

FIGURE 1A**Heavy Chain**Variable region shown **in bold**

CDRs highlighted in yellow

Affinity maturation mutated residues underlinedFc mutations (E→R and K→A) shown in red

10	20	30	40	50	60
EVQLQESGPG	LVKPSETLSL	TCTVSGDSIT	NGFWIWIRKP	PGNKLEYMGY	ISYSGSTYYN
70	80	90	100	110	120
PSLKSRISIS	RDTSKNQFSL	KLSSVTAADT	GVYYCAYRSY	GRTPIYYFDYW	GQGTTTLTVSS
130	140	150	160	170	180
ASTKGPSVFP	LAPSSKSTSG	GTAALGCLVK	DYFPEPVTVS	WNSGALTSGV	HTFPAVLQSS
190	200	210	220	230	240
GLYSLSSVVT	VPSSSLGTQT	YICNVNHKPS	NTKVDKKAEP	KSCDKTHTCP	PCPAPELLGG
250	260	270	280	290	300
PSVFLFPPKP	KDTLMISRTP	EVTCVVVDVS	HSDPEVKFNW	YVDGVEVHNA	KTKPREEQYN
310	320	330	340	350	360
STYRVVSVLT	VLHQDWLNGK	EYKCAVSNKA	LPAPIEKTIS	KAKGQPREPQ	VYTLPPSRDE
370	380	390	400	410	420
LTKNQVSLTC	LVKGFYPSDI	AVEWESNGQP	ENNYKTTPPV	LDSDGSFFLY	SKLTVDKSRW
430	440	450			
QQGNVFSCSV	MHEALHNHYT	QKSLSLSPGK			

FIGURE 1B

Light Chain

Variable region shown **in bold**

CDRs highlighted in yellow

Affinity maturation mutated residues underlined

10	20	30	40	50	60
DIVMTQSPSF	LSASVGDRV	ITCKASSNLG	HAWAYQQKP	GKSPKLLIYS	ASNRYTGVPD
70	80	90	100	110	120
RFSGSGSGTD	FTLTISSLQP	EDFADYFCQQ	YDDYPYTFGG	GTKLEIKRTV	AAPSVFIFPP
130	140	150	160	170	180
SDEQLKSGTA	SVVCLLNNFY	PREAKVQWKV	DNALQSGNSQ	ESVTEQDSKD	STYSLSSTLT
190	200	210			
LSKADYEKHK	VYACEVTHQG	LSSPVTKSFN	RGEC		

FIGURE 1C

INX021 Sequences

Variable Heavy (SEQ ID NO. 1)

EVQLQESGPGGLVKPSETLSLTCTVSGDSITNGFWIWIRKPPGNKLEYMGYISYSGSTYYNPSLKSRISSR
DTSKNQFSLKLSSVTAADTGVYYCAYRSYGRTPYFFDYWGQGTTLTVSS

Variable Light (SEQ ID NO. 2)

DIVMTQSPSFLSASVGDRVTITCKASSNLGHAVAWYQQKPGKSPKLLIYSASNRYTGVPDRFSGSGSGTD
TLTISSLQPEDFADYFCQQYDDYPYTFGGGTKLEIK

Constant Heavy (SEQ ID NO. 3)

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV
PSSSLGTQTYICNVNHKPSNTKVDKKAEPKSCDKHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV
TCVVDVSHRDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPA
PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSD
GSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

Constant Light (SEQ ID NO. 4)

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLSST
LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

INX021 Variable Heavy CDR1 (SEQ ID NO: 5)

GDSITNGFWI

INX021 Variable Heavy CDR2 (SEQ ID NO: 6)

YISYSGSTY

INX021 Variable Heavy CDR3 (SEQ ID NO: 7)

YRSYGRTPYYFDY

INX021 Variable Light CDR1 (SEQ ID NO: 8)

