FIGURE 1

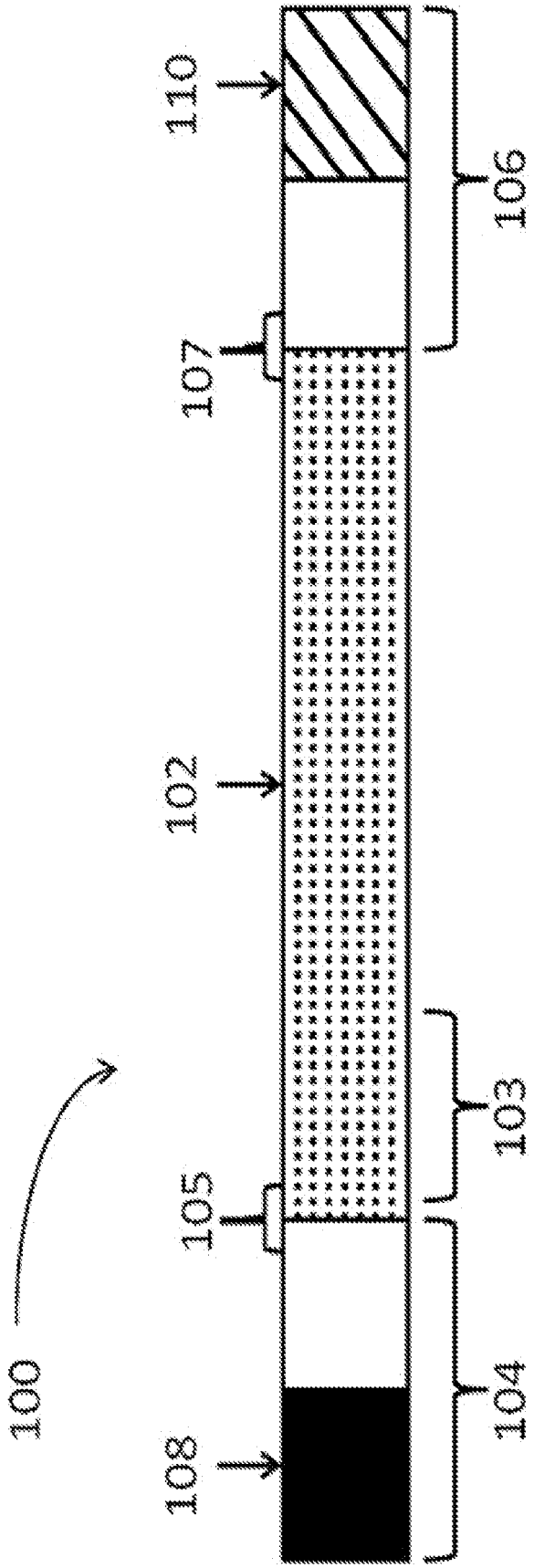


FIGURE 2

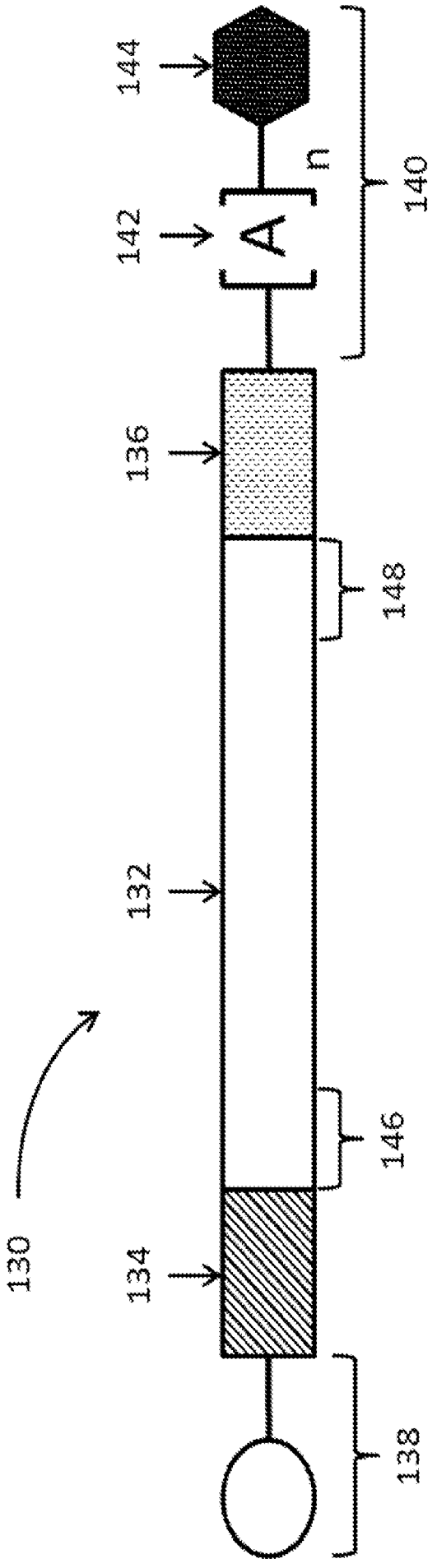


FIGURE 3

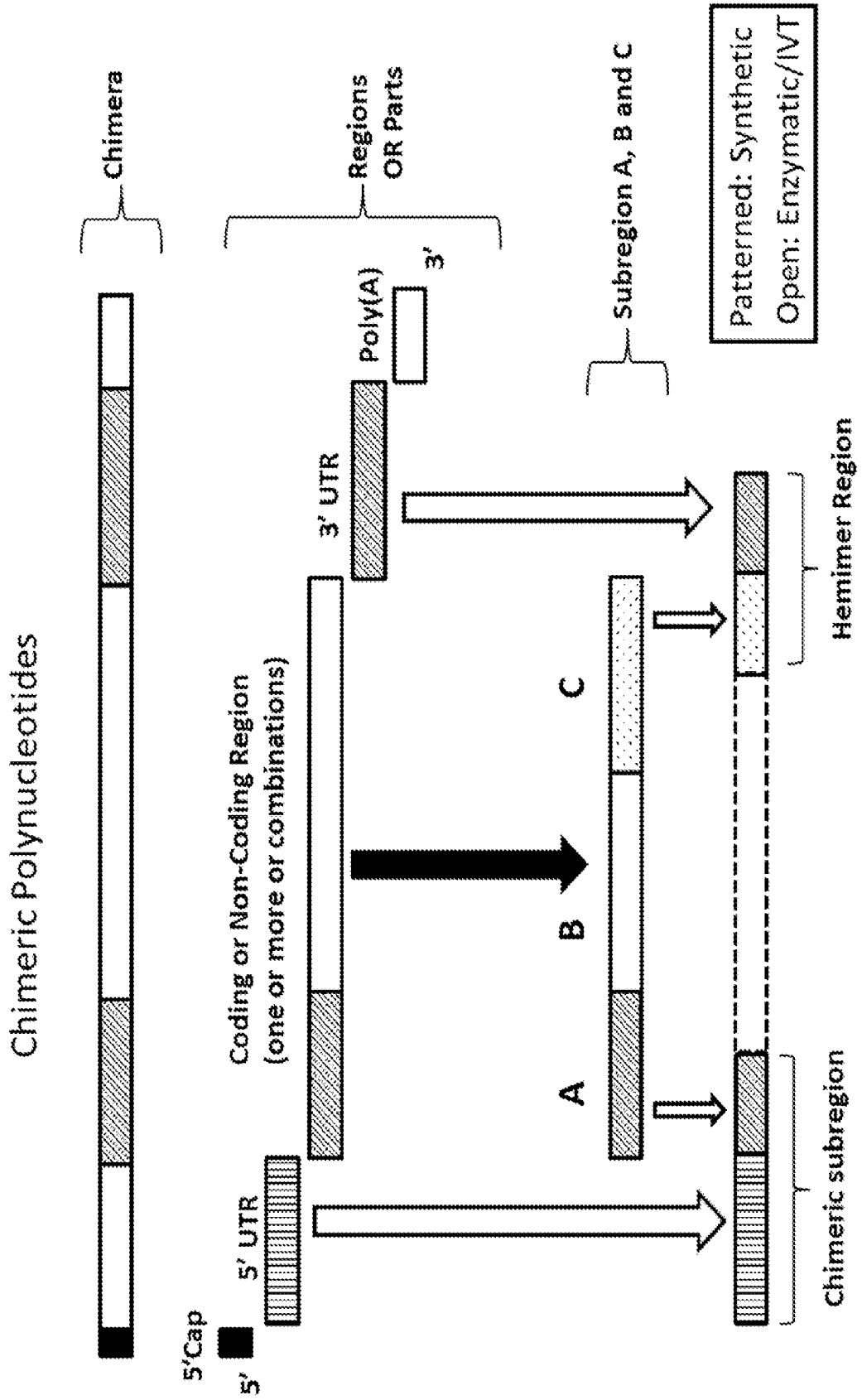

Chimeric Polynucleotides
Chimera
Regions
OR Parts
Subregion A, B and C
Patterned: Synthetic
Open: Enzymatic/IVT
5'Cap
5'
5' UTR
Coding or Non-Coding Region
(one or more or combinations)
3' UTR
Poly(A)
3'
A
B
C
Hemimer Region
Chimeric subregion

FIGURE 4

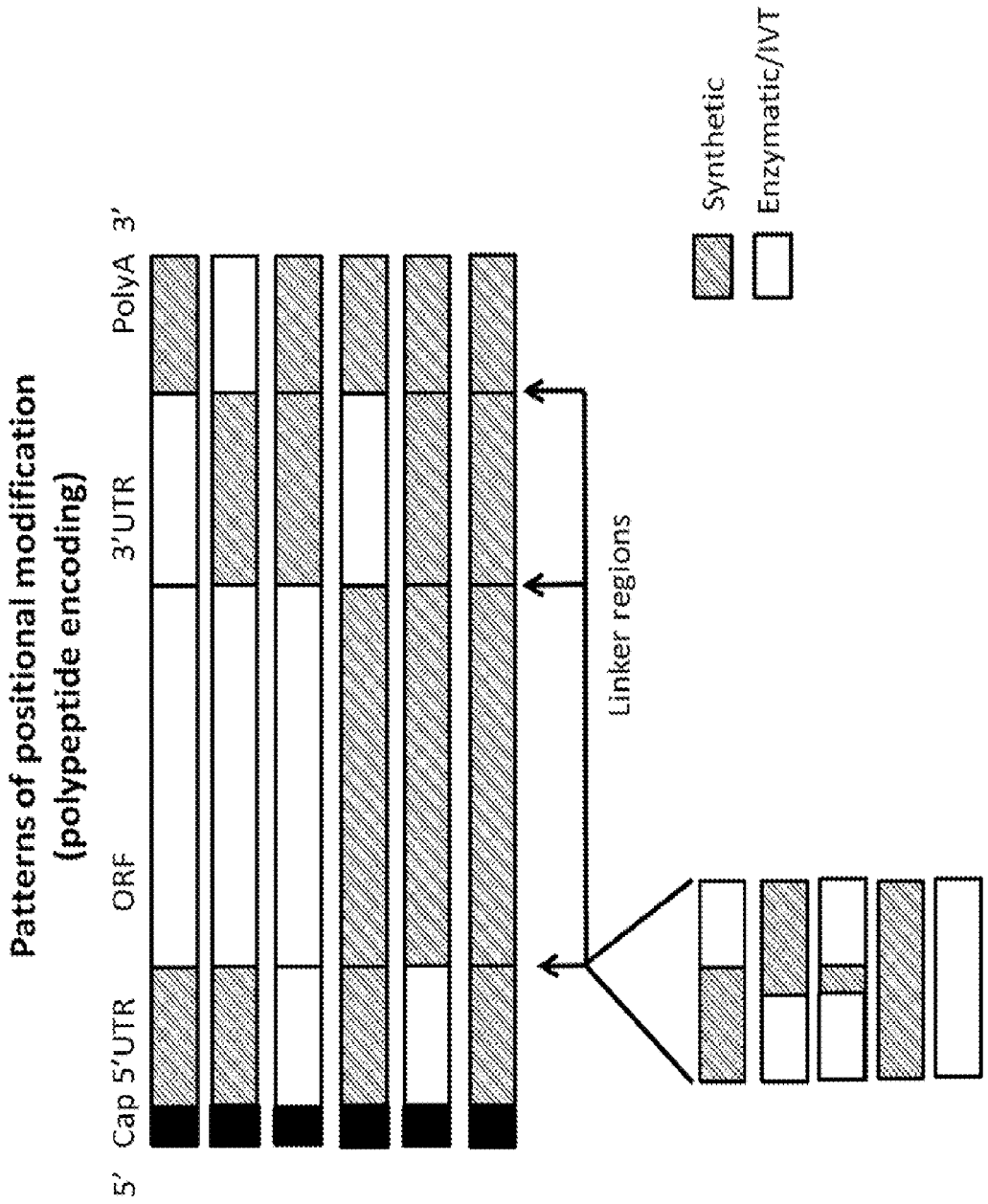

Patterns of positional modification
(polypeptide encoding)
5'
Cap
5'UTR
ORF
3'UTR
PolyA
3'
Linker regions
Synthetic
Enzymatic/IVT

FIGURE 5

Patterns of positional modification

A (L) B (L) C (L)
5′[NNNNN$_n$]$_x$ L1 [NNNNNNNNNNN$_o$]$_y$ L2 [XXXXXXXXXXXX$_p$]$_z$ L3 3′
5′[NNNNN$_n$]$_x$ L1 [XXXXXXXXXXXXXX$_o$]$_y$ L2 [XXXXXXXXXXXXX$_p$]$_z$ L3 3′
5′[XXXXXX$_n$]$_x$ L1 [XXXXXXXXXXXXXX$_o$]$_y$ L2 [XXXXXXXXXXXXX$_p$]$_z$ L3 3′
5′[NNNNN$_n$]$_x$ L1 [NNNNNNNNNNN$_o$]$_y$ L2 [XXXXXXXXXXXX$_p$]$_z$ L3 3′

A, B, C- Region or Part of chimeric polynucleotide
N-nucleoside
n, o, p-number of nucleosides
x, y, z-number of regions
X-selective placement nucleoside
L-linker (optional)

