FIG. 1A

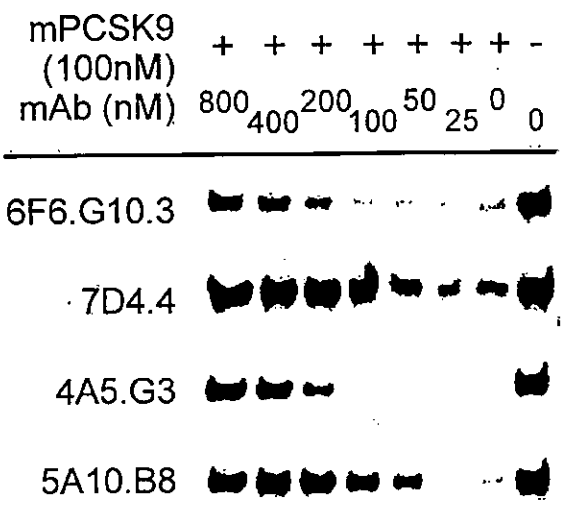


FIG. 1B

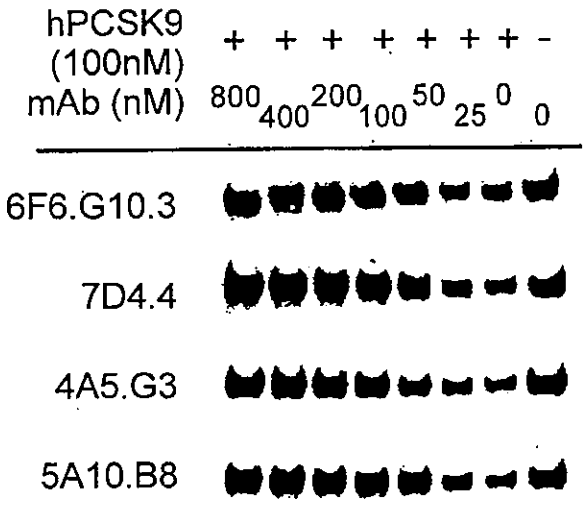


FIG. 2A

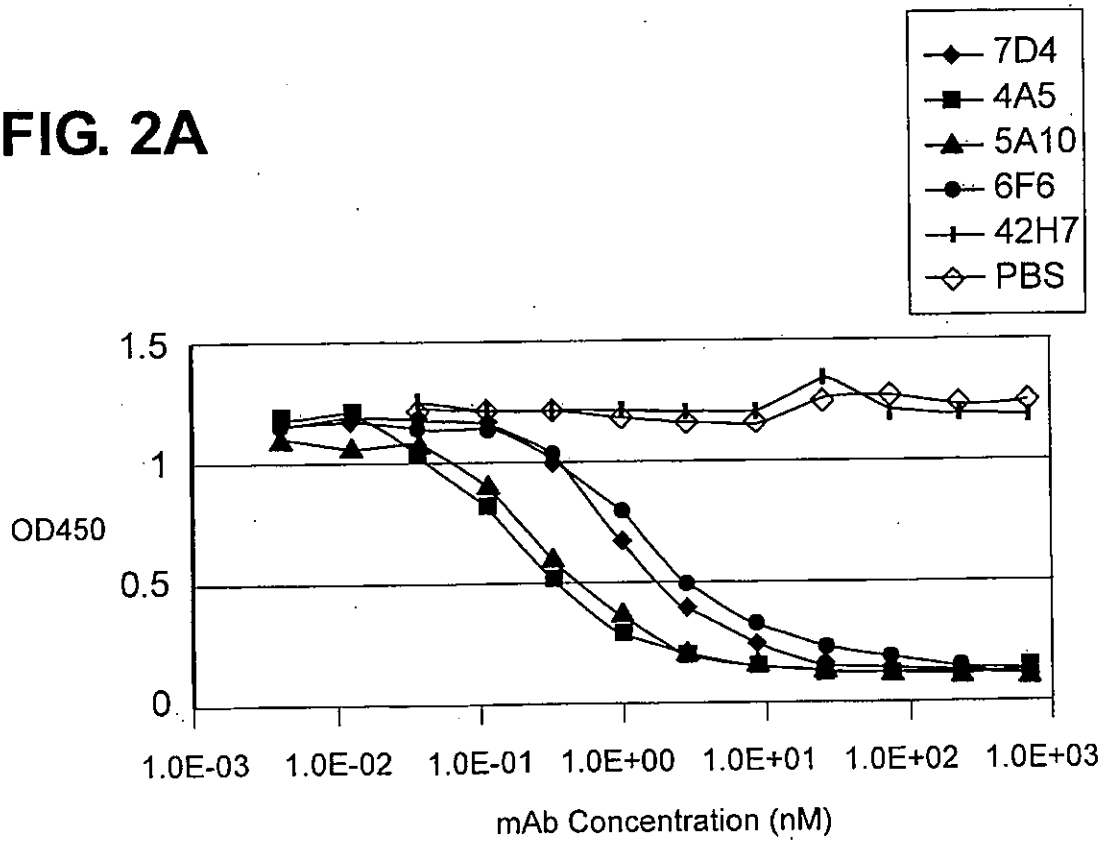


FIG. 2B

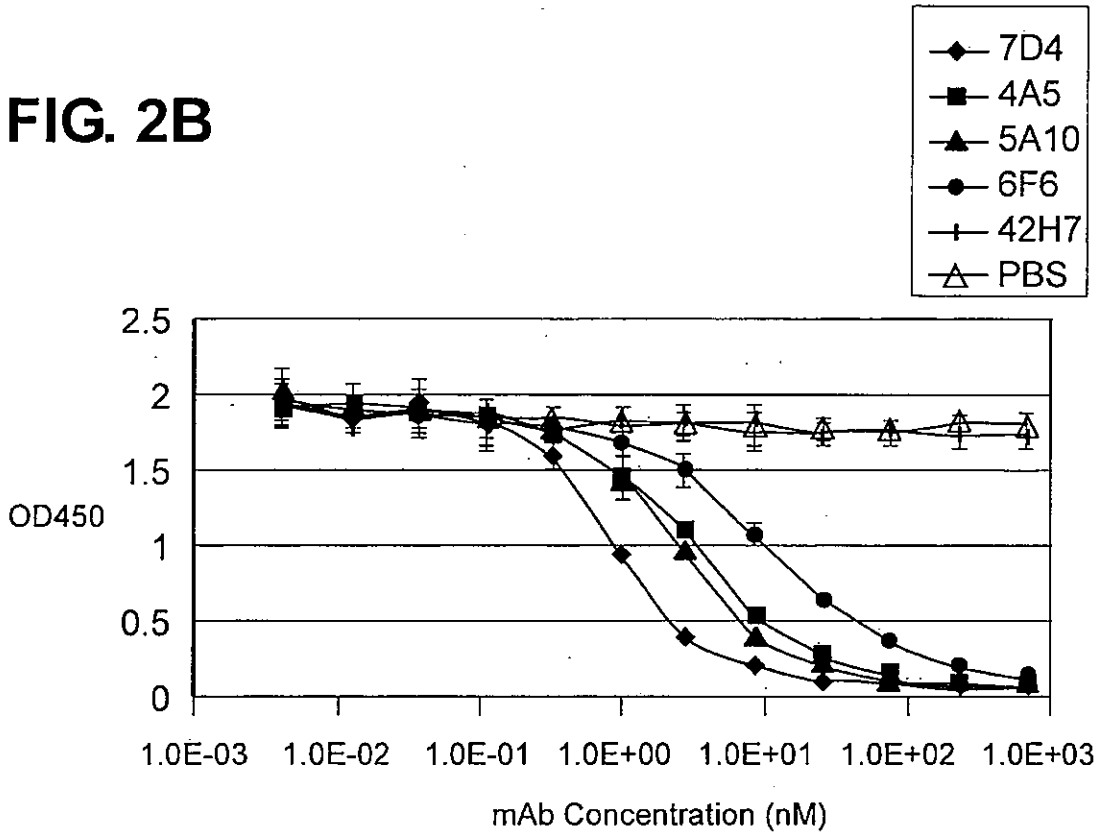

7D4
4A5
5A10
6F6
42H7
PBS
2.5
2
1.5
1
0.5
0
OD450
1.0E-03
1.0E-02
1.0E-01
1.0E+00
1.0E+01
1.0E+02
1.0E+03
mAb Concentration (nM)

FIG. 3

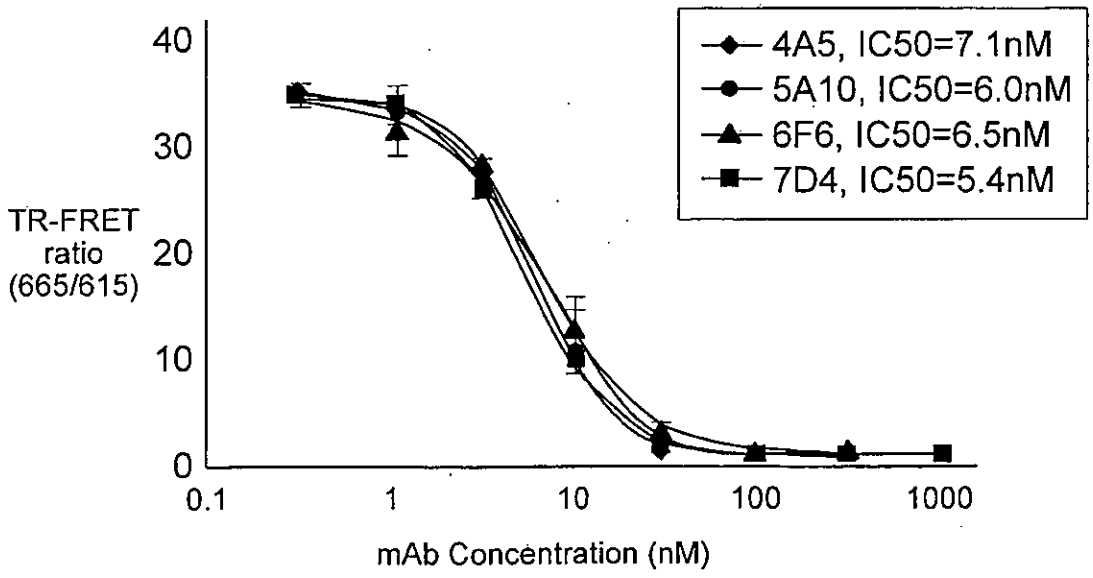

4A5, IC50=7.1nM
5A10, IC50=6.0nM
6F6, IC50=6.5nM
7D4, IC50=5.4nM
40
30
20
10
0
TR-FRET ratio (665/615)
0.1
1
10
100
1000
mAb Concentration (nM)

FIG. 4A

mAb	Epitope
3E1	ERITTPRY
4F1	SIPWNLERITPPRYRADE YQPPDG
5F6	Unknown, group 2
6D6	Unknown, group 1
4E1	Unknown
15F5	QEDEDGDYEELVLALRSEEDG LAEA
4G12	Unknown, group 1
4E4	AKDVINEAWFPEDQRVLTPNL
4A5	Unknown, group 4
5A10	Unknown, group 4
6F6	Unknown, group 4
7D4	Unknown, group 4

