Figure 1

Variable region sequences of parent mouse mAb LFU720

LFU720 Heavy Chain Variable Region

EVQLQQSGAELMKPGASVKLSCTASGFNIK**DMYMS**WVRQRPEQGLEWIG**RIDPAN**
GHTNYDPKFQAKATITTDTSSKTAYLHLSSLTSEDTAVYYCAR**SYYYYAMDY**WGQ
GTSVTVSS

LFU720 Light (kappa) Chain Variable Region

QIVLTQSPAIMSASPGEKVTMTC**SASSSVSYMH**WYQQKPGSSPRLWIY**LTFNLA**
SGVPARFSGSGSGTSYSLSISSMEAEDAATYYC**LQWSSDPPT**FGSGTKLEIK

Figure 2

Variable region sequences of Ab NVP-LGT209

pJG04 (Vh) +pJG10 (Vk)

pJG04 Vh

QVQLVQSGAEVKKPGASVKVSCKASGYTFS**TMYMS**WVRQAPGQGLEWMG**RIDPA**
NEHTNYAQKFQGRVTMTRDTSISTAYMELSRLTSDDTAVYYCAR**SYYYYNMDY**W
GQGTLVTVSS

pJG10 Vk

QIVLTQSPATLSVSPGERATLSC**RASQSVSYMH**WYQQKPGQAPRLLIY**GVFRRAT**GI
PDRFSGSGSGTDFTLTIGRLEPEDFAVYYC**LQWSSDPPT**FGQGTKLEIK

Figure 3

Variable region sequences of Ab NVP-LGT210

pJG04 (Vh) +pJG01 (Vk)

pJG04 Vh

QVQLVQSGAEVKKPGASVKVSCKASGYTFS**TMYMS**WVRQAPGQGLEWMG**RIDPA**
NEHTNYAQKFQGRVTMTRDTSISTAYMELSRLTSDDTAVYYCAR**SYYYYNMDY**W
GQGTLVTVSS

pJG01 Vk

EIVMTQSPATLSVSPGERATLSC**RASQSVSYMH**WYQQKPGQAPRLLIY**GVFRRAT**G
IPDRFSGSGSGTDFTLTIGRLEPEDFAVYYC**LQWSSDPPT**FGQGTKLEIK

Figure 4

Variable region sequences of Ab NVP-LGT211

pSR74 (Vh) +pJG10 (Vk)

pSR074 Vh

QVQLVQSGAEVKKPGASVKVSCKASGYTFS**TMYMS**WVRQAPGQGLEWMG**RIDPA**
NEHTNYAQKFQGRVTMTRDTSISTAYMELSRLTSDDTAVYYCAR**SYYYYAMDY**W
GQGTLVTVSS

pJG10 Vk

QIVLTQSPATLSVSPGERATLSC**RASQSVSYMH**WYQQKPGQAPRLLIY**GVFRRAT**GI
PDRFSGSGSGTDFTLTIGRLEPEDFAVYYC**LQWSSDPPT**FGQGTKLEIK

Figure 5A

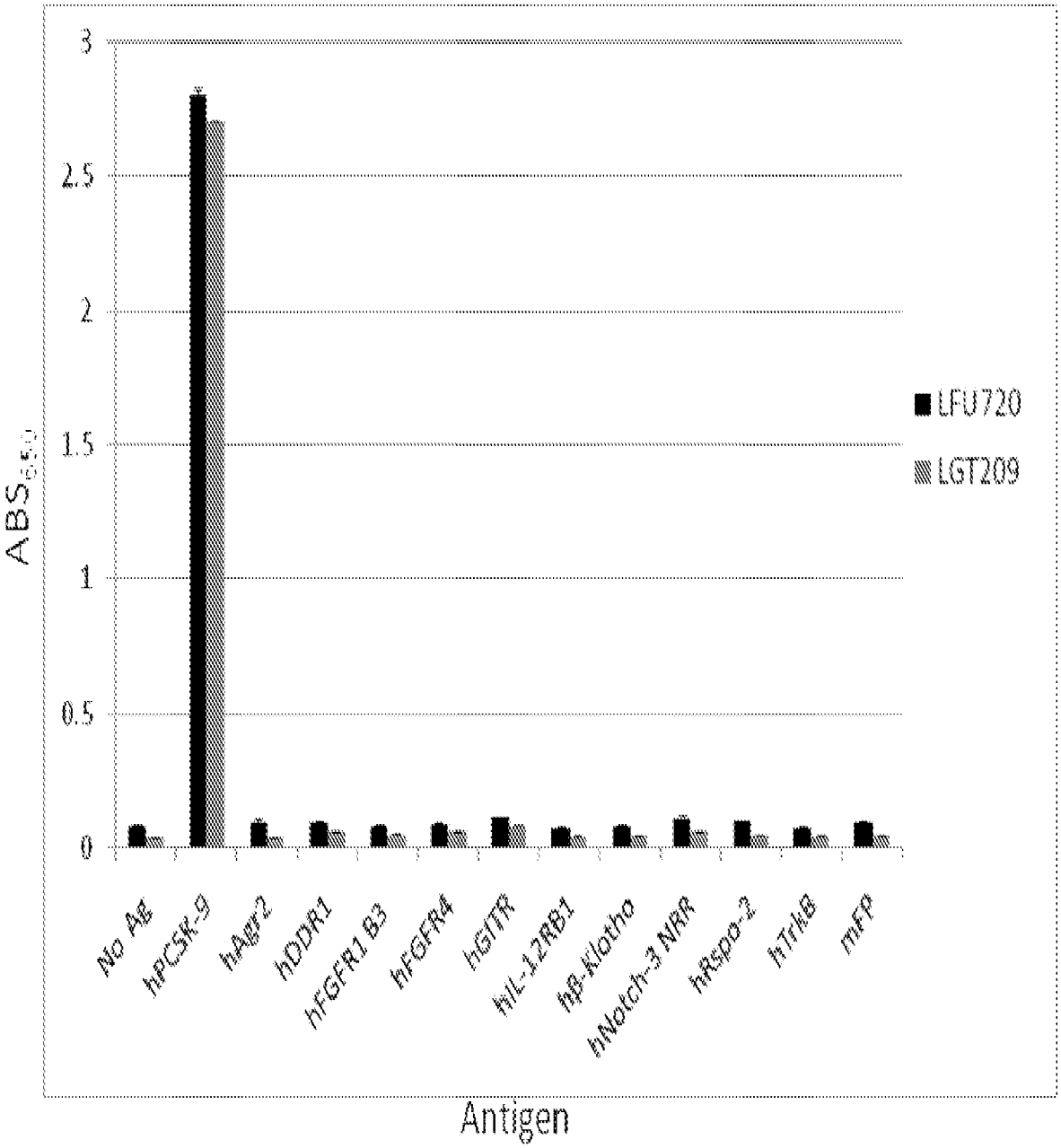

3
2.5
2
1.5
1
0.5
0
ABS450
LFU720
LGT209
No AG
hPCSK-9
hAgr2
hDDR1
hFGFR1 B3
hFGFR4
hGITR
hIL-12RB1
hβ-Klotho
hNotch-3 NRR
hRspo-2
hTrkB
mFP
Antigen