FIGURE 6

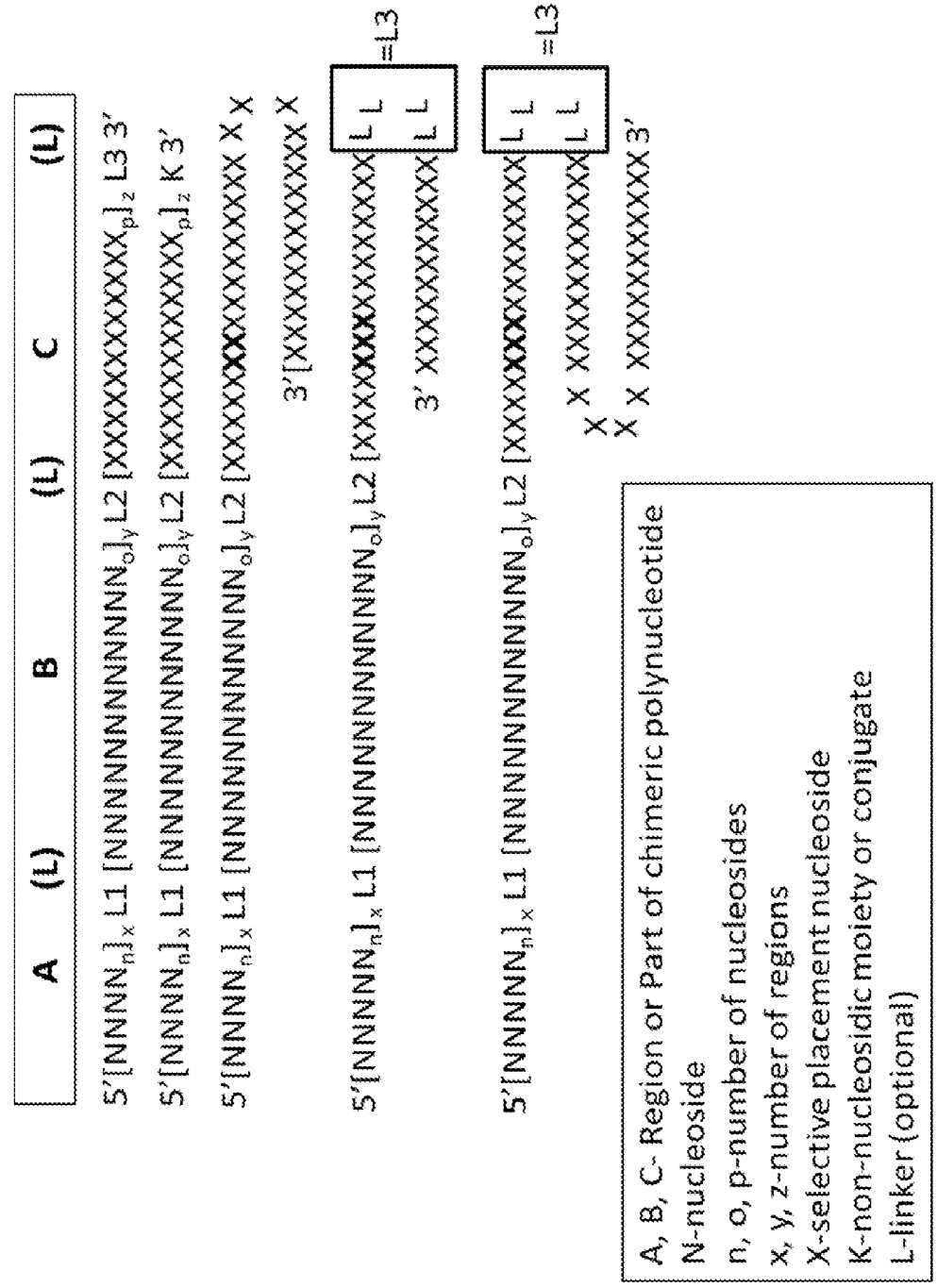

Blocked or structured 3' termini
A (L) B (L) C (L)
5'[NNNNn]x L1 [NNNNNNNNNNNNo]y L2 [XXXX