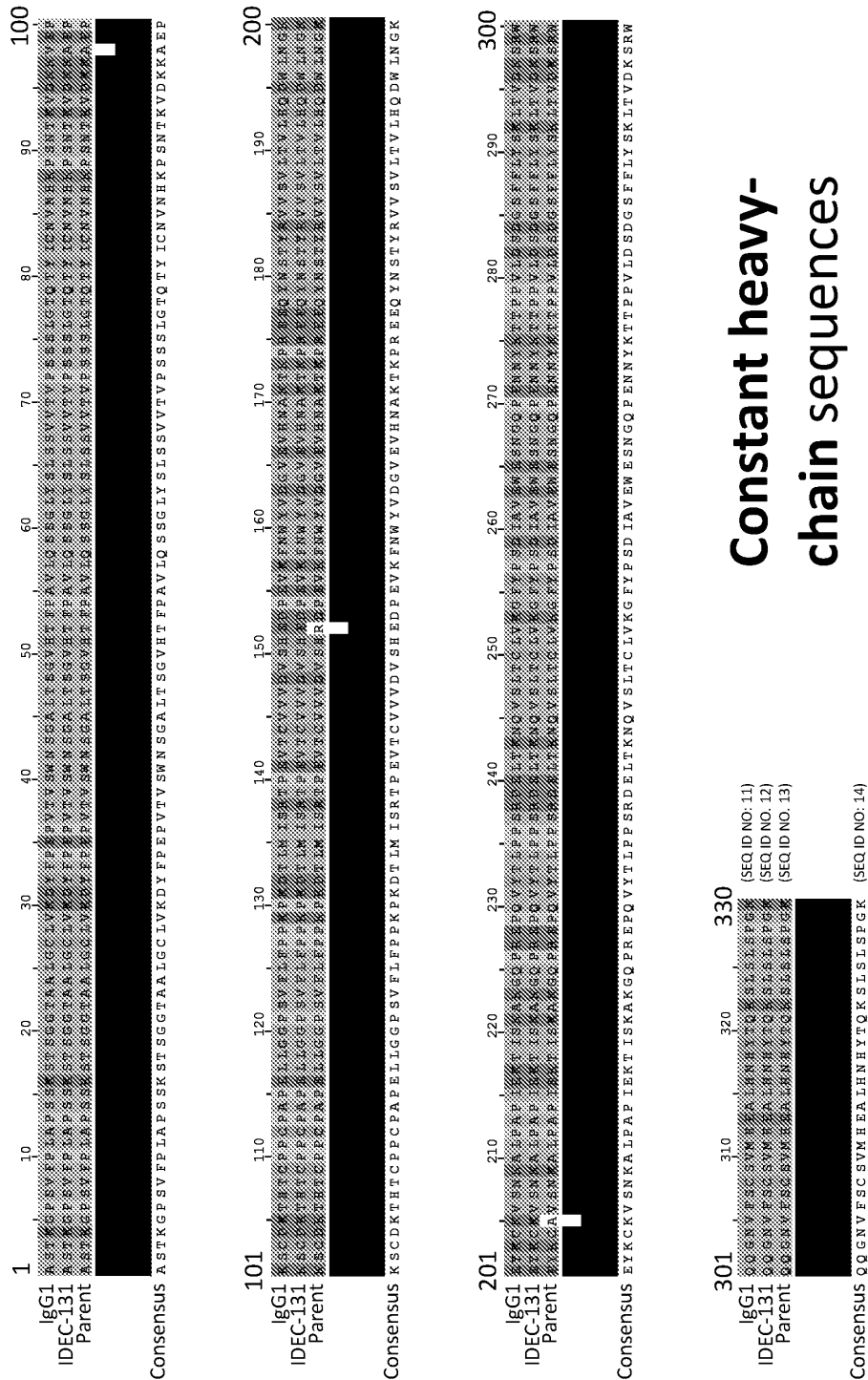
KASSNLGHAVA

INX021 Variable Light CDR2 (SEQ ID NO: 9)

SASNRYT

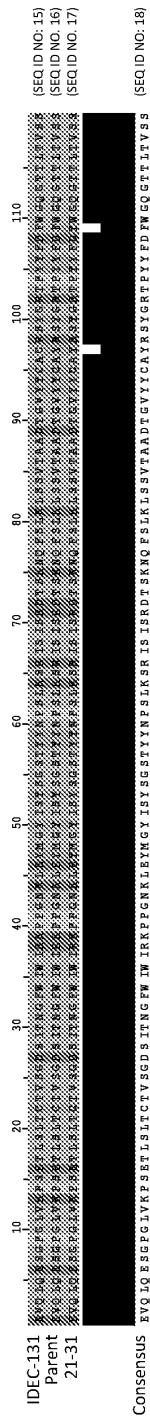
INX021 Variable Light CDR3 (SEQ ID NO: 10)

