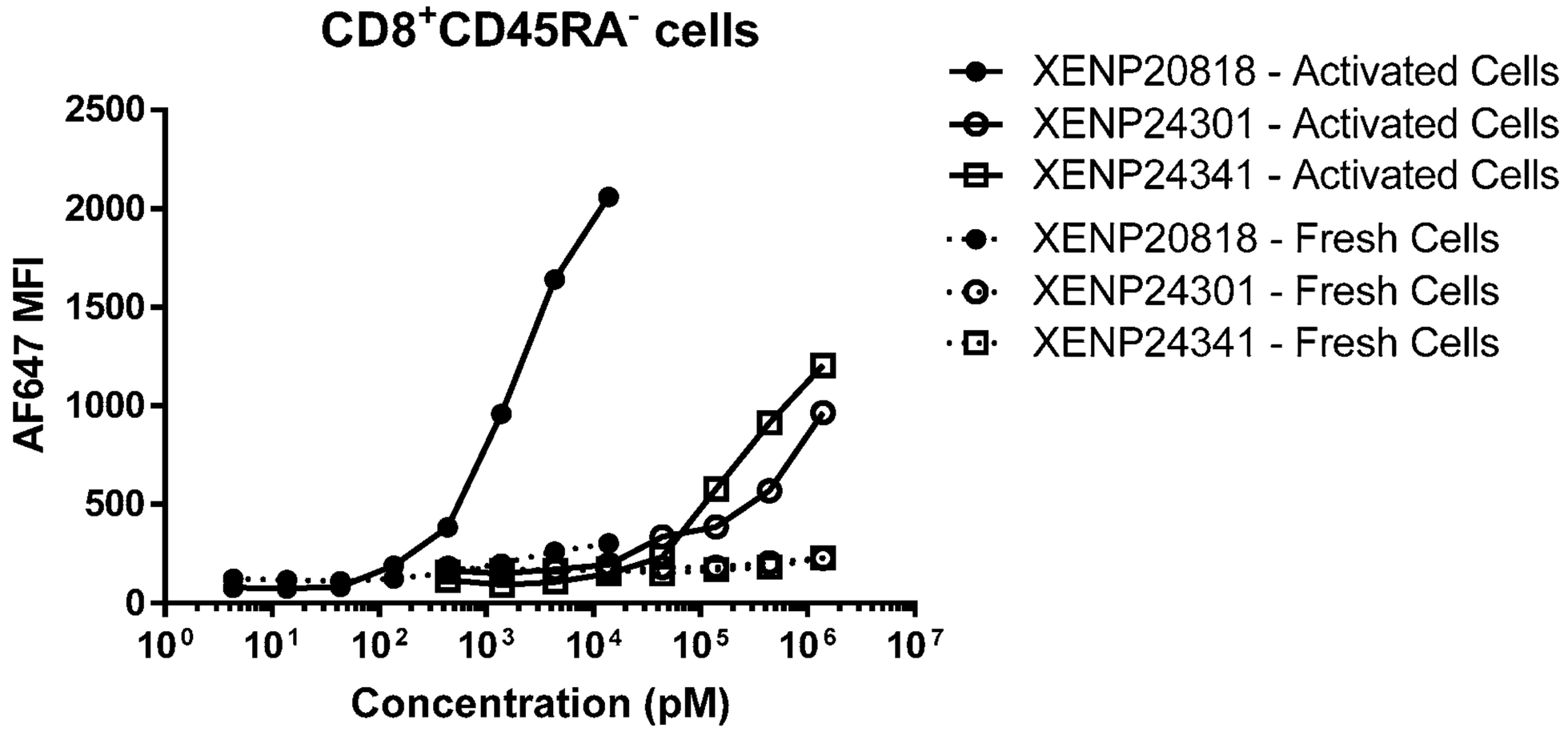


Figure 114B

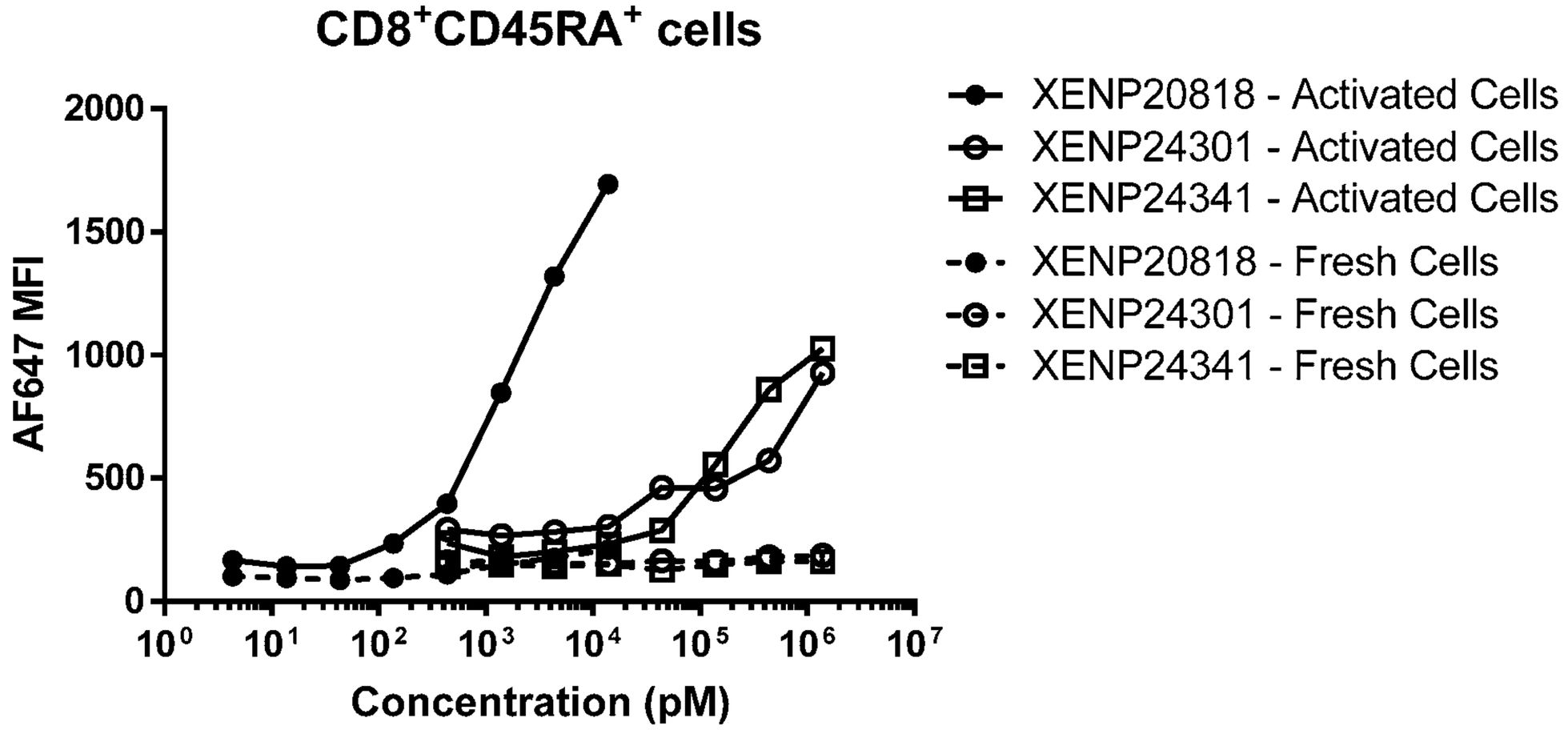


Figure 114C

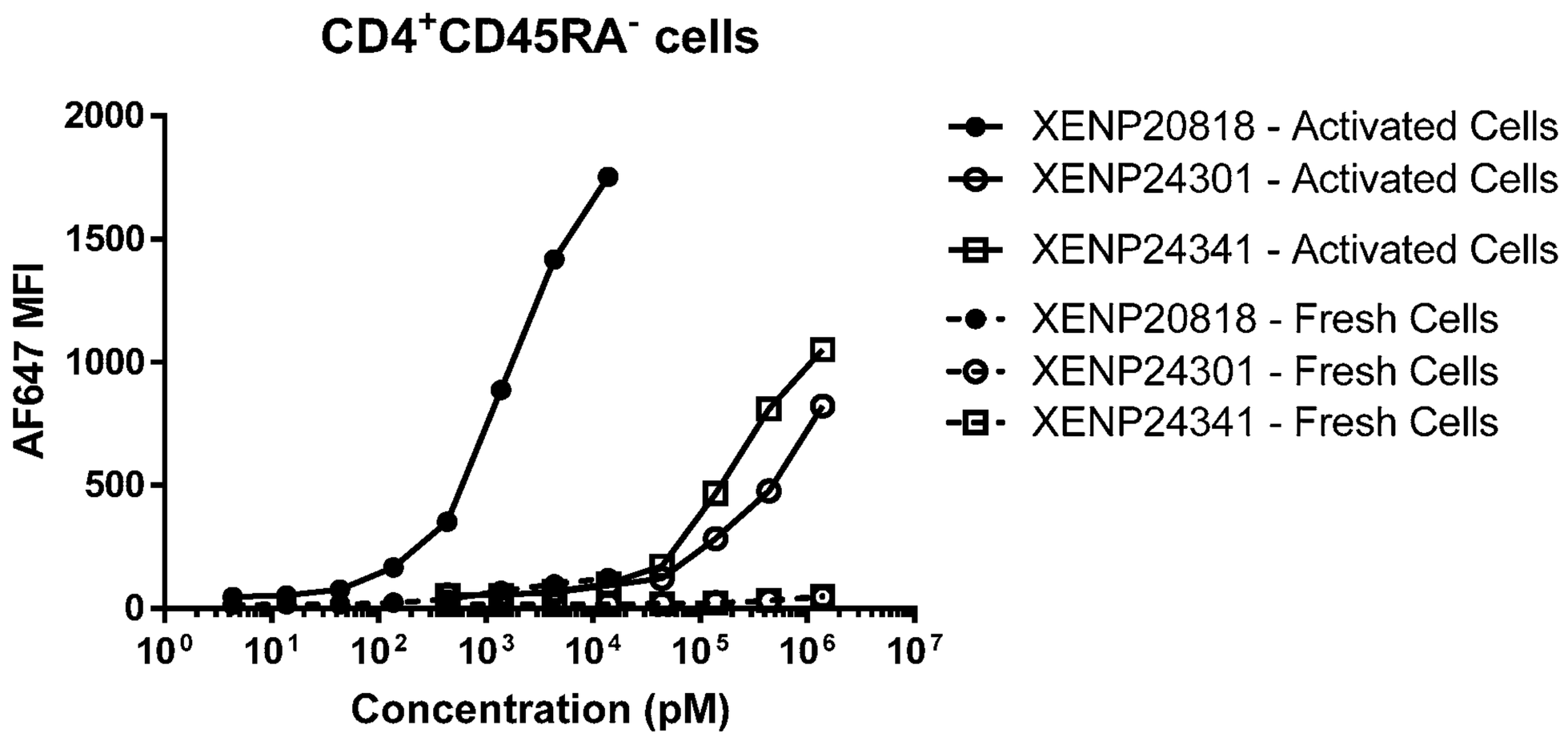


Figure 114D

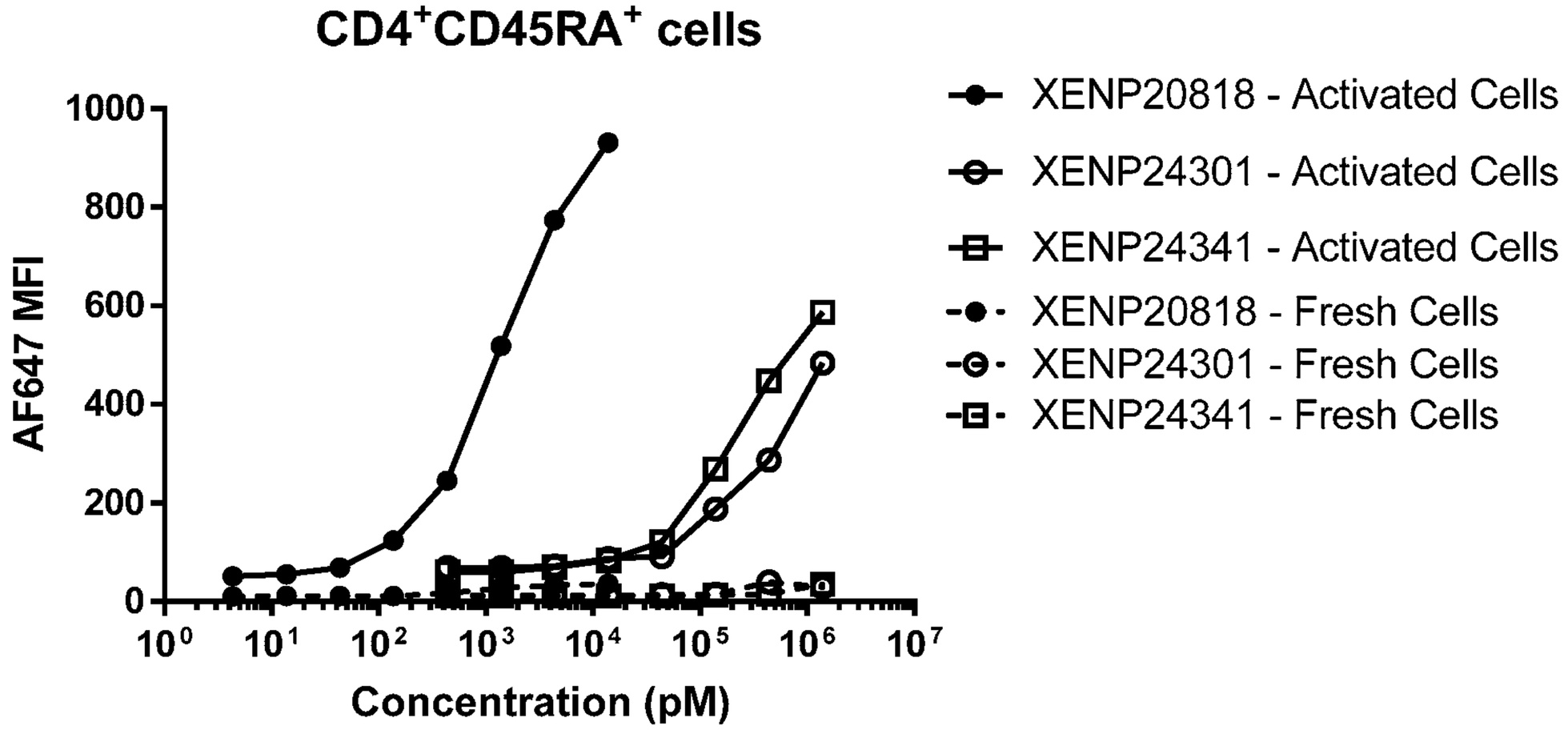


Figure 114E

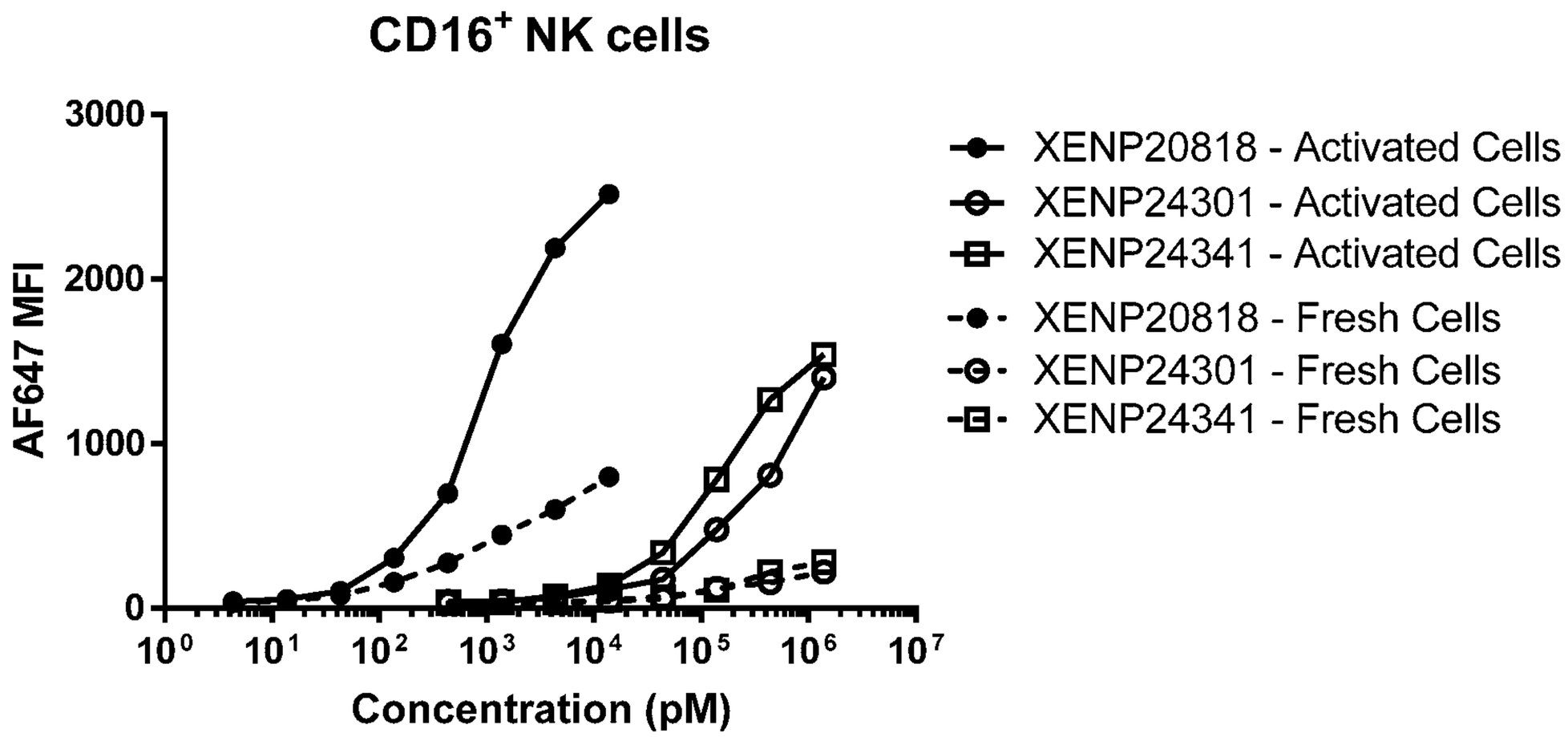


Figure 114F

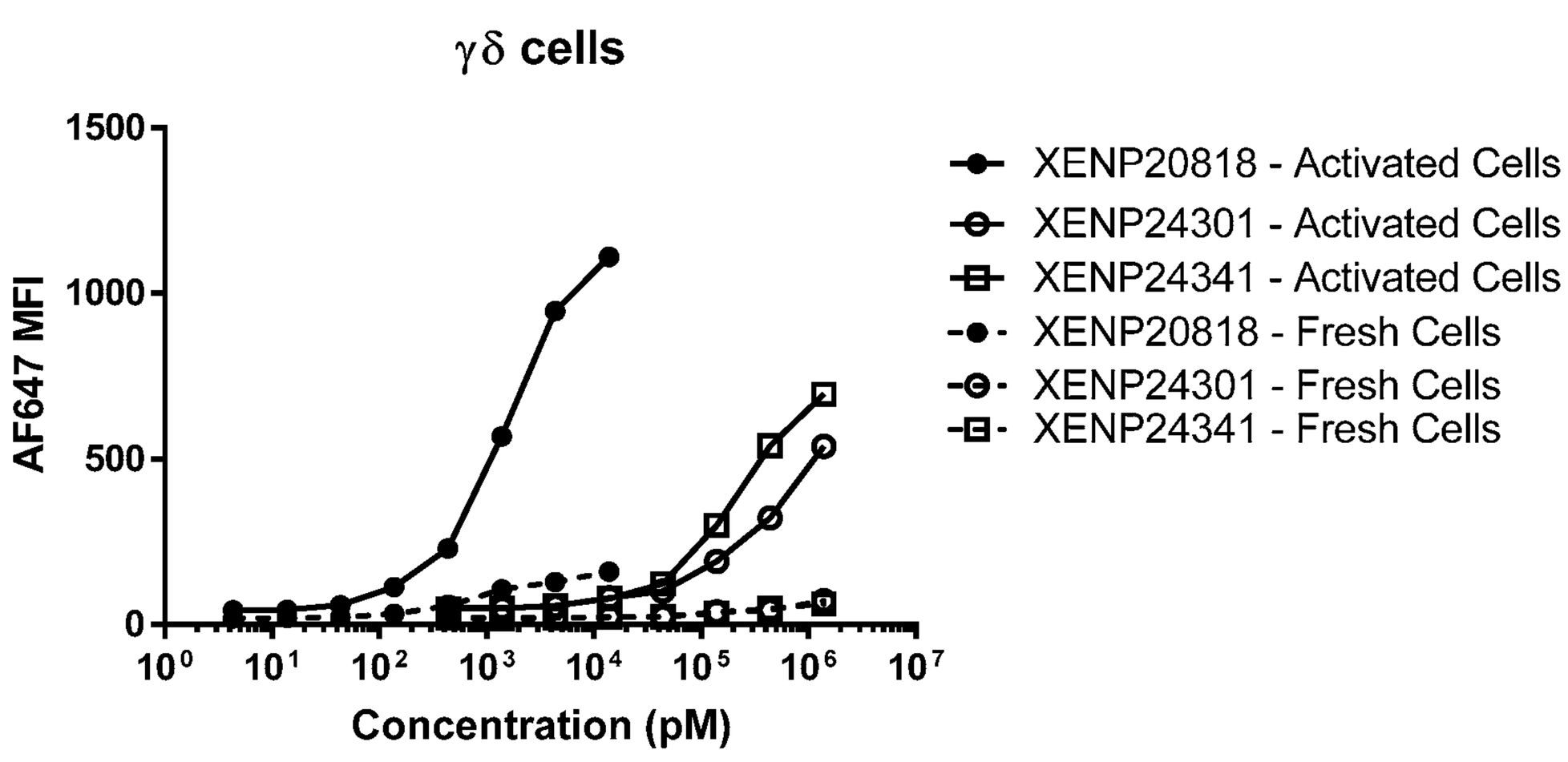


Figure 115A

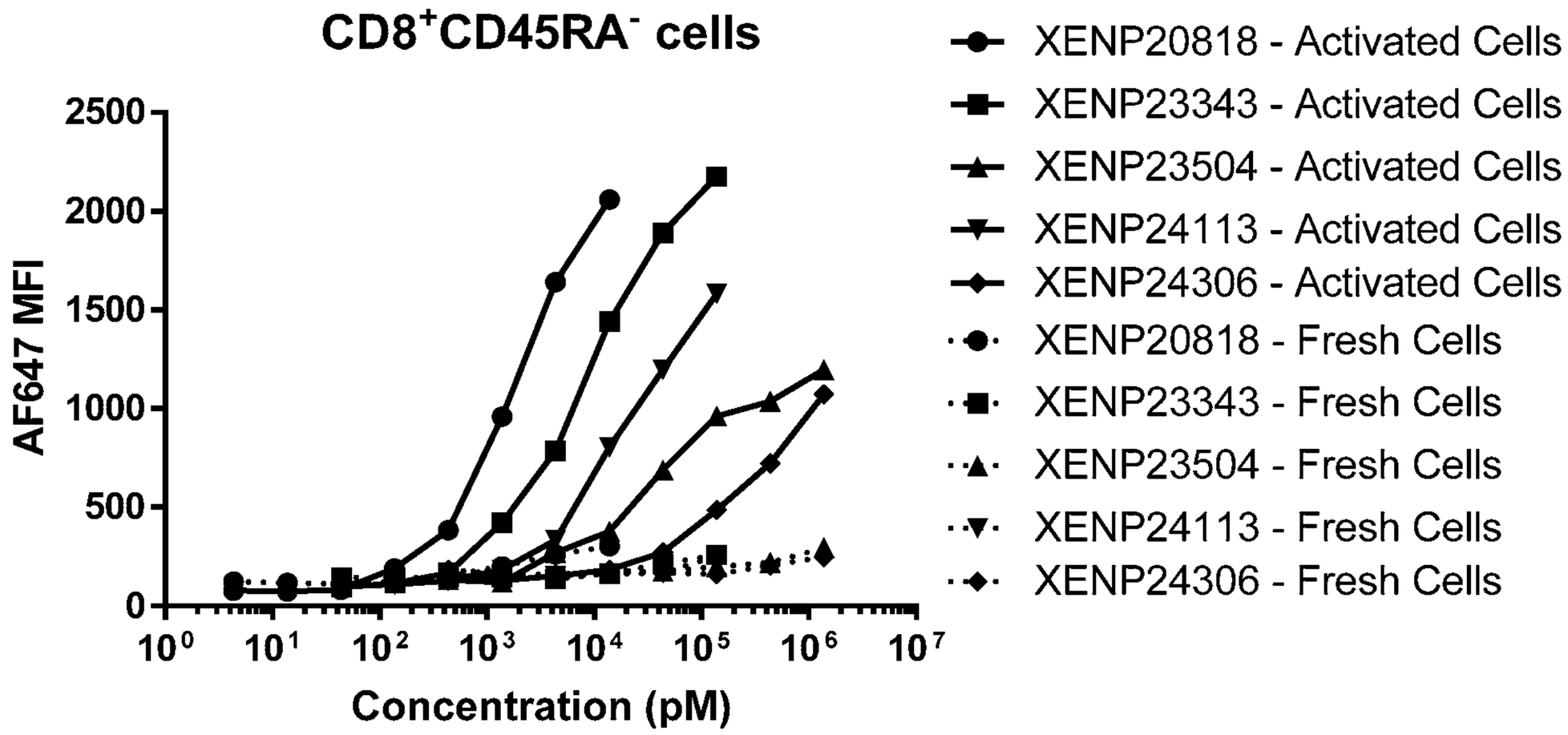


Figure 115B

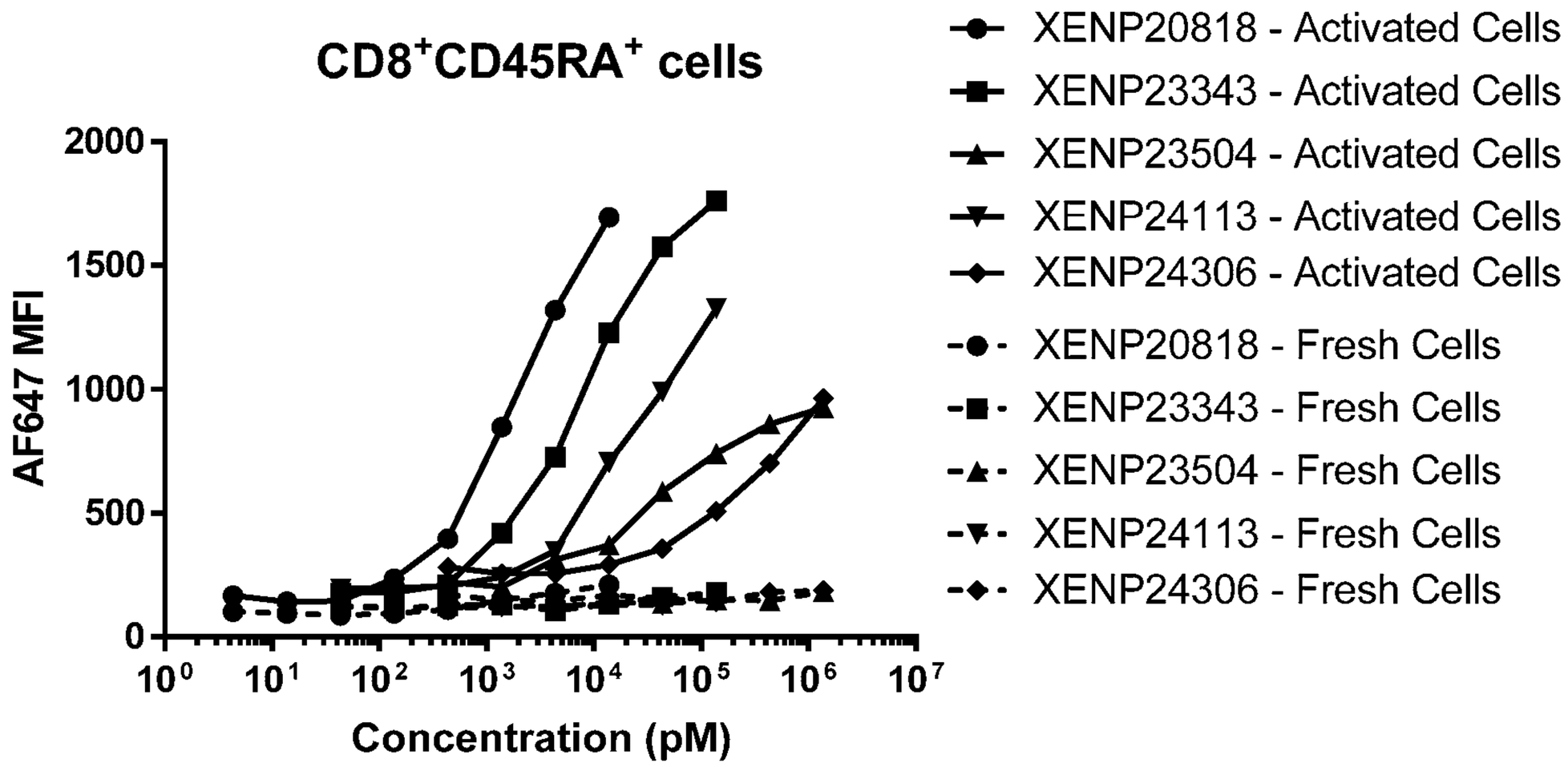


Figure 115C

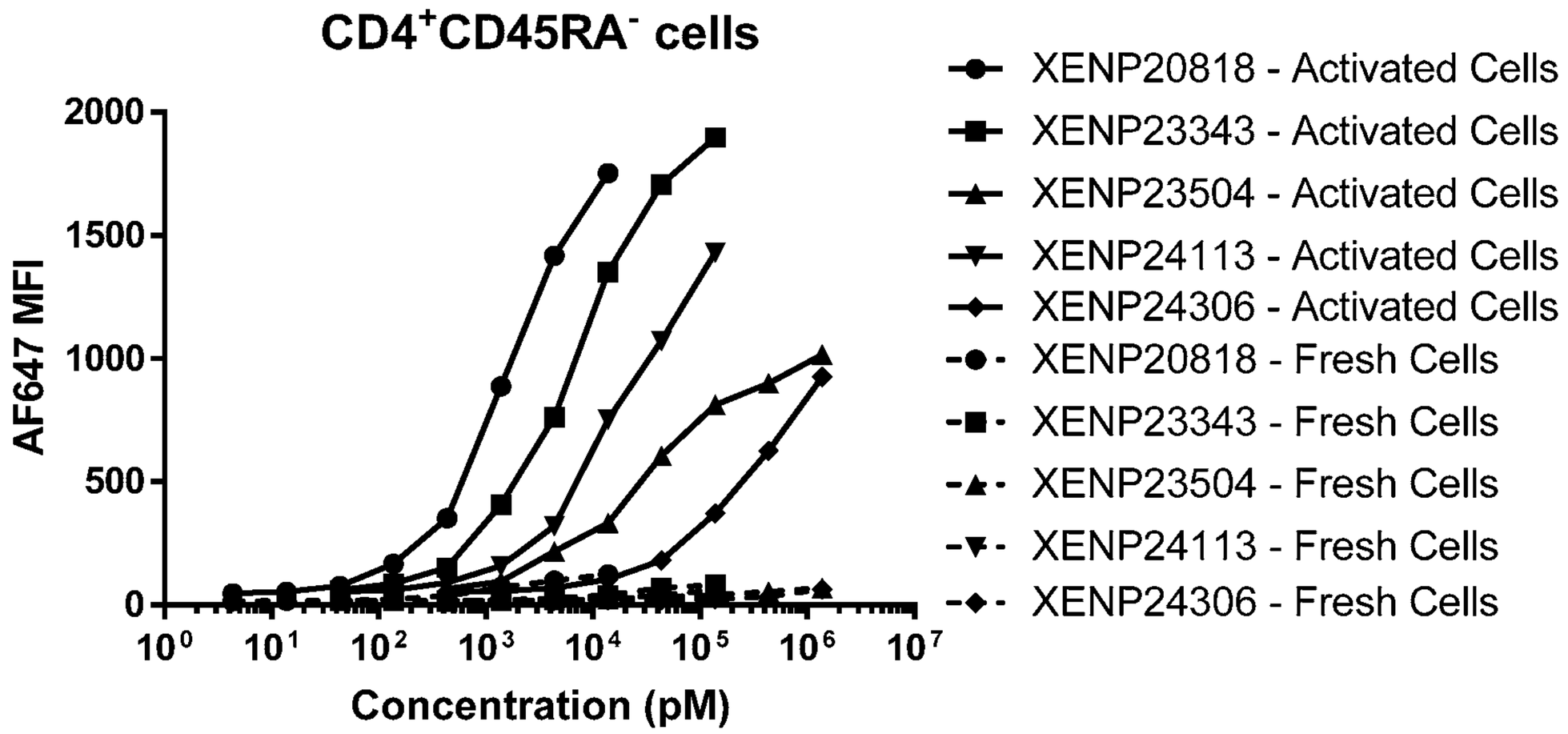
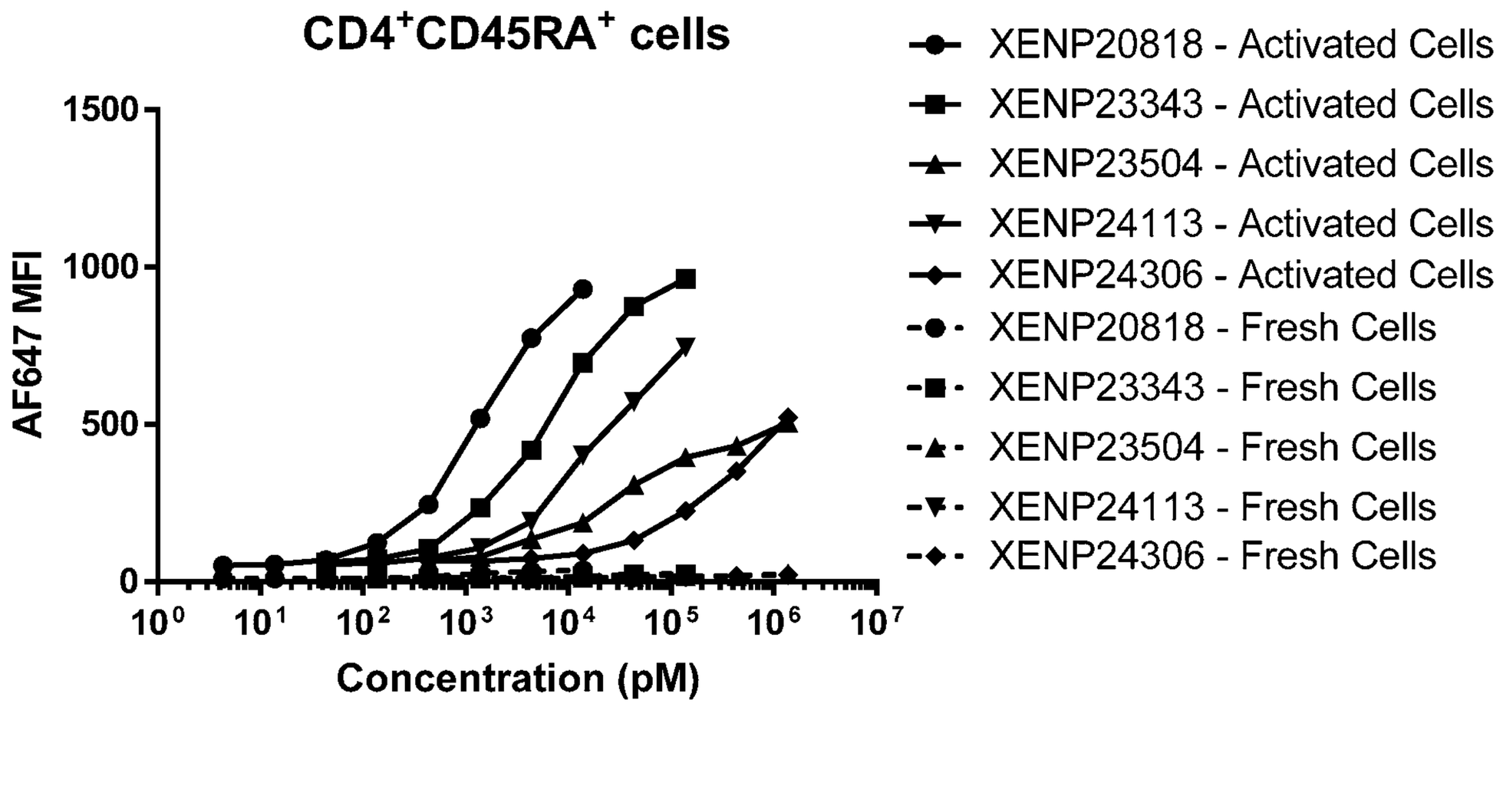


Figure 115D



igure 115E

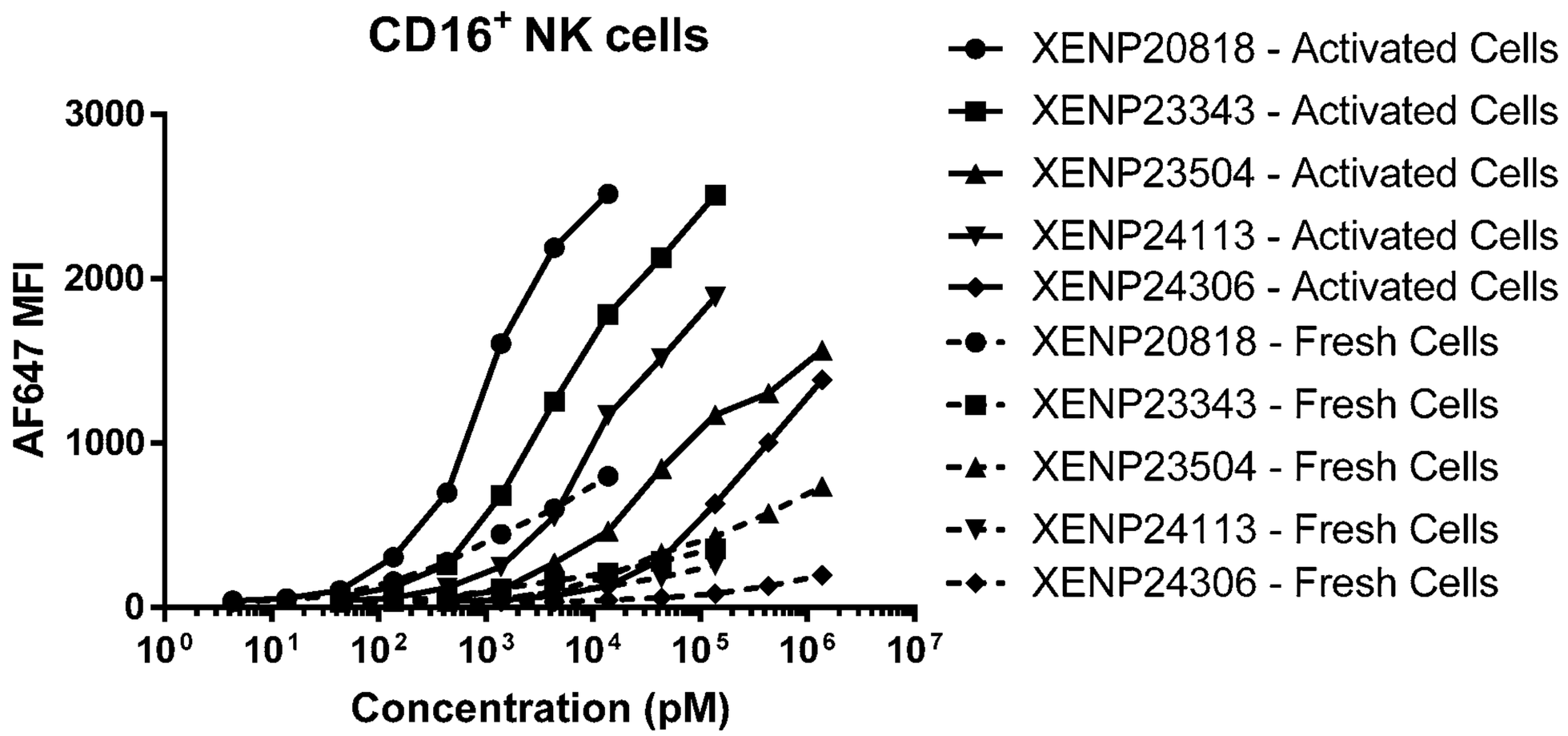


Figure 115F

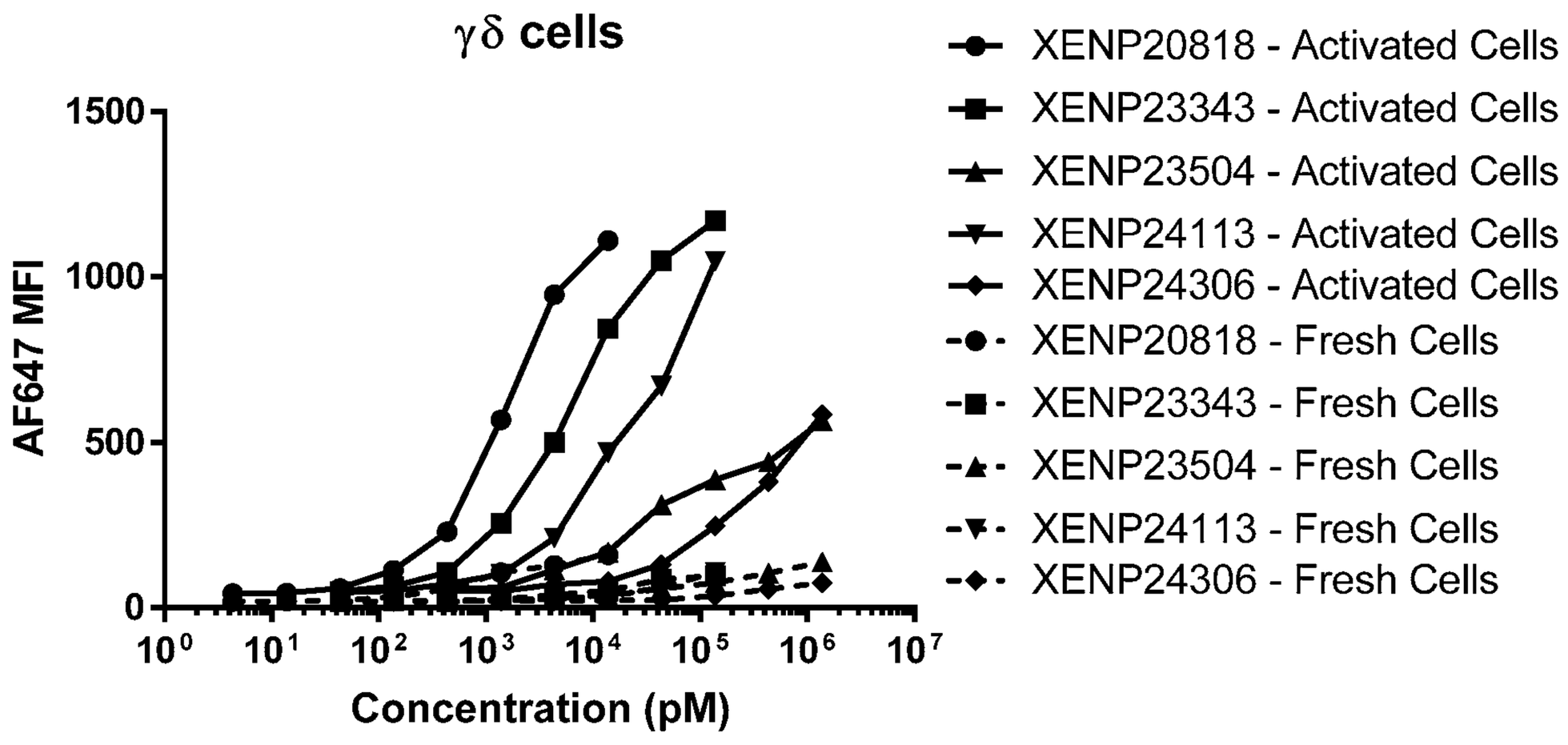


Figure 116A

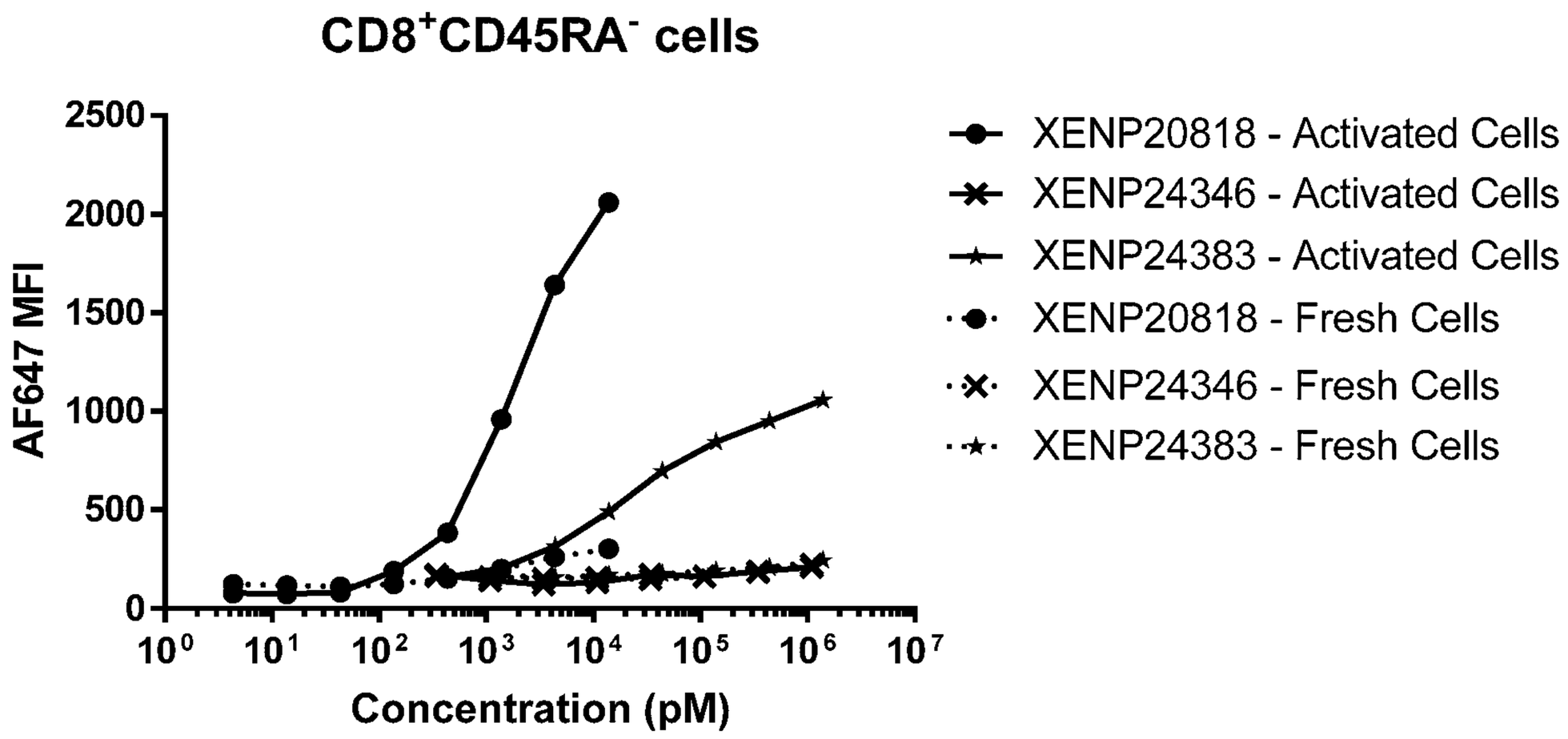


Figure 116B

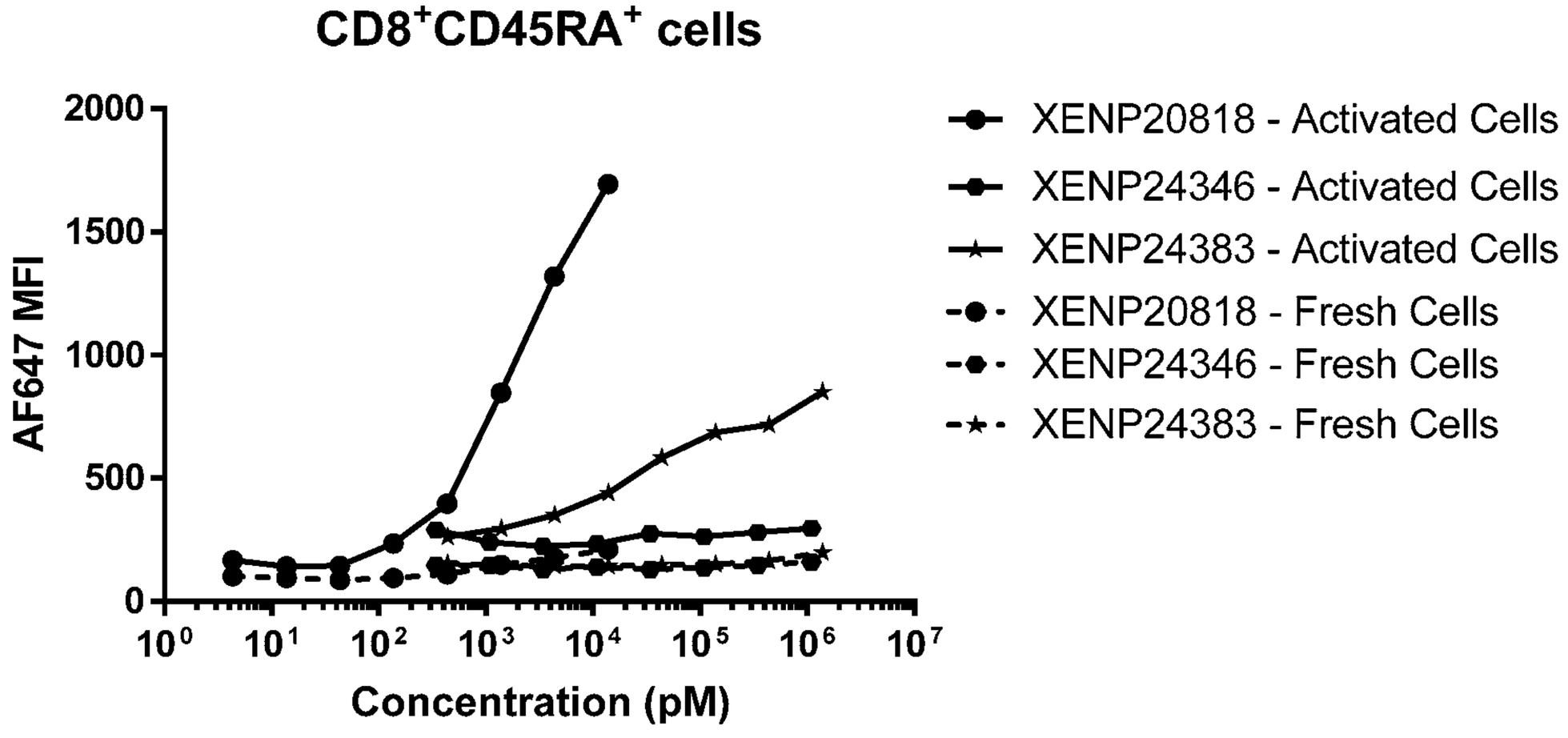


Figure 116C

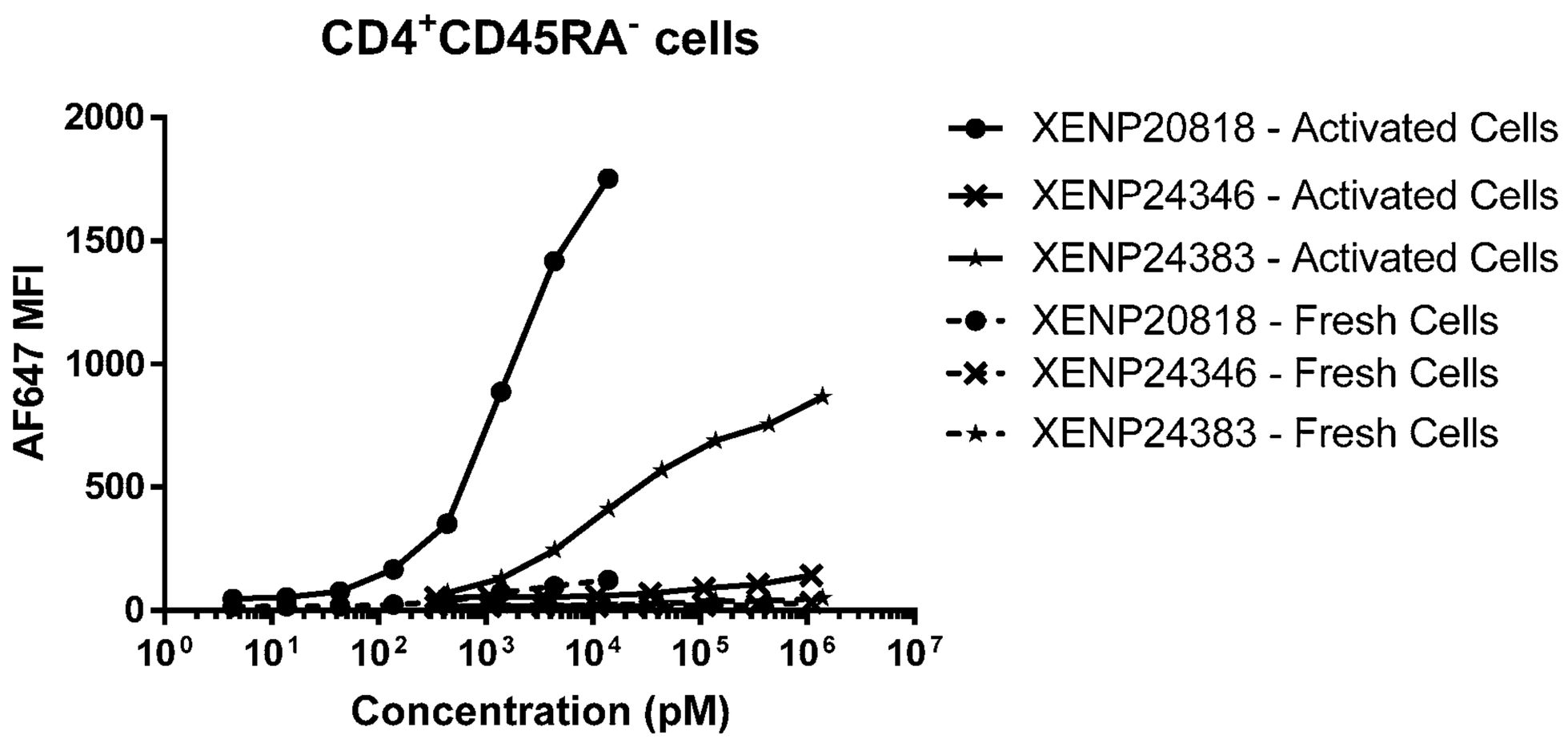


Figure 116D

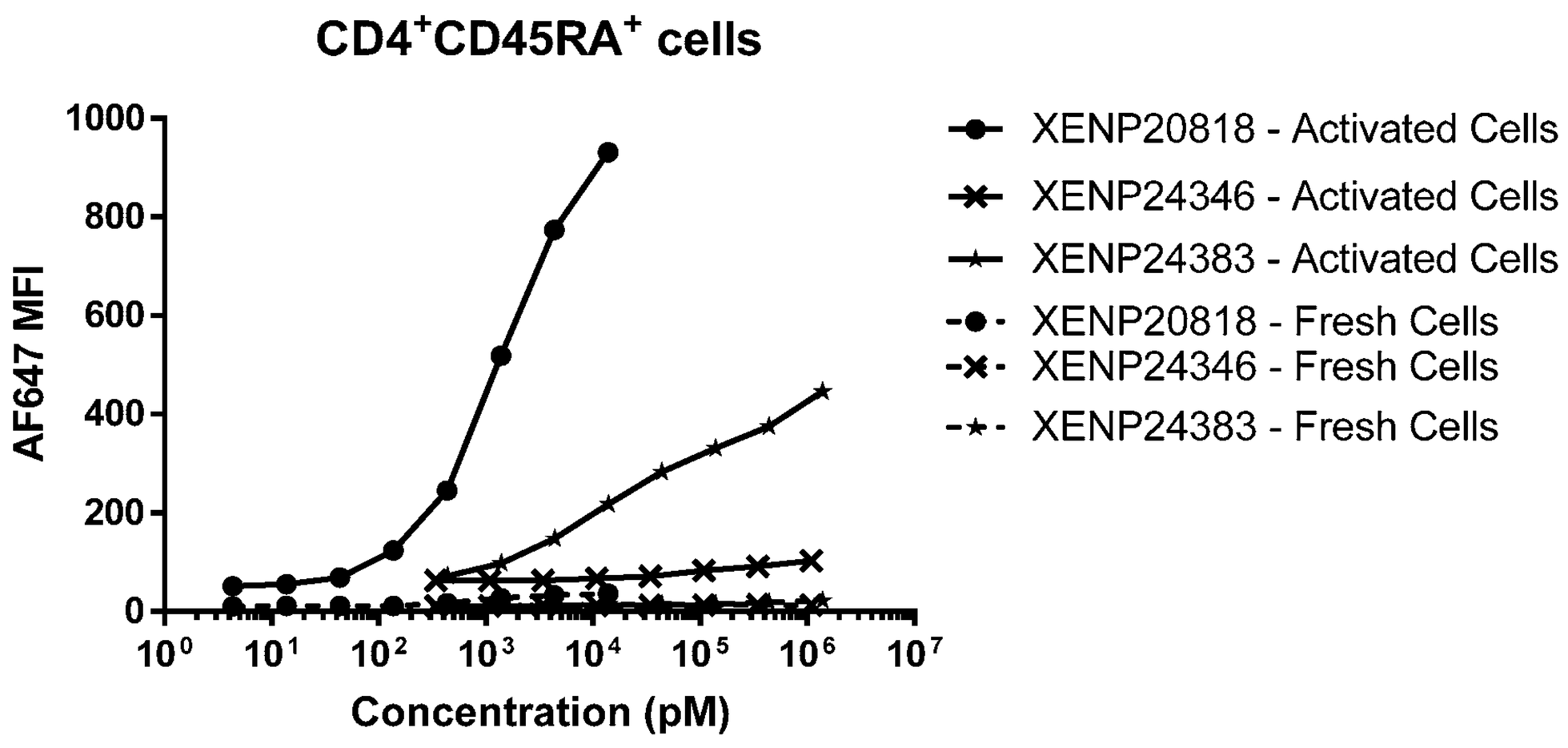


Figure 116E

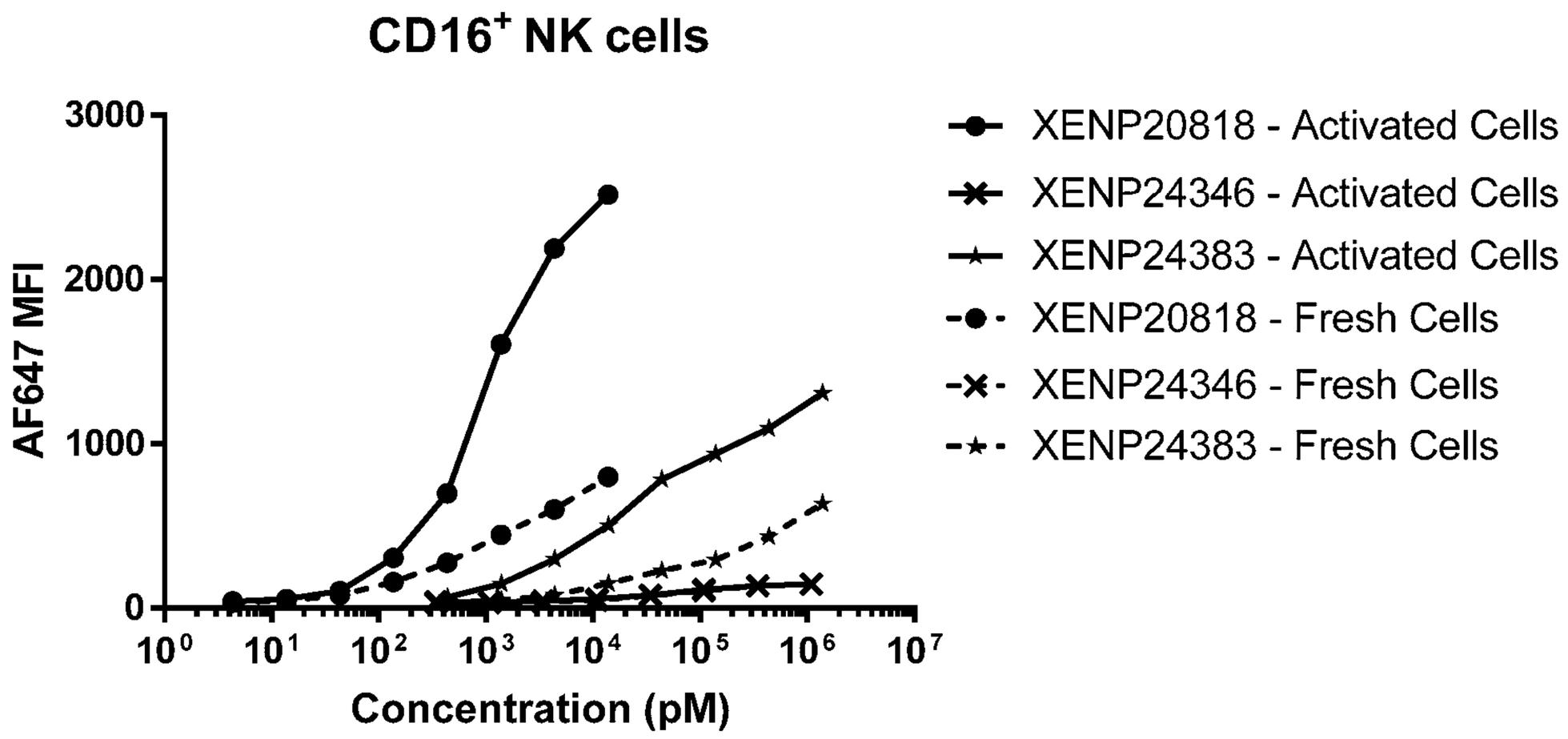


Figure 116F

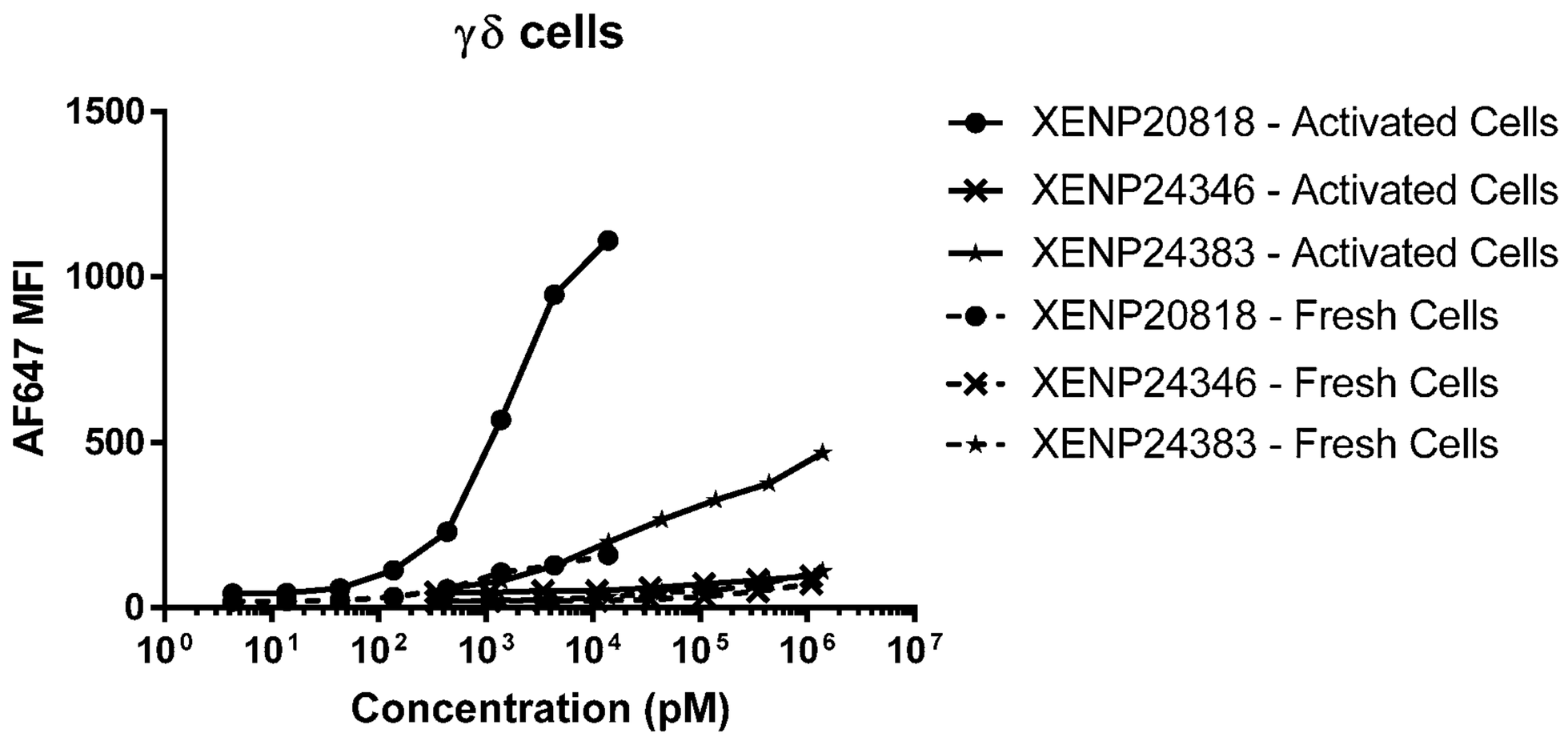


Figure 117

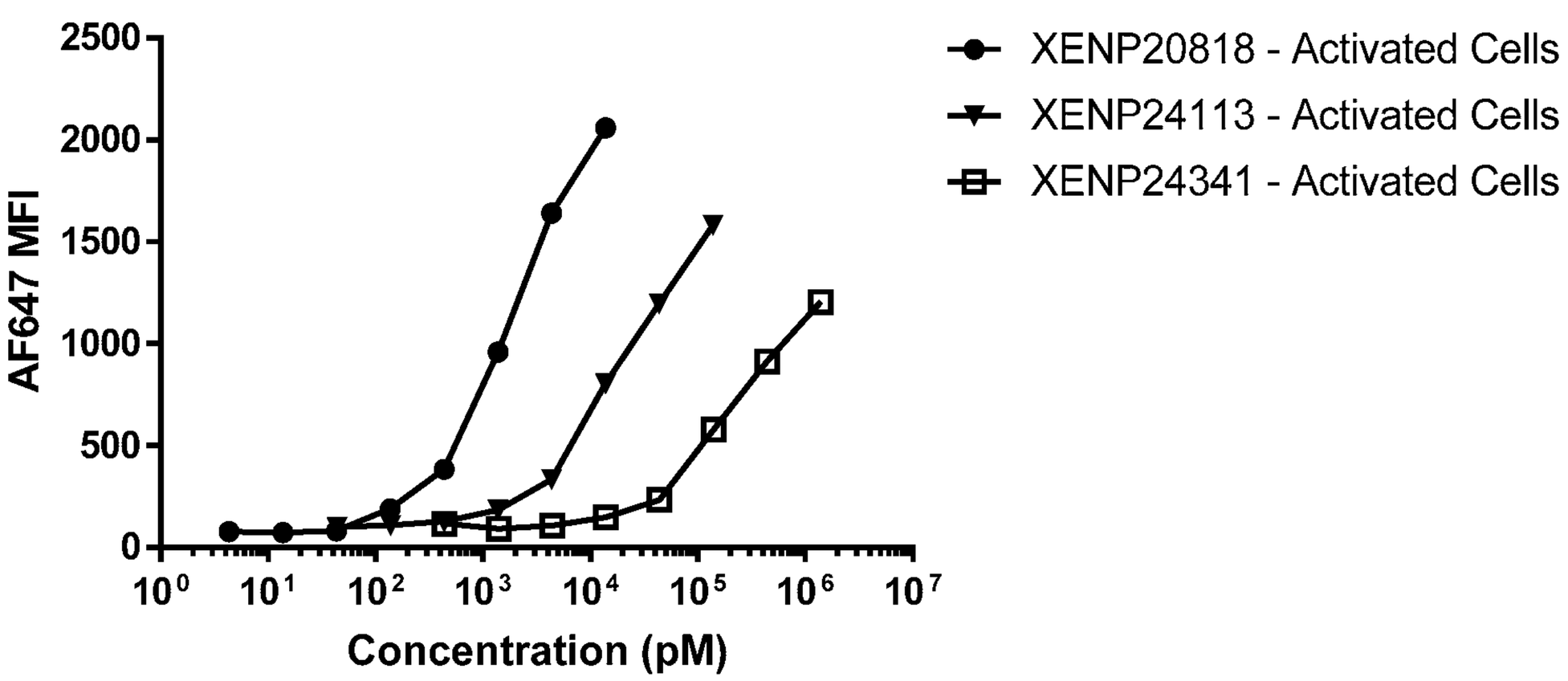

CD8+CD45RA- cells
XENP20818 - Activated Cells
XENP24113 - Activated Cells
XENP24341 - Activated Cells
AF647 MFI
2500
2000
1500
1000
500
0
10^0
10^1
10^2
10^3
10^4
10^5
10^6
10^7
Concentration (pM)