FIGURE 7

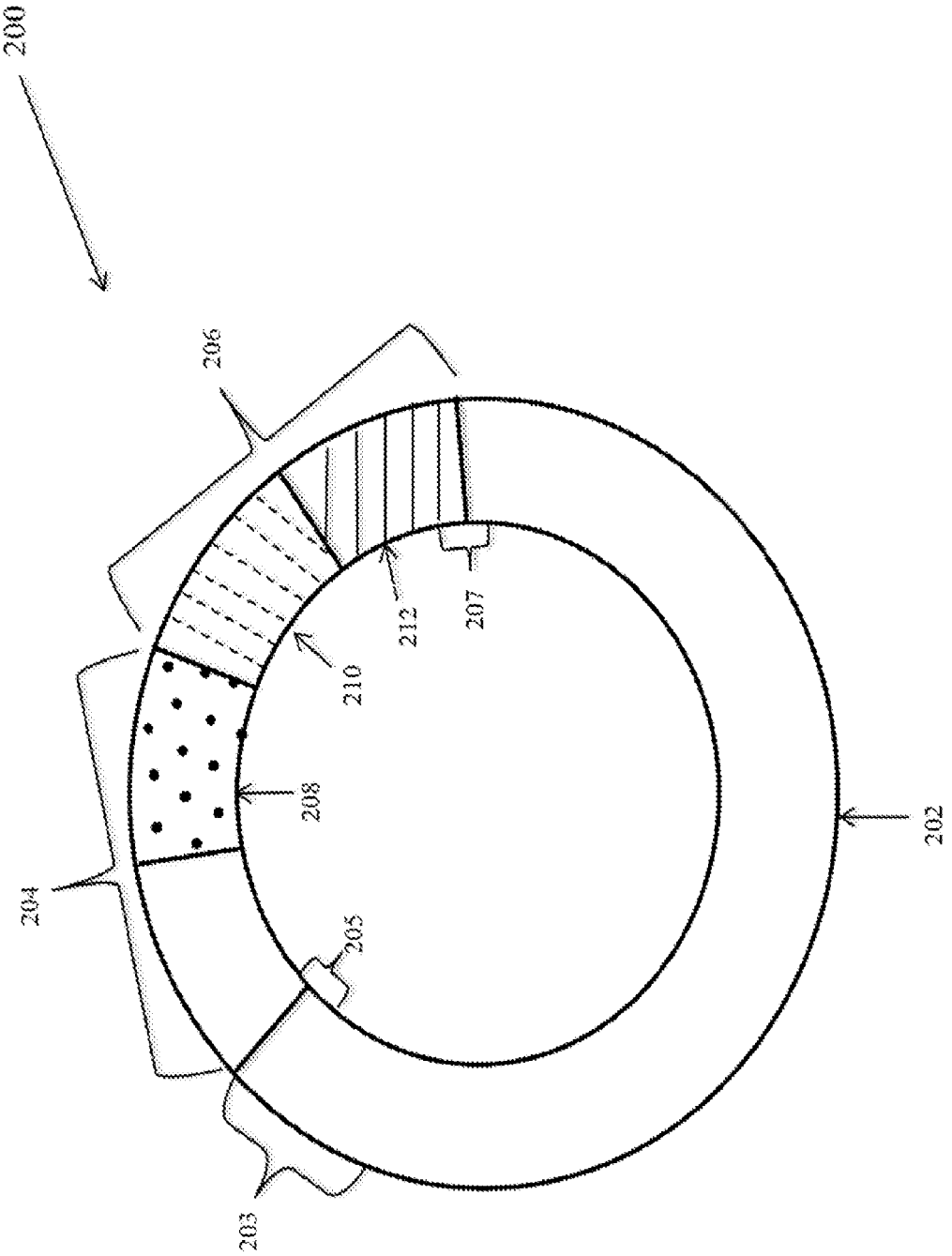


FIGURE 8

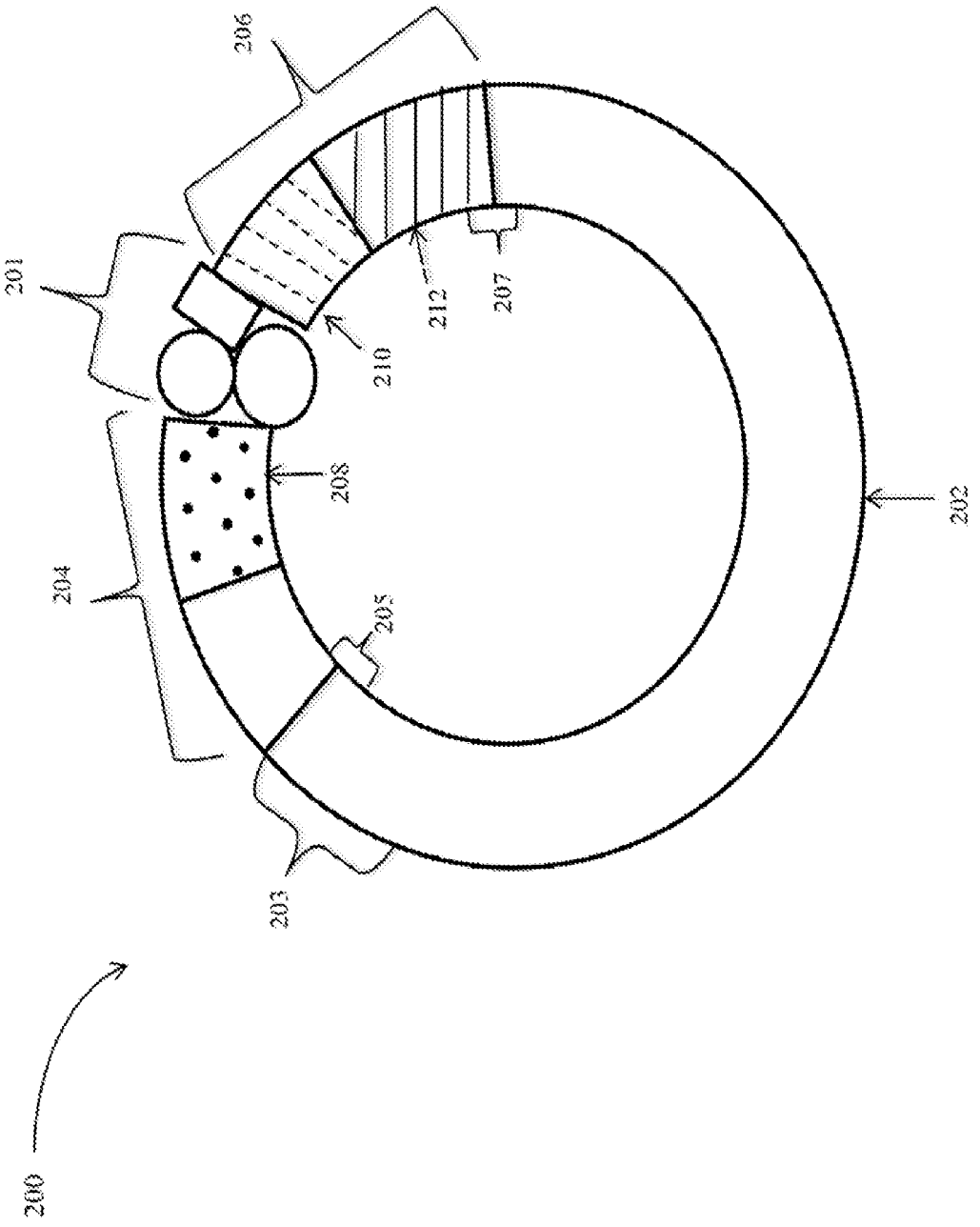


FIGURE 9