FIG. 4B

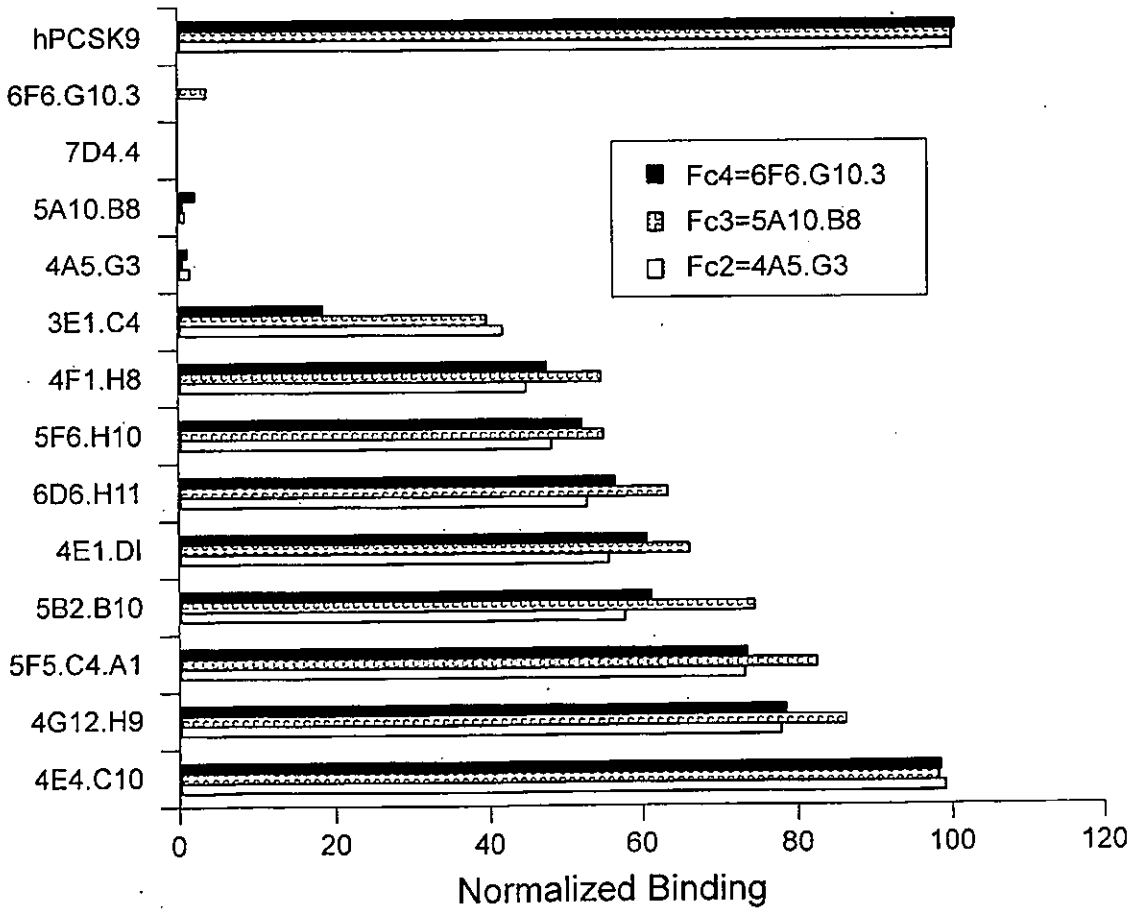


FIG. 5

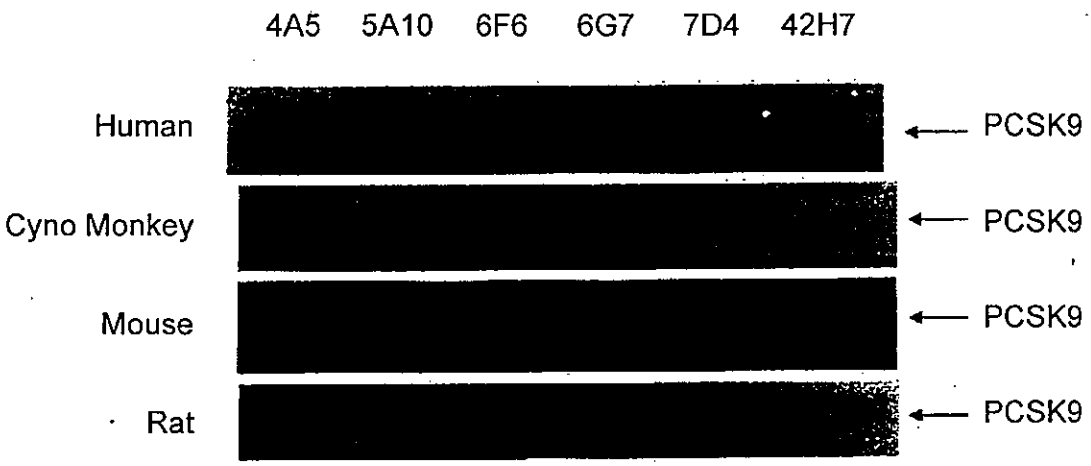

4A5
5A10
6F6
6G7
7D4
42H7
Human
Cyno Monkey
Mouse
Rat
PCSK9
PCSK9
PCSK9
PCSK9

FIG. 6

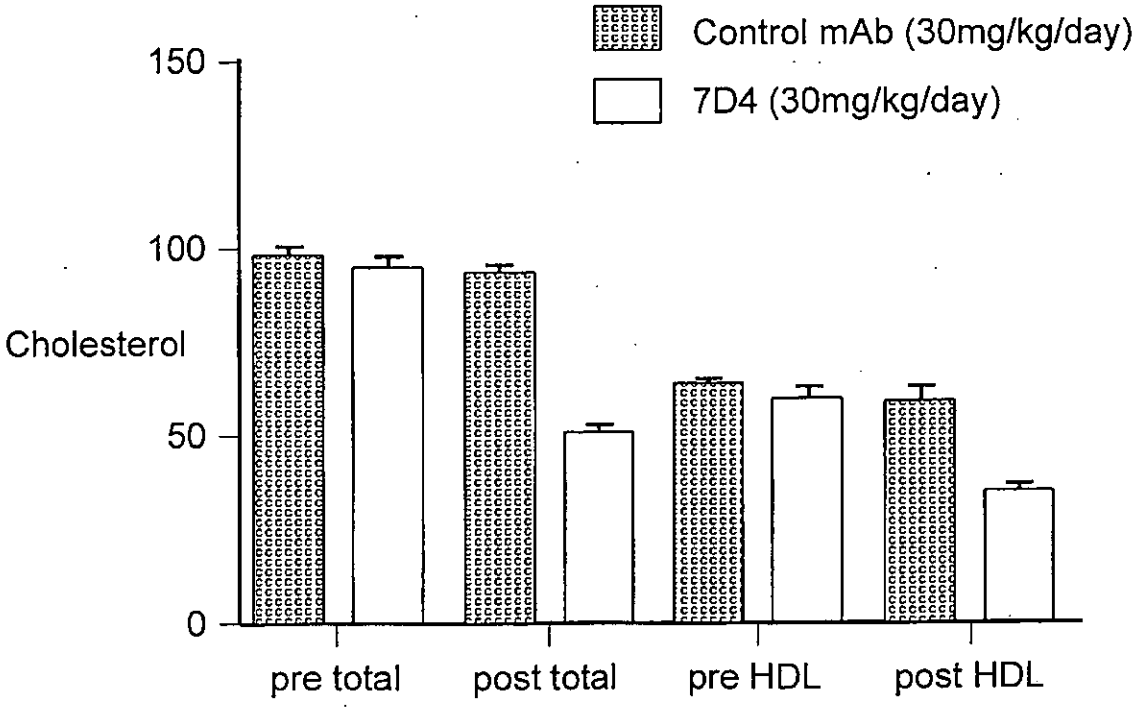

Control mAb (30mg/kg/day)
7D4 (30mg/kg/day)
150
100
50
0
Cholesterol
pre total
post total
pre HDL
post HDL

FIG. 7A

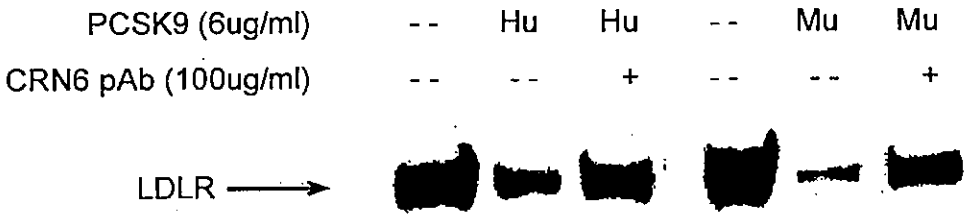

PCSK9 (6ug/ml) -- Hu Hu -- Mu Mu
CRN6 pAb (100ug/ml) -- -- + -- -- +
LDLR

FIG. 7B

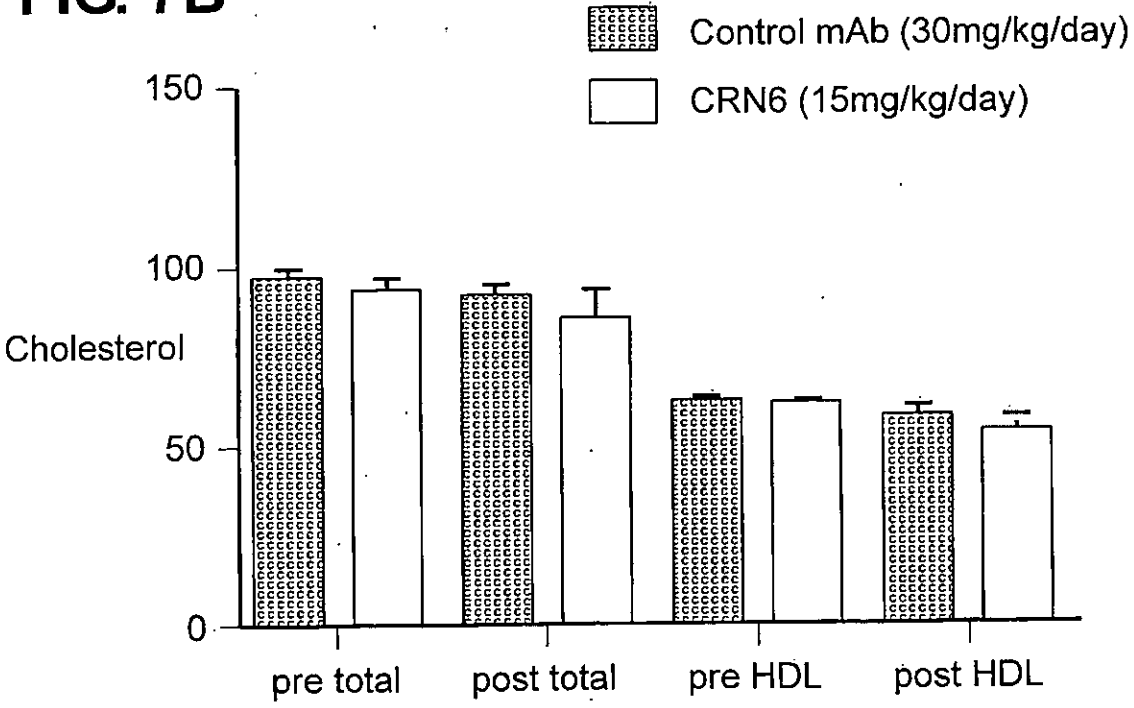

Control mAb (30mg/kg/day)
CRN6 (15mg/kg/day)
150
100
50
0
Cholesterol
pre total
post total
pre HDL
post HDL