Figure 118A

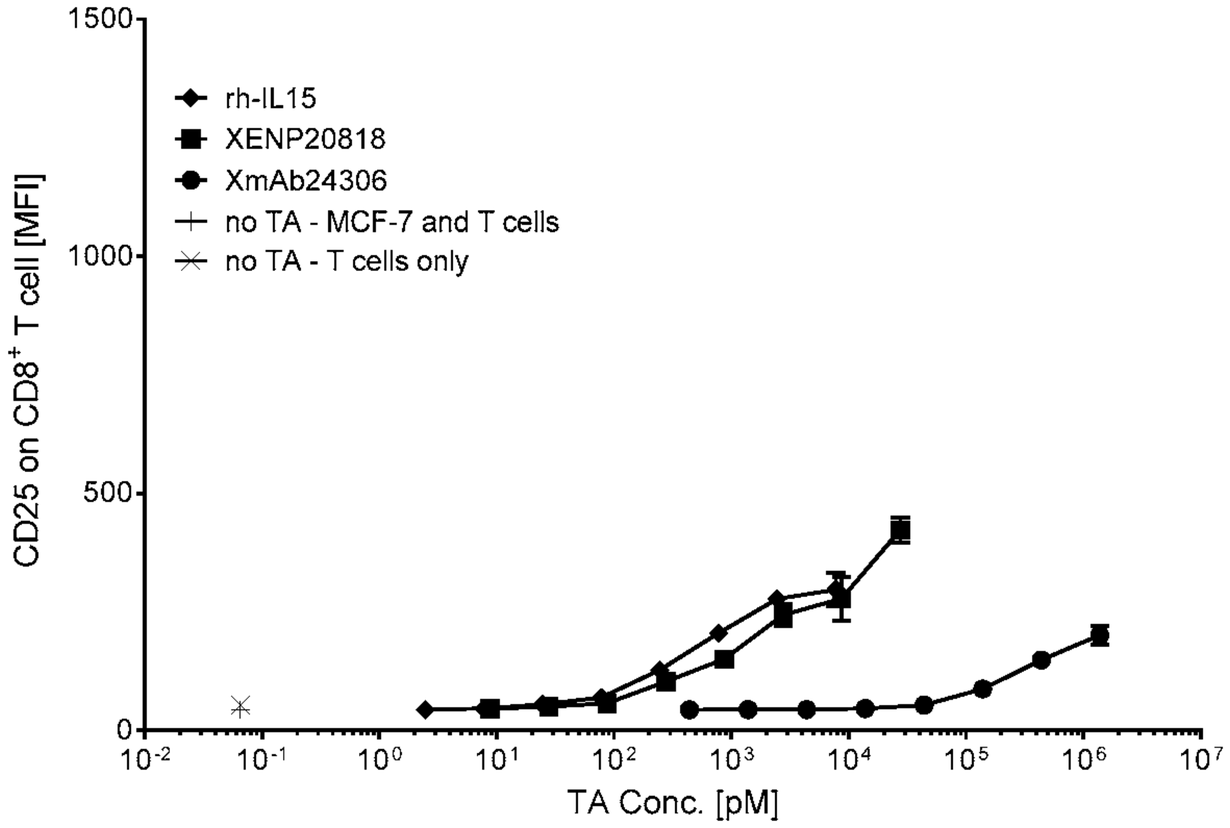


Figure 118B

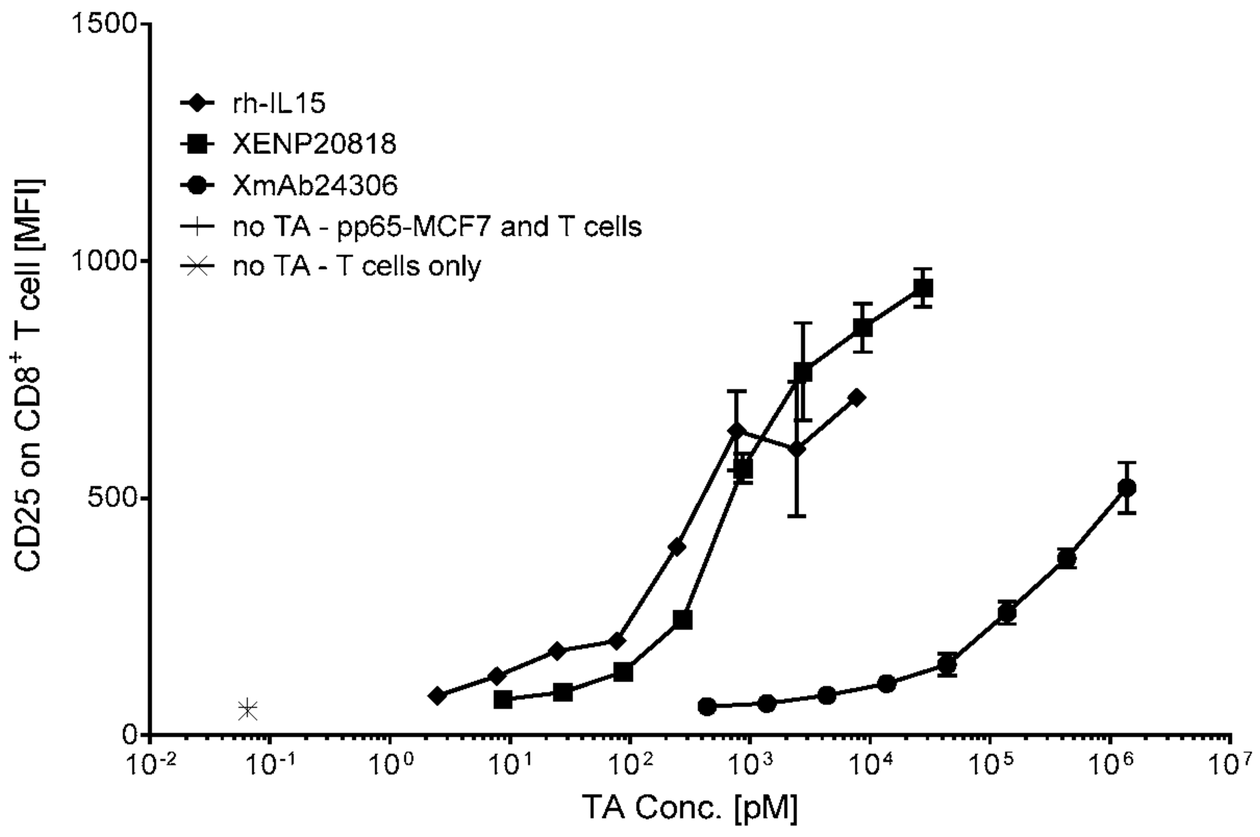


Figure 119A

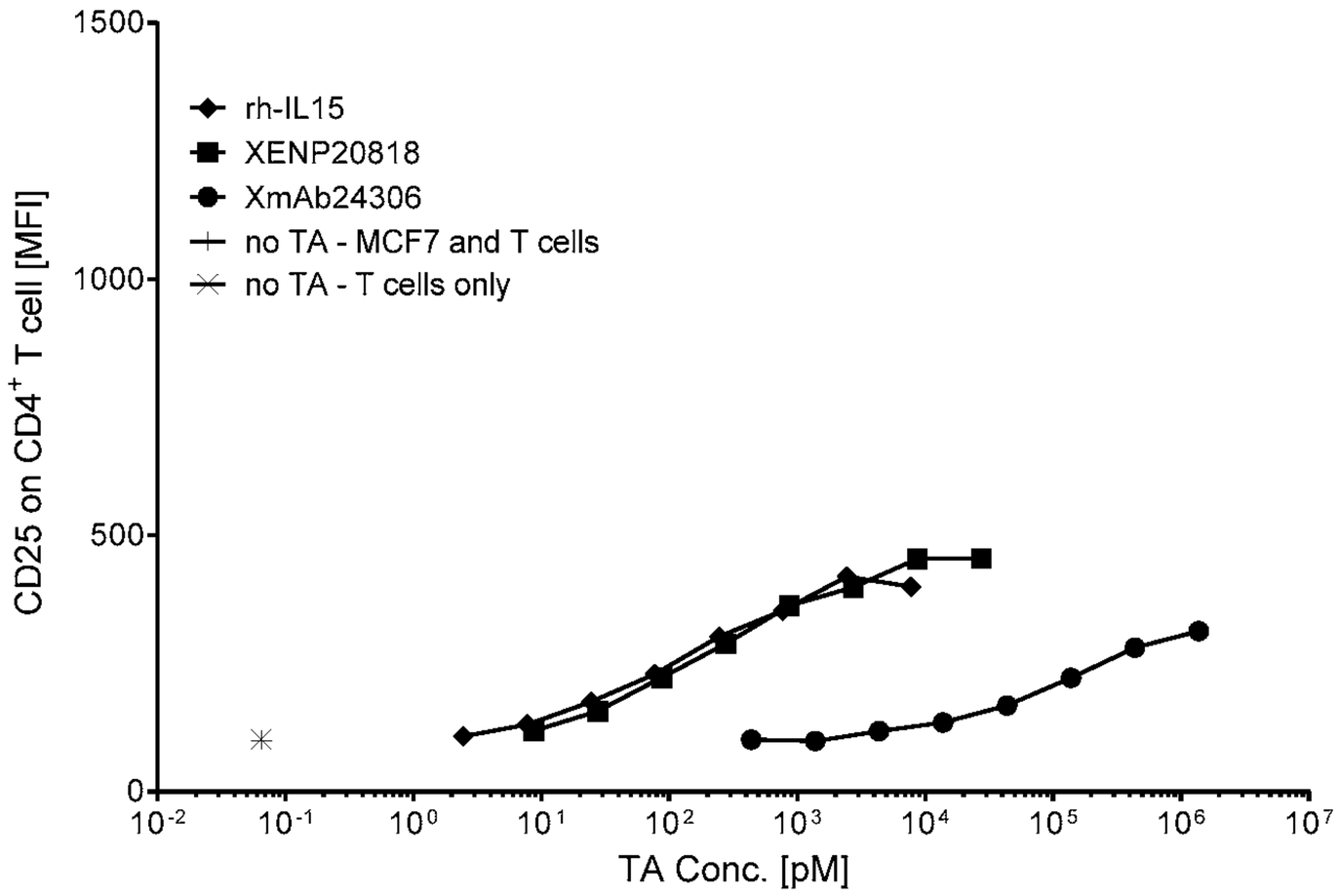


Figure 119B

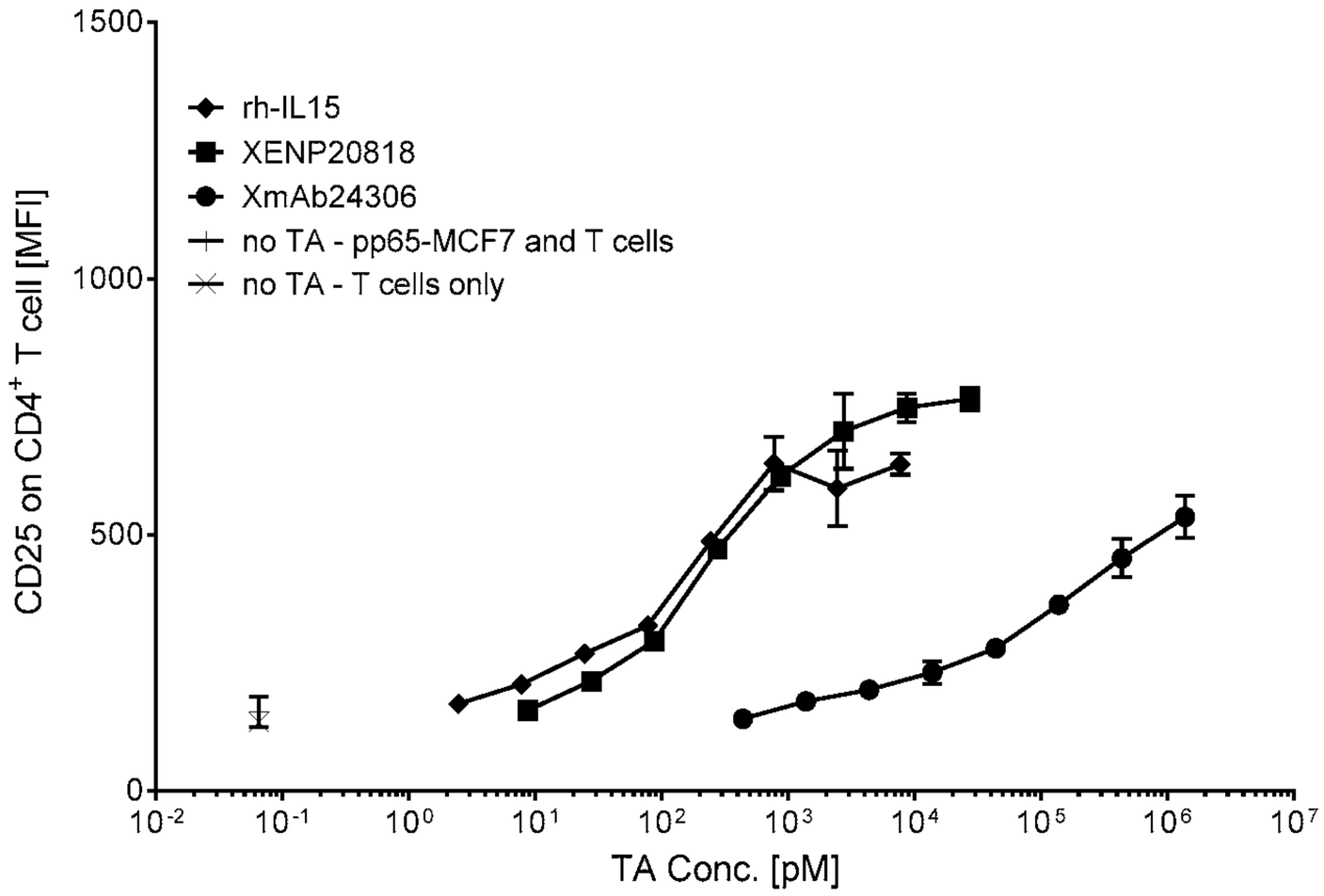


Figure 120A

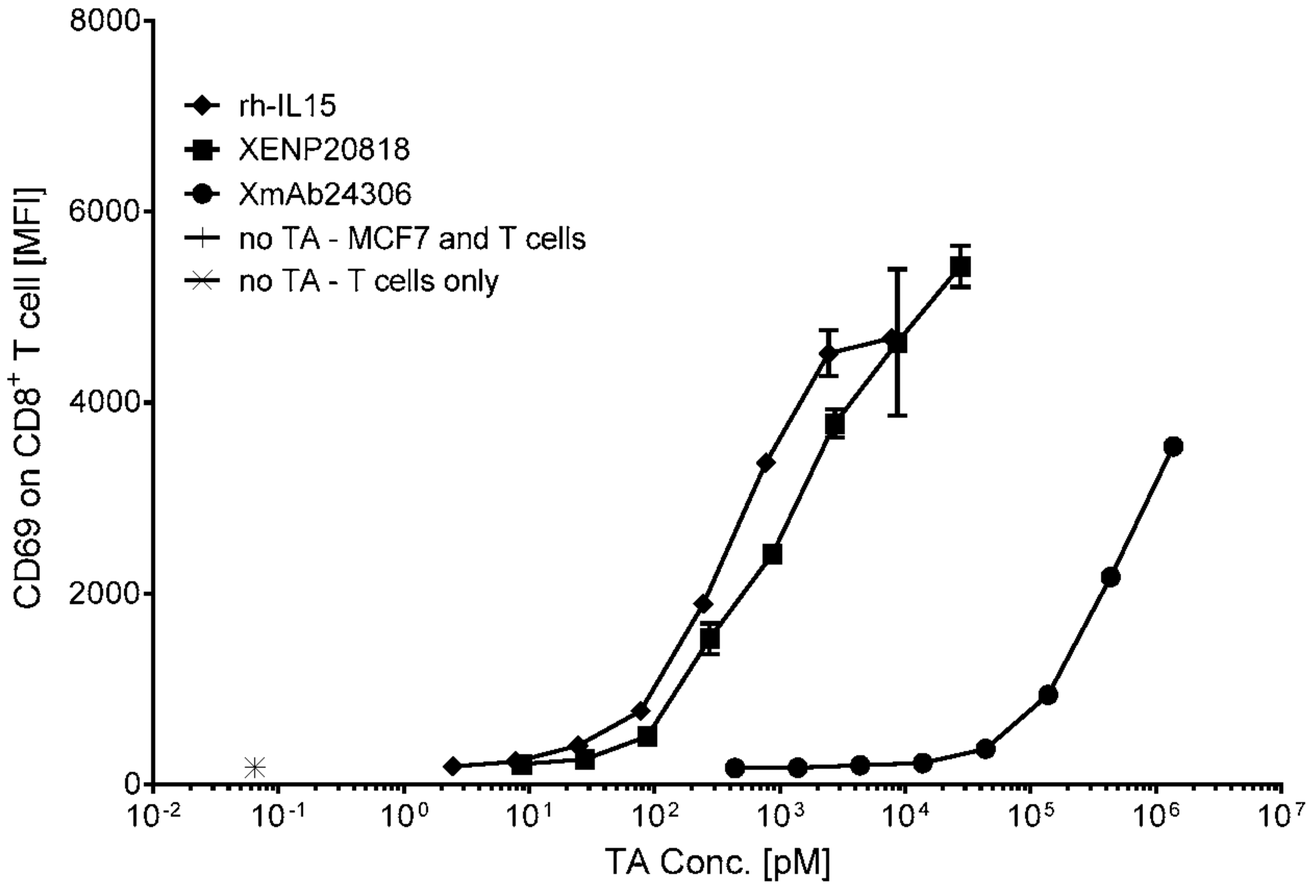


Figure 120B

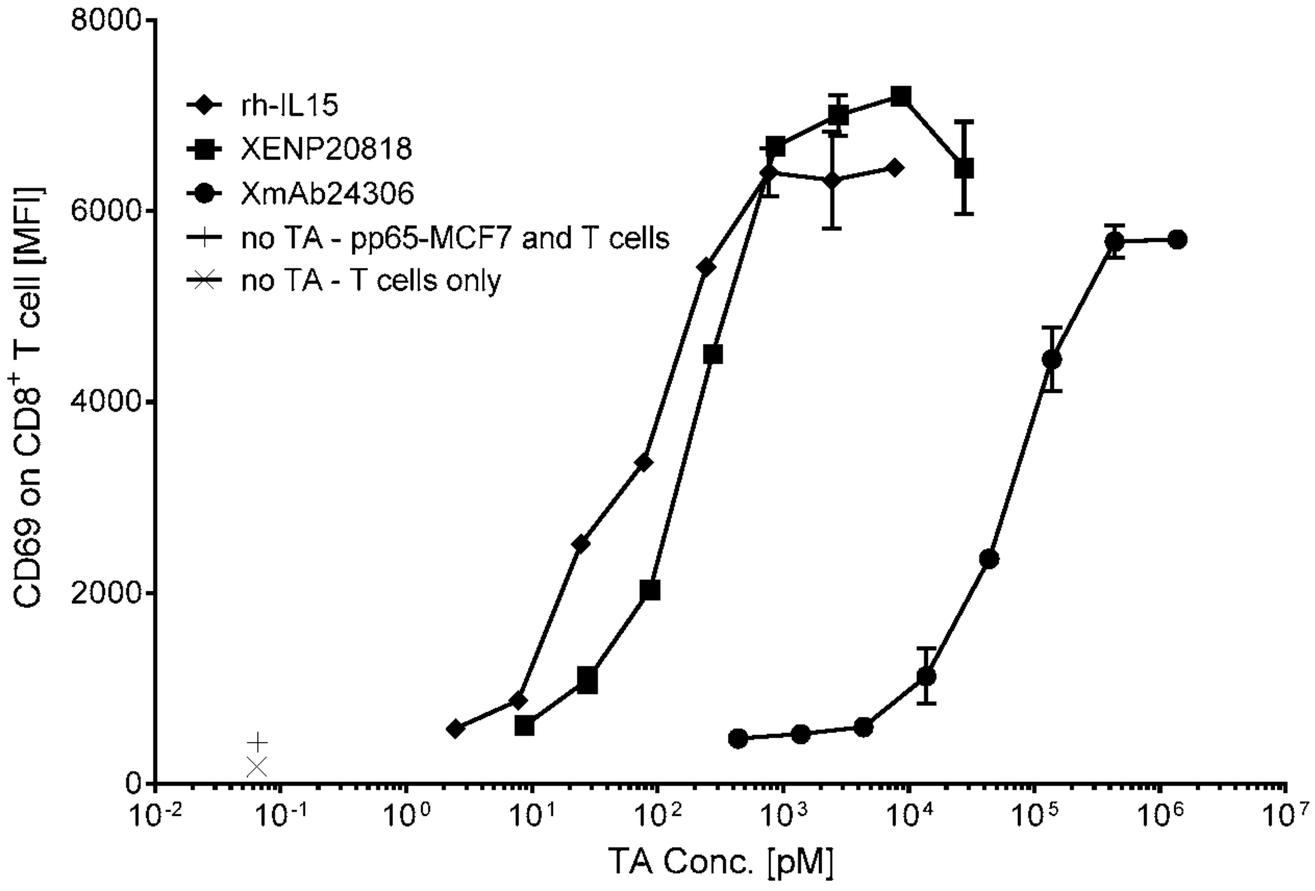


Figure 121A

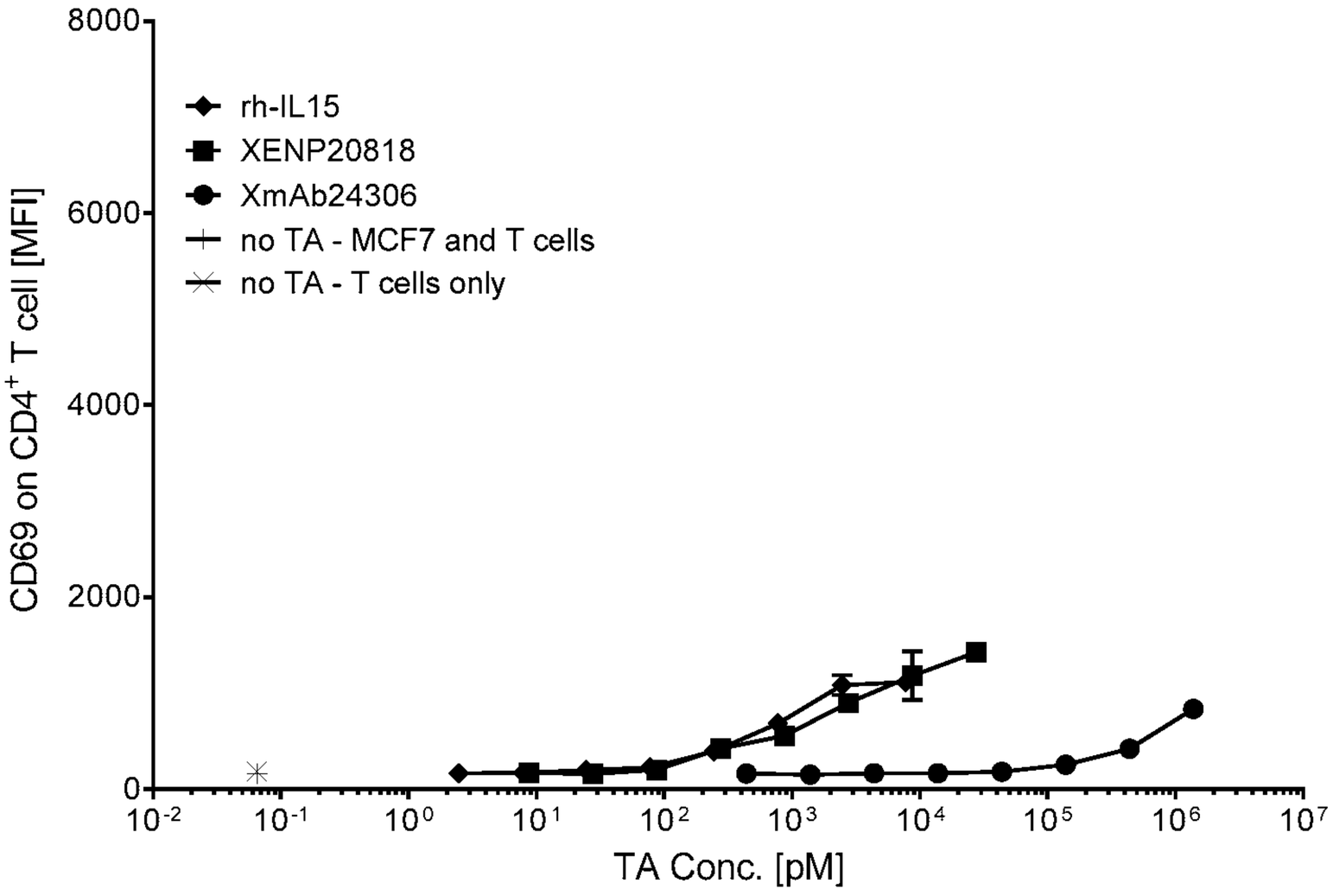


Figure 121B

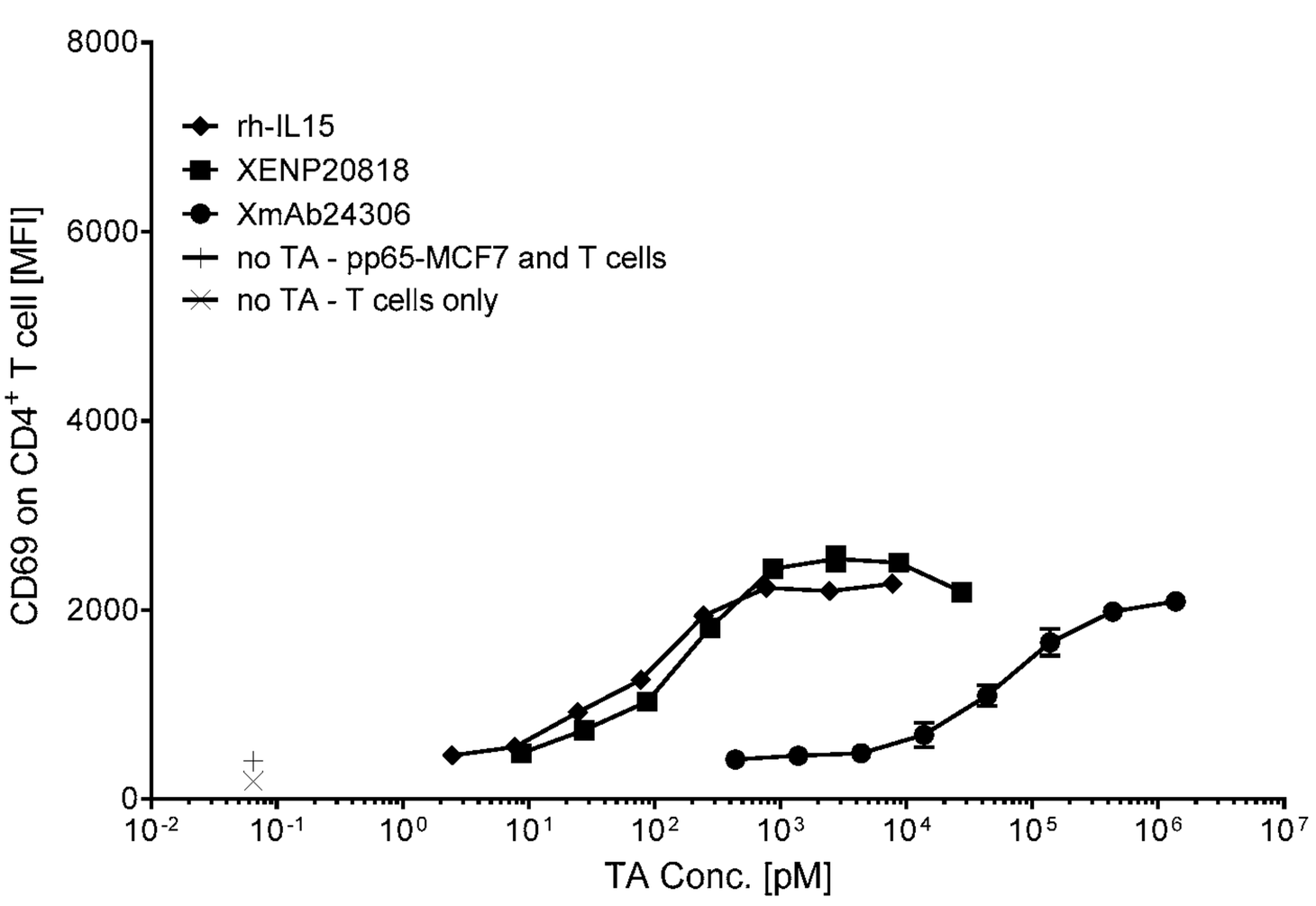


Figure 122A

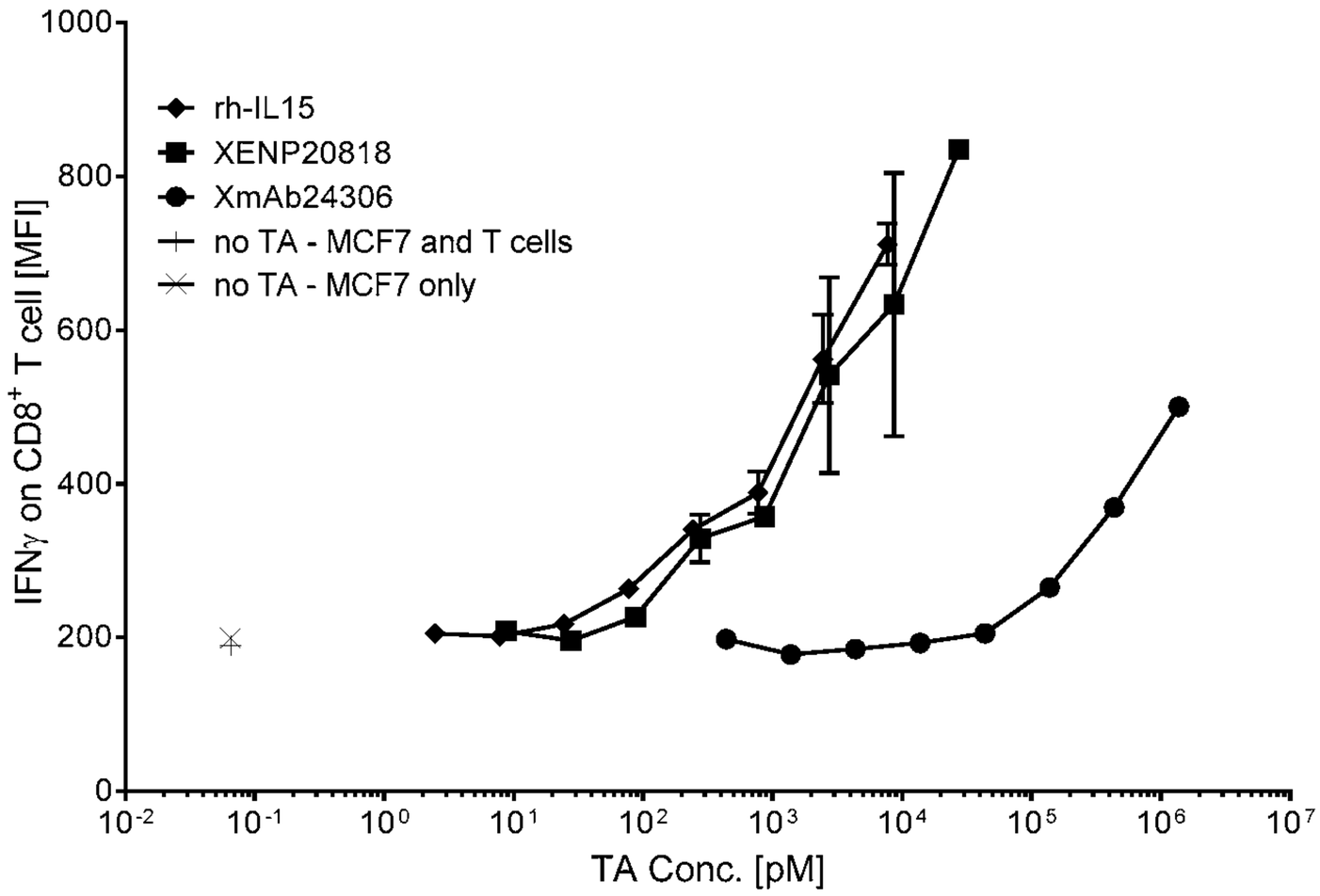


Figure 122B

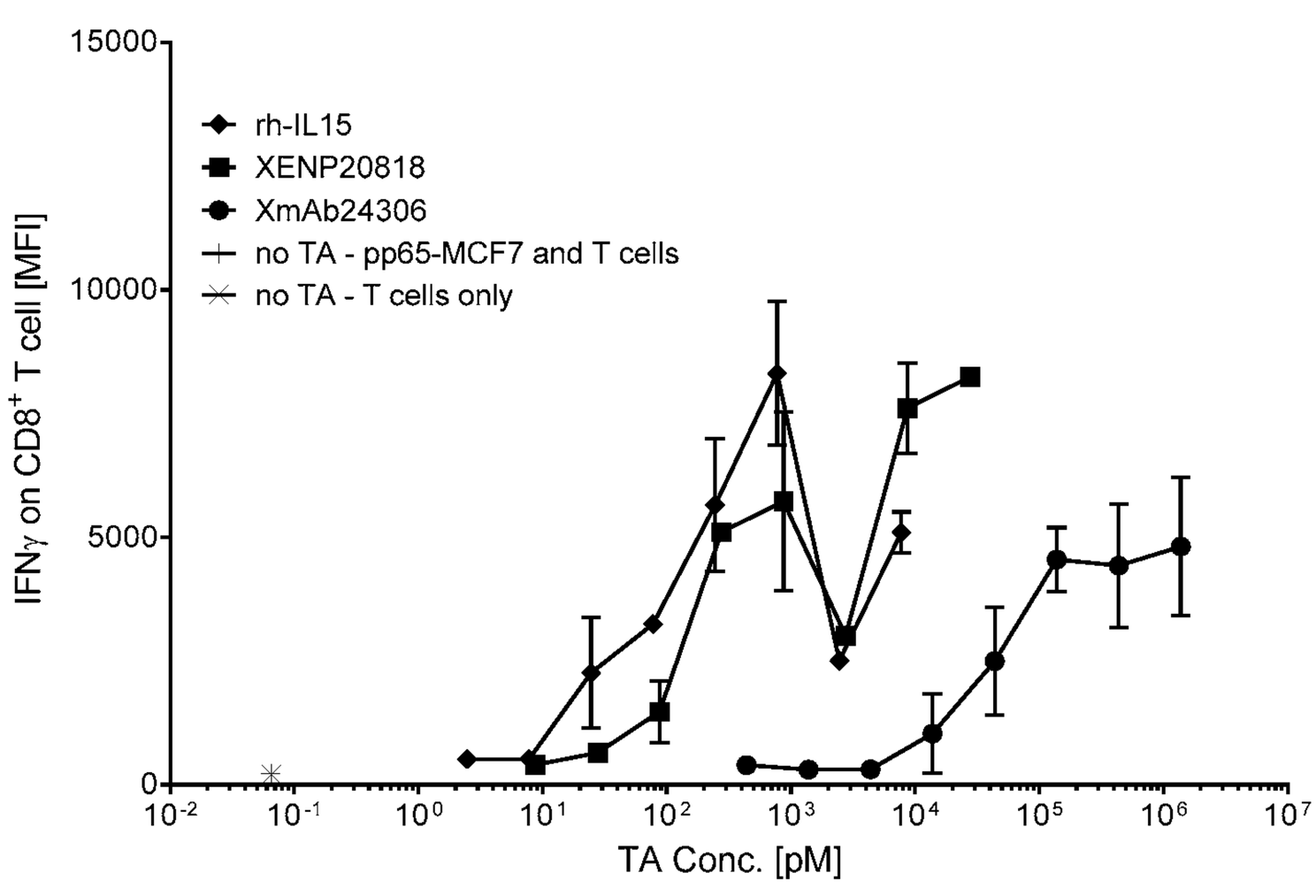


Figure 123A

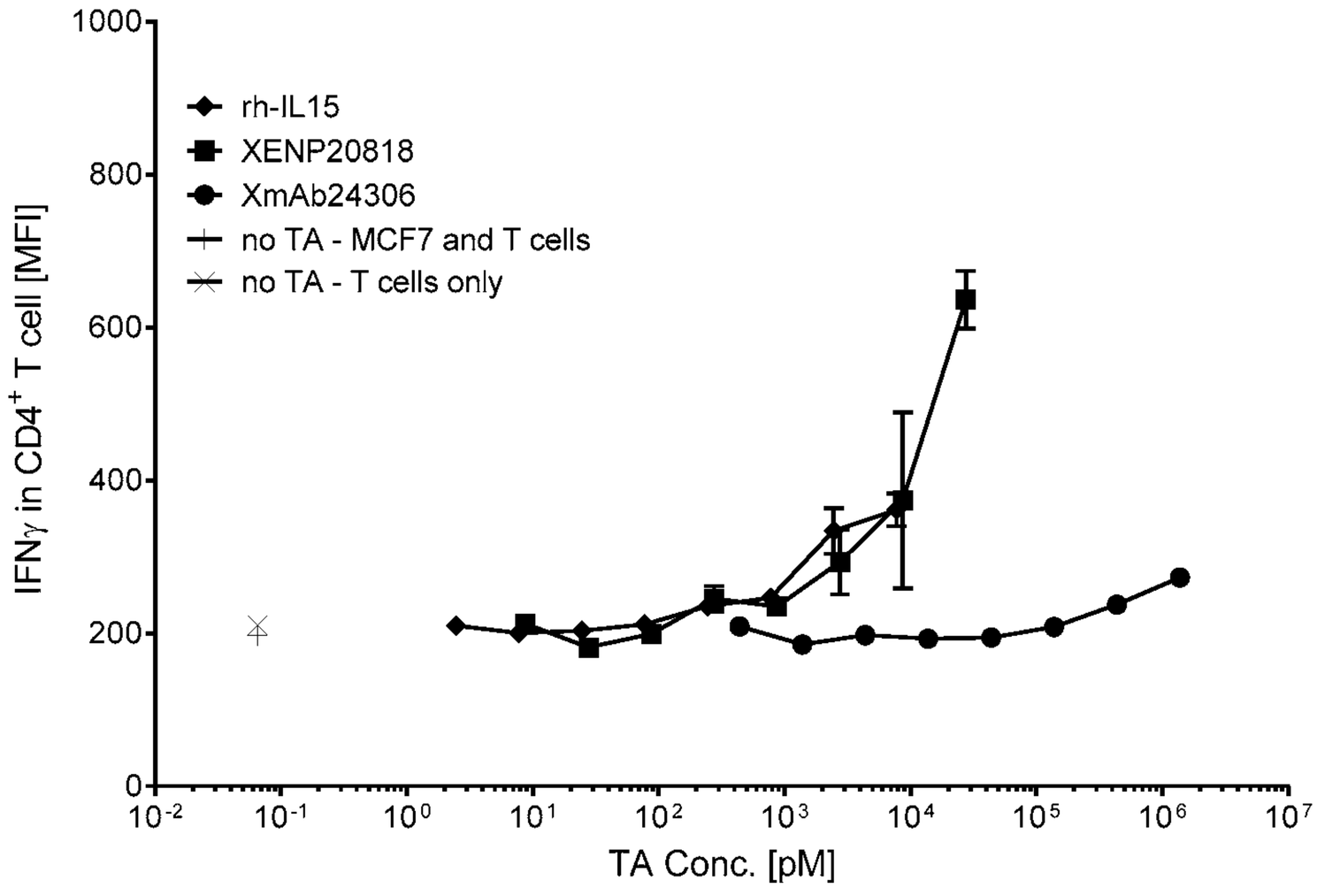


Figure 123B

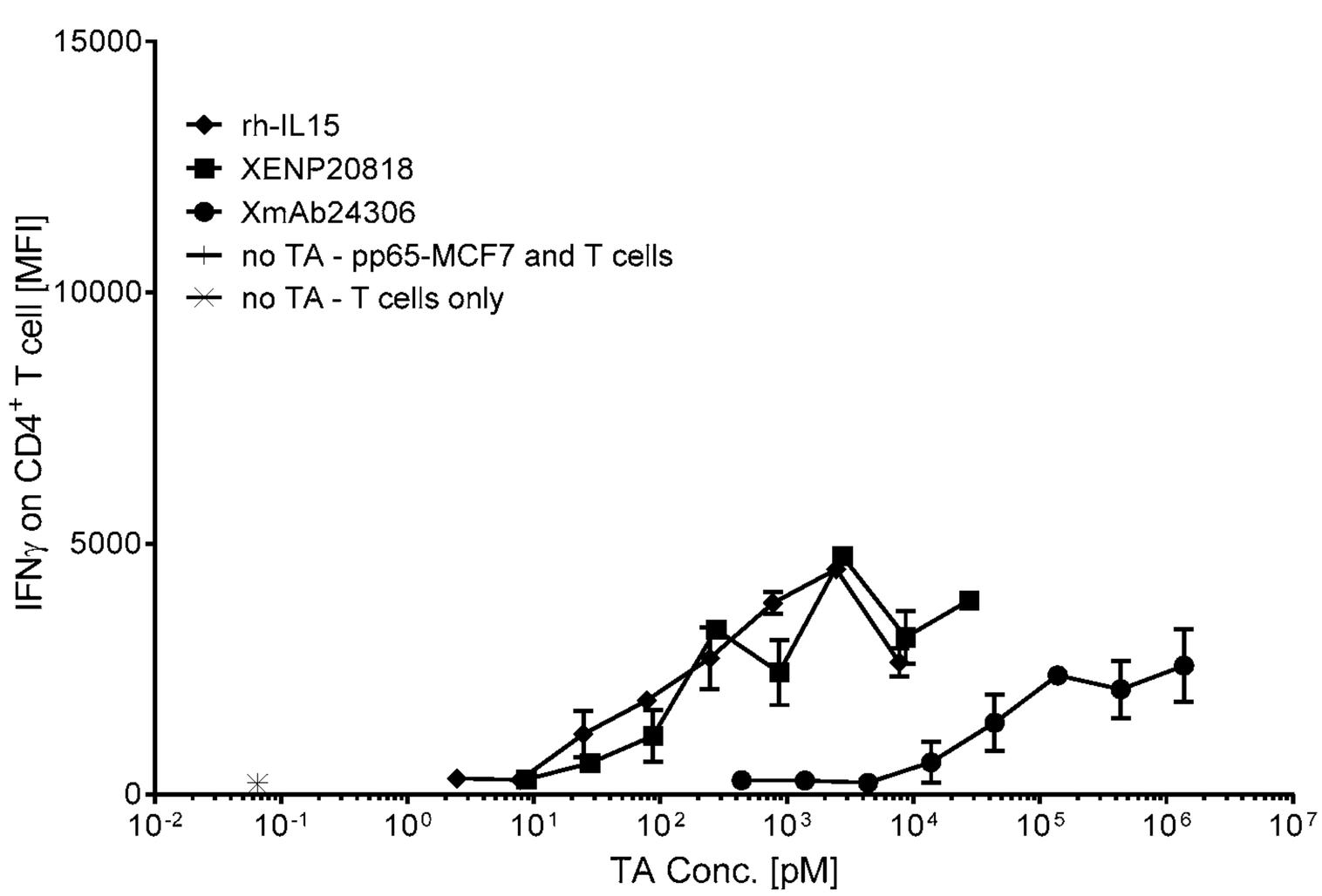


Figure 124A

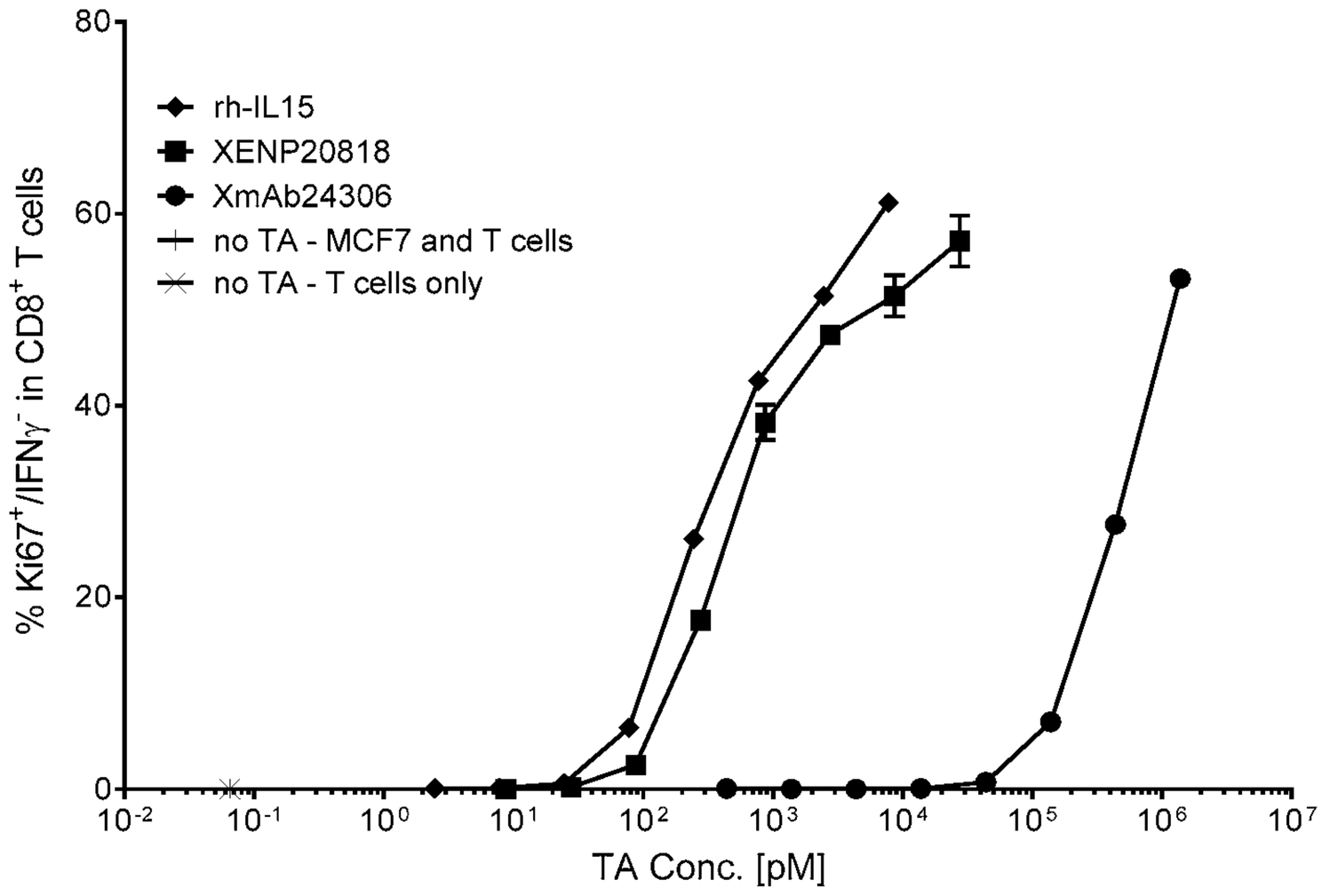


Figure 124B

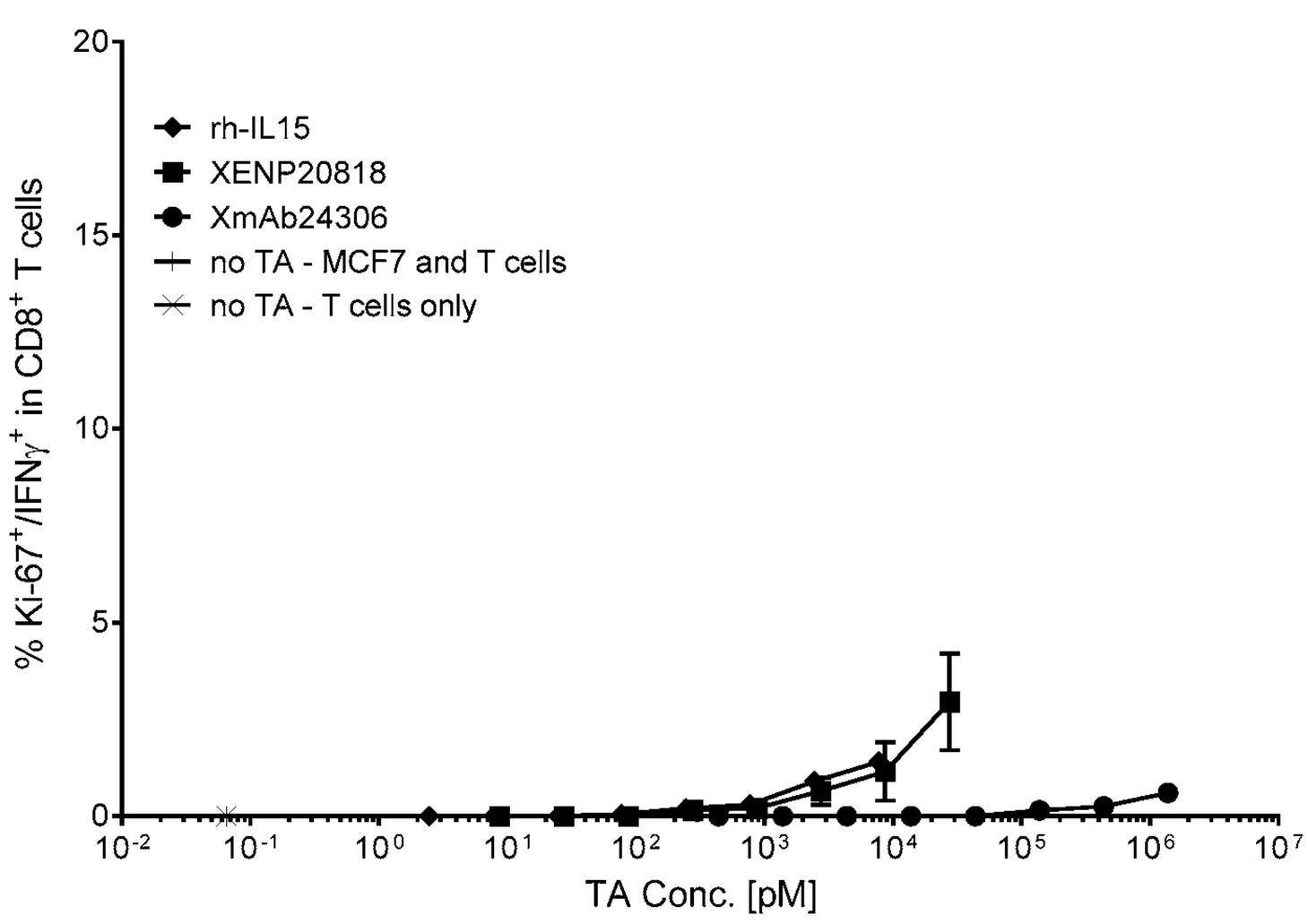


Figure 124C

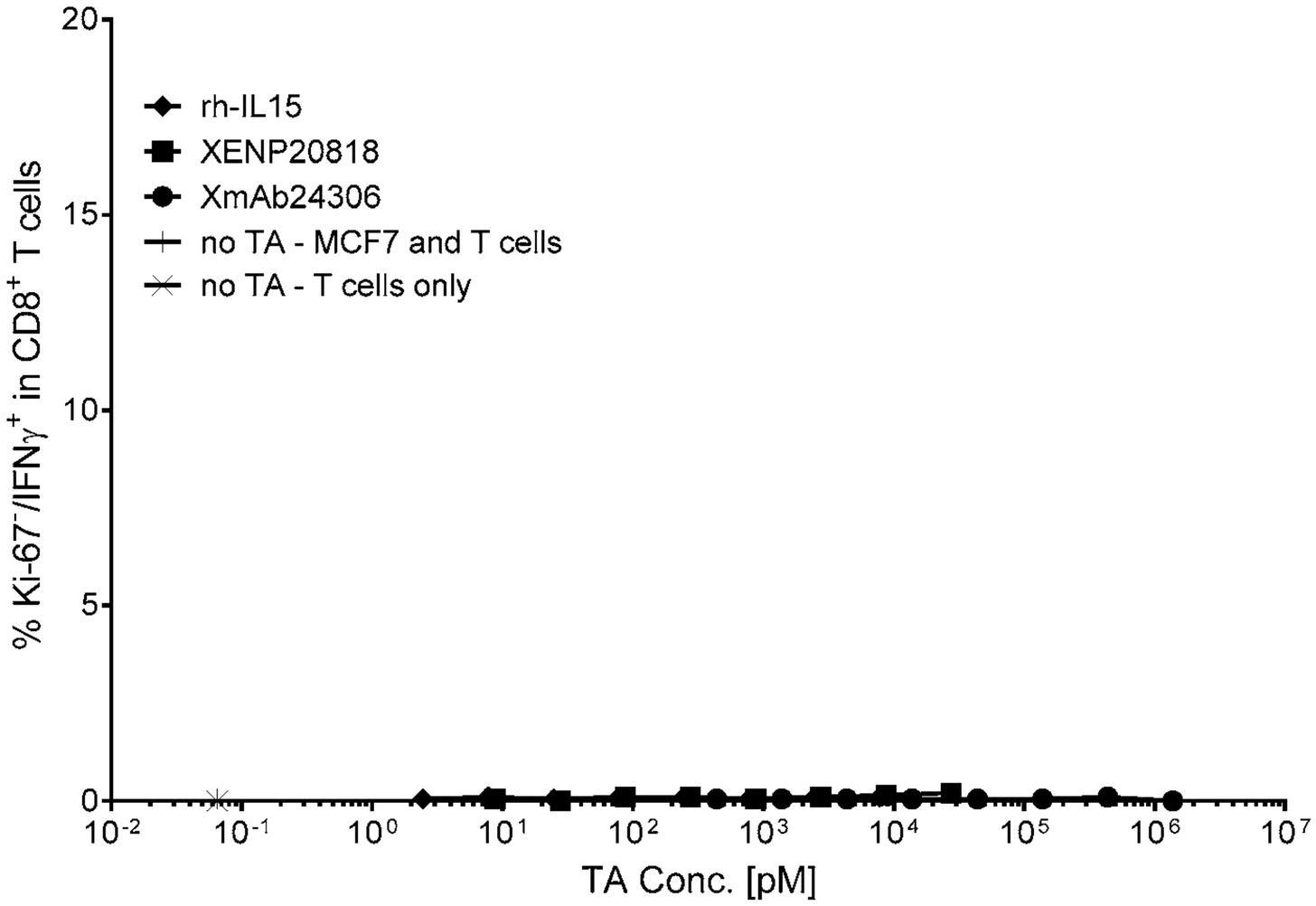

20
15
10
5
0
rh-IL15
XENP20818
XmAb24306
no TA - MCF7 and T cells
no TA - T cells only
% Ki-67+/IFNγ+ in CD8+ T cells
10-2
10-1
100
101
102
103
104
105
106
107
TA Conc. [pM]

Figure 125A

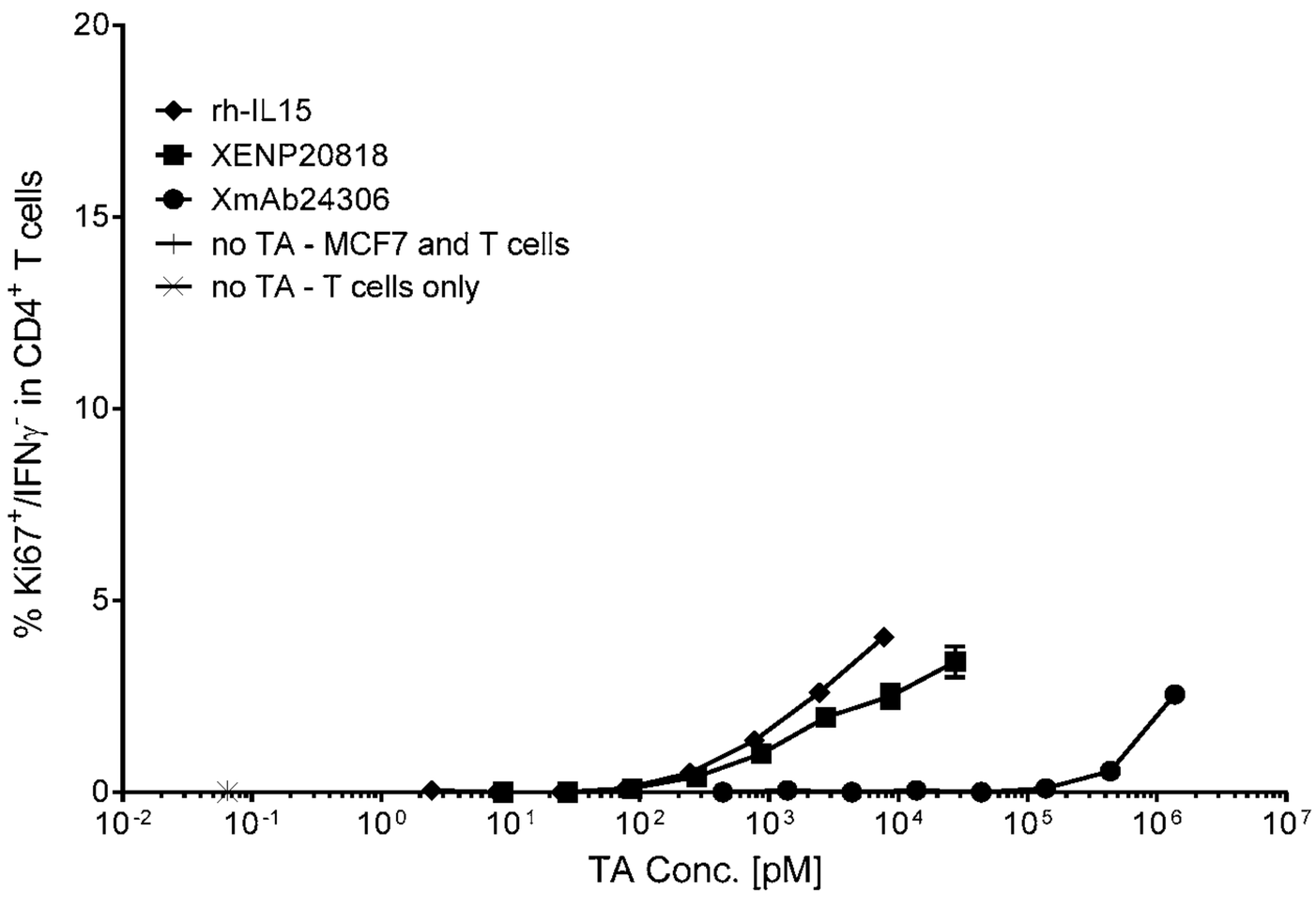


Figure 125B

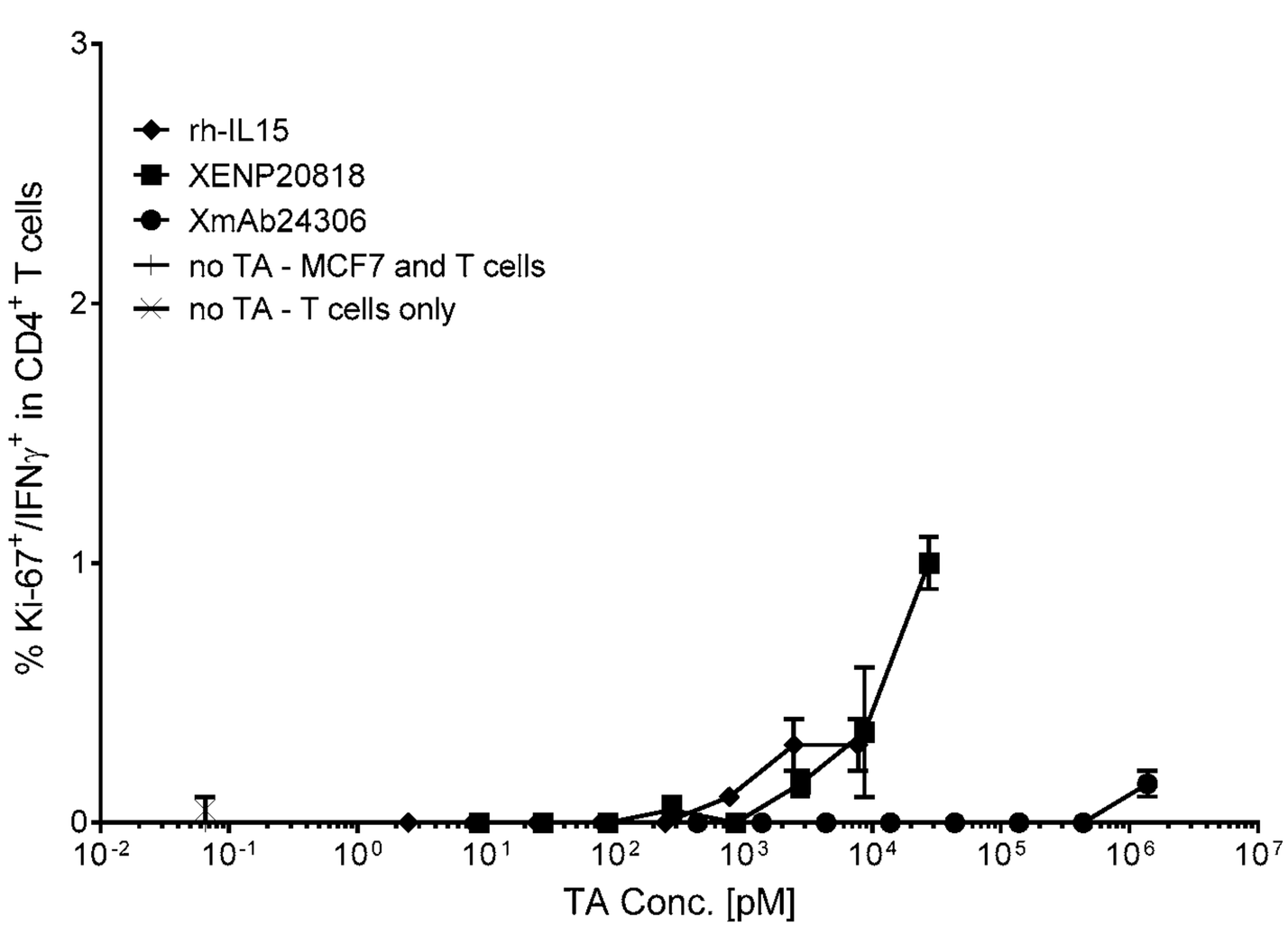


Figure 125C

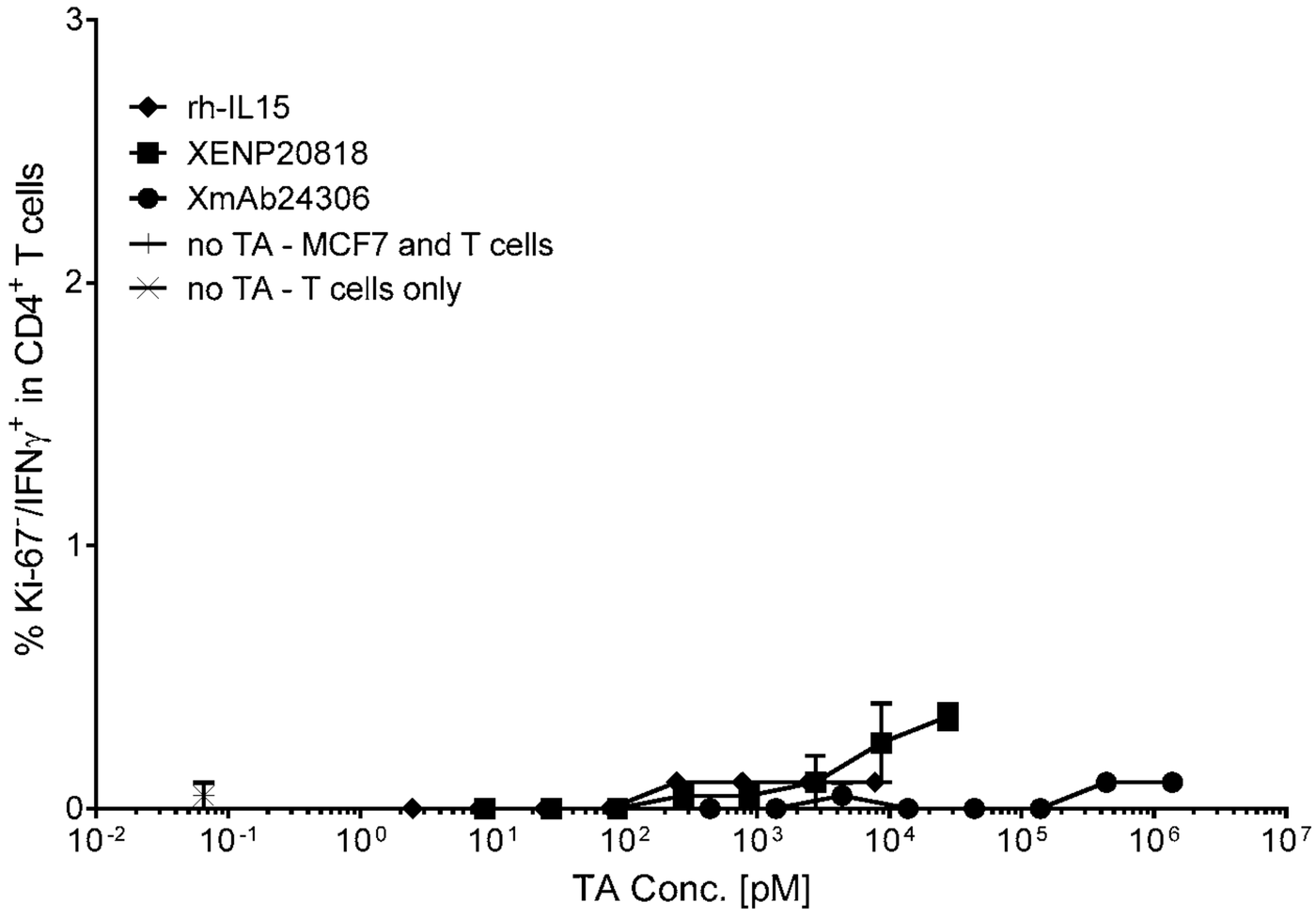

rh-IL15
XENP20818
XmAb24306
no TA - MCF7 and T cells
no TA - T cells only
% Ki-67⁻/IFNγ⁺ in CD4⁺ T cells
0
1
2
3
10⁻²
10⁻¹
10⁰
10¹
10²
10³
10⁴
10⁵
10⁶
10⁷
TA Conc. [pM]

Figure 126A

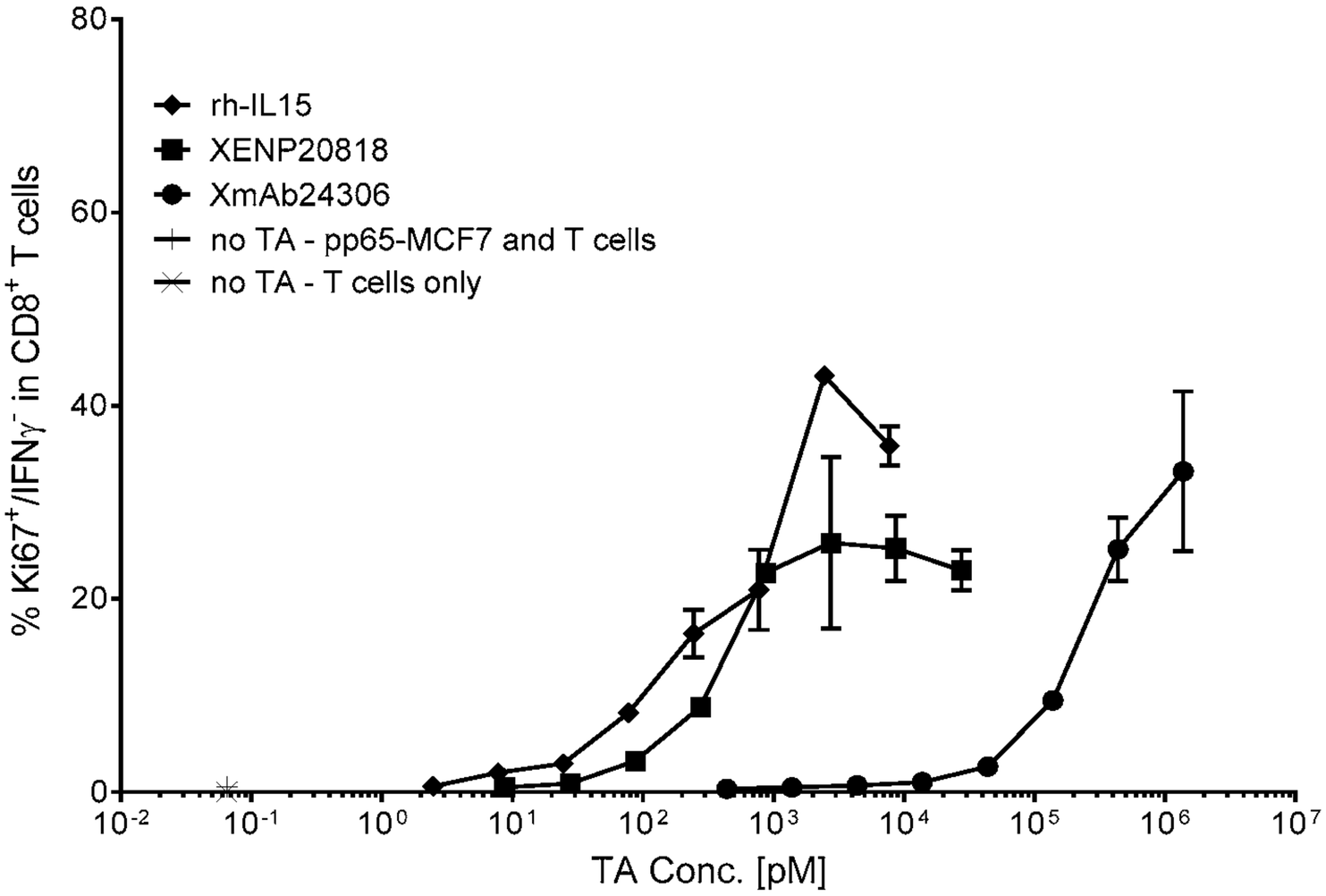


Figure 126B

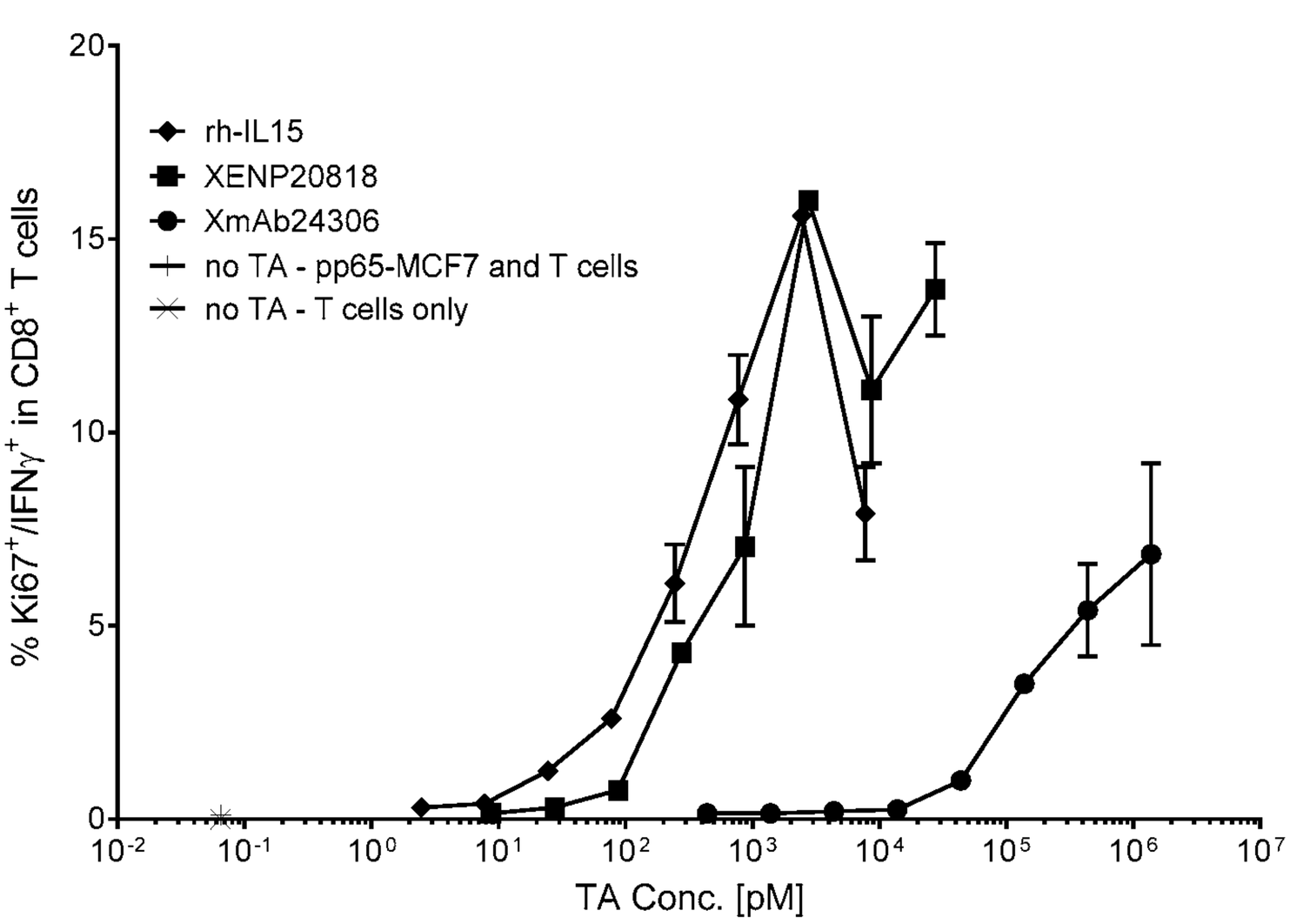


Figure 126C

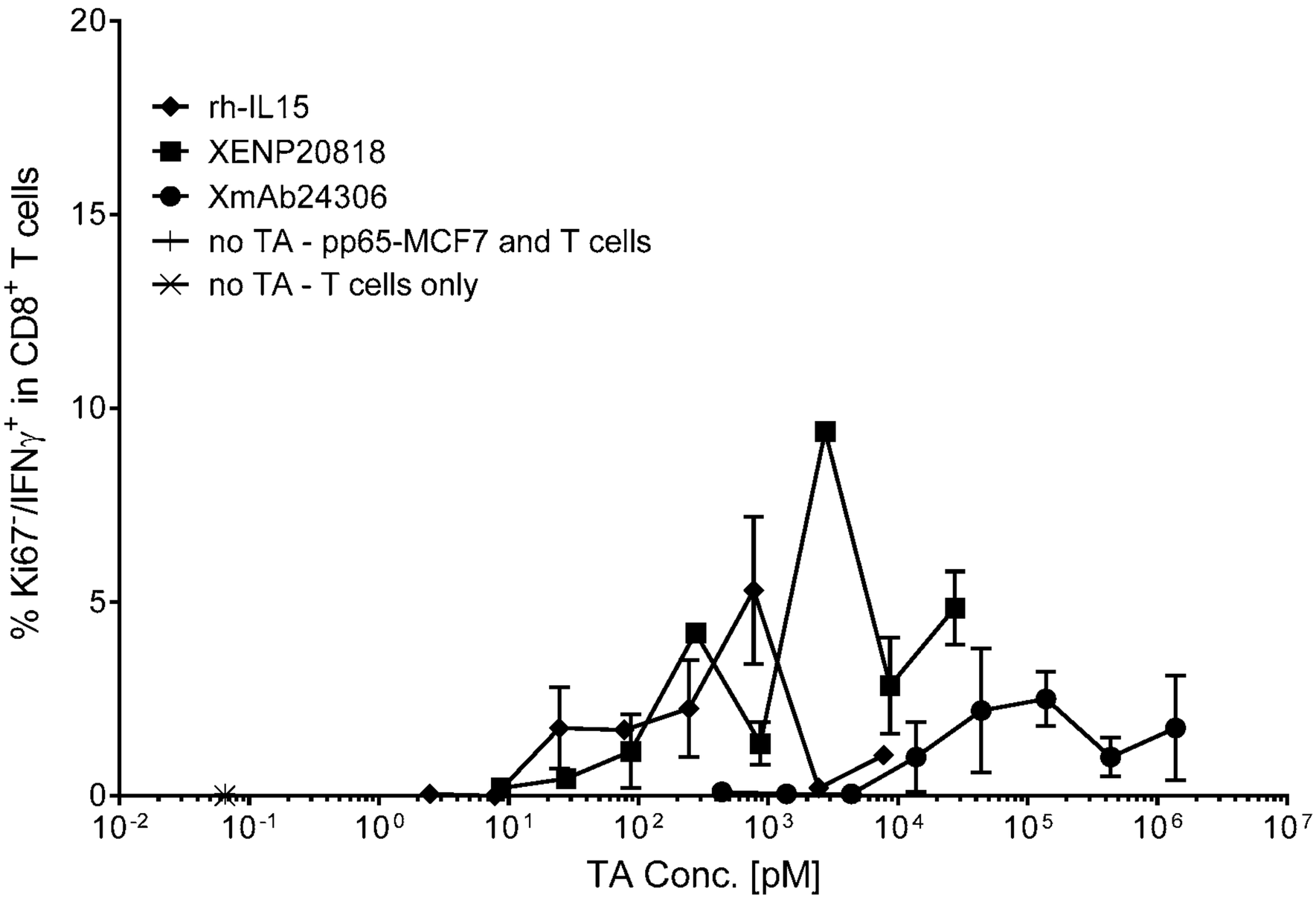

20
15
10
5
0
% Ki67-/IFNγ+ in CD8+ T cells
rh-IL15
XENP20818
XmAb24306
no TA - pp65-MCF7 and T cells
no TA - T cells only
10-2
10-1
100
101
102
103
104
105
106
107
TA Conc. [pM]

Figure 127A

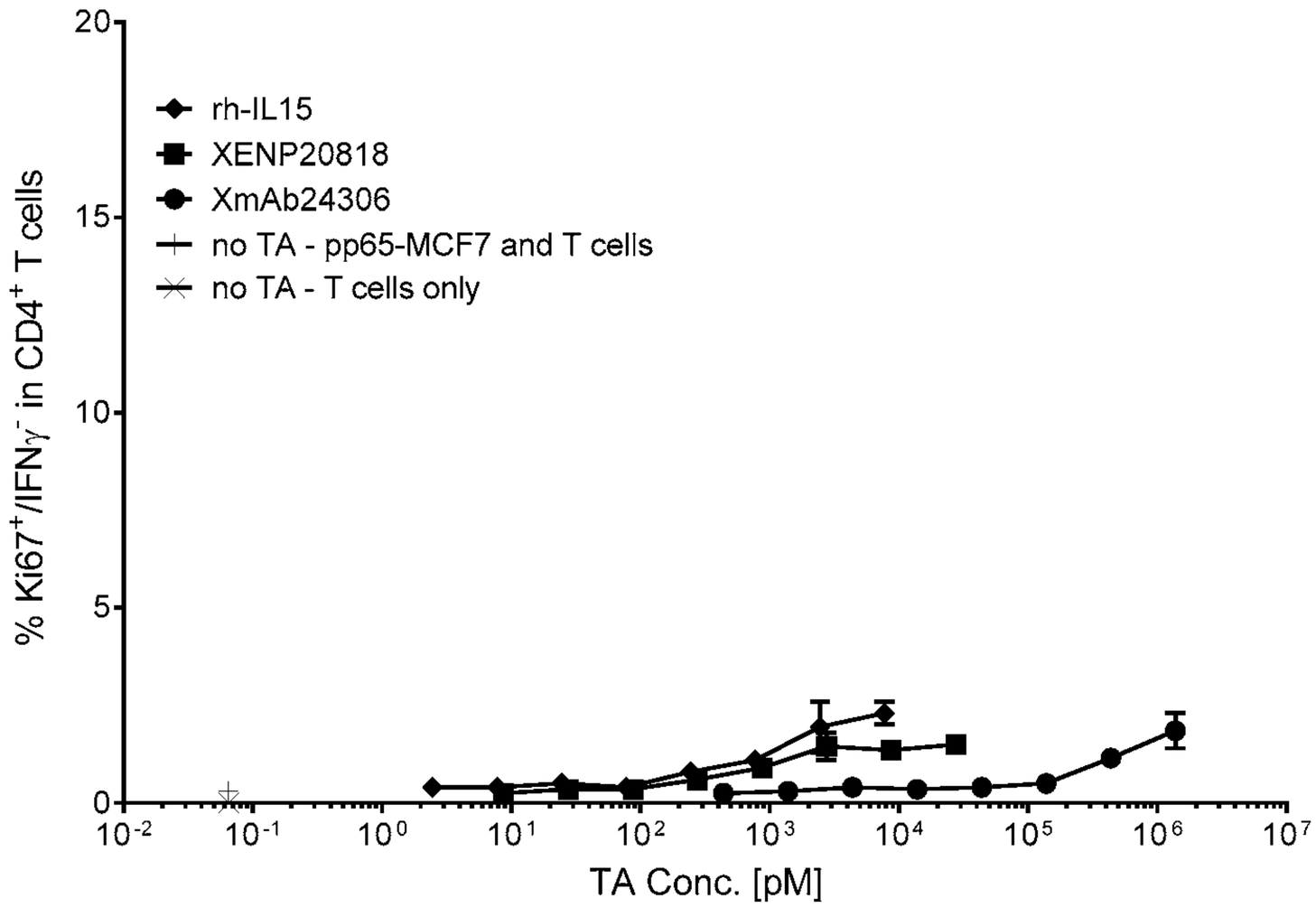


Figure 127B

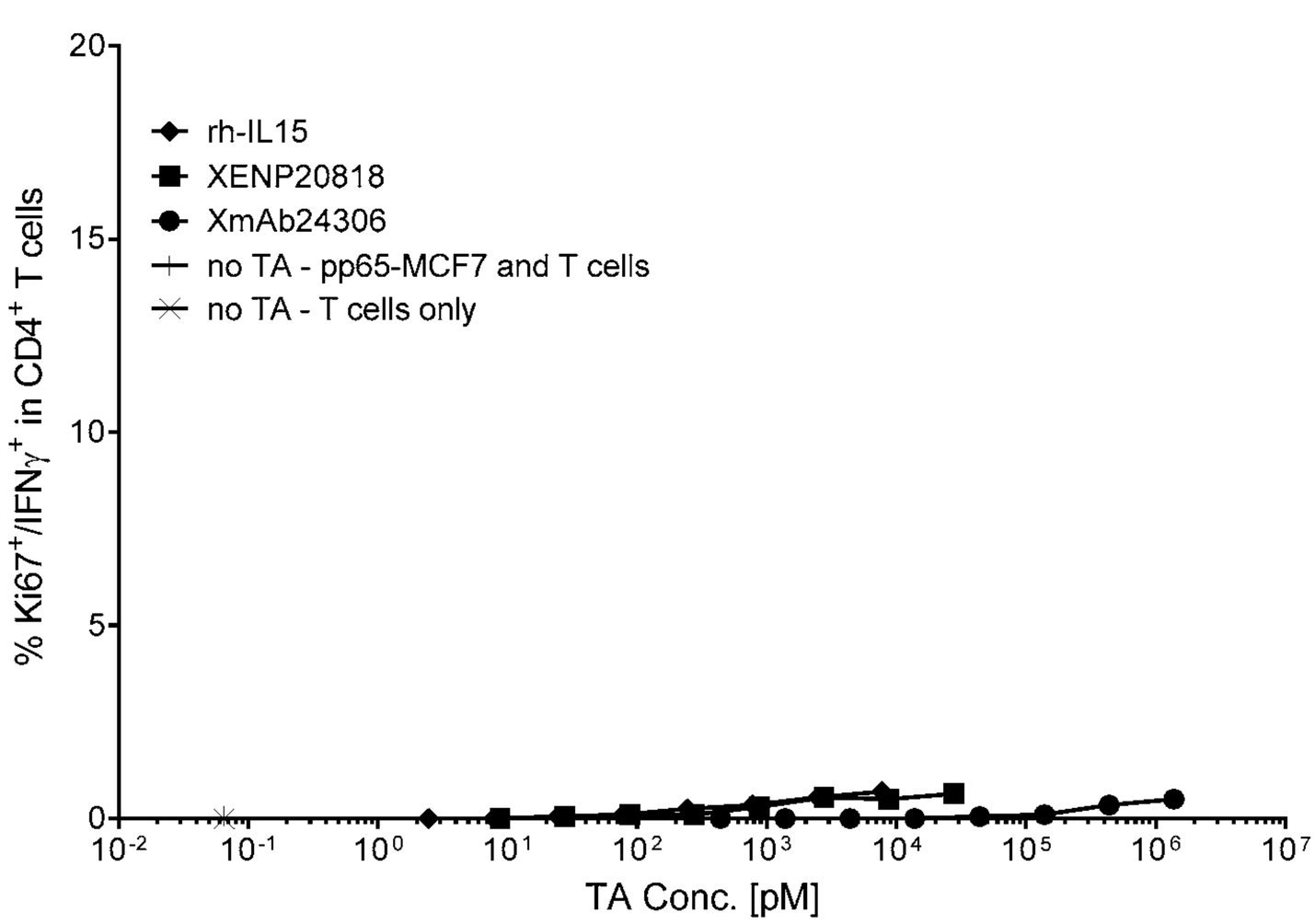


Figure 127C

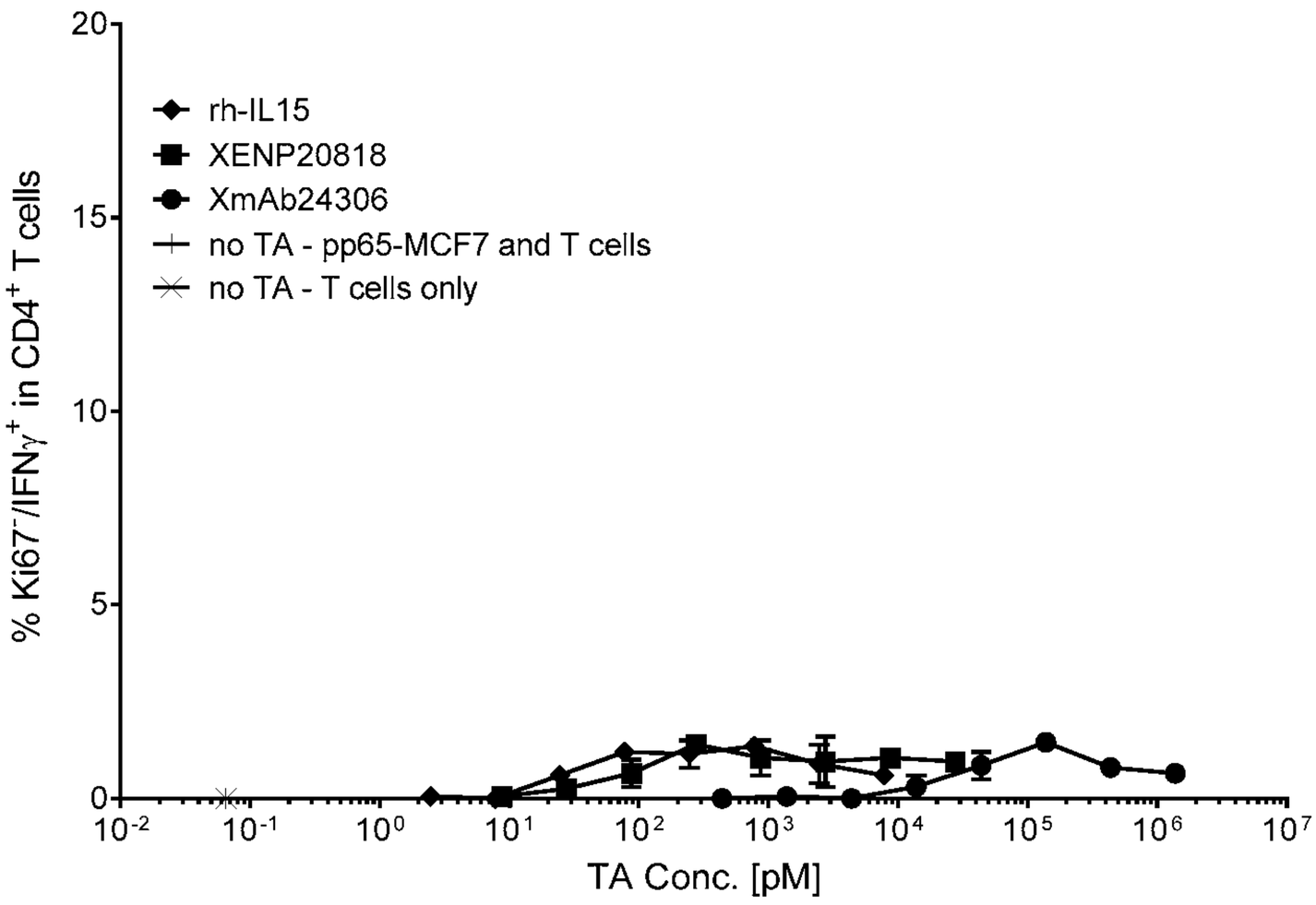

rh-IL15
XENP20818
XmAb24306
no TA - pp65-MCF7 and T cells
no TA - T cells only
% Ki67⁻/IFNγ⁺ in CD4⁺ T cells
TA Conc. [pM]
0
5
10
15
20
10⁻²
10⁻¹
10⁰
10¹
10²
10³
10⁴
10⁵
10⁶
10⁷