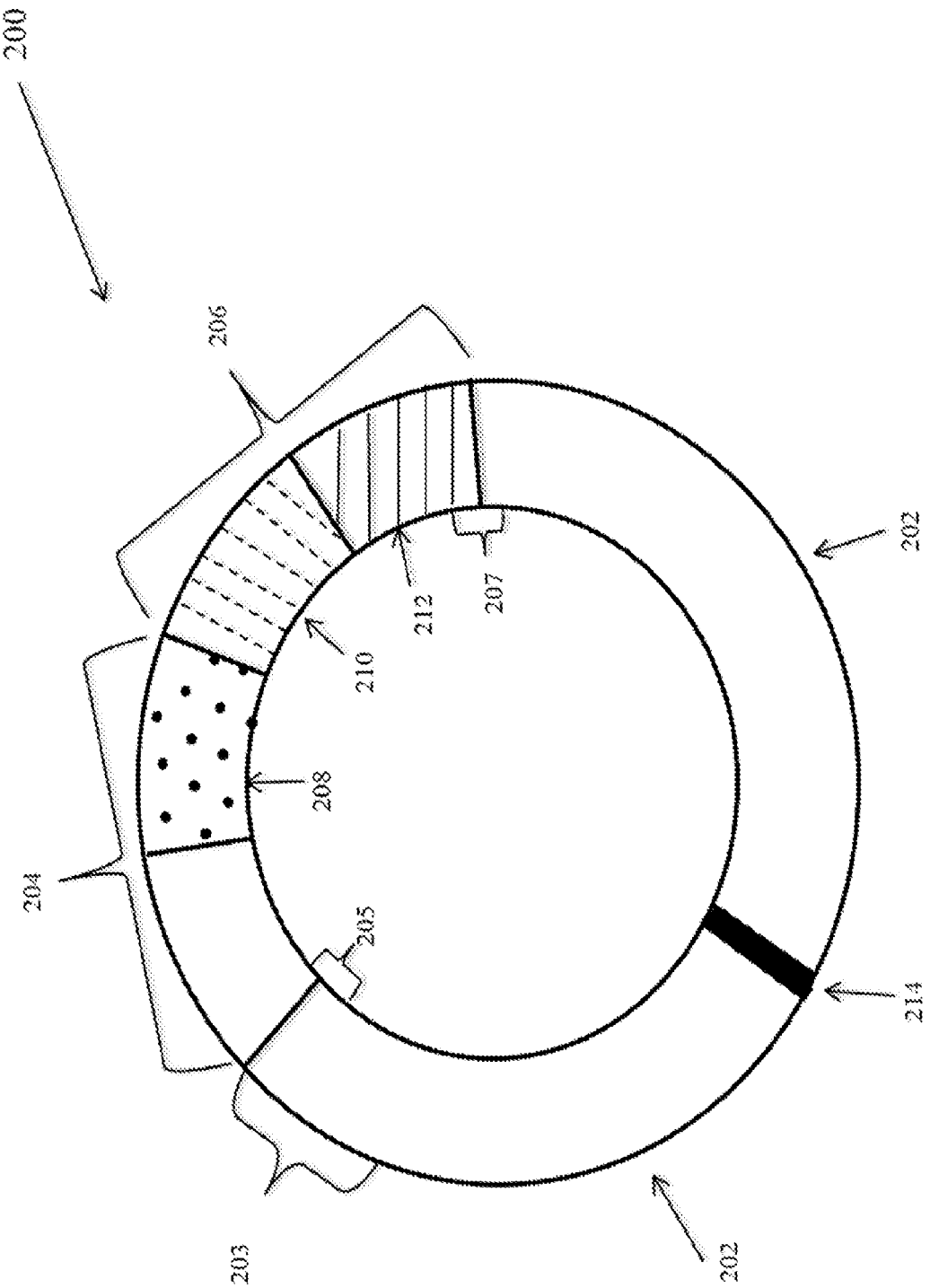


FIGURE 10

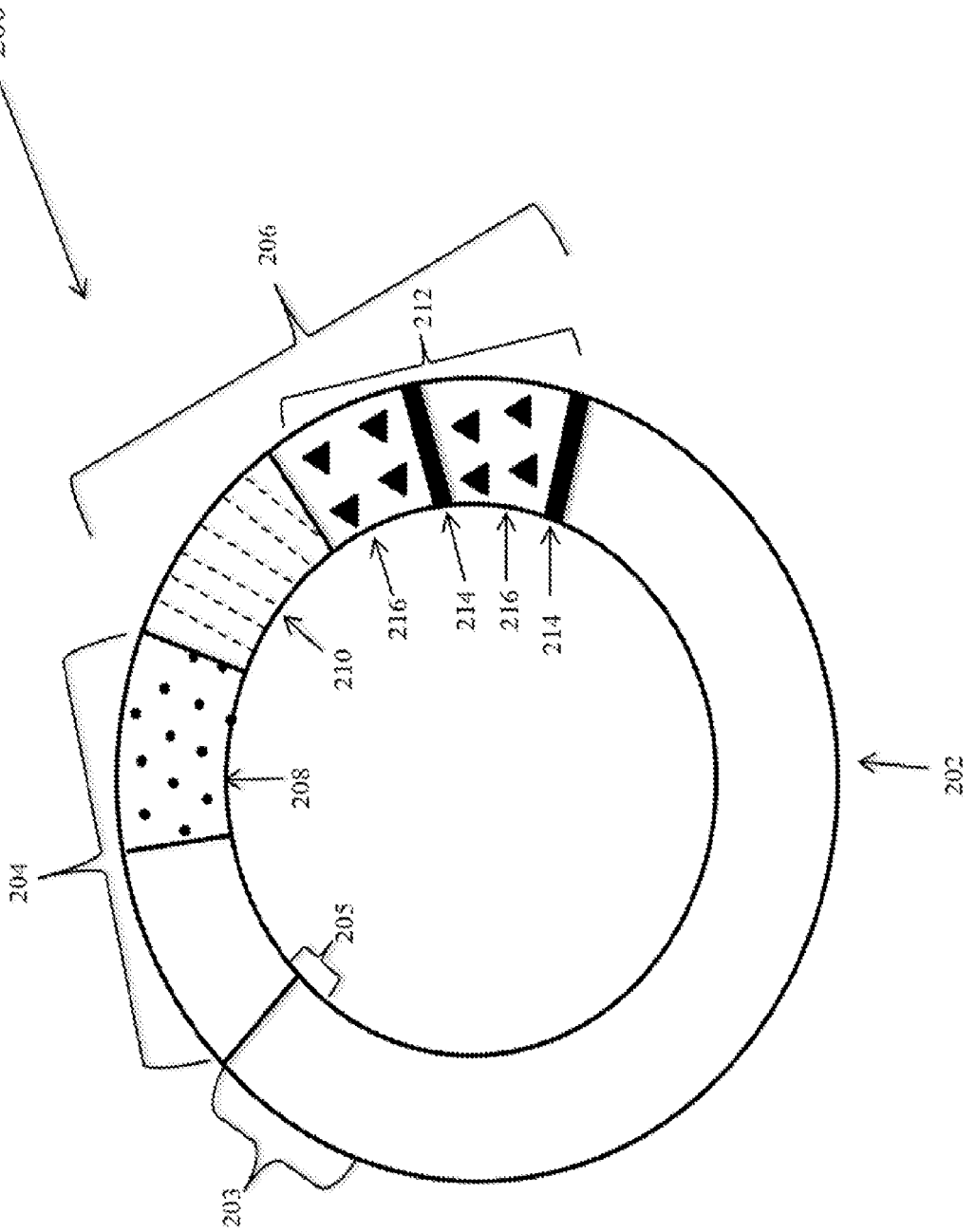


FIGURE 11