QQYDDYPYT



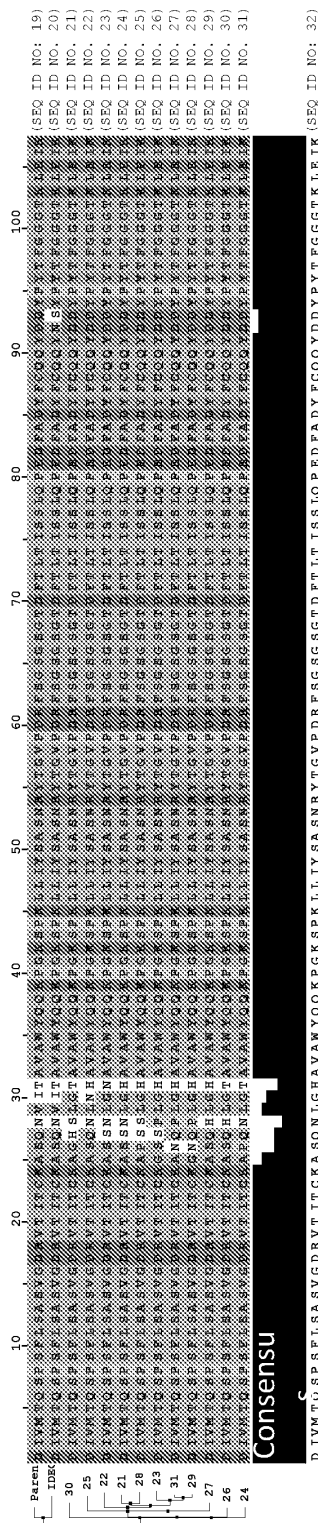
Constant heavy-
chain sequences

FIG. 2A



Variable heavy-
chain sequences

FIG. 2B



Improved potency: using IDEC epitope

FIG. 3

INX021 shows better binding to CD40L on T cells

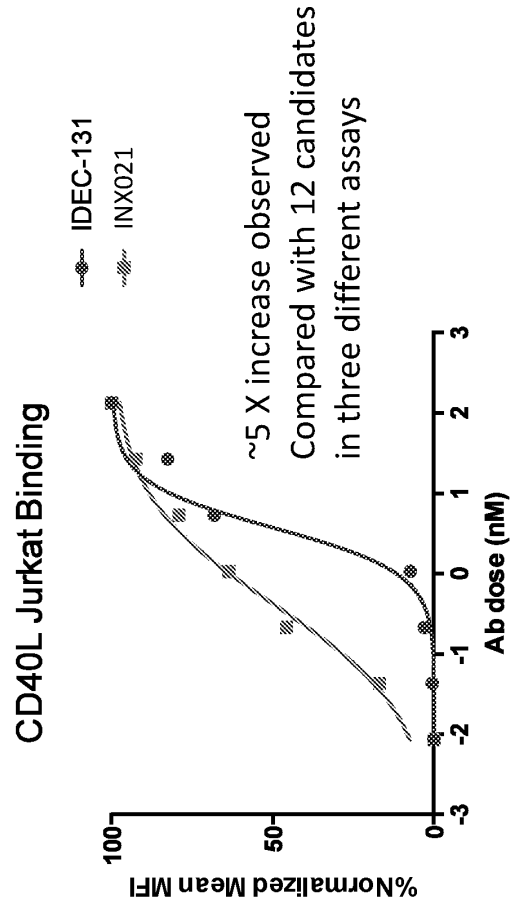
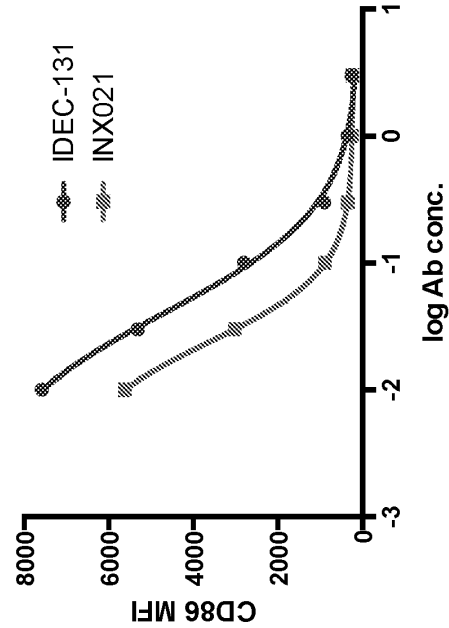