Figure 128A

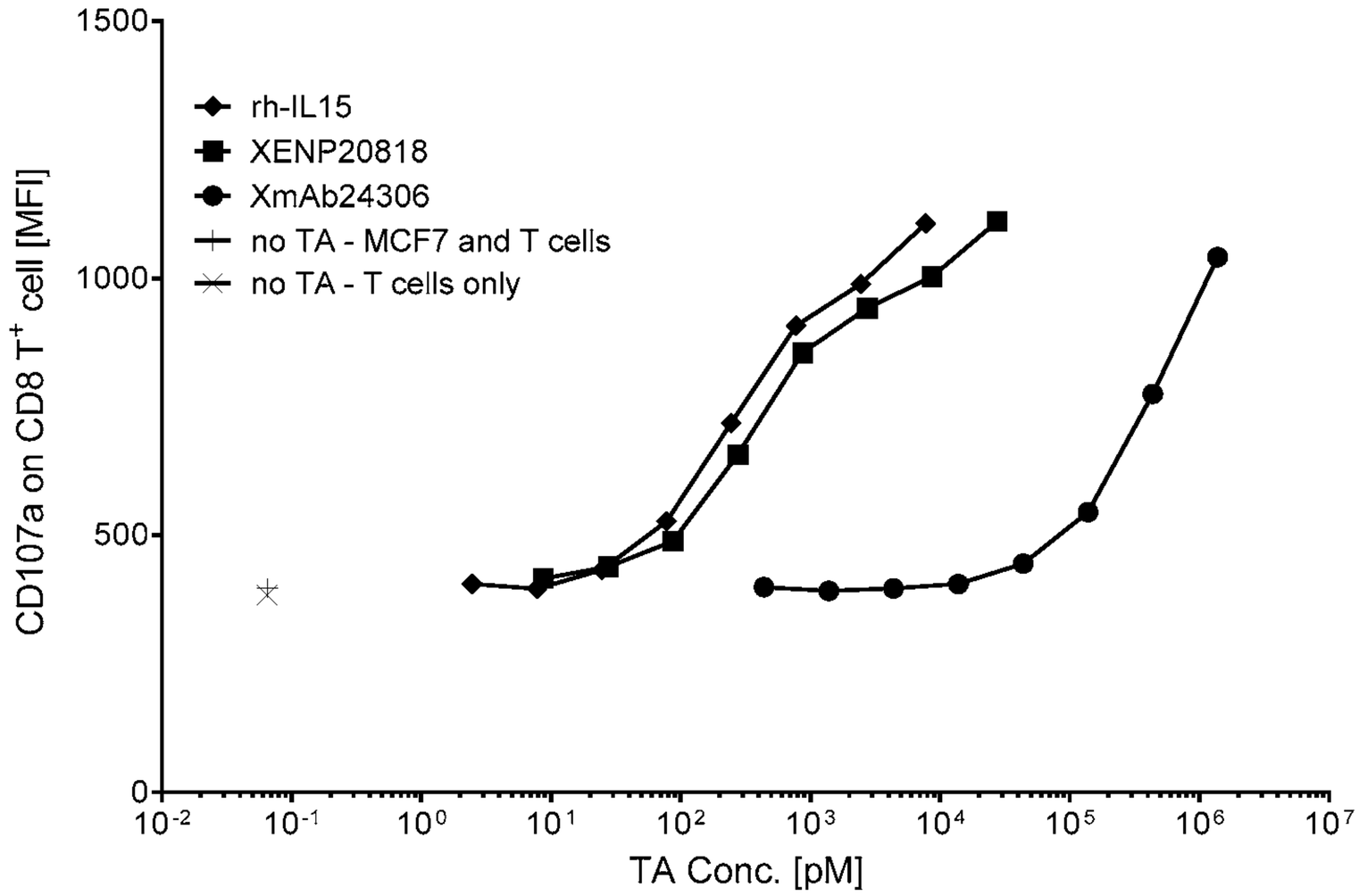


Figure 128B

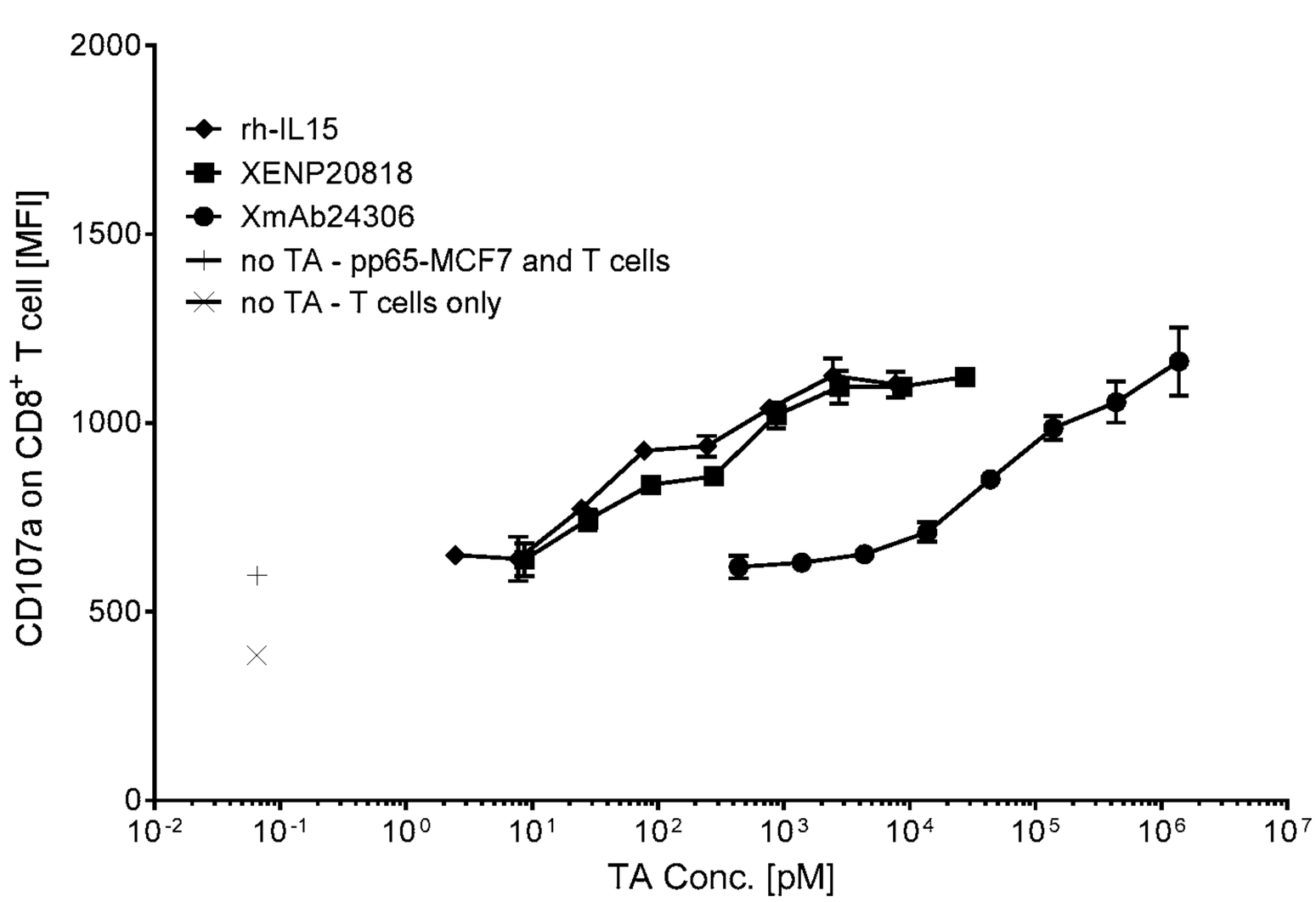


Figure 129A

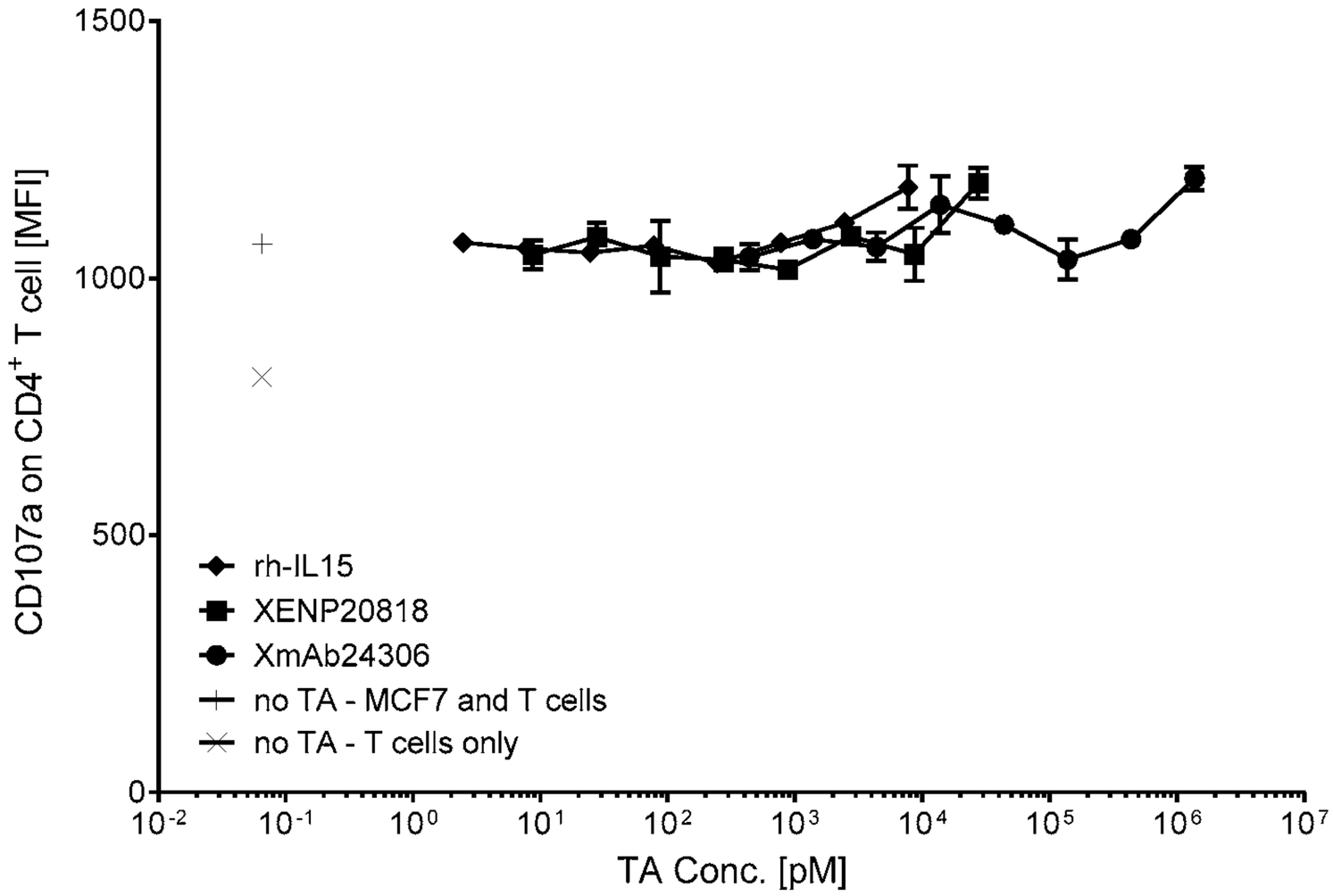


Figure 129B

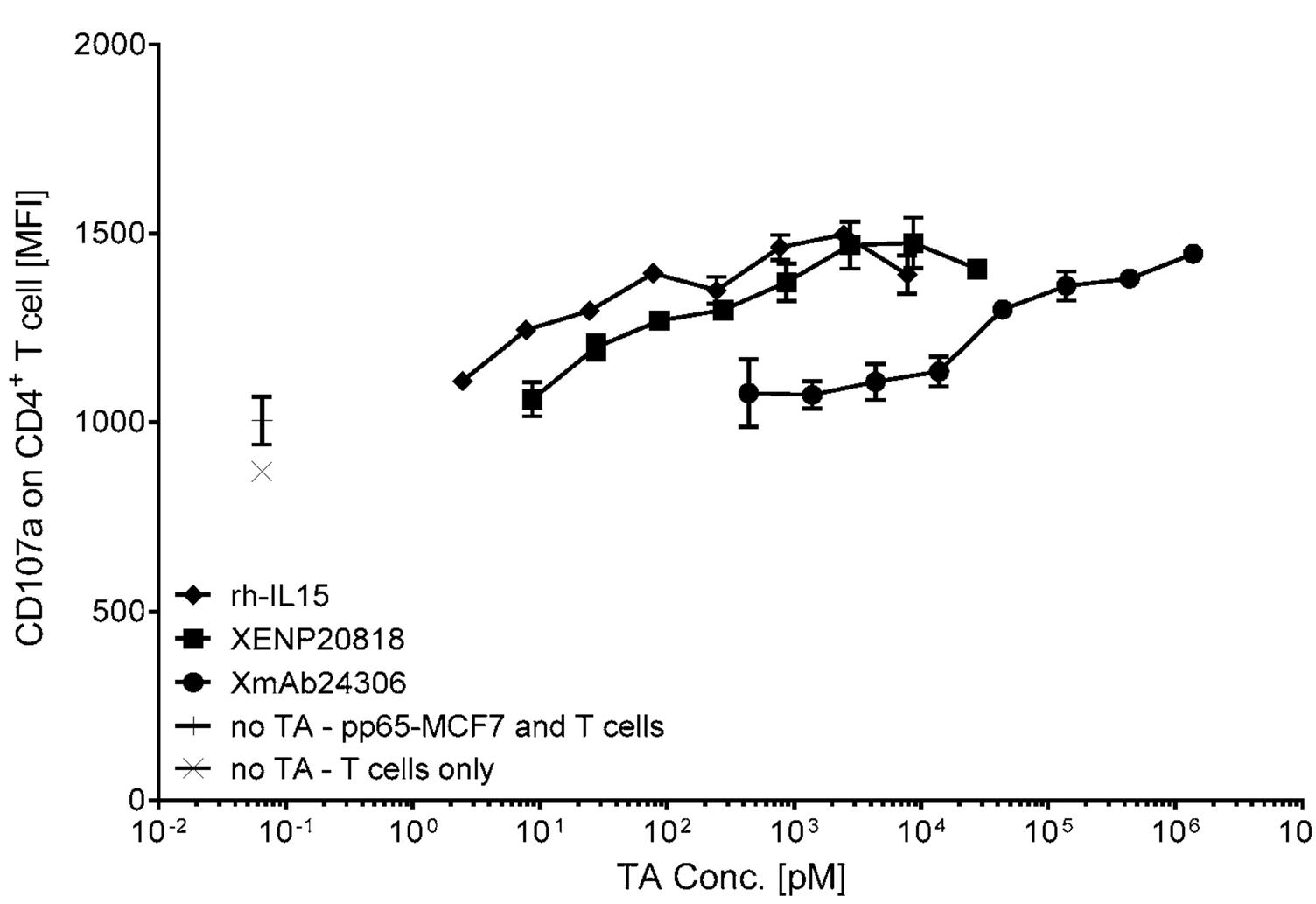


Figure 130A

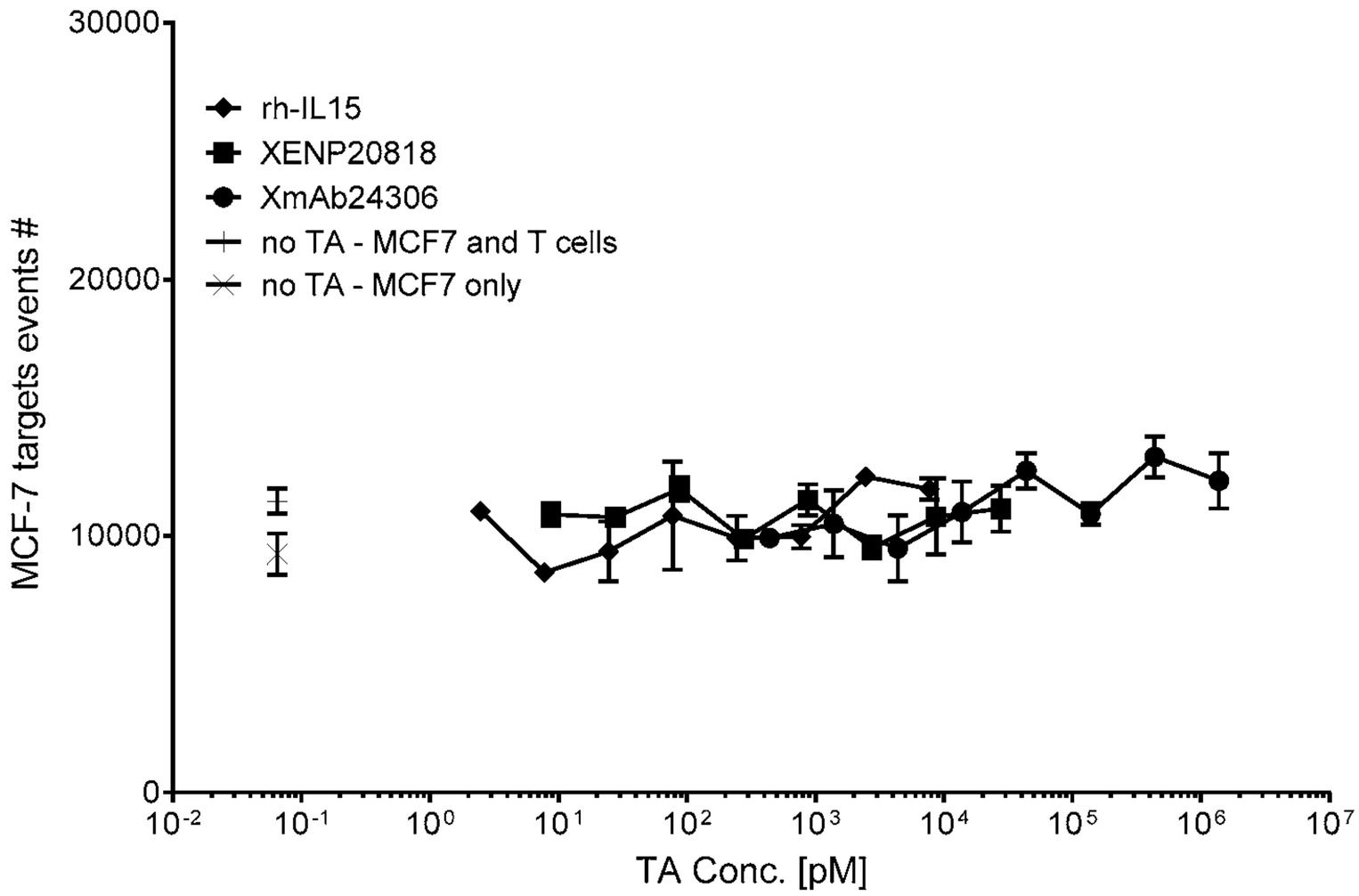


Figure 130B

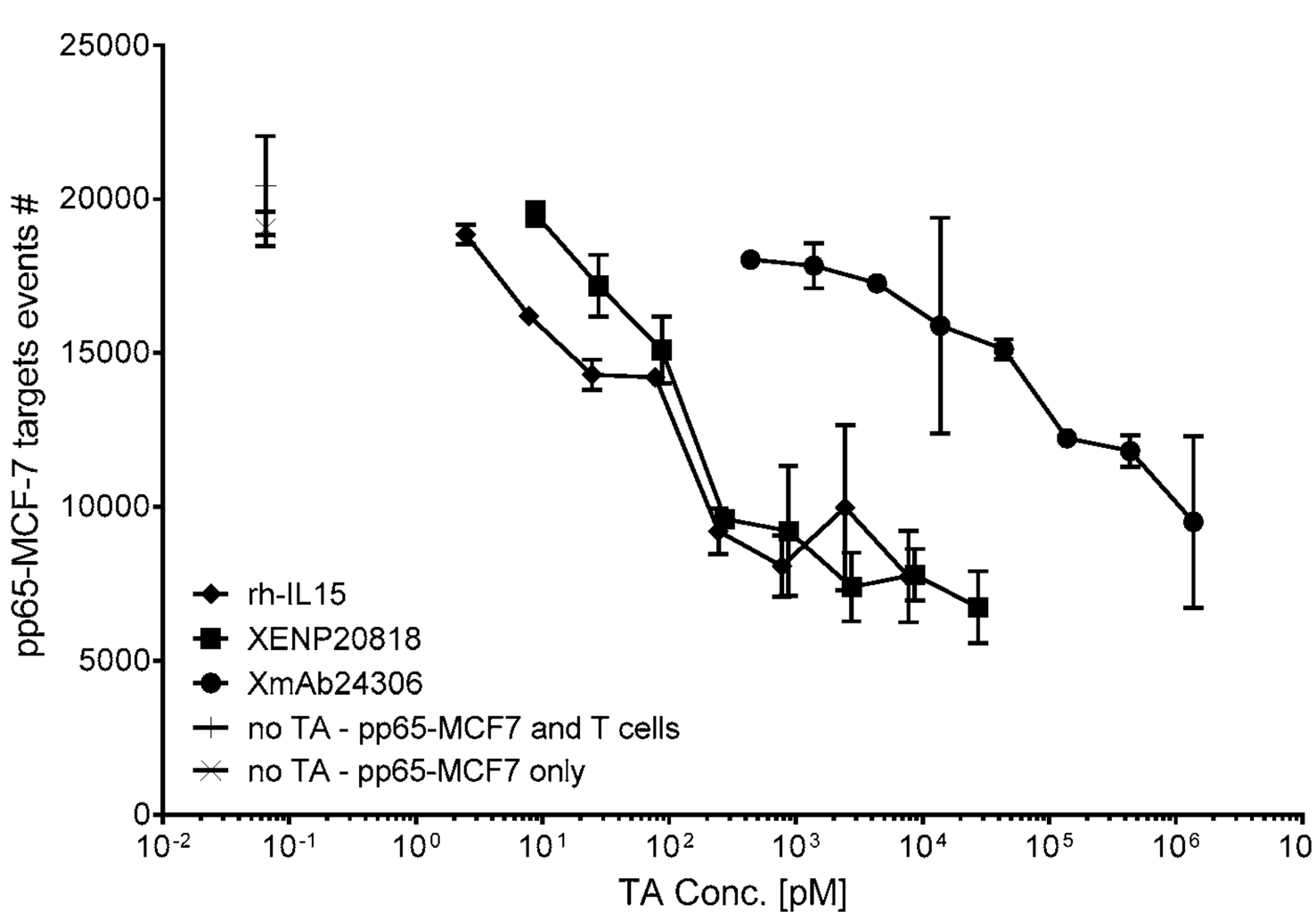


Figure 131A

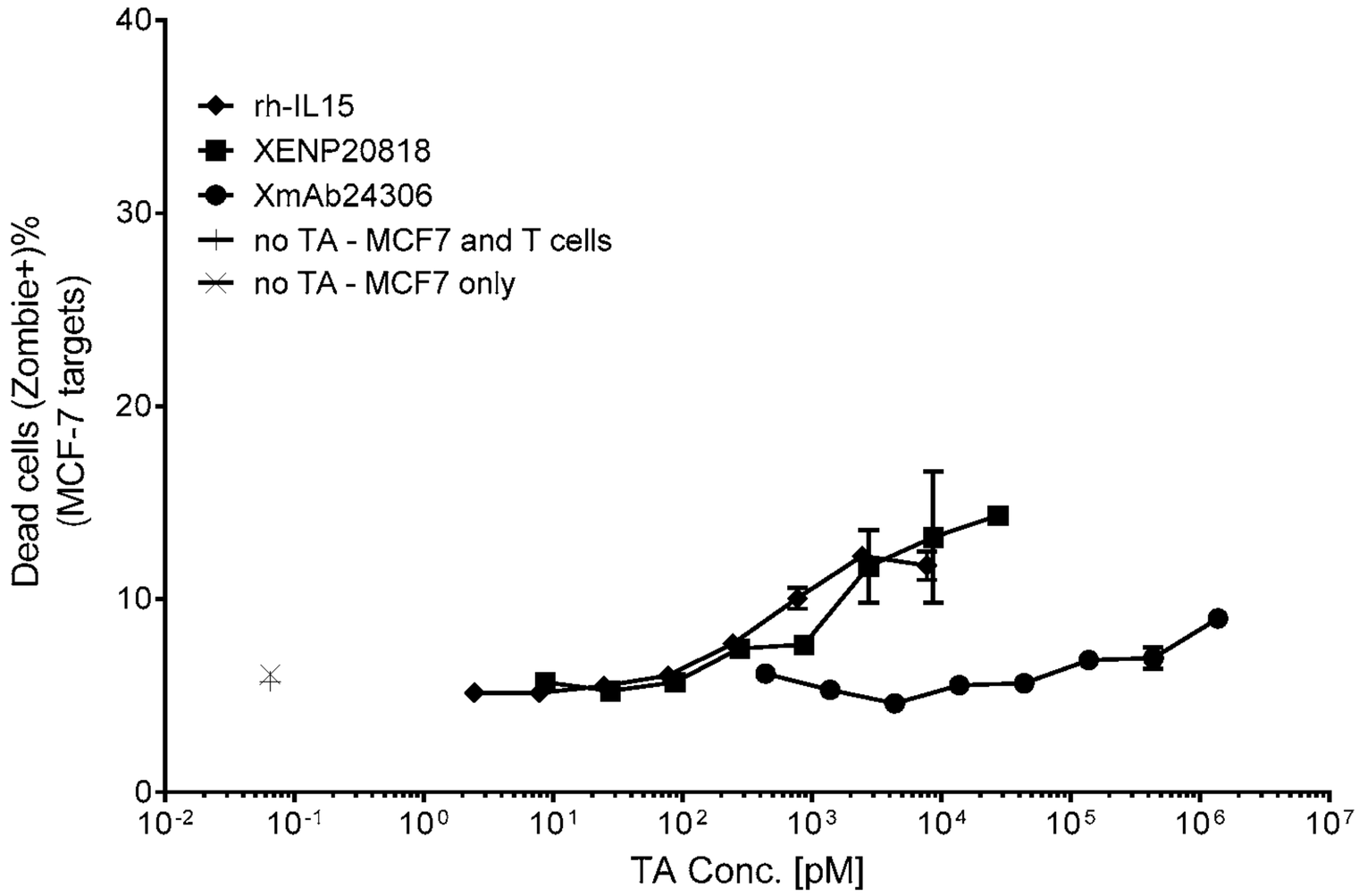


Figure 131B

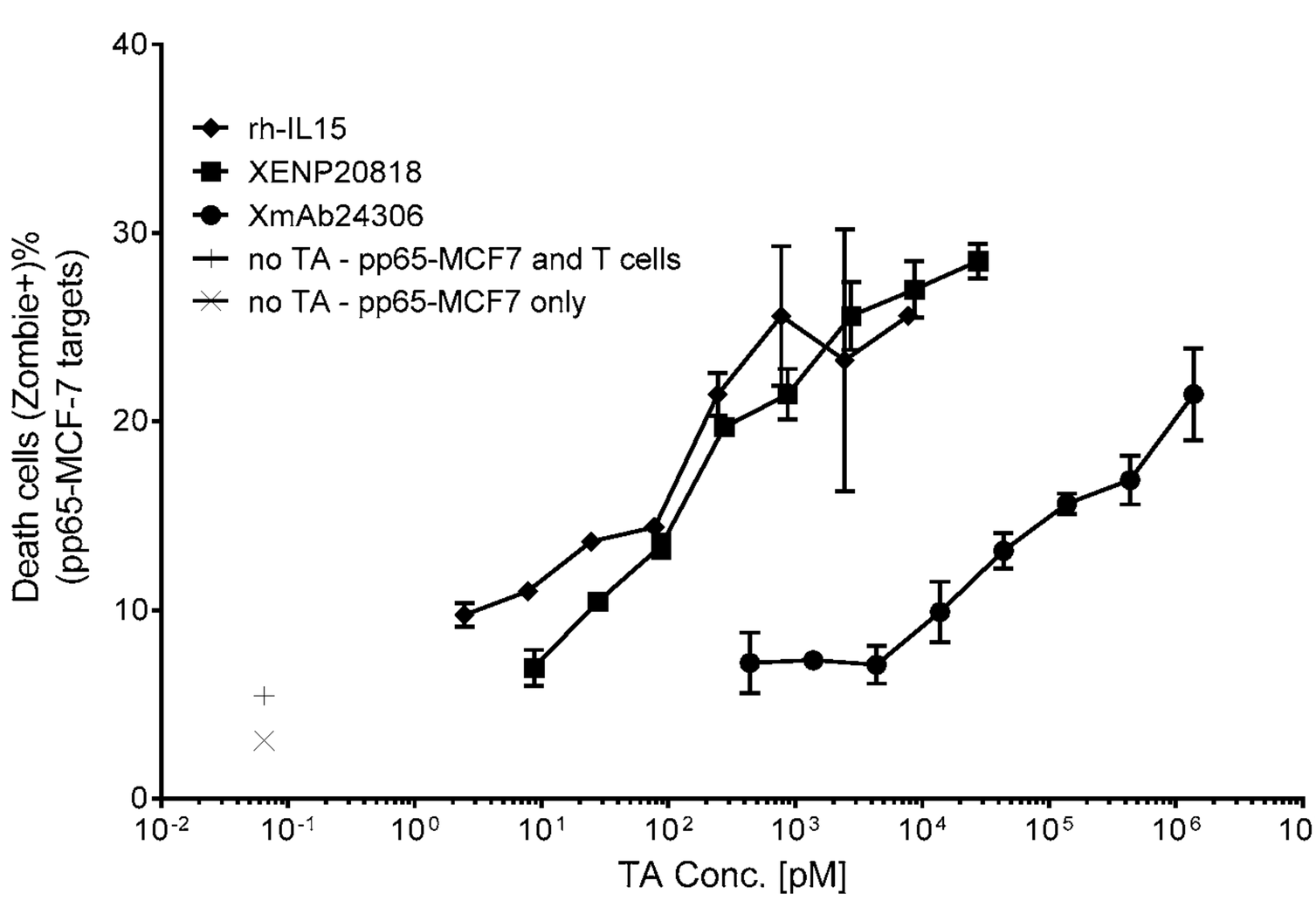


Figure 132

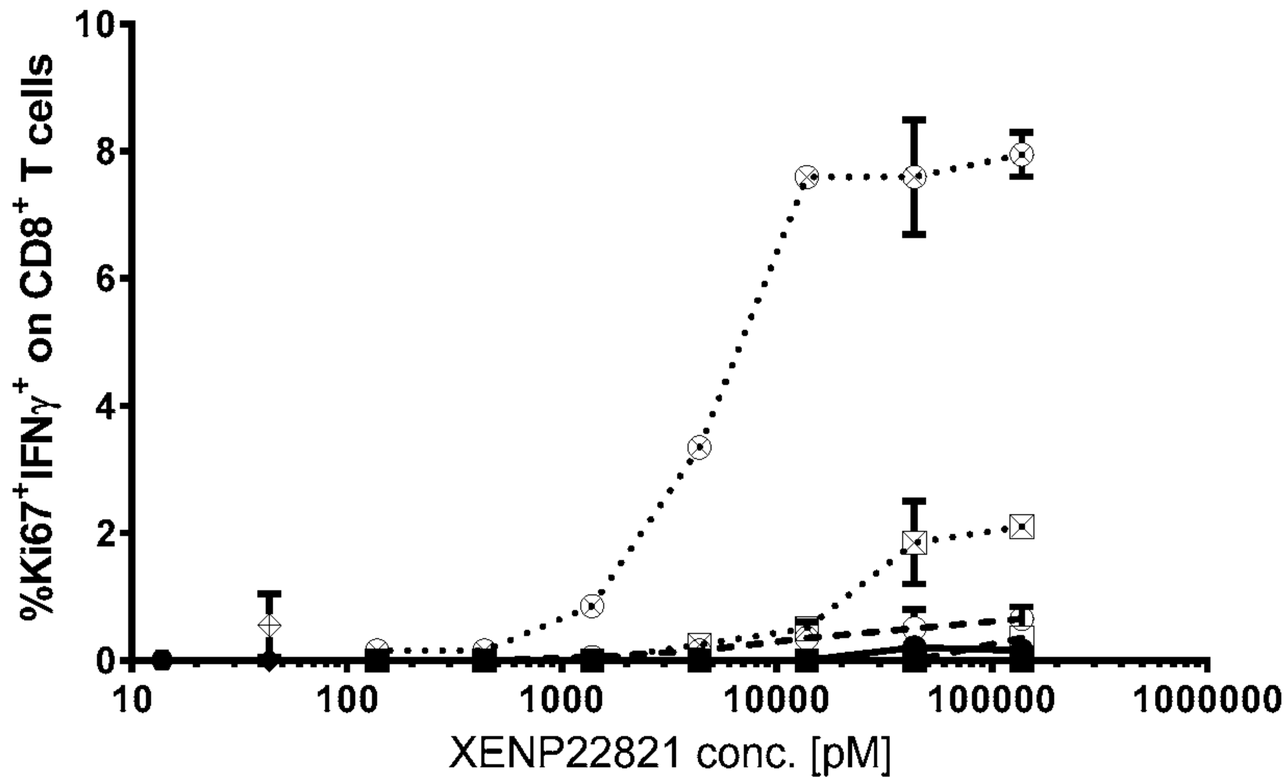

%Ki67+IFNγ+ on CD8+ T cells
10
8
6
4
2
0
10
100
1000
10000
100000
1000000
XENP22821 conc. [pM]
XENP22821/T cells/pp65/MCF7
XENP22821/T cells/parental MCF7
XENP22821/T cells
T cells/pp65-MCF7
T cells/parental MCF7
T cells
XENP22821/T cells (anti-HLA-A treated)/pp65-MCF7
XENP22821/T cells (anti-HLA-A treated)/parental MCF7
XENP22821/T cells (anti-HLA-A treated)
T cells (anti-HLA-A treated)/pp65-MCF7
T cells (anti-HLA-A treated)/parental MCF7
T cells (anti-HLA-A treated)

Figure 133

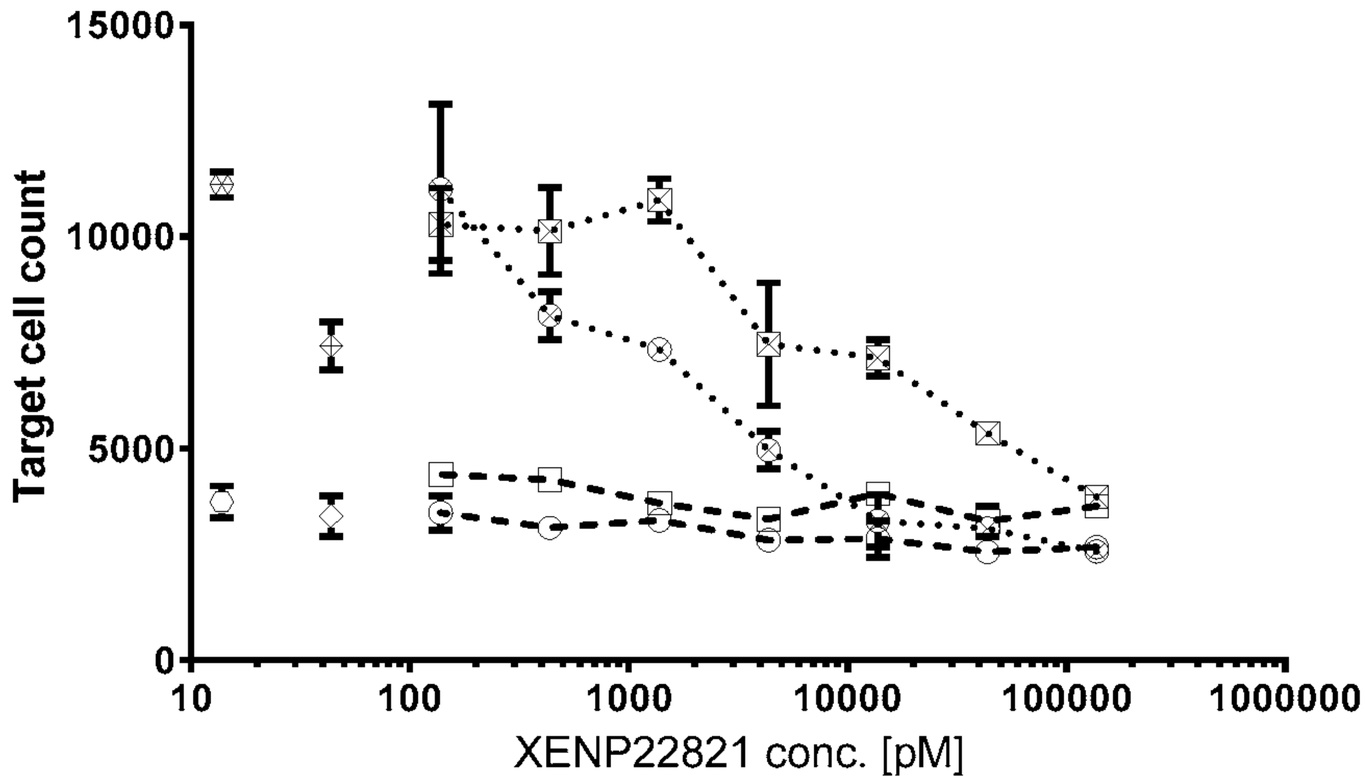

15000
10000
5000
0
Target cell count
10
100
1000
10000
100000
1000000
XENP22821 conc. [pM]
XENP22821/T cells/pp65-MCF7
XENP22821/T cells/parental MCF7
T cells/pp65-MCF7
T cells/parental MCF7
XENP22821/T cells (anti-HLA-A treated)/pp65-MCF7
XENP22821/T cells (anti-HLA-A treated)/parental MCF7
T cells (anti-HLA-A treated)/pp65-MCF7
T cells (anti-HLA-A treated)/parental MCF7

Figure 134A

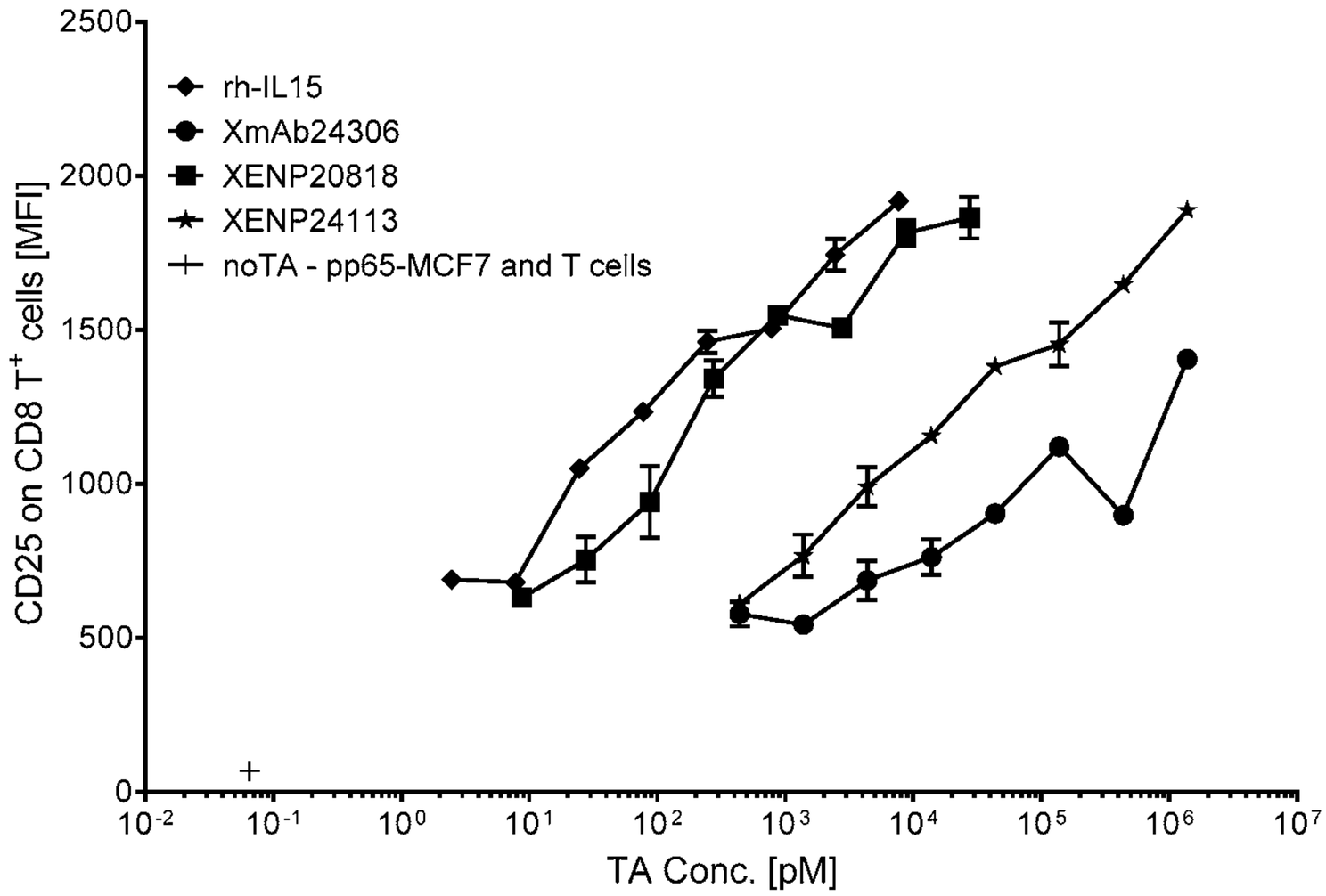


Figure 134B

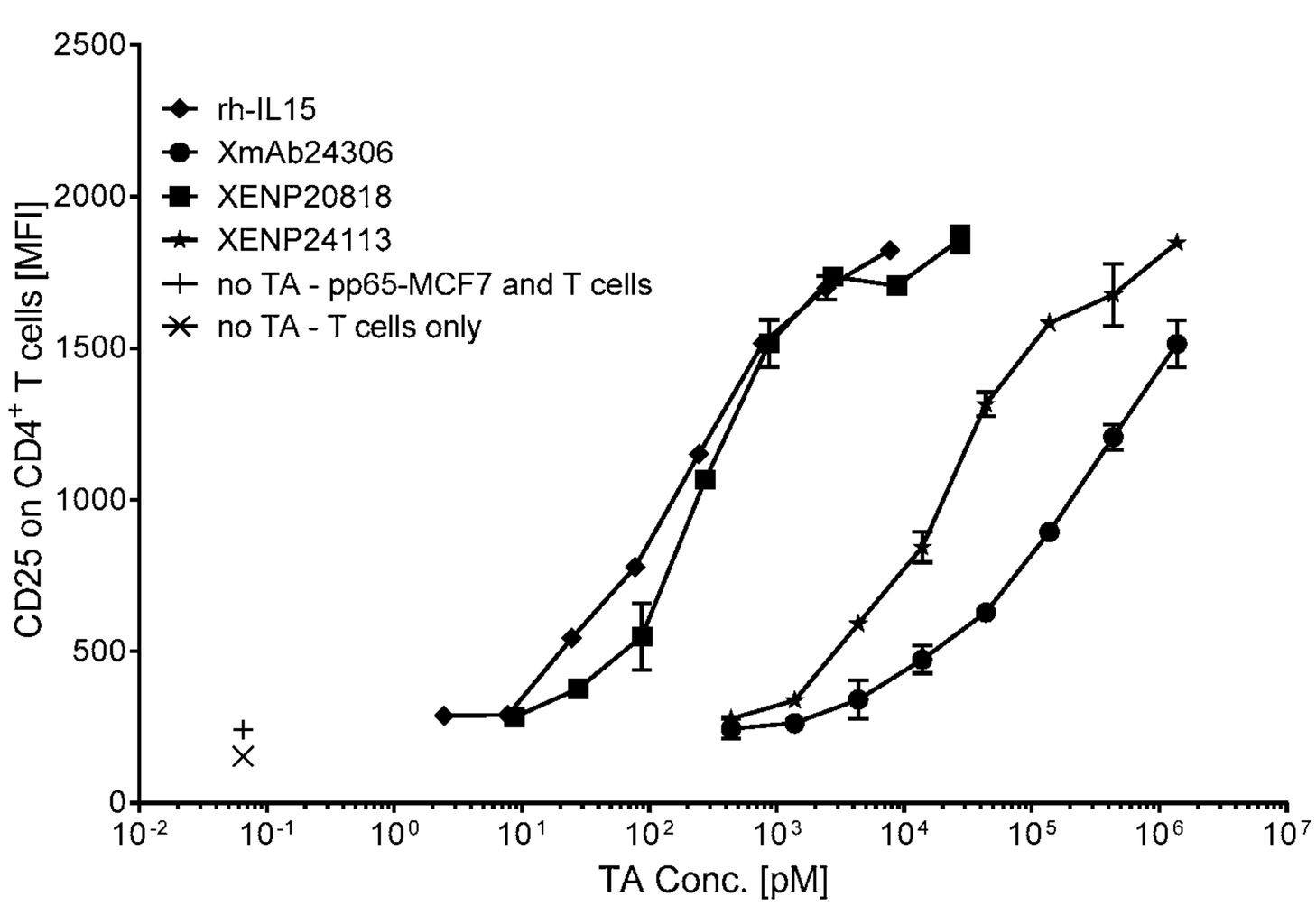


Figure 135A

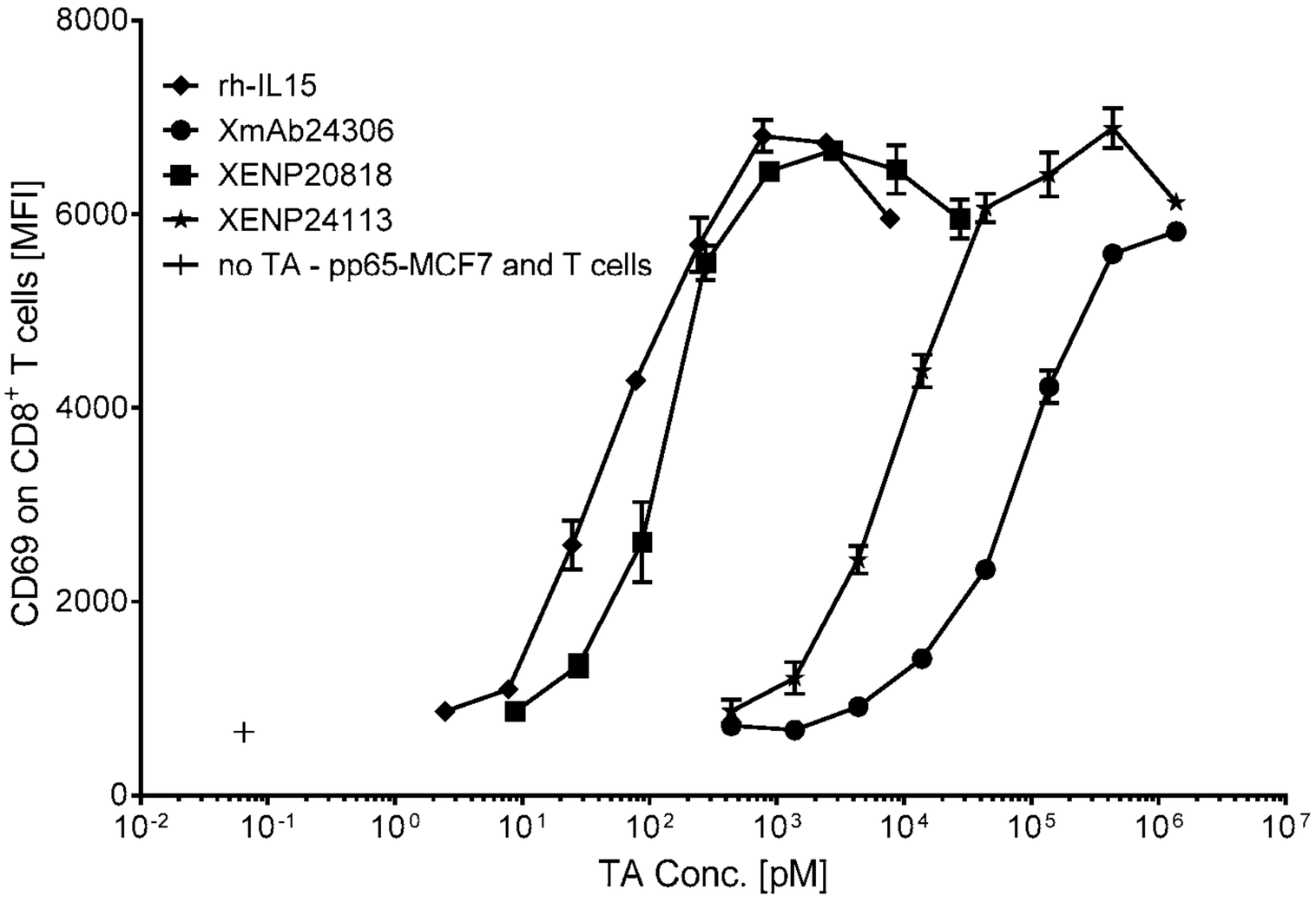


Figure 135B

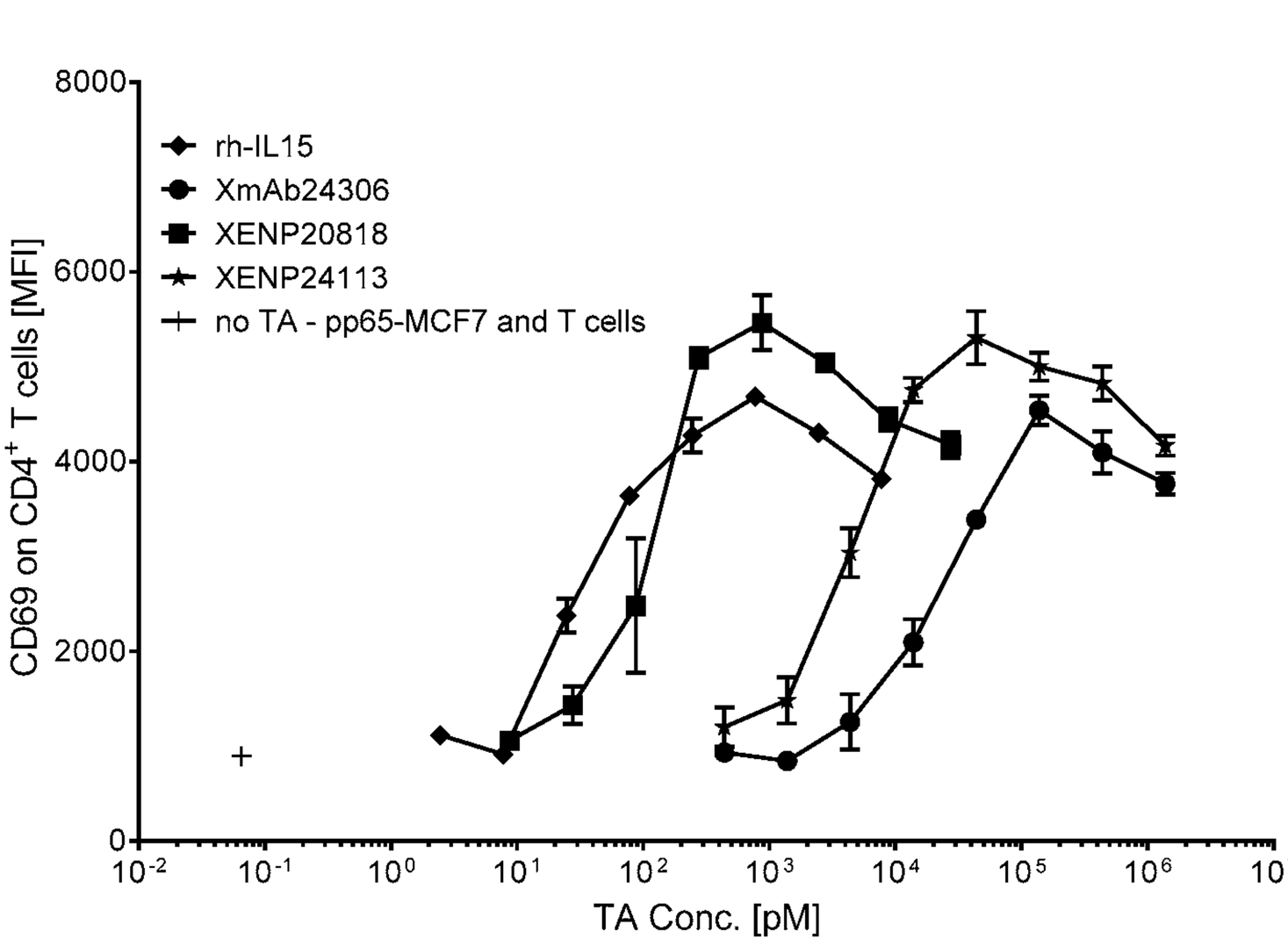


Figure 136A

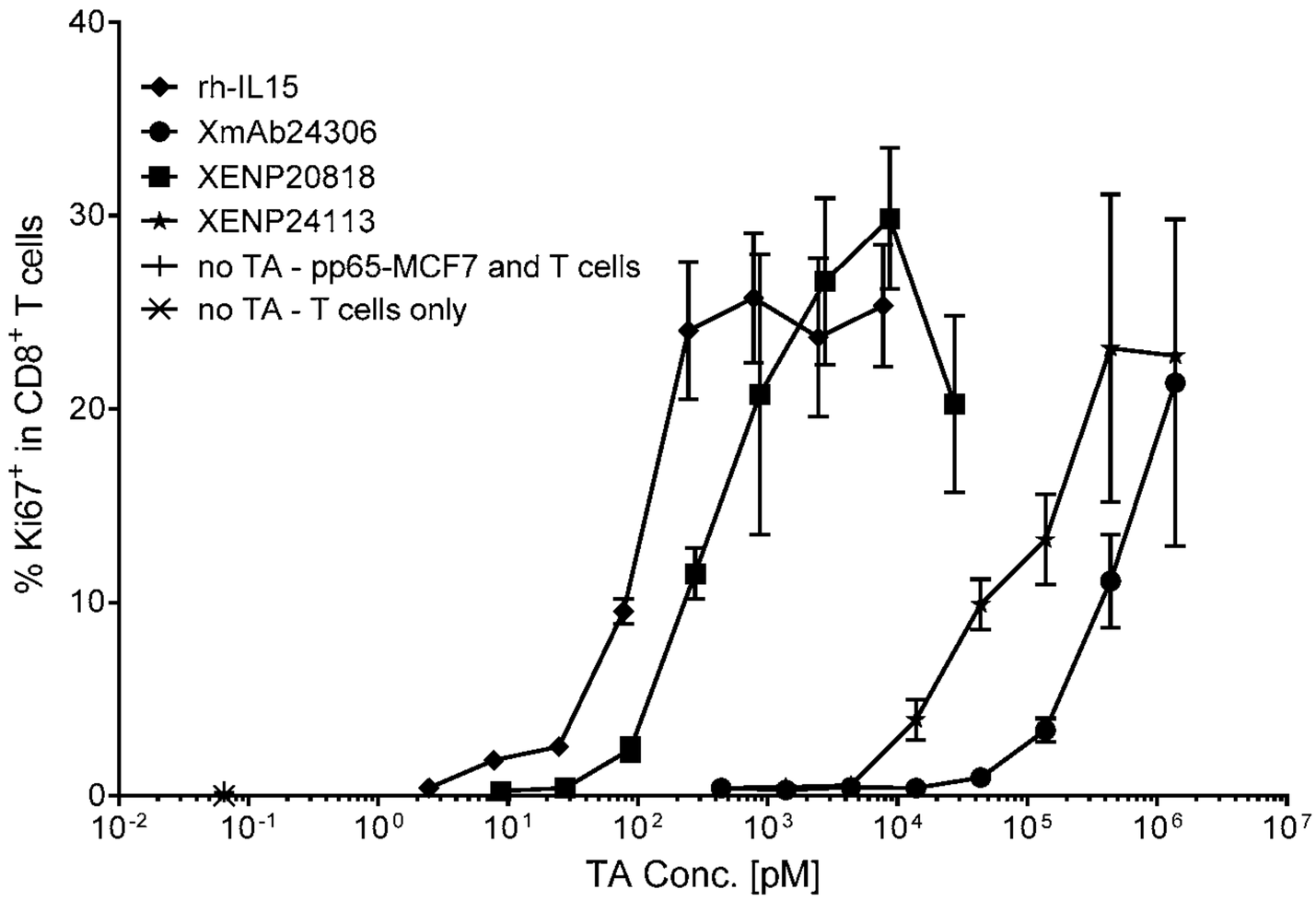


Figure 136B

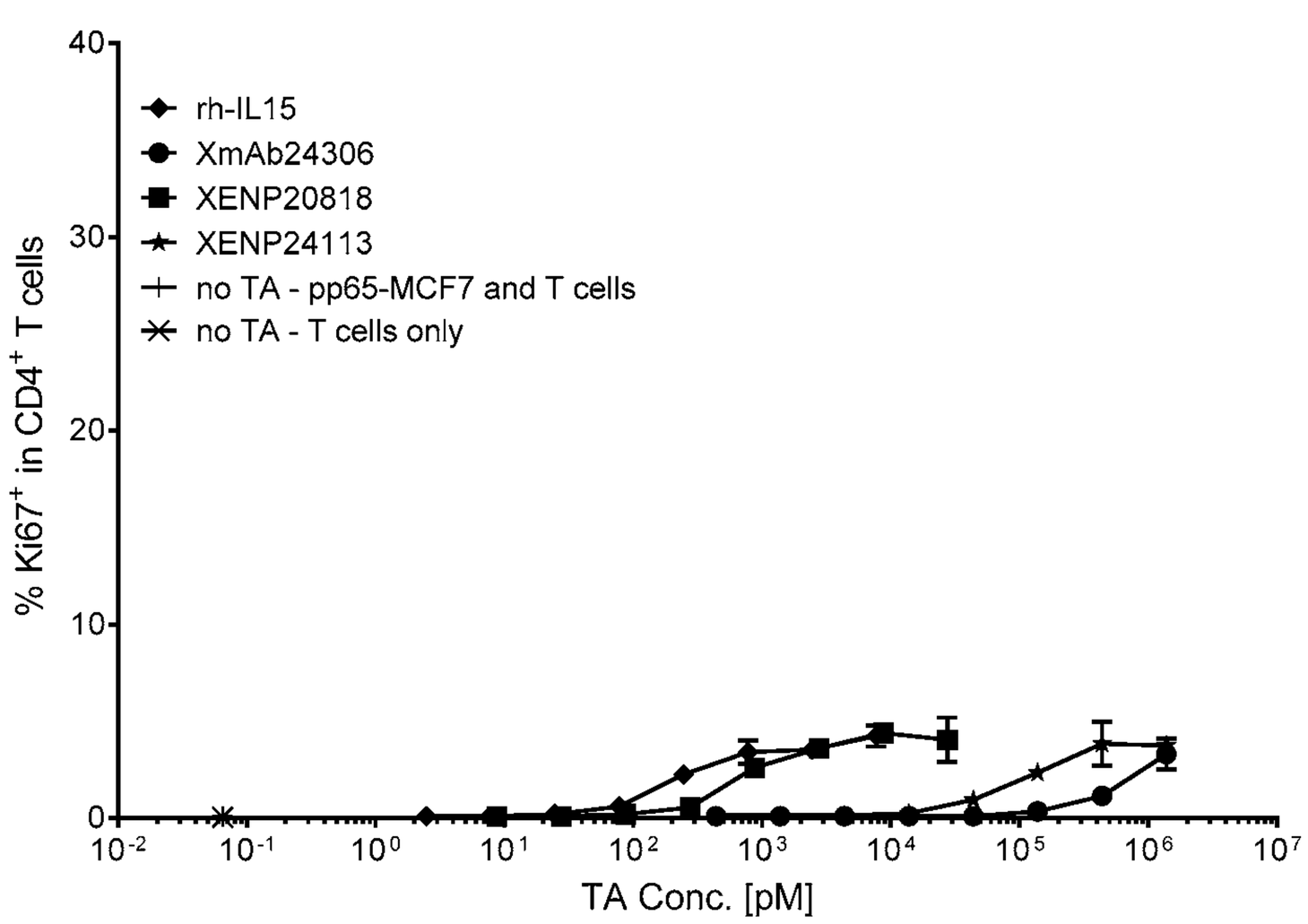


Figure 137A

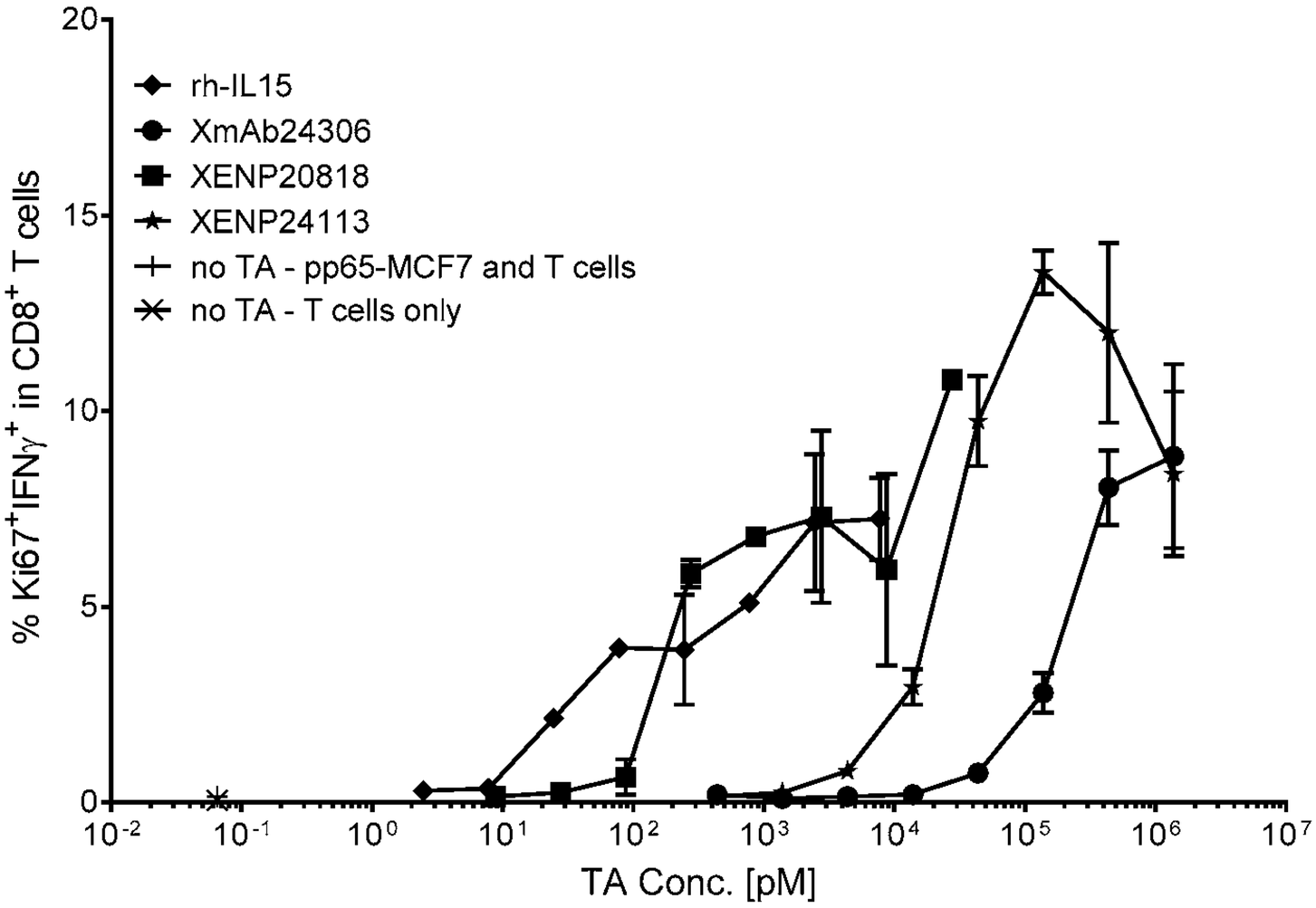


Figure 137B

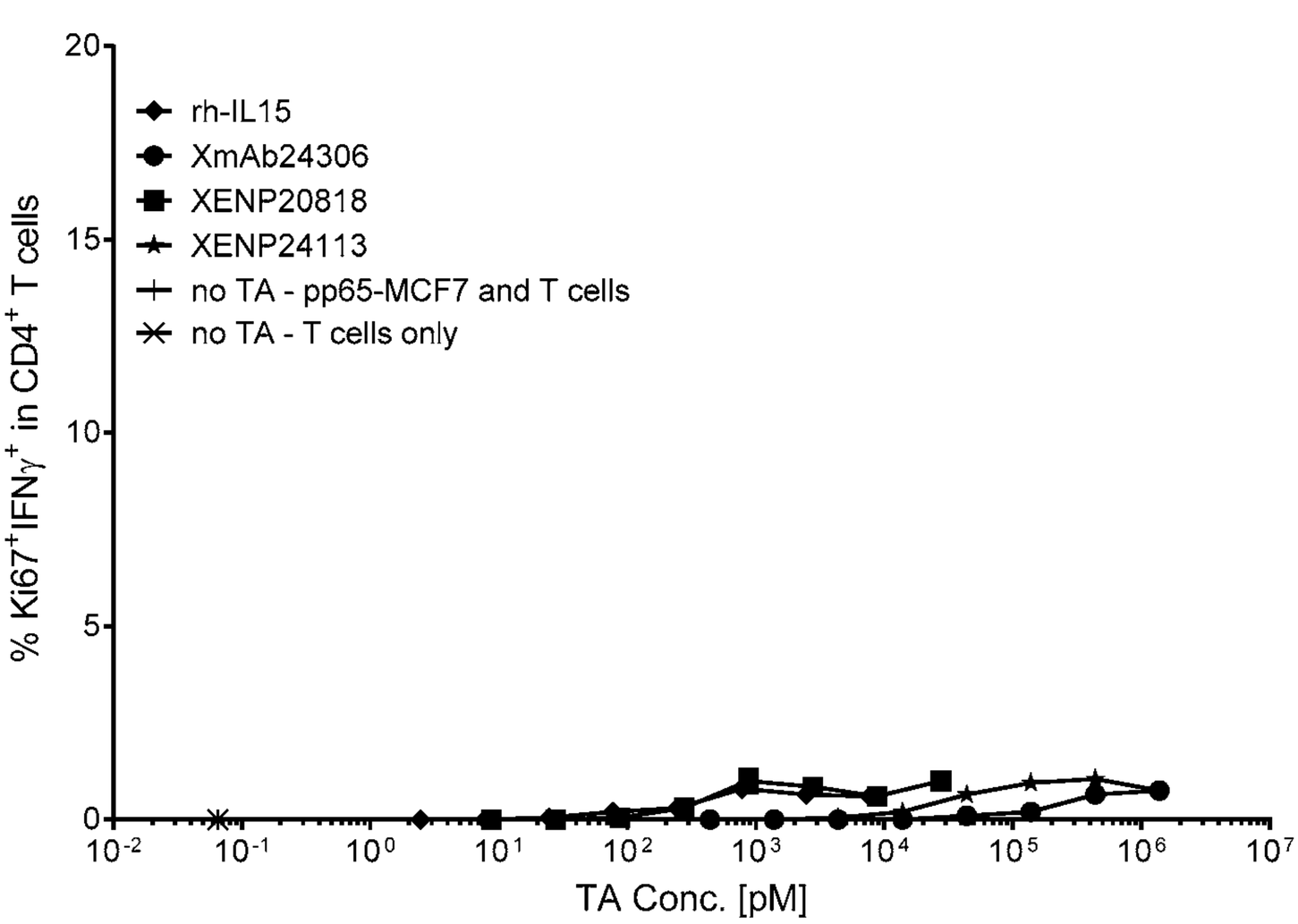


Figure 138A

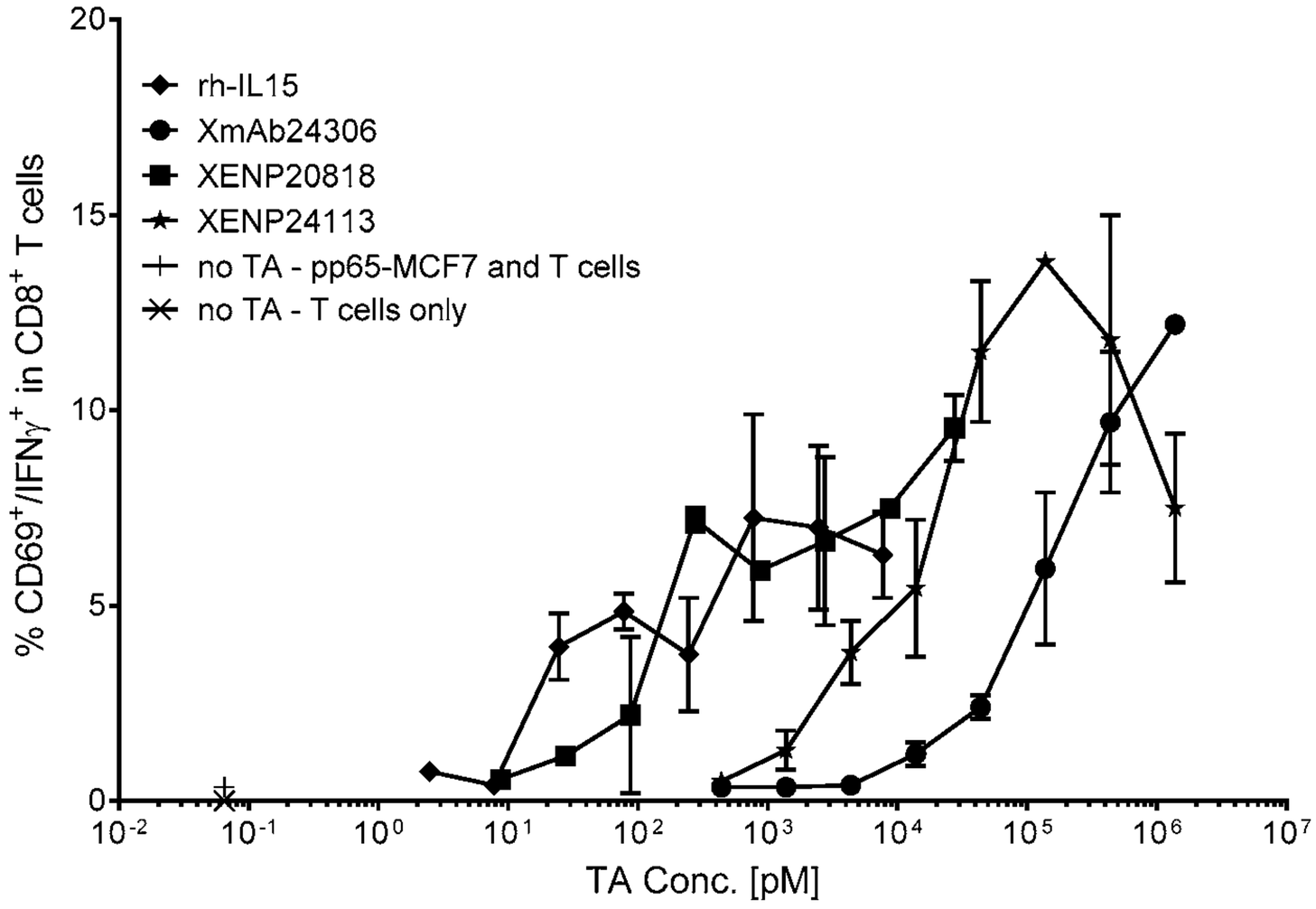


Figure 138B

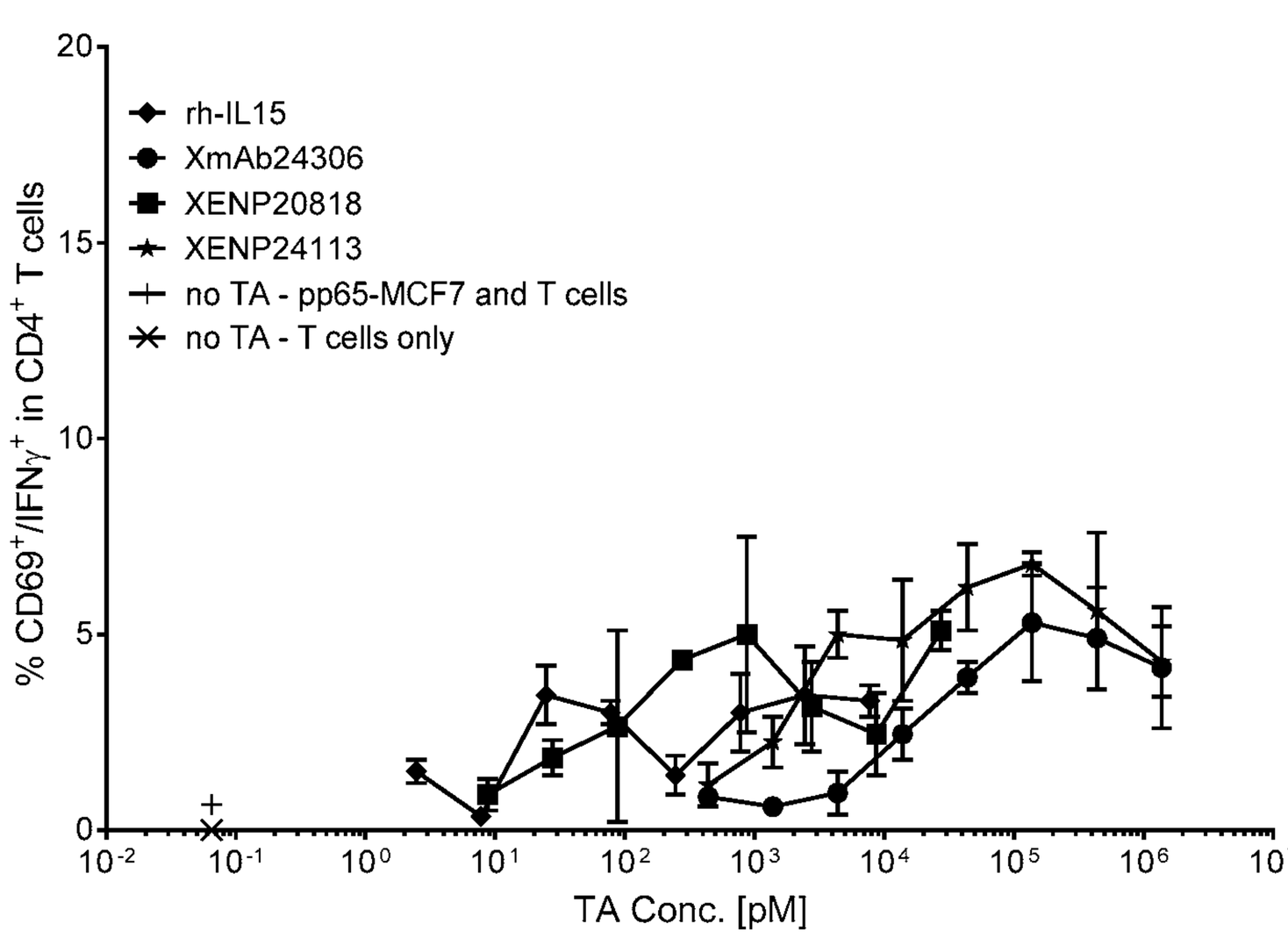


Figure 139A

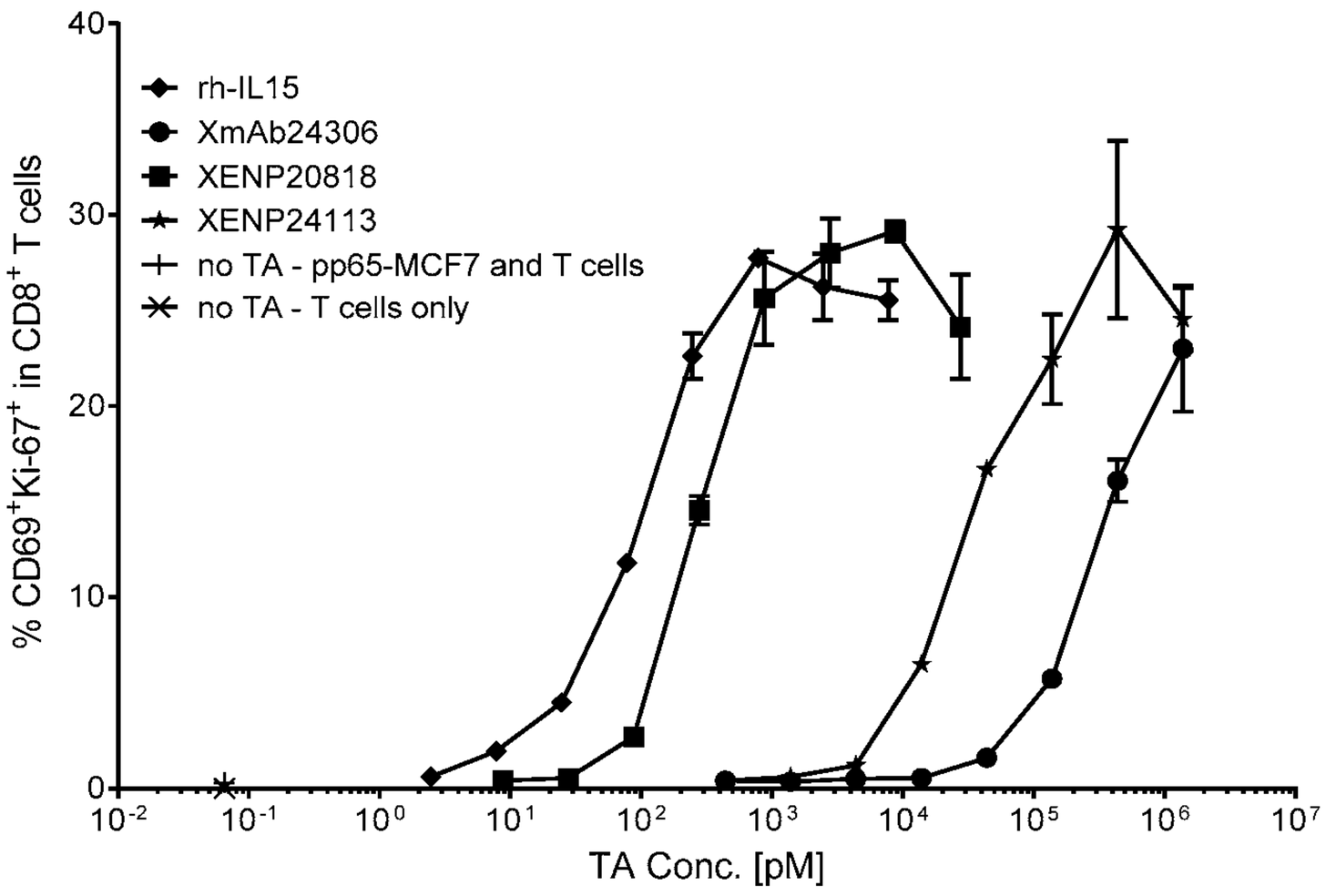


Figure 139B

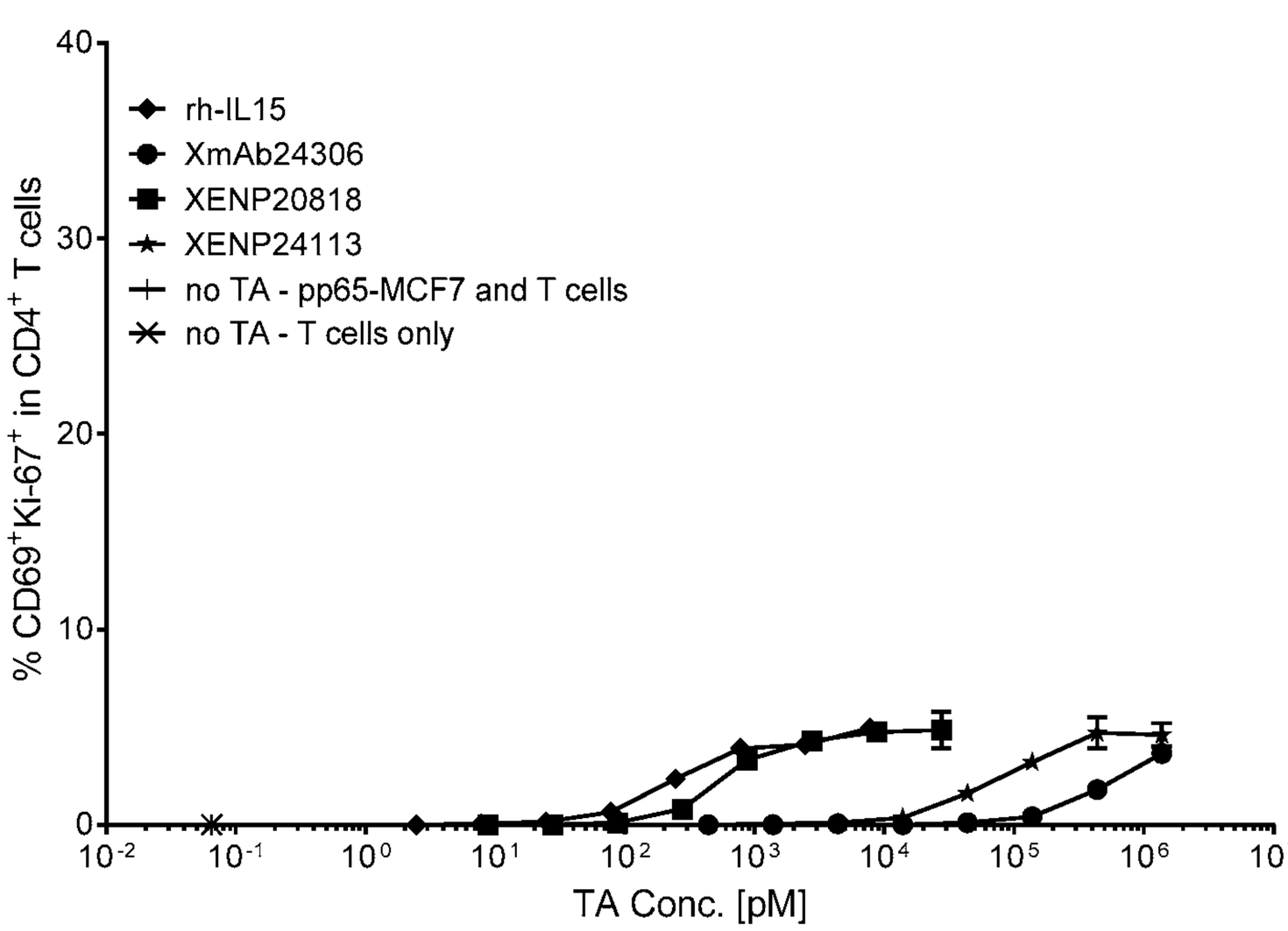


Figure 140

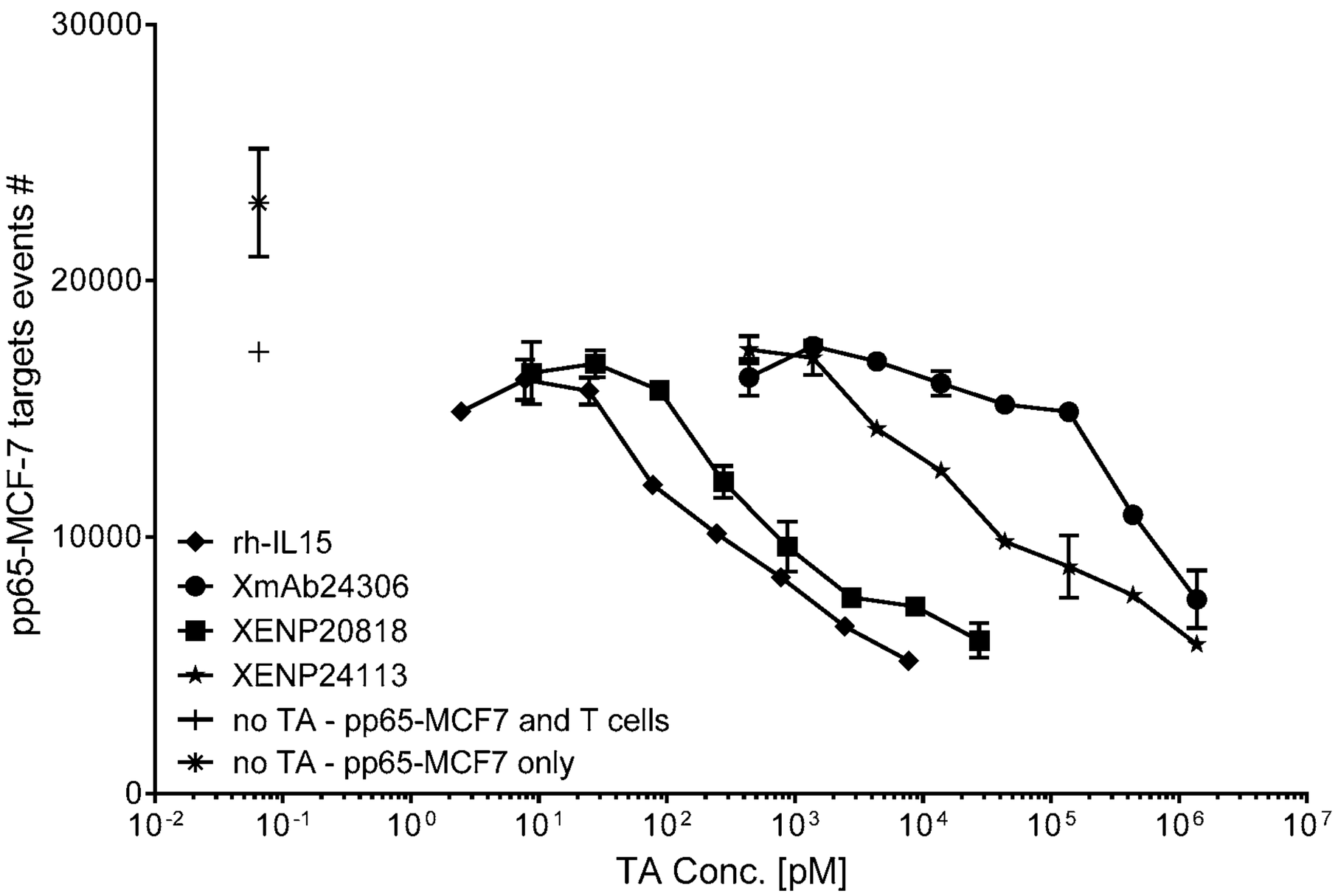

30000
20000
10000
0
pp65-MCF-7 targets events #
rh-IL15
XmAb24306
XENP20818
XENP24113
no TA - pp65-MCF7 and T cells
no TA - pp65-MCF7 only
10-2
10-1
100
101
102
103
104
105
106
107
TA Conc. [pM]