FIG. 8A

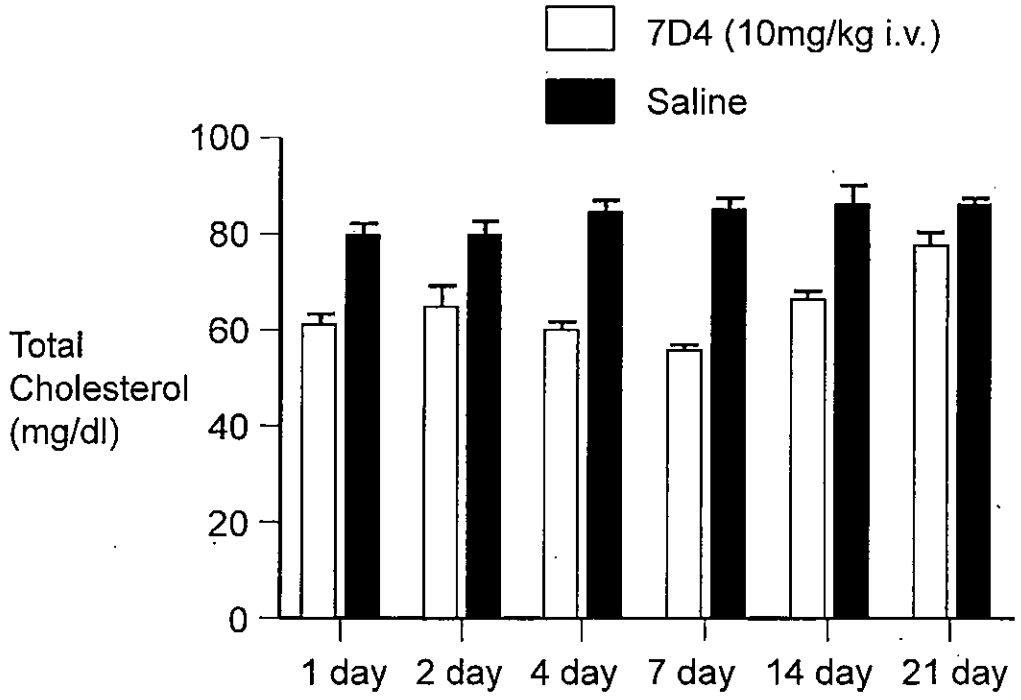

7D4 (10mg/kg i.v.)
Saline
Total Cholesterol (mg/dl)
100
80
60
40
20
0
1 day
2 day
4 day
7 day
14 day
21 day

FIG. 8B

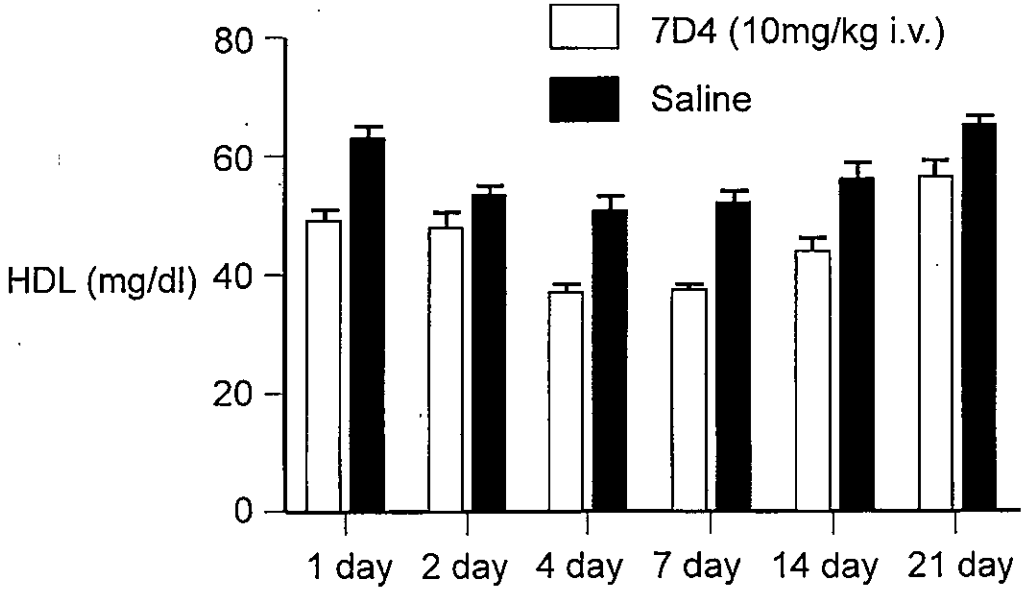

7D4 (10mg/kg i.v.)
Saline
HDL (mg/dl)
80
60
40
20
0
1 day
2 day
4 day
7 day
14 day
21 day