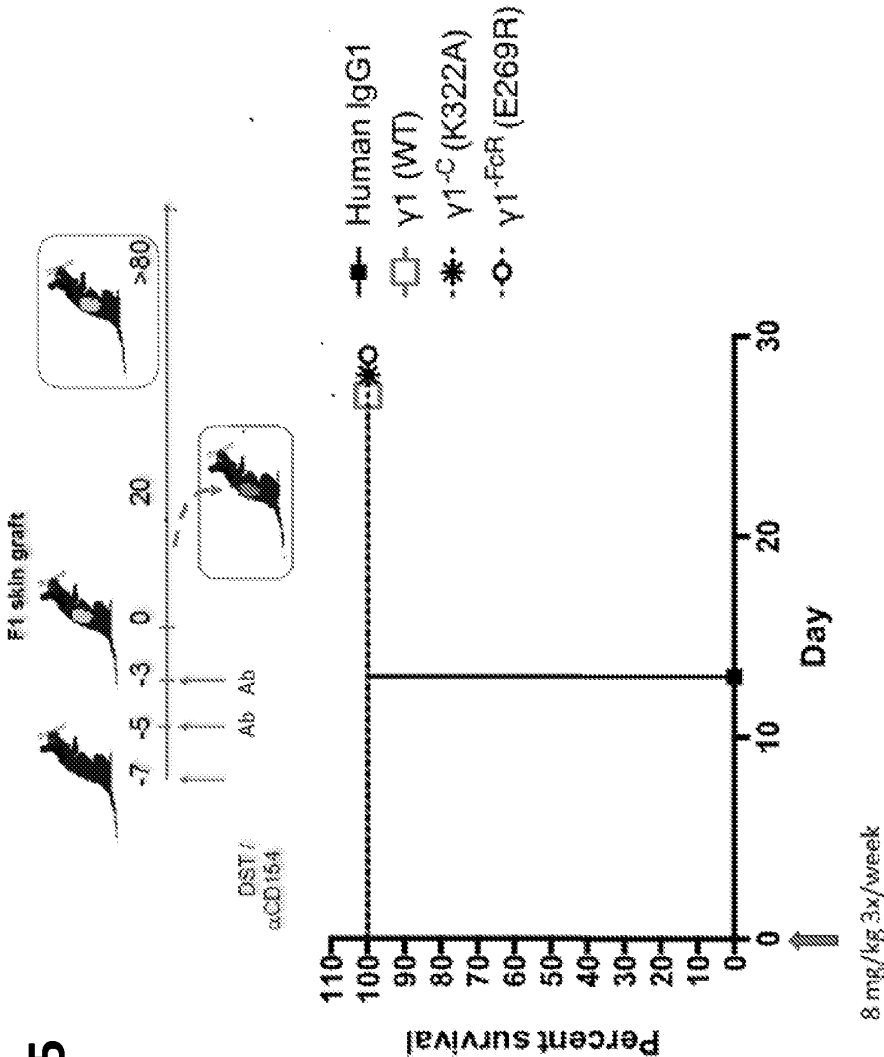
FIG. 4

INX021 shows more potent inhibition of T cell CD40L-driven B cell activation

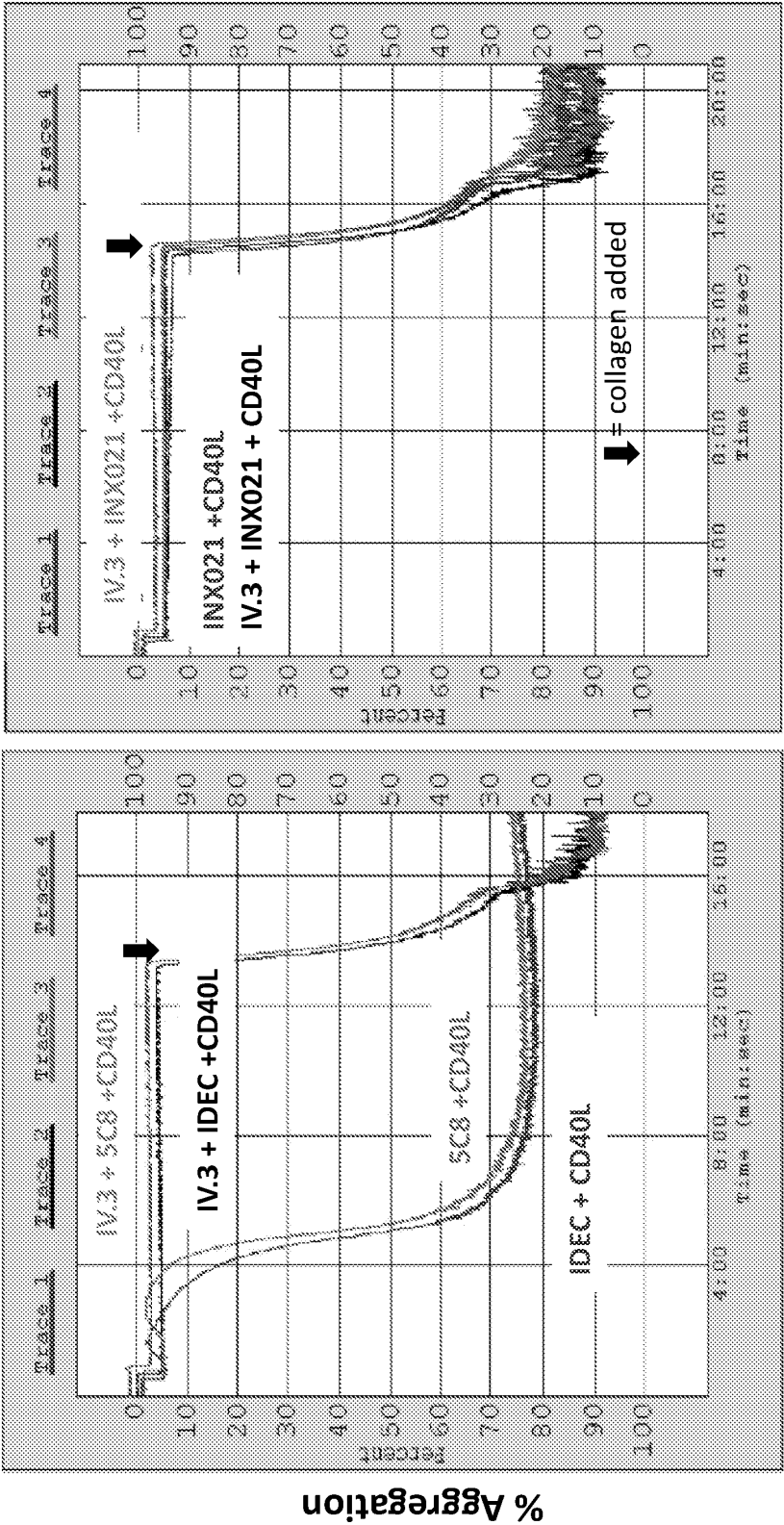


FcR mutants of hlgG anti-mCD40L induce tolerance

FIG. 5



FcR mutants of hIgG1 anti-CD40L do not induce platelet aggregation

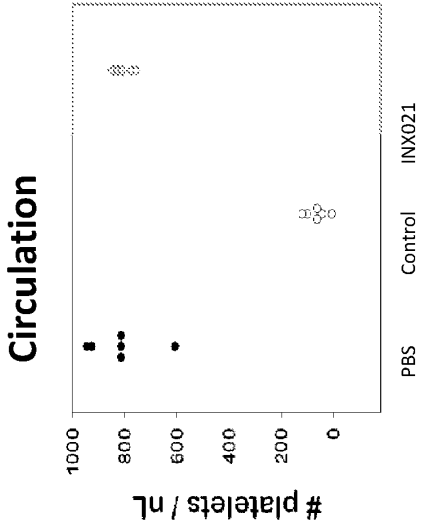
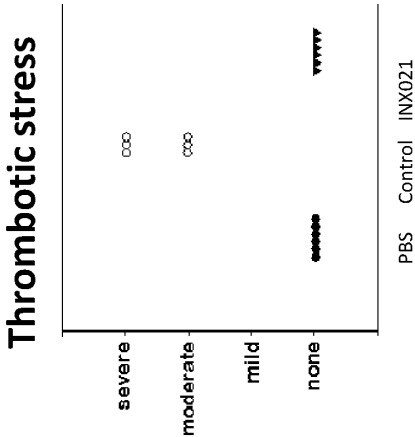


Immune Complexes of FcR mutants did not induce isolated mouse and human platelet activation in vitro.