Figure 141

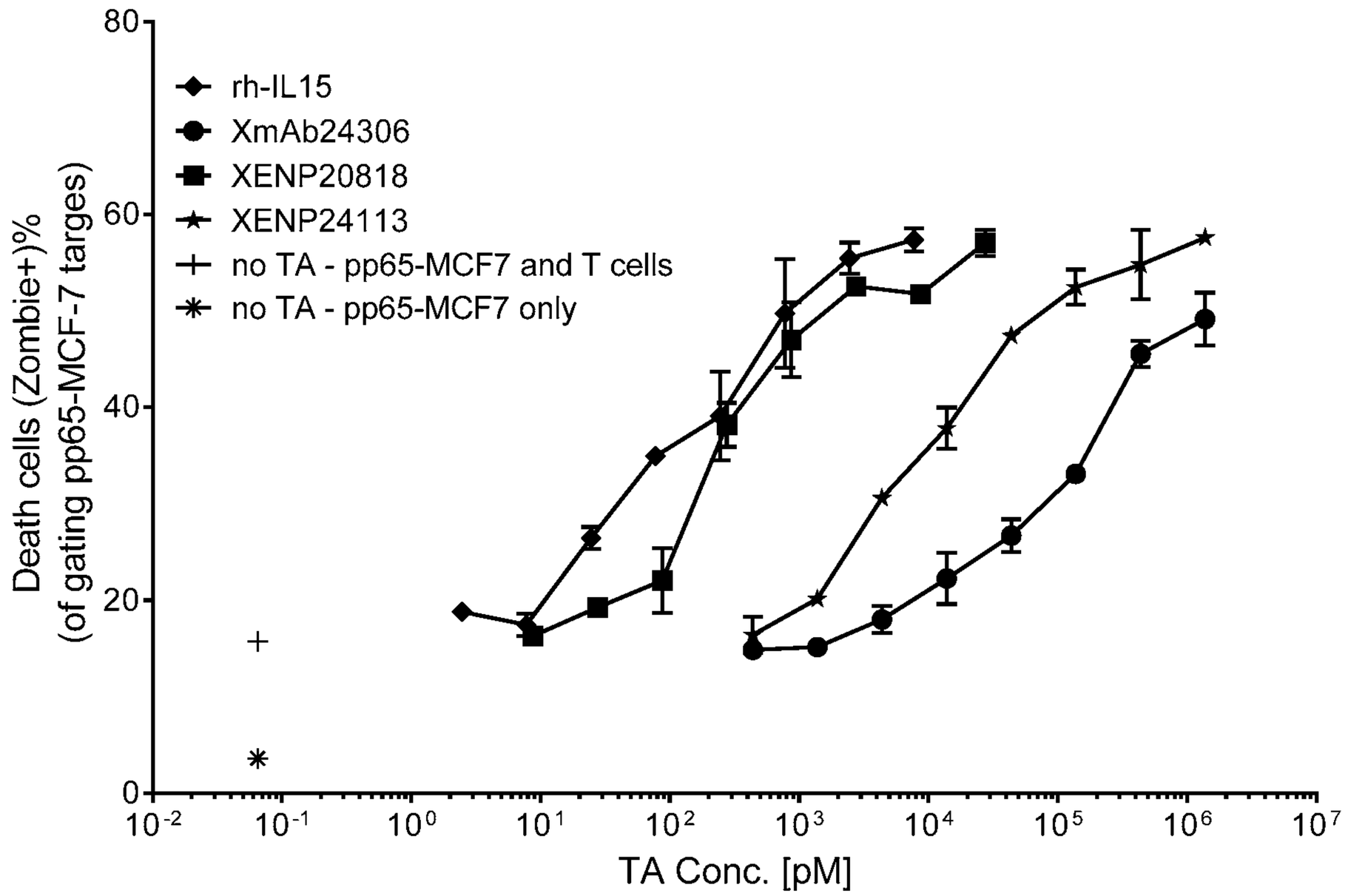

rh-IL15
XmAb24306
XENP20818
XENP24113
no TA - pp65-MCF7 and T cells
no TA - pp65-MCF7 only
Death cells (Zombie+)%
(of gating pp65-MCF-7 targets)
0
20
40
60
80
10-2
10-1
100
101
102
103
104
105
106
107
TA Conc. [pM]

Figure 142A

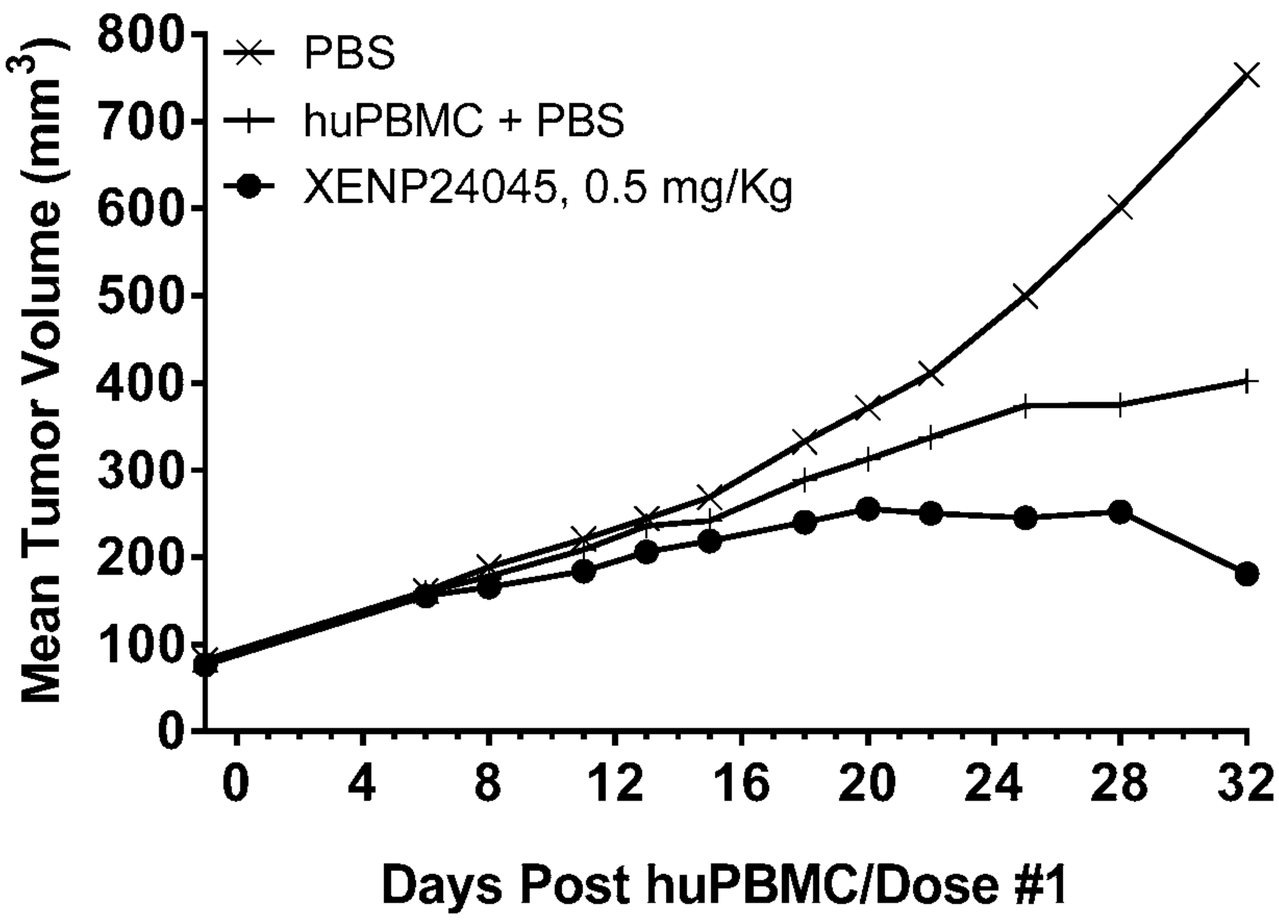


Figure 142B

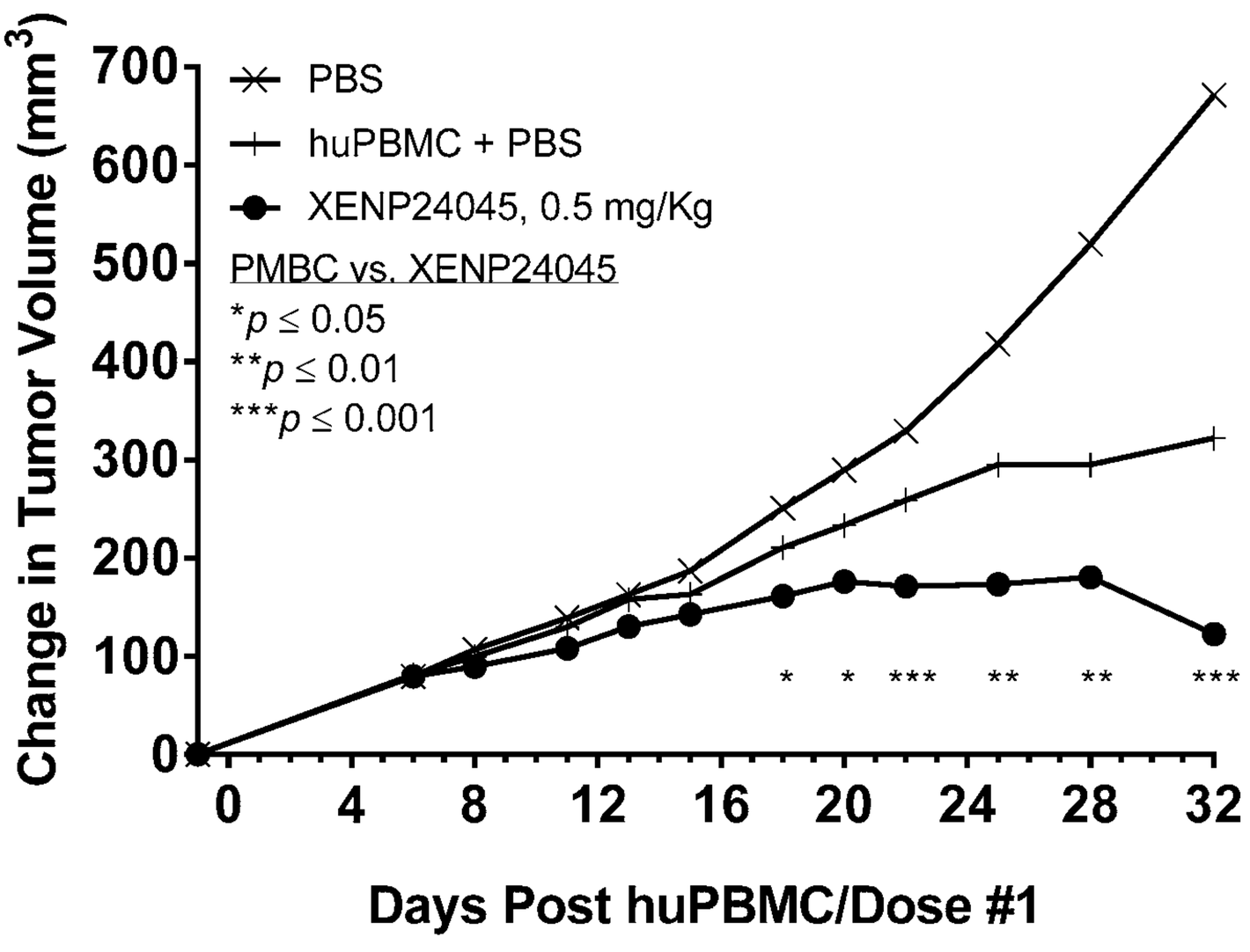


Figure 143A

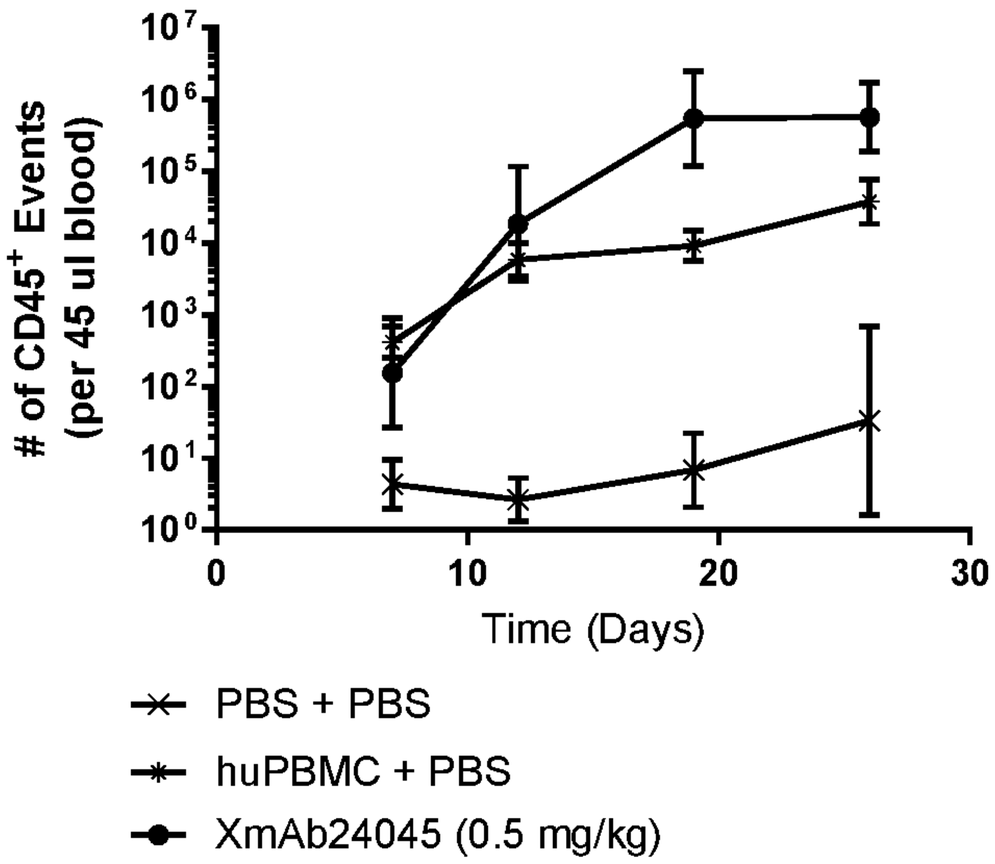


Figure 143B

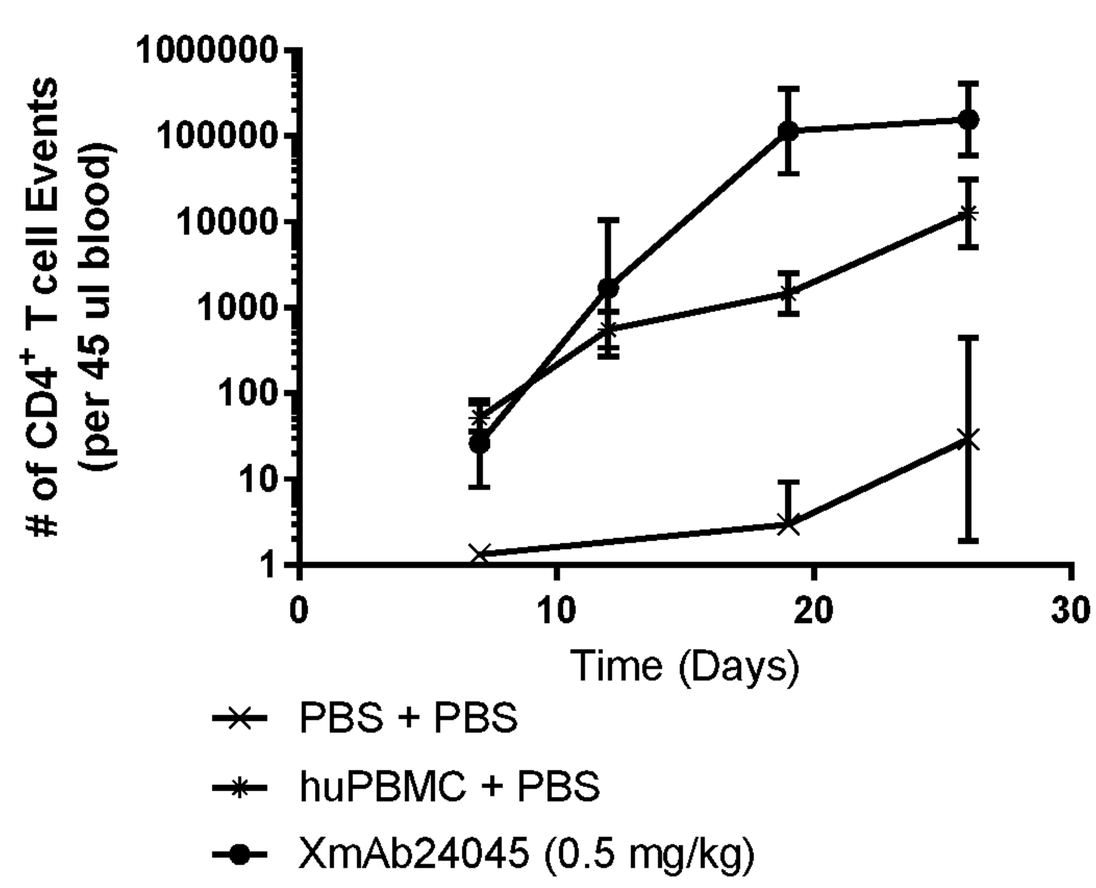
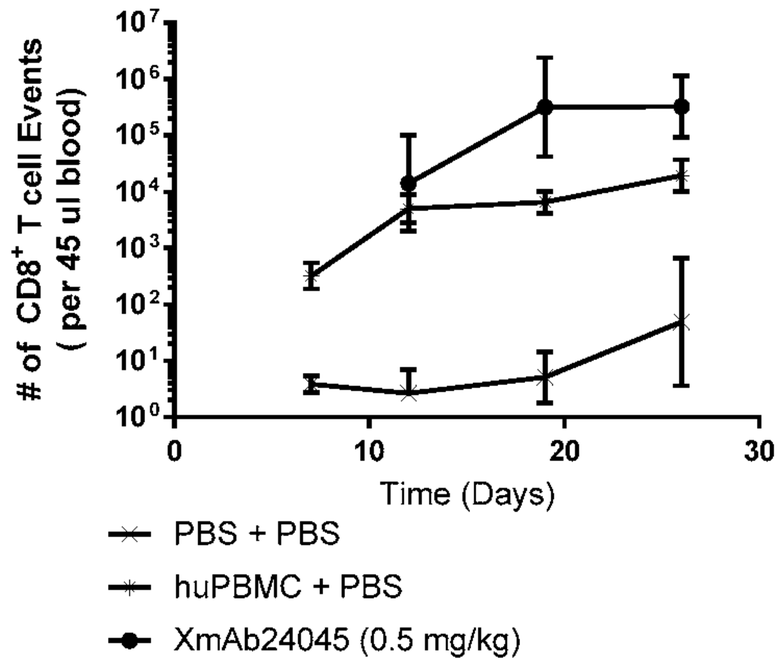


Figure 143C


of CD8+ T cell Events
(per 45 ul blood)
10^7
10^6
10^5
10^4
10^3
10^2
10^1
10^0
0
10
20
30
Time (Days)
PBS + PBS
huPBMC + PBS
XmAb24045 (0.5 mg/kg)

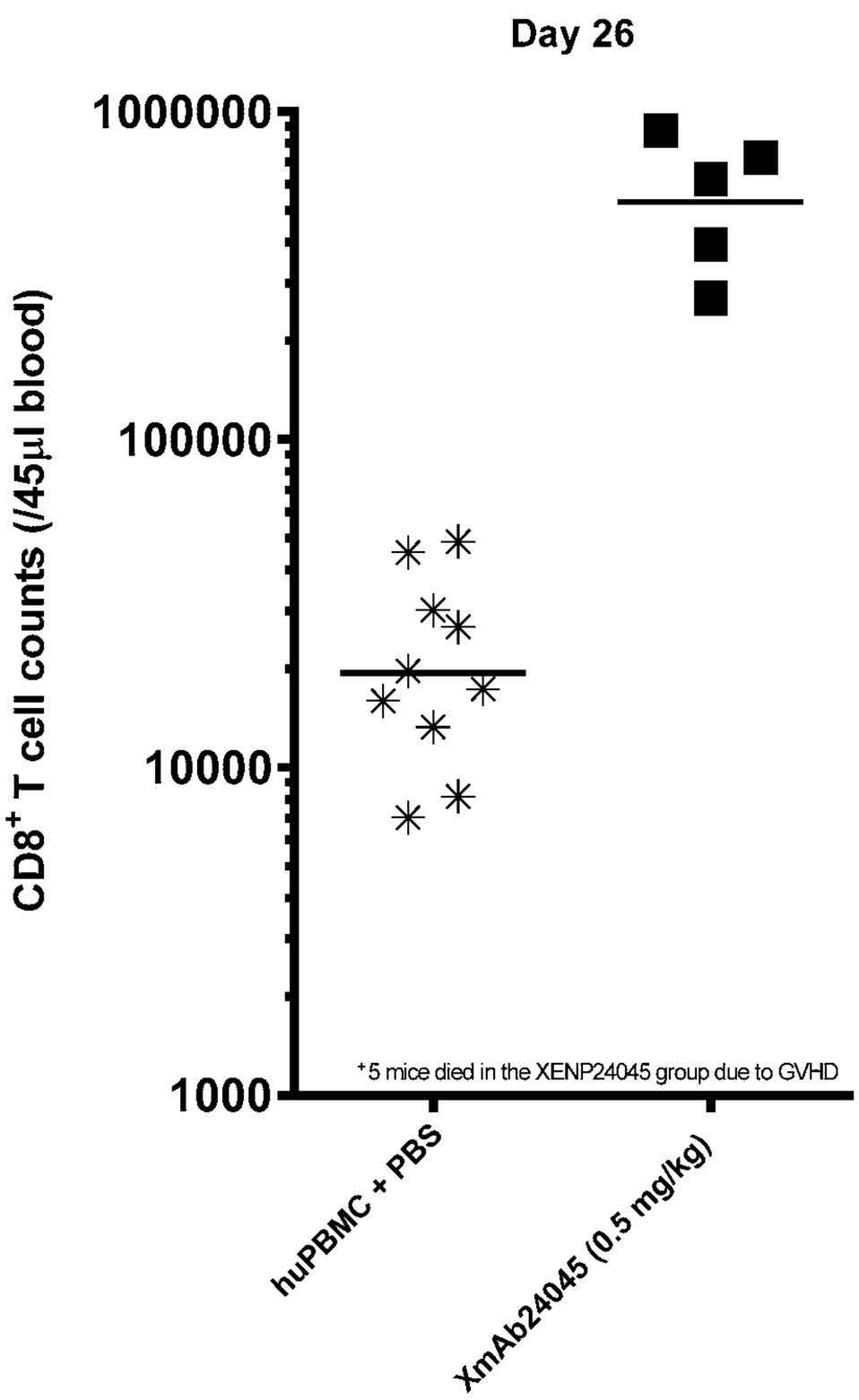
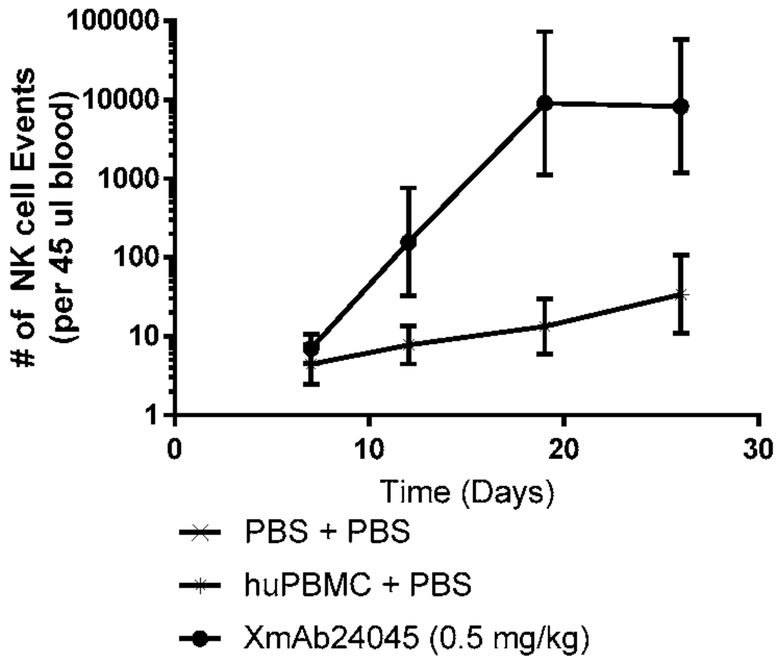

Day 26
1000000
100000
10000
1000
CD8+ T cell counts (/45µl blood)
+5 mice died in the XENP24045 group due to GVHD
huPBMC + PBS
XmAb24045 (0.5 mg/kg)

Figure 143D


100000
10000
1000
100
10
1
of NK cell Events
(per 45 ul blood)
0
10
20
30
Time (Days)
PBS + PBS
huPBMC + PBS
XmAb24045 (0.5 mg/kg)

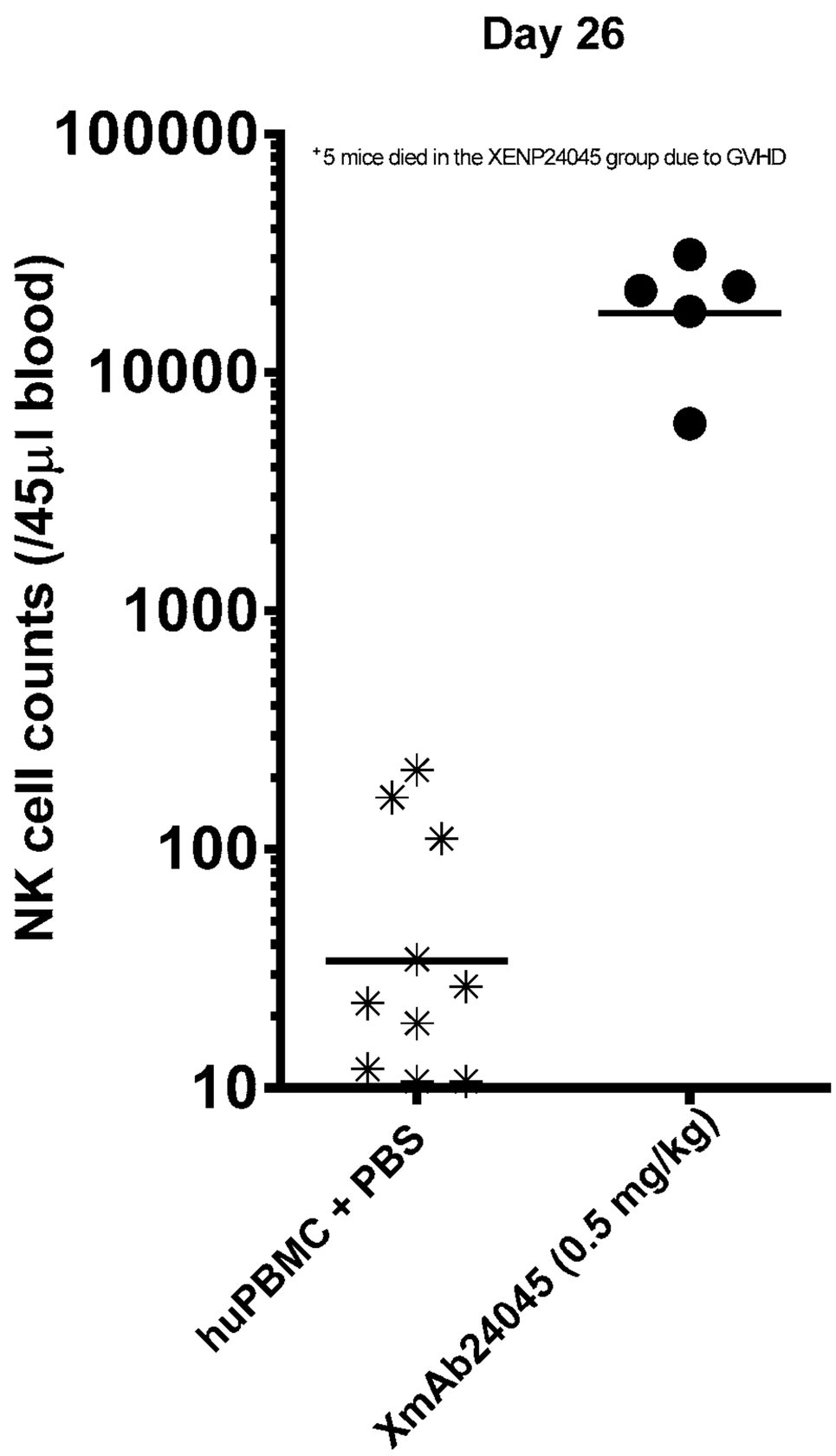

Day 26
+5 mice died in the XENP24045 group due to GVHD
100000
10000
1000
100
10
NK cell counts (/45µl blood)
huPBMC + PBS
XmAb24045 (0.5 mg/kg)

Figure 144

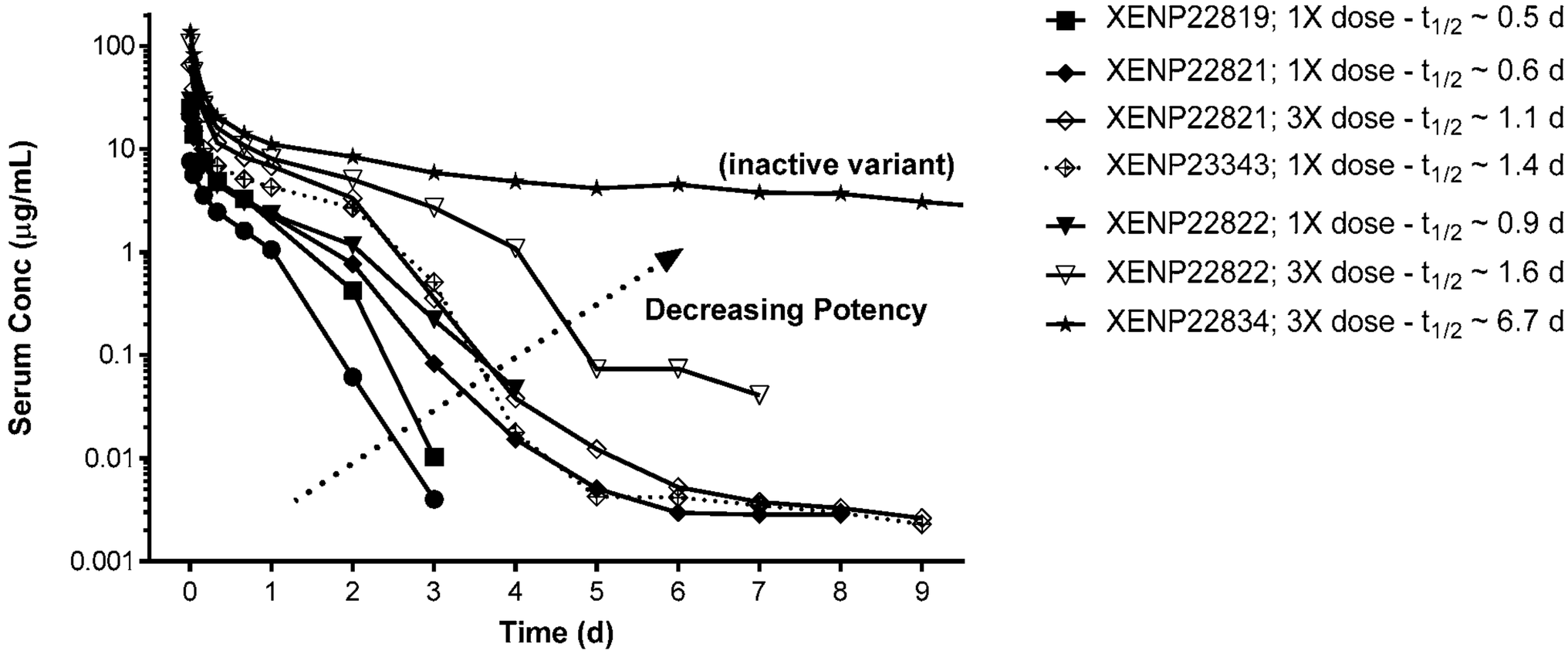

Serum Conc (µg/mL)
100
10
1
0.1
0.01
0.001
0
1
2
3
4
5
6
7
8
9
Time (d)
(inactive variant)
Decreasing Potency
XENP20818; 0.3X dose - t1/2 ~ 0.6 d
XENP22819; 1X dose - t1/2 ~ 0.5 d
XENP22821; 1X dose - t1/2 ~ 0.6 d
XENP22821; 3X dose - t1/2 ~ 1.1 d
XENP23343; 1X dose - t1/2 ~ 1.4 d
XENP22822; 1X dose - t1/2 ~ 0.9 d
XENP22822; 3X dose - t1/2 ~ 1.6 d
XENP22834; 3X dose - t1/2 ~ 6.7 d

Figure 145

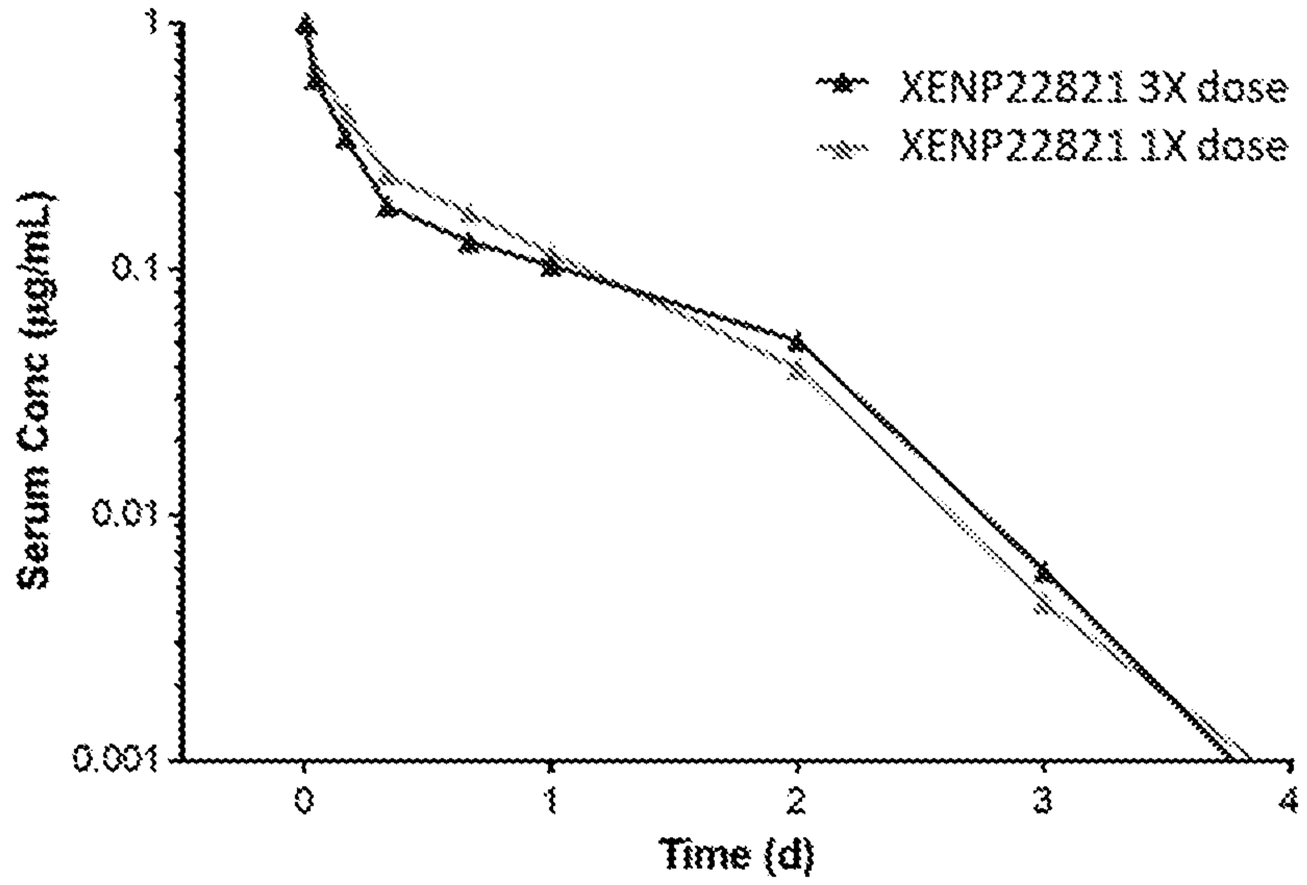

XENP22821 3X dose
XENP22821 1X dose
Serum Conc (µg/mL)
0.1
0.01
0.001
0
1
2
3
4
Time (d)

Figure 146A

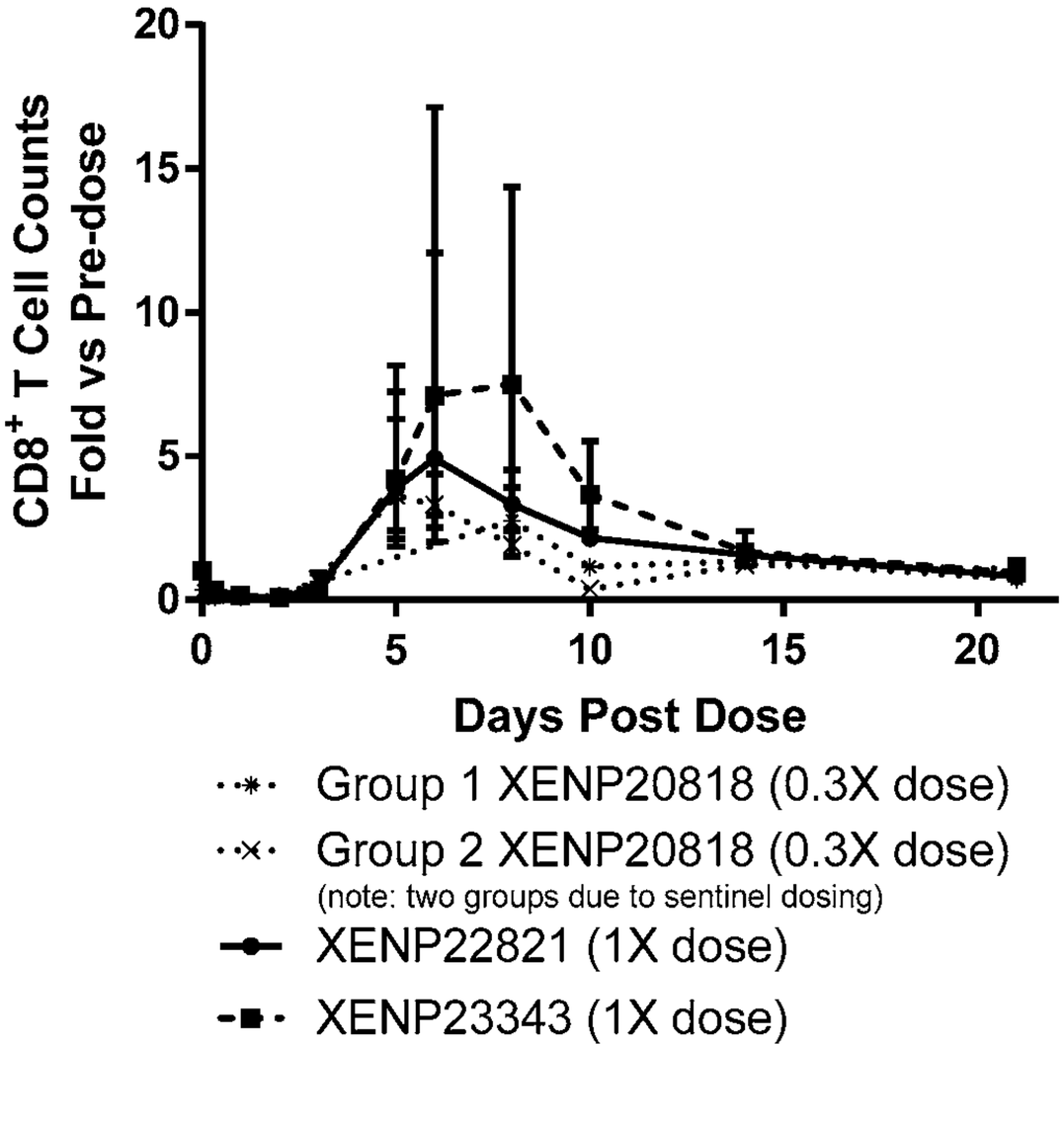


Figure 146B

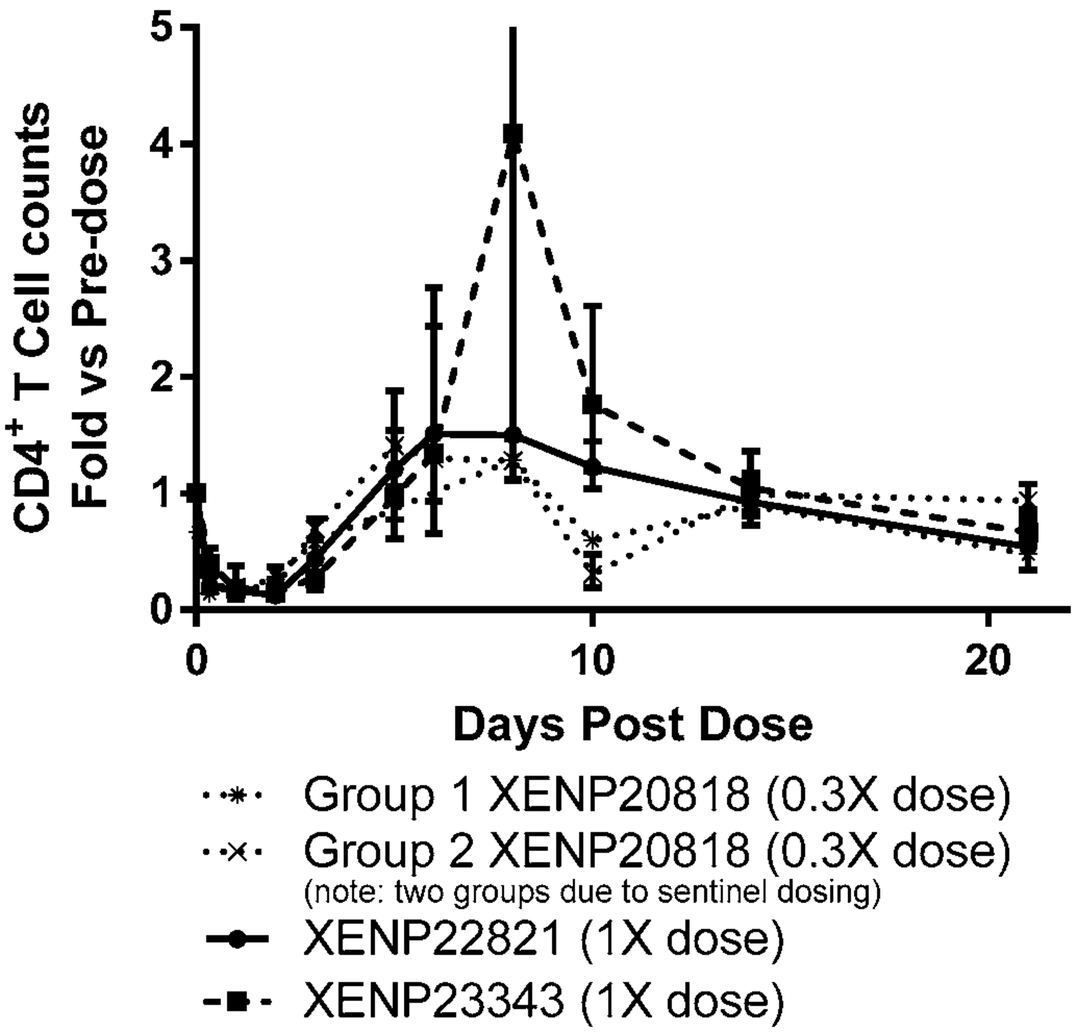


Figure 146C

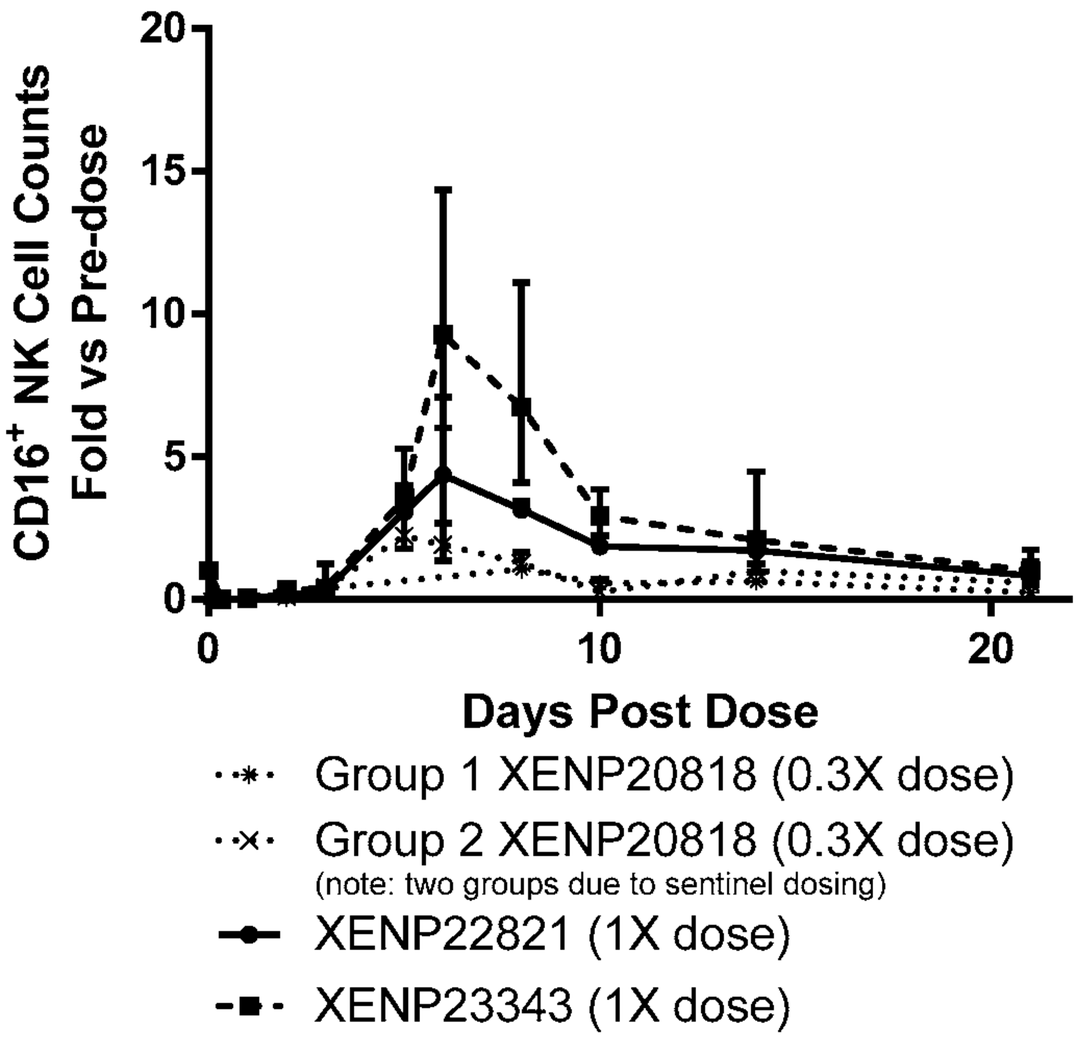


Figure 146D

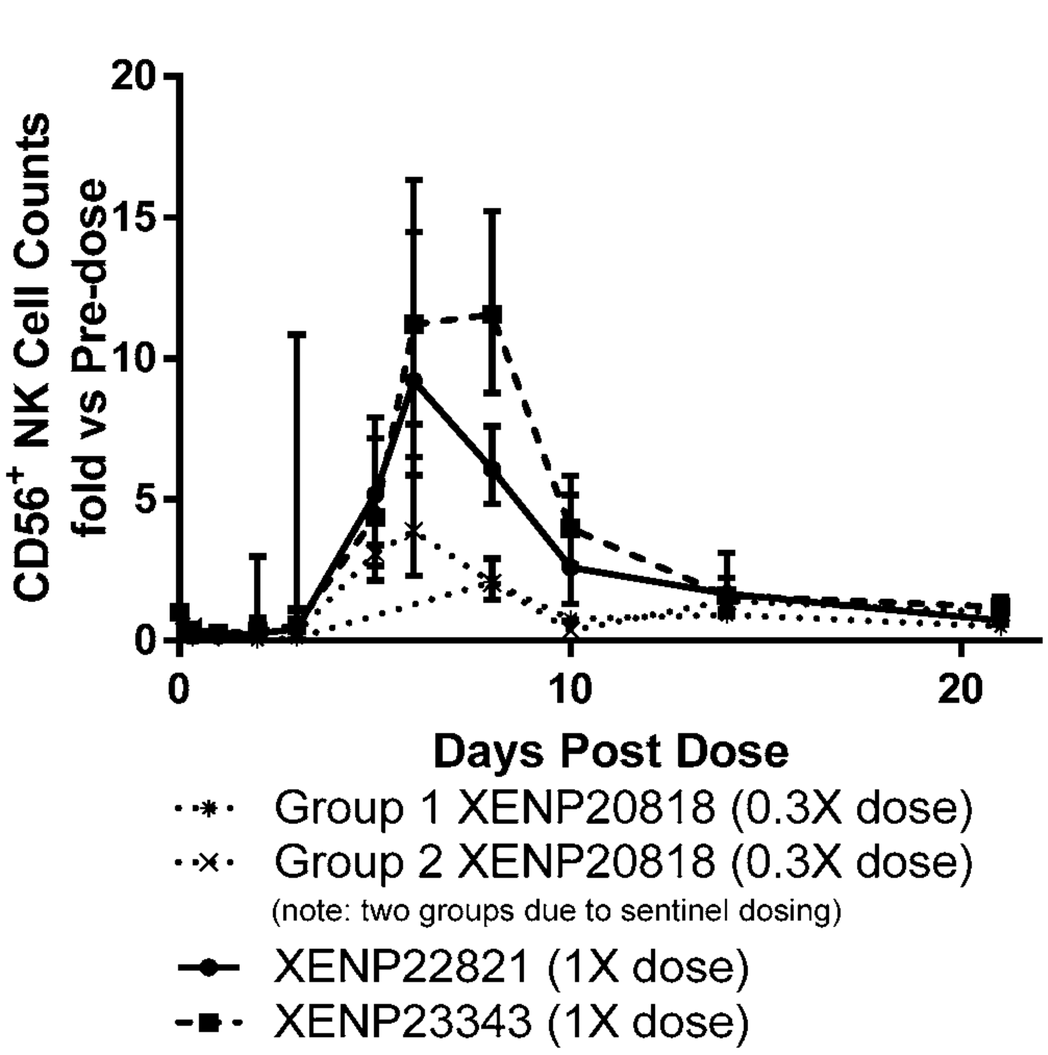


Figure 146E

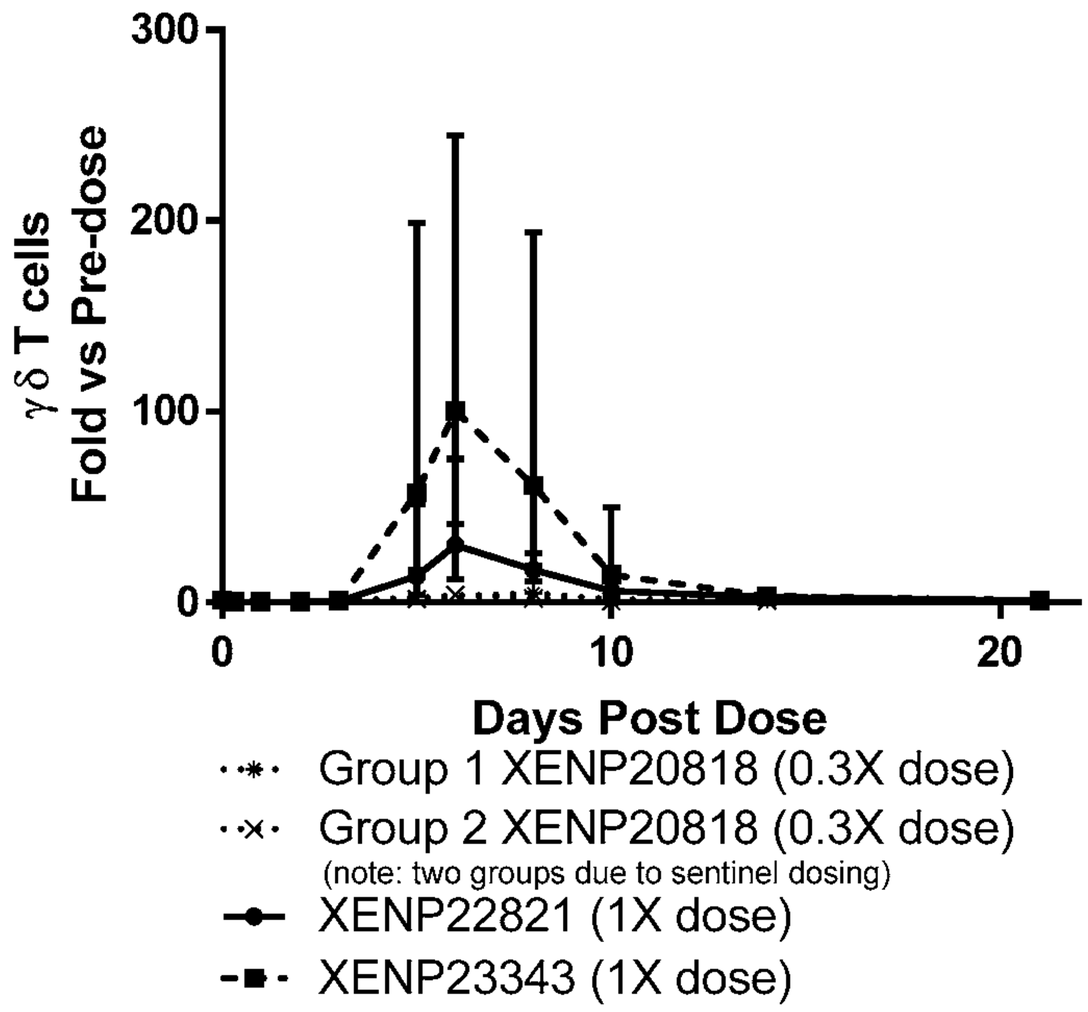

300
200
100
0
γδ T cells
Fold vs Pre-dose
0
10
20
Days Post Dose
Group 1 XENP20818 (0.3X dose)
Group 2 XENP20818 (0.3X dose)
(note: two groups due to sentinel dosing)
XENP22821 (1X dose)
XENP23343 (1X dose)

Figure 147A

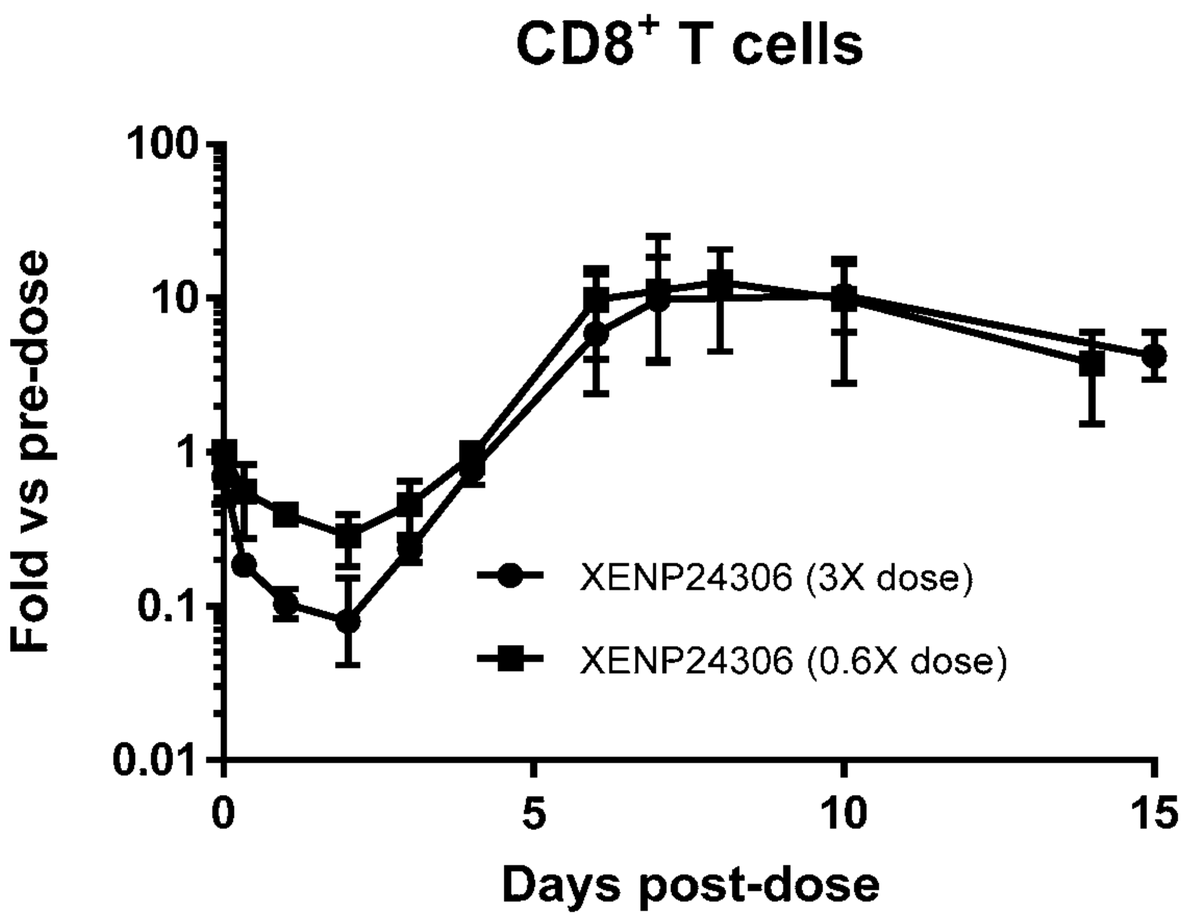


Figure 147B

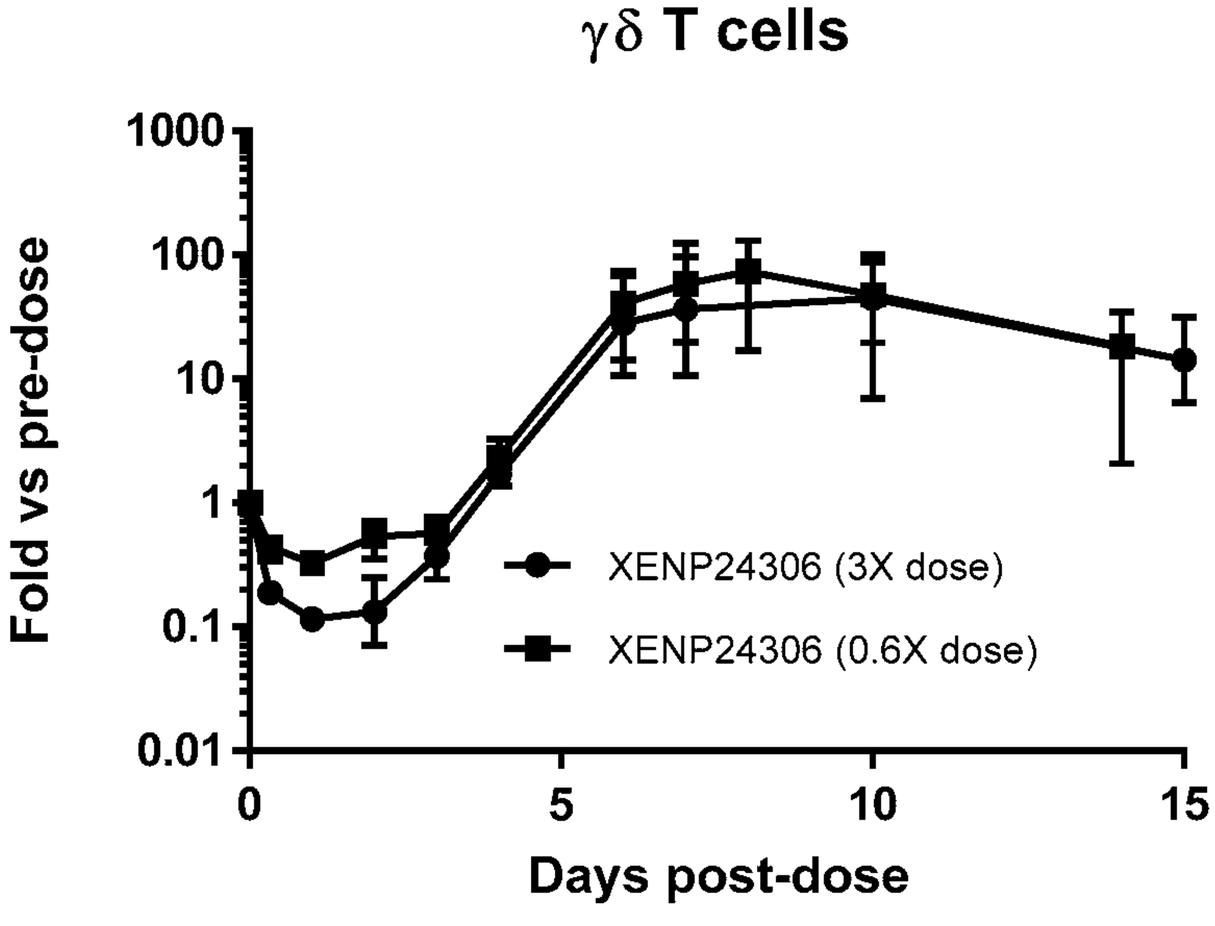


Figure 148

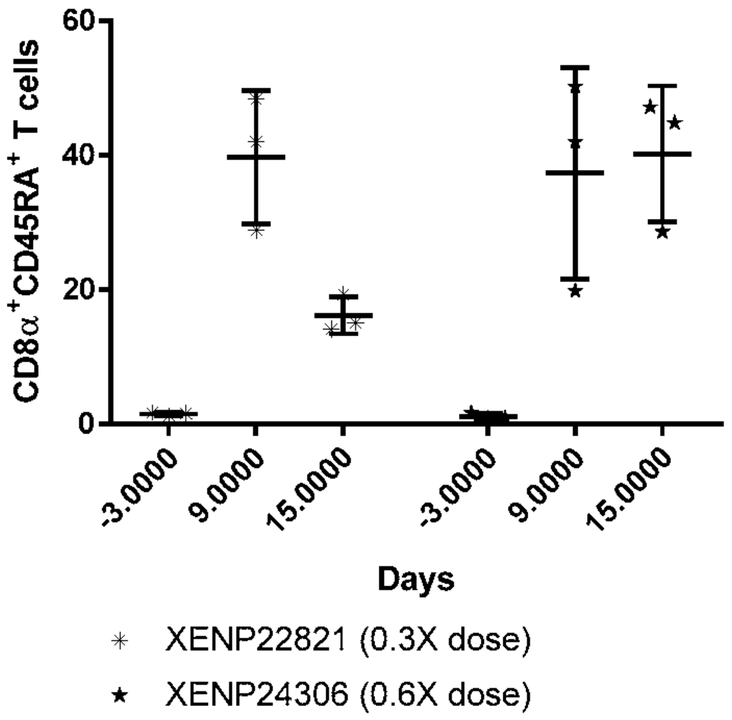

Ki-67% of CD8α+CD45RA+ T cells
60
40
20
0
-3.0000
9.0000
15.0000
-3.0000
9.0000
15.0000
Days
XENP22821 (0.3X dose)
XENP24306 (0.6X dose)

Figure 149

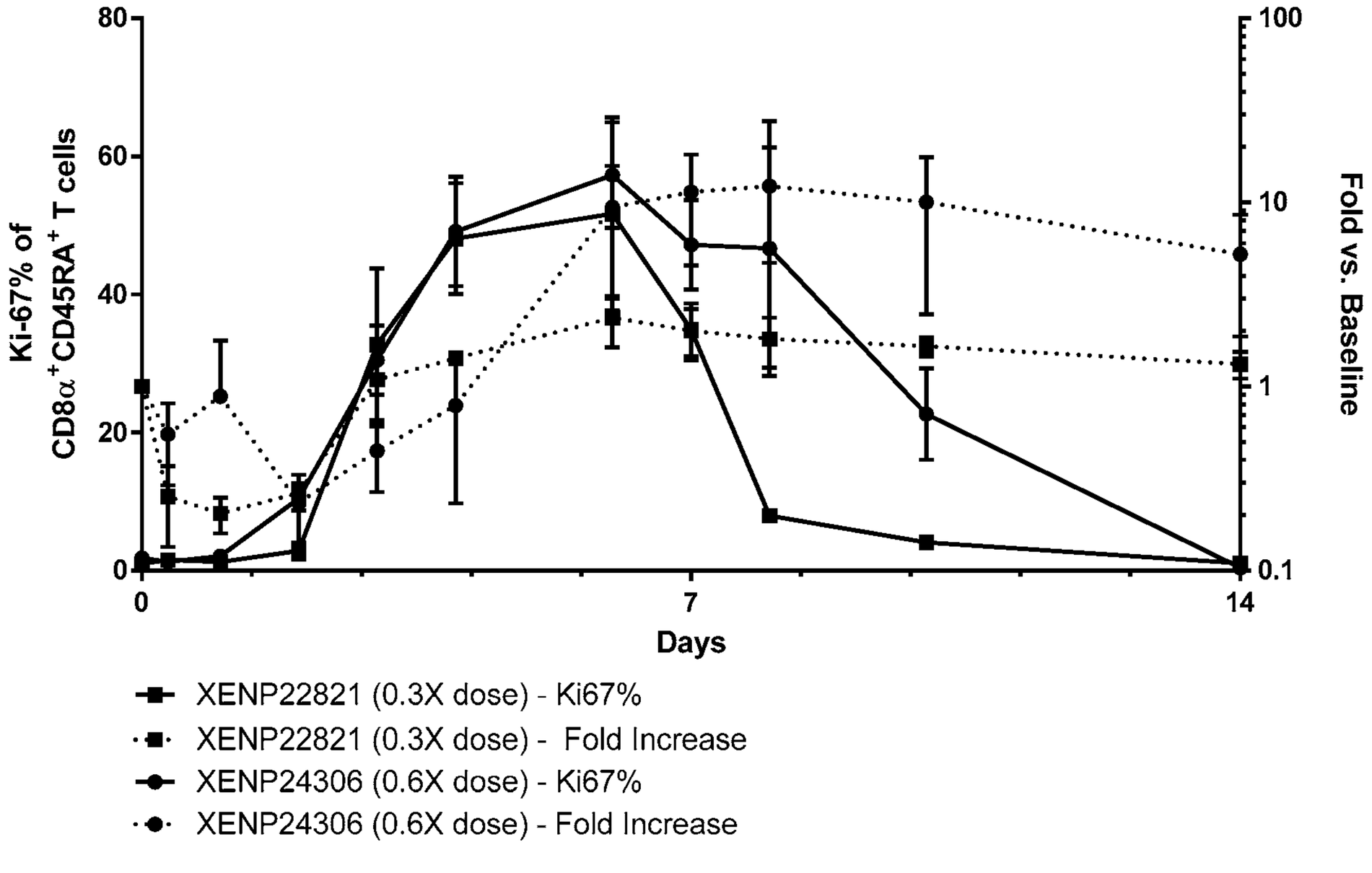

Ki-67% of CD8α+CD45RA+ T cells
Fold vs. Baseline
Days
0
7
14
0
20
40
60
80
0.1
1
10
100
XENP22821 (0.3X dose) - Ki67%
XENP22821 (0.3X dose) - Fold Increase
XENP24306 (0.6X dose) - Ki67%
XENP24306 (0.6X dose) - Fold Increase

Figure 150

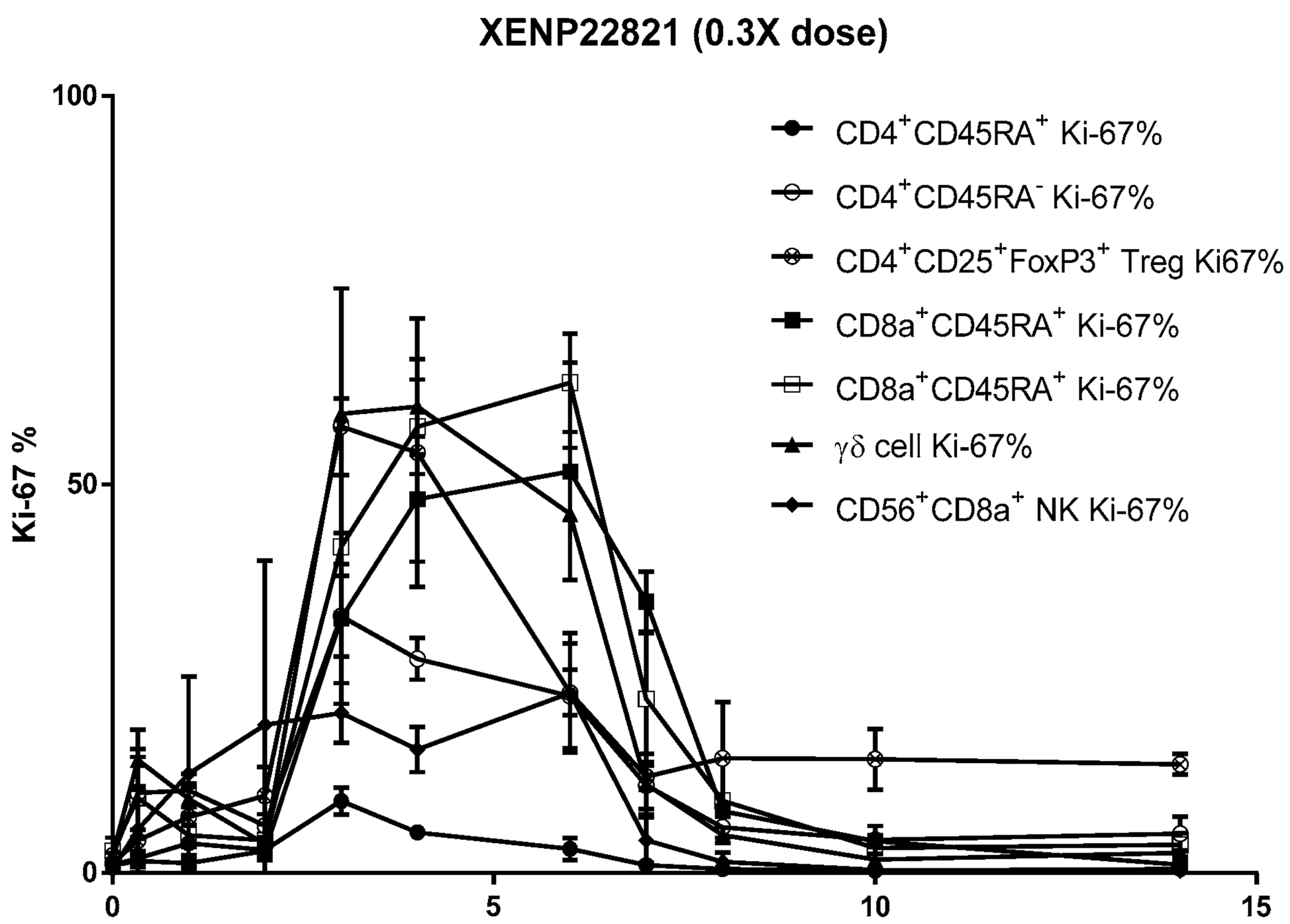

XENP22821 (0.3X dose)
100
50
0
Ki-67 %
0
5
10
15
days
CD4+CD45RA+ Ki-67%
CD4+CD45RA- Ki-67%
CD4+CD25+FoxP3+ Treg Ki67%
CD8a+CD45RA+ Ki-67%
CD8a+CD45RA+ Ki-67%
γδ cell Ki-67%
CD56+CD8a+ NK Ki-67%

Figure 151

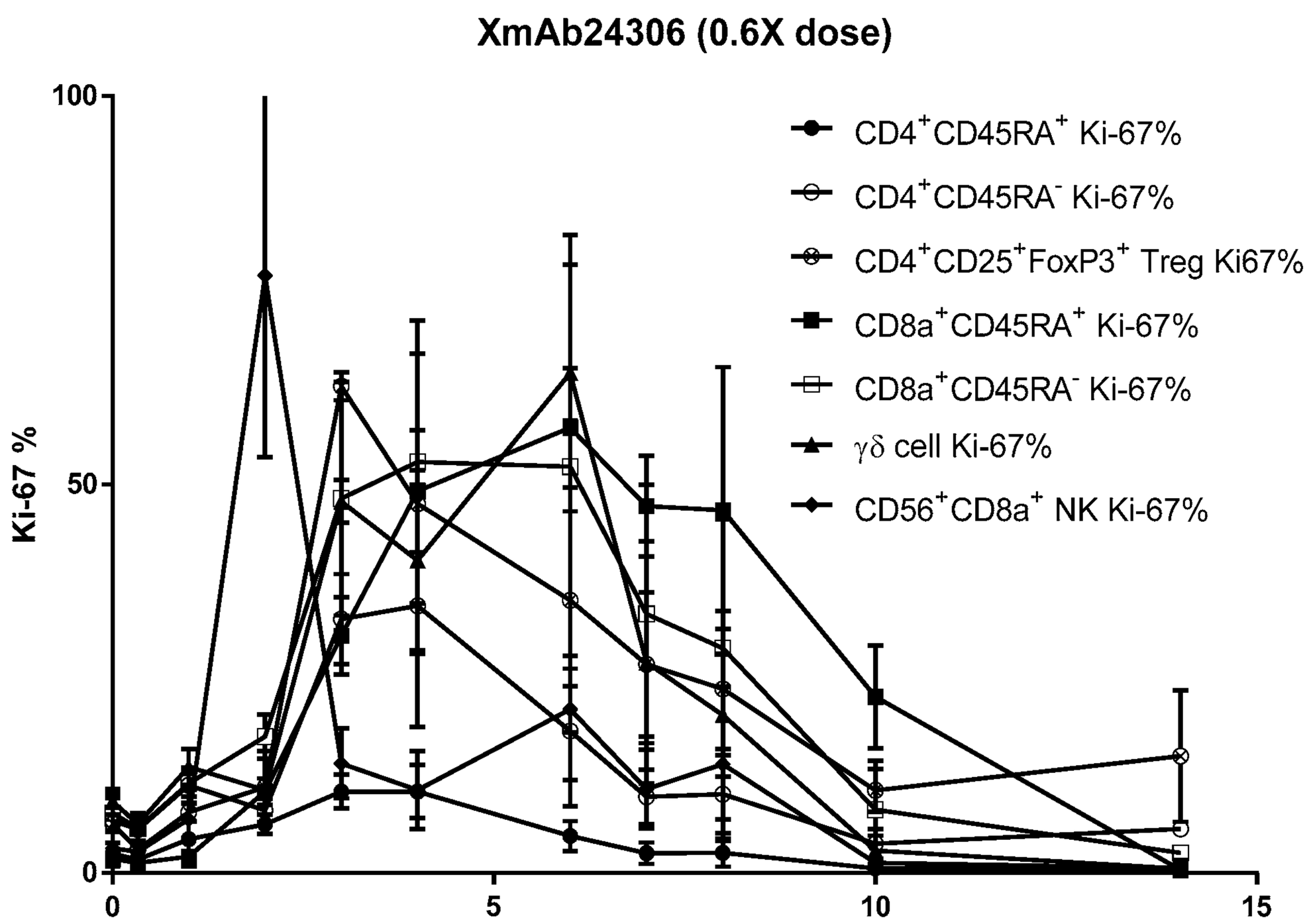

XmAb24306 (0.6X dose)
100
50
0
Ki-67 %
0
5
10
15
days
CD4+CD45RA+ Ki-67%
CD4+CD45RA- Ki-67%
CD4+CD25+FoxP3+ Treg Ki67%
CD8a+CD45RA+ Ki-67%
CD8a+CD45RA- Ki-67%
γδ cell Ki-67%
CD56+CD8a+ NK Ki-67%

Figure 152

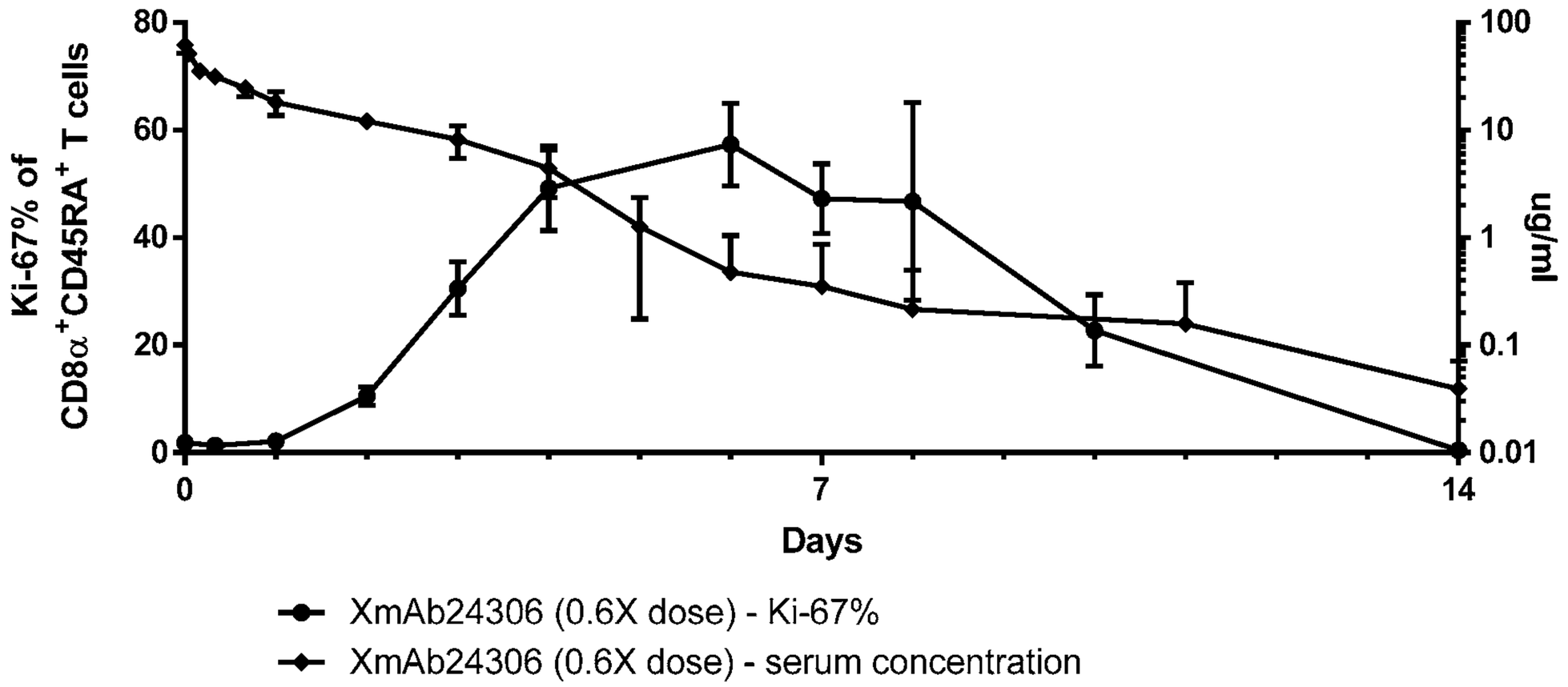

Ki-67% of CD8α+CD45RA+ T cells
80
60
40
20
0
0
7
14
Days
100
10
1
0.1
0.01
μg/ml
XmAb24306 (0.6X dose) - Ki-67%
XmAb24306 (0.6X dose) - serum concentration

Figure 153

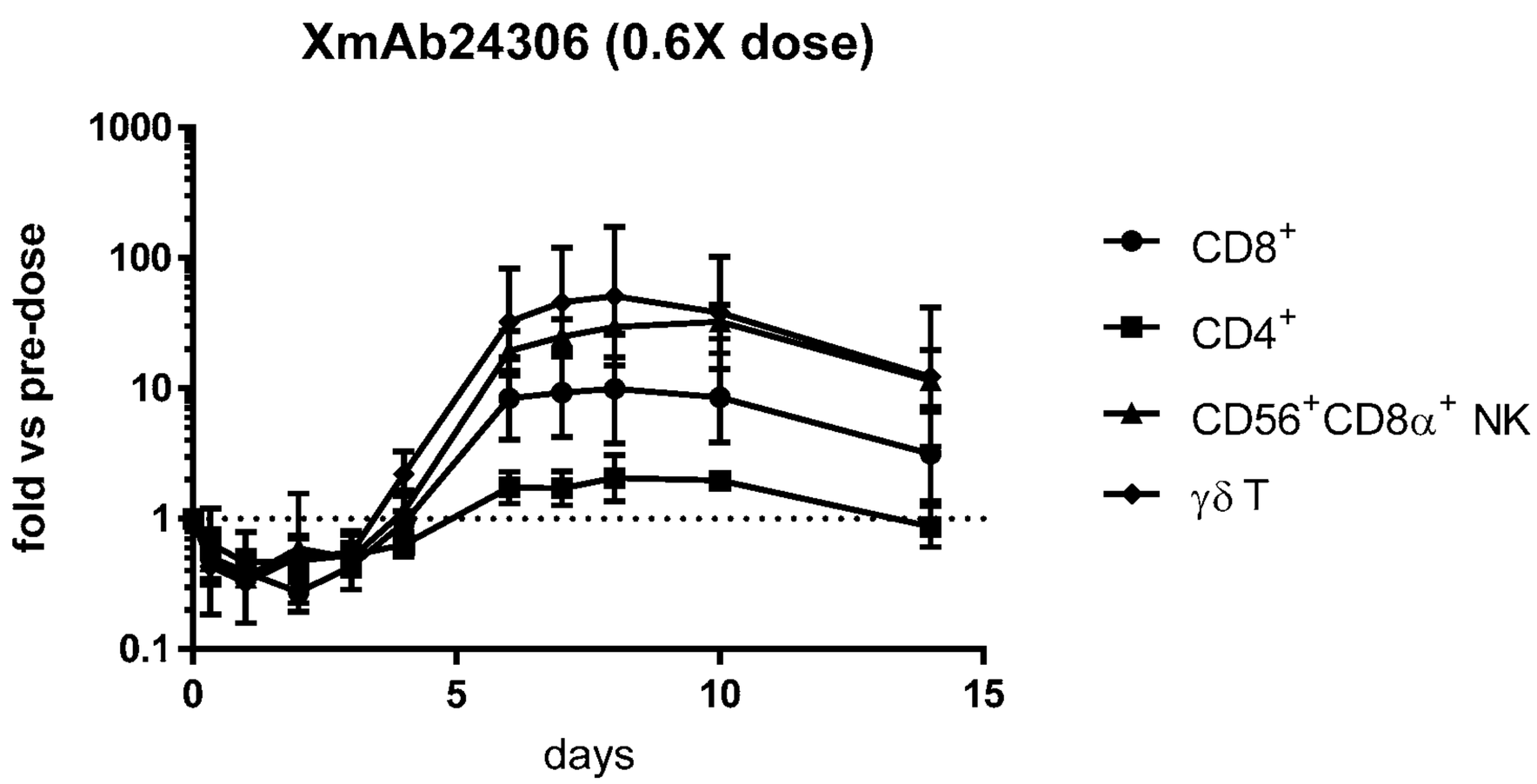

XmAb24306 (0.6X dose)
1000
100
10
1
0.1
fold vs pre-dose
0
5
10
15
days
CD8+
CD4+
CD56+CD8α+ NK
γδ T