Figure 5B

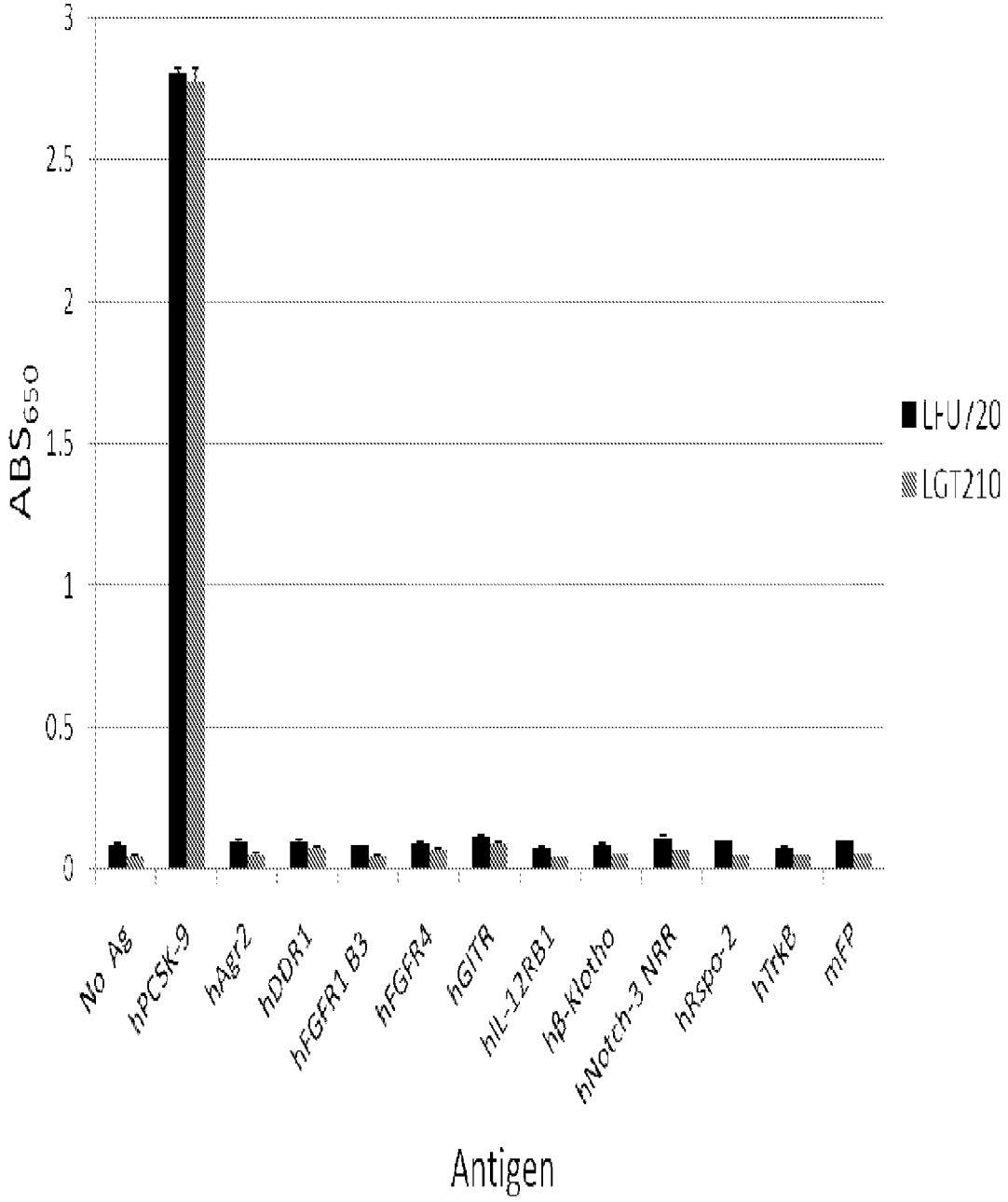

3
2.5
2
1.5
1
0.5
0
ABS650
LFU/20
LGT210
No Ag
hPCSK-9
hAgT2
hDDR1
hFGFR1 B3
hFGFR4
hGITR
hIL-12RB1
hβ-Klotho
hNotch-3 NRR
hRspo-2
hTrkB
mFP
Antigen