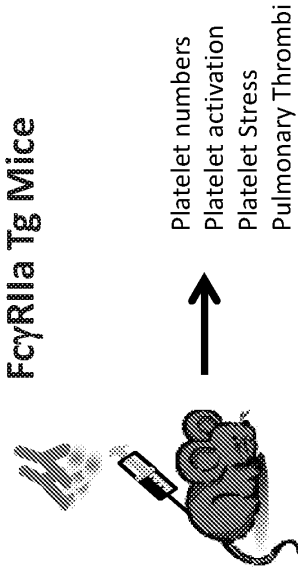
FIG. 6

Lack of platelet activities by FcR mutants of hlgG1 anti-huCD40L in vivo

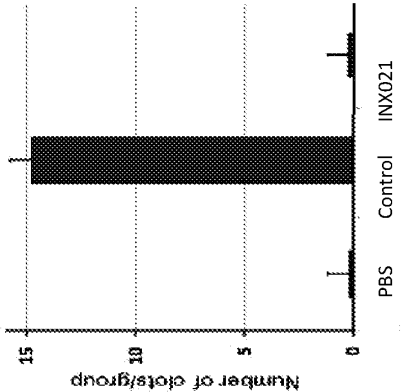
FcR mutants did not induce thrombotic stress, reduced platelet number, or clots in the lung.



Immune complex induced thrombocytopenia model:



Emboli



Activity of FcR/C1q mutant anti-mCD40L abs

FcR/C1q-binding mutants are still active in models of interest such as EAE, tolerance and immune response to MOG.