Figure 154

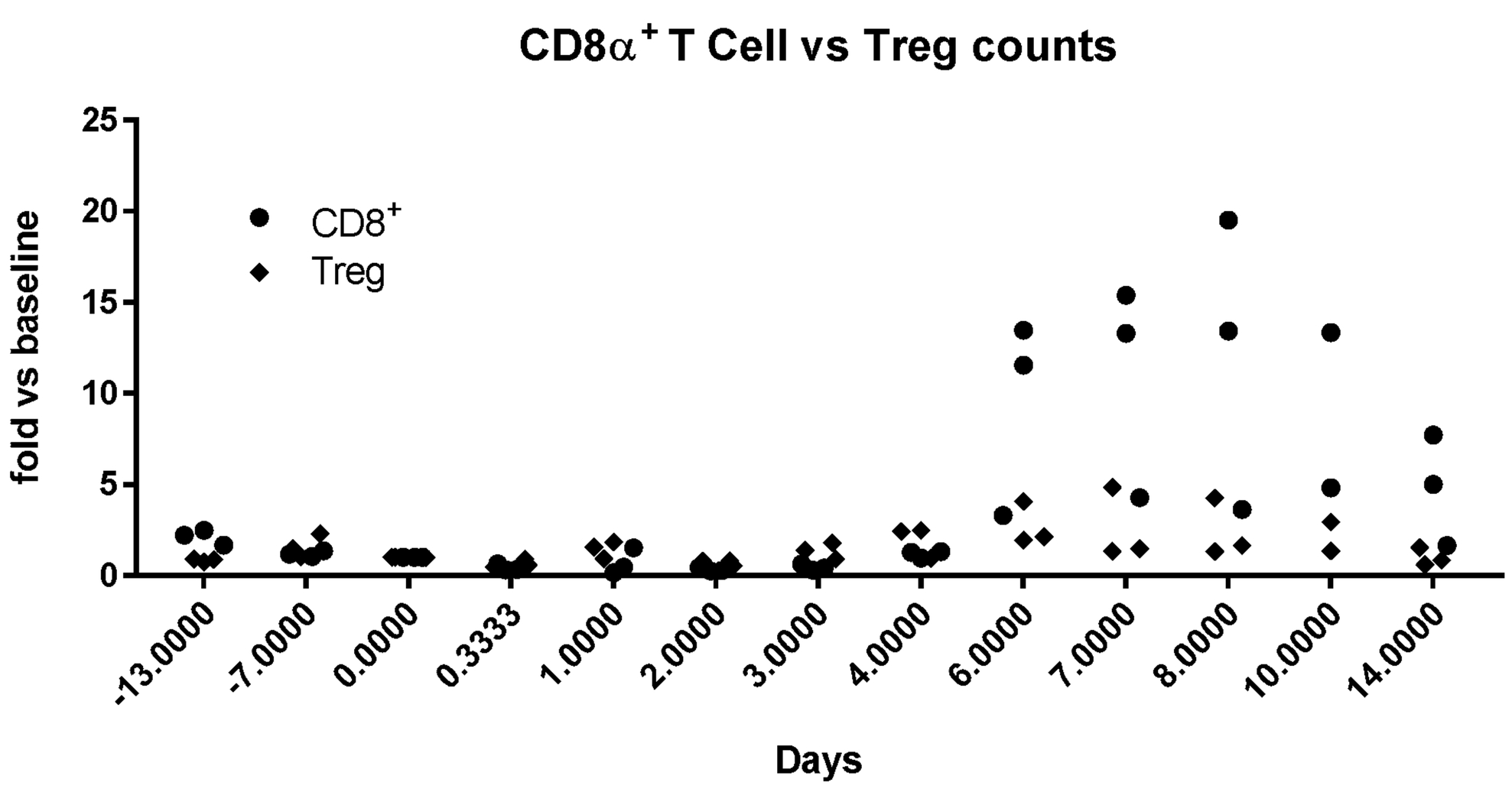

CD8α+ T Cell vs Treg counts
fold vs baseline
25
20
15
10
5
0
CD8+
Treg
-13.0000
-7.0000
0.0000
0.3333
1.0000
2.0000
3.0000
4.0000
6.0000
7.0000
8.0000
10.0000
14.0000
Days

Figure 155A

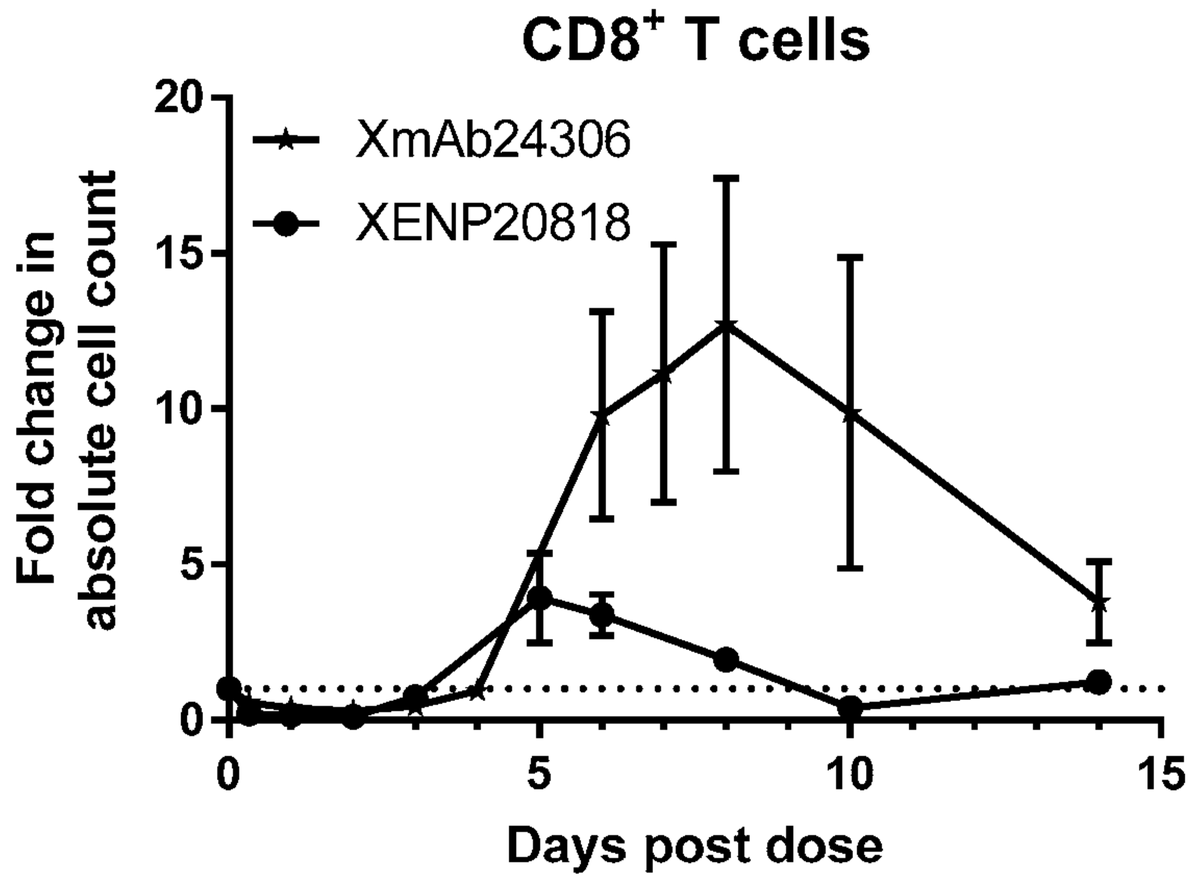


Figure 155B

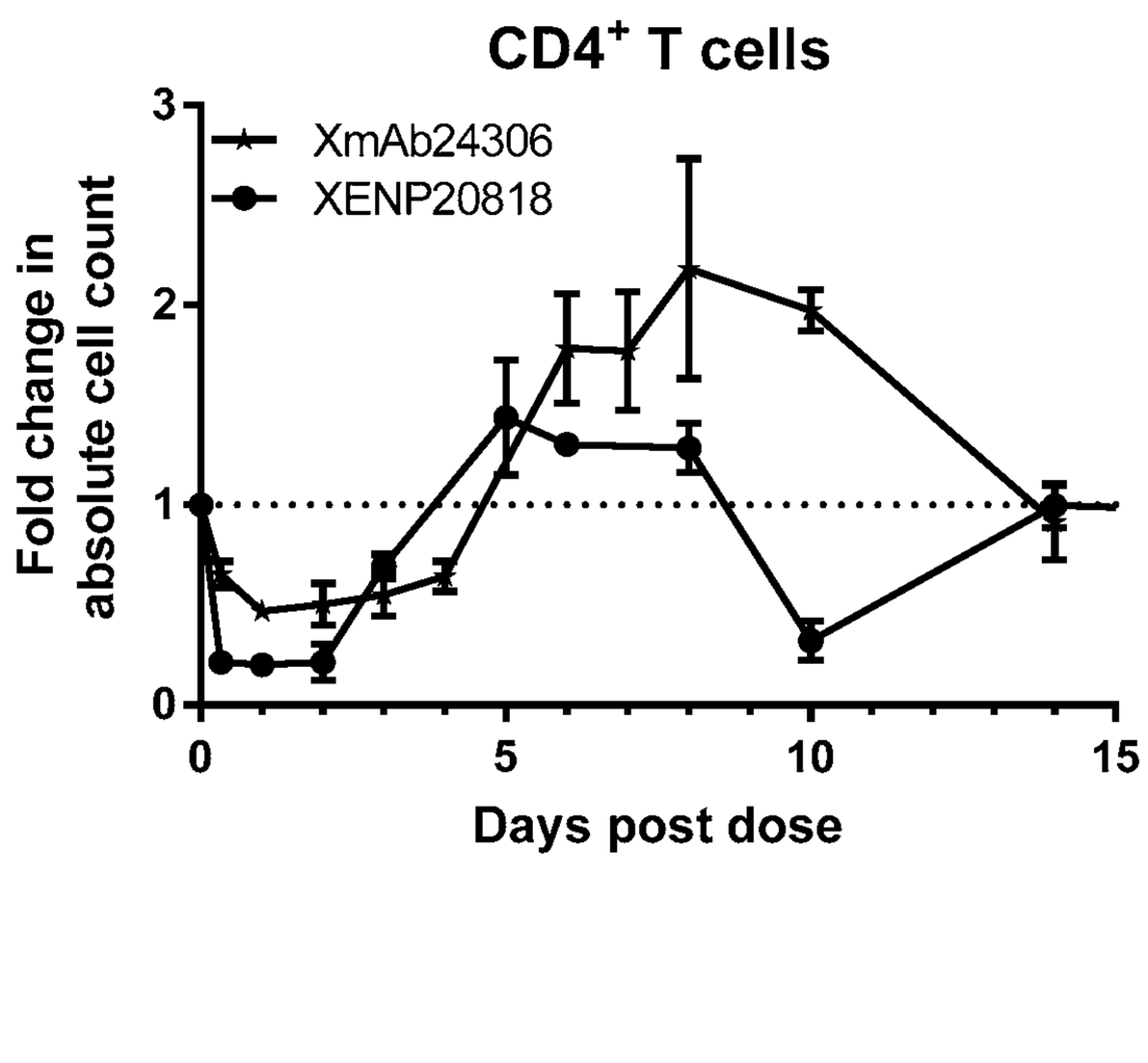


Figure 155C

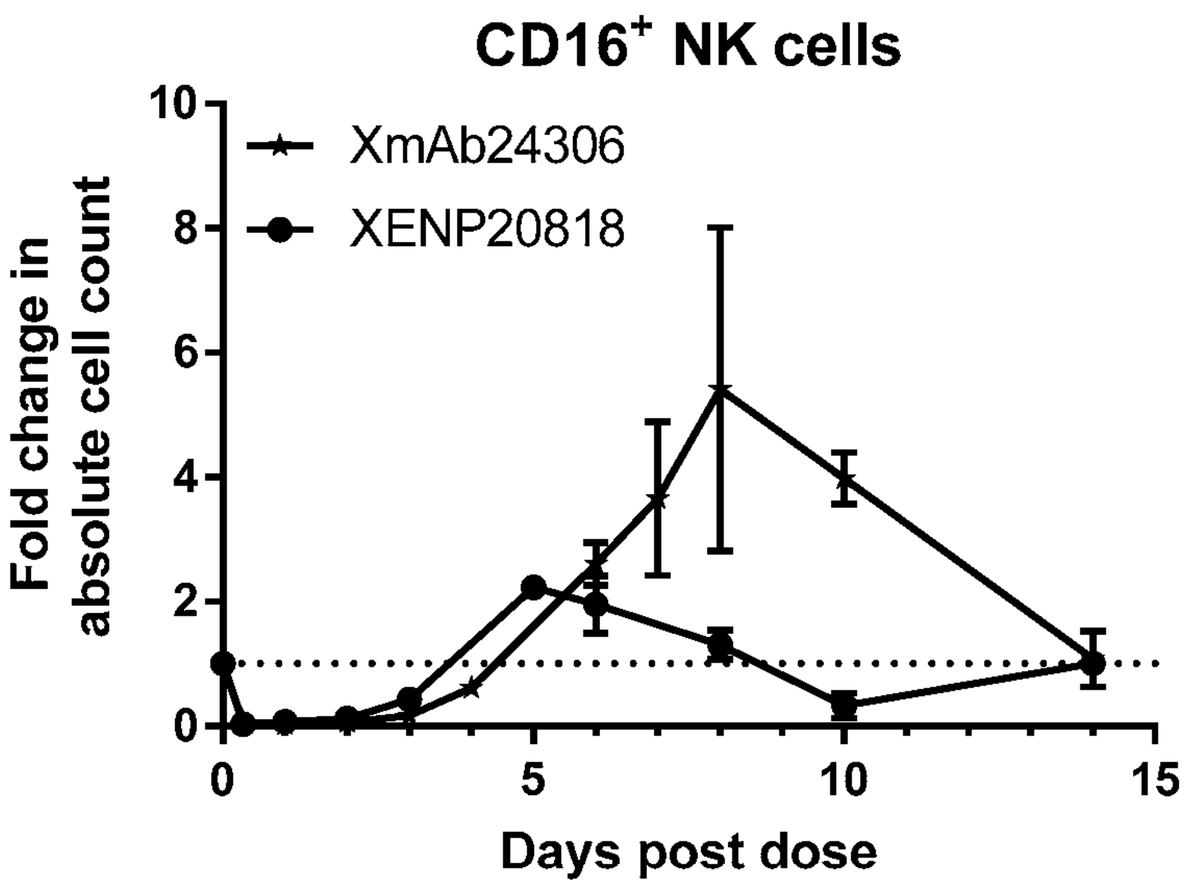

CD16+ NK cells
XmAb24306
XENP20818
Fold change in absolute cell count
0
2
4
6
8
10
0
5
10
15
Days post dose

Figure 156A

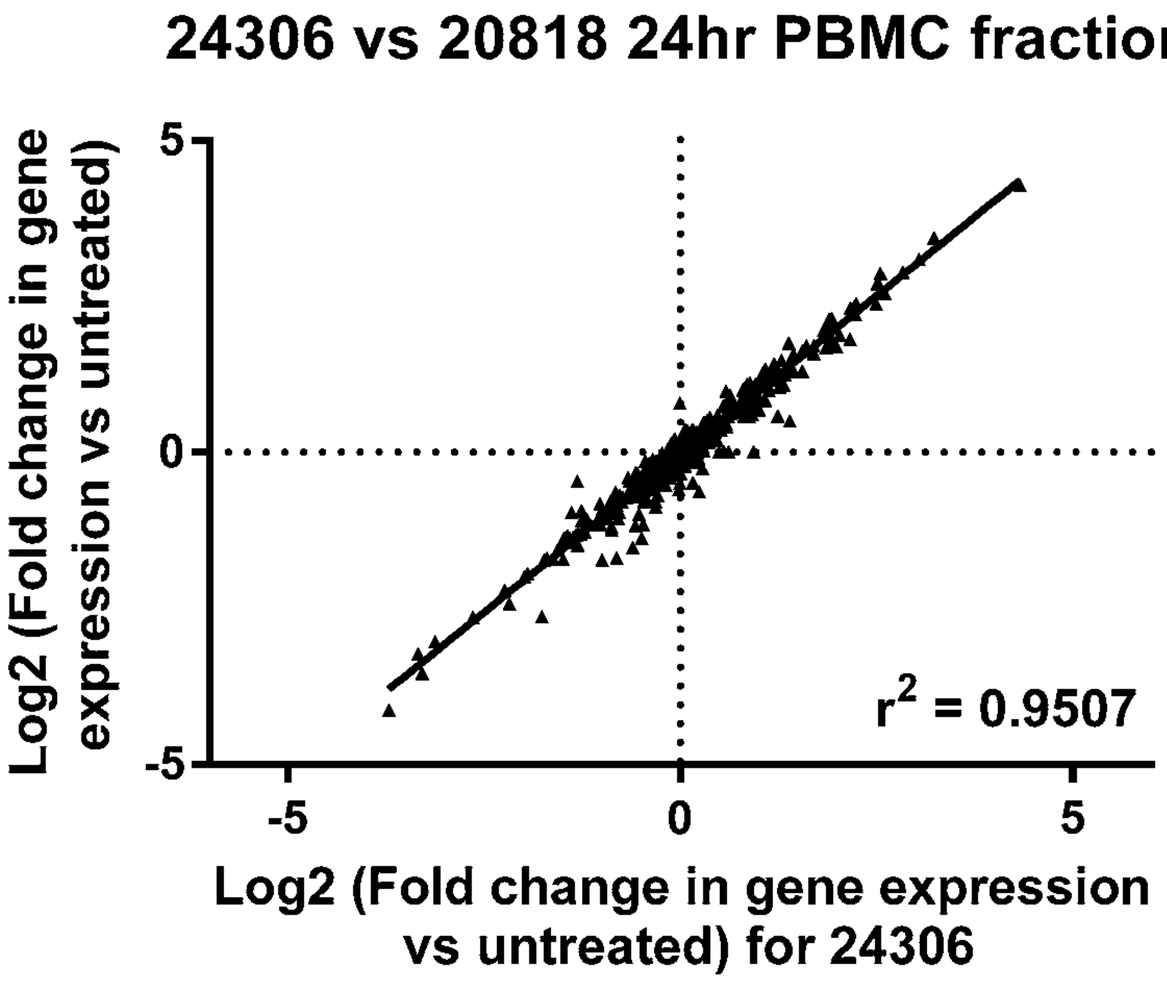


Figure 156B

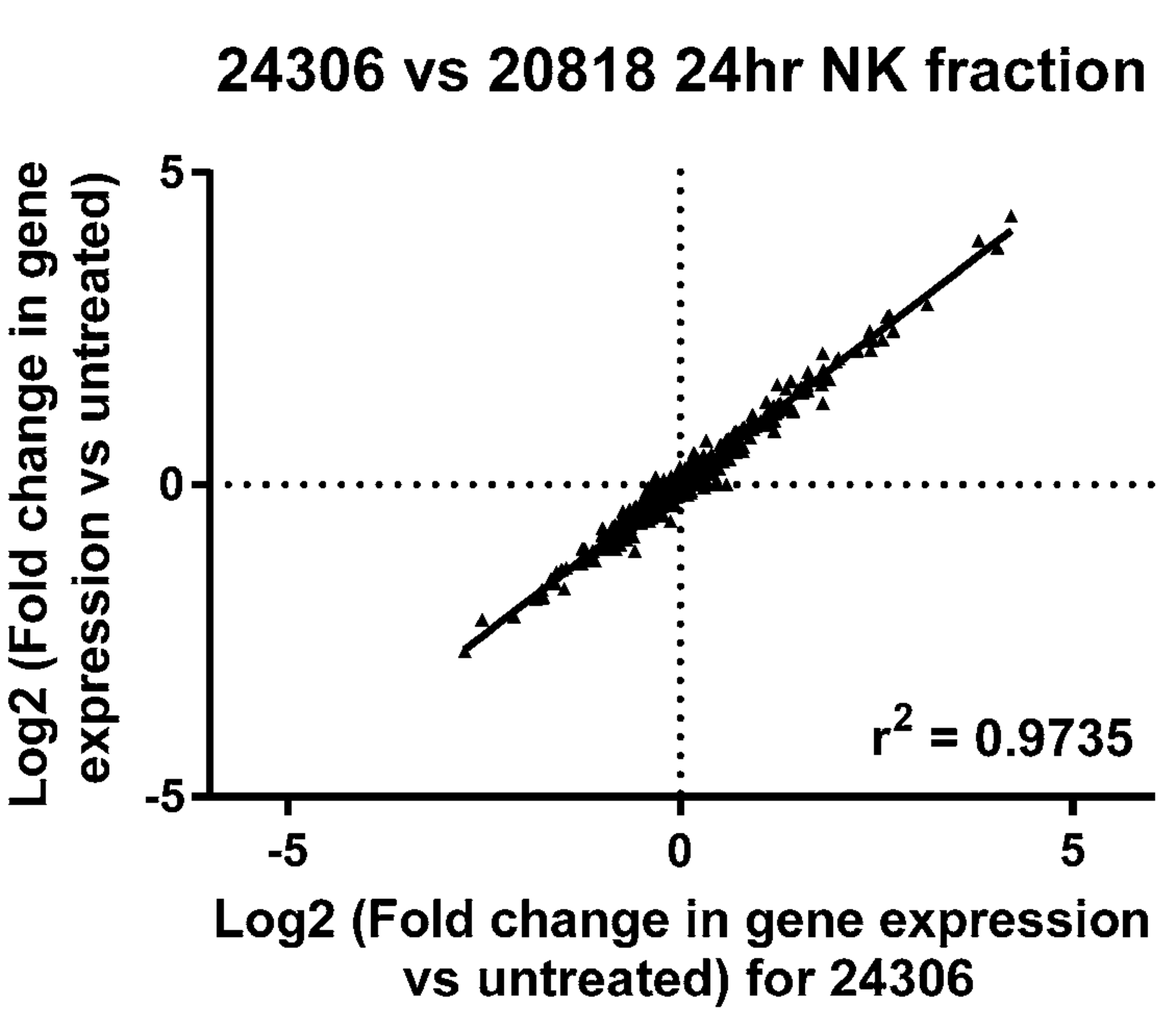


Figure 156C

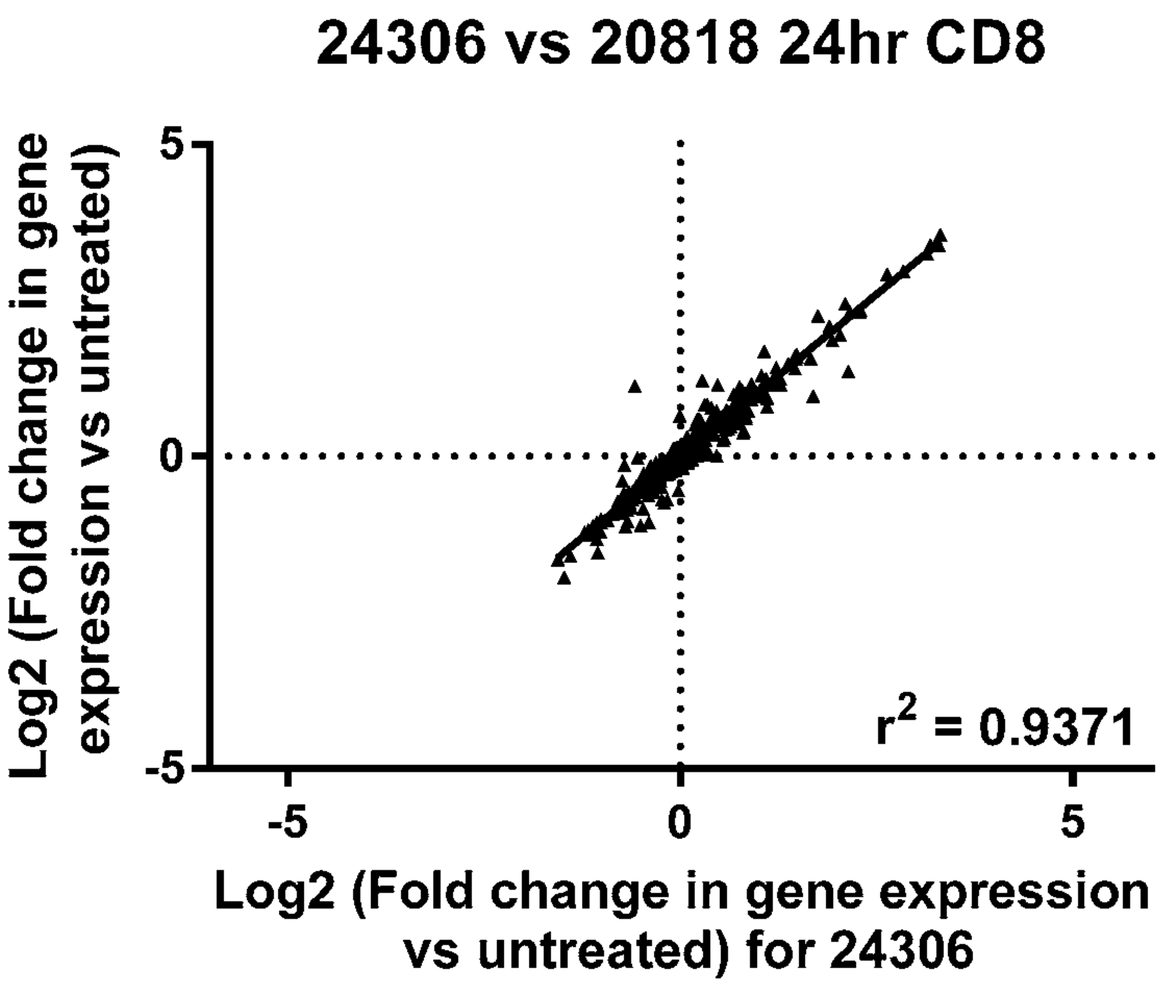

24306 vs 20818 24hr CD8
Log2 (Fold change in gene expression vs untreated)
5
0
-5
-5
0
5
r2 = 0.9371
Log2 (Fold change in gene expression vs untreated) for 24306

Figure 157A

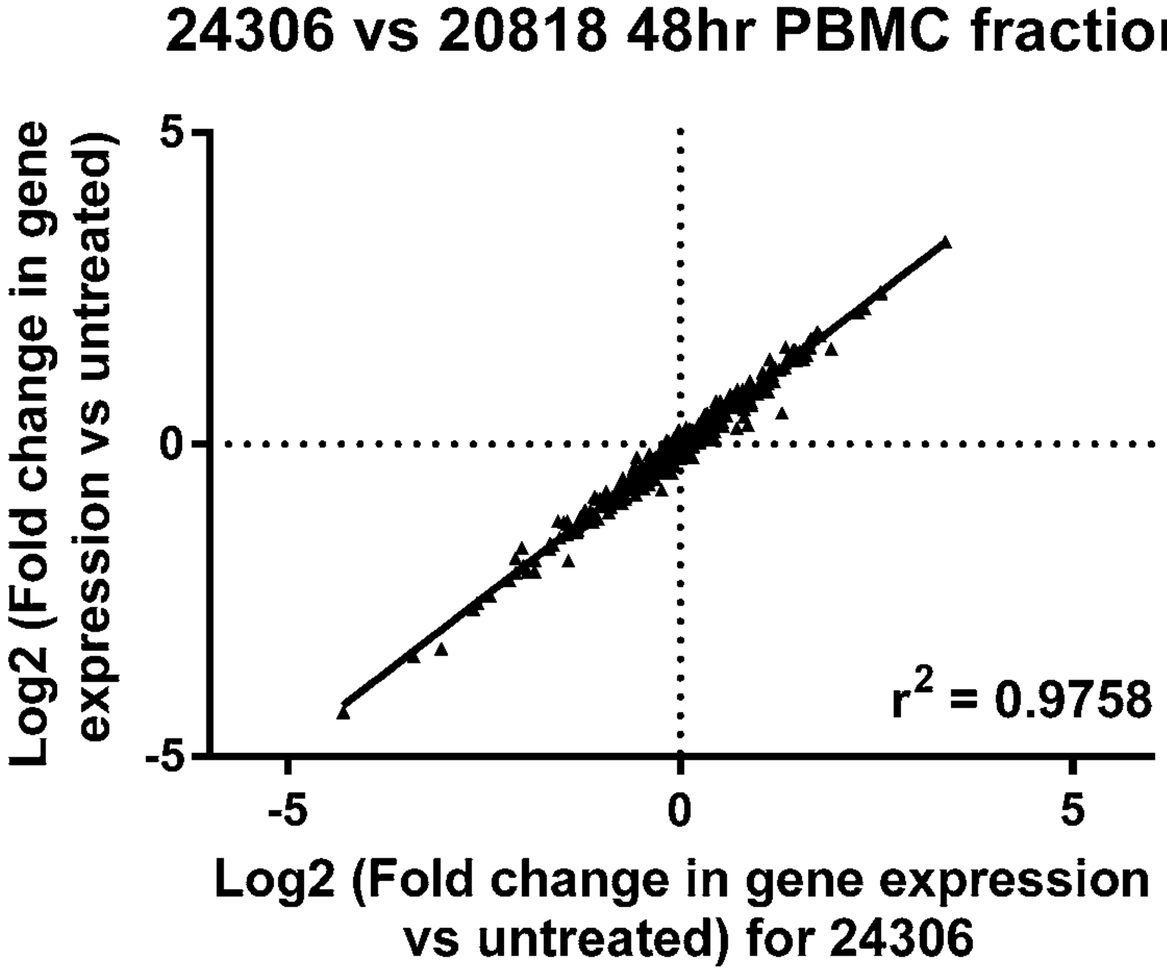


Figure 157B

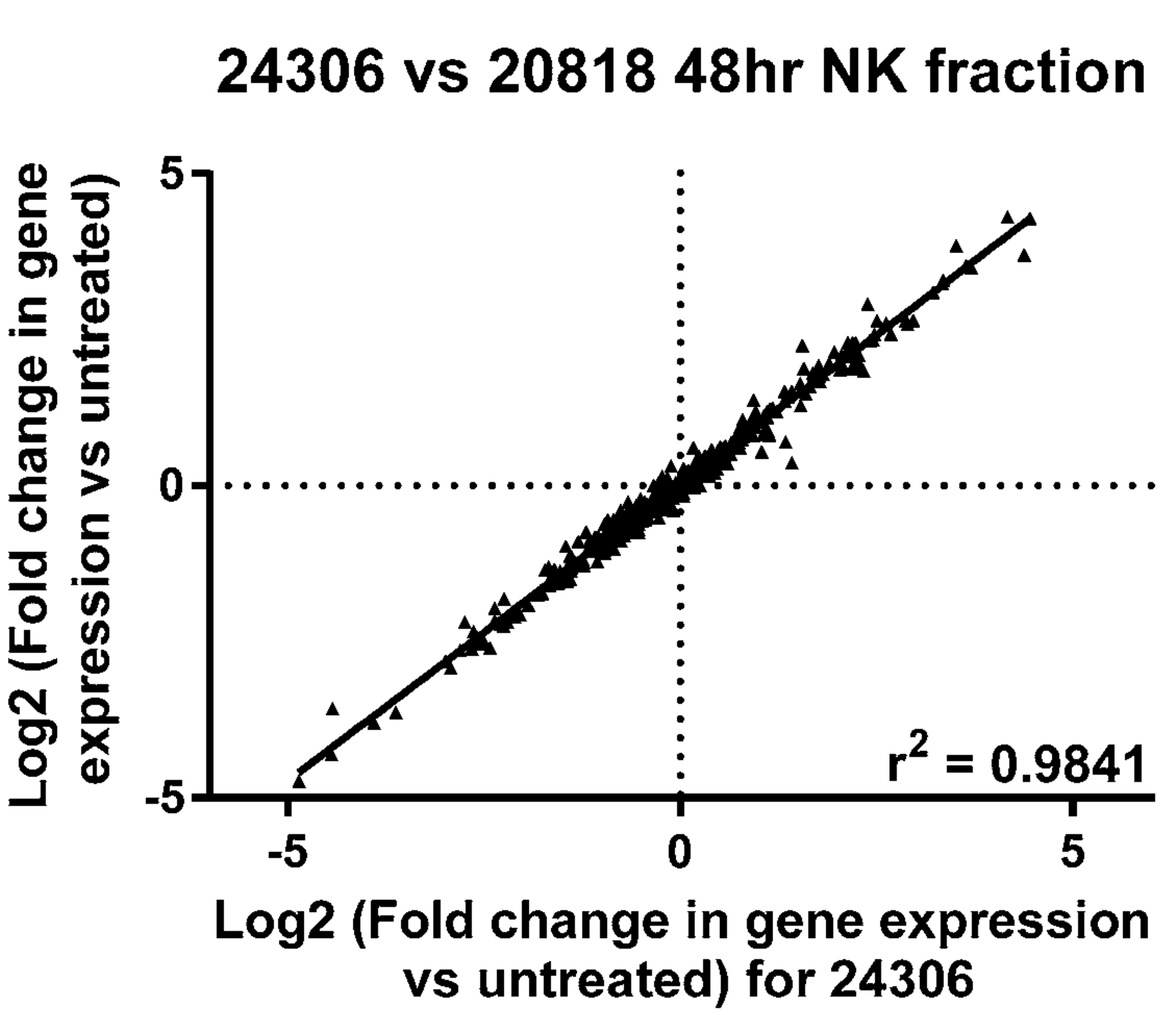


Figure 157C

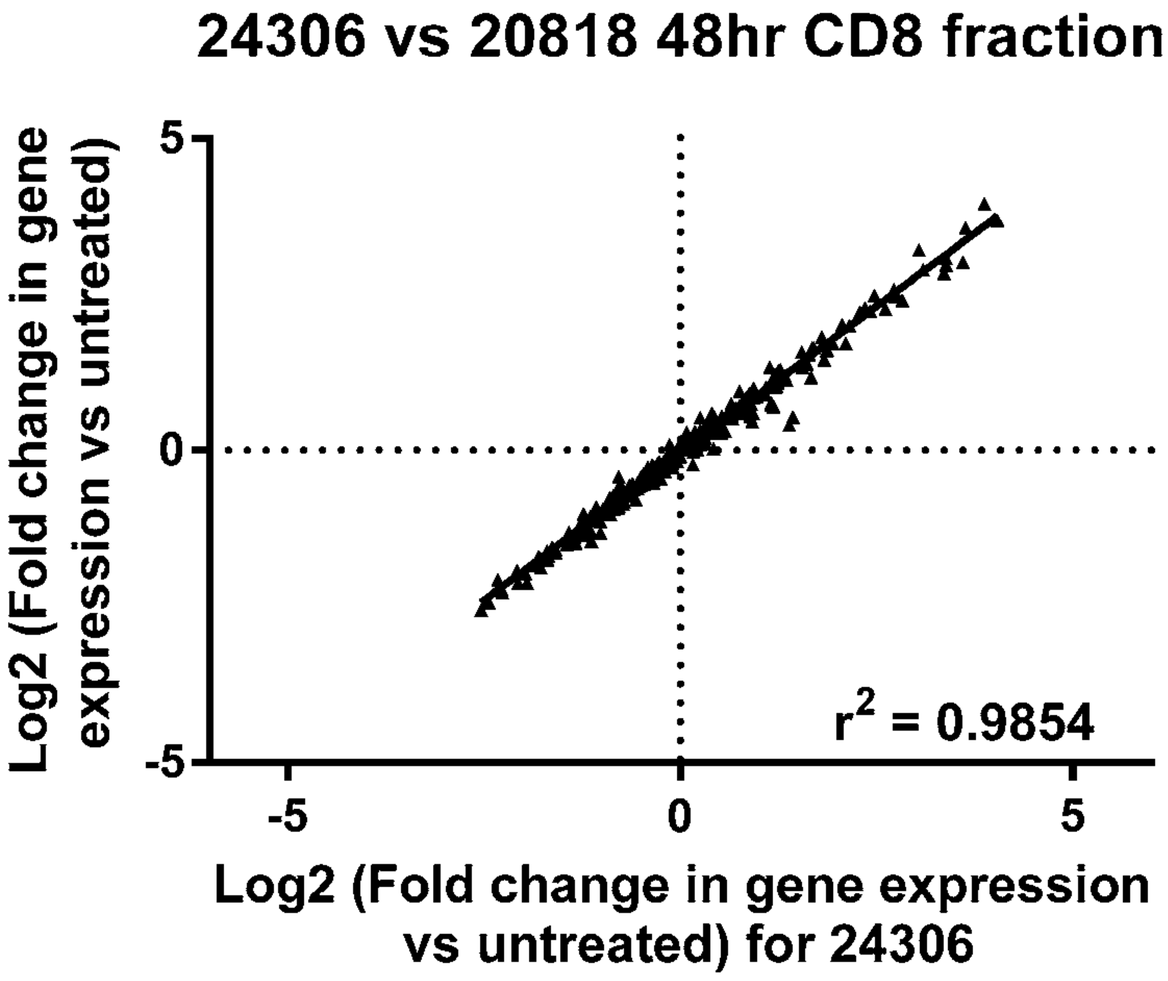

24306 vs 20818 48hr CD8 fraction
Log2 (Fold change in gene expression vs untreated)
5
0
-5
-5
0
5
r2 = 0.9854
Log2 (Fold change in gene expression vs untreated) for 24306

Figure 158A

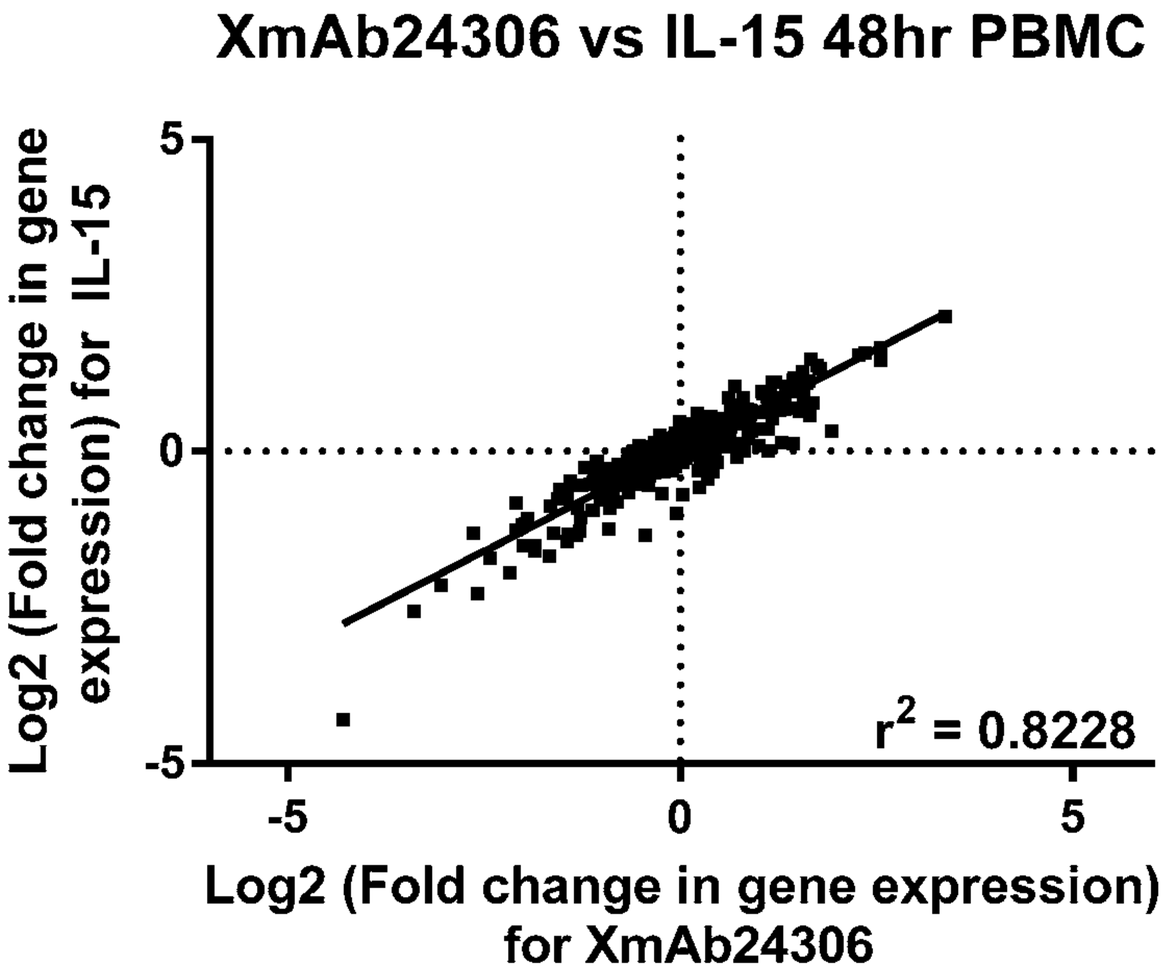


Figure 158B

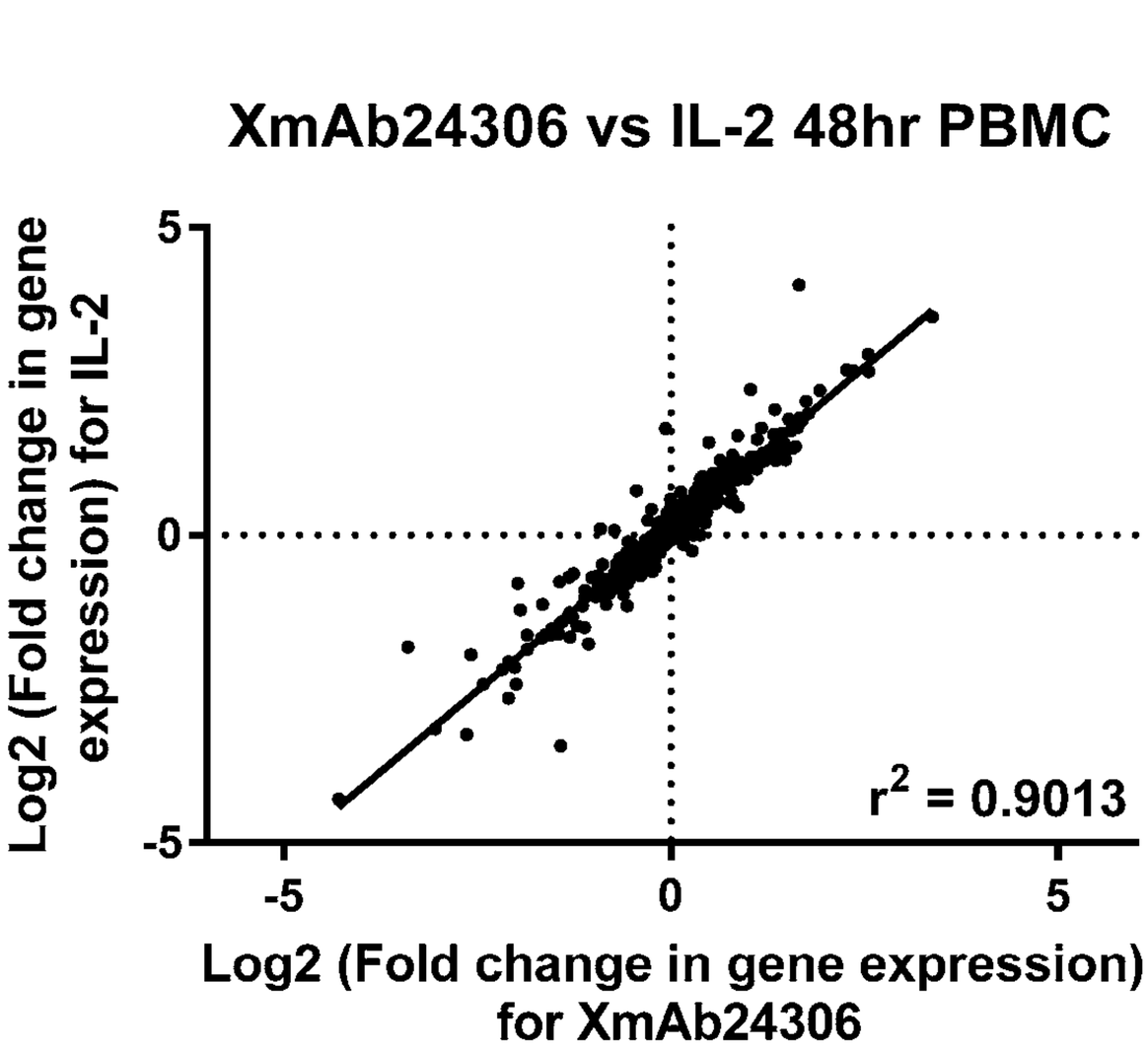


Figure 159A

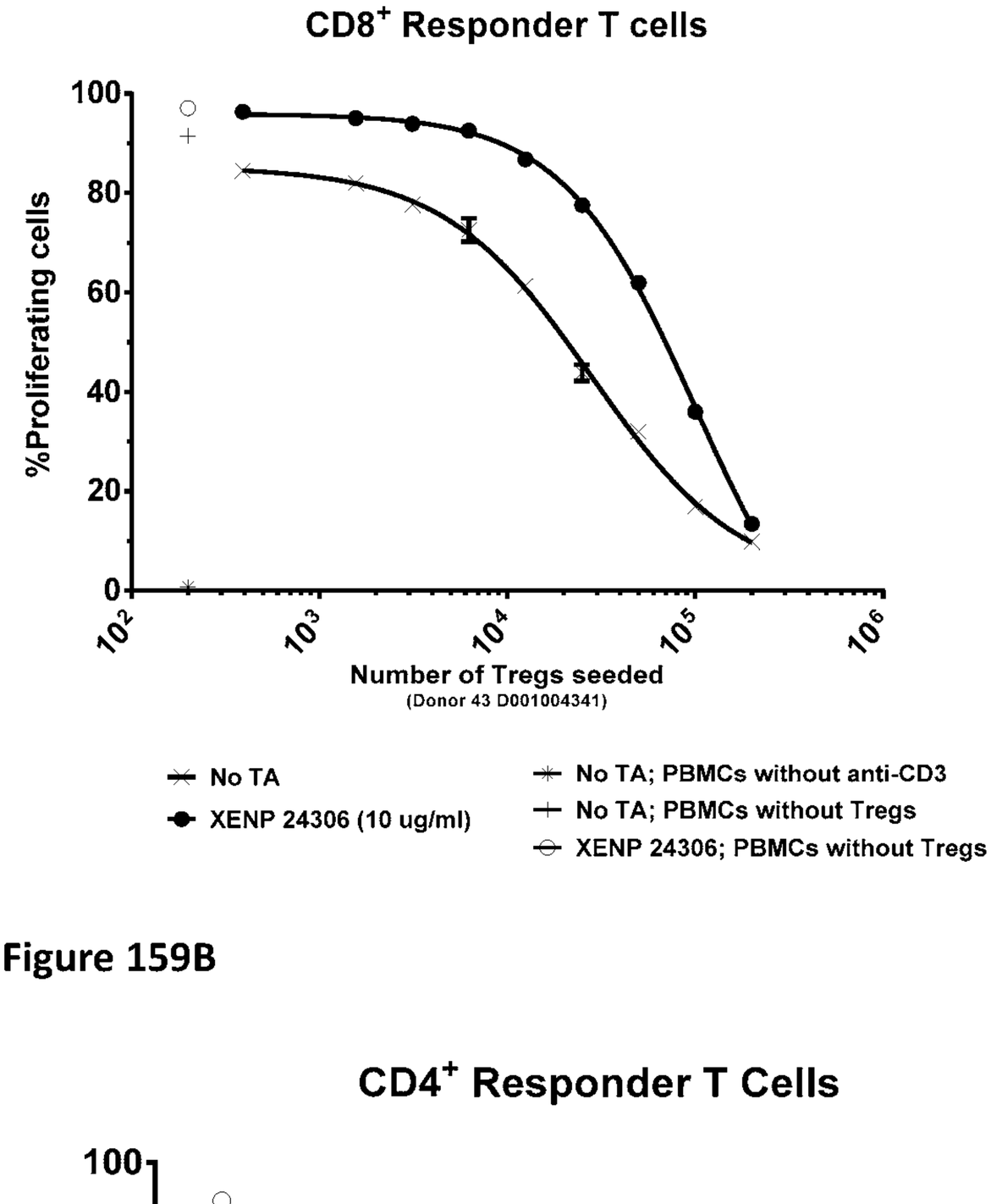


Figure 159B

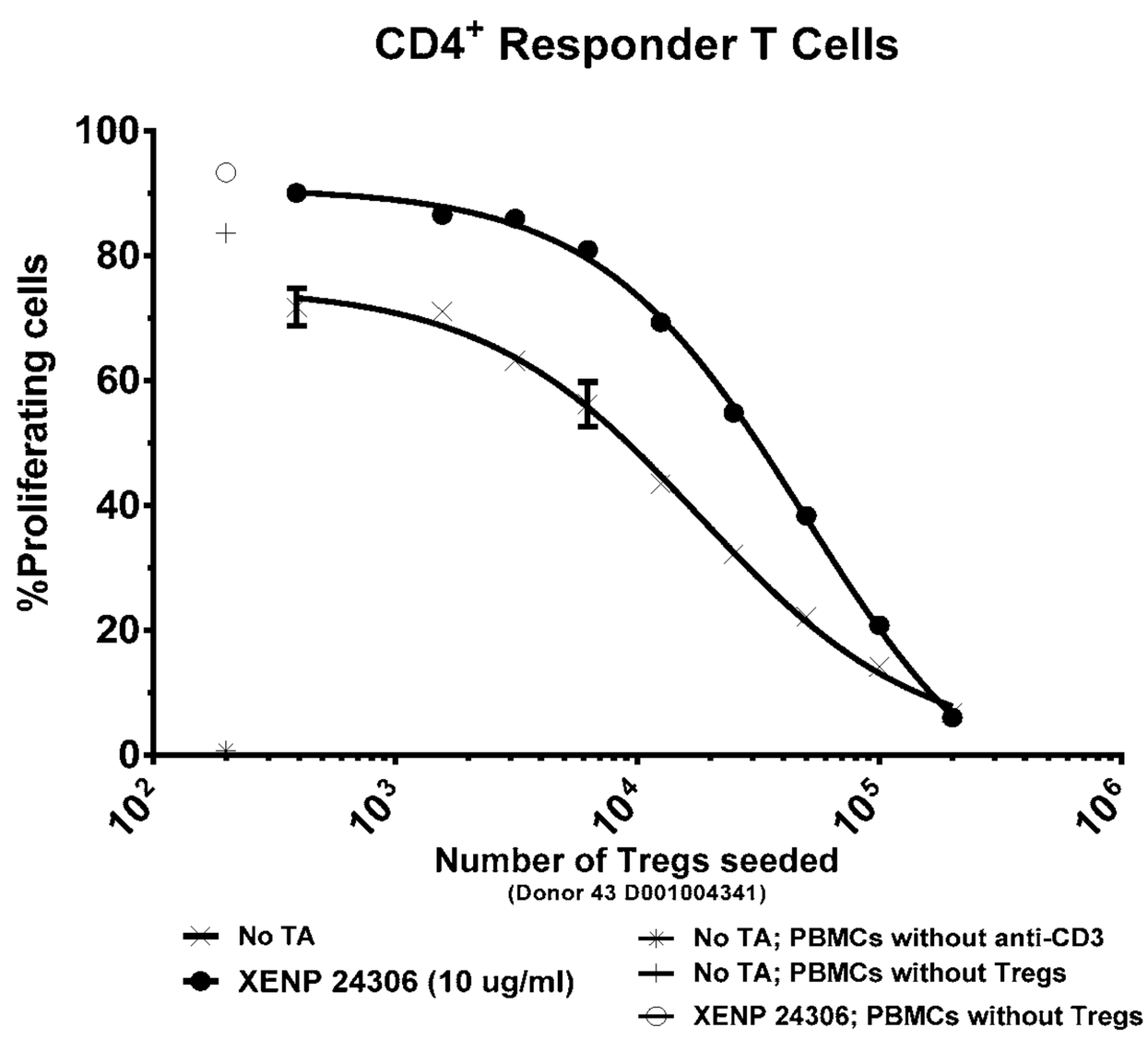


Figure 160

XENP016432 Nivolumab_H0L0_IgG1_PVA_/S267K Heavy Chain (SEQ ID NO: 266)

QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWYDGSKRYYADSVKGRFTISRDNSK
NTLFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSS/ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPPVAG
PSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP
PVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

XENP016432 Nivolumab_H0L0_IgG1_PVA_/S267K Light Chain (SEQ ID NO: 267)

EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPED
FAVYYCQQSSNWPRTFGQGTKVEIK/RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Figure 161A

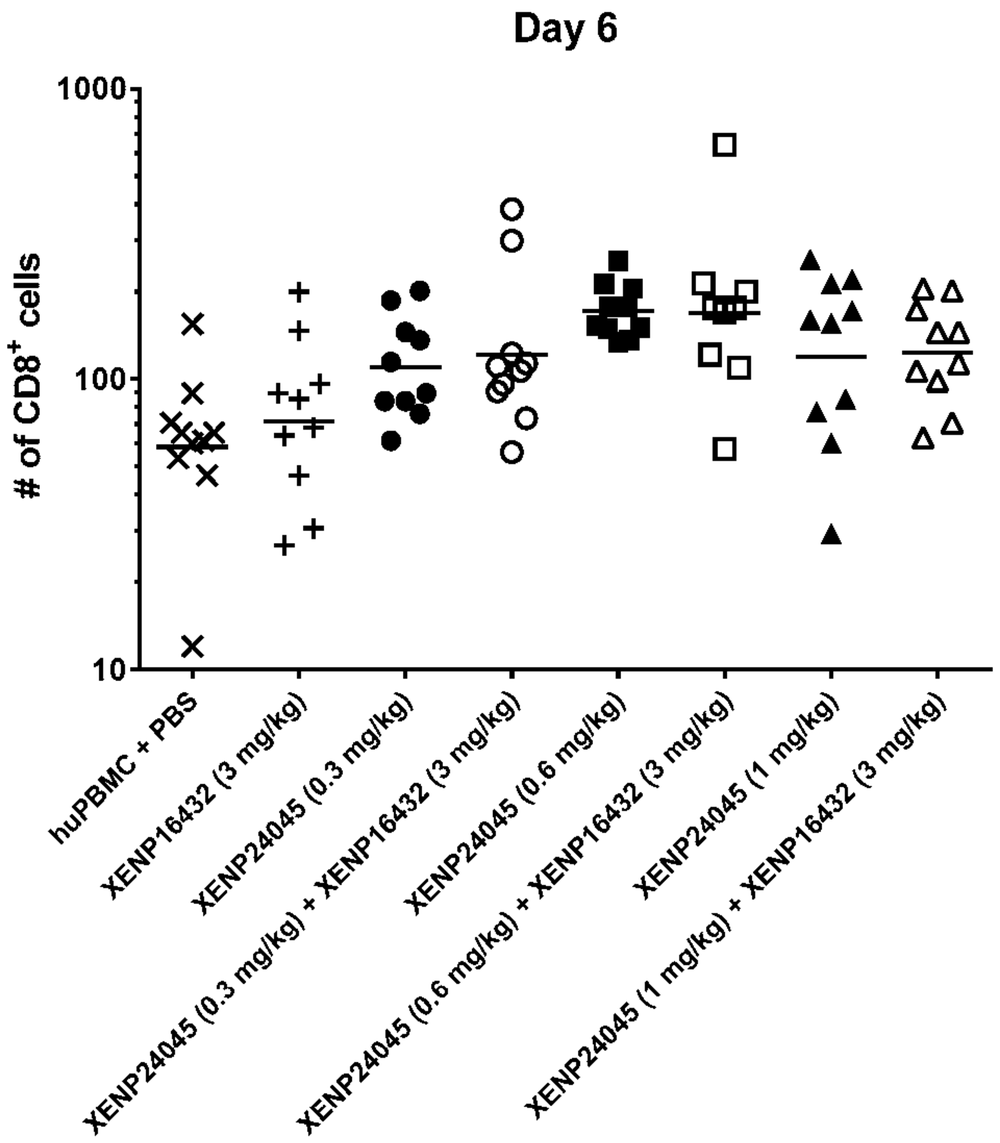


Figure 161B

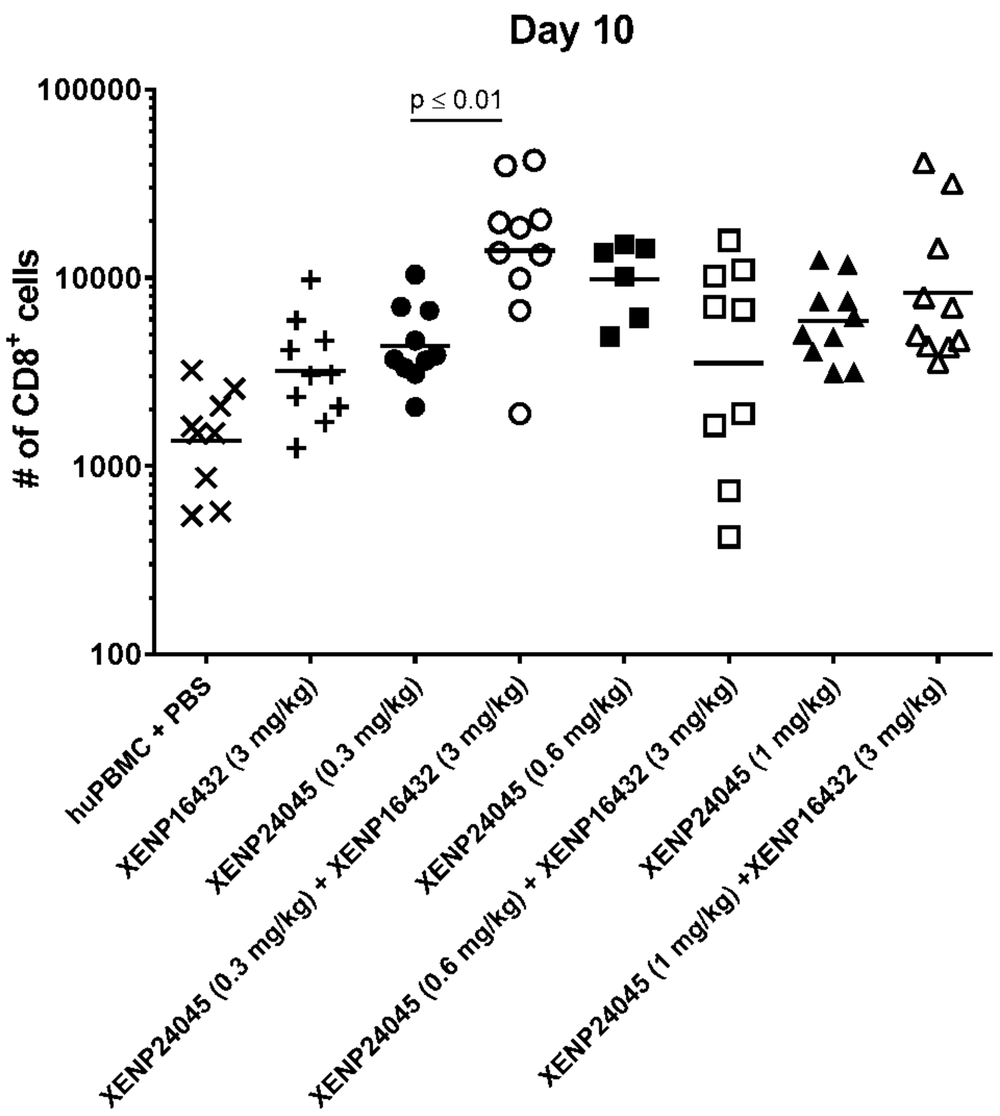


Figure 162A

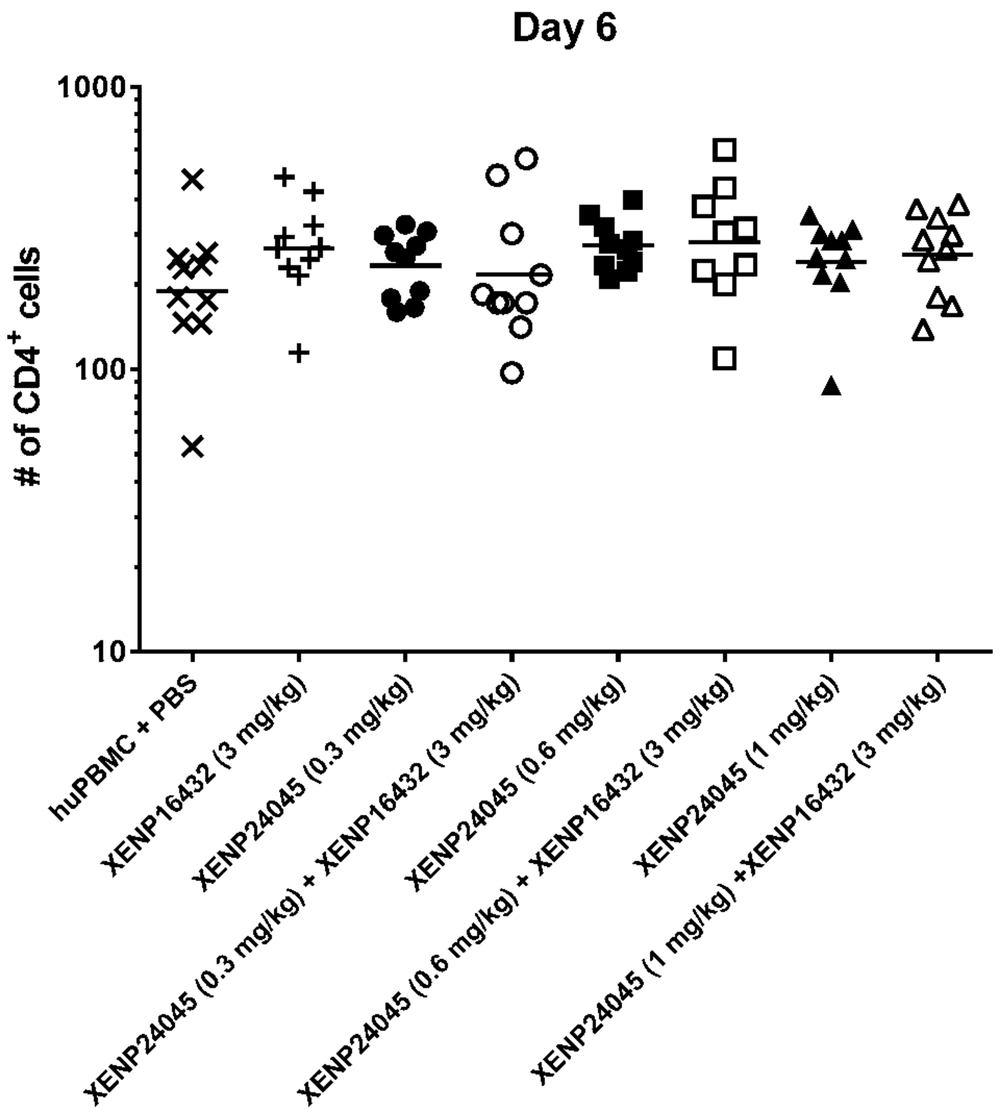
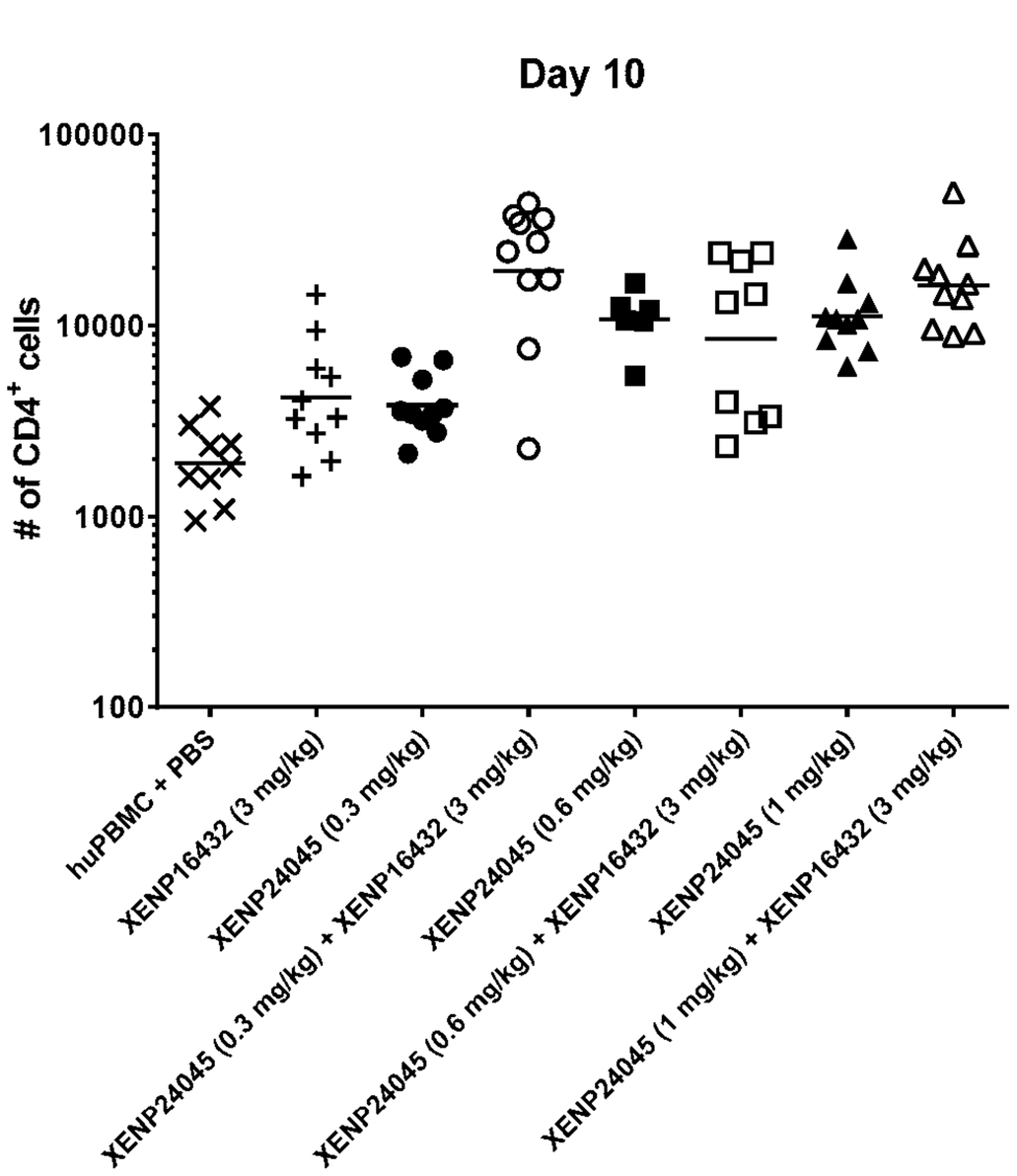


Figure 162B



Figures 163A-163B depict $CD45^+$ T cells in whole blood of mice on (Figure 163A) Day 6 and (Figure 163B) Day 10 after first dose of the indicated test articles.

Figure 163A

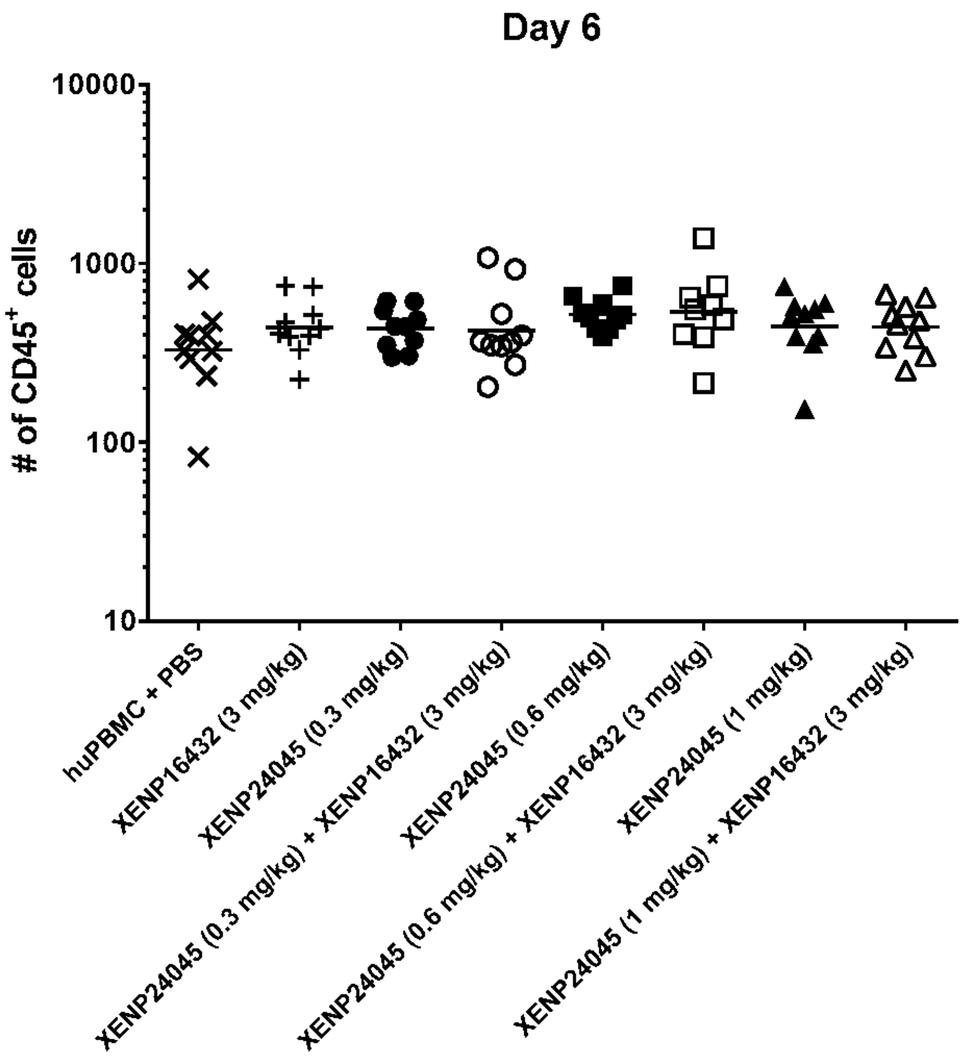


Figure 163B

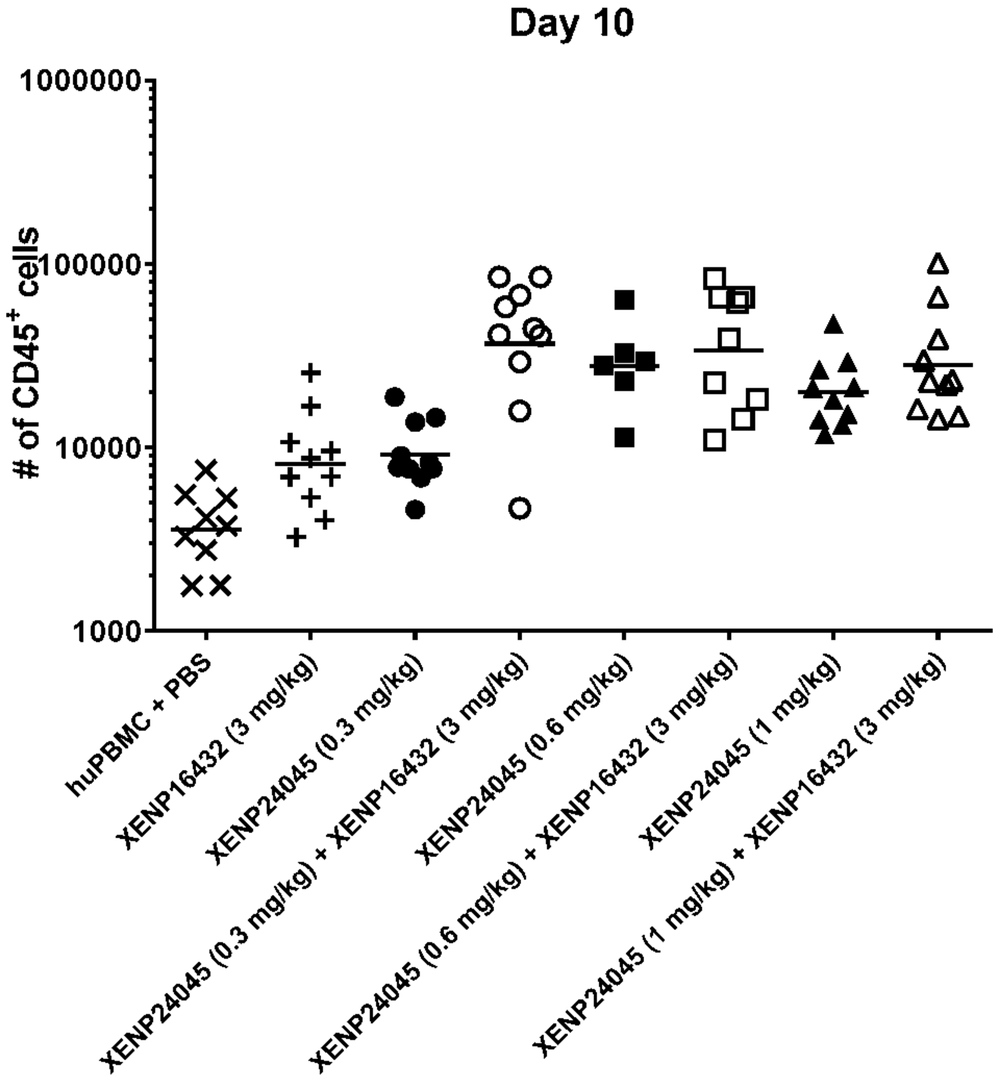


Figure 164A

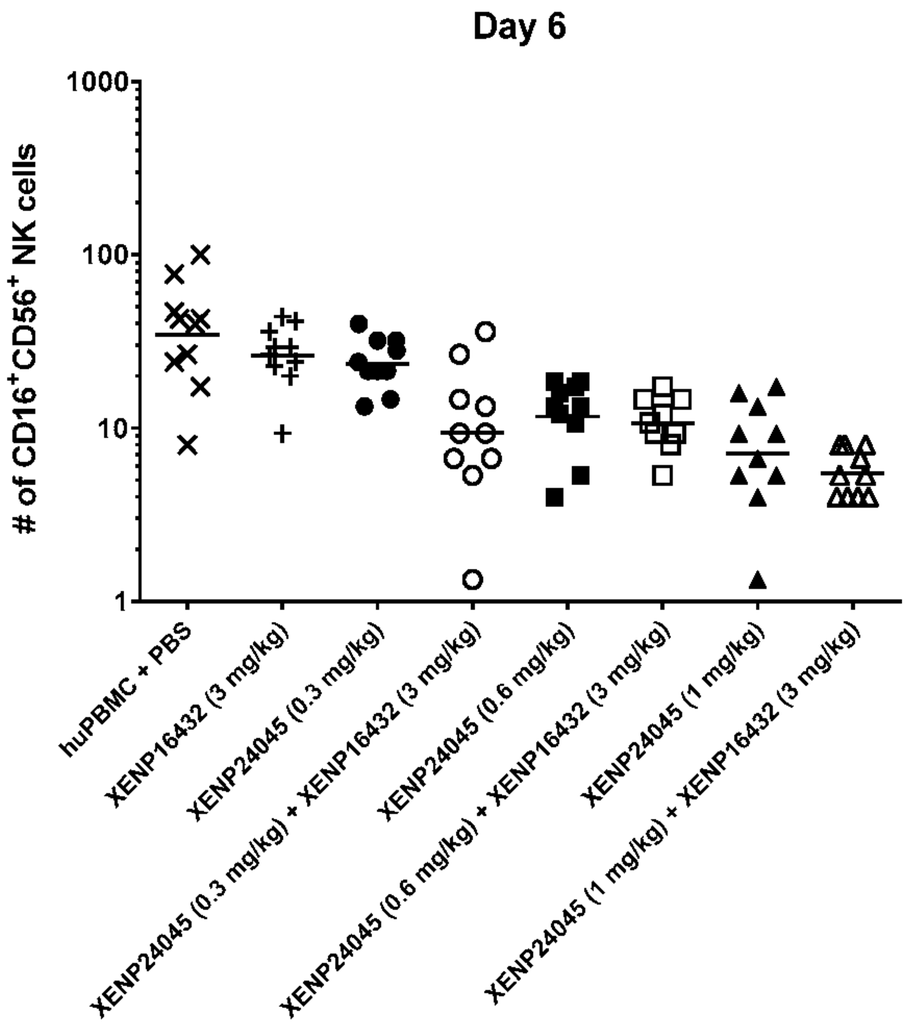


Figure 164B

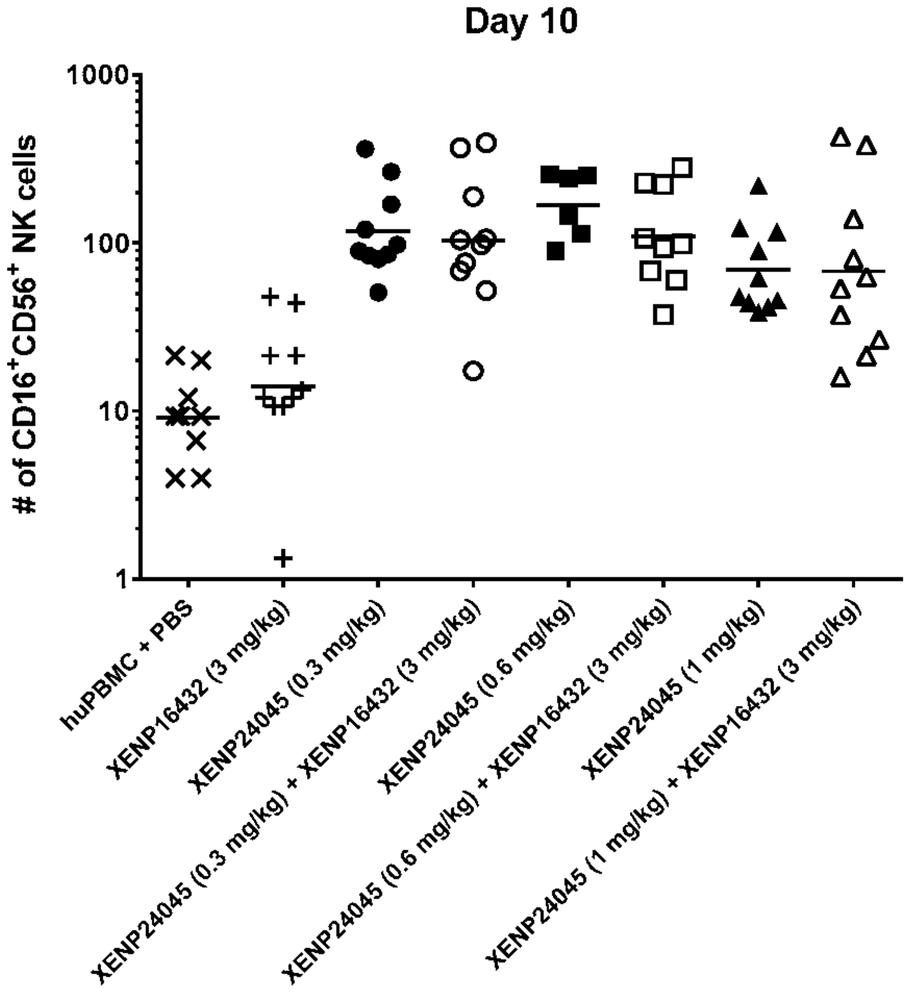


Figure 165

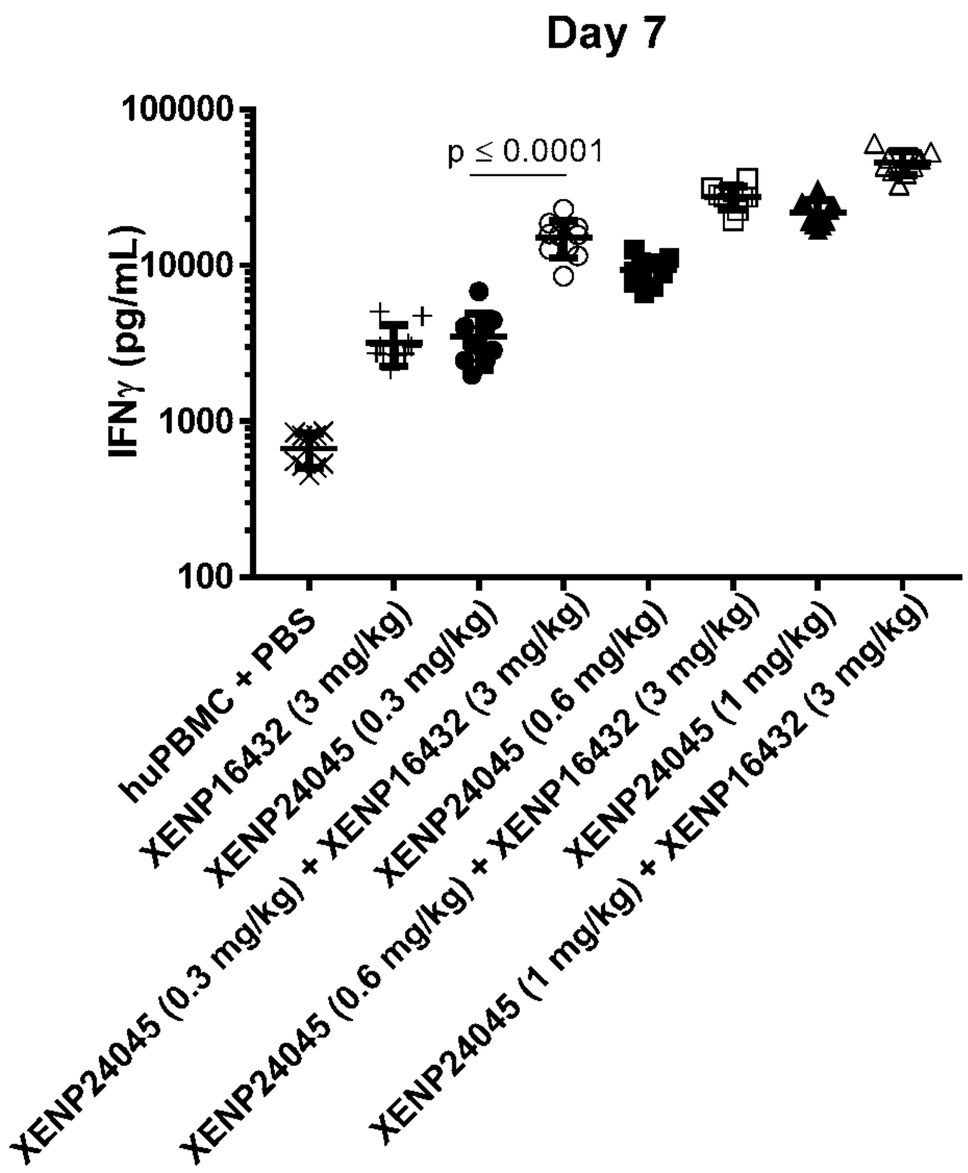

Day 7
IFNγ (pg/mL)
100000
10000
1000
100
p ≤ 0.0001
huPBMC + PBS
XENP16432 (3 mg/kg)
XENP24045 (0.3 mg/kg)
XENP24045 (0.3 mg/kg) + XENP16432 (3 mg/kg)
XENP24045 (0.6 mg/kg)
XENP24045 (0.6 mg/kg) + XENP16432 (3 mg/kg)
XENP24045 (1 mg/kg)
XENP24045 (1 mg/kg) + XENP16432 (3 mg/kg)