Figure 5C

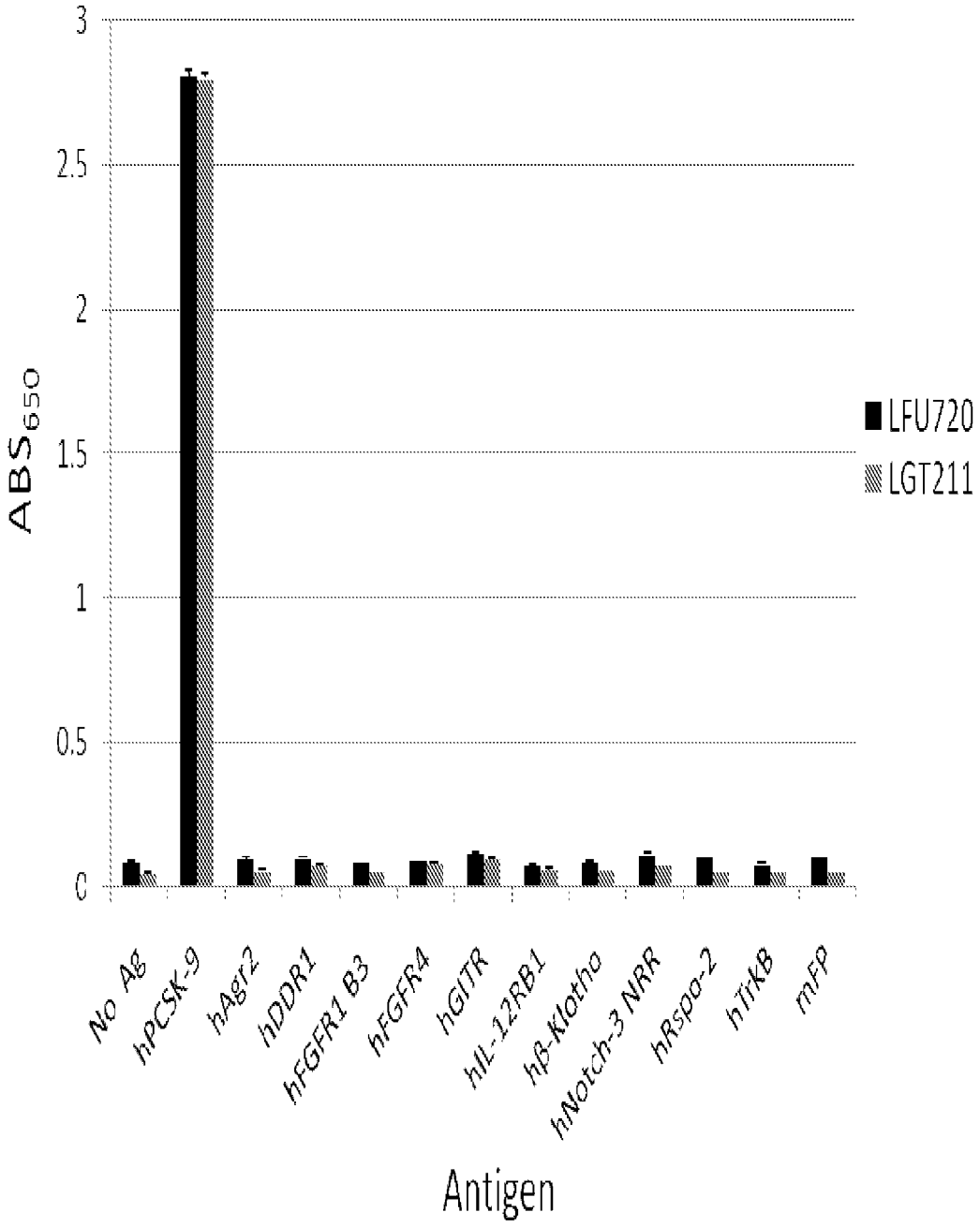

3
2.5
2
1.5
1
0.5
0
ABS650
LFU720
LGT211
No Ag
hPCSK-9
hAgr2
hDDR1
hFGFR1 B3
hFGFR4
hGITR
hIL-12RB1
hβ-Klotho
hNotch-3 NRR
hRspo-2
hTrkB
mFp
Antigen

Figure 6A

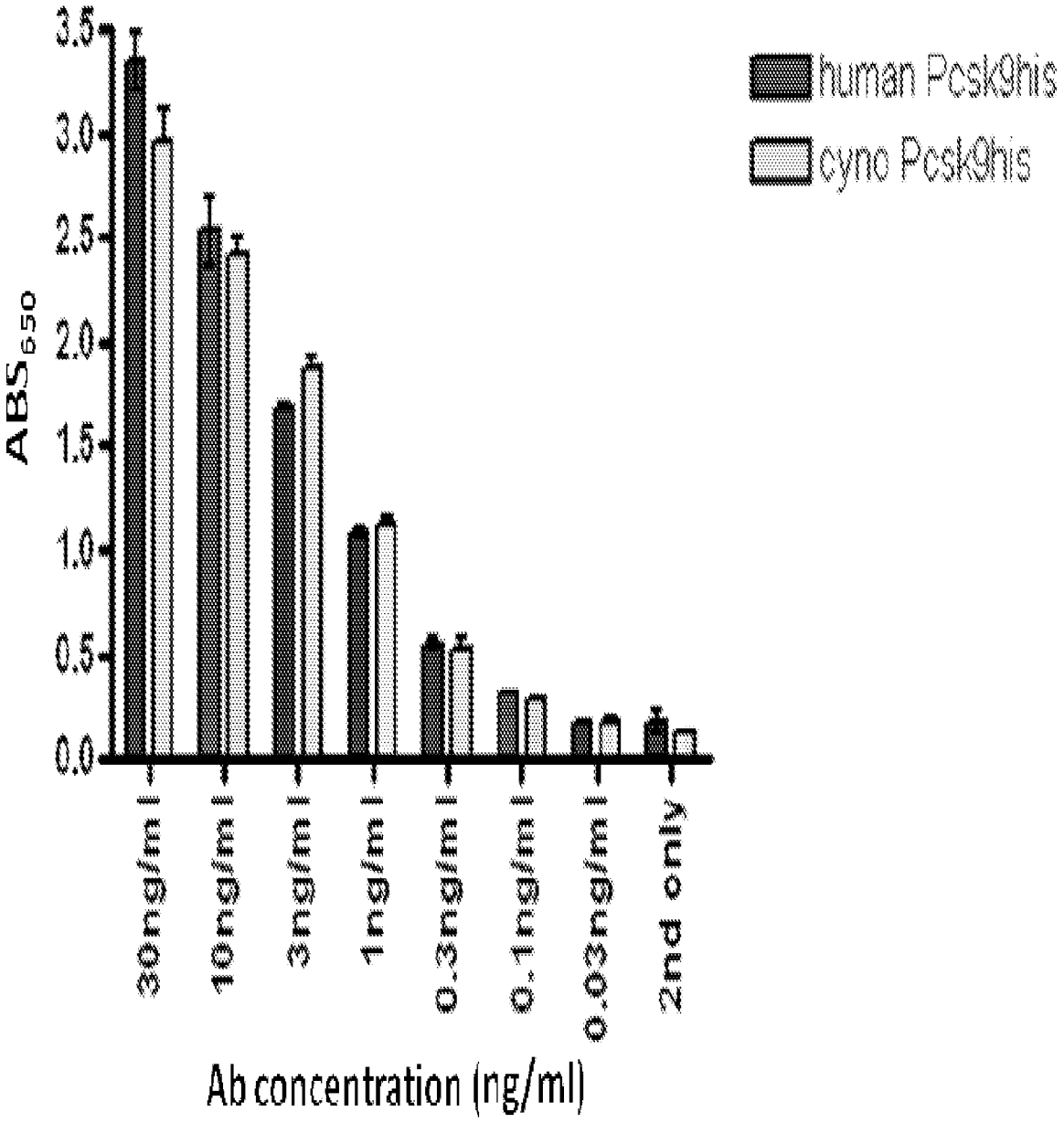

human Pcsk9his
cyno Pcsk9his
ABS650
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
30ng/ml
10ng/ml
3ng/ml
1ng/ml
0.3ng/ml
0.1ng/ml
0.03ng/ml
2nd only
Ab concentration (ng/ml)