FIG. 9A

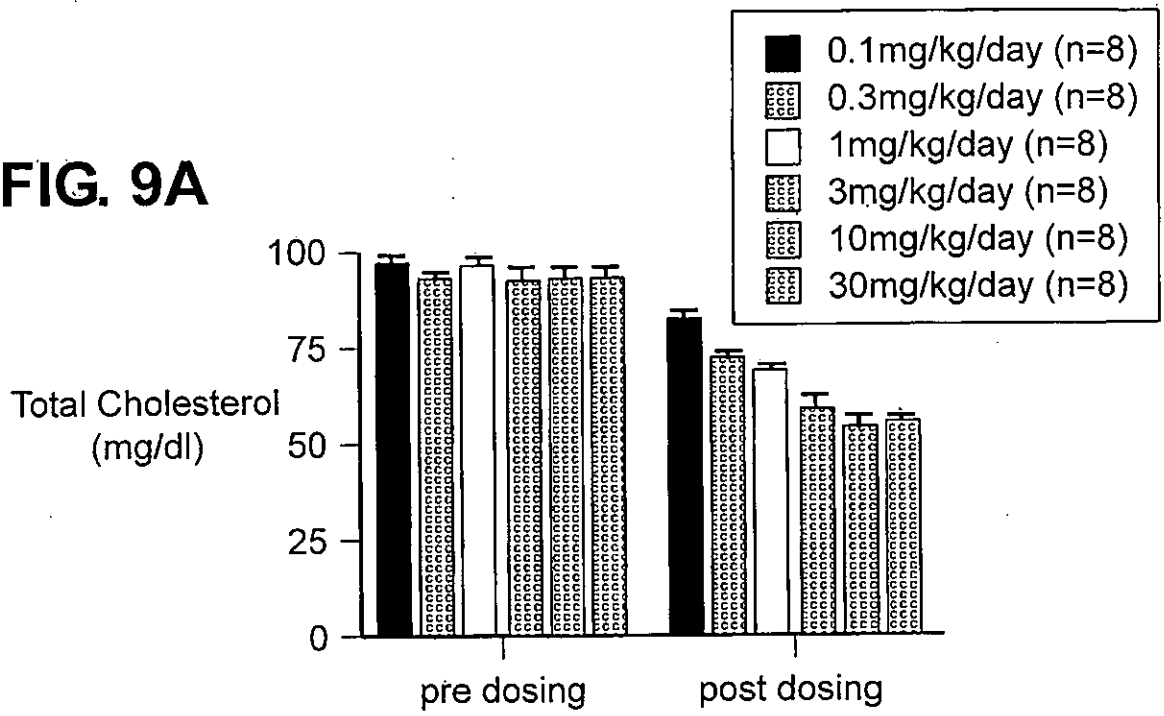


FIG. 9B

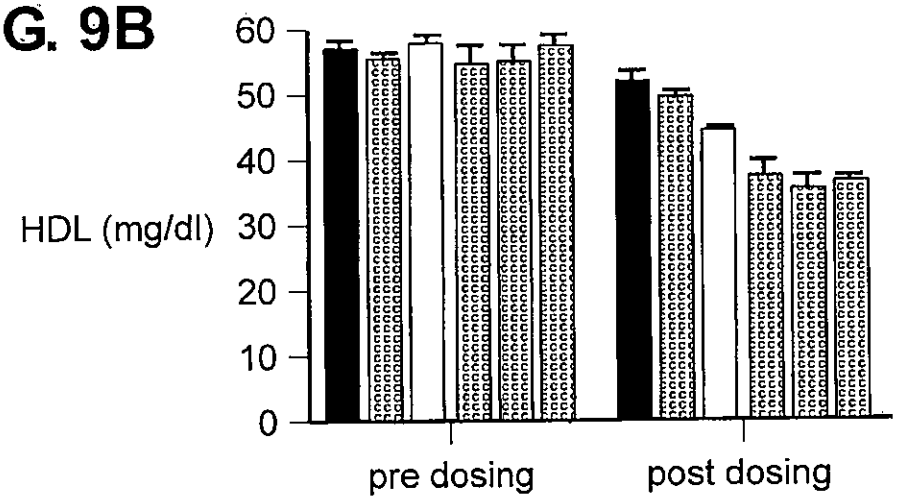


FIG. 9C

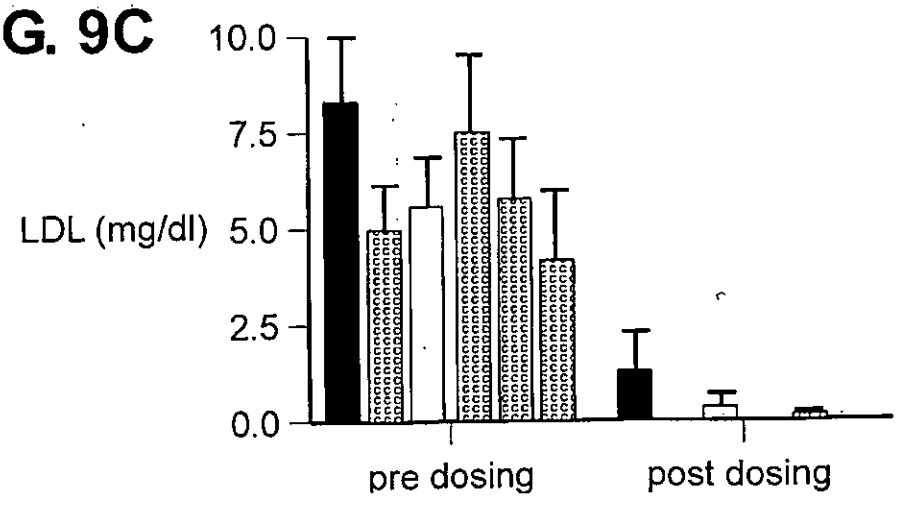


FIG. 10A

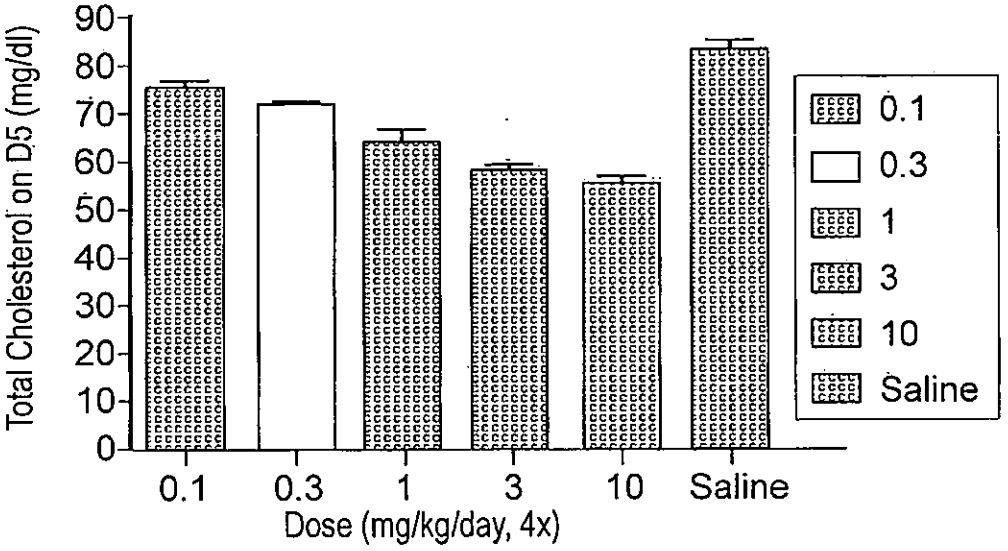


FIG. 10B

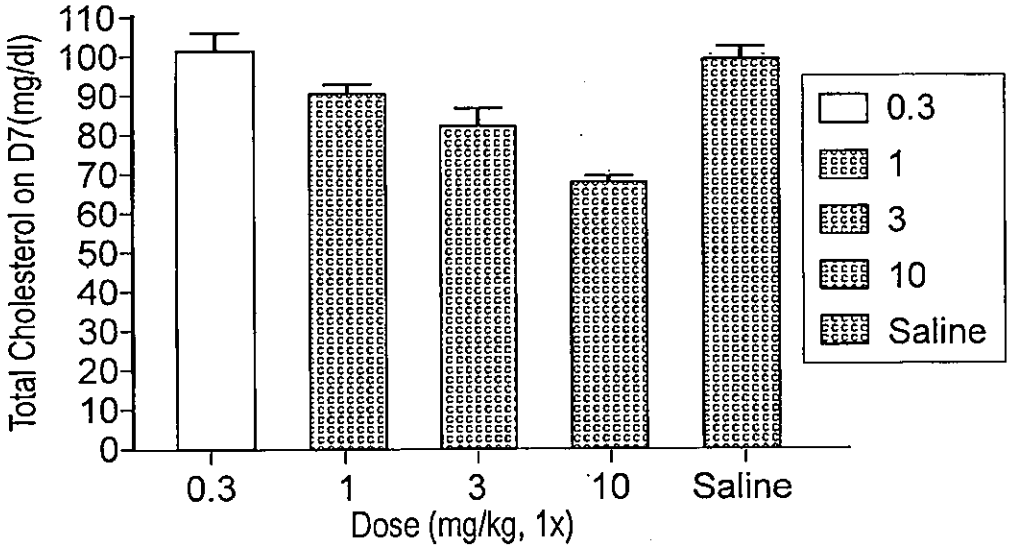


FIG. 11

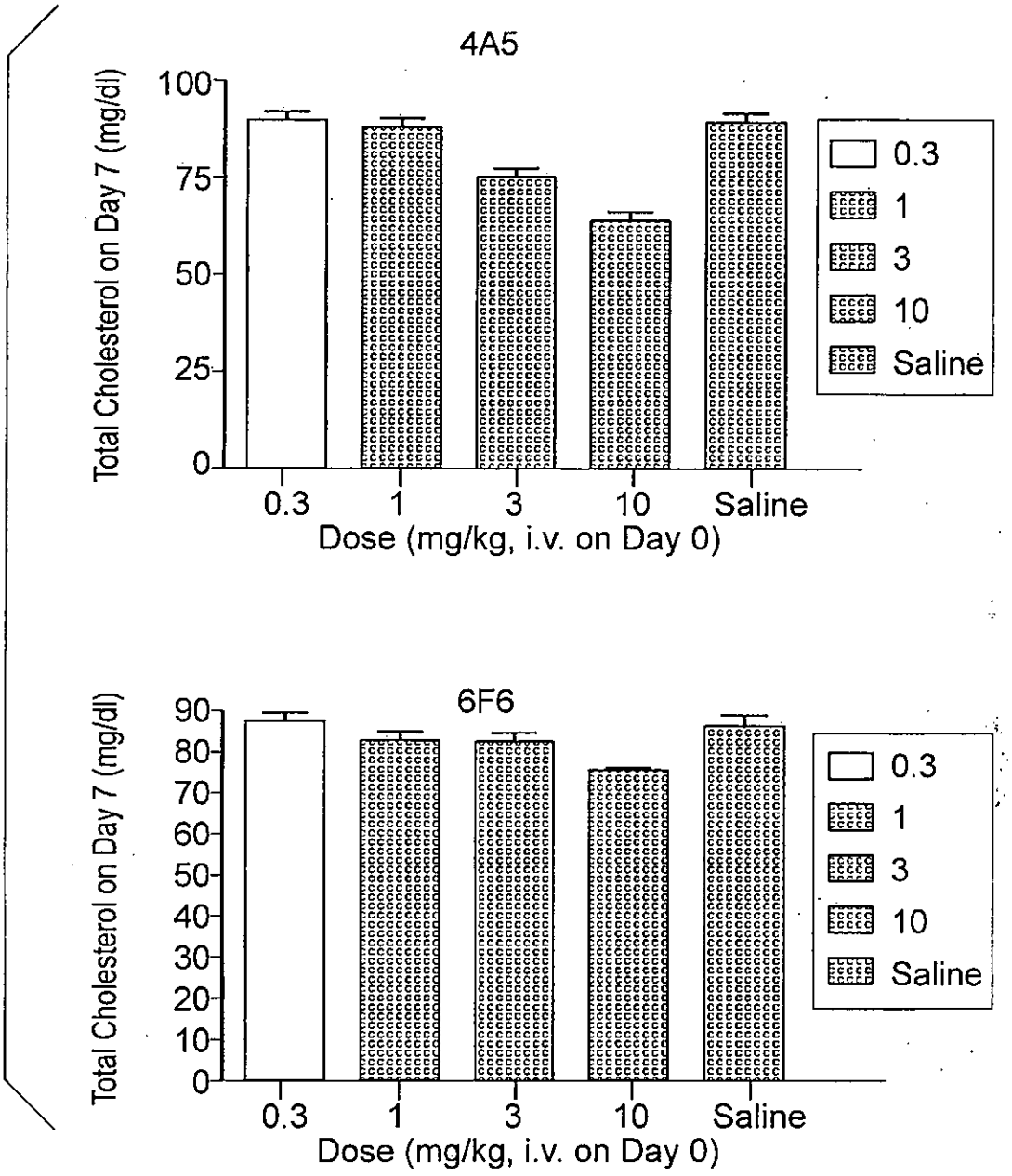

4A5
Total Cholesterol on Day 7 (mg/dl)
100
75
50
25
0
0.3
1
3
10
Saline
Dose (mg/kg, i.v. on Day 0)
6F6
Total Cholesterol on Day 7 (mg/dl)
90
80
70
60
50
40
30
20
10
0
0.3
1
3
10
Saline
Dose (mg/kg, i.v. on Day 0)

FIG. 12

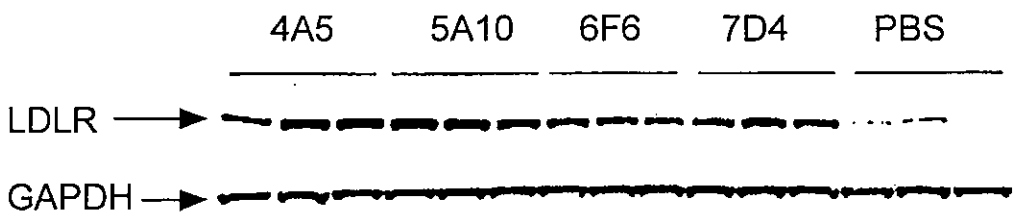

4A5
5A10
6F6
7D4
PBS
LDLR
GAPDH

FIG. 13

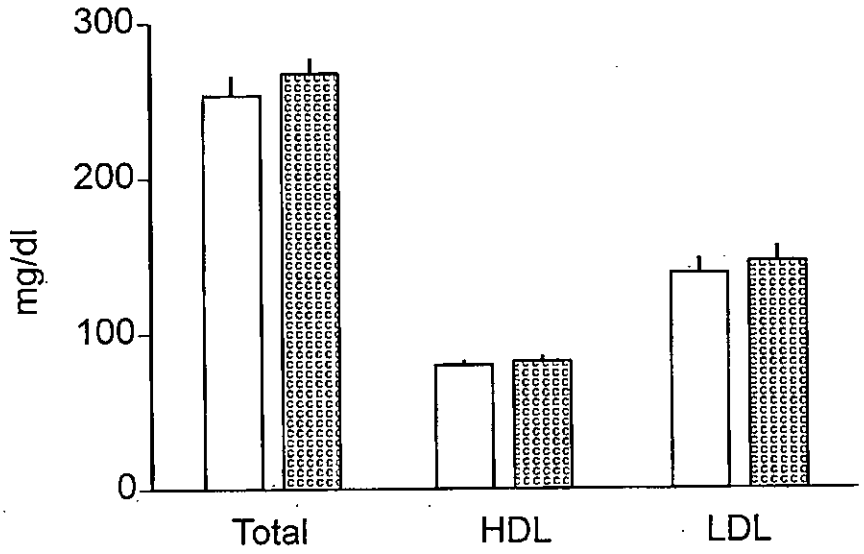

300
200
100
0
mg/dl
Total
HDL
LDL

FIG. 14

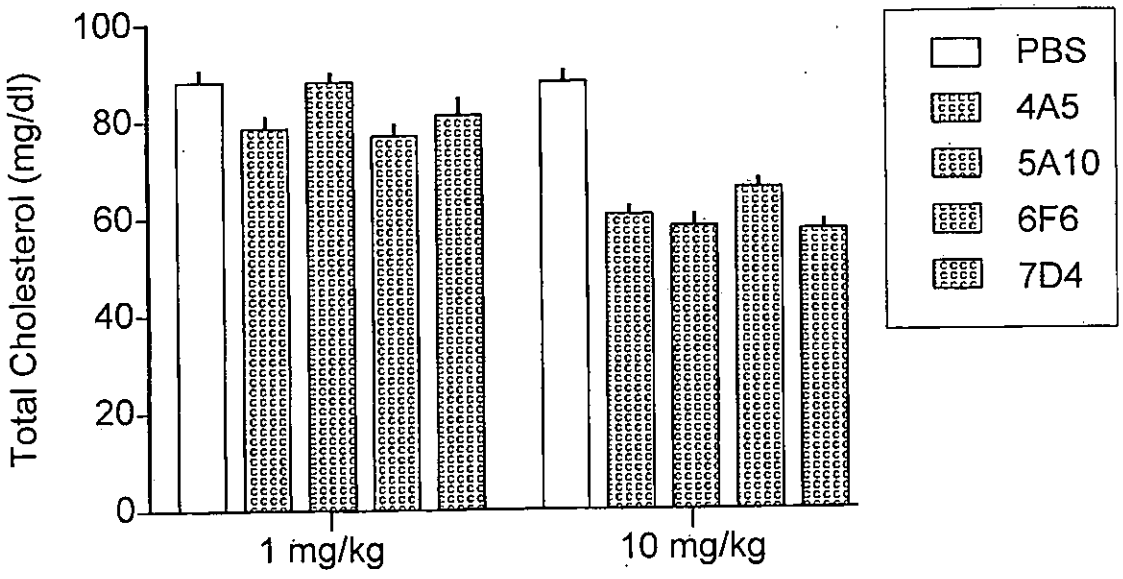

100
80
60
40
20
0
Total Cholesterol (mg/dl)
1 mg/kg
10 mg/kg
PBS
4A5
5A10
6F6
7D4