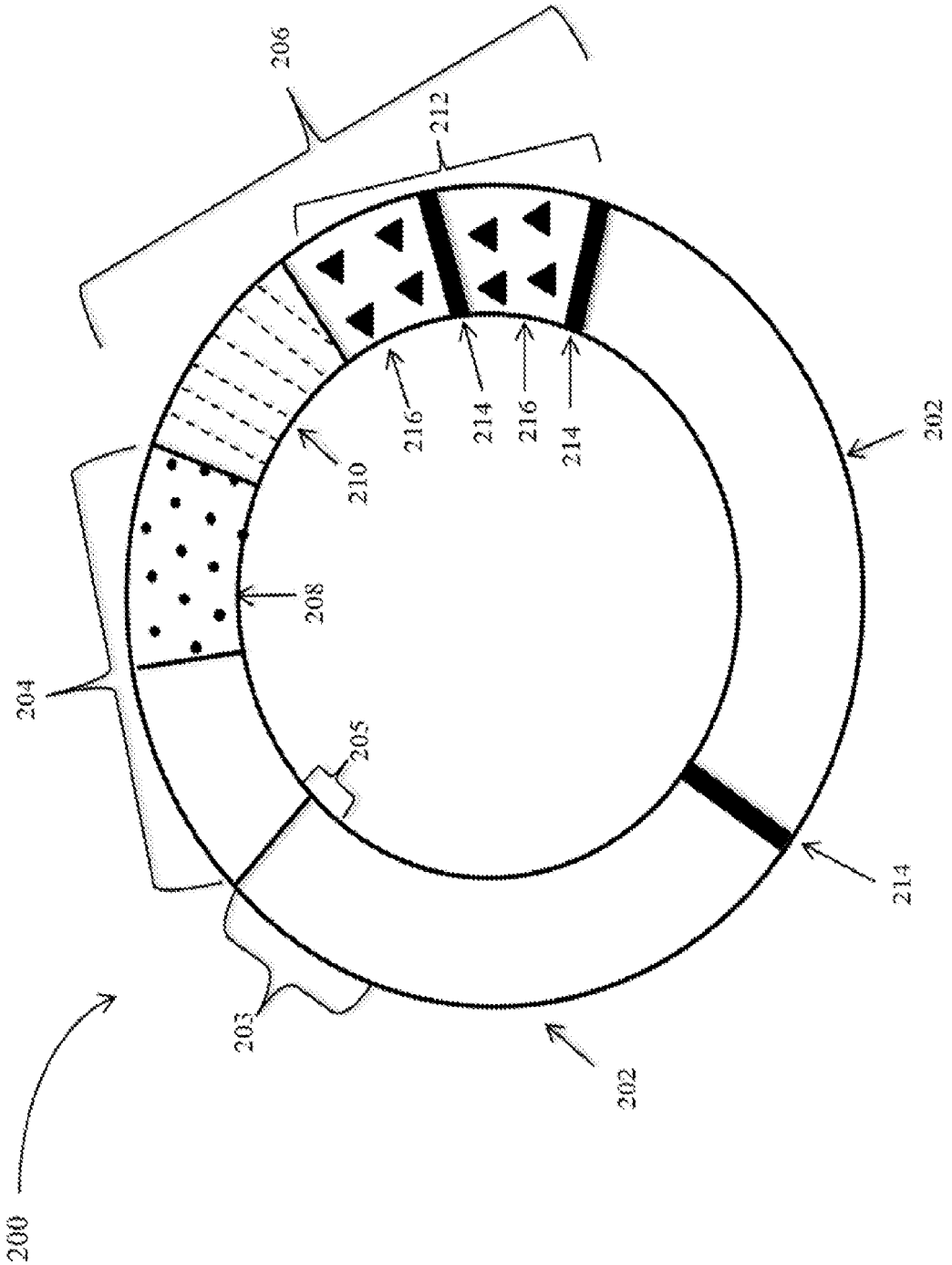


FIGURE 12

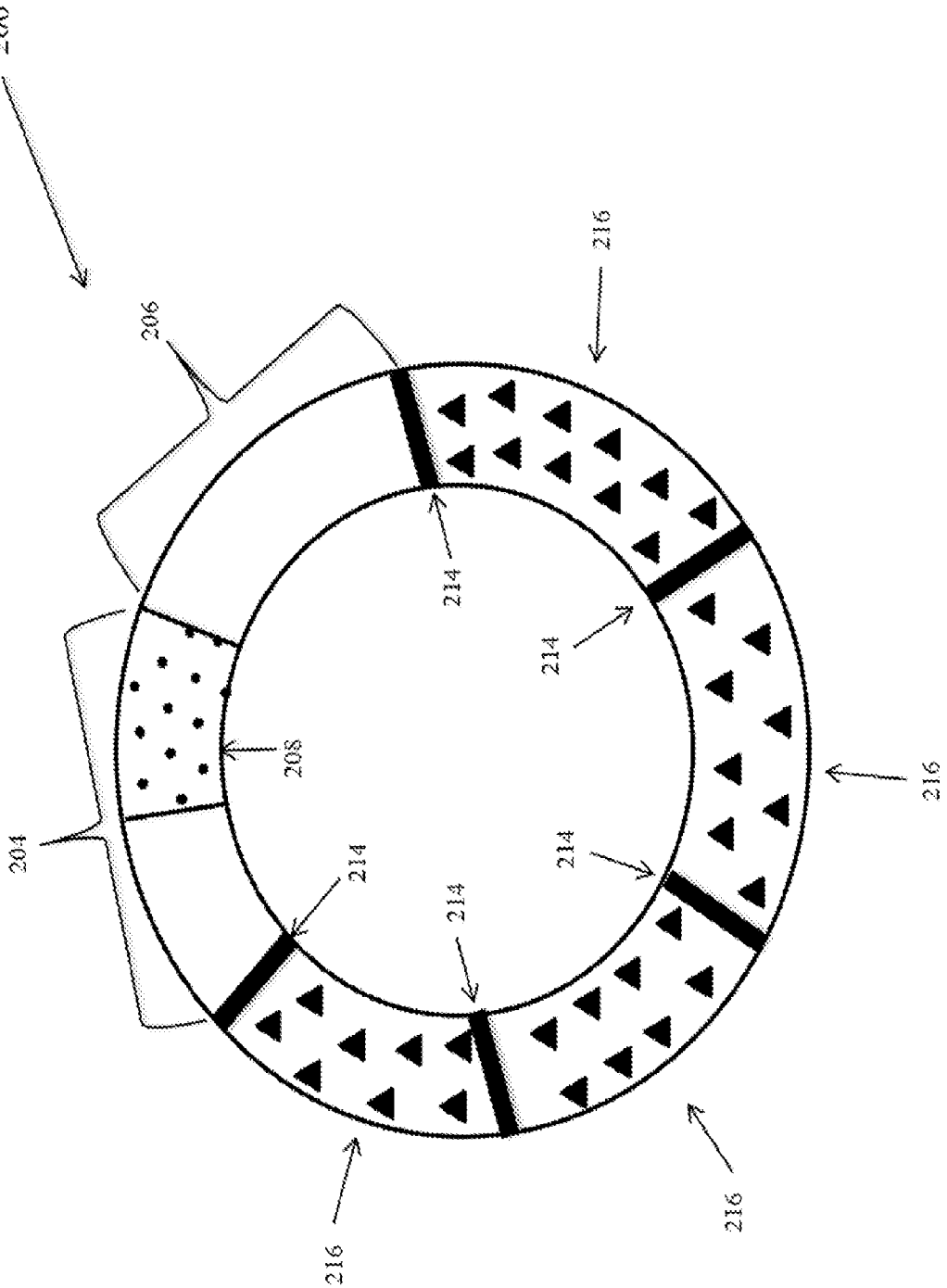


FIGURE 13