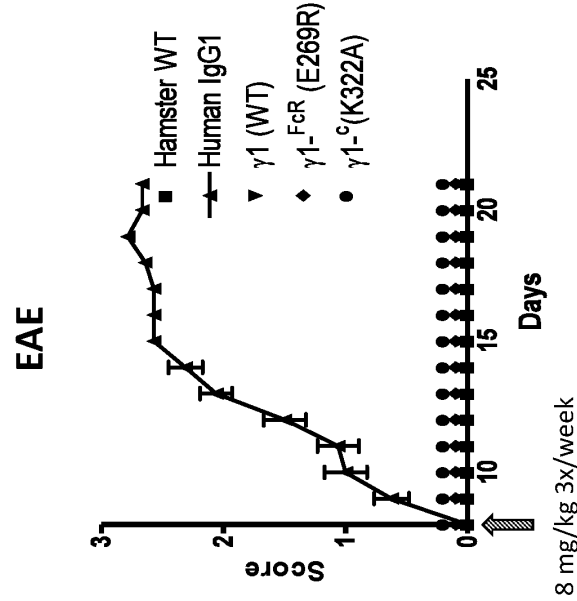


FIG. 8A

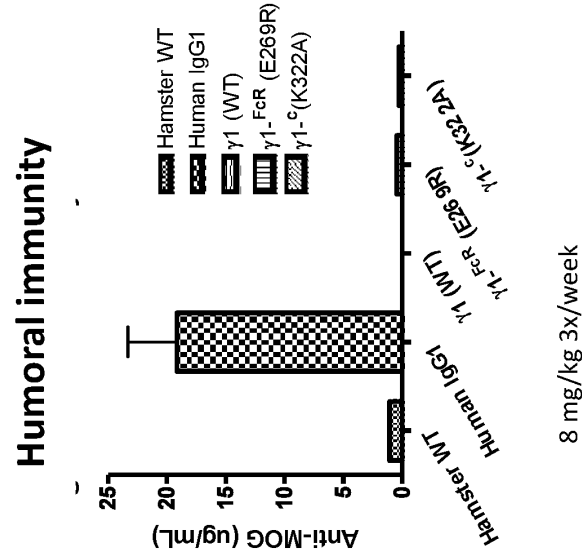


FIG. 8B

FIG. 9

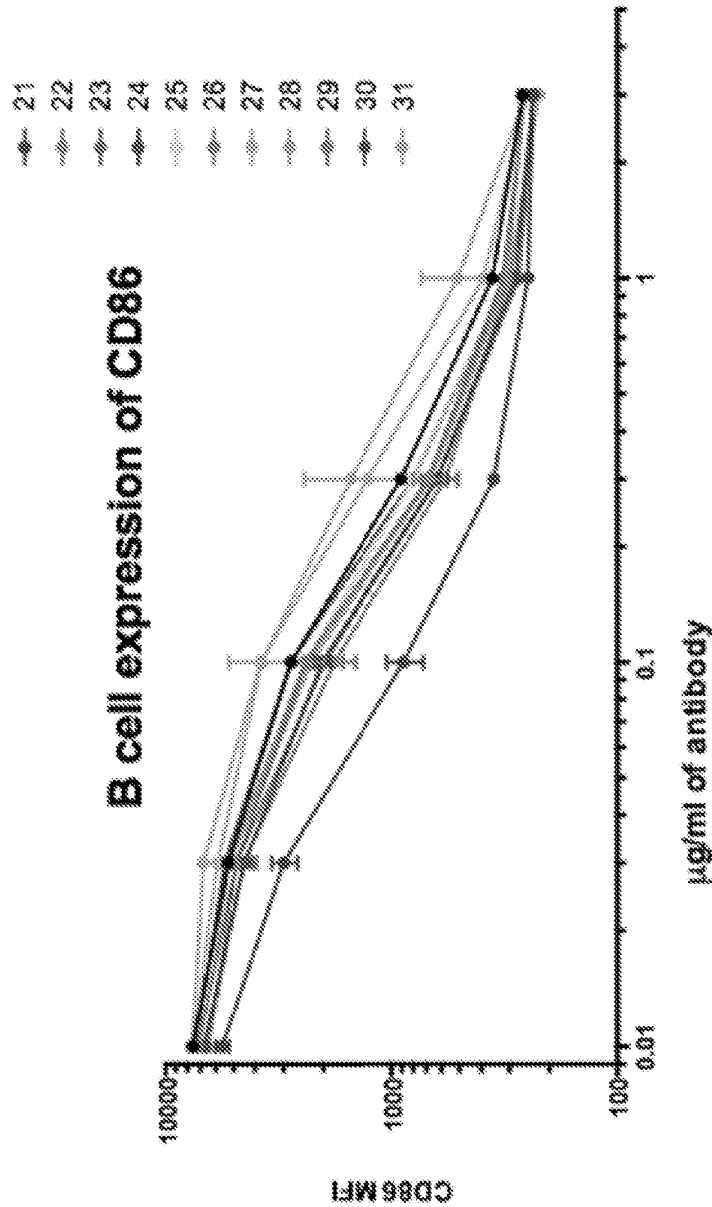