Figure 166A

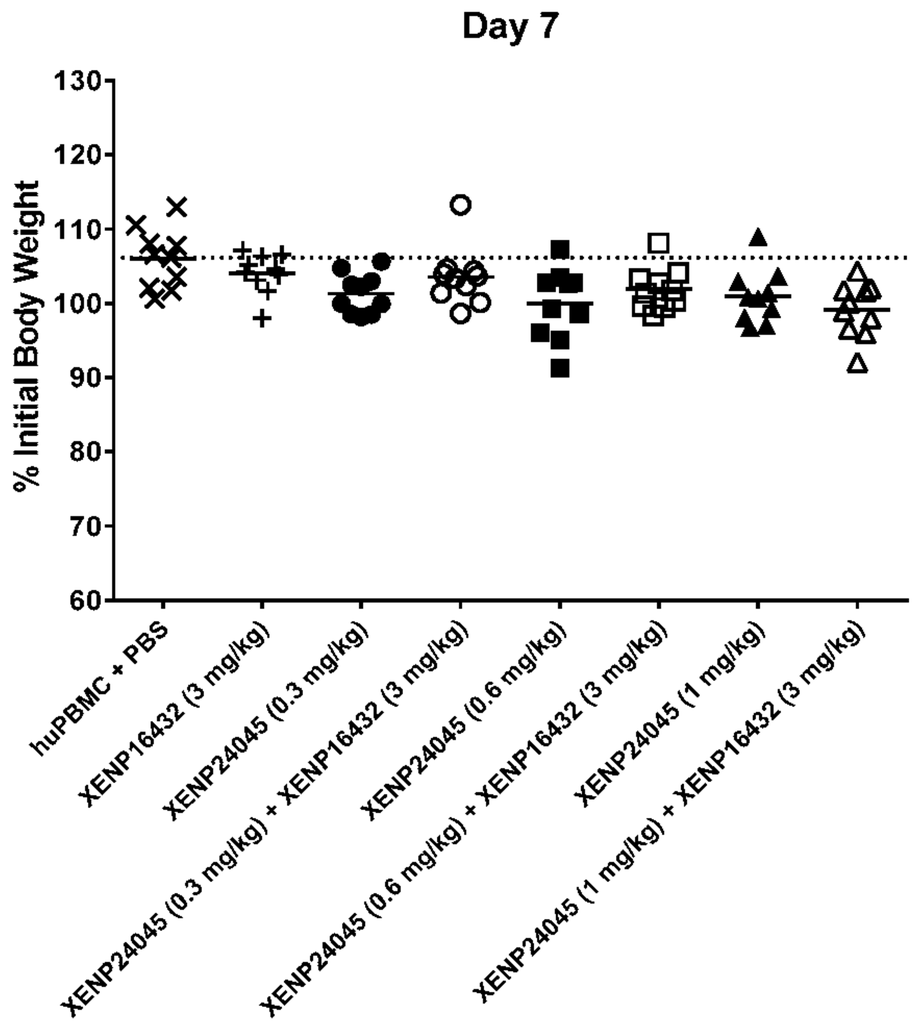


Figure 166B

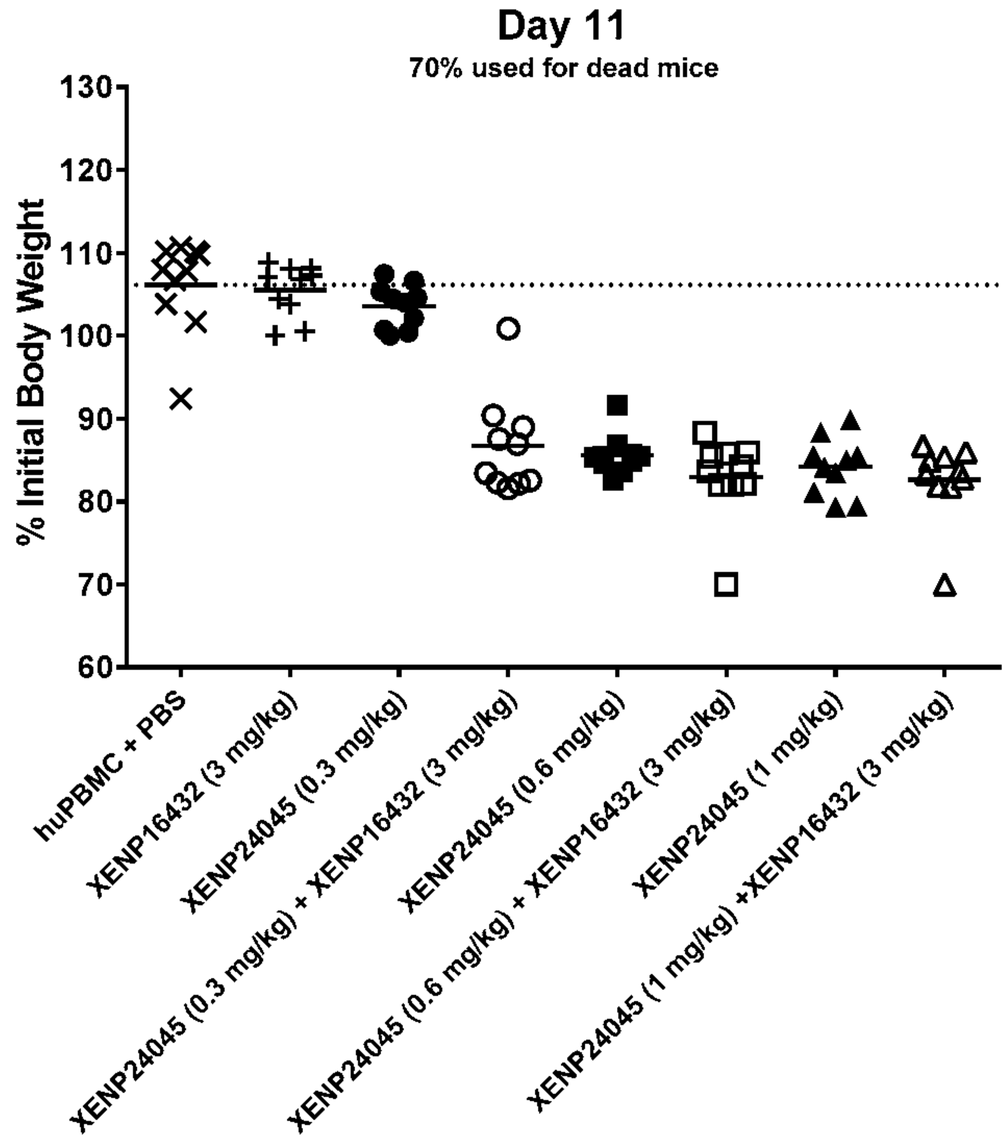


Figure 166C

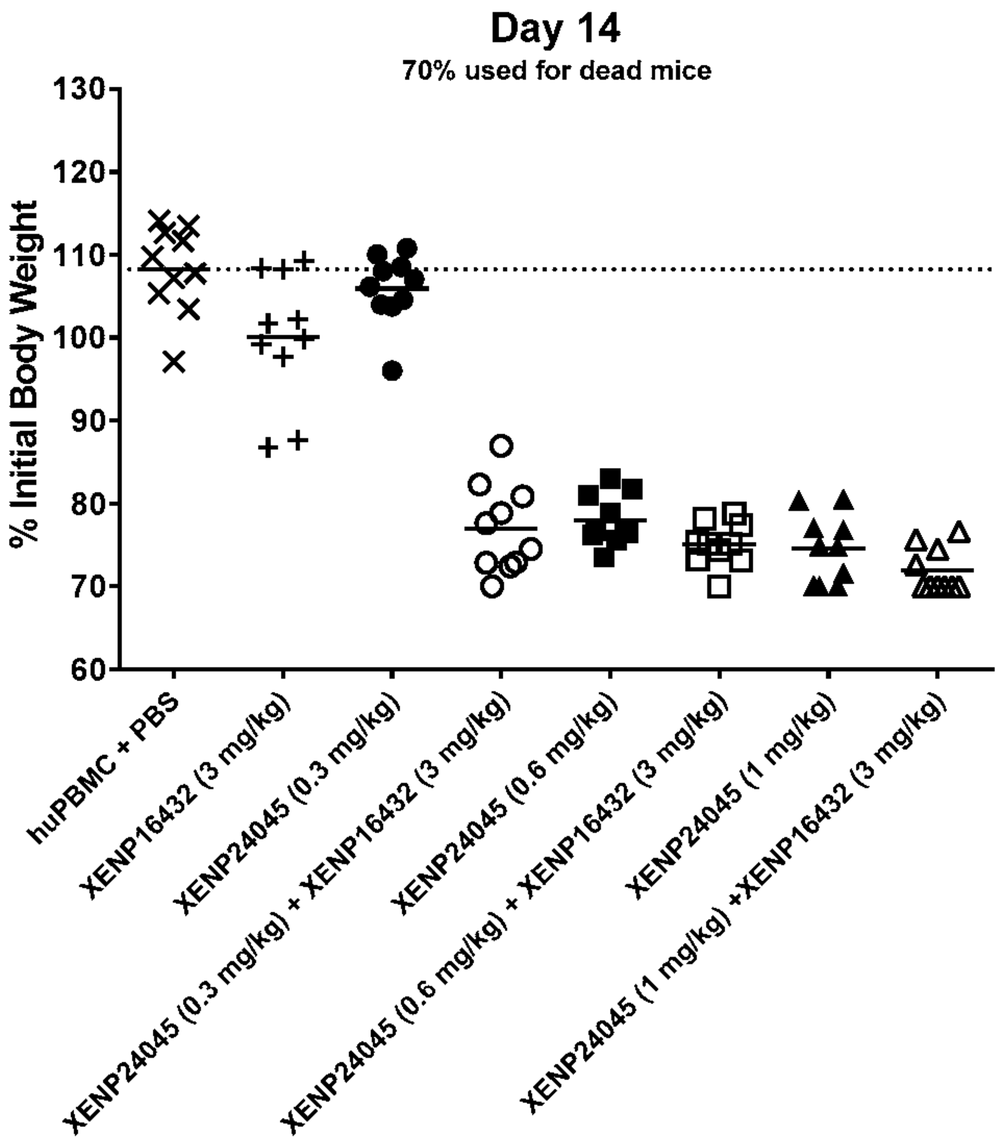


Figure 166D

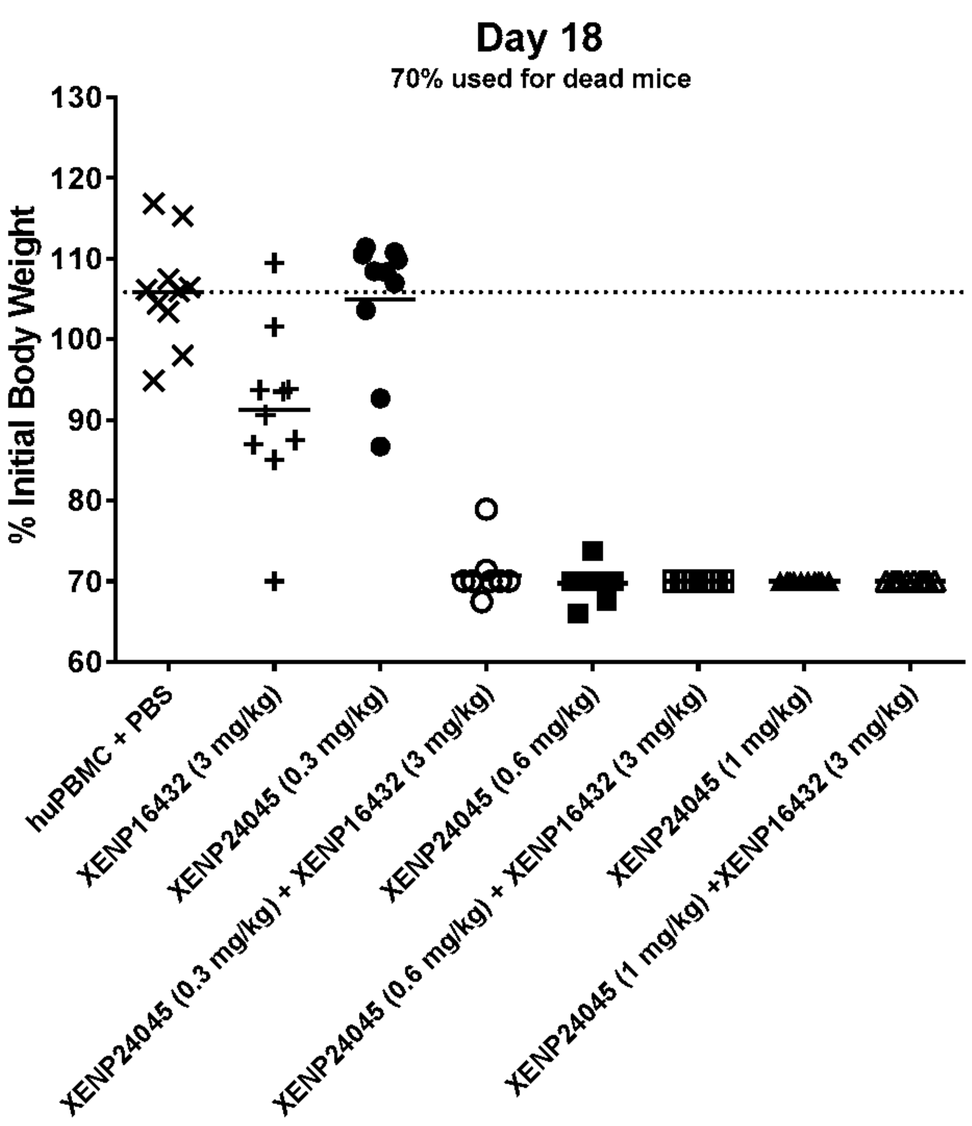


Figure 167

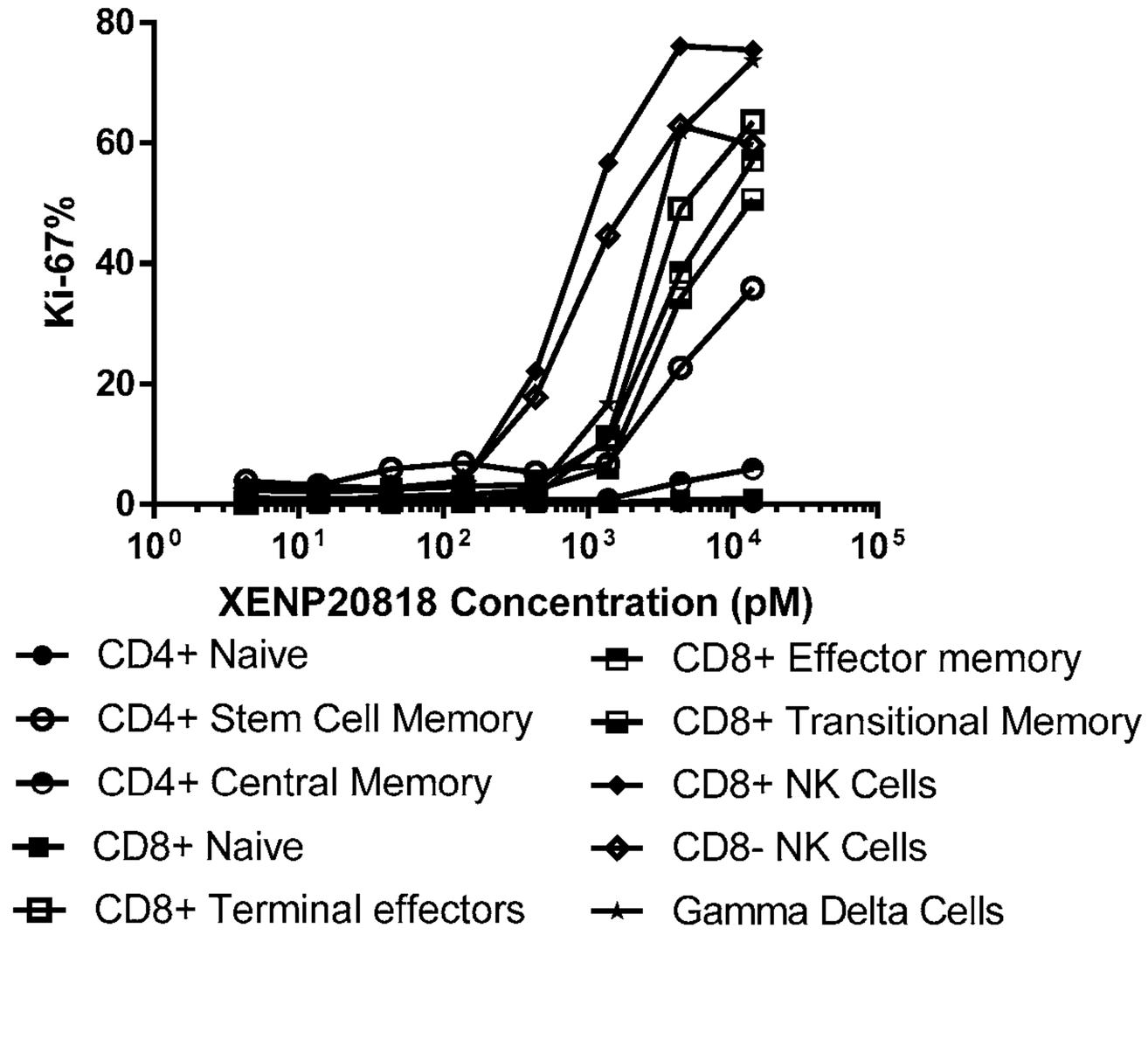

80
60
40
20
0
Ki-67%
10^0
10^1
10^2
10^3
10^4
10^5
XENP20818 Concentration (pM)
CD4+ Naive
CD4+ Stem Cell Memory
CD4+ Central Memory
CD8+ Naive
CD8+ Terminal effectors
CD8+ Effector memory
CD8+ Transitional Memory
CD8+ NK Cells
CD8- NK Cells
Gamma Delta Cells

Figure 168

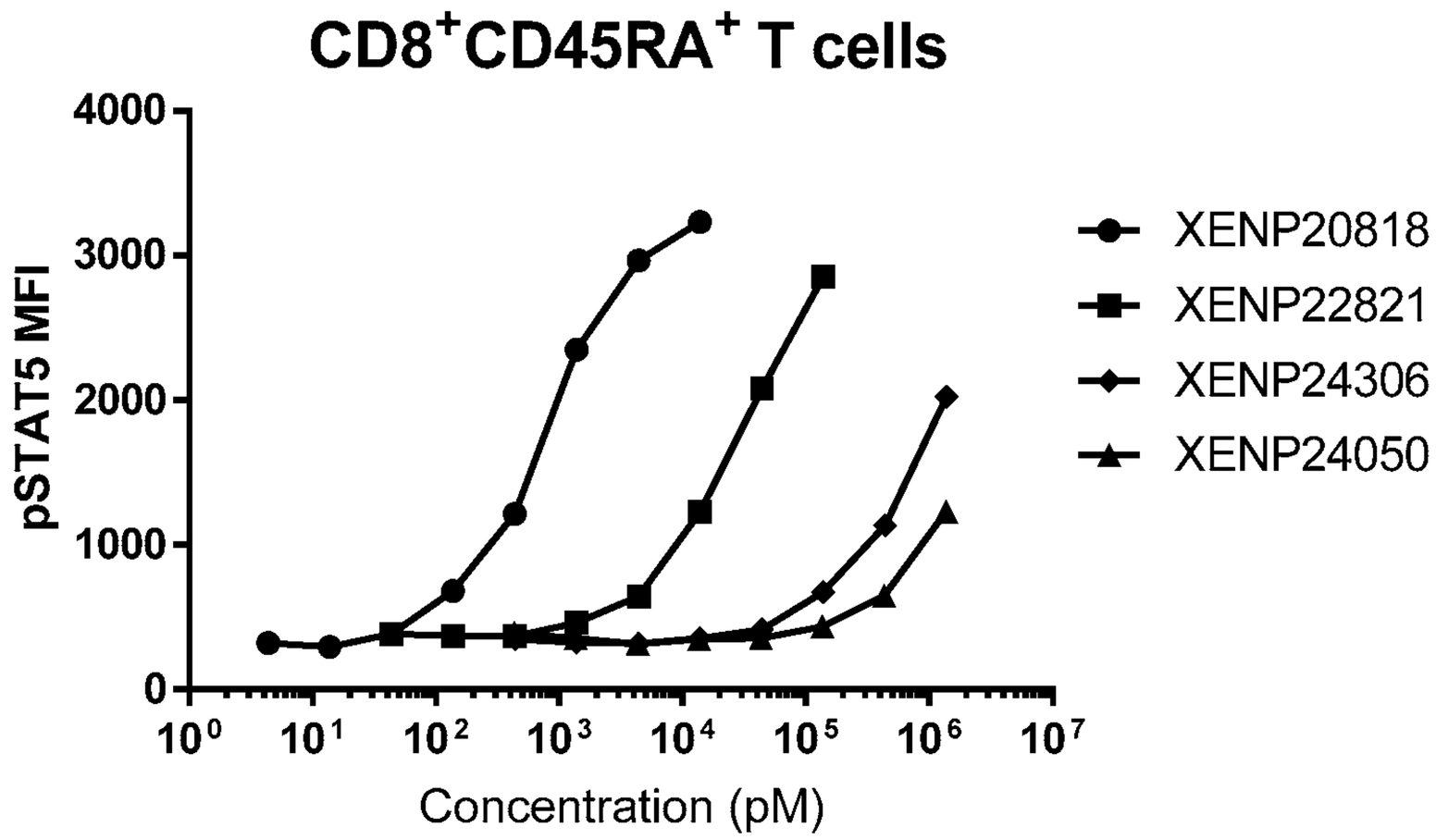


Figure 169

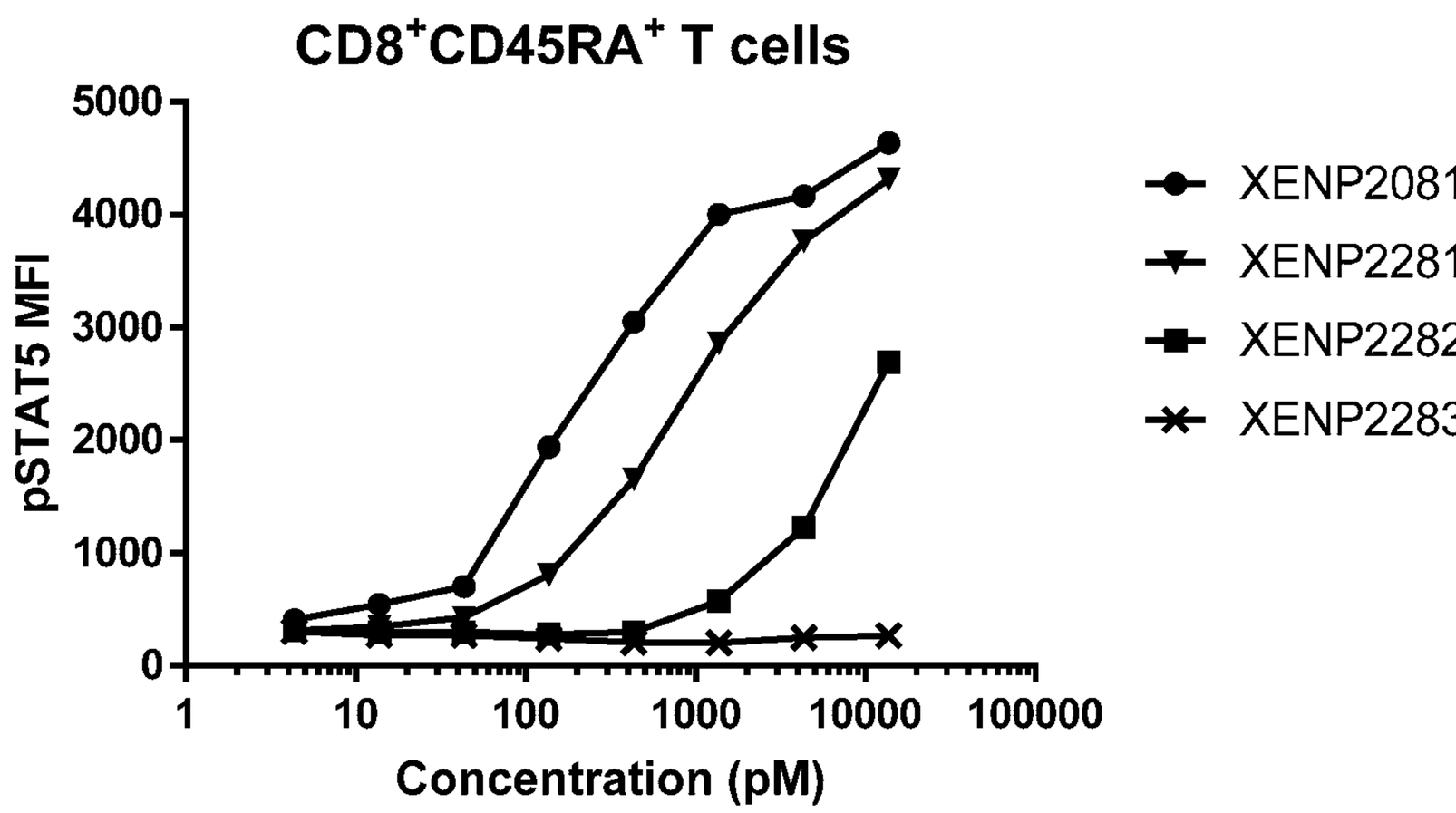


Figure 170

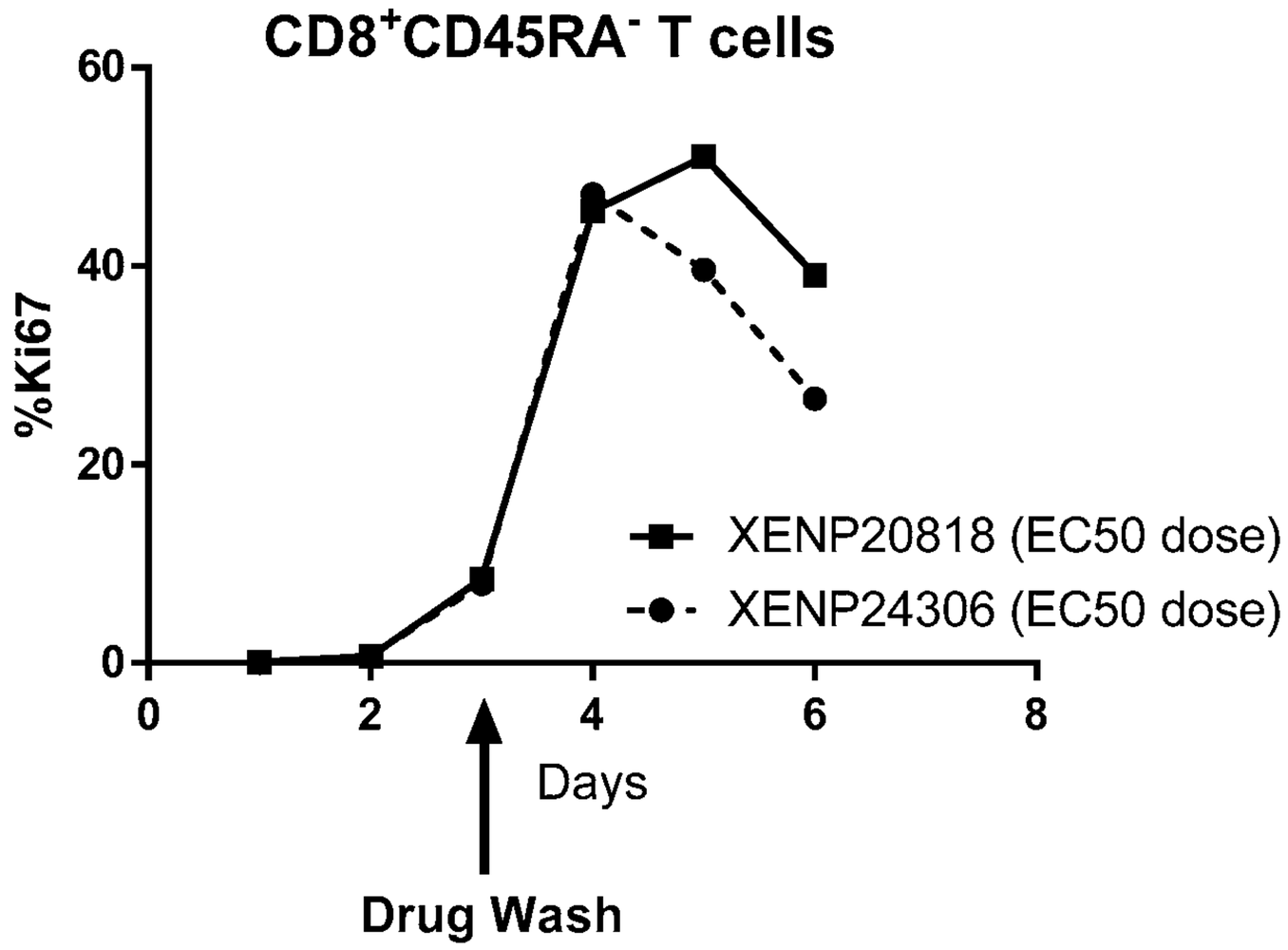


Figure 171

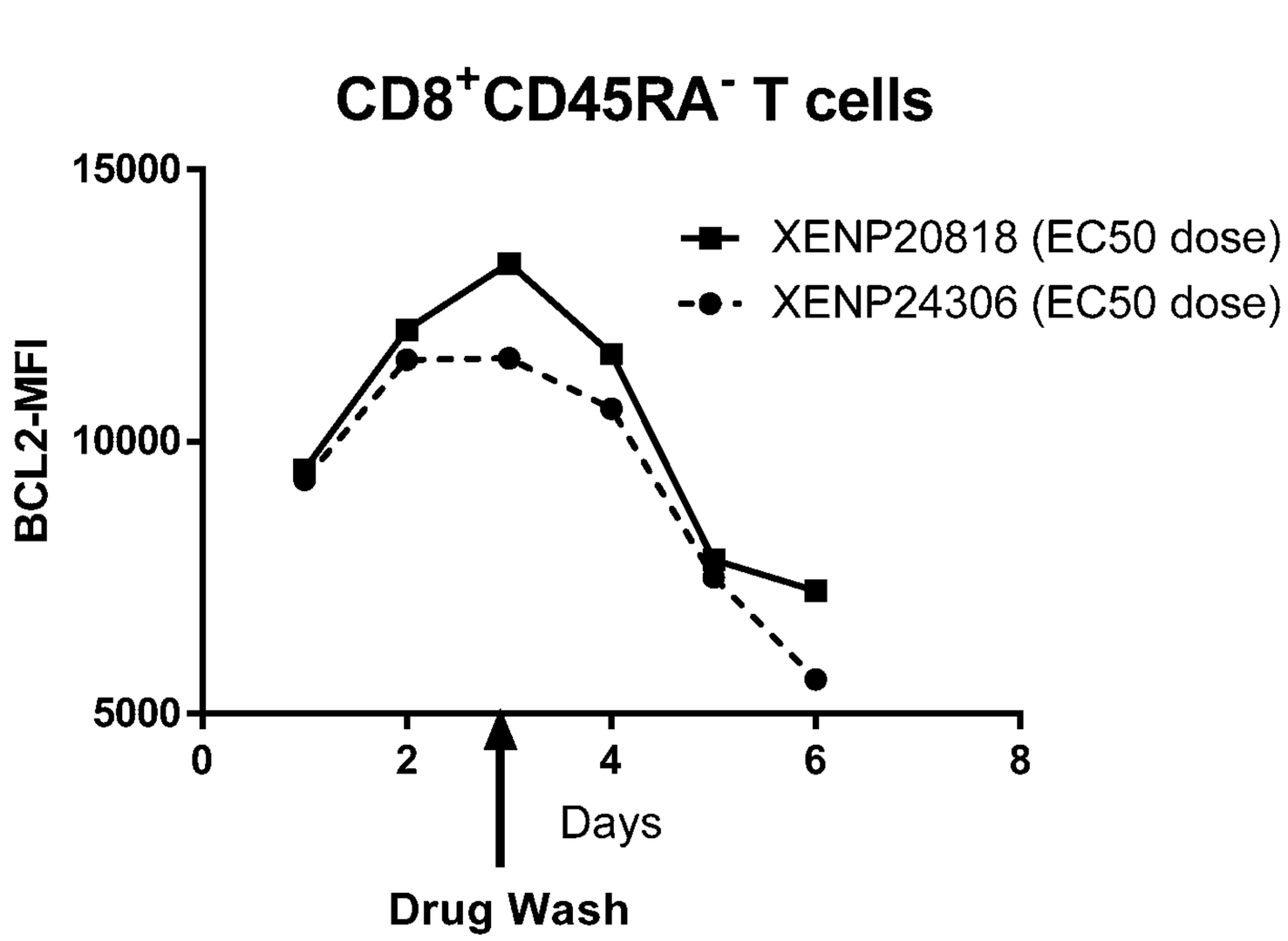


Figure 172

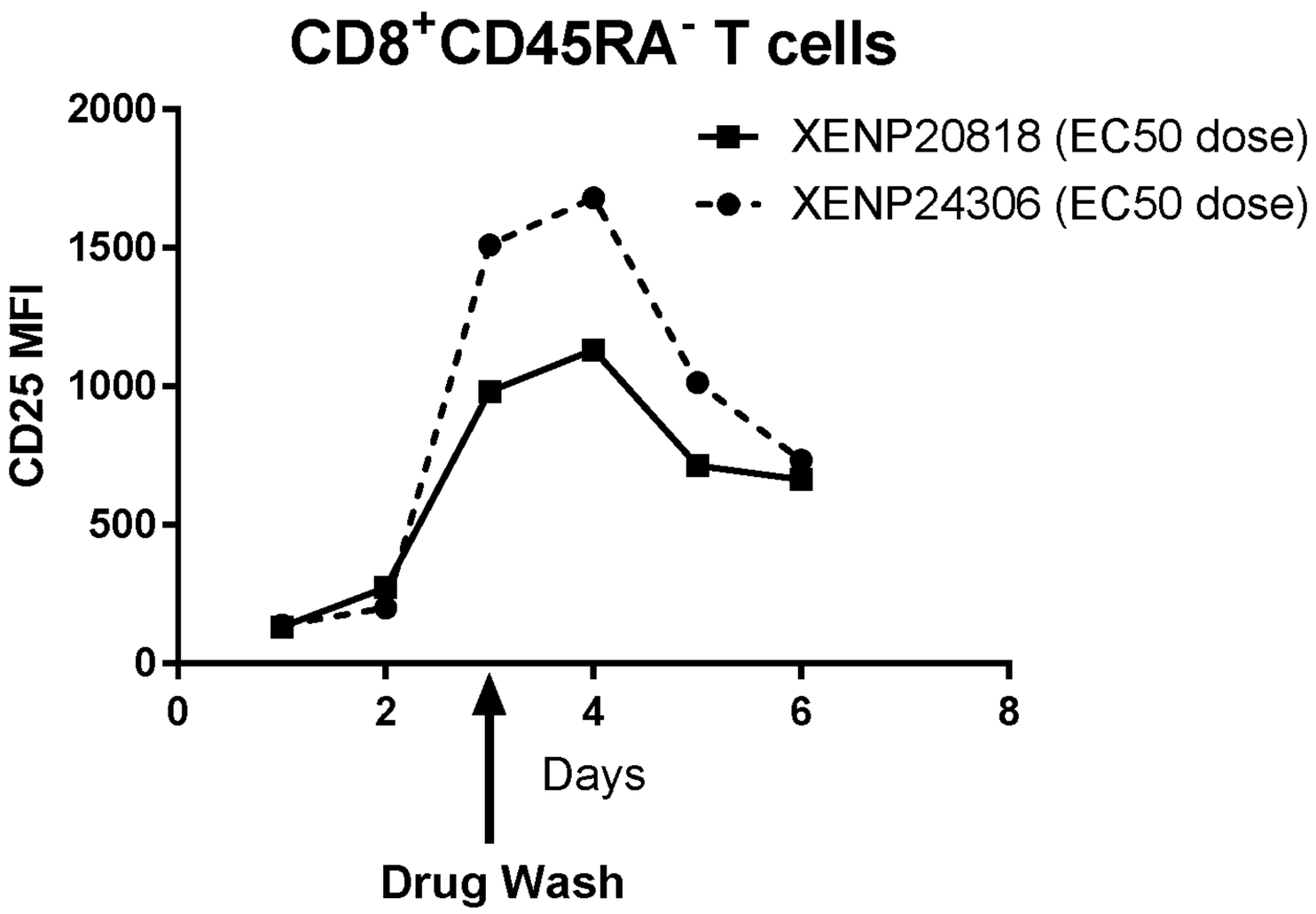


Figure 173

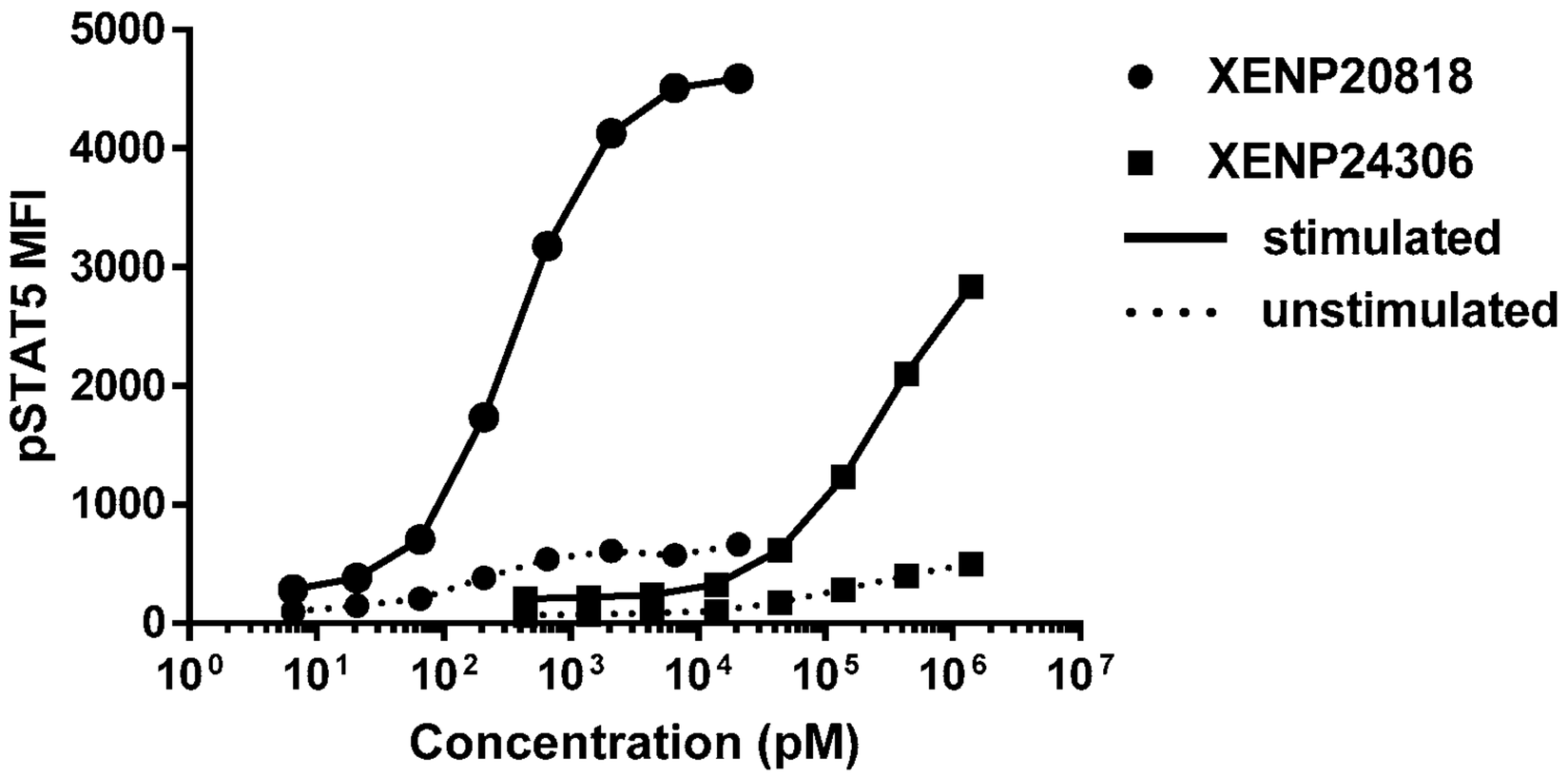


Figure 174

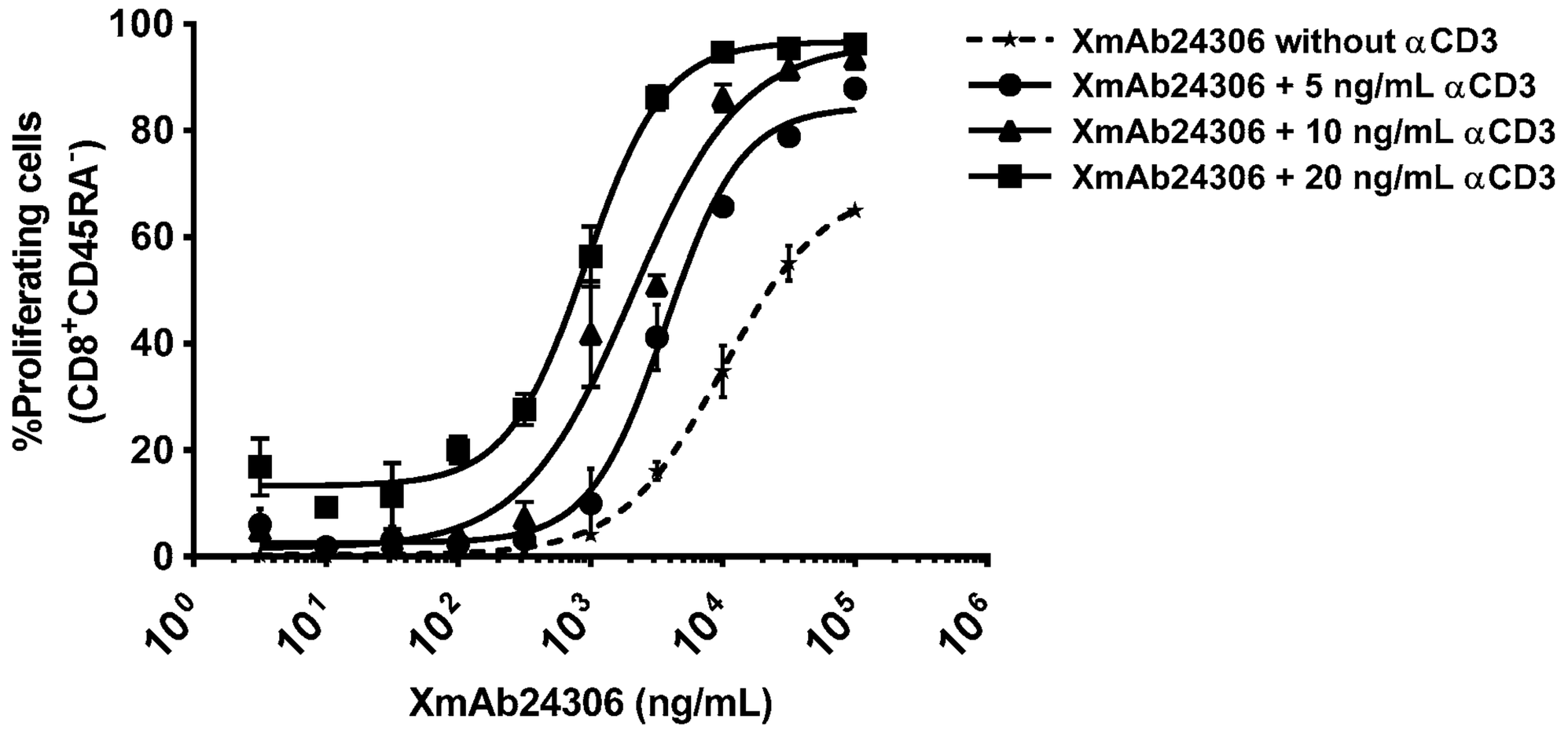


Figure 175

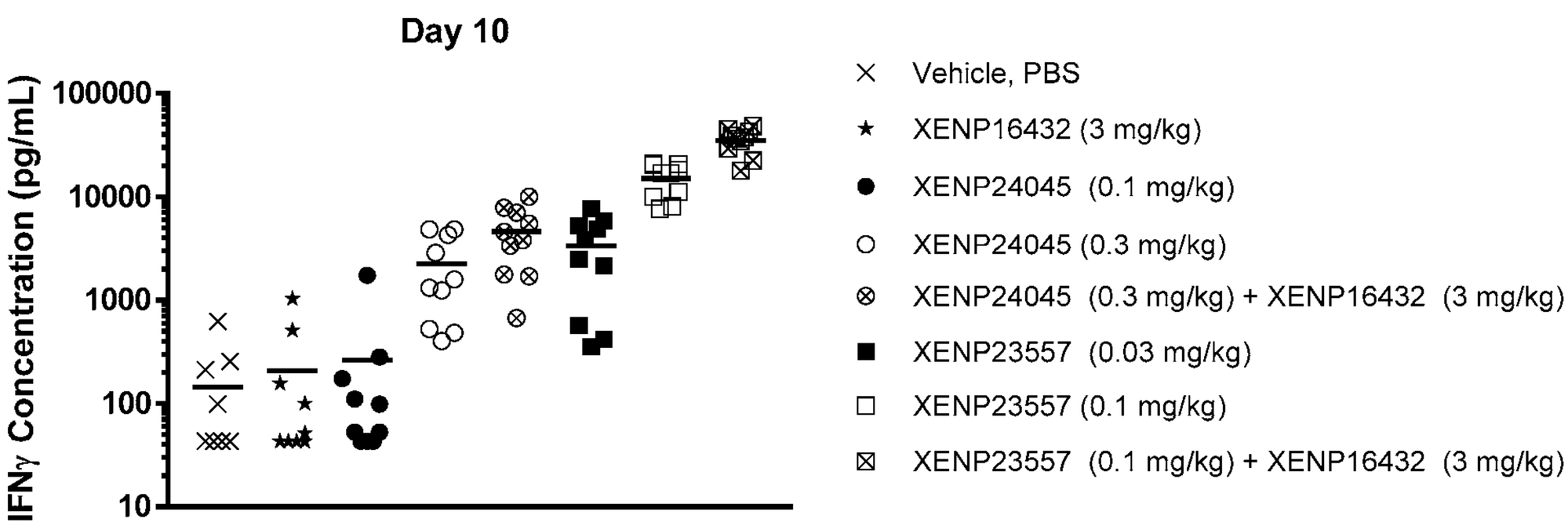


Figure 176

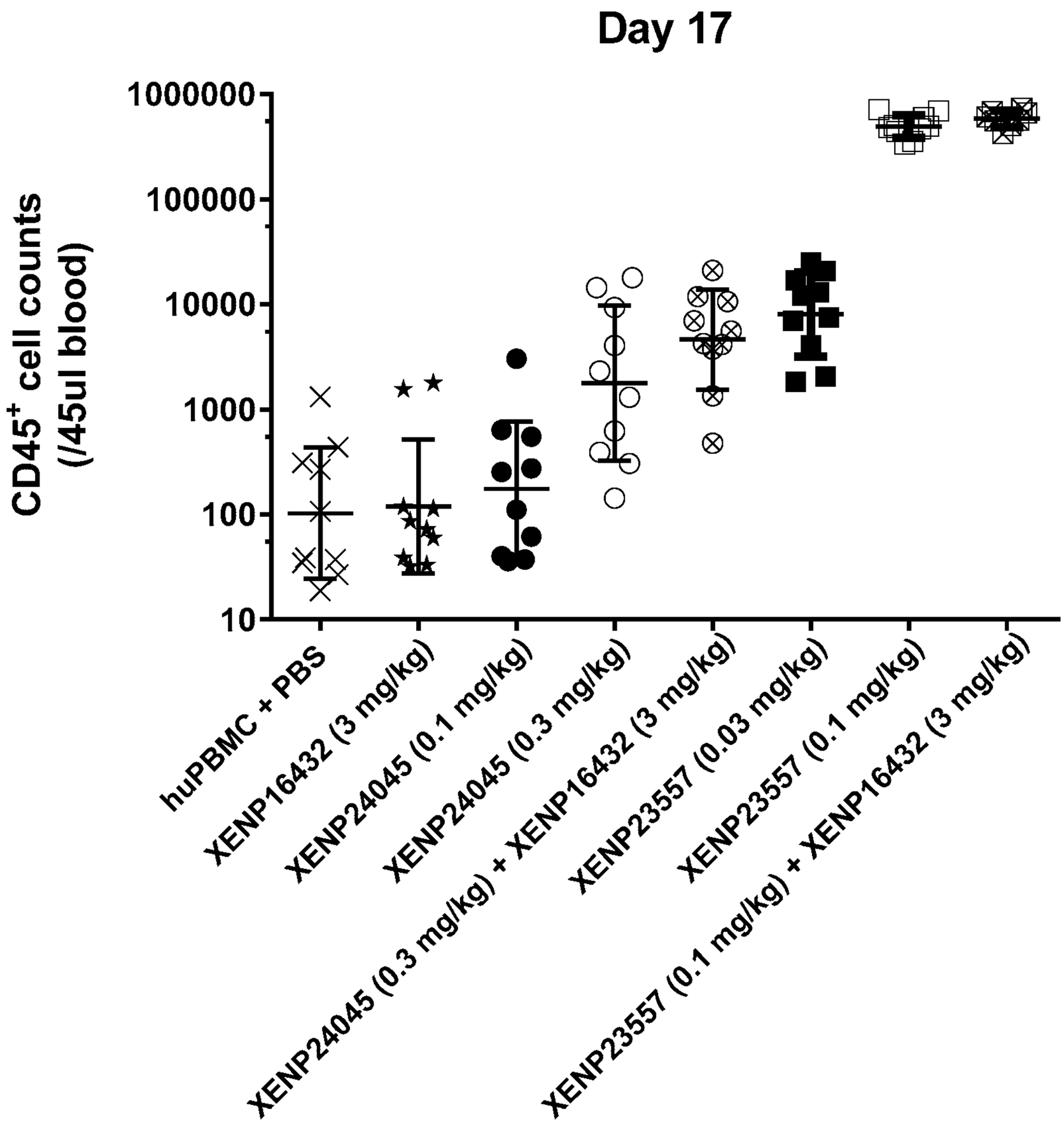

Day 17
CD45+ cell counts (/45ul blood)
1000000
100000
10000
1000
100
10
huPBMC + PBS
XENP16432 (3 mg/kg)
XENP24045 (0.1 mg/kg)
XENP24045 (0.3 mg/kg)
XENP24045 (0.3 mg/kg) + XENP16432 (3 mg/kg)
XENP23557 (0.03 mg/kg)
XENP23557 (0.1 mg/kg)
XENP23557 (0.1 mg/kg) + XENP16432 (3 mg/kg)

Figure 177

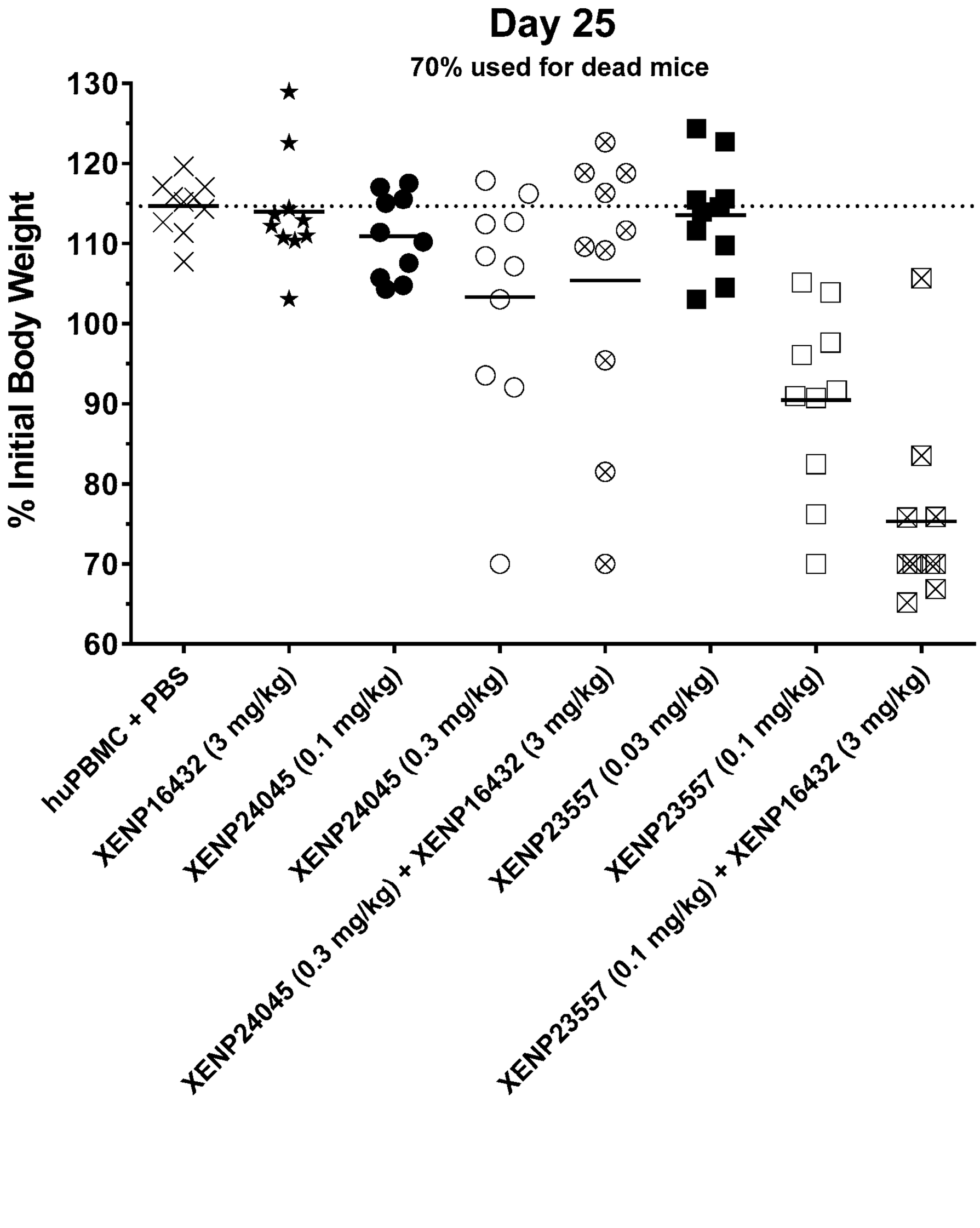

Day 25
70% used for dead mice
% Initial Body Weight
130
120
110
100
90
80
70
60
huPBMC + PBS
XENP16432 (3 mg/kg)
XENP24045 (0.1 mg/kg)
XENP24045 (0.3 mg/kg)
XENP24045 (0.3 mg/kg) + XENP16432 (3 mg/kg)
XENP23557 (0.03 mg/kg)
XENP23557 (0.1 mg/kg)
XENP23557 (0.1 mg/kg) + XENP16432 (3 mg/kg)

Figure 178

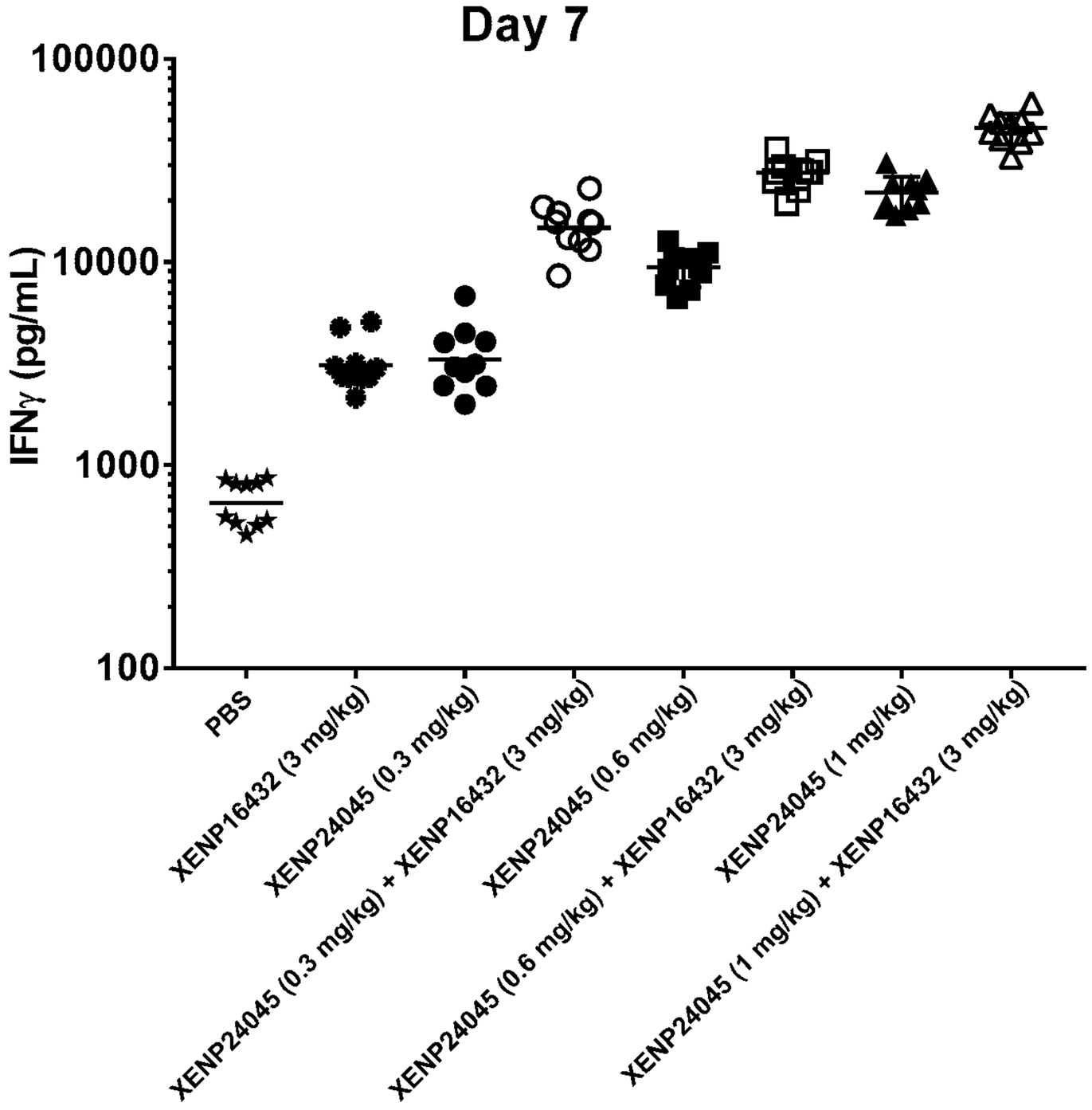

Day 7
IFNγ (pg/mL)
100000
10000
1000
100
PBS
XENP16432 (3 mg/kg)
XENP24045 (0.3 mg/kg)
XENP24045 (0.3 mg/kg) + XENP16432 (3 mg/kg)
XENP24045 (0.6 mg/kg)
XENP24045 (0.6 mg/kg) + XENP16432 (3 mg/kg)
XENP24045 (1 mg/kg)
XENP24045 (1 mg/kg) + XENP16432 (3 mg/kg)

Figure 179A

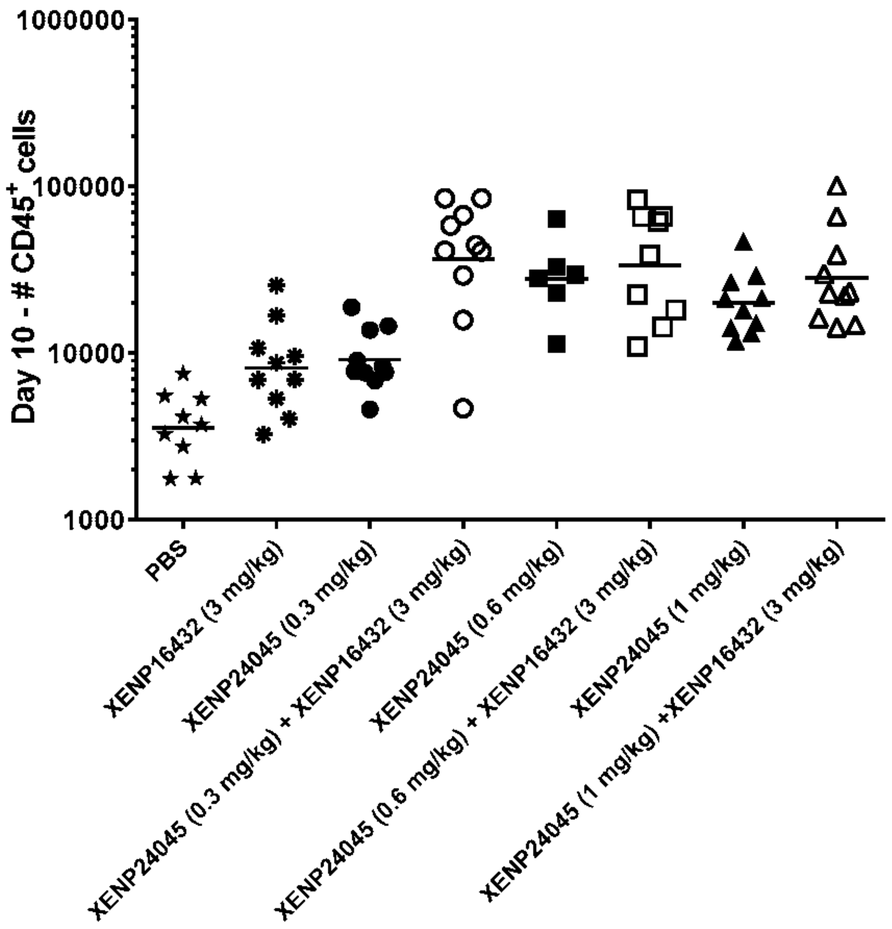


Figure 179B

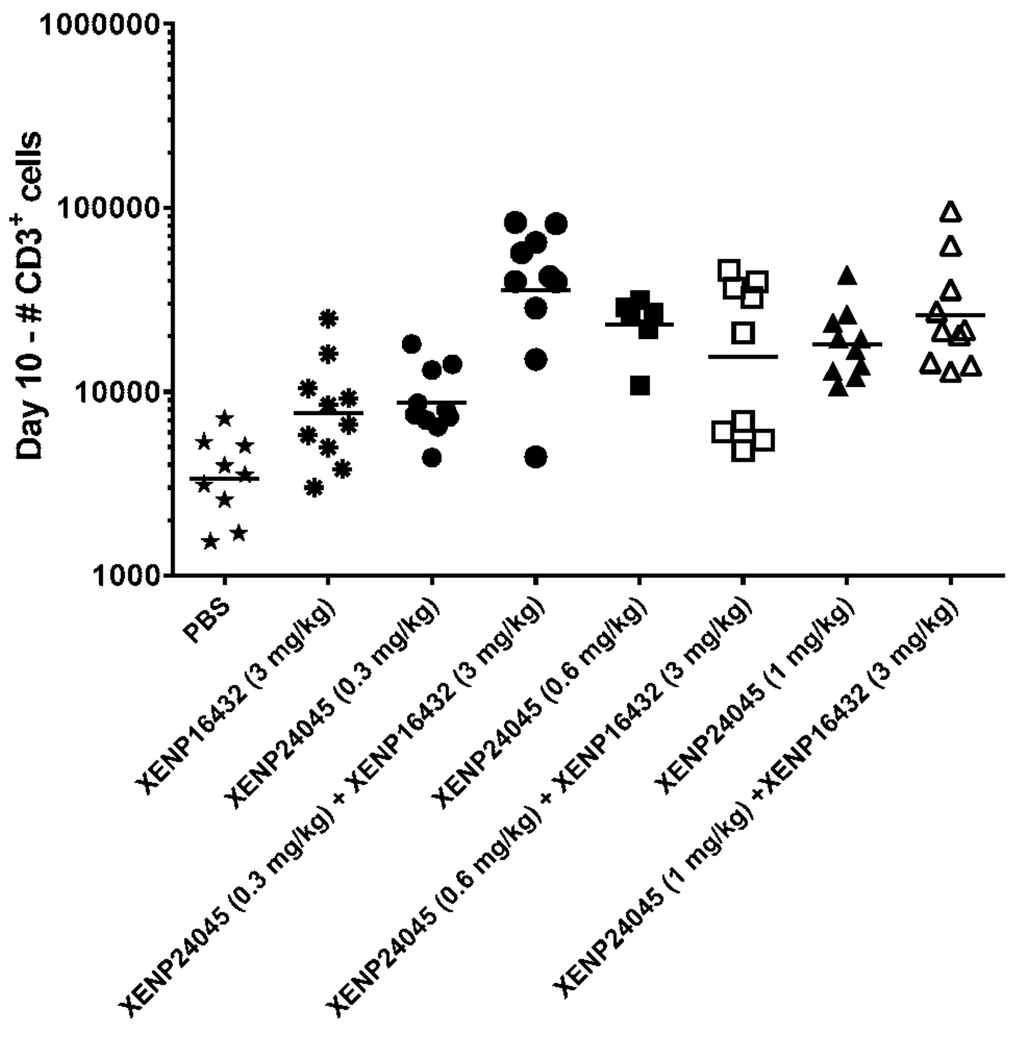


Figure 179C

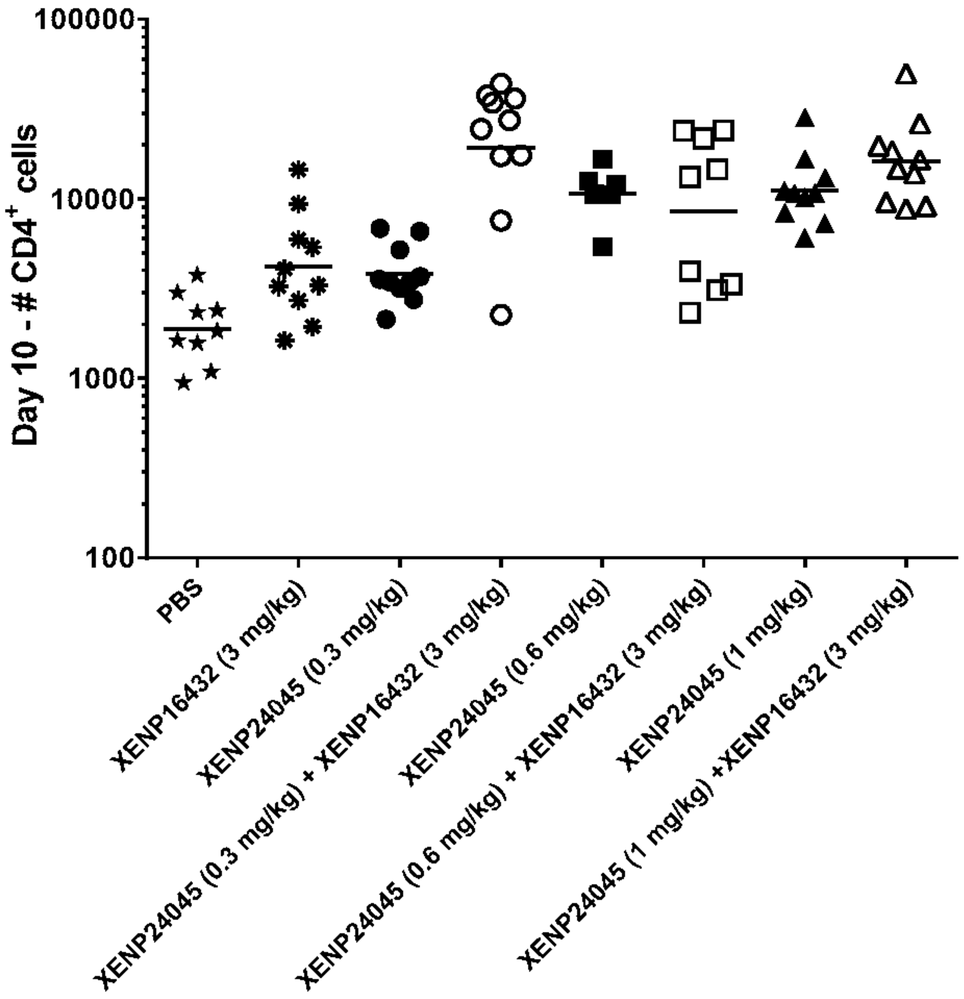


Figure 179D

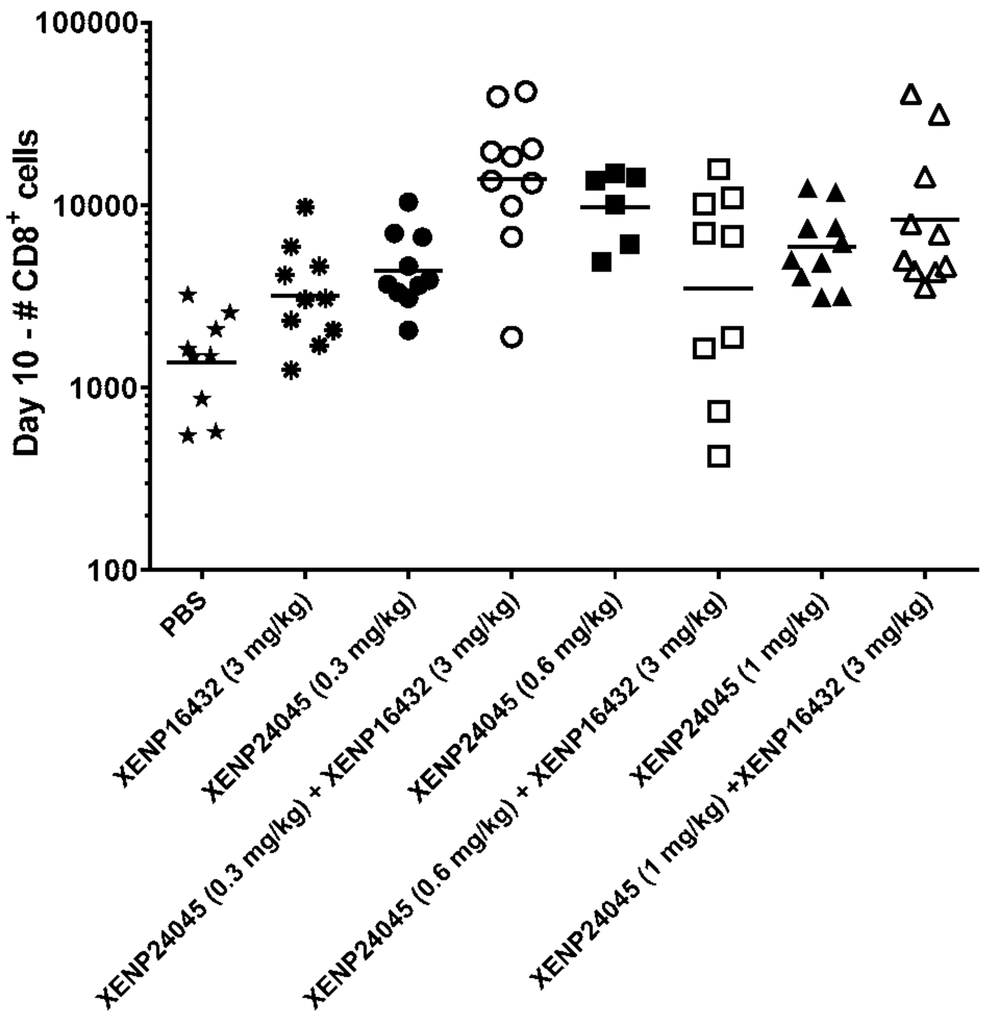


Figure 180

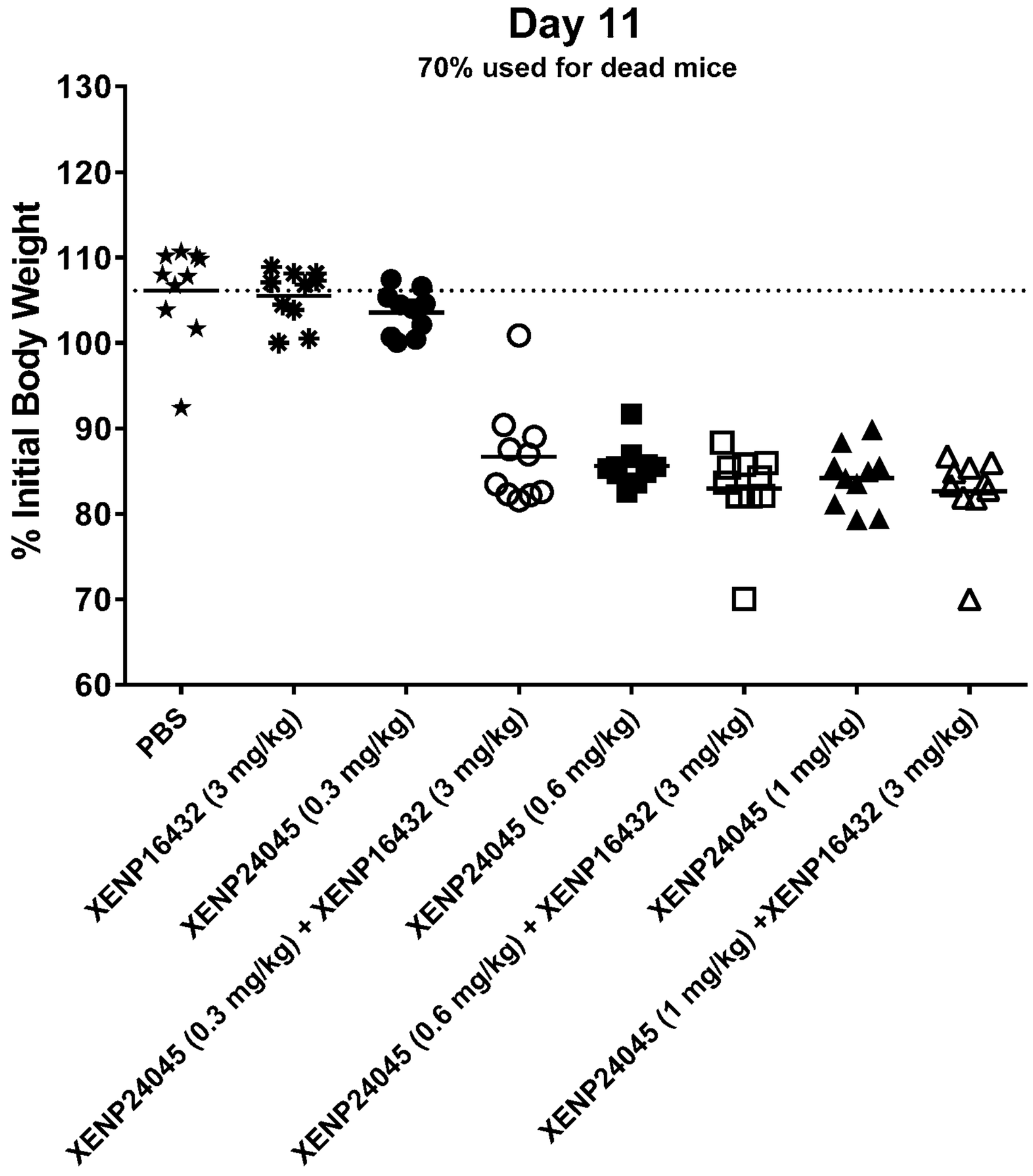

Day 11
70% used for dead mice
% Initial Body Weight
130
120
110
100
90
80
70
60
PBS
XENP16432 (3 mg/kg)
XENP24045 (0.3 mg/kg)
XENP24045 (0.3 mg/kg) + XENP16432 (3 mg/kg)
XENP24045 (0.6 mg/kg)
XENP24045 (0.6 mg/kg) + XENP16432 (3 mg/kg)
XENP24045 (1 mg/kg)
XENP24045 (1 mg/kg) +XENP16432 (3 mg/kg)

Figure 181

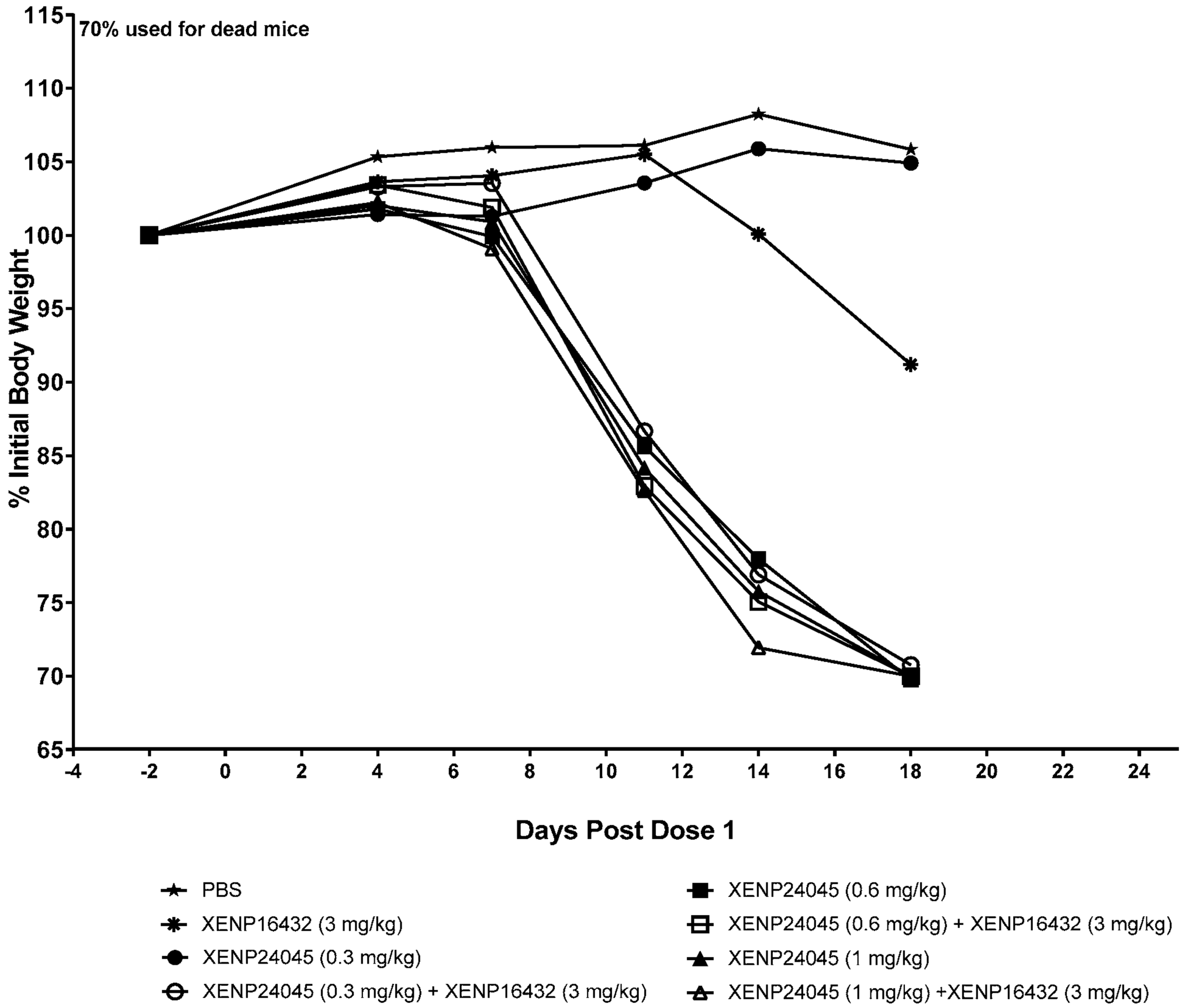

70% used for dead mice
% Initial Body Weight
115
110
105
100
95
90
85
80
75
70
65
-4
-2
0
2
4
6
8
10
12
14
16
18
20
22
24
Days Post Dose 1
PBS
XENP16432 (3 mg/kg)
XENP24045 (0.3 mg/kg)
XENP24045 (0.3 mg/kg) + XENP16432 (3 mg/kg)
XENP24045 (0.6 mg/kg)
XENP24045 (0.6 mg/kg) + XENP16432 (3 mg/kg)
XENP24045 (1 mg/kg)
XENP24045 (1 mg/kg) +XENP16432 (3 mg/kg)