FIG. 15A

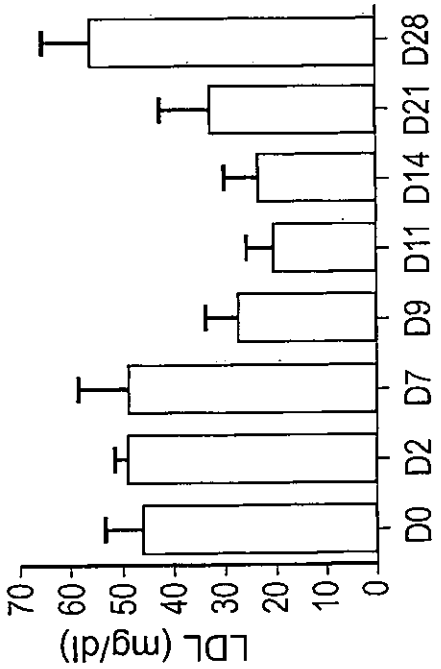


FIG. 15B

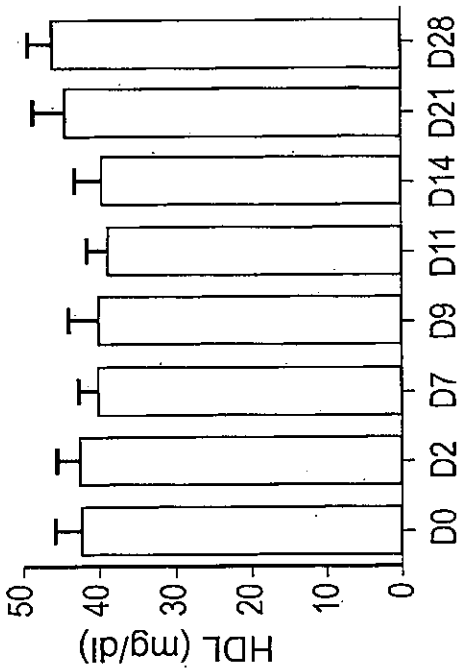


FIG. 15C

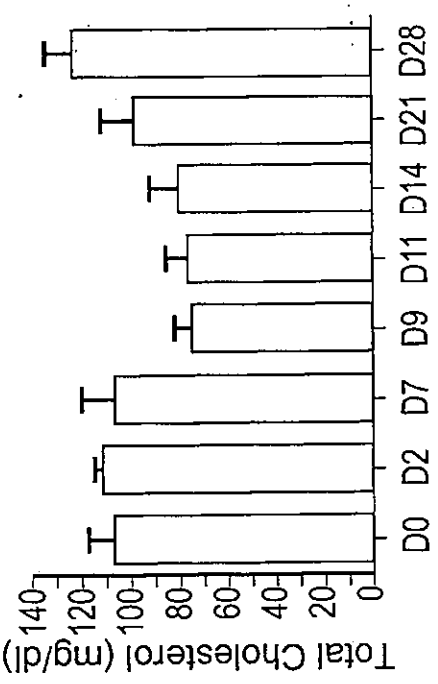


FIG. 15D

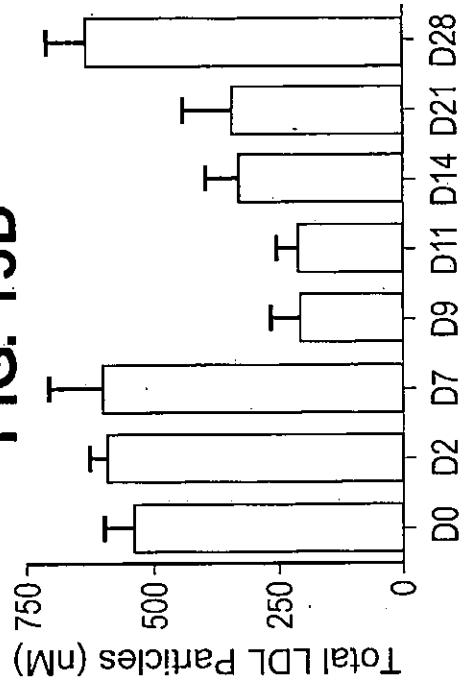


FIG. 15E

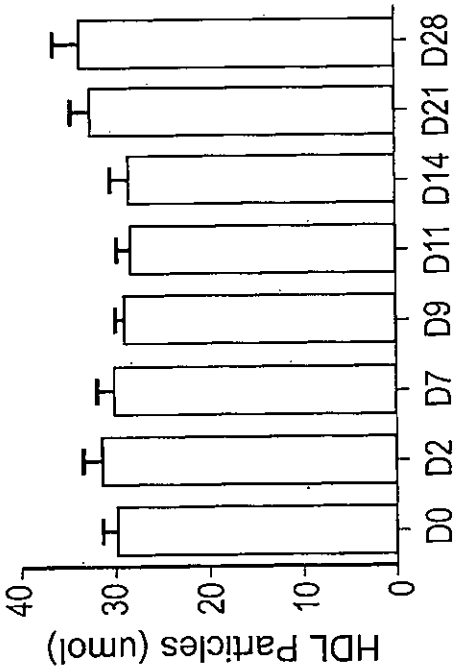


FIG. 15F

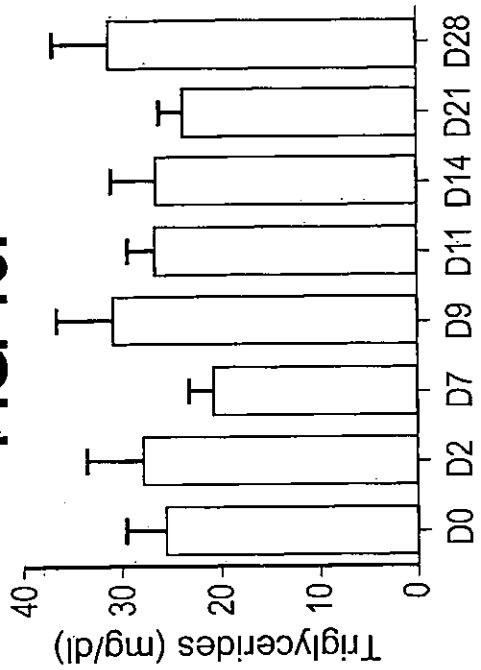


FIG. 15G

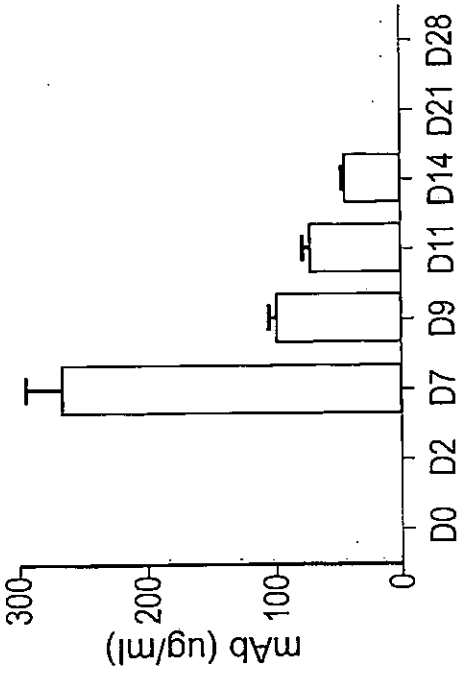


FIG. 15H

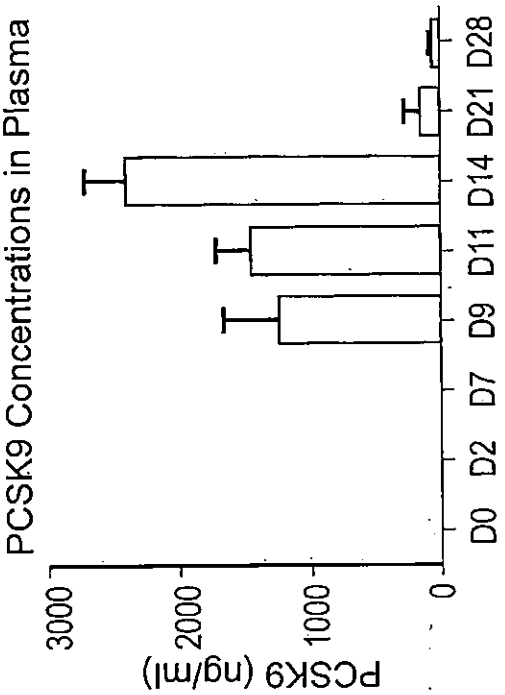


FIG. 16

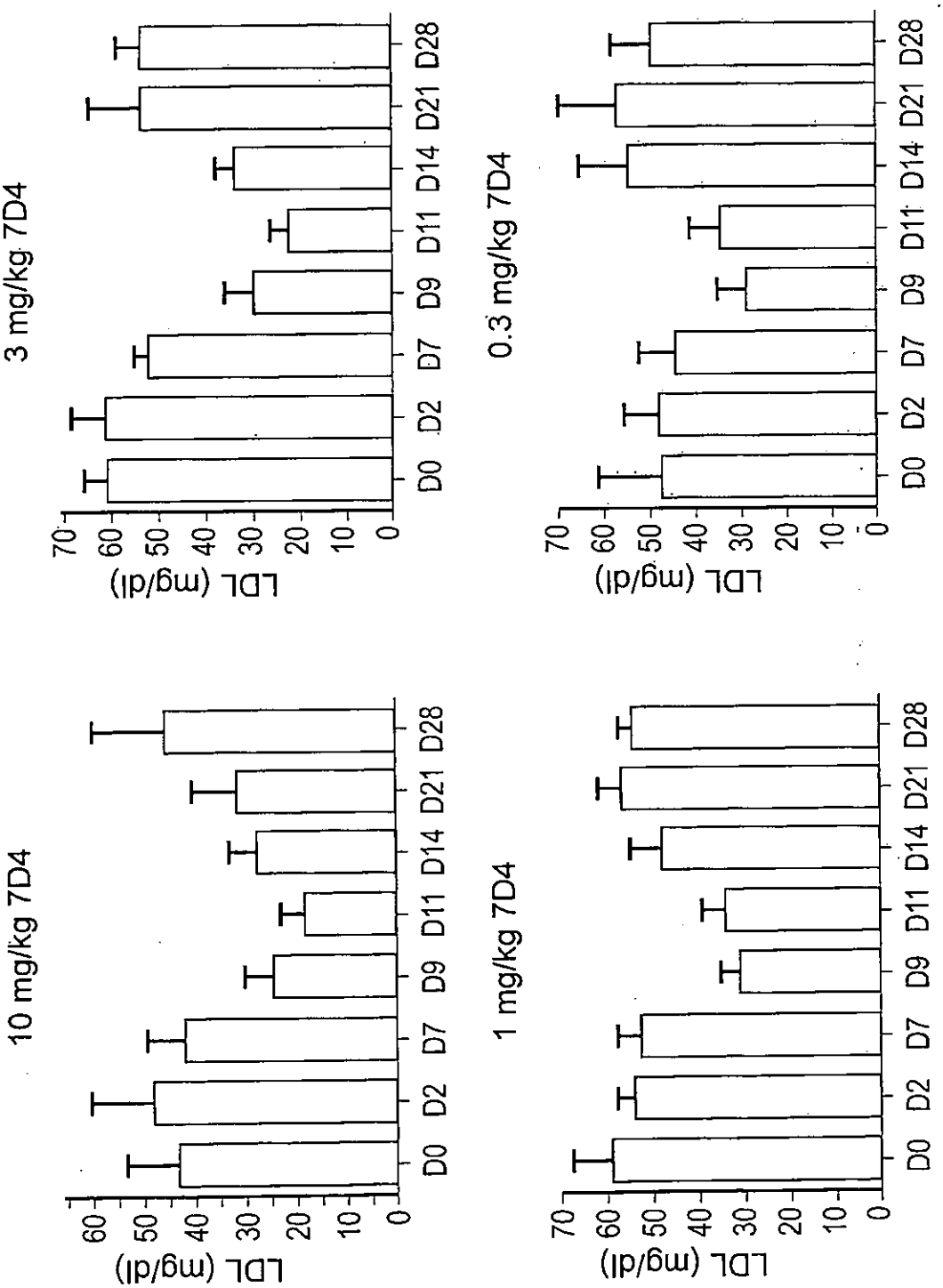

3 mg/kg 7D4
0.3 mg/kg 7D4
10 mg/kg 7D4
1 mg/kg 7D4
LDL (mg/dl)
0
10
20
30
40
50
60
70
D0
D2
D7
D9
D11
D14
D21
D28