Figure 6B

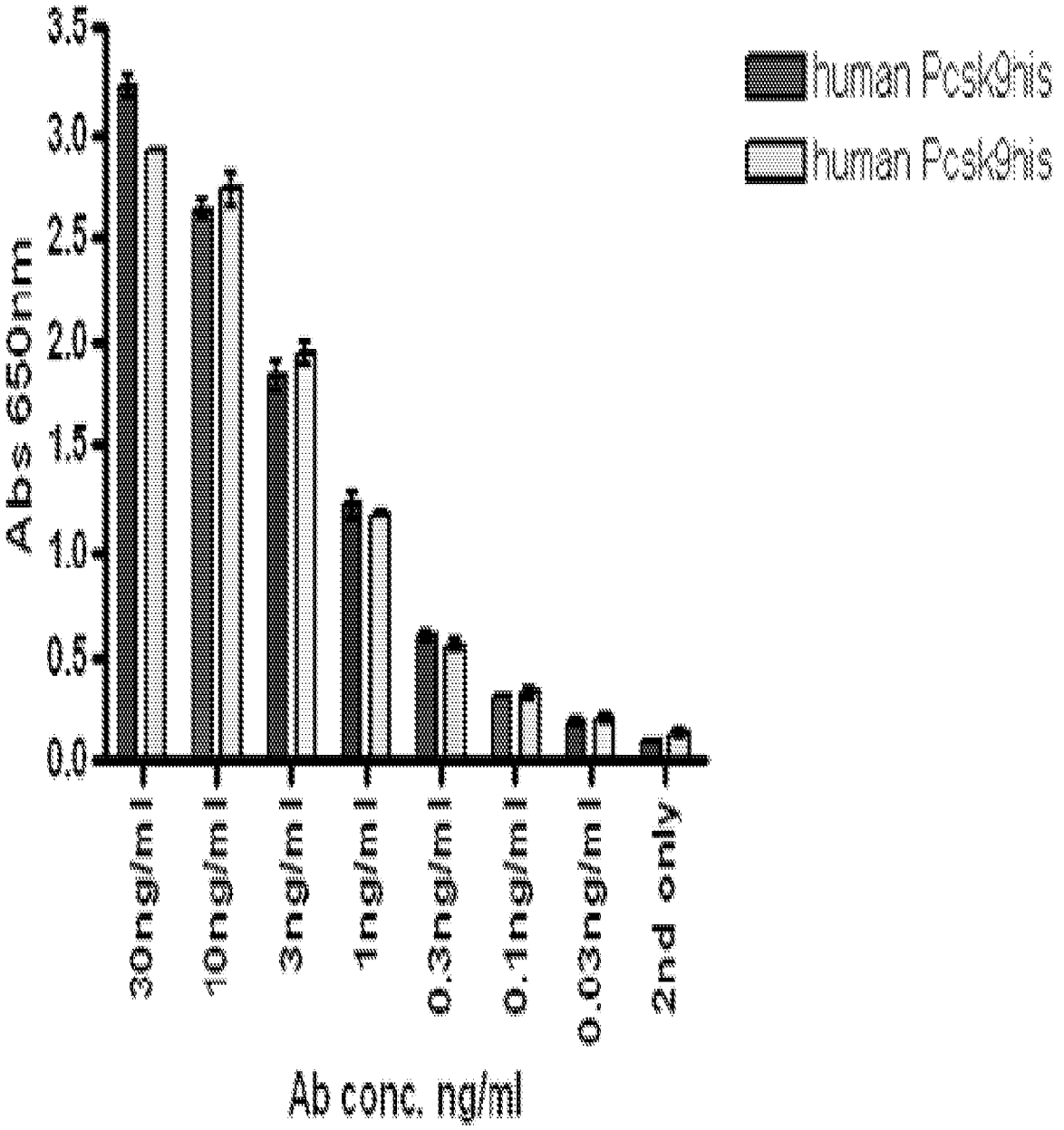
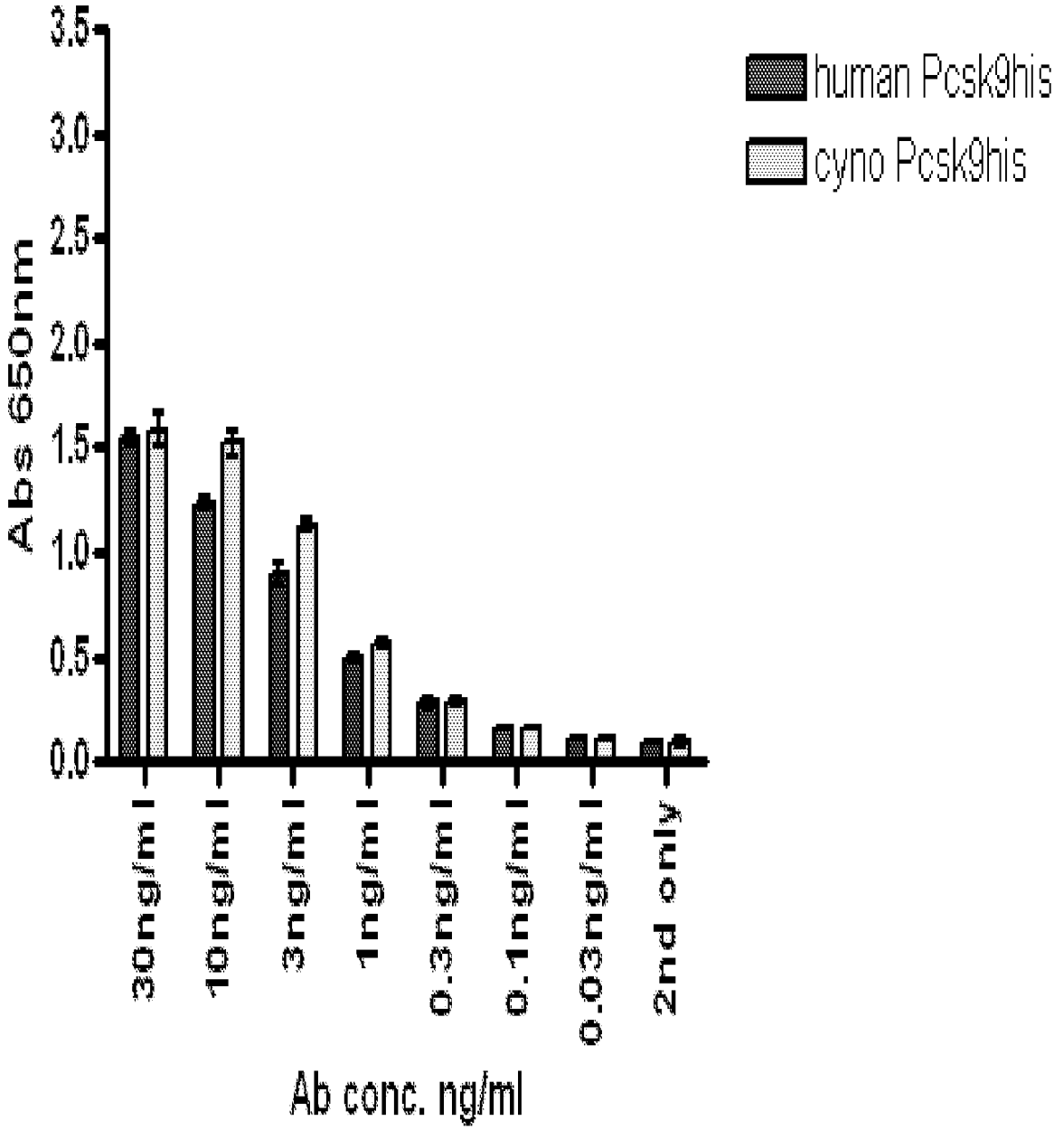

human Pcsk9his
human Pcsk9his
Abs 650nm
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
30ng/ml
10ng/ml
3ng/ml
1ng/ml
0.3ng/ml
0.1ng/ml
0.03ng/ml
2nd only
Ab conc. ng/ml

Figure 6C


human Pcsk9his
cyno Pcsk9his
Abs 650nm
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
30ng/ml
10ng/ml
3ng/ml
1ng/ml
0.3ng/ml
0.1ng/ml
0.03ng/ml
2nd only
Ab conc. ng/ml