FIGURE 10A

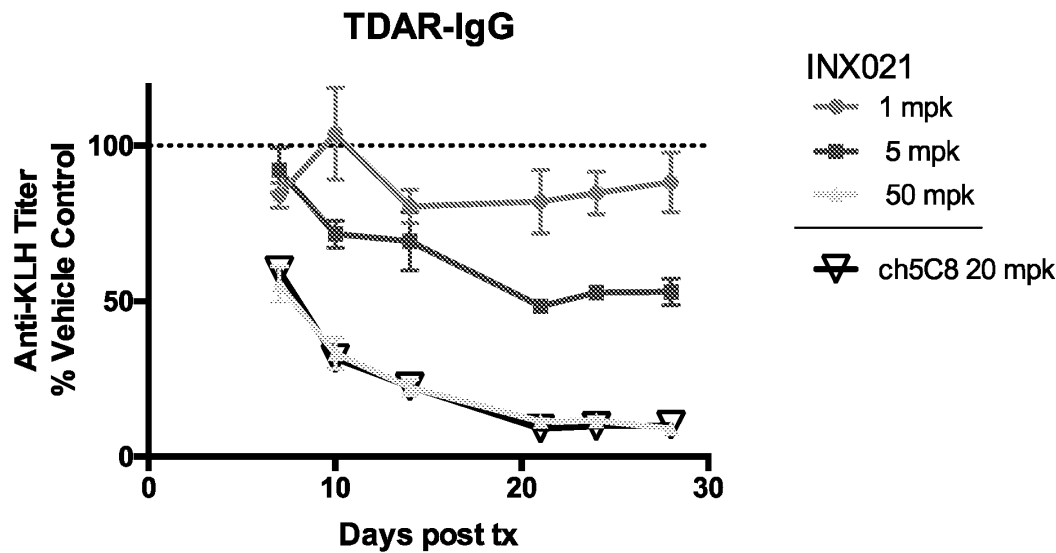
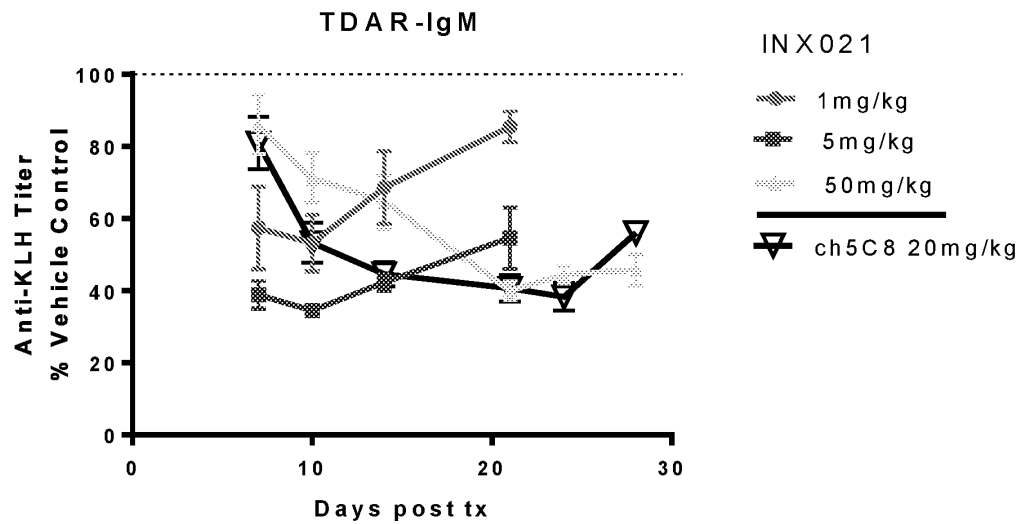
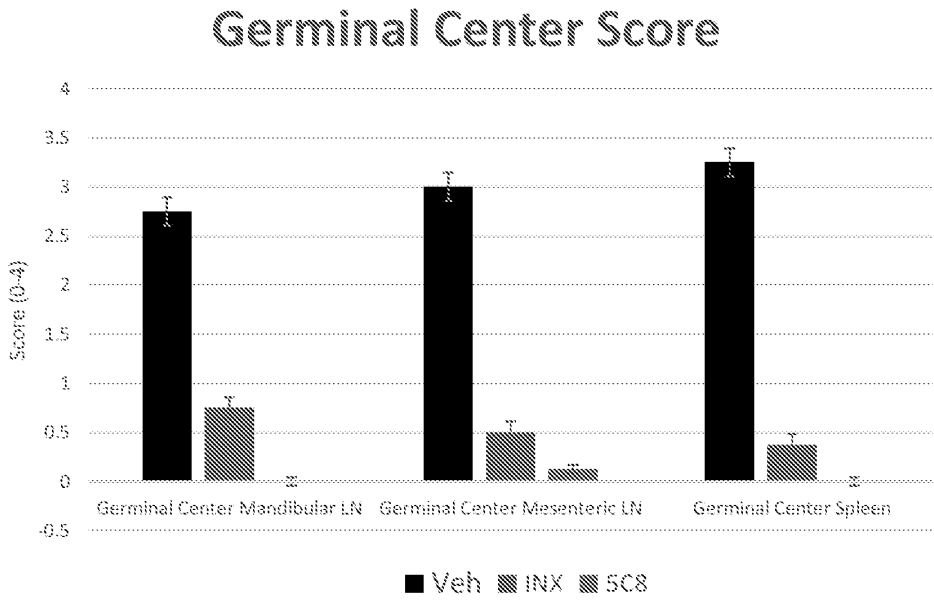