FIG. 17

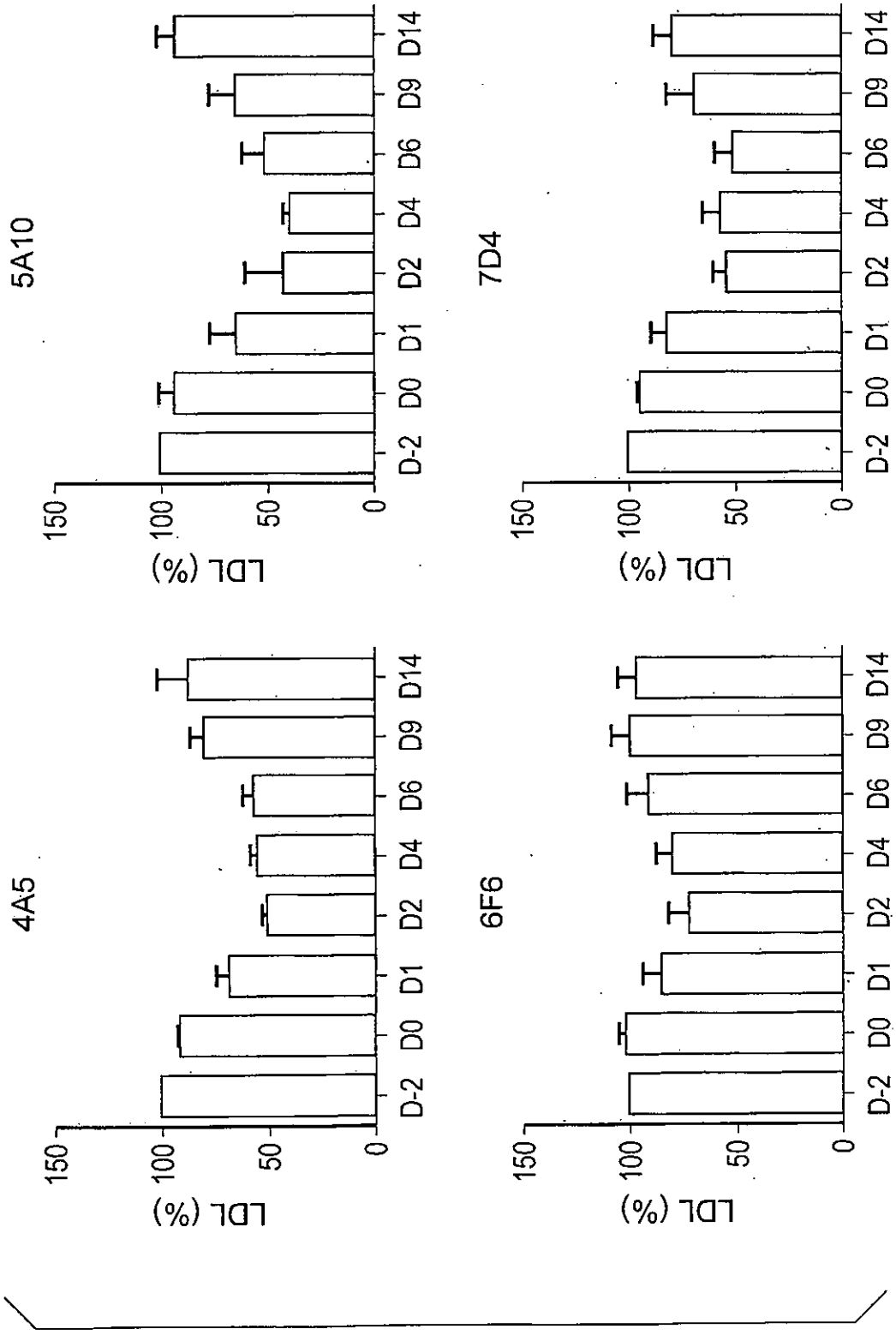


FIG. 18

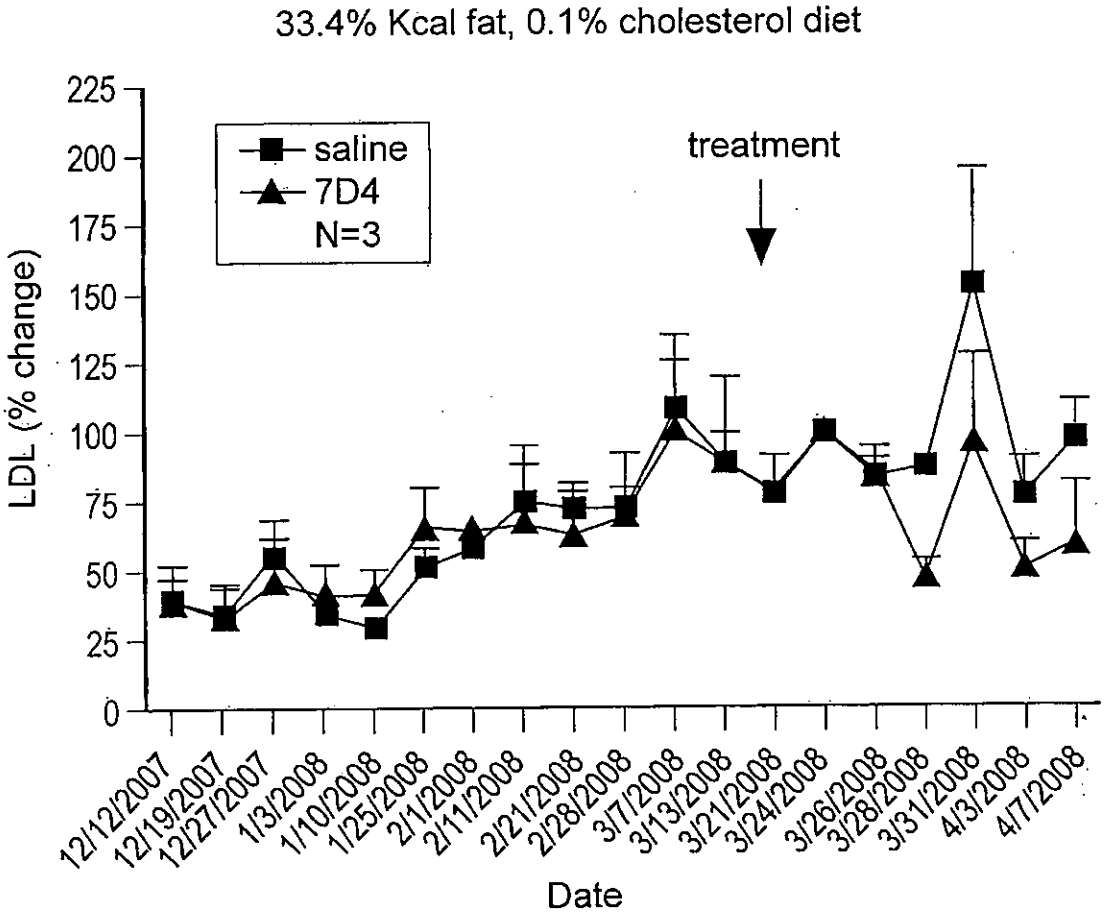

33.4% Kcal fat, 0.1% cholesterol diet
LDL (% change)
225
200
175
150
125
100
75
50
25
0
saline
7D4
N=3
treatment
12/12/2007
12/19/2007
12/27/2007
1/3/2008
1/10/2008
1/25/2008
2/1/2008
2/11/2008
2/21/2008
2/28/2008
3/7/2008
3/13/2008
3/21/2008
3/24/2008
3/26/2008
3/28/2008
3/31/2008
4/3/2008
4/7/2008
Date

FIG. 19

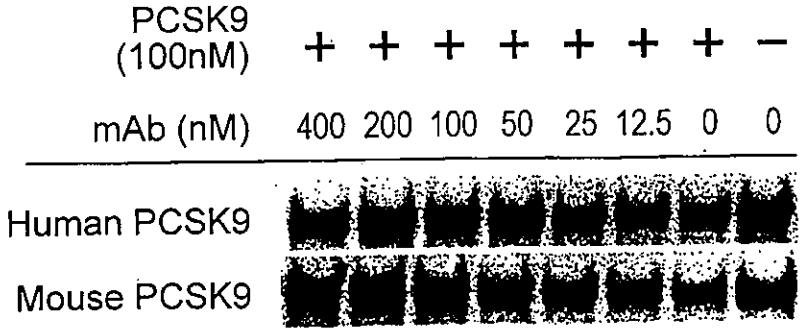

PCSK9 (100nM)
+ + + + + + + −
mAb (nM)
400 200 100 50 25 12.5 0 0
Human PCSK9
Mouse PCSK9