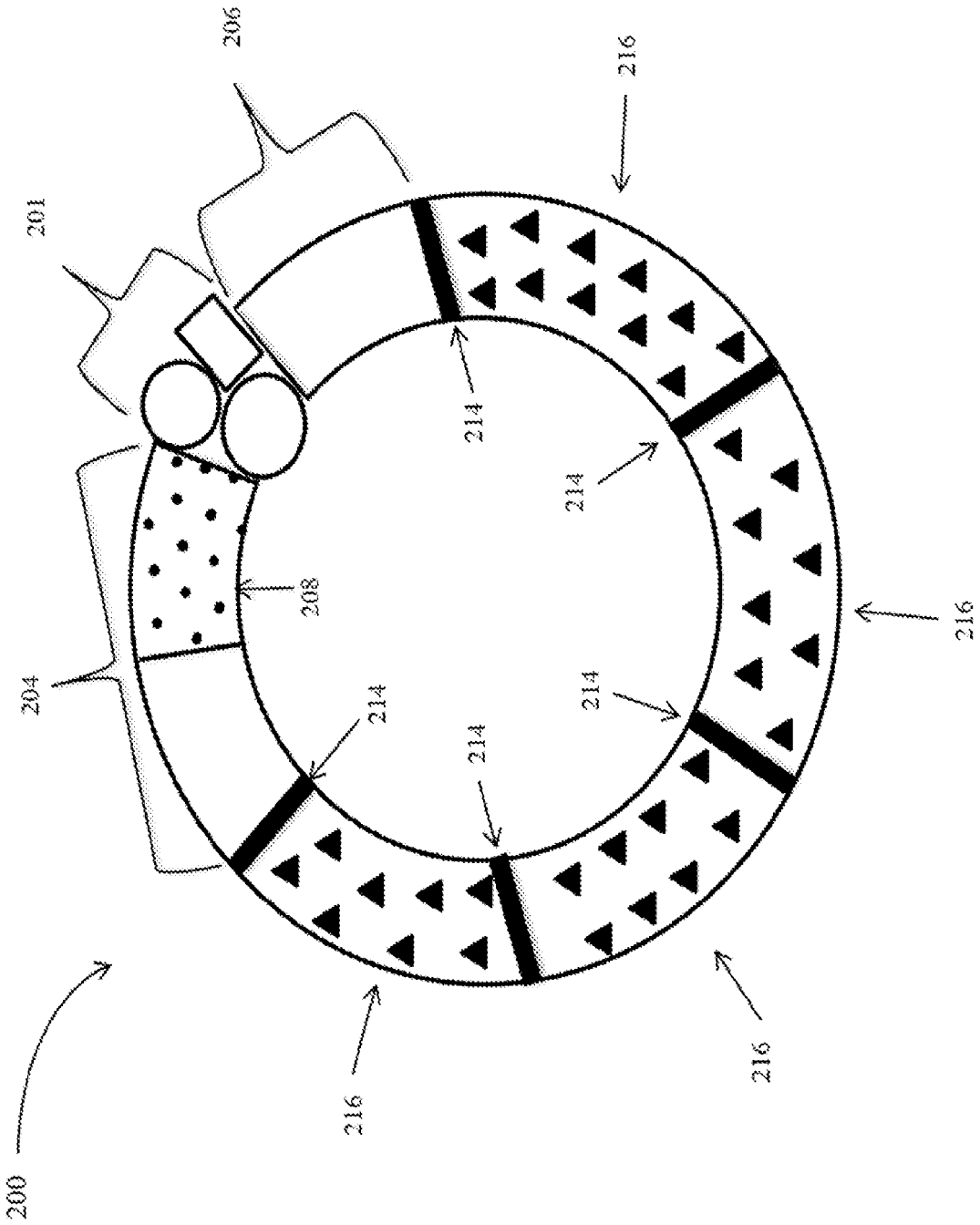
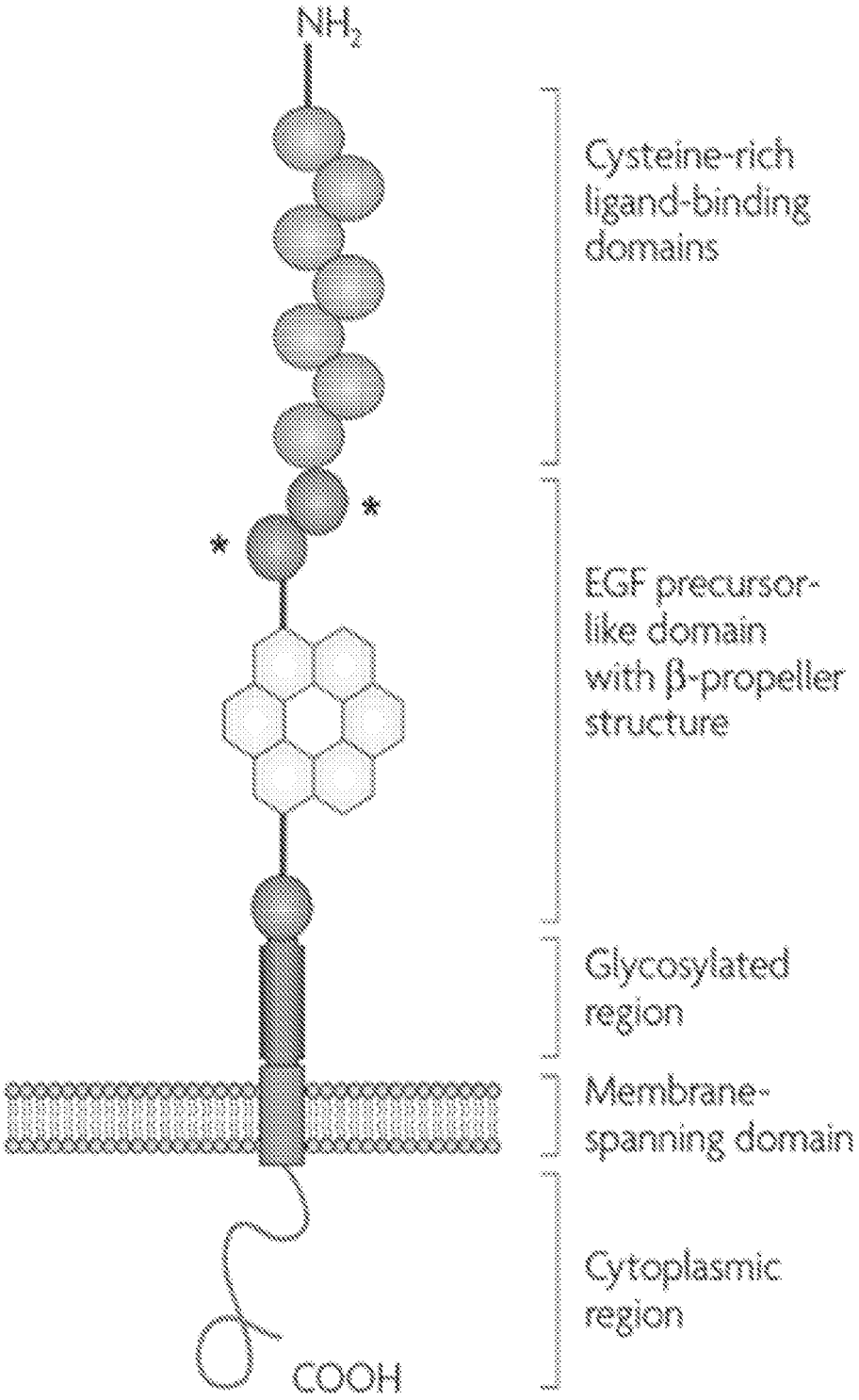
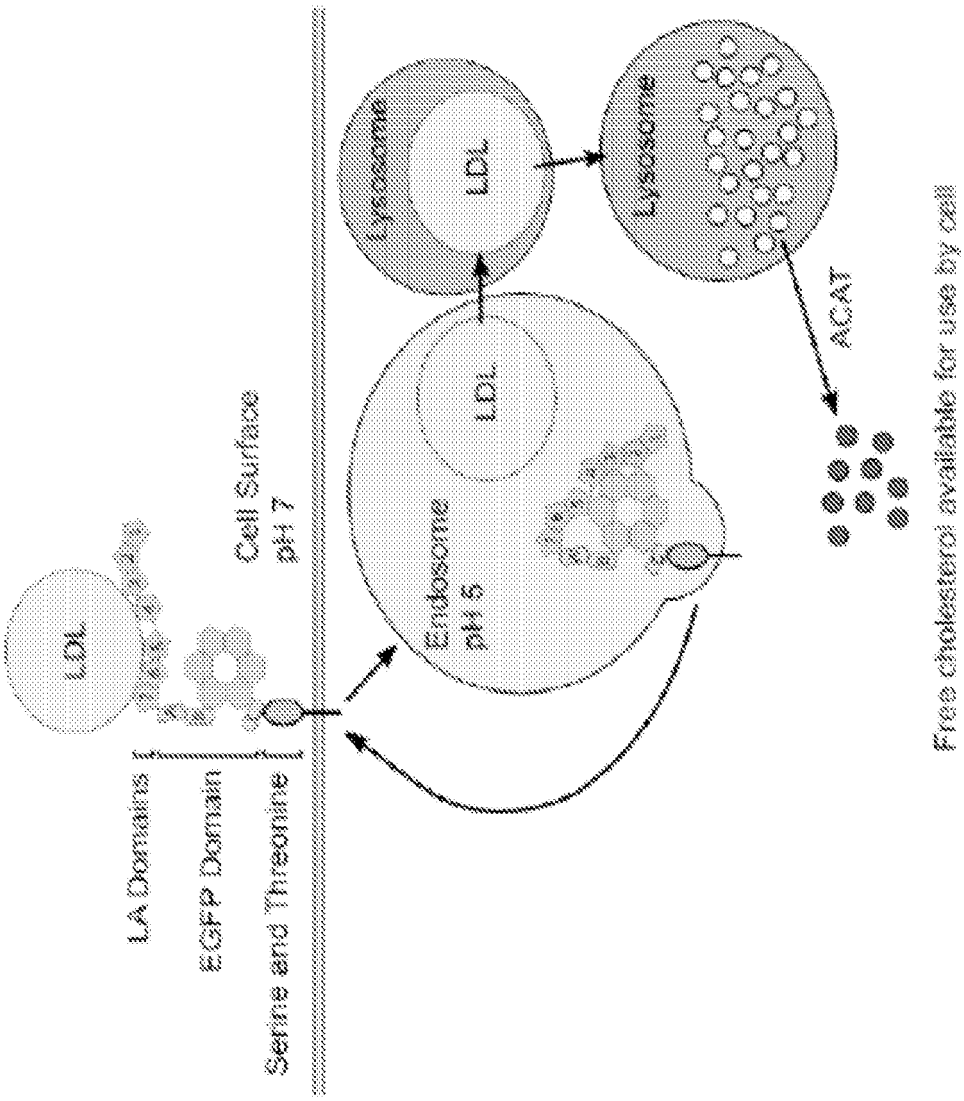