FIGURE 10B



TDAR results: IgG TDAR (TOP) compared with saline controls (dotted line). IgM TDAR (bottom) compared with saline controls (dotted line).

FIGURE 11A



Germinal Center scores (above): Number and degree of cellularity of the germinal centers in spleen and LN of treated animals.

FIGURE 11B

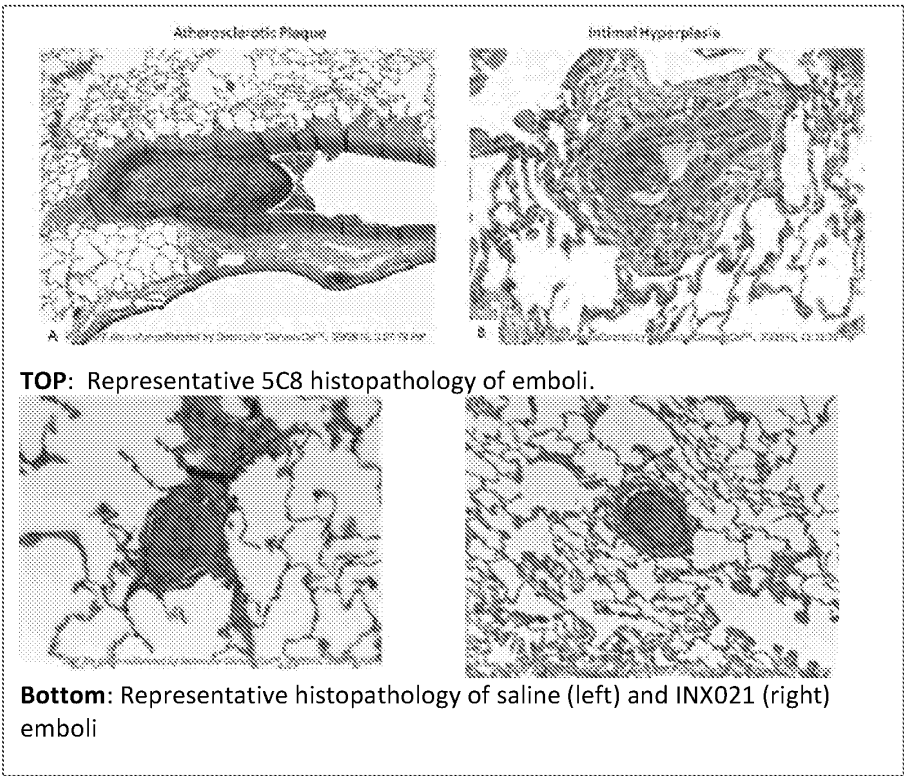


FIGURE 12

Summary of lesion frequency compared with published UCB emboli data:

(CDP7657, an anti-CD40L antibody lacking an Fc domain, inhibits CD40L-dependent immune responses without thrombotic complications: an in vivo study Arthritis Res Ther. 2015; 17(1): 234.)

	Dose Group	Animals affected (%)	Total lung sections examined	Lung sections affected (%)
Historic Controls				
	Saline	7 (50%)	406	2.5%
Biogen/UCB Pegylated Fab				
	Saline	1 (25%)	116	0.9%
	Peg-Fab CDP765	3 (37.5%)	203	2.0%
	Aglycosyl 5C8	3 (37.5%)	232	1.3%
	hu5C8	5 (62.5%)	232	17.6%
ImmuNext INX021				
	Vehicle	2 (50%)	174	1.7%
	INX021	3 (37.5%)	232	3.4%
	ch5C8	6 (75%)	232	3.8%