FIG. 20A 0.36nM Human PCSK9 pH 7.5

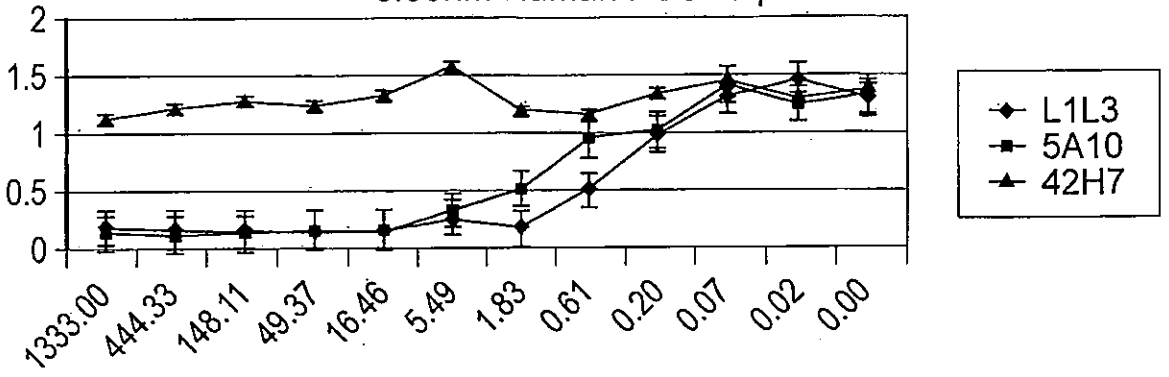


FIG. 20B 0.36nM Human PCSK9 pH 5.3

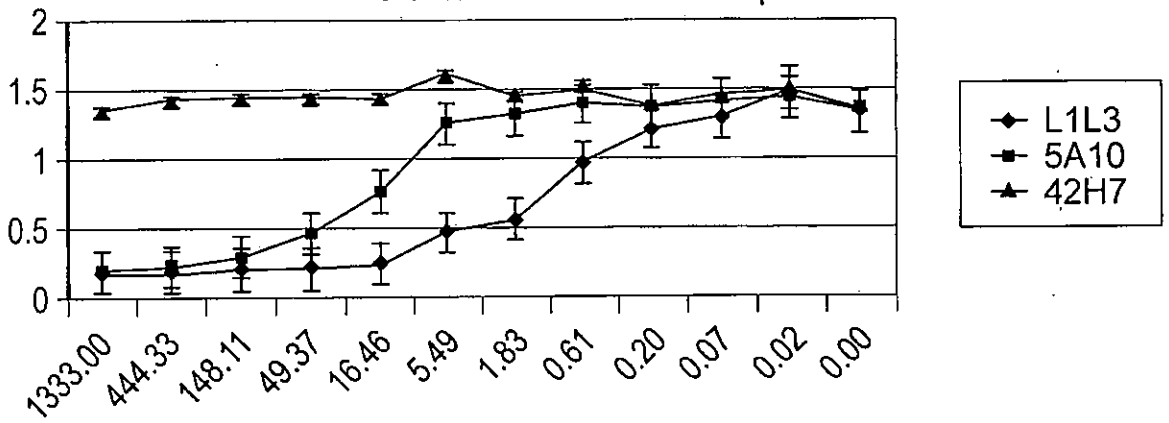


FIG. 20C 0.31nM Mouse PCSK9 pH 7.5

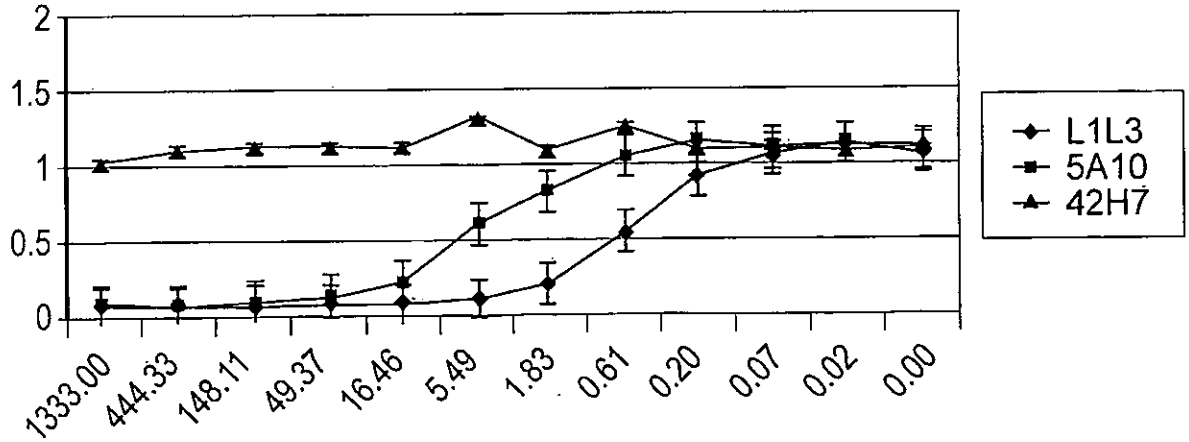


FIG. 20D

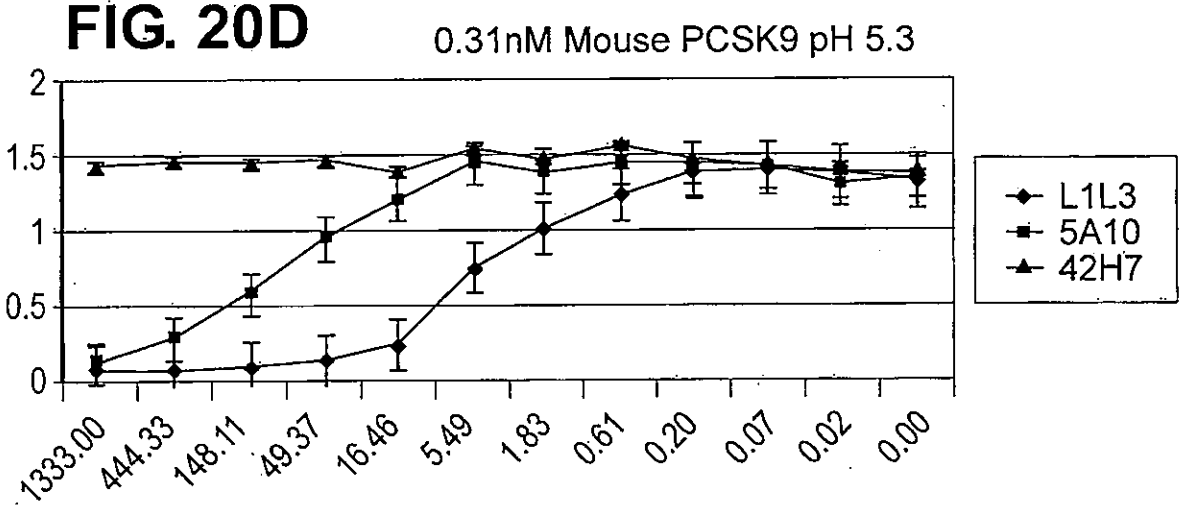


FIG. 21

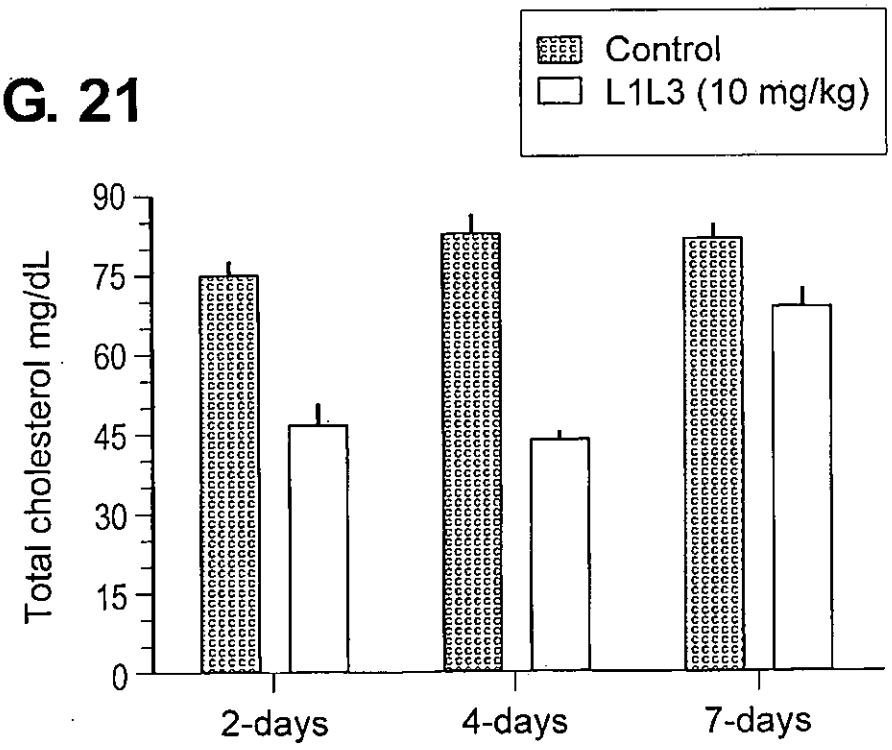


FIG. 22

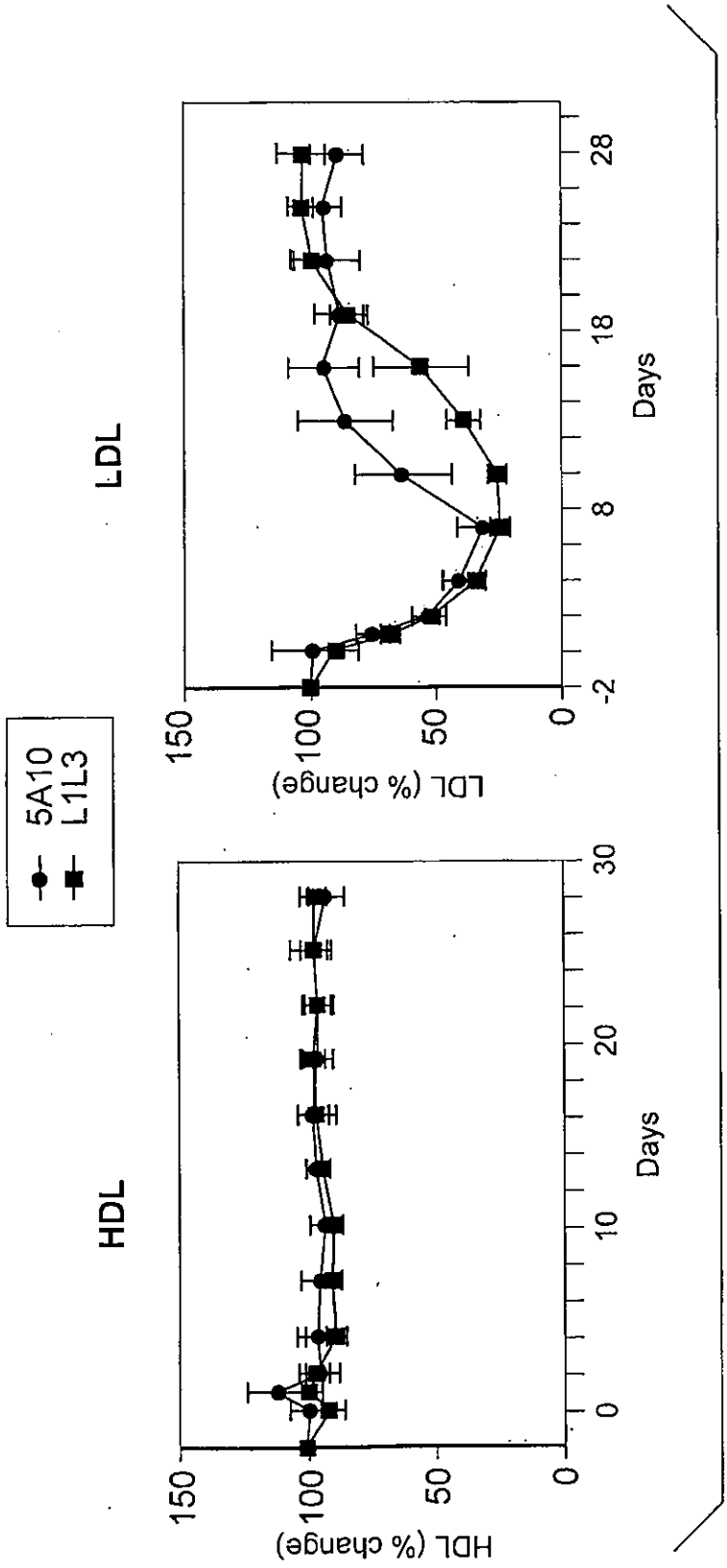

LDL
LDL (% change)
150
100
50
0
-2
8
18
28
Days
5A10
L1L3
HDL
HDL (% change)
150
100
50
0
0
10
20
30
Days

FIG. 23A

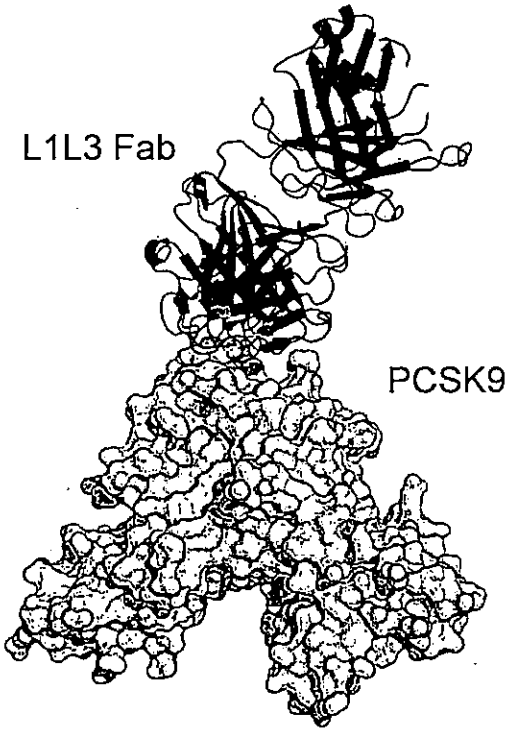


FIG. 23B

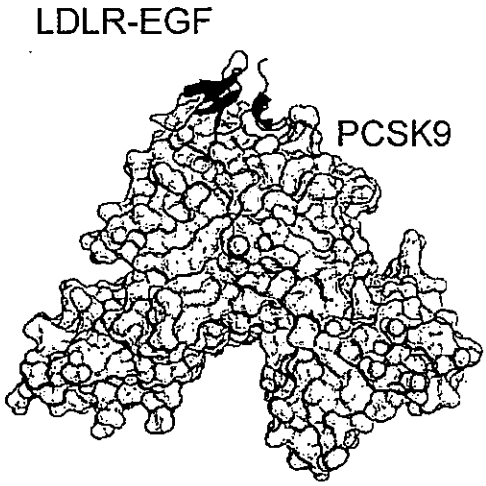
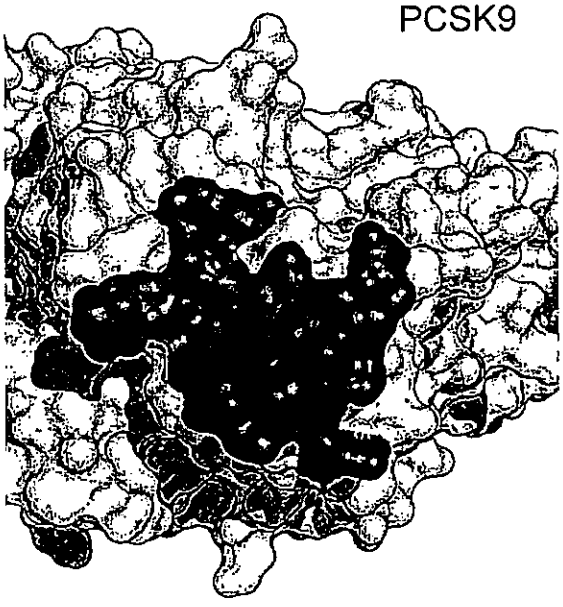
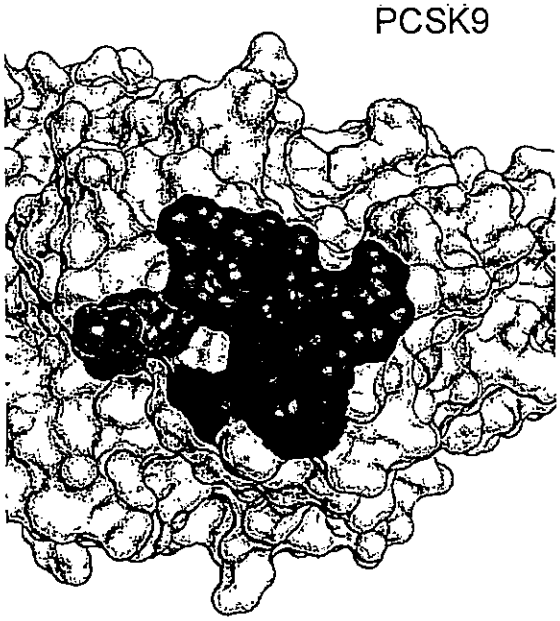