11/18

Figure 7

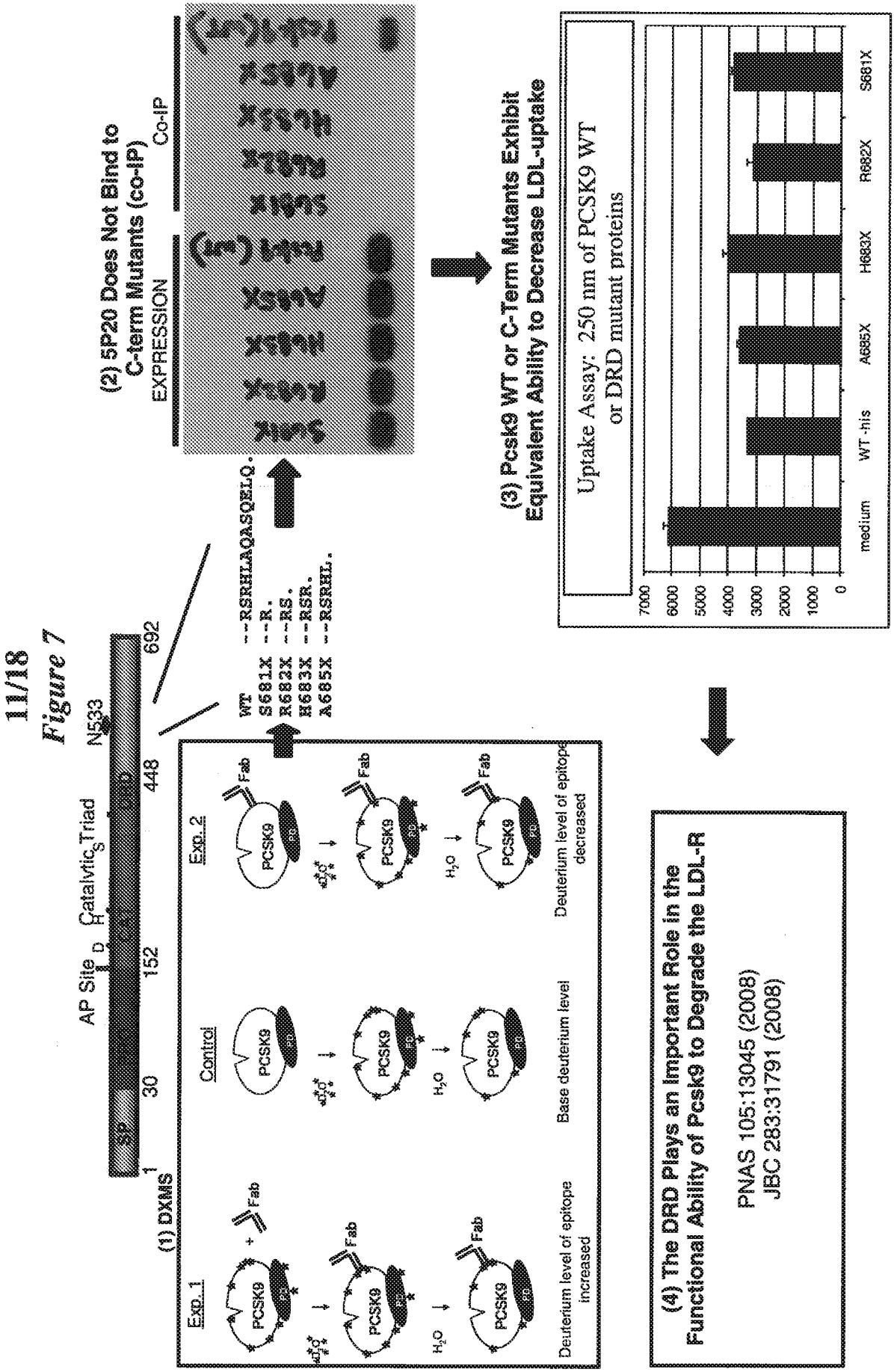


Figure 8

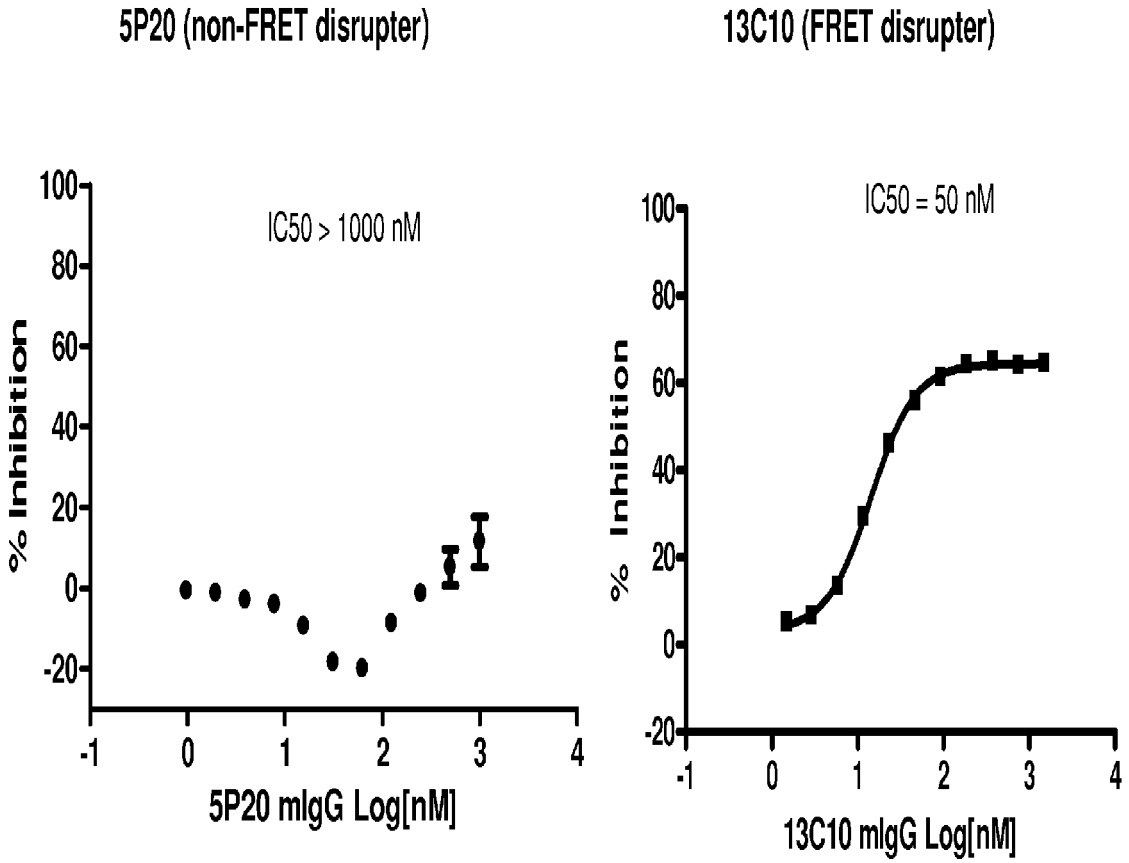
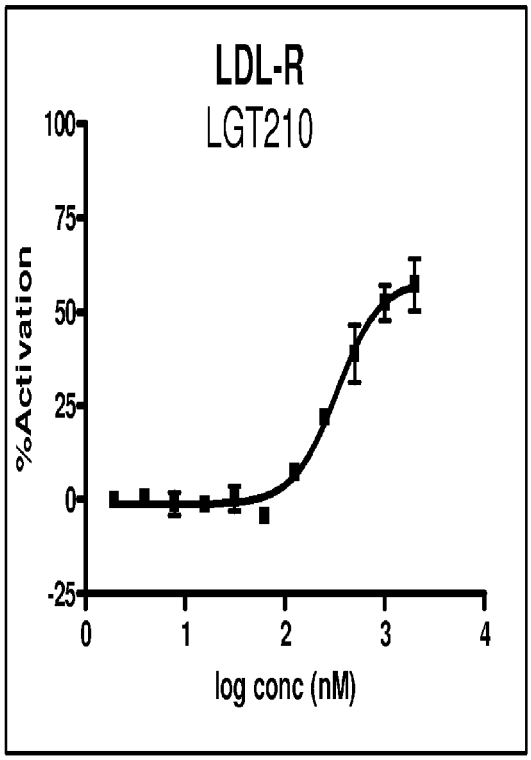