Figure 182

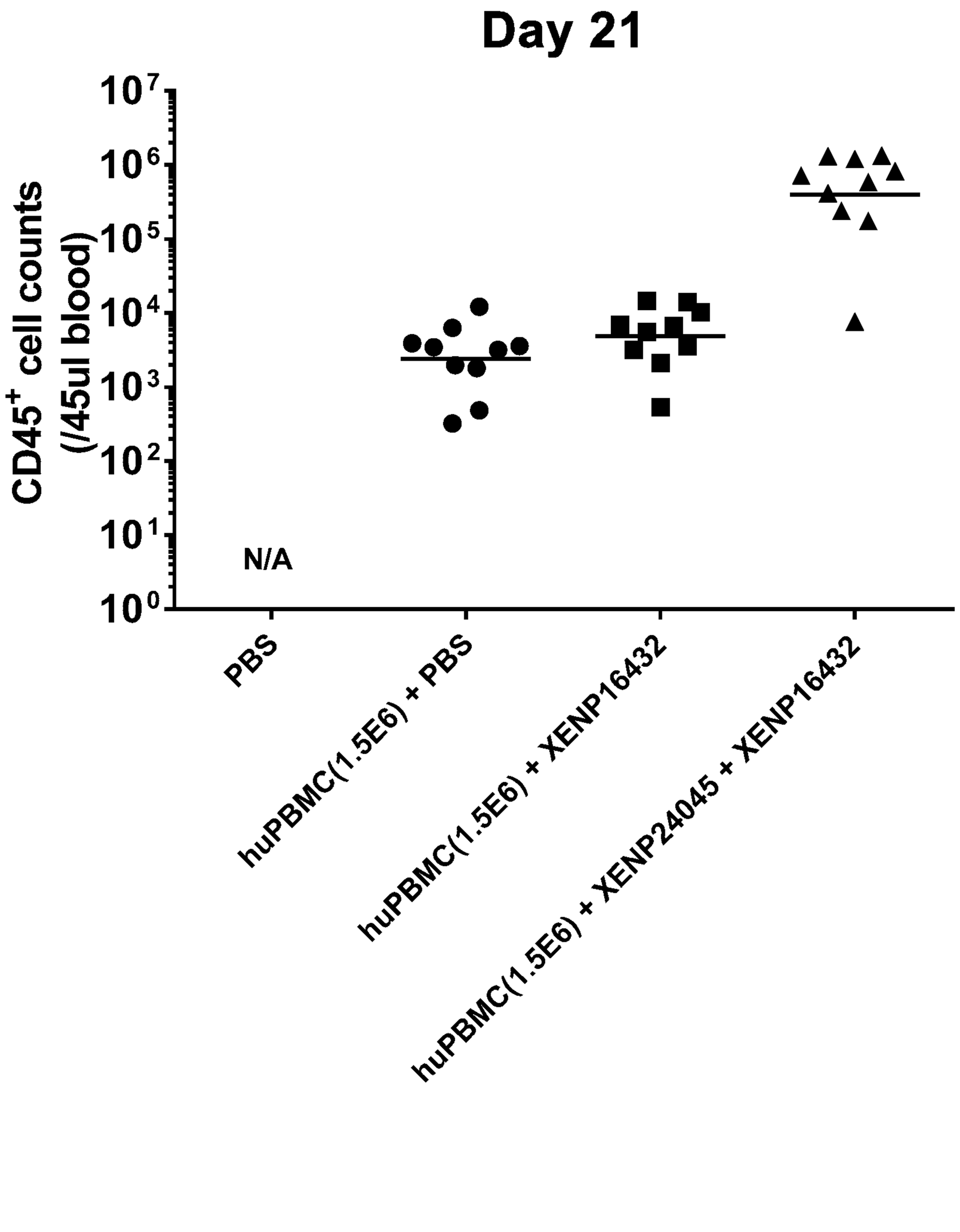

Day 21
CD45+ cell counts (/45ul blood)
10^7
10^6
10^5
10^4
10^3
10^2
10^1
10^0
N/A
PBS
huPBMC(1.5E6) + PBS
huPBMC(1.5E6) + XENP16432
huPBMC(1.5E6) + XENP24045 + XENP16432

Figure 183

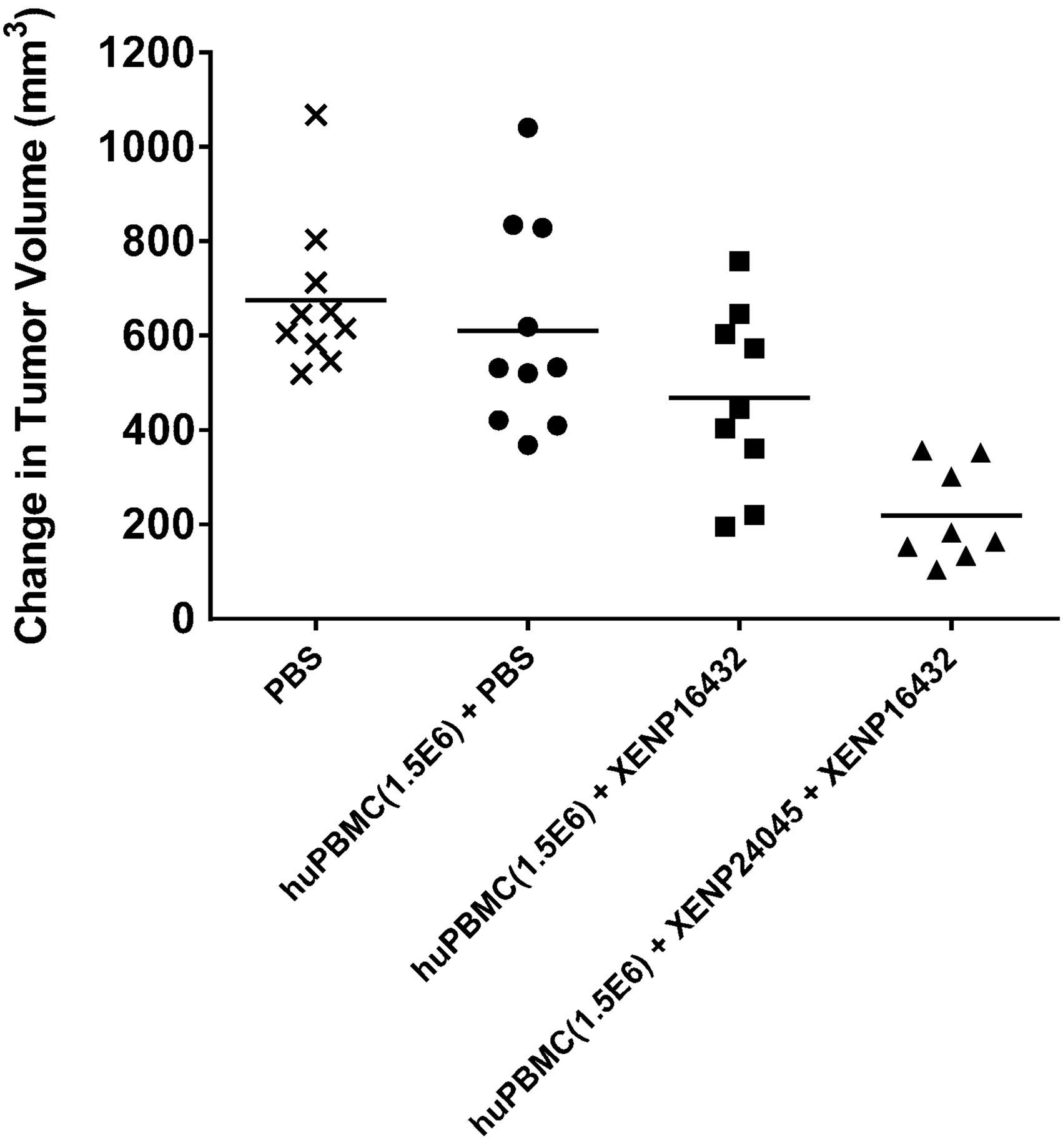

Change in Tumor Volume (mm3)
1200
1000
800
600
400
200
0
PBS
huPBMC(1.5E6) + PBS
huPBMC(1.5E6) + XENP16432
huPBMC(1.5E6) + XENP24045 + XENP16432

Figure 184

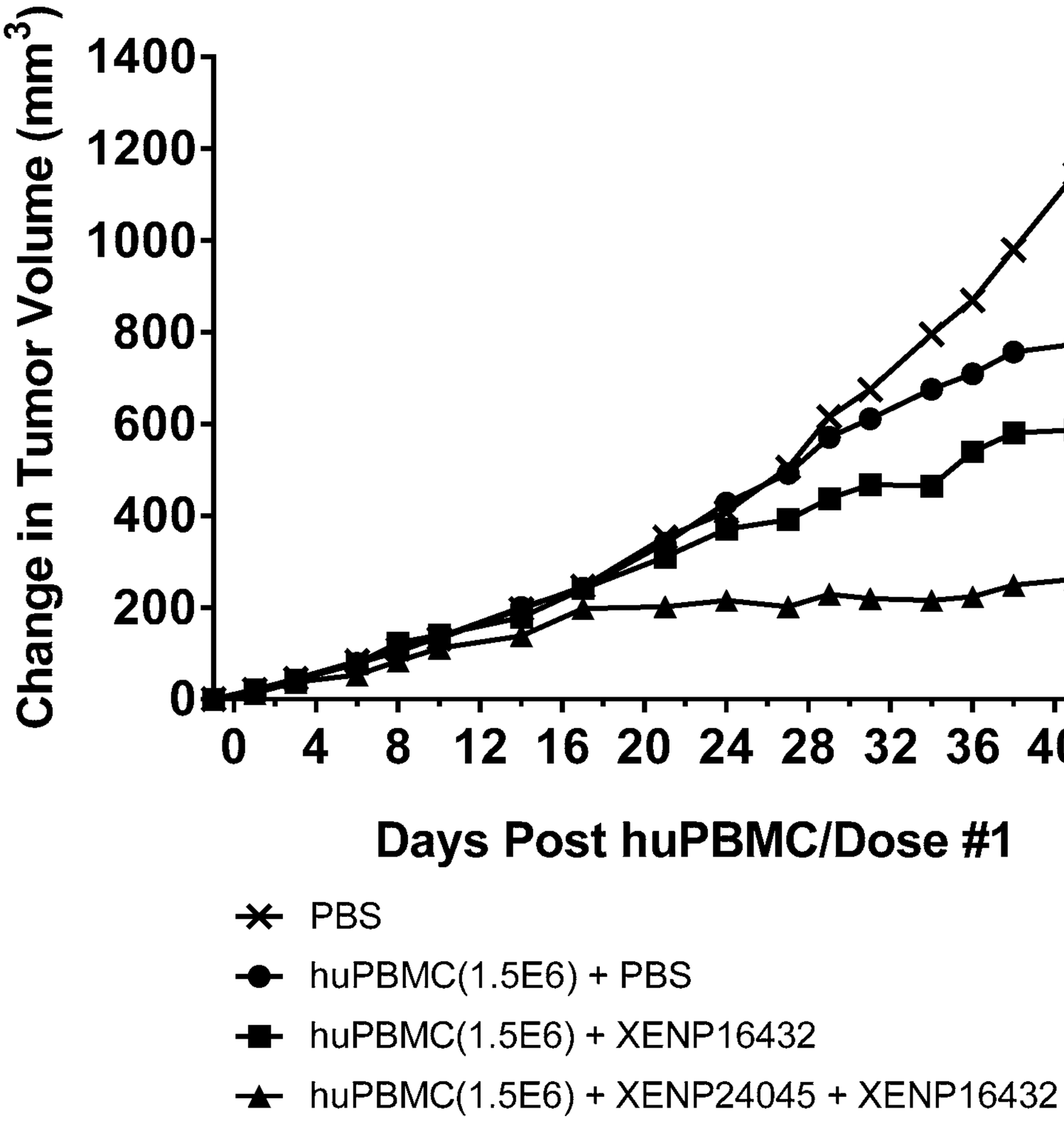

Change in Tumor Volume (mm3)
1400
1200
1000
800
600
400
200
0
0 4 8 12 16 20 24 28 32 36 40 44
Days Post huPBMC/Dose #1
PBS
huPBMC(1.5E6) + PBS
huPBMC(1.5E6) + XENP16432
huPBMC(1.5E6) + XENP24045 + XENP16432

Figure 185

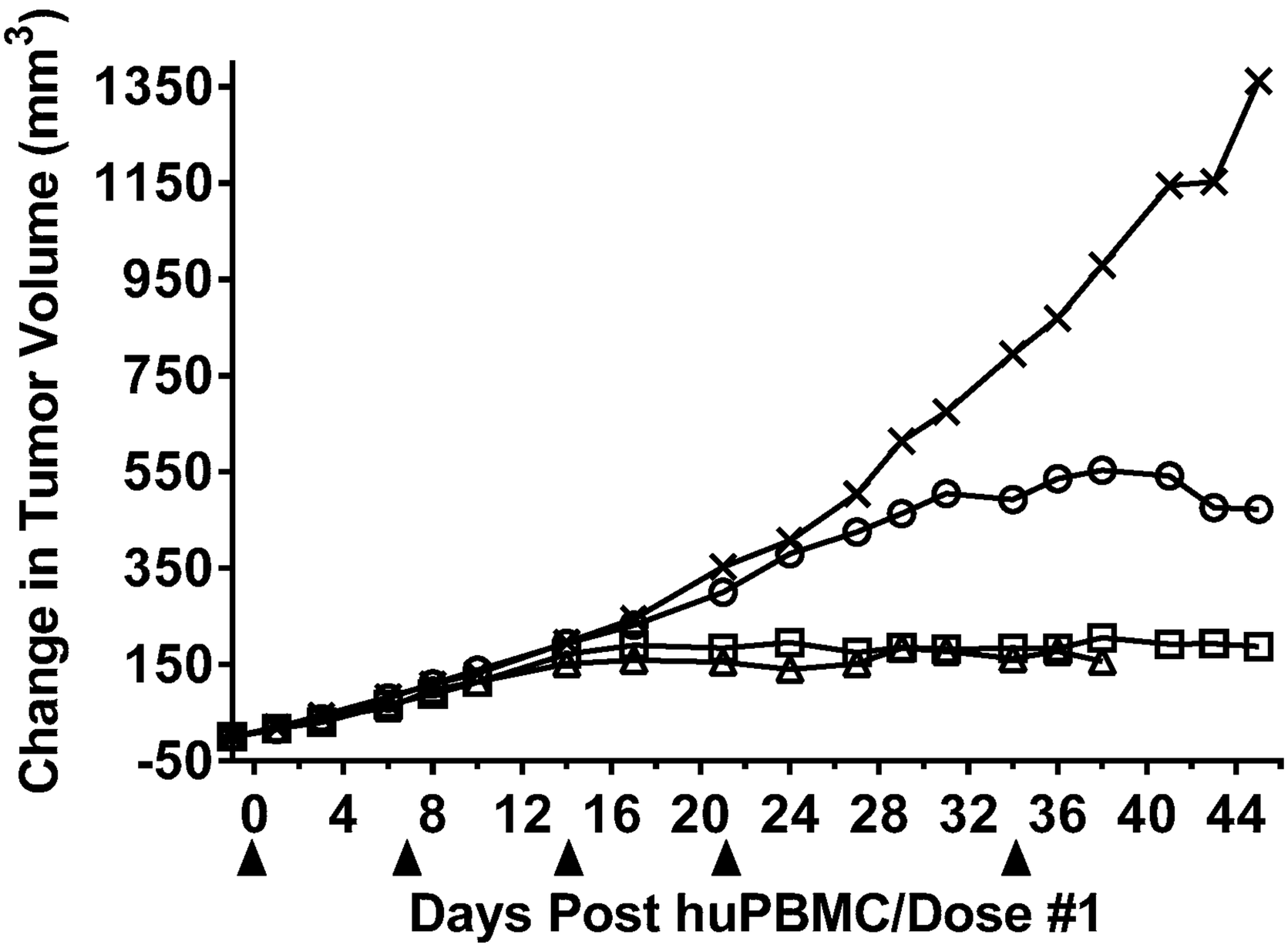

Change in Tumor Volume (mm3)
1350
1150
950
750
550
350
150
-50
0
4
8
12
16
20
24
28
32
36
40
44
Days Post huPBMC/Dose #1
PBS
huPBMC(5E6) + PBS
huPBMC(5E6) + XENP16432
huPBMC(5E6) + XENP24045 + XENP16432

Figure 186

>XENP21993 human_IL15Ra(sushi)_(GGGGS)5-human_IL15(single-Chain)-empty-Fc_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

XENP21993 Chain 1 - human_IL15Ra(sushi)_(GGGGS)5-human_IL15(single-Chain)_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:268)

ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGSGGGGSGGGGSGGGGSGGGGS/NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

XENP21993 Chain 2 - empty-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:269)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Figure 187

>XENP22853 human_IL15_(GGGGS)1-human_IL15Ra(Sushi)_(GGGGS)1_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S/M428L/N434S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q/M428L/N434S

XENP22853 Chain 1 - human_IL15_(GGGGS)1-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S/M428L/N434S (SEQ ID NO:270)
NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK

XENP22853 Chain 2 - human_IL15Ra(Sushi)_(GGGGS)1-
Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q/M428L/N434S (SEQ ID NO:271)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 188

>XENP24294 human_IL15Ra(sushi)_(GGGGS)5-human_IL15_N4D/N65D_(single-Chain)-empty-Fc_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S/M428L/N434S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q/M428L/N434S

XENP24294 Chain 1 - human_IL15Ra(sushi)_(GGGGS)5-human_IL15_N4D/N65D_(single-Chain)-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S/M428L/N434S (SEQ ID NO:272)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGSGGGGSGGGGSGGGGSGGGGS/NWVDVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVLHEALHSHYTQKSLSLSPGK

XENP24294 Chain 2 - empty-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q/M428L/N434S (SEQ ID NO:273)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQKSLSLSPGK

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 189

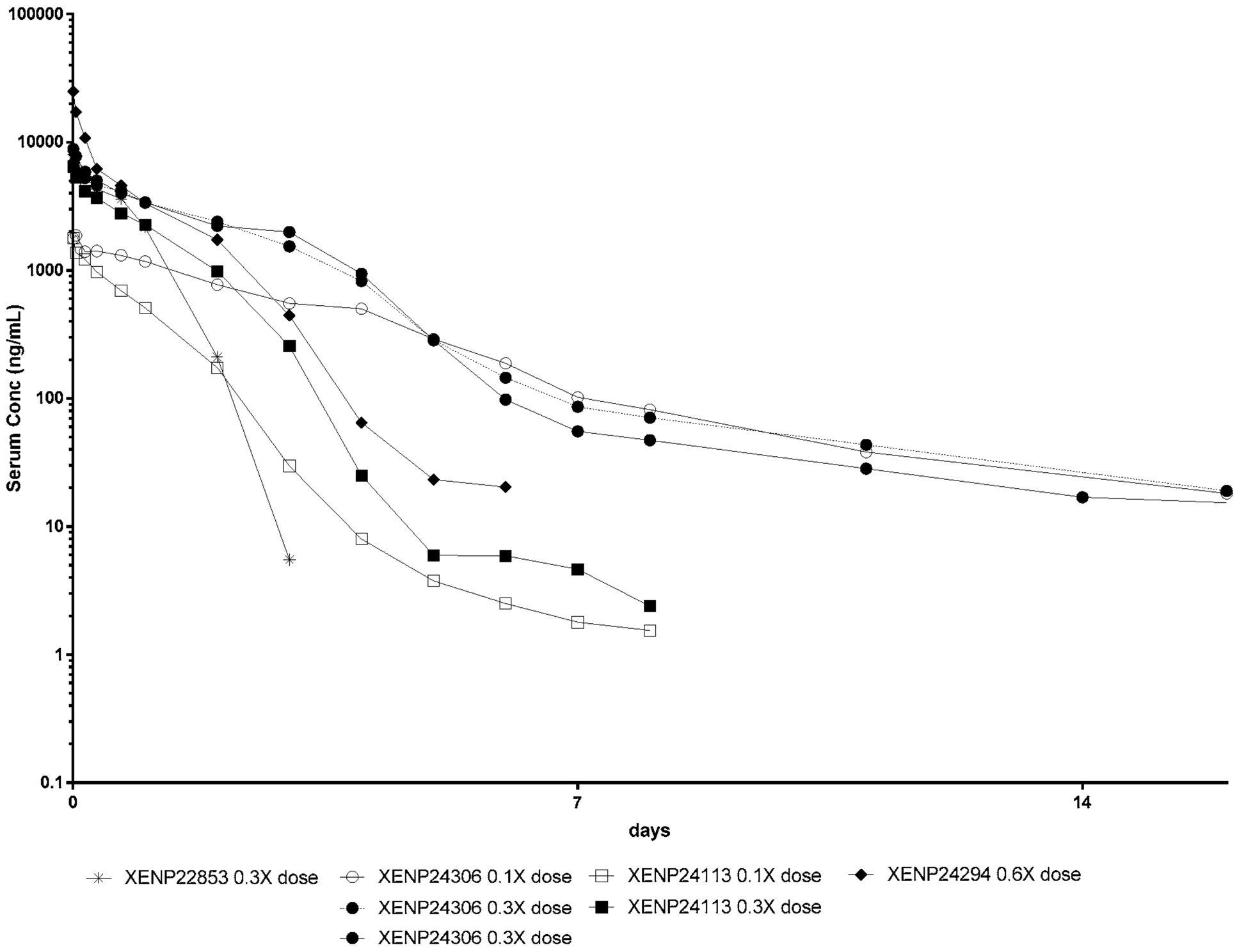

100000
10000
1000
100
10
1
0.1
Serum Conc (ng/mL)
0
7
14
days
XENP22853 0.3X dose
XENP24306 0.1X dose
XENP24306 0.3X dose
XENP24306 0.3X dose
XENP24113 0.1X dose
XENP24113 0.3X dose
XENP24294 0.6X dose

Figure 190

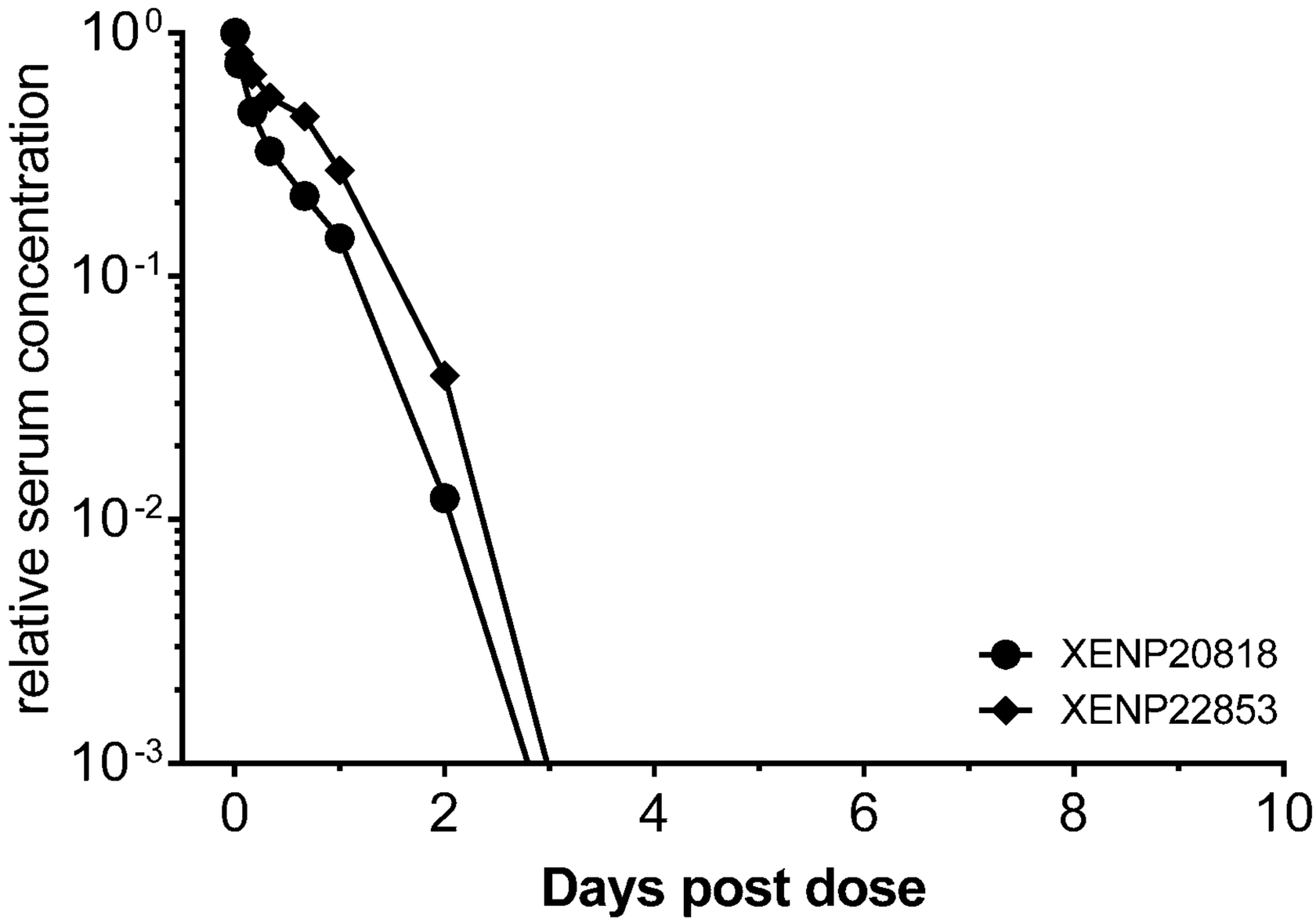

relative serum concentration
10^0
10^-1
10^-2
10^-3
0
2
4
6
8
10
Days post dose
XENP20818
XENP22853

Figure 191

D30N (SEQ ID NO:274)
NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILA
NNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS

N1D/D30N (SEQ ID NO:275)
DWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILA
NNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS

N4D/D30N (SEQ ID NO:276)
NWVDVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILA
NNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS

D30N/E64Q (SEQ ID NO:277)
NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHDTVQNLIILA
NNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS

D30N/N65D (SEQ ID NO:278)
NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILA
NNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS

D30N/E64Q/N65D (SEQ ID NO:279)
NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHDTVQDLIILA
NNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS

Figure 192A

>XENP29281 human_IL15Ra(sushi)_(GGGGS)5-human_IL15_D30N_(single-Chain)-empty-Fc_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

XENP29281 Chain 1 - human_IL15Ra(sushi)_(GGGGS)5-human_IL15_D30N_(single-Chain)-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:280)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGG
SGGGGSGGGGSGGGGSGGGGS/NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQ
VISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/EPK
SSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKT
KPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT
KNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMH
EALHNHYTQKSLSLSPGK

XENP29281 Chain 2 - empty-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:281)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE
QMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPGK

>XENP29282 human_IL15Ra(sushi)_(GGGGS)5-human_IL15_N1D/D30N_(single-Chain)-empty-Fc_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

XENP29282 Chain 1 - human_IL15Ra(sushi)_(GGGGS)5-human_IL15_N1D/D30N_(single-Chain)-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:282)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGG
SGGGGSGGGGSGGGGSGGGGS/DWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQ
VISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/EPK
SSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKT
KPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT
KNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMH
EALHNHYTQKSLSLSPGK

XENP29282 Chain 2 - empty-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:283)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE
QMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPGK

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 192B

>XENP29283 human_IL15Ra(sushi)_(GGGGS)5-human_IL15_N4D/D30N_(single-Chain)-empty-Fc_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

XENP29283 Chain 1 - human_IL15Ra(sushi)_(GGGGS)5-human_IL15_N4D/D30N_(single-Chain)-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:284)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGSGGGGSGGGGSGGGGSGGGGS/NWVDVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

XENP29283 Chain 2 - empty-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:285)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>XENP29284 human_IL15Ra(sushi)_(GGGGS)5-human_IL15_D30N/E64Q_(single-Chain)-empty-Fc_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

XENP29284 Chain 1 - human_IL15Ra(sushi)_(GGGGS)5-human_IL15_D30N/E64Q_(single-Chain)-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:286)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGSGGGGSGGGGSGGGGSGGGGS/NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHDTVQNLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

XENP29284 Chain 2 - empty-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:287)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 192C

>XENP29285 human_IL15Ra(sushi)_(GGGGS)5-human_IL15_D30N/N65D_(single-Chain)-empty-Fc_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

XENP29285 Chain 1 - human_IL15Ra(sushi)_(GGGGS)5-human_IL15_D30N/N65D_(single-Chain)-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:288)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGSGGGGSGGGGSGGGGSGGGGS/NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHDTVEDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

XENP29285 Chain 2 - empty-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q (SEQ ID NO:289)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

>XENP29286 human_IL15Ra(sushi)_(GGGGS)5-human_IL15_D30N/E64Q/N65D_(single-Chain)-empty-Fc_Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S-Fc(216)_IgG1_C220S/PVA_/S267K/S364K/E357Q

XENP29286 Chain 1 - human_IL15Ra(sushi)_(GGGGS)5-human_IL15_D30N/E64Q/N65D_(single-Chain)-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:290)
ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVLNKATNVAHWTTPSLKCIR/GGGGSGGGGSGGGGSGGGGSGGGGS/NWVNVISDLKKIEDLIQSMHIDATLYTESNVHPSCKVTAMKCFLLELQVISLESGDASIHDTVQDLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS/EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALHNHYTQKSLSLSPGK

XENP29286 Chain 2 - empty-Fc(216)_IgG1_pI(-)_Isosteric_A_C220S/PVA_/S267K/L368D/K370S (SEQ ID NO:291)
EPKSSDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREQMTKNQVKLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

RECTIFIED SHEET (RULE 91) ISA/EP

Figure 193A

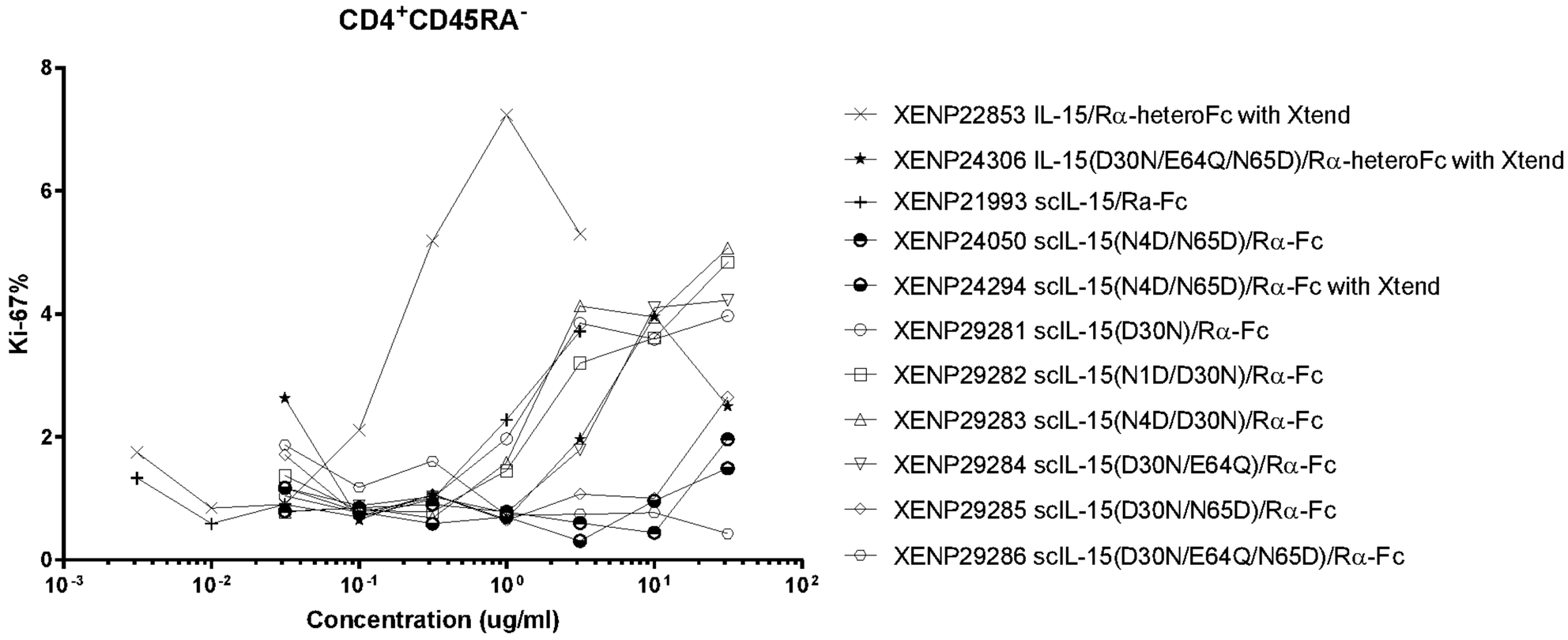


Figure 193B

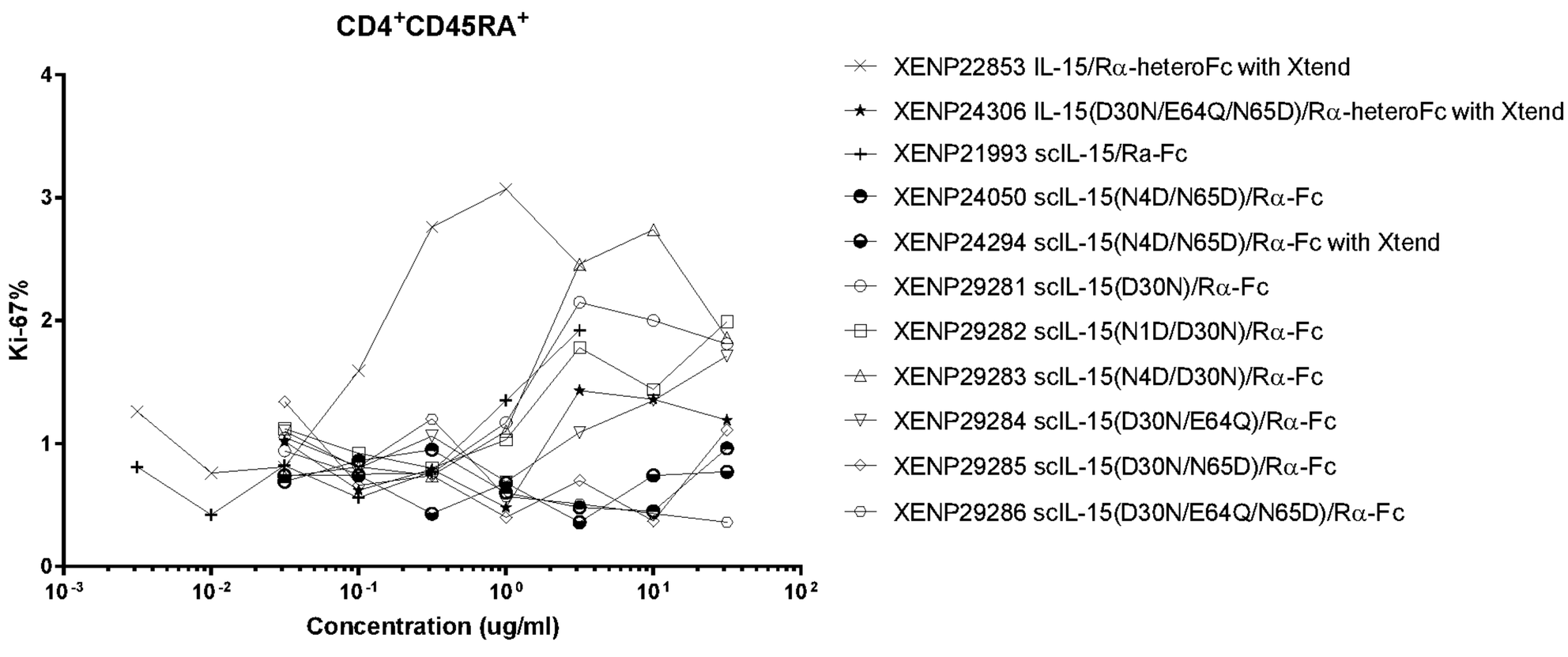


Figure 193C

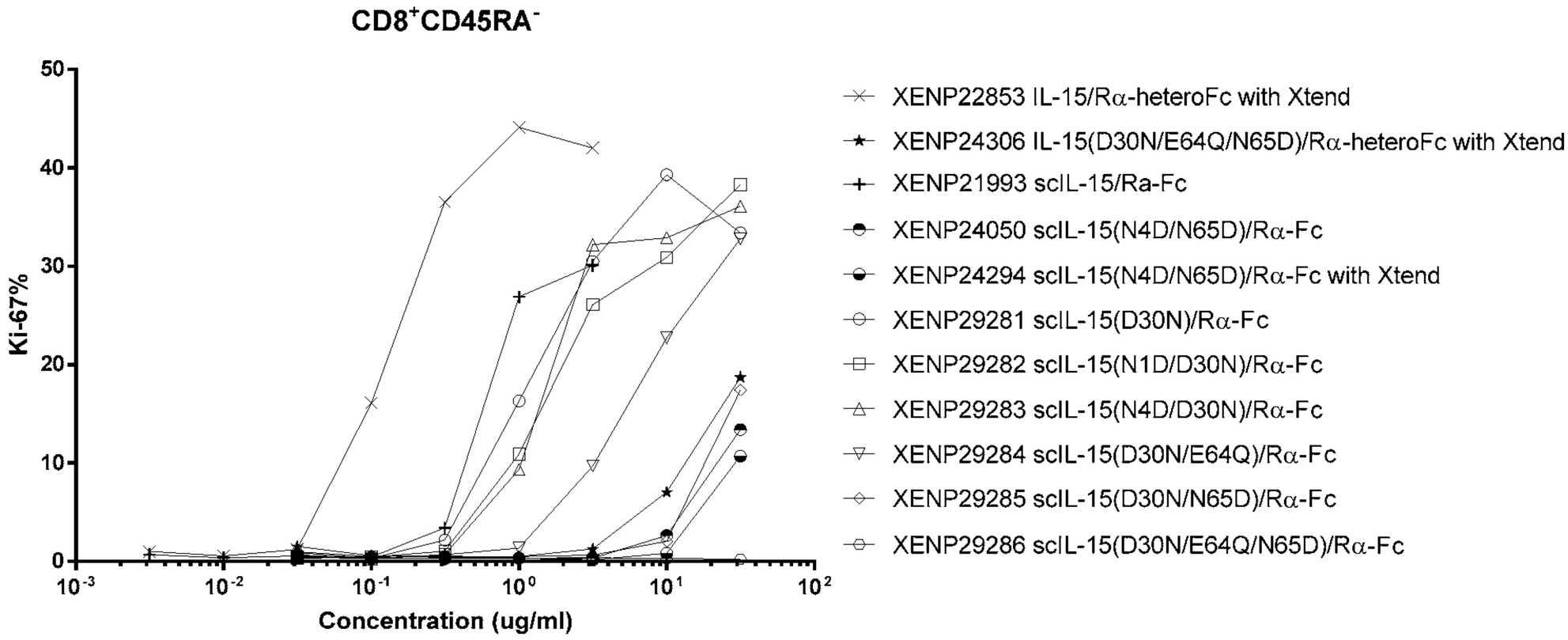


Figure 193D

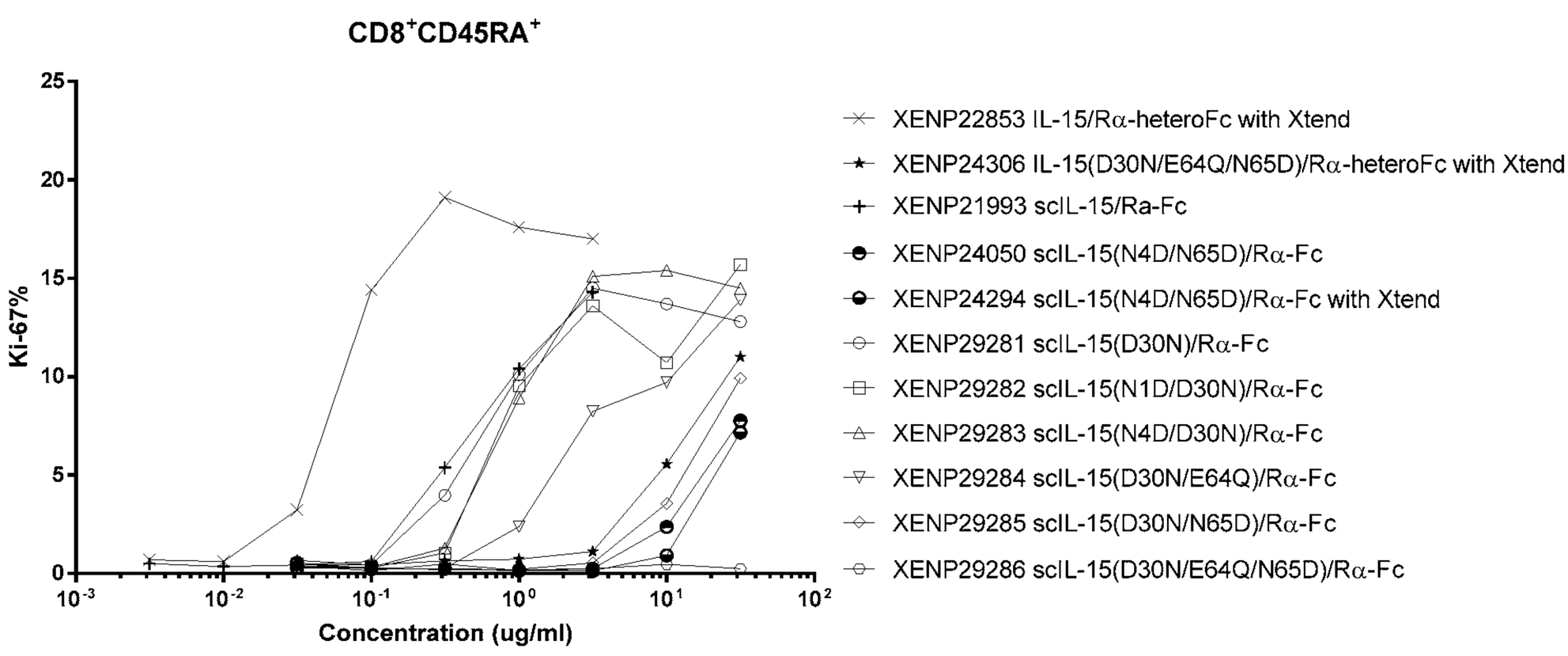


Figure 193E

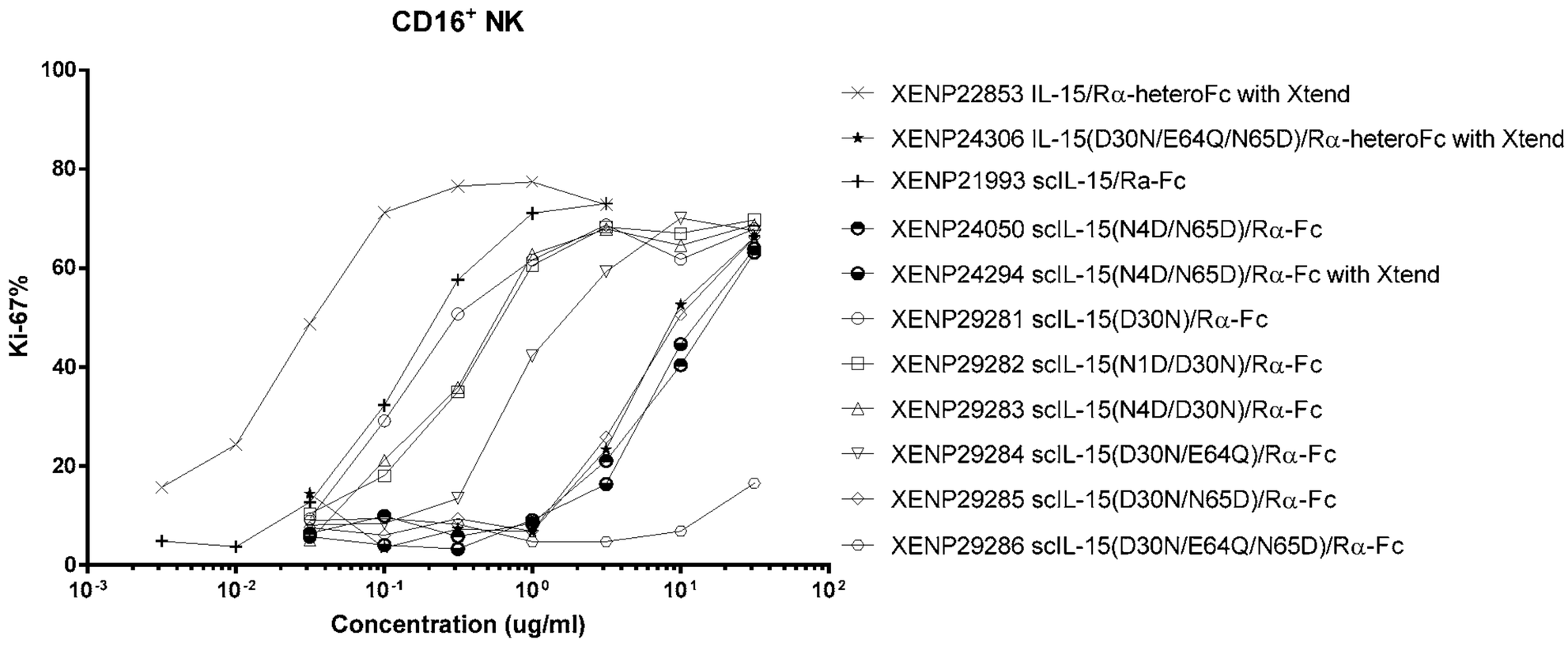


Figure 193F

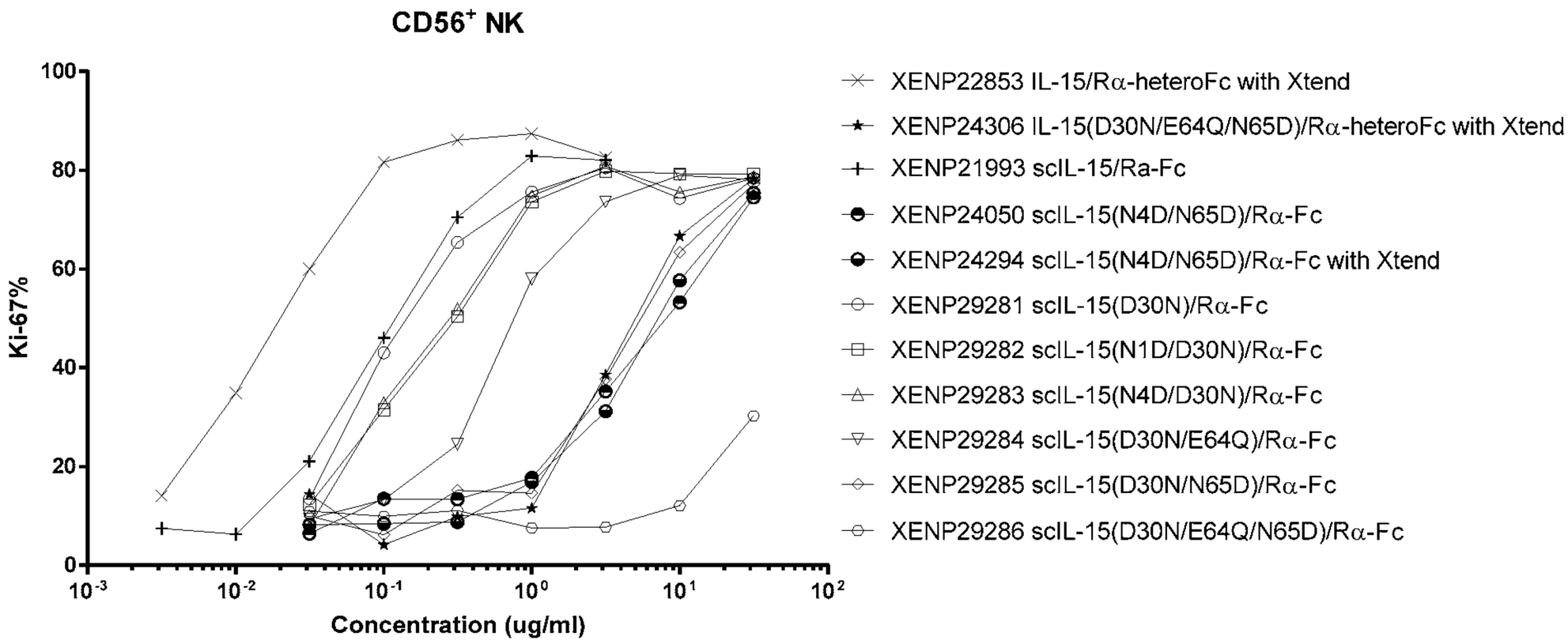
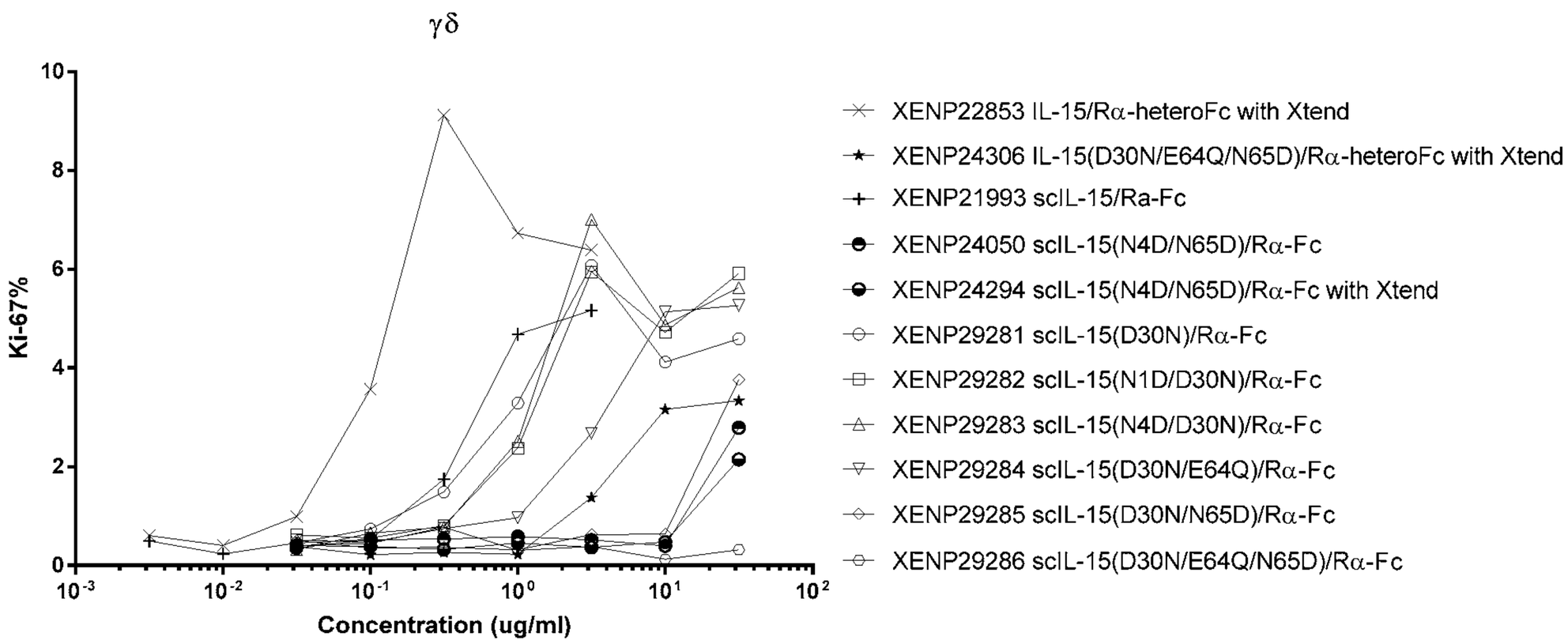


Figure 193G


γδ
Ki-67%
Concentration (ug/ml)
XENP22853 IL-15/Rα-heteroFc with Xtend
XENP24306 IL-15(D30N/E64Q/N65D)/Rα-heteroFc with Xtend
XENP21993 scIL-15/Ra-Fc
XENP24050 scIL-15(N4D/N65D)/Rα-Fc
XENP24294 scIL-15(N4D/N65D)/Rα-Fc with Xtend
XENP29281 scIL-15(D30N)/Rα-Fc
XENP29282 scIL-15(N1D/D30N)/Rα-Fc
XENP29283 scIL-15(N4D/D30N)/Rα-Fc
XENP29284 scIL-15(D30N/E64Q)/Rα-Fc
XENP29285 scIL-15(D30N/N65D)/Rα-Fc
XENP29286 scIL-15(D30N/E64Q/N65D)/Rα-Fc

Figures 194A-194E

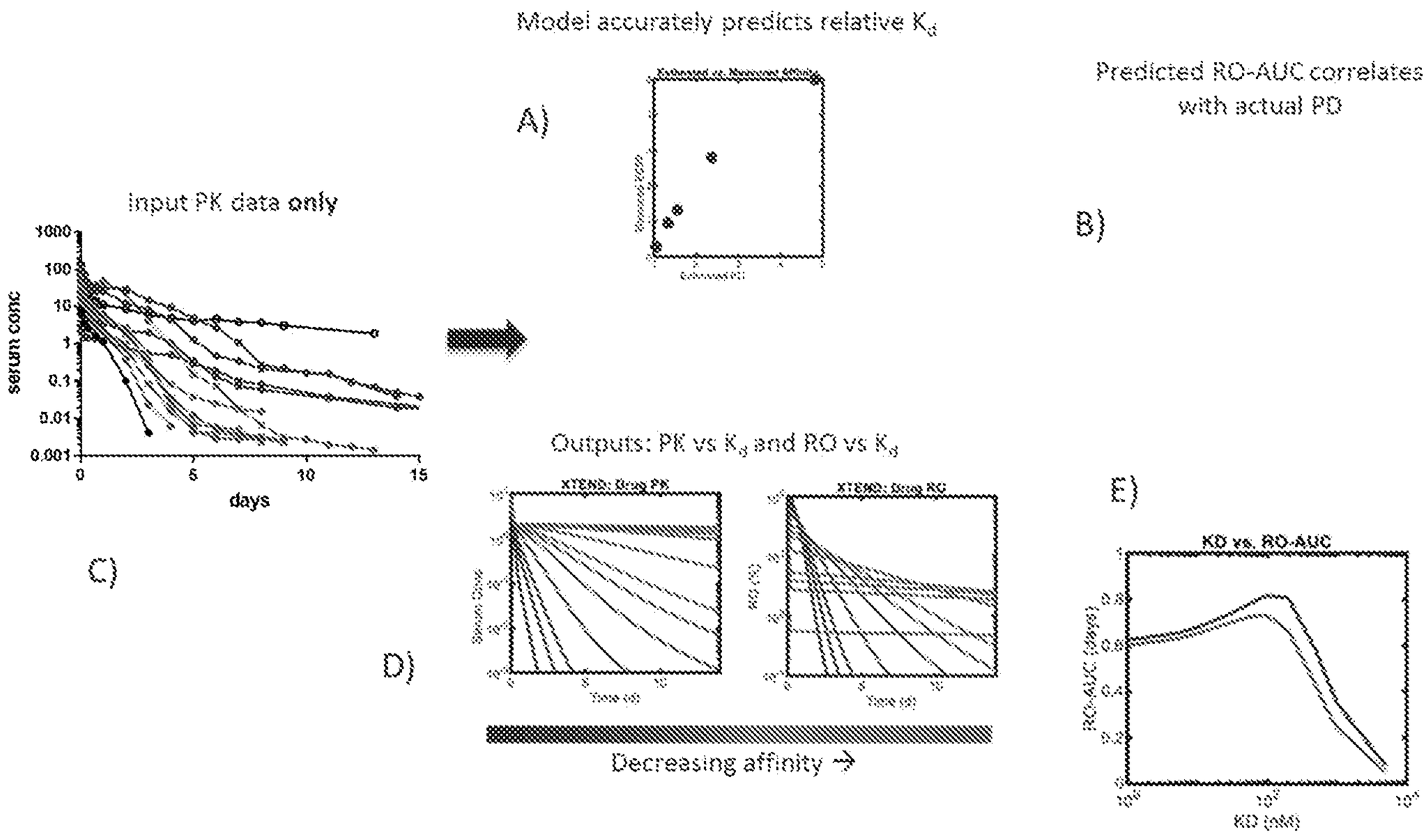


Figure 195

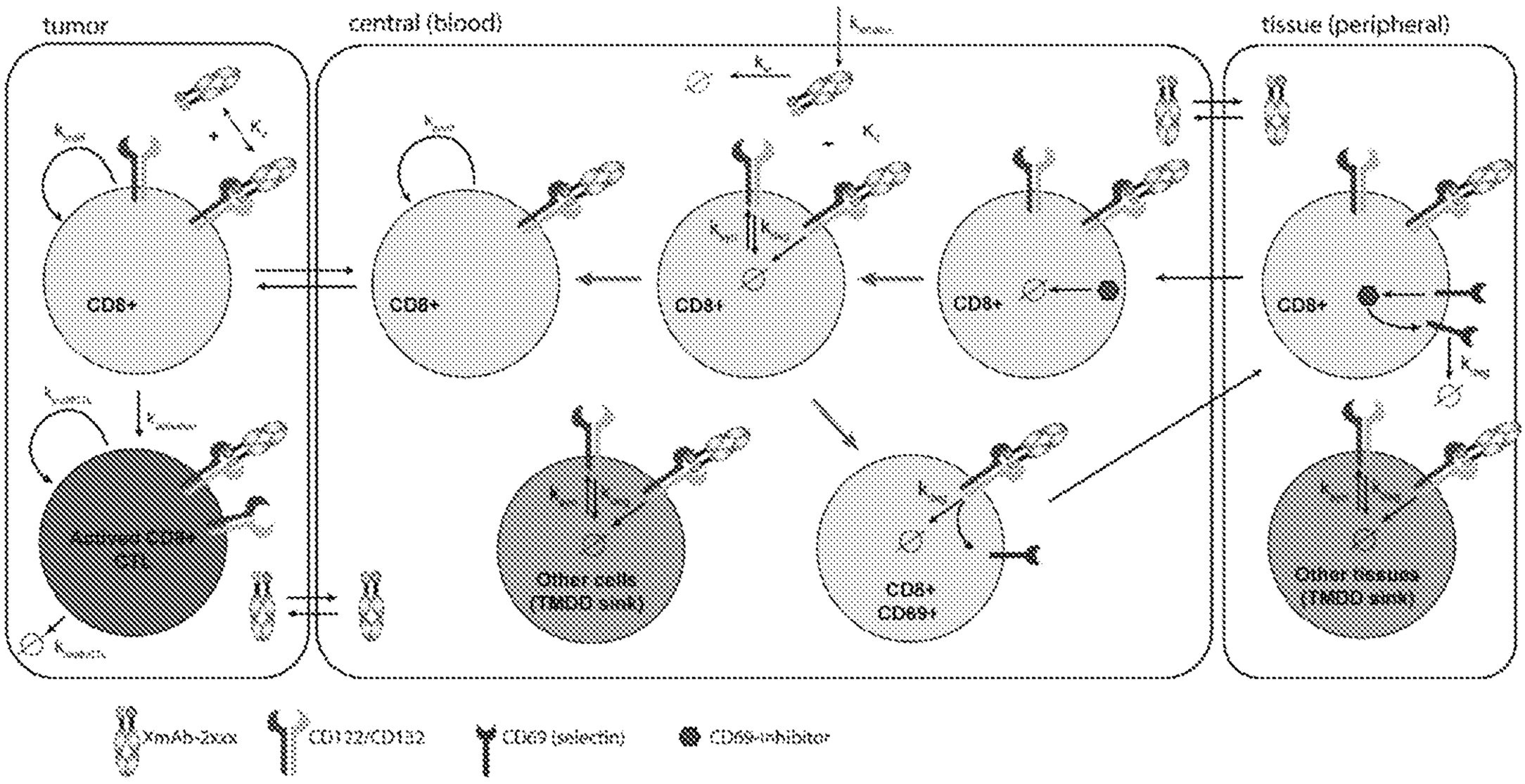

tumor
central (blood)
tissue (peripheral)
CD8+
CD8+
CD8+
CD8+
CD8+
CD8+
Other cells
(TMDD sink)
CD8+
CD69+
Other tissues
(TMDD sink)
XmAb-2xxx
CD122/CD132
CD69 (selectin)
CD69-inhibitor

Figure 196

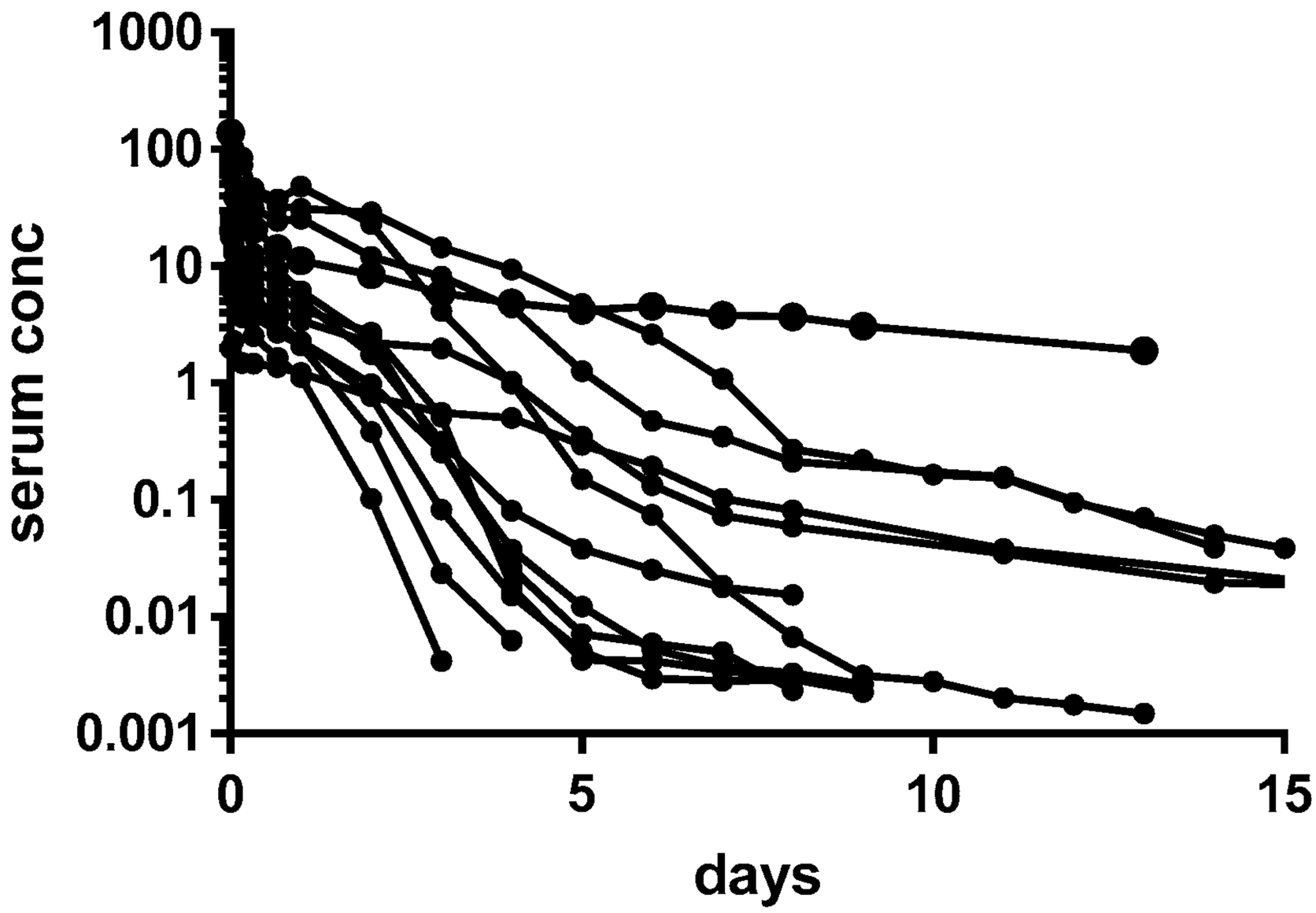


Figure 197

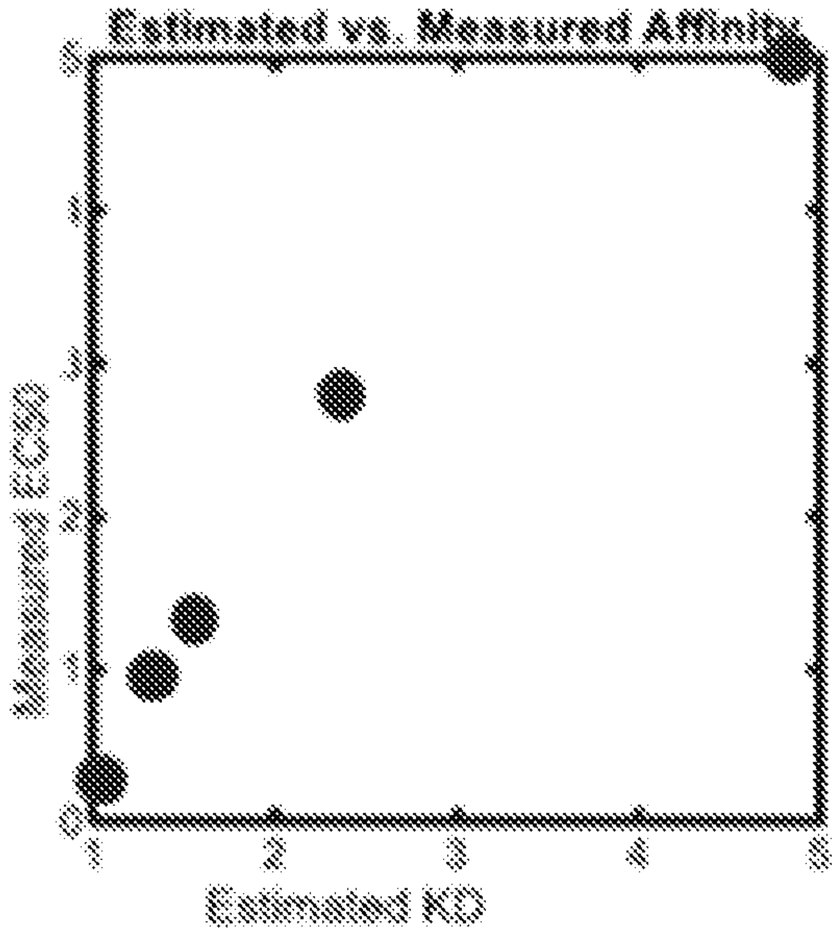
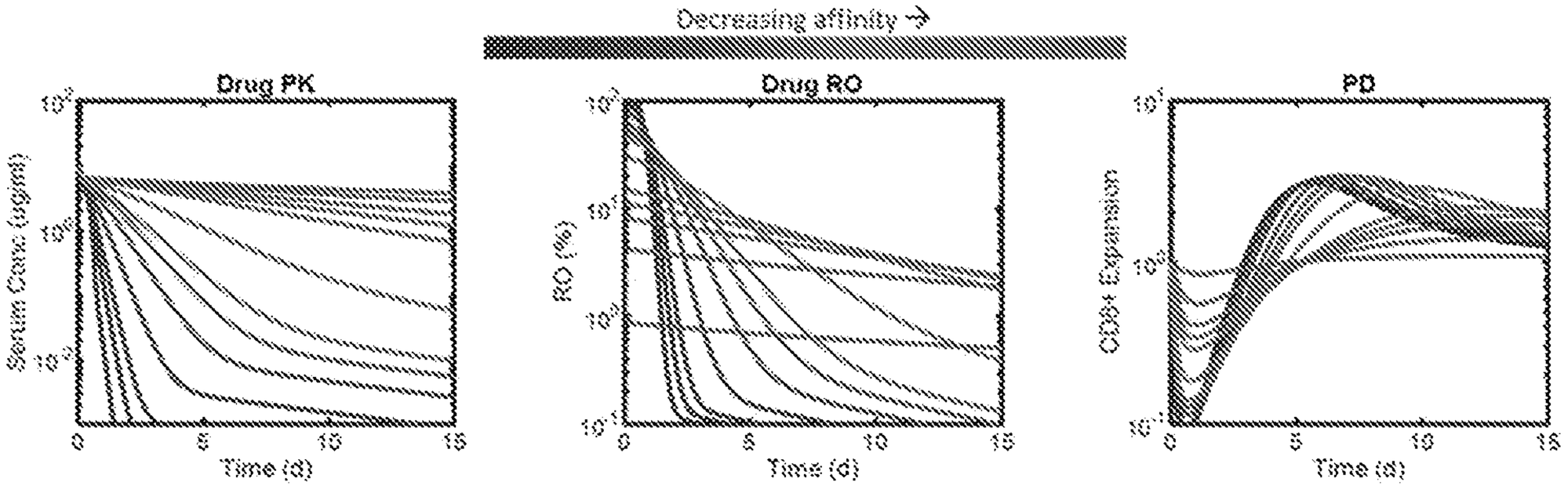


Figure 198



Figures 199A-199F

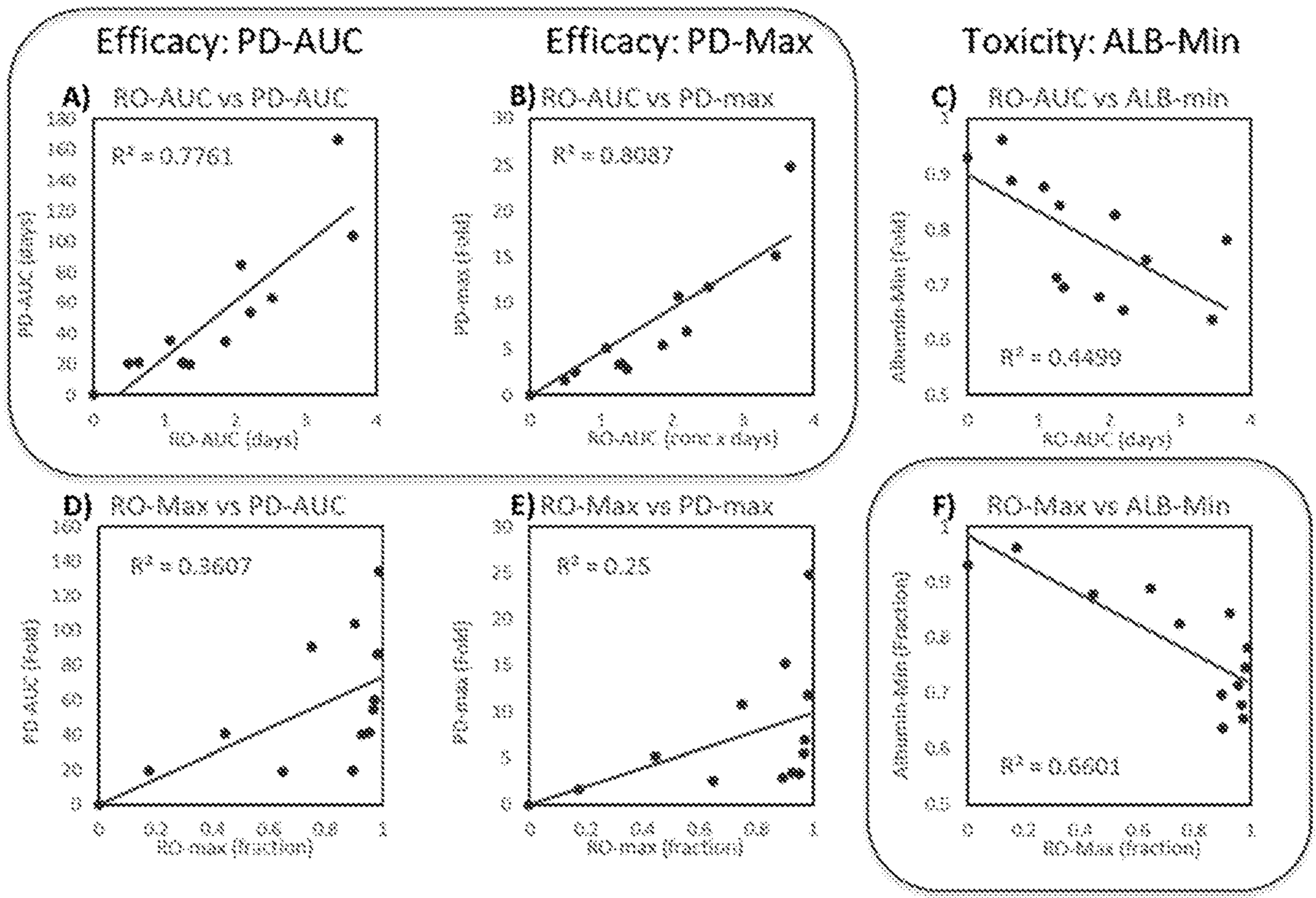


Figure 200

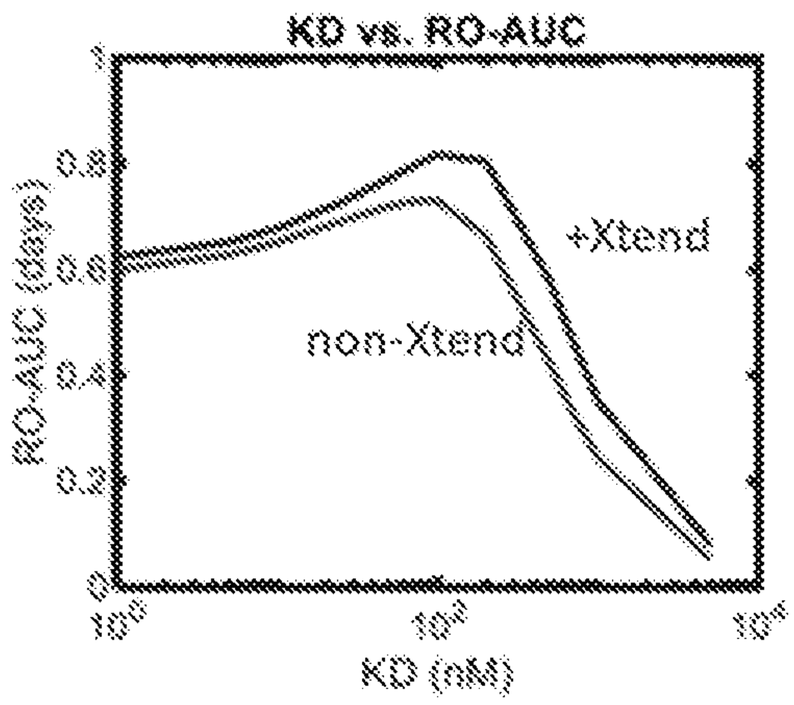
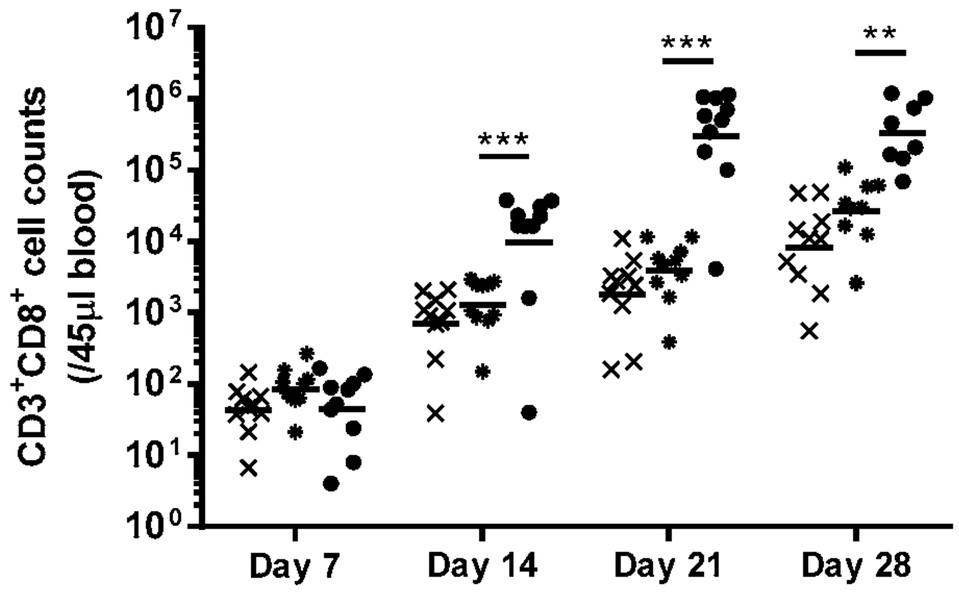


Figure 201A

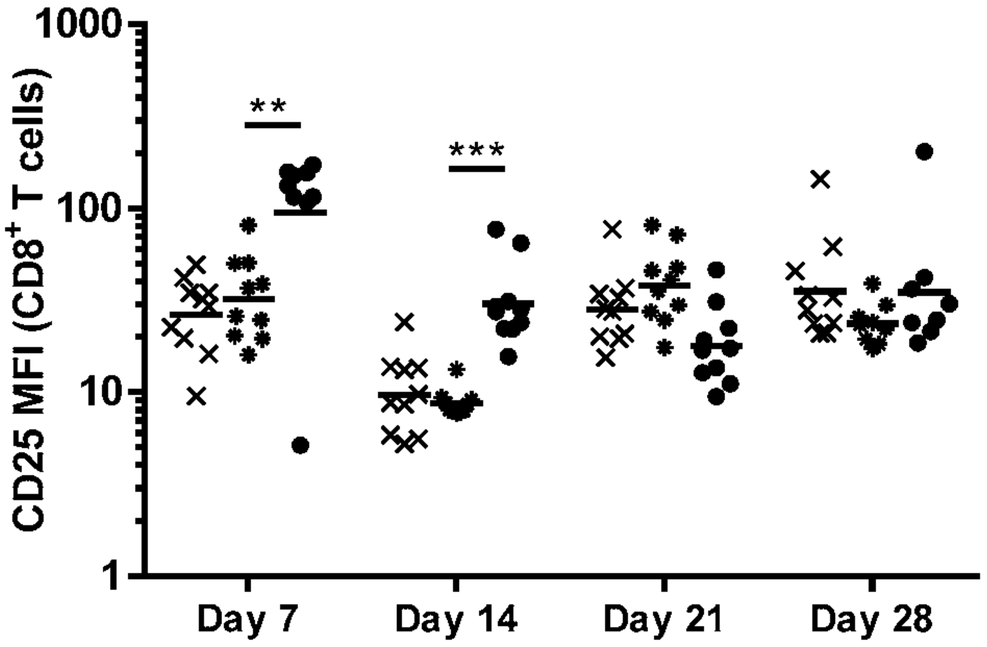


× PBMC only

* PBMC + XENP16432 (3 mg/kg)

• PBMC + XENP16432 (3 mg/kg) + XENP24045 (0.5 mg/kg)

Figure 201B



× PBMC

* PBMC + XENP16432 (3 mg/kg)

• PBMC + XENP16432 (3 mg/kg) + XENP24045 (0.5 mg/kg)