FIG. 23C



L1L3 Epitope

FIG. 23D



LDLR-EGF Epitope

FIG. 24A

L1	L2	L3	H1	H2	H3	k_{off} [1/s]	K_D [pM]
KASQDVSTAVA 30	SASYRYT 12	QQRYSTPRT 31	GYTFTSYWMH 57	EINPSNGRTNYNEKFKS 44	ERPLYAMDY 45		1100
QDVSTAVA 62							620000
GGTRVVSTAVA 63							
RGDFVSTAVA 64							
KASQDVSTAVA 30	SASYRYT 12	QQRYSTPRT 31	GYTFTSY**Y**MH 59	EINPSNGRTNYNEKFKS 44	ERPLYAMDY 45	$9x10^{-4}$	
				EINPS**G**GRTNYNEKFKS 65		$1x10^{-3}$	
				EINPS**S**GRTNYNEKFKS 66		$1x10^{-3}$	
				EINPS**T**GRTNYNEKFKS 67		$1x10^{-3}$	
				EINPS**I**GRTNYNEKFKS 68		$8x10^{-4}$	
				EINPS**DS**RTNYNEKFKS 69		$1x10^{-3}$	
				EINPS**GN**RTNYNEKFKS 70		$1x10^{-3}$	
				EINPS**SS**RTNYNEKFKS 71		$1x10^{-3}$	
KASQDVSTAVA 30	SASYRYT 12	QQRYSTPRT 31	GYTFTSY**Y**MH 59	EINPSNGRTNYNEKFKS 44	ERPLYAMDY 72	$9x10^{-4}$	
					ERPLYA**A**DY 73	$9x10^{-4}$	
					ERPLYA**I**DY 74	$3x10^{-3}$	
					ERPLYA**R**DY 75	$5x10^{-3}$	
					ERPLYA**G**DY 76	$1x10^{-3}$	
					ERPLYA**K**DY 77	$1x10^{-3}$	
					ERPLYA**P**DY 78	$7x10^{-3}$	
					ERPLYA**S**DY 79	$8x10^{-3}$	
					ERPLYA**L**DY 80	$1x10^{-3}$	
					ERPLYA**V**DY 81	$2x10^{-3}$	
					ERPLYA**W**DY 82	$2x10^{-3}$	
					ERPLYA**H**DY 83	$9x10^{-3}$	

SUBSTITUTE SHEET (RULE 26)

FIG. 24B

L1	L2	L3	H1	H2	H3	k_{off} [1/s]	K_D [pM]
					ERPLYAFDY 84	$2x10^{-3}$	
					ERPLYATDY 85	$1x10^{-3}$	
KASQDVSTAVA 30	SASYRYT 12	QQRYSTPRT 31	GYTFTSYYMH 59	EINPSGGRTNYNEKFKS 65	ERPLYAMDY 45	$5x10^{-4}$	
		QQRFSTPRT 86				$2x10^{-4}$	
		QQRYSDWRT 87				$5x10^{-4}$	
		QQRYSSWRT 88				$4x10^{-4}$	
		QQRYSTART 89				$7x10^{-4}$	
		QQRYSLYRT 90				$6x10^{-4}$	
		QQRYSLWRT 13				$4x10^{-4}$	
		QQRYSFWRT 91				$4x10^{-4}$	
		QQRYSPWRT 92				$4x10^{-4}$	
		QQRYSGWRT 93				$4x10^{-4}$	
		QQRYSIWRT 94				$4x10^{-4}$	
		QQRYSAWRT 95				$4x10^{-4}$	
		QQRYSLFRT 96				$4x10^{-4}$	
		QQRYSTRRT 97				$4x10^{-4}$	
		QQRYSTLYT 98				$4x10^{-4}$	
		QQRYSTWRT 99				$5x10^{-4}$	
		QQRYSLART 100				$5x10^{-4}$	
		QQRYSSERT 101				$5x10^{-4}$	
		QQRYGTART 102				$5x10^{-4}$	
		QQRYSQART 103				$5x10^{-4}$	
		QQRYSLHRT 104				$6x10^{-4}$	

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FIG. 24C

L1	L2	L3	H1	H2	H3	k_{off} [1/s]	K_D [pM]
		QQRYSG**V**RT 105				$6x10^{-4}$	
		QQRYS**Q**S**R**T 106				$6x10^{-4}$	
		QQRYS**A**E**R**T 107				$6x10^{-4}$	
		QQRYS**Q**F**R**T 108				$6x10^{-4}$	
		QQRYS**S**R**R**T 109				$4x10^{-4}$	
		QQRYS**C**S**R**T 110				$3x10^{-4}$	
		QQRYST**NRR** 111				$4x10^{-4}$	
		QQRYS**R**W**R**T 112				$4x10^{-4}$	
		QQRYS**P**Y**R**T 113				$4x10^{-4}$	
		QQRYS**Y**W**R**T 114				$5x10^{-4}$	
		QQRYSG**F**RT 115				$5x10^{-4}$	
		QQRYS**Y**W**R**T 116				$5x10^{-4}$	
		QQRYS**F**K**R**T 117				$5x10^{-4}$	
		QQRYSA**R**RT 118				$5x10^{-4}$	
		QQRYS**R**Y**R**T 119				$6x10^{-4}$	
		QQRYSL**Q**RT 120				$6x10^{-4}$	
		QQRYST**S**RT 121				$6x10^{-4}$	
		QQRYSH**A**RT 122				$6x10^{-4}$	
		QQRYSK**Y**RT 123				$6x10^{-4}$	
		QQRYS**Q**S**R**T 124				$6x10^{-4}$	
		QQRYST**A**F**T** 125				$6x10^{-4}$	
		QQRYST**C**C**T** 126				$6x10^{-4}$	
		QQRYST**D**RT 127				$7x10^{-4}$	
		QQRYS**ED**RT 128				$7x10^{-4}$	

FIG. 24D

L1	L2	L3	H1	H2	H3	k_{off} [1/s]	K_D [pM]
		QQRY**VG**RT 129				$7x10^{-4}$	
		QQRYS**LS**RT 130				$7x10^{-4}$	
		QQRYS**LG**RT 131				$7x10^{-4}$	
		QQRYS**RA**RT 132				$8x10^{-4}$	
		QQRYS**HA**RT 133				$8x10^{-4}$	
		QQRYSTP**D**T 134				$9x10^{-4}$	
		QQRY**QQ**PRT 135				$9x10^{-4}$	
KASQDVSTAVA 30	SASYRYT 12	QQRYSTPRT 31	GYTFTSY**Y**MH 59	EINPSGGRTNYNEKFKS 65	ERPLYAMDY 45	$5x10^{-4}$	
				EI**QV**SGGRTNYNEKFKS 136		$9x10^{-4}$	
				EINP**WQ**GRTNYNEKFKS 137		$4x10^{-4}$	
				EINP**VQ**GRTNYNEKFKS 138		$6x10^{-4}$	
				EI**SPF**GGRTNYNEKFKS 9		$2x10^{-4}$	
				EI**SPY**GGRTNYNEKFKS 139		$3x10^{-4}$	
				EI**QE**SGGRTNYNEKFKS 140		$3x10^{-4}$	
				EI**SPI**GGRTNYNEKFKS 141		$4x10^{-4}$	
				EINP**EH**GRTNYNEKFKS 142		$4x10^{-4}$	
				EINP**SE**GRTNYNEKFKS 143		$4x10^{-4}$	
				EINP**WM**GRTNYNEKFKS 144		$5x10^{-4}$	
				EINP**Q**GGRTNYNEKFKS 145		$5x10^{-4}$	
				EINP**VK**GRTNYNEKFKS 146		$5x10^{-4}$	
				EI**GPW**GGRTNYNEKFKS 147		$5x10^{-4}$	
				EINP**I**GGRTNYNEKFKS 148		$6x10^{-4}$	
				EI**QI**SGGRTNYNEKFKS 149		$7x10^{-4}$	

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FIG. 24E

L1	L2	L3	H1	H2	H3	k_{off} [1/s]	K_D [pM]
				EINPQGTRTNYNEKFKS 150		$8x10^{-4}$	
KASQDVSTAVA 30	SASYRYT 12	QQRYSTPRT 31	GYTFTSYYMH 59	EINPSGGRTNYNEKFKS 65	ERPLYAMDY 45	$5x10^{-4}$	
					ERPLYASDS 151	$2x10^{-4}$	
					ERPLYASDR 152	$2x10^{-4}$	
					ERPLYAMDR 153	$2x10^{-4}$	
					ERPLYANDA 154	$3x10^{-4}$	
					ERPLYANDV 155	$3x10^{-4}$	
					ERPLYAHDV 156	$4x10^{-4}$	
					ERPLYASDY 157	$4x10^{-4}$	
					ERPLYASDL 10	$3x10^{-4}$	
					ERPLYASDV 158	$5x10^{-4}$	
					ERPLYASDA 159	$5x10^{-4}$	
					ERPLYANDS 160	$5x10^{-4}$	
					ERPLYATDL 161	$3x10^{-4}$	
					ERPLYASDS 162	$6x10^{-4}$	
					ERPLYANDM 163	$3x10^{-4}$	
					ERPLYAHDL 164	$4x10^{-4}$	
					ERPLYAHDI 165	$6x10^{-4}$	
KASQDVSTAVA 30	SASYRYT 12	QQRYSTPRT 31	GYTFTSYYMH 59	EINPSGGRTNYNEKFKS 65	ERPLYAMDY 45		1470
					ERPLYANDV 166		342
					ERPLYASDY 167		755
					ERPLYASDL 10		343
					ERPLYASDR 168		271

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FIG 24F

L1	L2	L3	H1	H2	H3	k_{off} [1/s]	K_D [pM]
					ERPLYASDV 169		286
					ERPLYAHDV 170		385
					ERPLYANDM 171		413
					ERPLYAHDL 172		376
				EINPWQGRTNYNEKFKS 173			1390
				EINPVQGRTNYNEKFKS 174			439
				EISPYGGRTNYNEKFKS 175			216
				EISPFGGRTNYNEKFKS 9			239
				EIGPWGGRTNYNEKFKS 176			363
		QQRYSDWRT 177					616
		QQRYSSWRT 178					728
		QQRYSAERT 179					345
		QQRYSLHRT 180					228
		QQRYSLWRT 13					94
		QQRYSSERT 181					886
		QQRYSLQRT 182					497
		QQRYSTRRT 183					297
							KD at 37C
		QQRYSLWRT 13		EISPFGGRTNYNEKFKS 9			343
		QQRYSLWRT 13			ERPLYASDL 10		384
				EISPFGGRTNYNEKFKS 9	ERPLYASDL 10		253
		QQRYSLWRT 13		EISPFGGRTNYNEKFKS 9	ERPLYASDL 10		183
		QQRYSDWRT 184			ERPLYASDL 10		466

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FIG. 24G

L1	L2	L3	H1	H2	H3	k_{off} [1/s]	K_D [pM]
					ERPLYASDL 10		703
							KD at 37C
				EISPFGGRTNYNEKFKS 9	ERPLYASDL 10		155
		QQRYSLWRT 13		EISPFGGRTNYNEKFKS 9	ERPLYASDL 10		79
				EISPYGGRTNYNEKFKS 185	ERPLYASDL 10		215
		QQRYSRSRT 186			ERPLYASDL 10		621
					ERPLYASDL 10		968
KASQDVSTAVA 30	SASYRYT 12	QQRYSTPRT 31	GYTFTSYYMH 59	EINPSGGRTNYNEKFKS 65	ERPLYAMDY 45		1470
RASQGISSALA 11							1660
	GASYLHS 186						9890
	DASNRAT 187						105000
RASQGISSALA 11	SASYRYT 12	QQRYSLWRT 13	GYTFTSYYMH 59	EISPFGGRTNYNEKFKS 9	ERPLYASDL 10		7

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