5P20 (non-FRET disrupter)
IC50 > 1000 nM
% Inhibition
100
80
60
40
20
0
-20
-1
0
1
2
3
4
5P20 mIgG Log[nM]
13C10 (FRET disrupter)
IC50 = 50 nM
% Inhibition
100
80
60
40
20
0
-20
-1
0
1
2
3
4
13C10 mIgG Log[nM]

Figure 9

Antibody	LDL-R Elevation	LDL-uptake
LGT209	480 ± 64	255 ± 25
LGT210	480 ± 48	259 ± 22
LGT211	430 ± 60	230 ± 17
NVP-LFU720	520 ± 28	294 ± 62



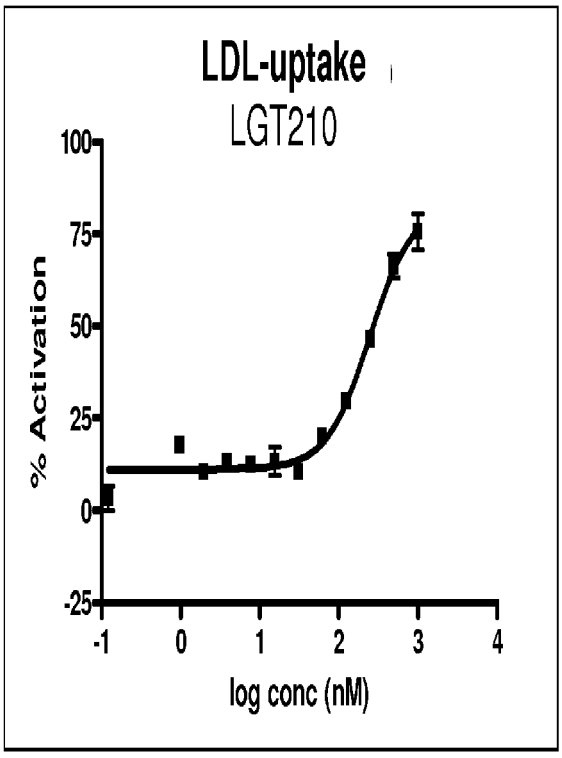
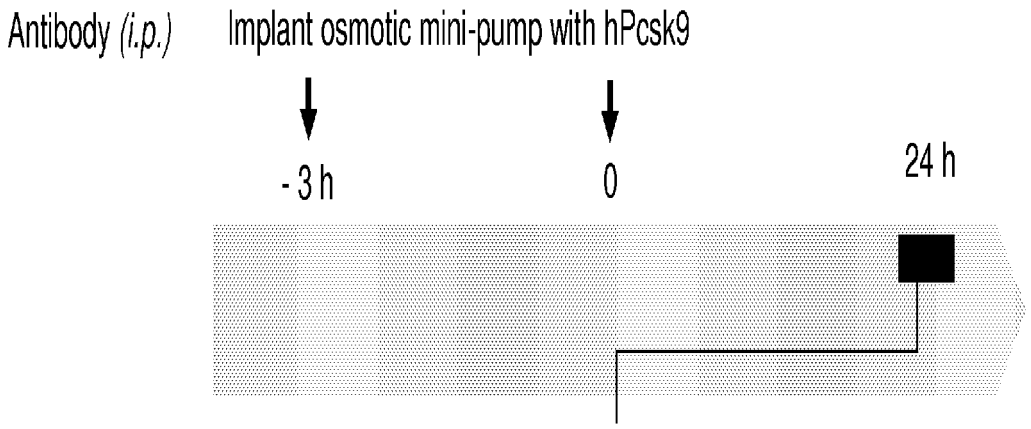


Figure 10



- Wild-type C57BL/6J mice (9 wks old)
- Alzet: 2001D (8 µl/h, 24h pump, 0.2 ml)
- i.v. infusion – mini-pump implanted *s.c.* with jugular vein catheter

■ Non-HDL-C (Helena)
Total cholesterol (Olympus)
hPcsk9 (ELISA)
Antibody (ELISA)

Groups	Number of Mice
PBS (*i.p.*) + PBS (3 µg/h *i.v.*)	7
PBS (*i.p.*) + hPcsk9 (3 µg/h; *i.v.*)	7
mIgG (20 mpk *i.p.*) + hPcsk9 (3 µg/h; *i.v.*)	5
LGT209 (20 mpk *i.p.*) + hPcsk9 (3 µg/h *i.v.*)	7
LGT210 (20 mpk *i.p.*) + hPcsk9 (3 µg/h *i.v.*)	5
LGT211 (20 mpk *i.p.*) + hPcsk9 (3 µg/h *i.v.*)	7