Figure 202A

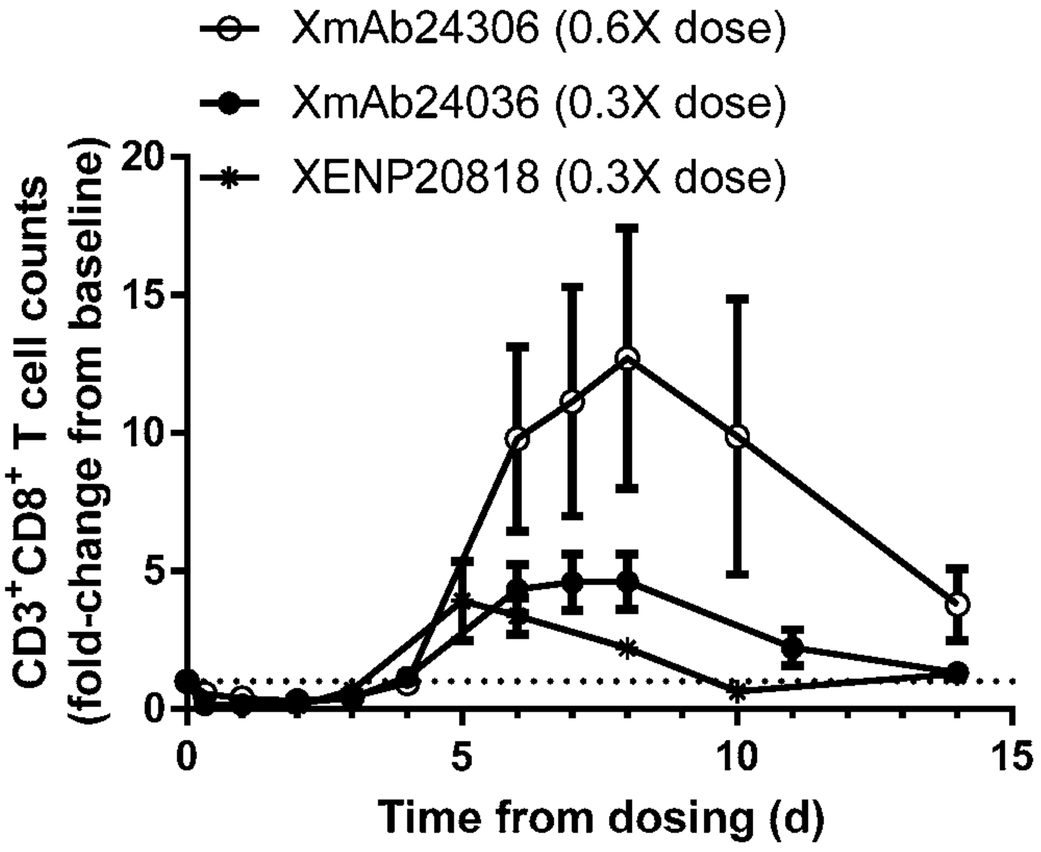


Figure 202B

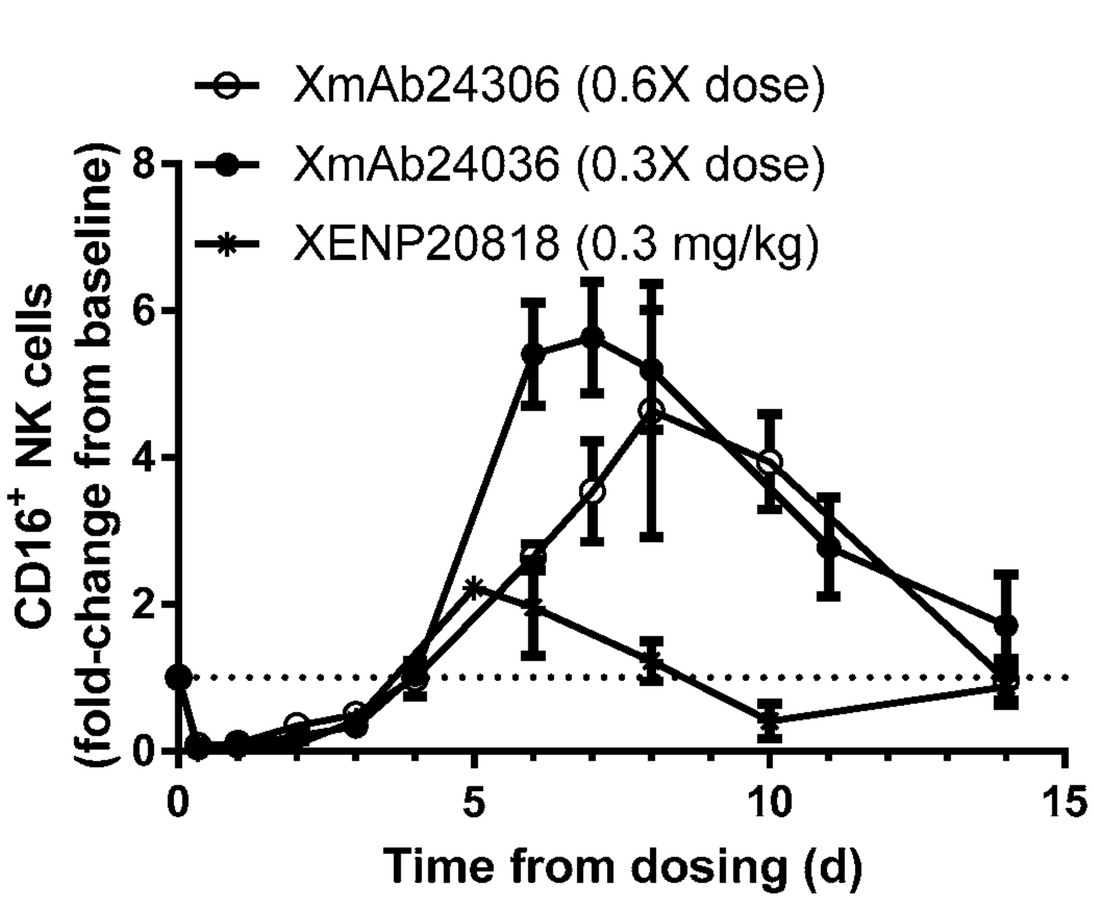


Figure 202C

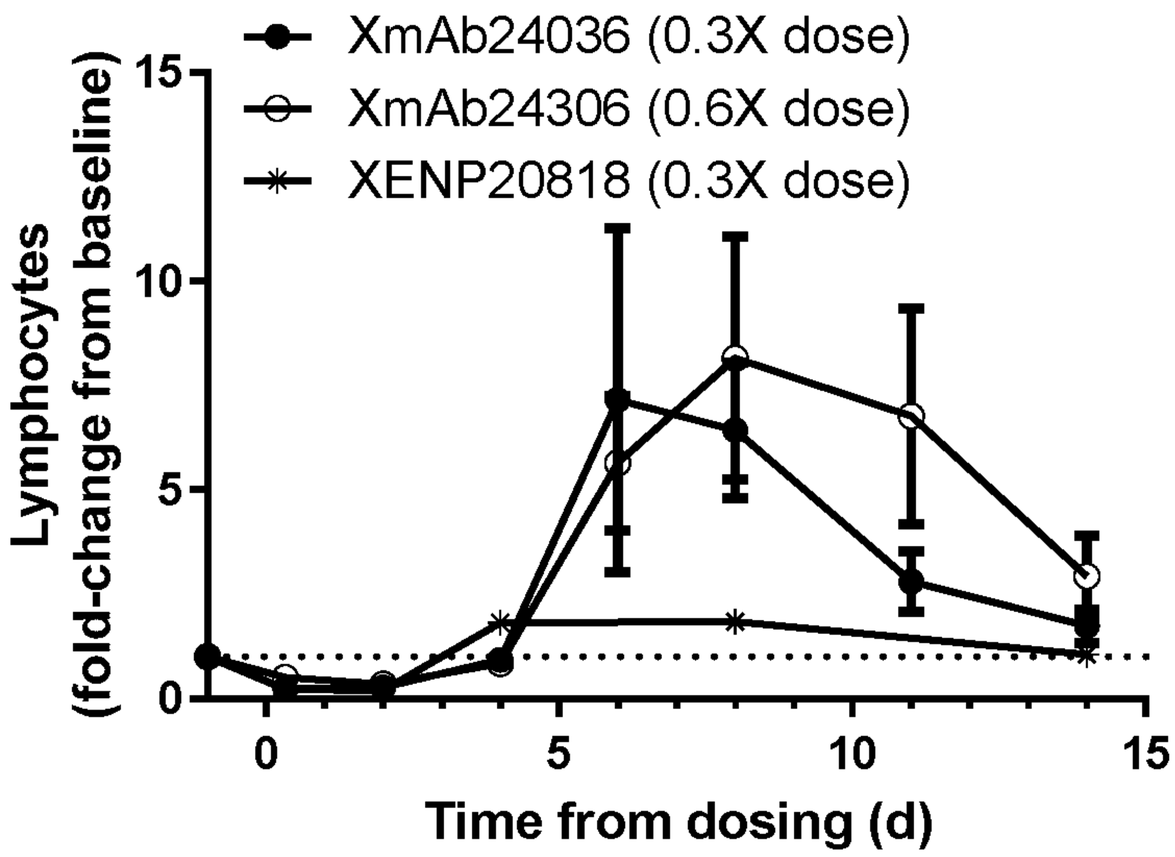


Figure 203

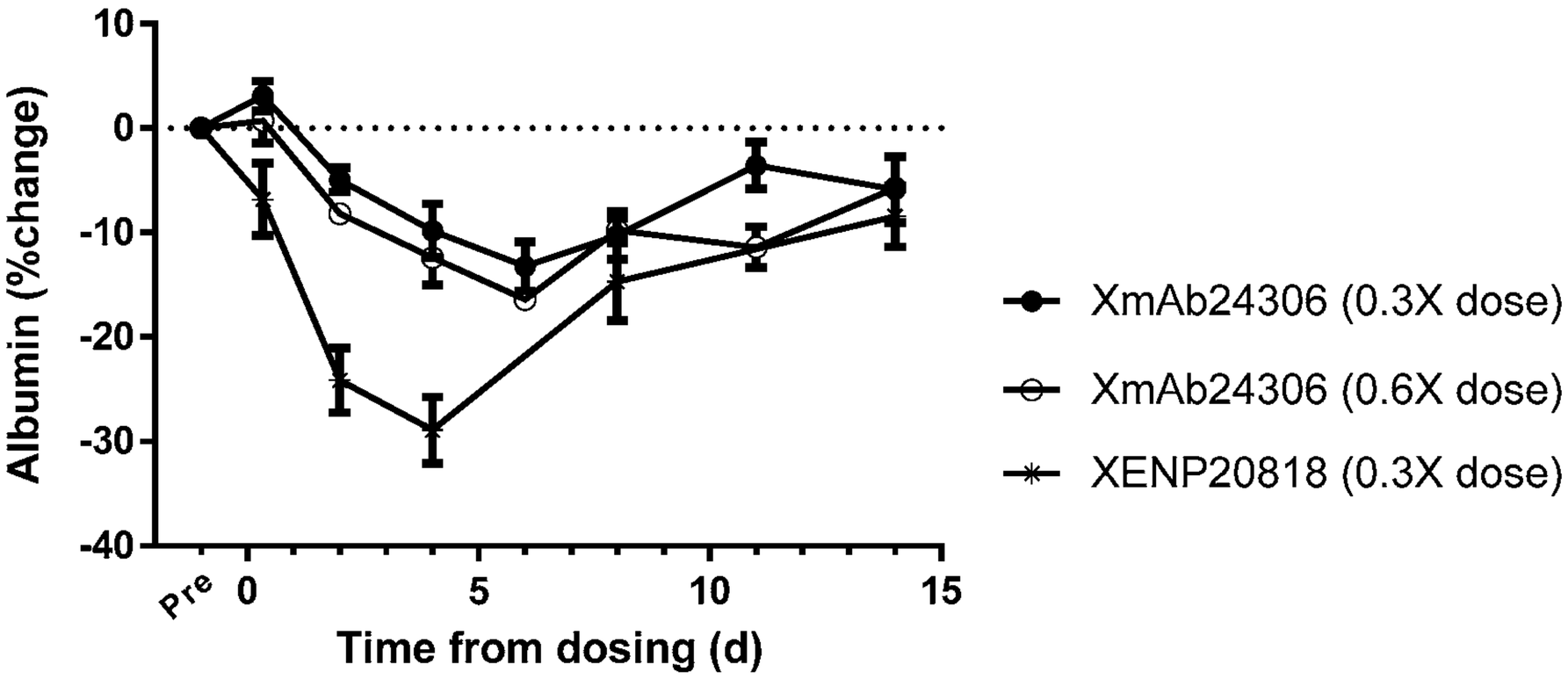


Figure 204A-Figure 204F

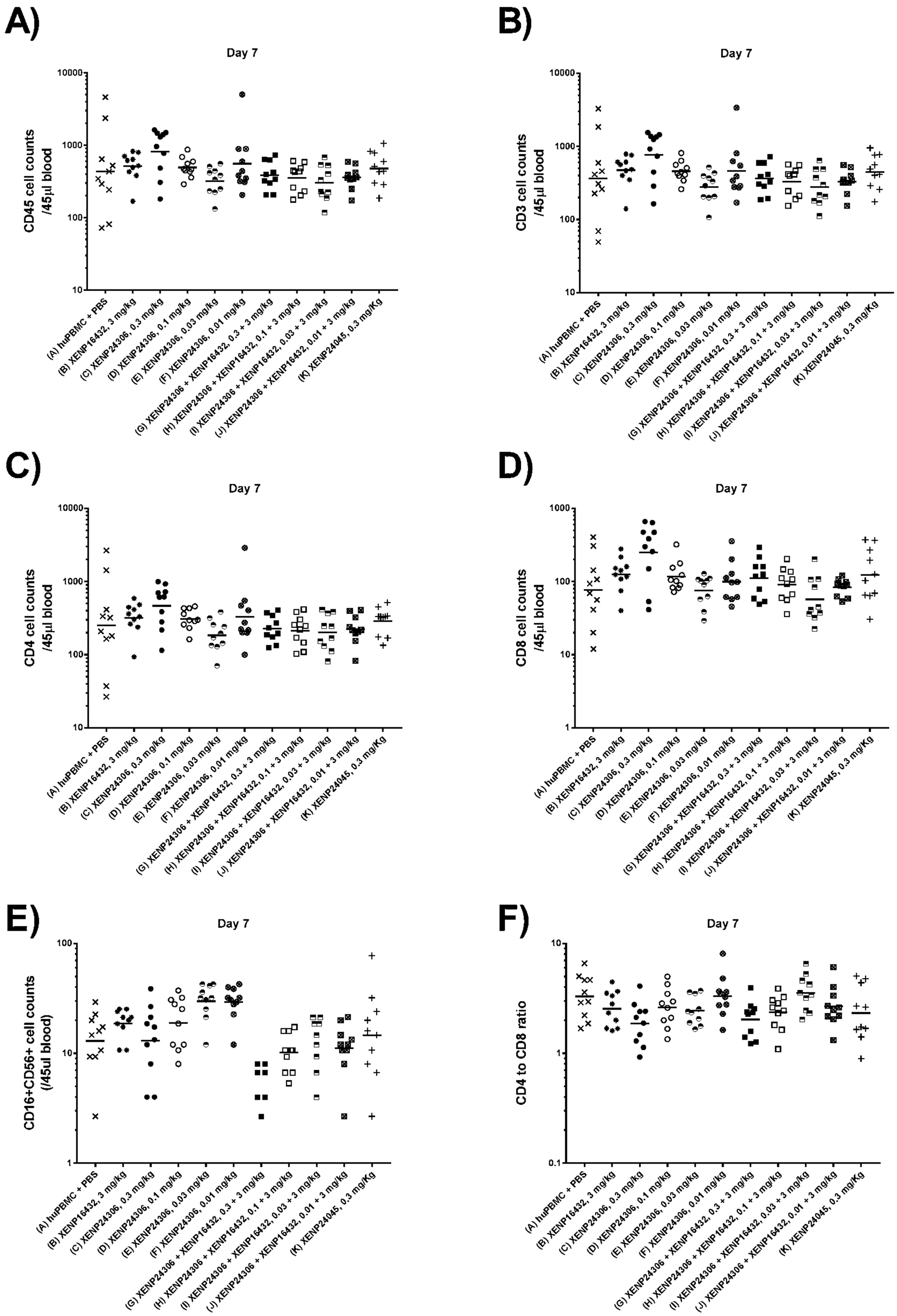


Figure 205A-Figure 205F

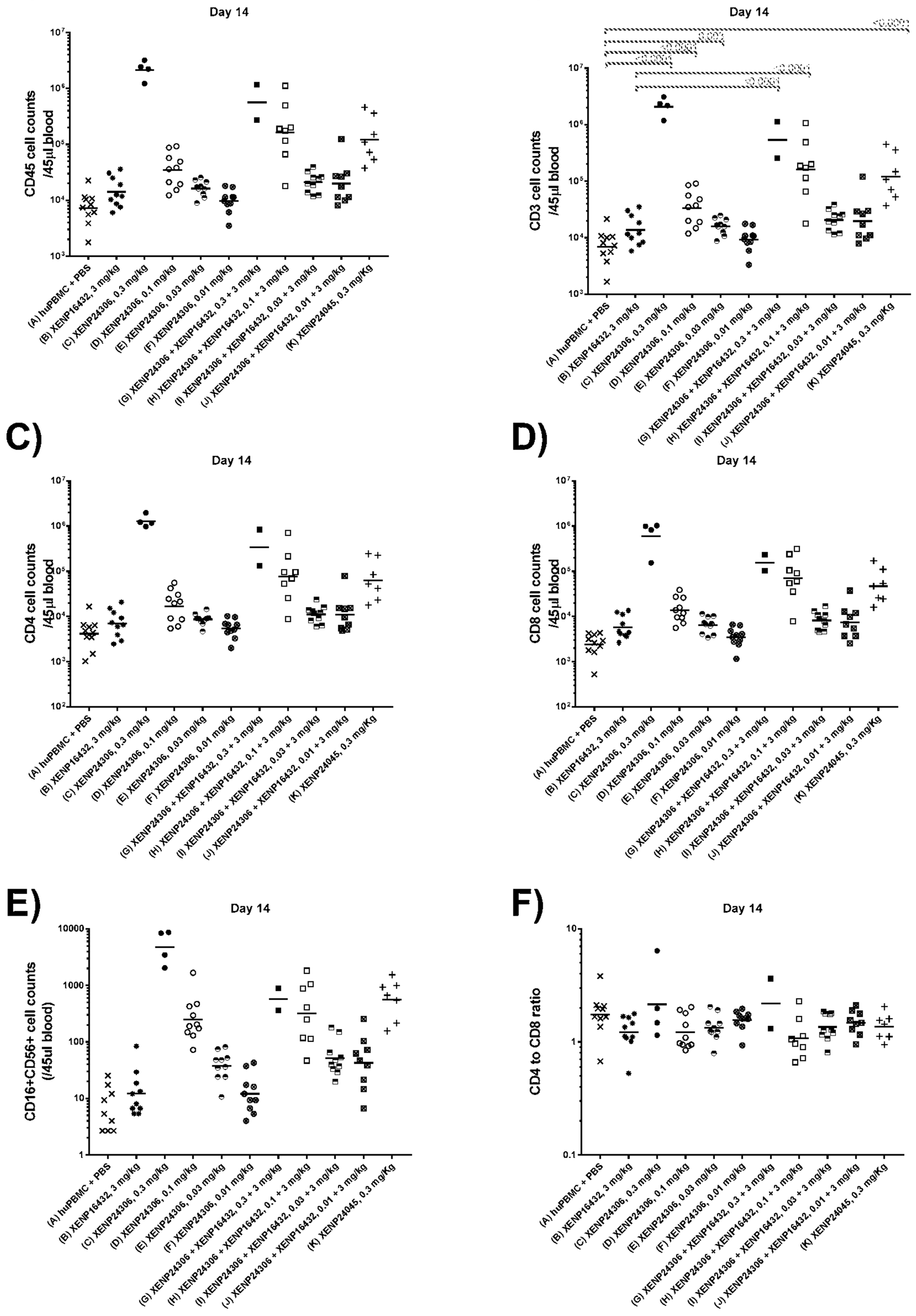


Figure 206A-Figure 206F

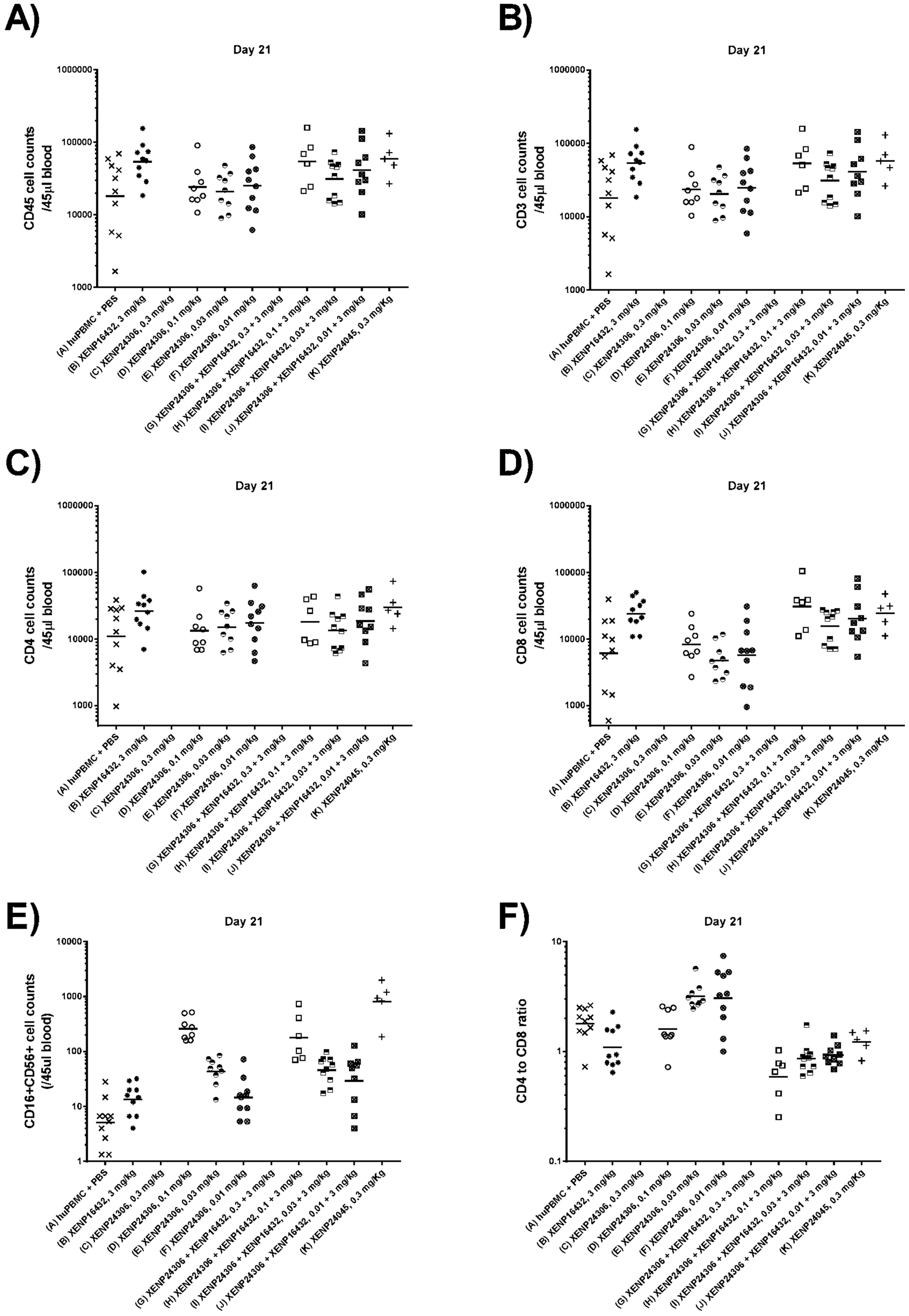


Figure 207A-Figure 207D

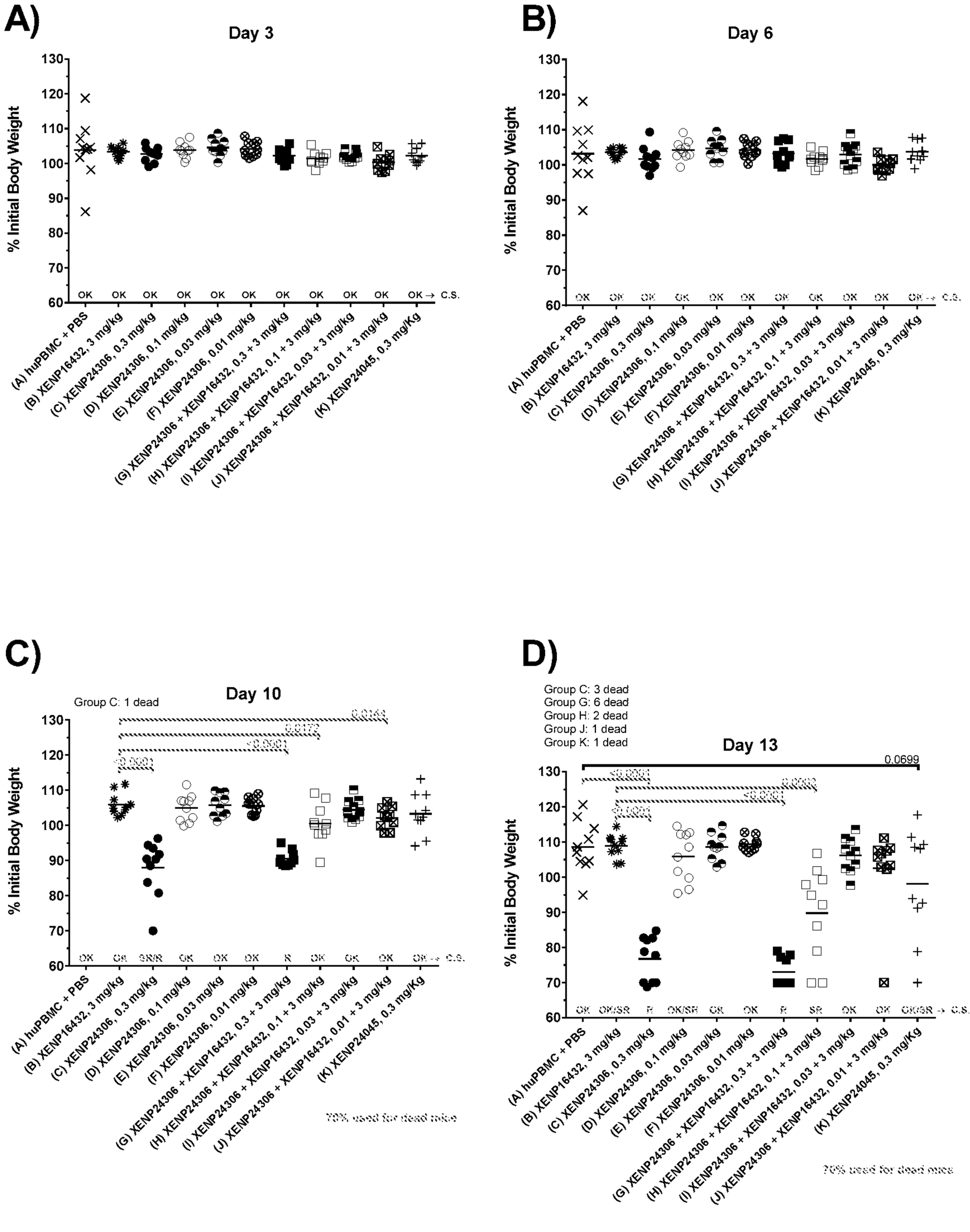
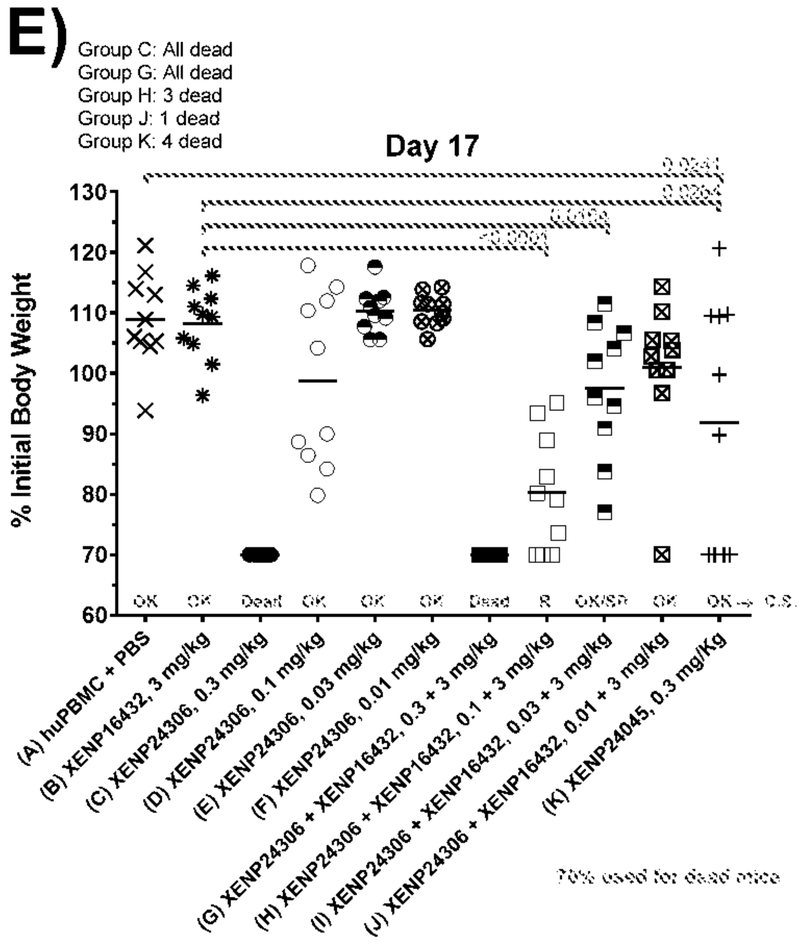
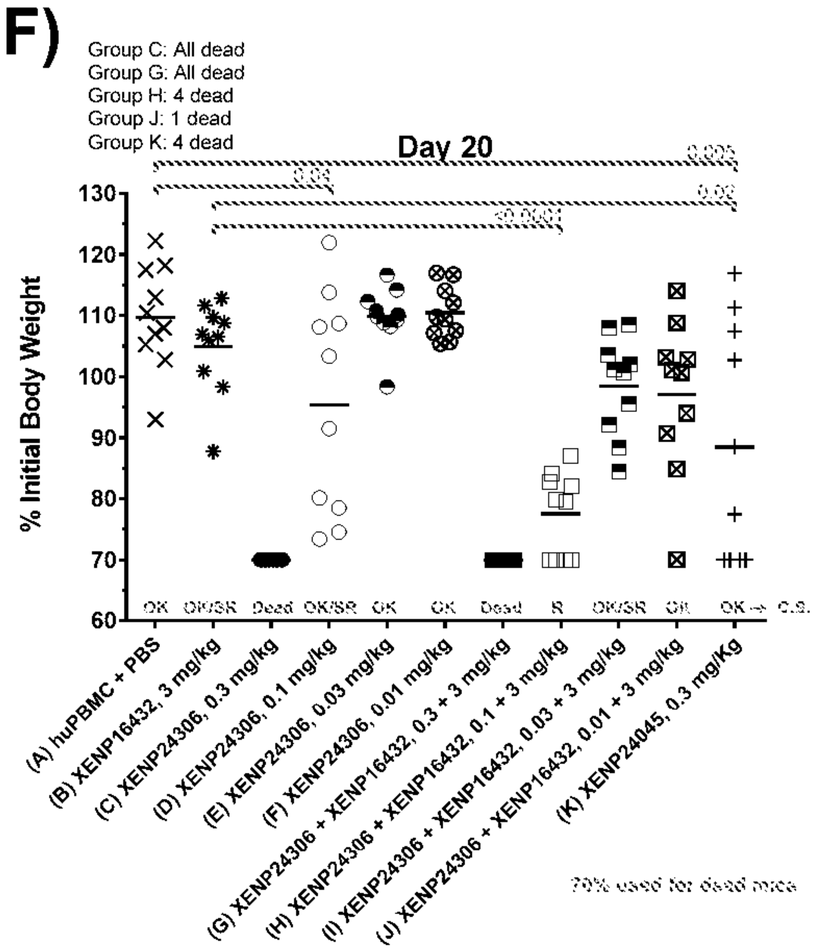


Figure 207E-Figure 207H

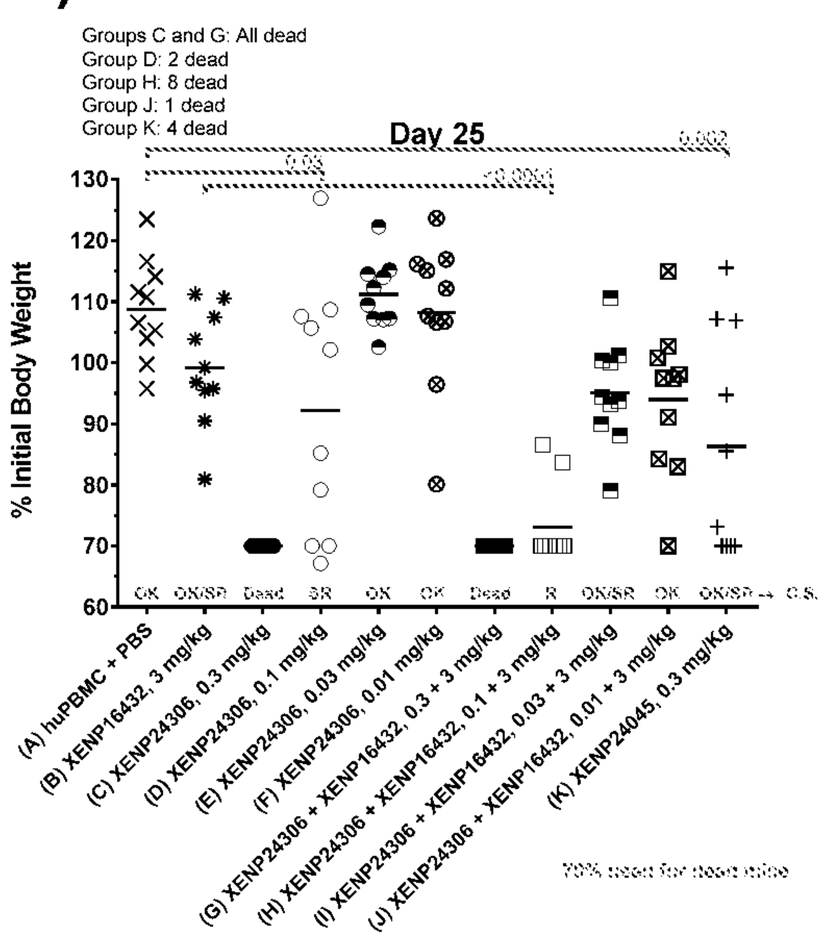
E)



F)



G)



H)

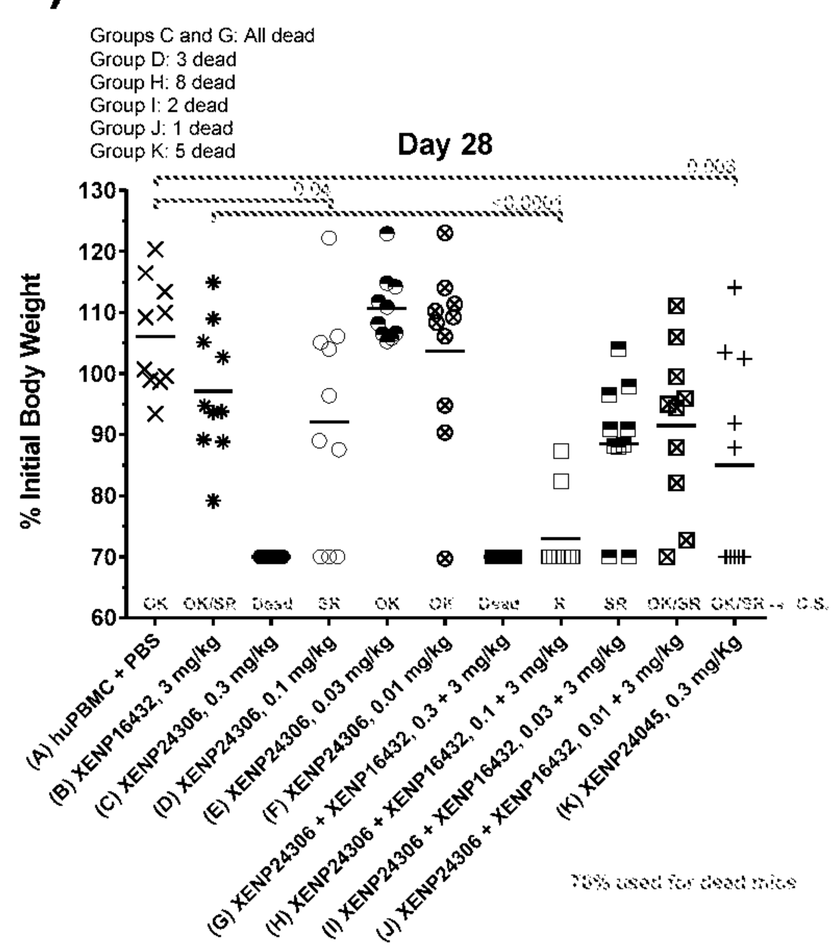


Figure 207I

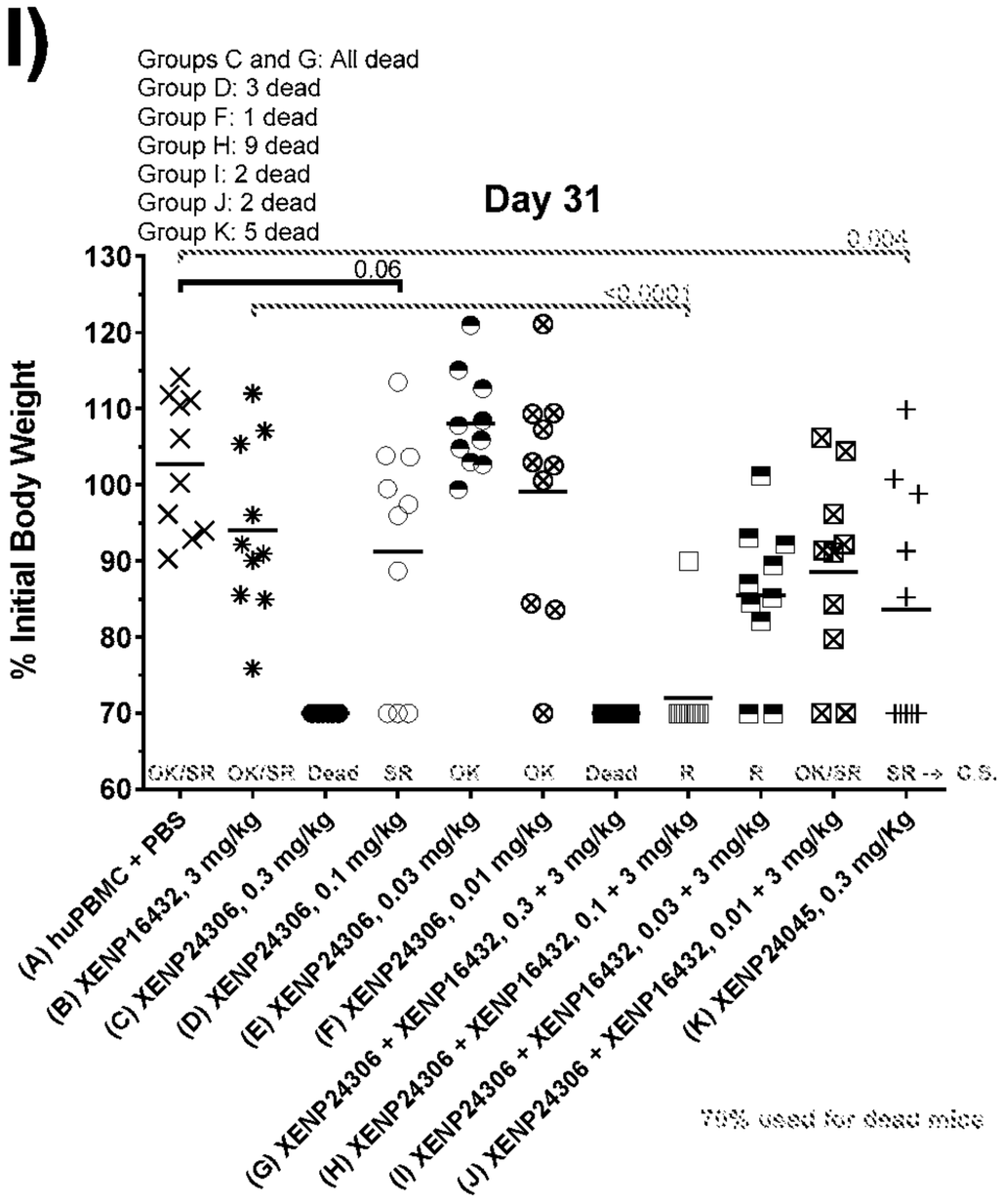

I)
Groups C and G: All dead
Group D: 3 dead
Group F: 1 dead
Group H: 9 dead
Group I: 2 dead
Group J: 2 dead
Group K: 5 dead
Day 31
0.004
0.06
<0.0001
% Initial Body Weight
130
120
110
100
90
80
70
60
OK/SR
OK/SR
Dead
SR
OK
OK
Dead
R
R
OK/SR
SR -> C.S.
(A) huPBMC + PBS
(B) XENP16432, 3 mg/kg
(C) XENP24306, 0.3 mg/kg
(D) XENP24306, 0.1 mg/kg
(E) XENP24306, 0.03 mg/kg
(F) XENP24306, 0.01 mg/kg
(G) XENP24306 + XENP16432, 0.3 + 3 mg/kg
(H) XENP24306 + XENP16432, 0.1 + 3 mg/kg
(I) XENP24306 + XENP16432, 0.03 + 3 mg/kg
(J) XENP24306 + XENP16432, 0.01 + 3 mg/kg
(K) XENP24045, 0.3 mg/Kg
79% used for dead mice

Figure 208

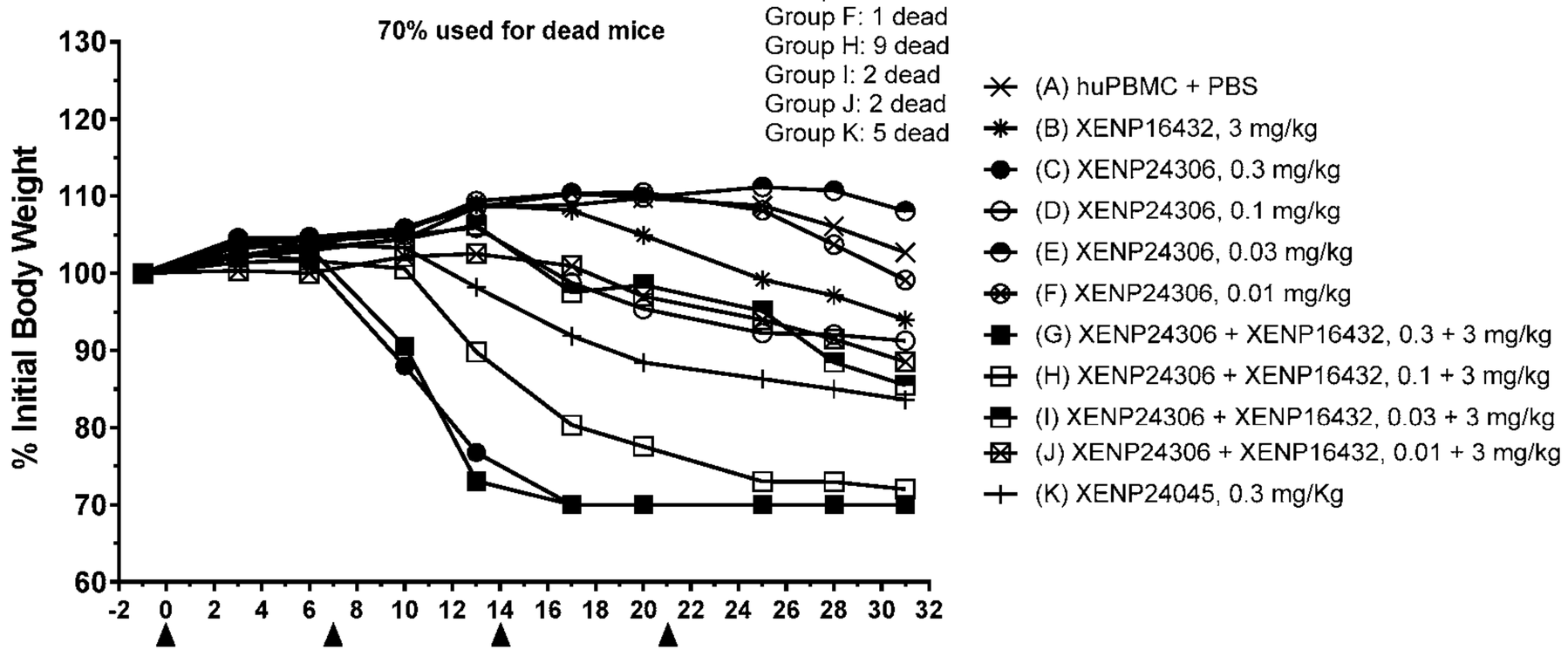
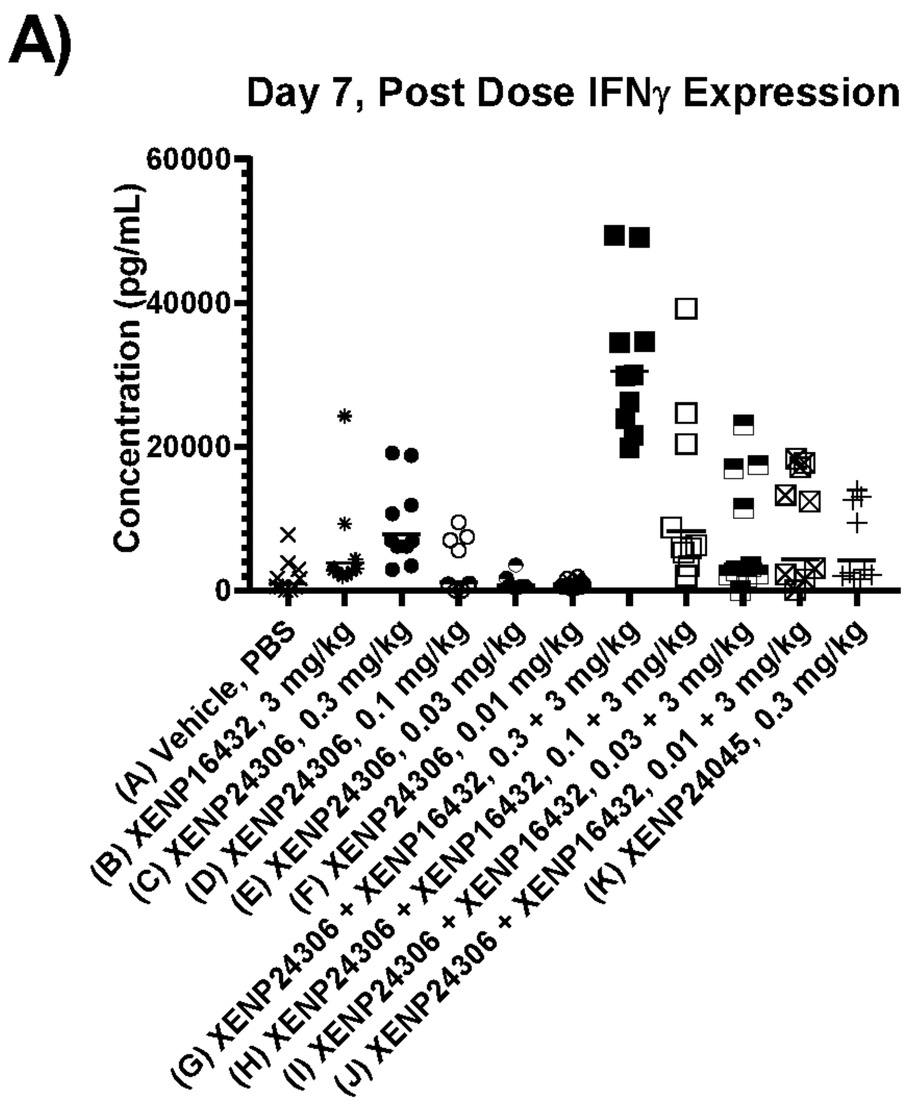
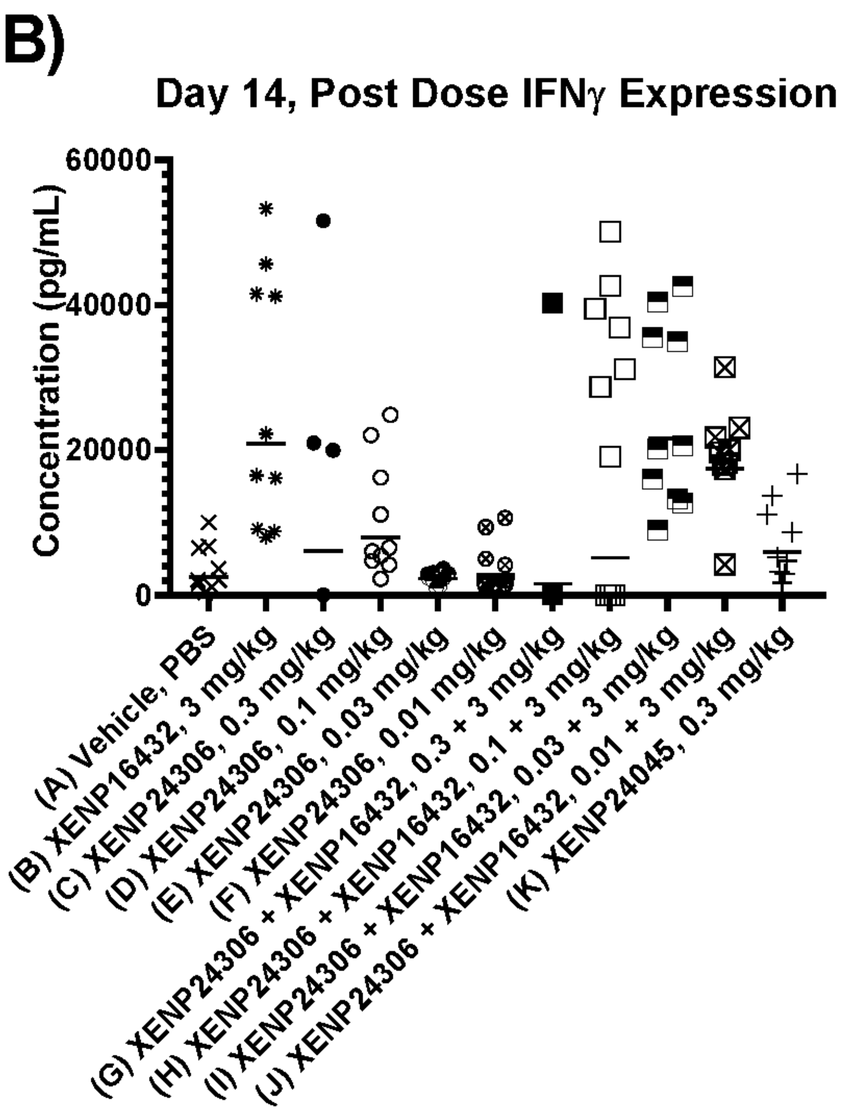

70% used for dead mice
Groups C and G: All dead
Group D: 3 dead
Group F: 1 dead
Group H: 9 dead
Group I: 2 dead
Group J: 2 dead
Group K: 5 dead
% Initial Body Weight
130
120
110
100
90
80
70
60
-2 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32
(A) huPBMC + PBS
(B) XENP16432, 3 mg/kg
(C) XENP24306, 0.3 mg/kg
(D) XENP24306, 0.1 mg/kg
(E) XENP24306, 0.03 mg/kg
(F) XENP24306, 0.01 mg/kg
(G) XENP24306 + XENP16432, 0.3 + 3 mg/kg
(H) XENP24306 + XENP16432, 0.1 + 3 mg/kg
(I) XENP24306 + XENP16432, 0.03 + 3 mg/kg
(J) XENP24306 + XENP16432, 0.01 + 3 mg/kg
(K) XENP24045, 0.3 mg/Kg

Figure 209A-Figure 209C





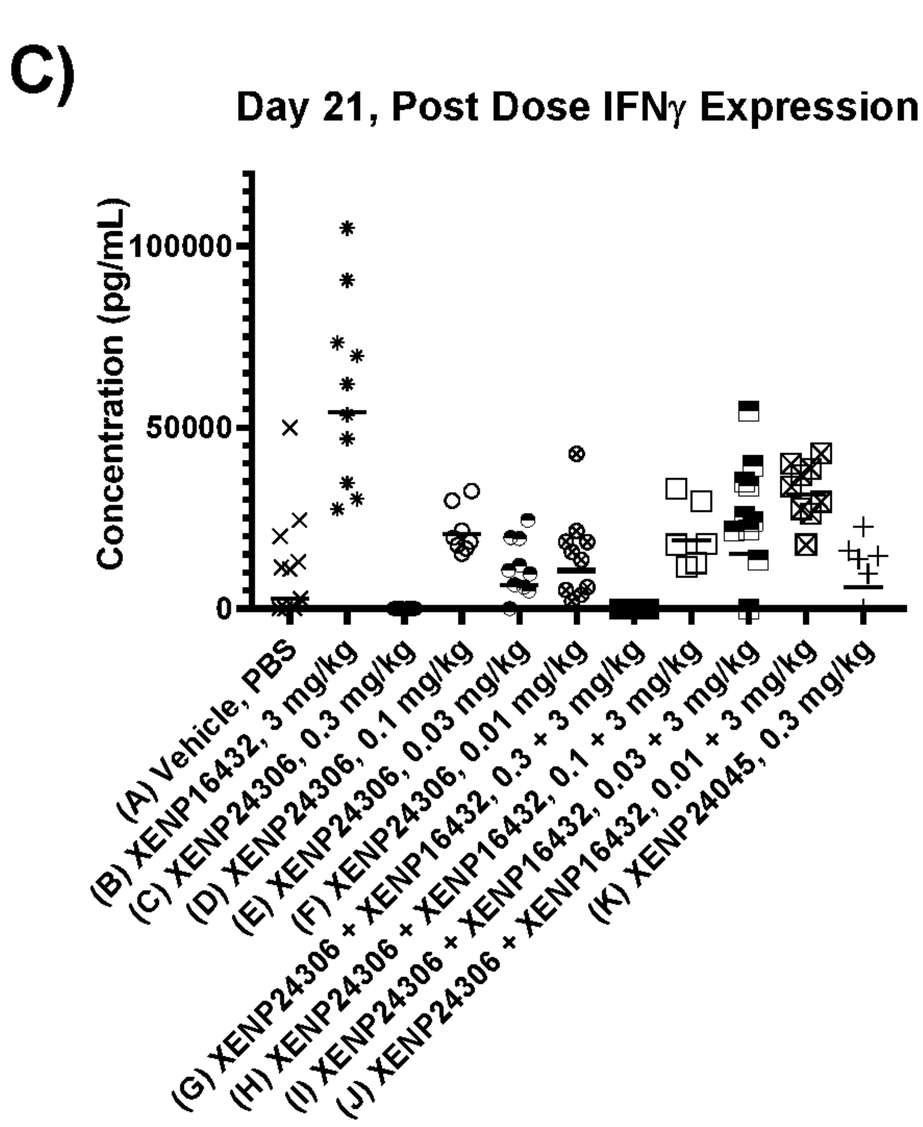


Figure 210A-Figure 210F

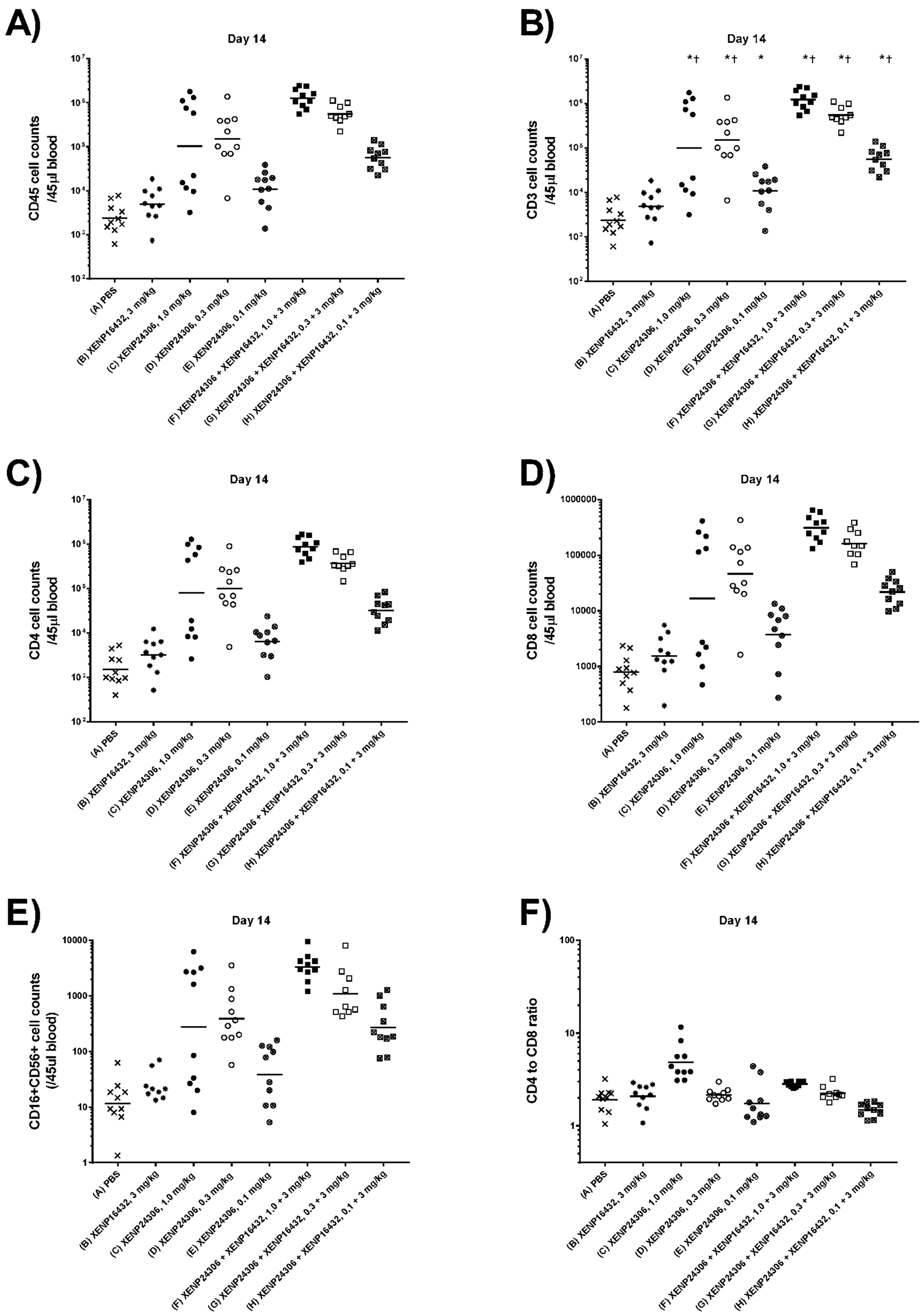


Figure 211A-Figure 211F

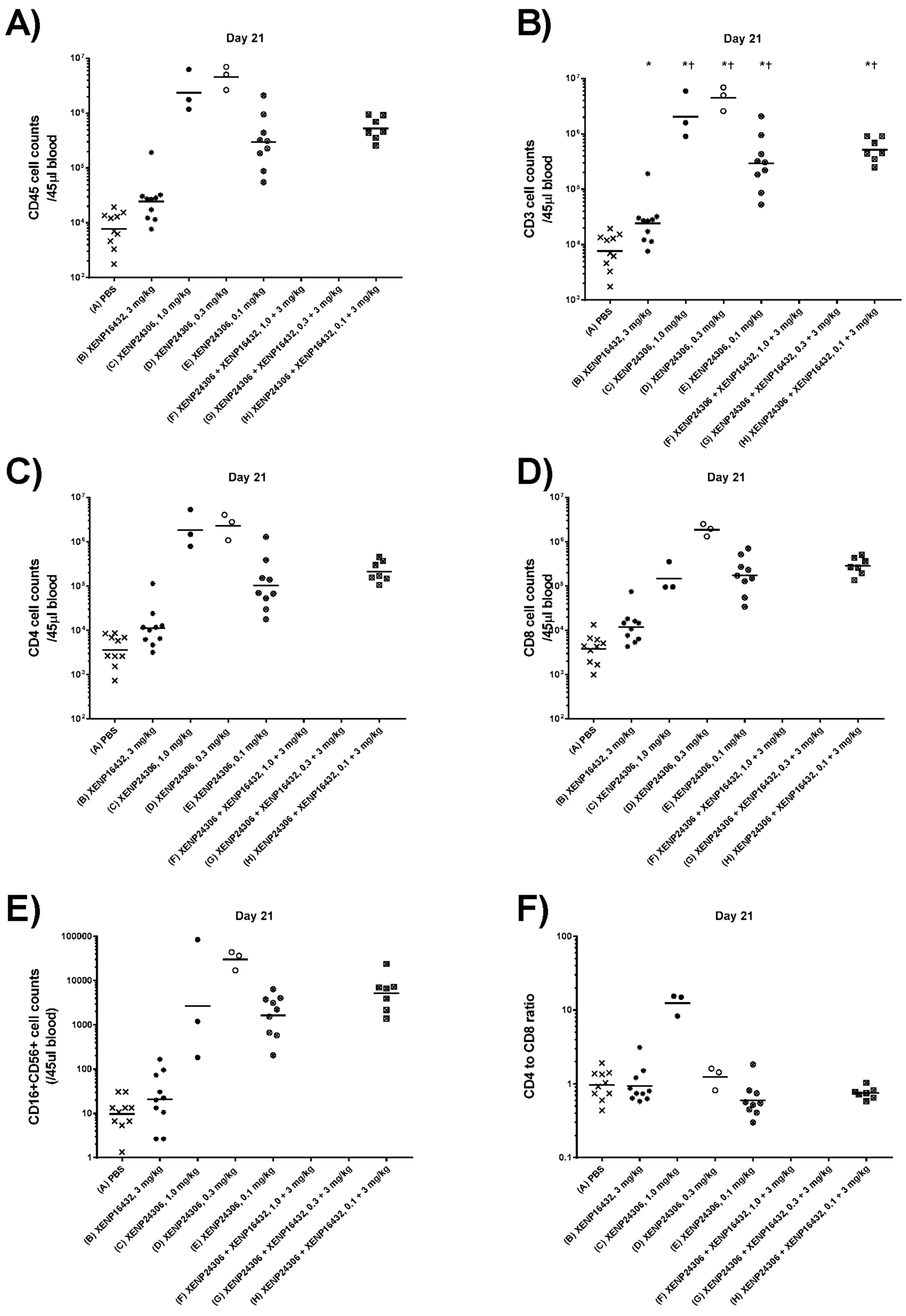


Figure 212A-Figure 212D

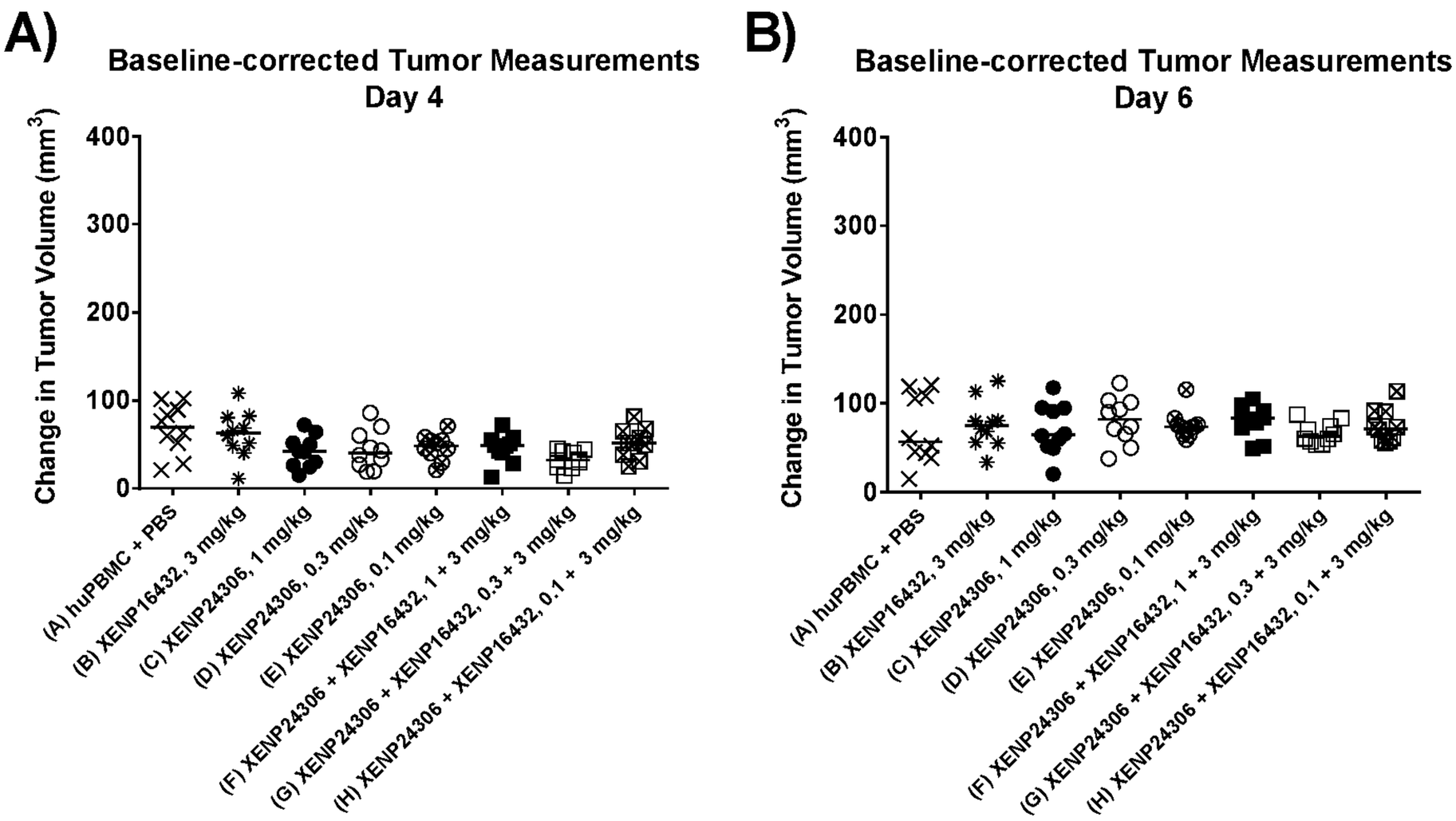
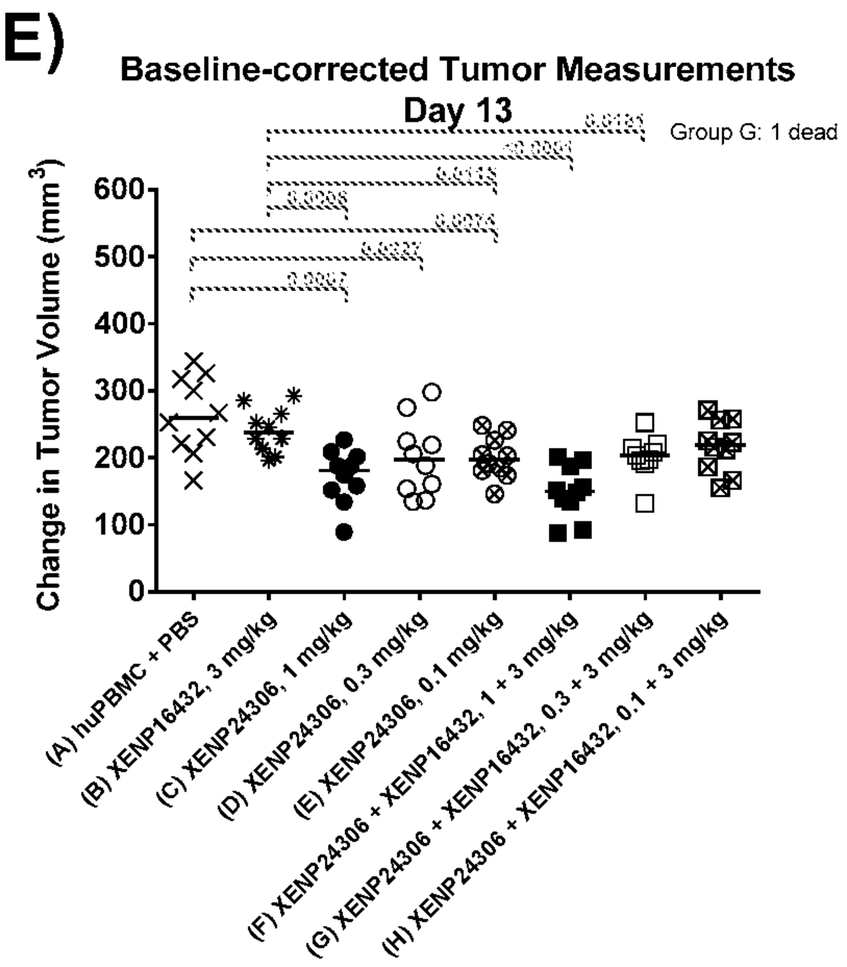
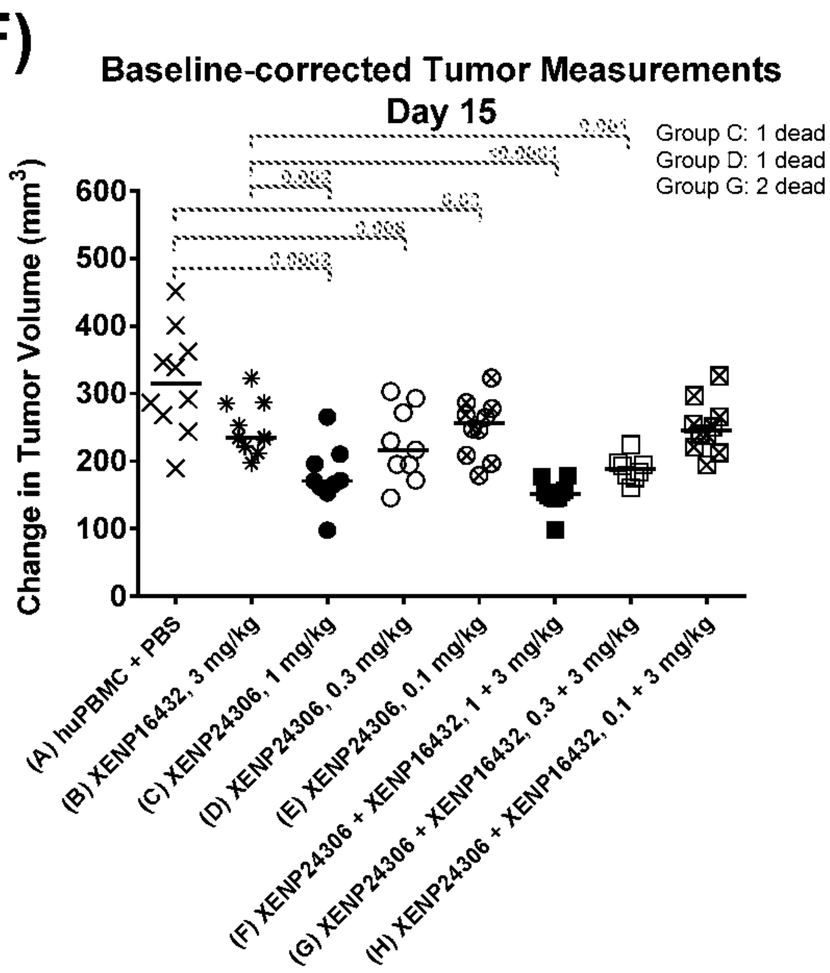
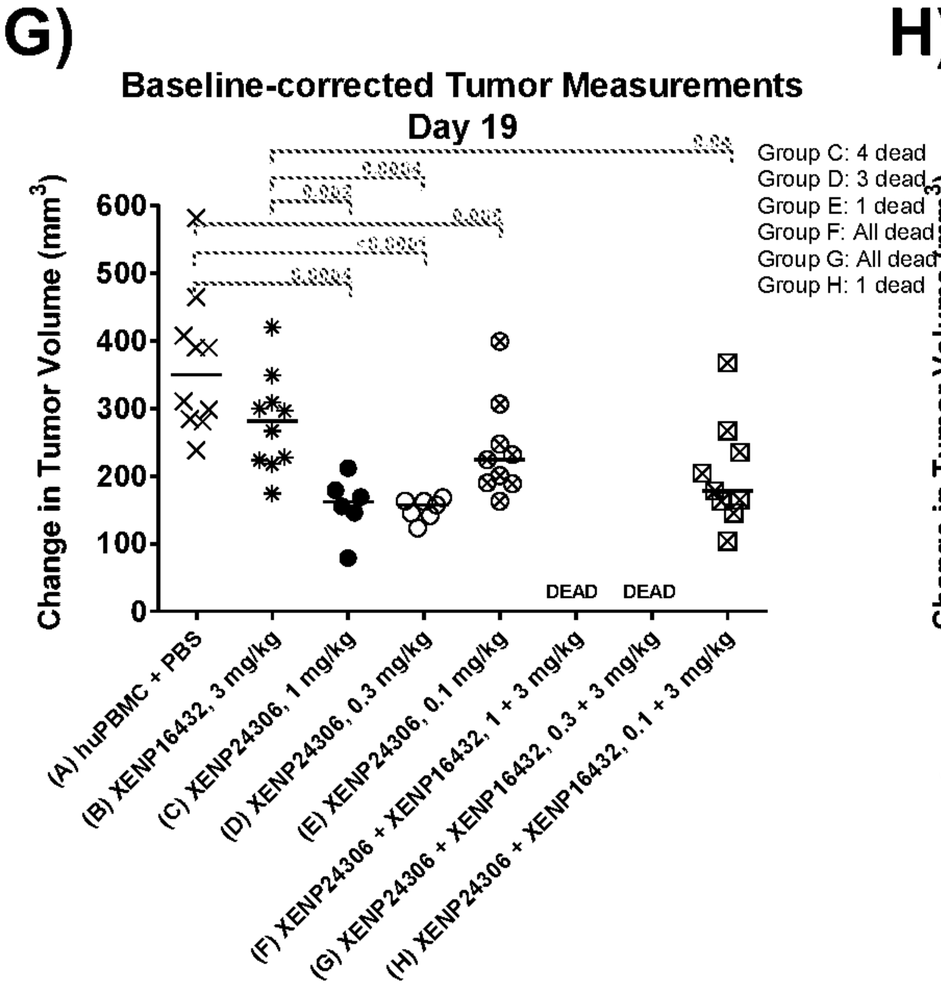


Figure 212E-Figure 212H







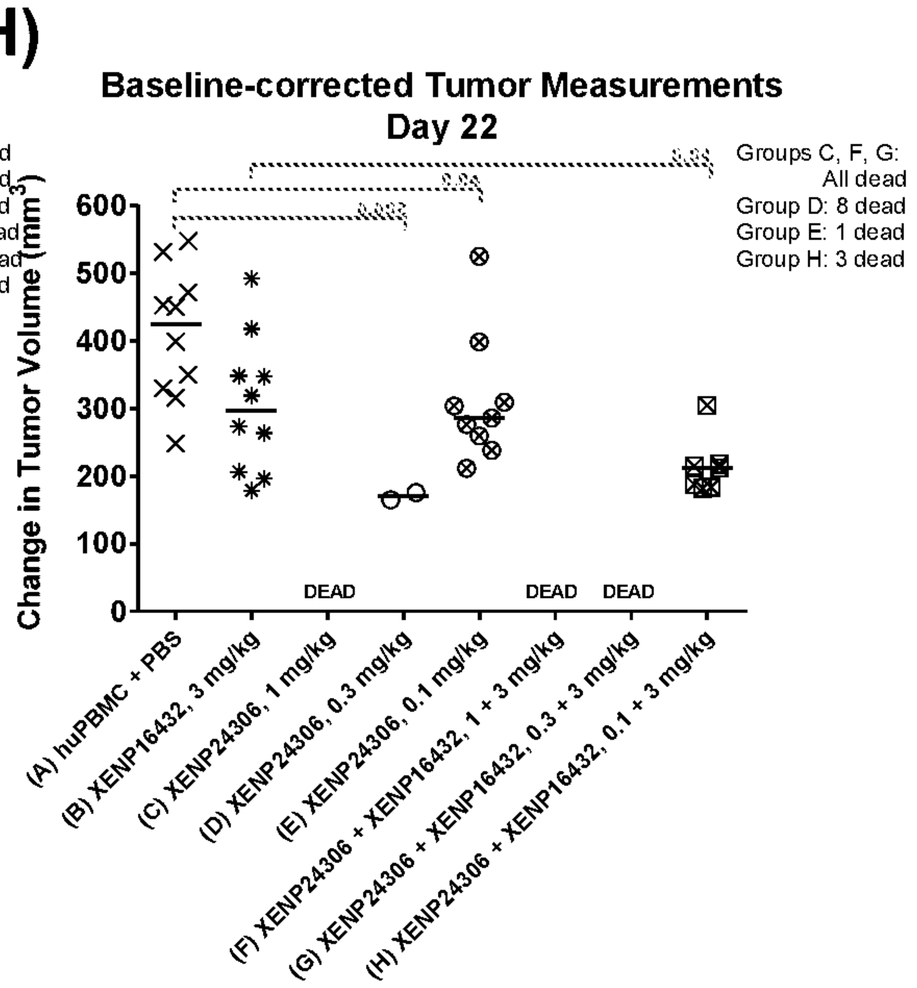


Figure 212I

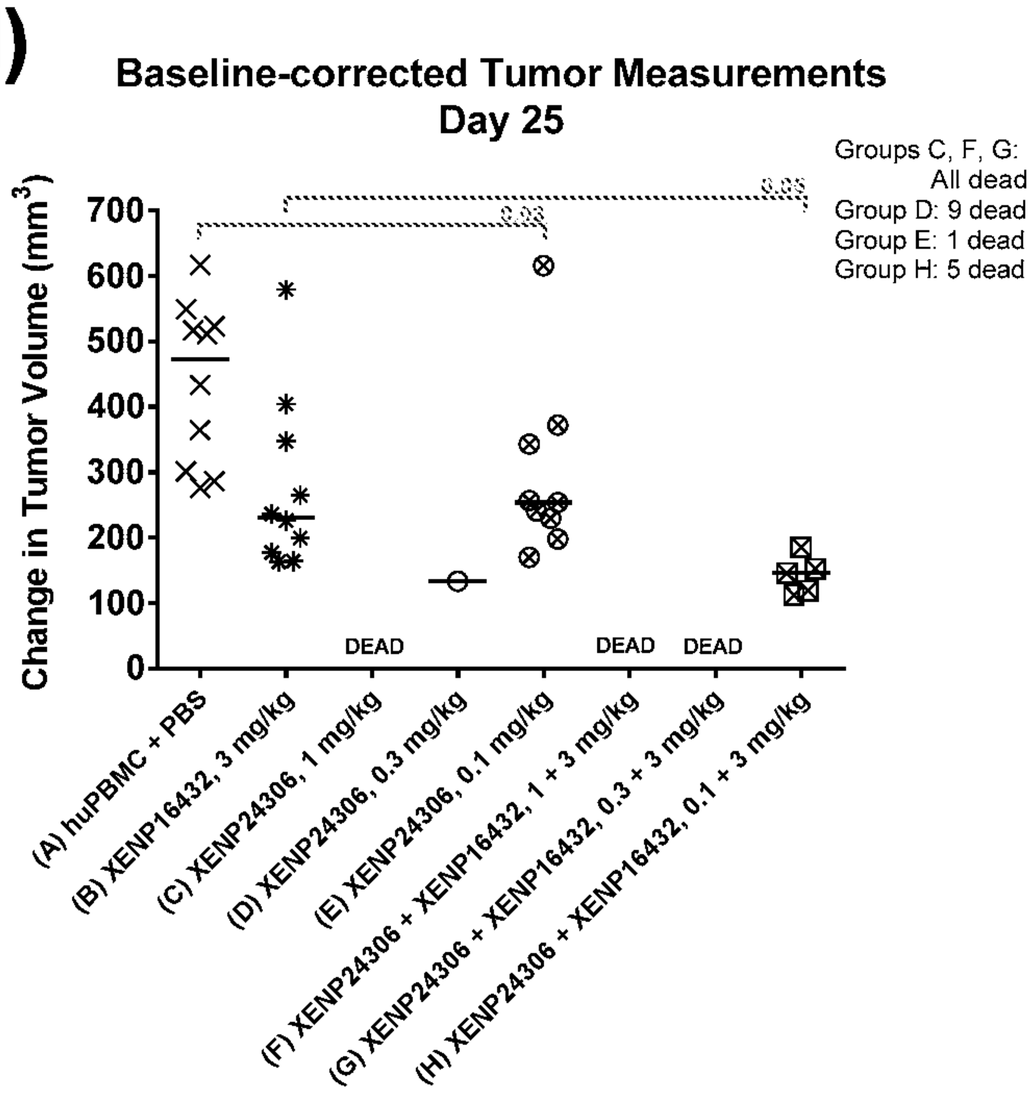

I)
Baseline-corrected Tumor Measurements
Day 25
Groups C, F, G:
All dead
Group D: 9 dead
Group E: 1 dead
Group H: 5 dead
0.05
0.05
Change in Tumor Volume (mm3)
700
600
500
400
300
200
100
0
DEAD
DEAD
DEAD
(A) huPBMC + PBS
(B) XENP16432, 3 mg/kg
(C) XENP24306, 1 mg/kg
(D) XENP24306, 0.3 mg/kg
(E) XENP24306, 0.1 mg/kg
(F) XENP24306 + XENP16432, 1 + 3 mg/kg
(G) XENP24306 + XENP16432, 0.3 + 3 mg/kg
(H) XENP24306 + XENP16432, 0.1 + 3 mg/kg

Figure 213A-213B

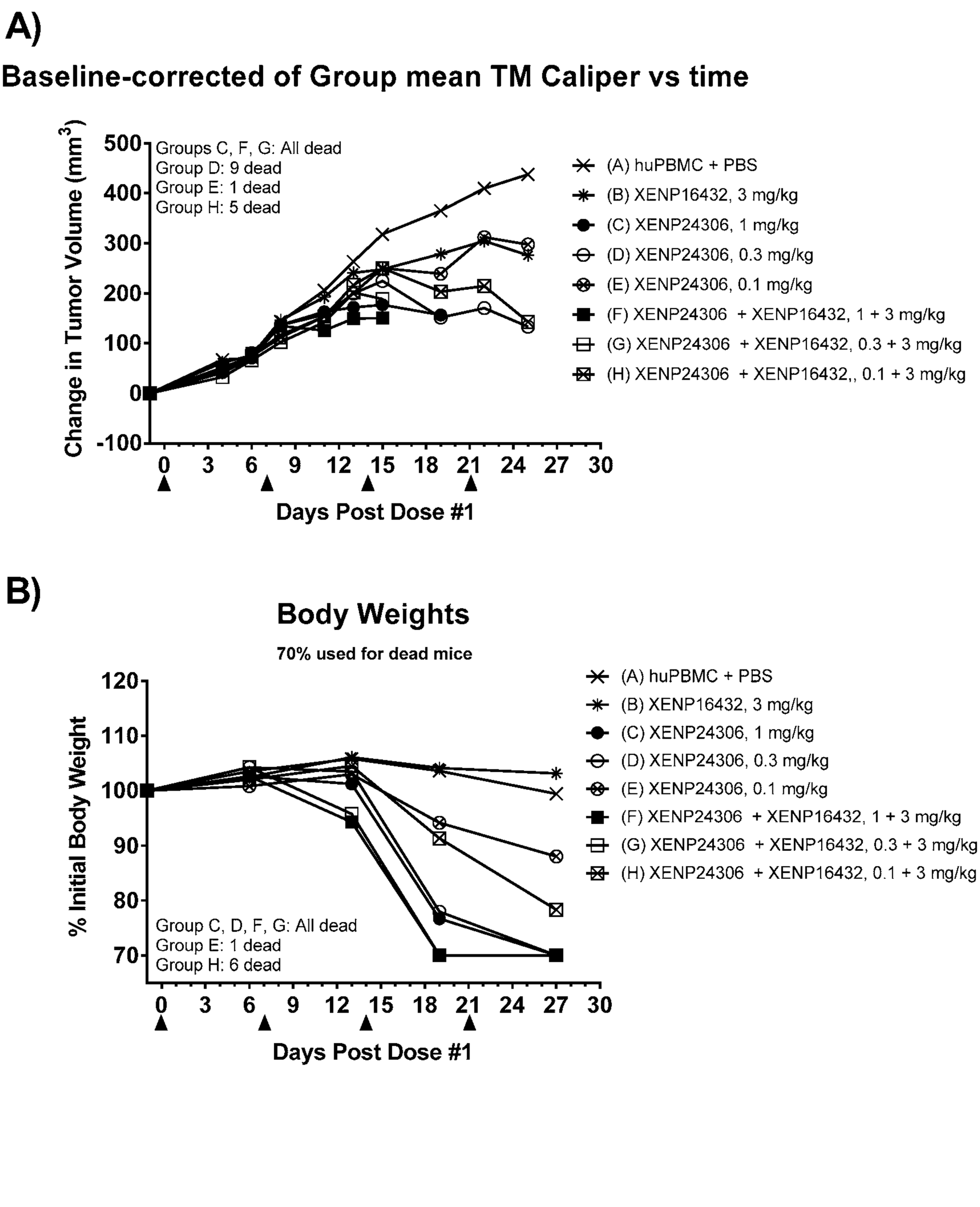


Figure 214A-214C