Figure 11

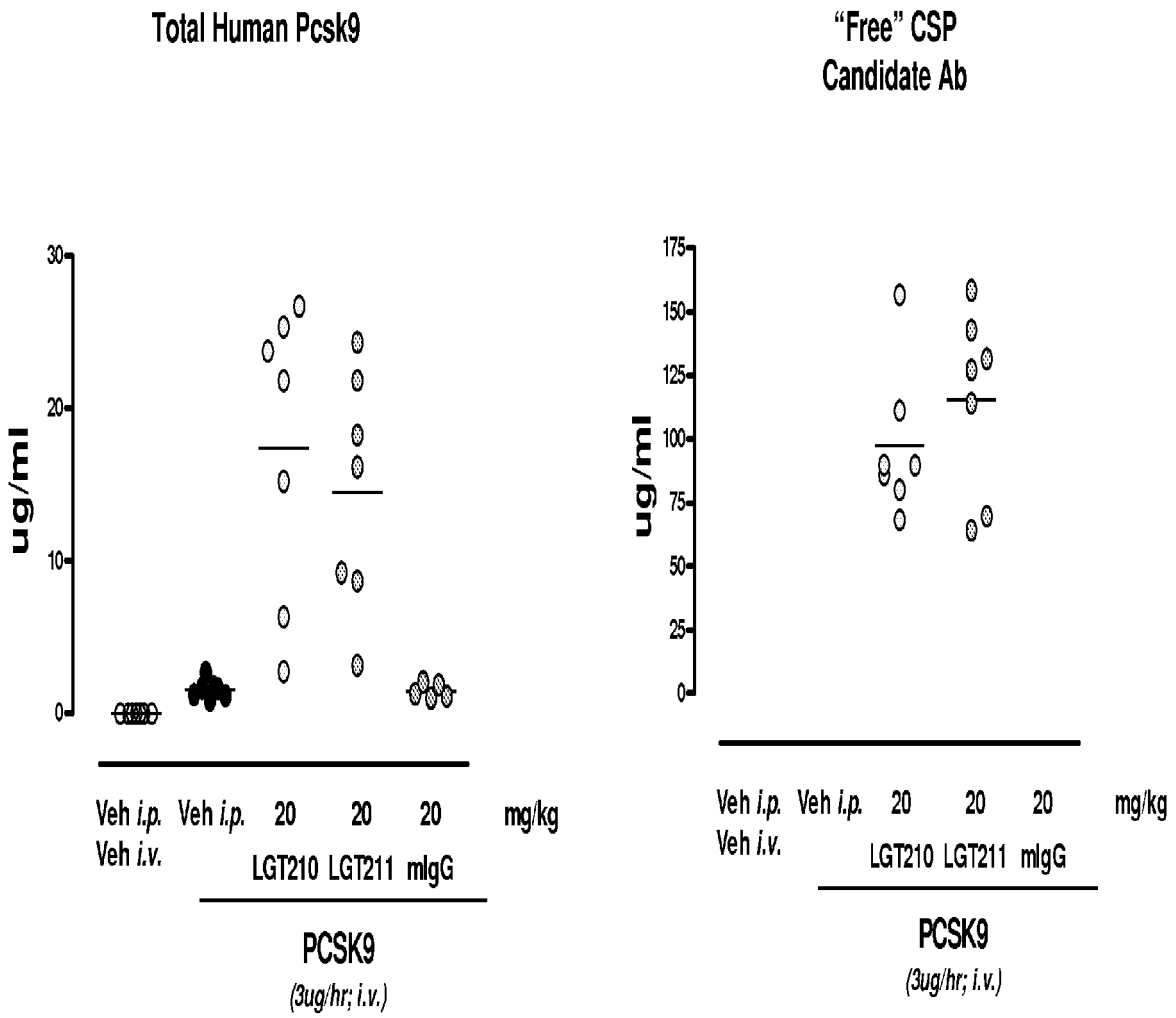

Total Human Pcsk9
ug/ml
30
20
10
0
Veh i.p.
Veh i.v.
Veh i.p.
20
20
20
mg/kg
LGT210
LGT211
mIgG
PCSK9
(3ug/hr; i.v.)
"Free" CSP
Candidate Ab
ug/ml
175
150
125
100
75
50
25
0
Veh i.p.
Veh i.v.
Veh i.p.
20
20
20
mg/kg
LGT210
LGT211
mIgG
PCSK9
(3ug/hr; i.v.)

Figure 12

LDL-R Western Blot of Liver Membrane Preparations

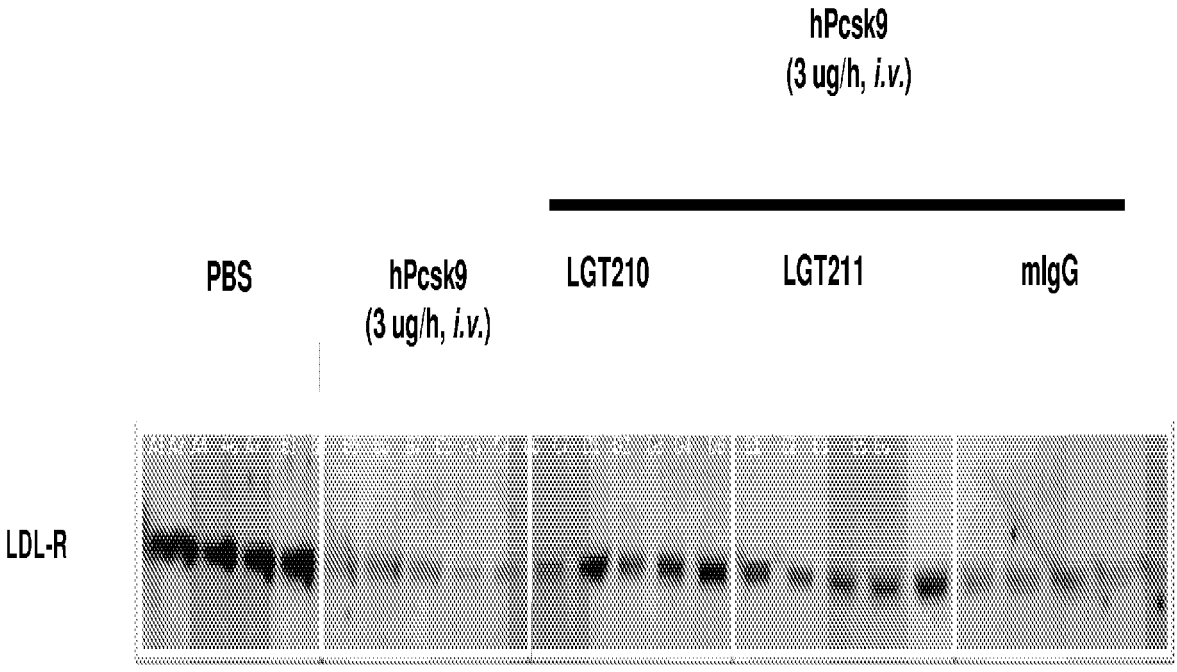
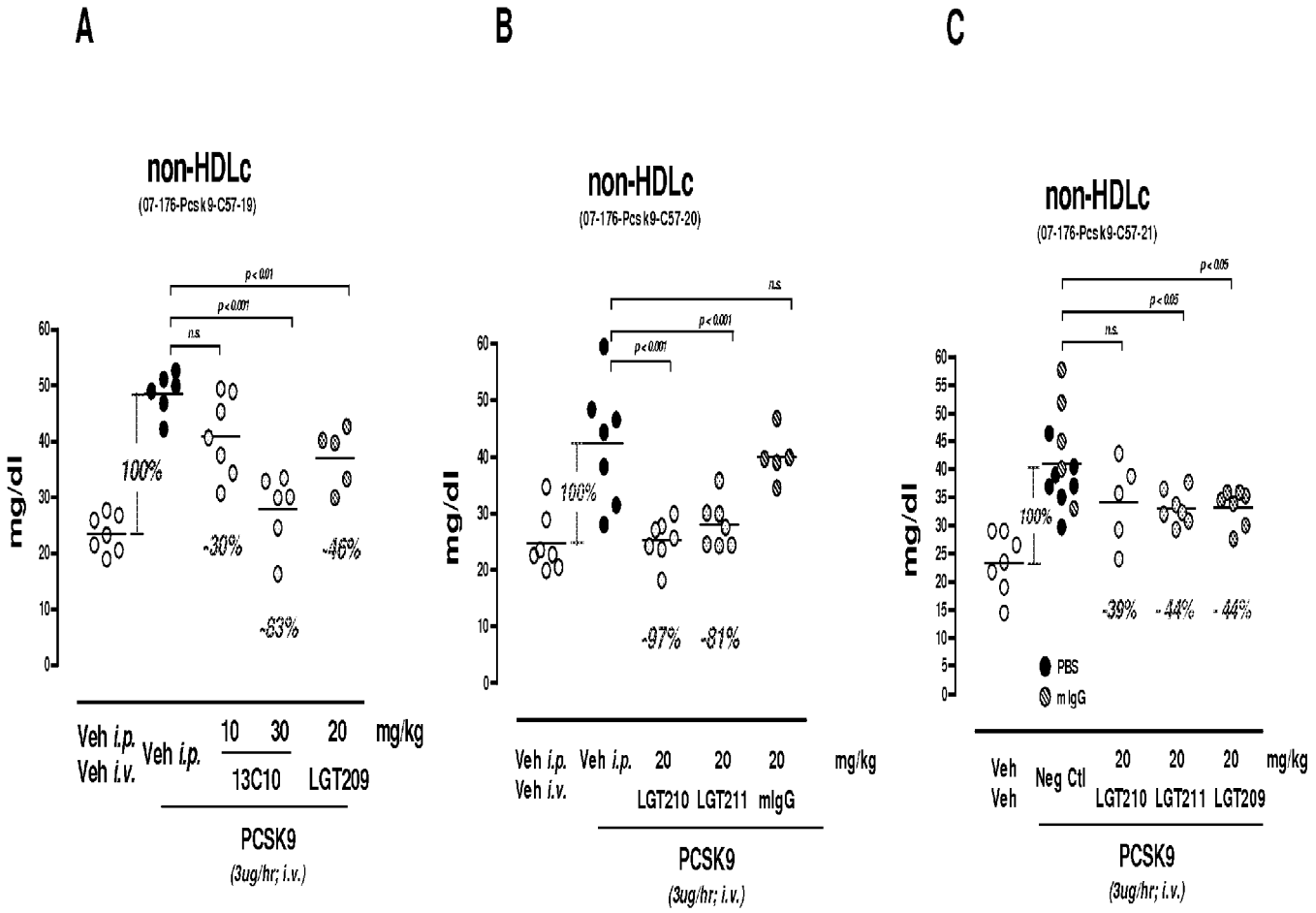
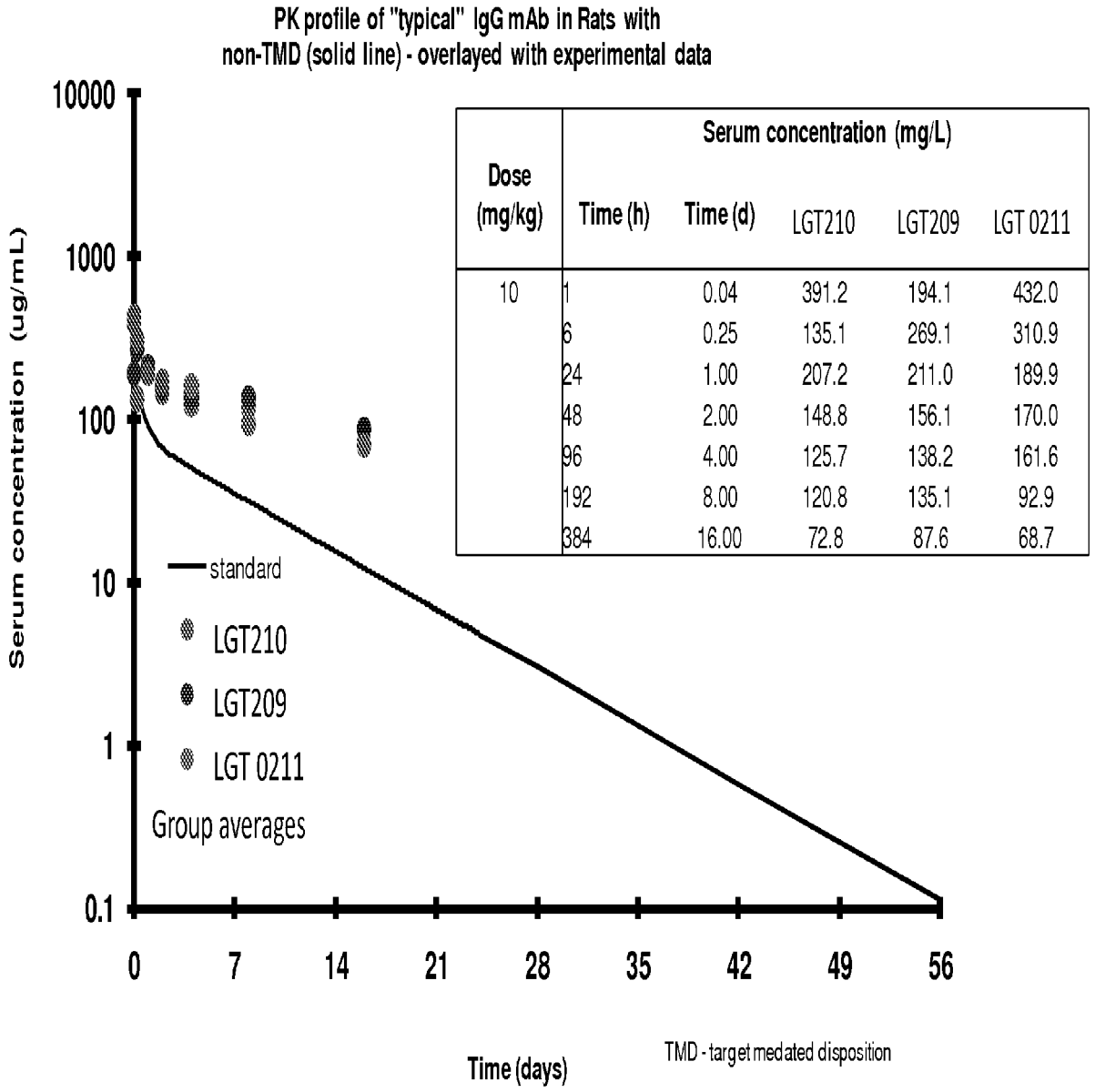


Figure 13



Antibody	non-HDL-C A	non-HDL-C B	non-HDL-C C
LGT209	- 46% ($p < 0.01$)	-	- 44% ($p < 0.05$)
LGT210	-	- 97% ($p < 0.001$)	- 39% (*n.s.*)
LGT211	-	- 81% ($p < 0.001$)	- 44% ($p < 0.05$)

Figure 14



Dose (mg/kg)	Serum concentration (mg/L)				
	Time (h)	Time (d)	LGT210	LGT209	LGT 0211
10	1	0.04	391.2	194.1	432.0
	6	0.25	135.1	269.1	310.9
	24	1.00	207.2	211.0	189.9
	48	2.00	148.8	156.1	170.0
	96	4.00	125.7	138.2	161.6
	192	8.00	120.8	135.1	92.9
	384	16.00	72.8	87.6	68.7