FIGURE 14



PRIOR ART

FIGURE 15



PRIOR ART

FIGURE 16

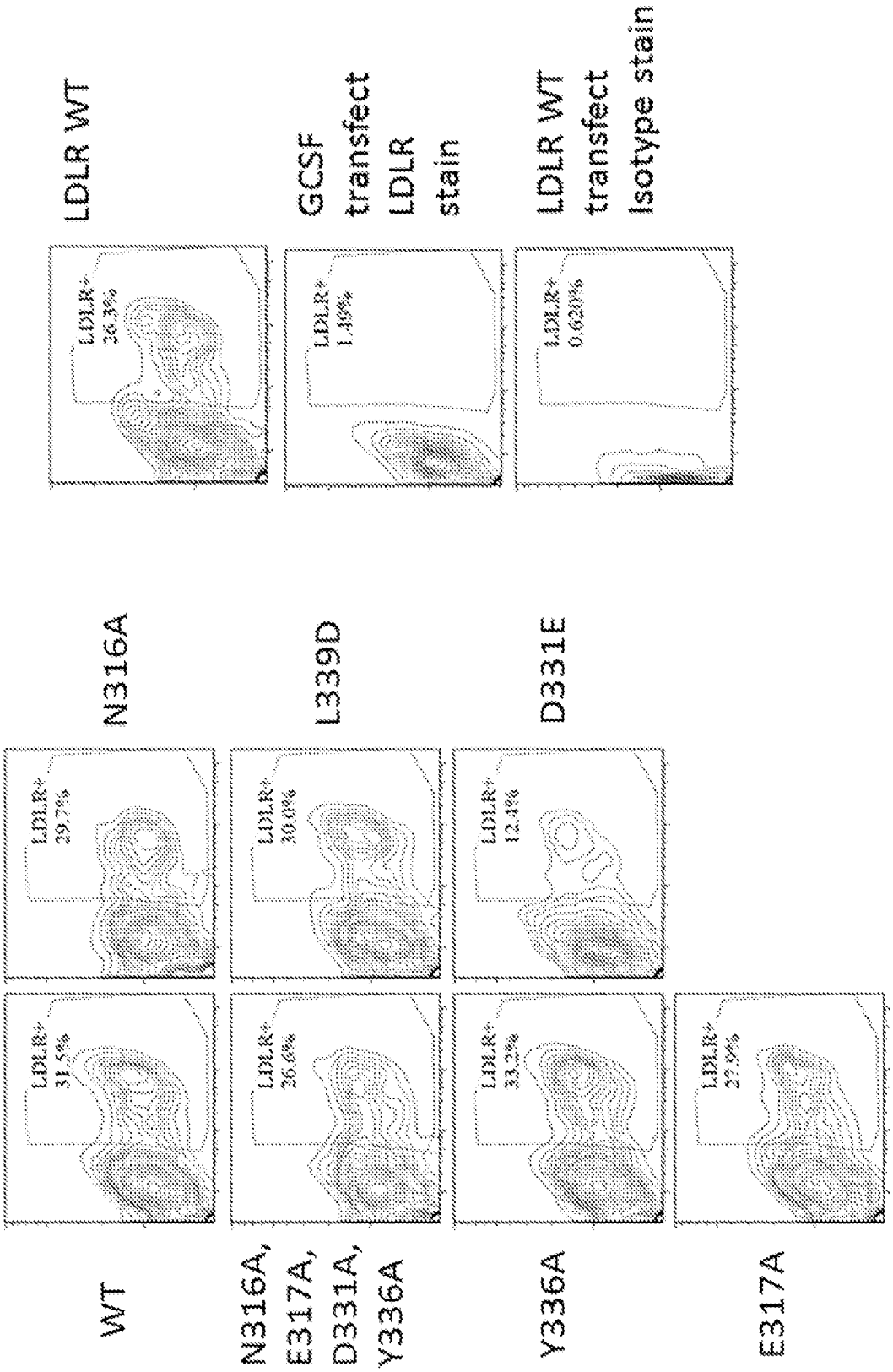

LDLR WT
GCSF transfect LDLR stain
LDLR WT transfect Isotype stain
LDLR+ 26.3%
LDLR+ 1.49%
LDLR+ 0.620%
N316A
L339D
D331E
LDLR+ 29.7%
LDLR+ 30.0%
LDLR+ 12.4%
WT
N316A, E317A, D331A, Y336A
Y336A
E317A
LDLR+ 31.5%
LDLR+ 26.6%
LDLR+ 33.2%
LDLR+ 27.9%

FIGURE 17

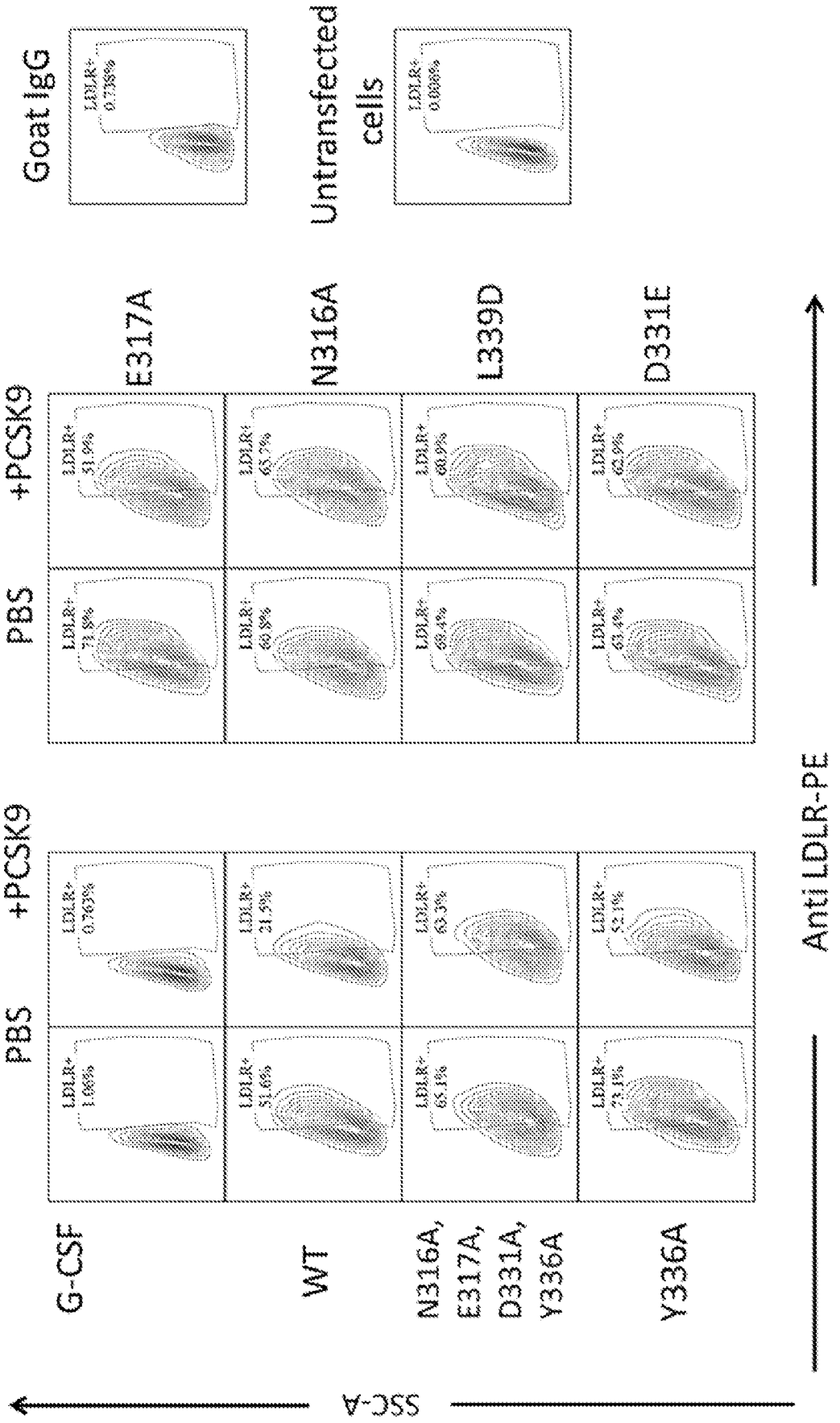

Goat IgG
Untransfected cells
E317A
N316A
L339D
D331E
PBS
+PCSK9
G-CSF
WT
N316A, E317A, D331A, Y336A
Y336A
SSC-A
Anti LDLR-PE

FIGURE 18A

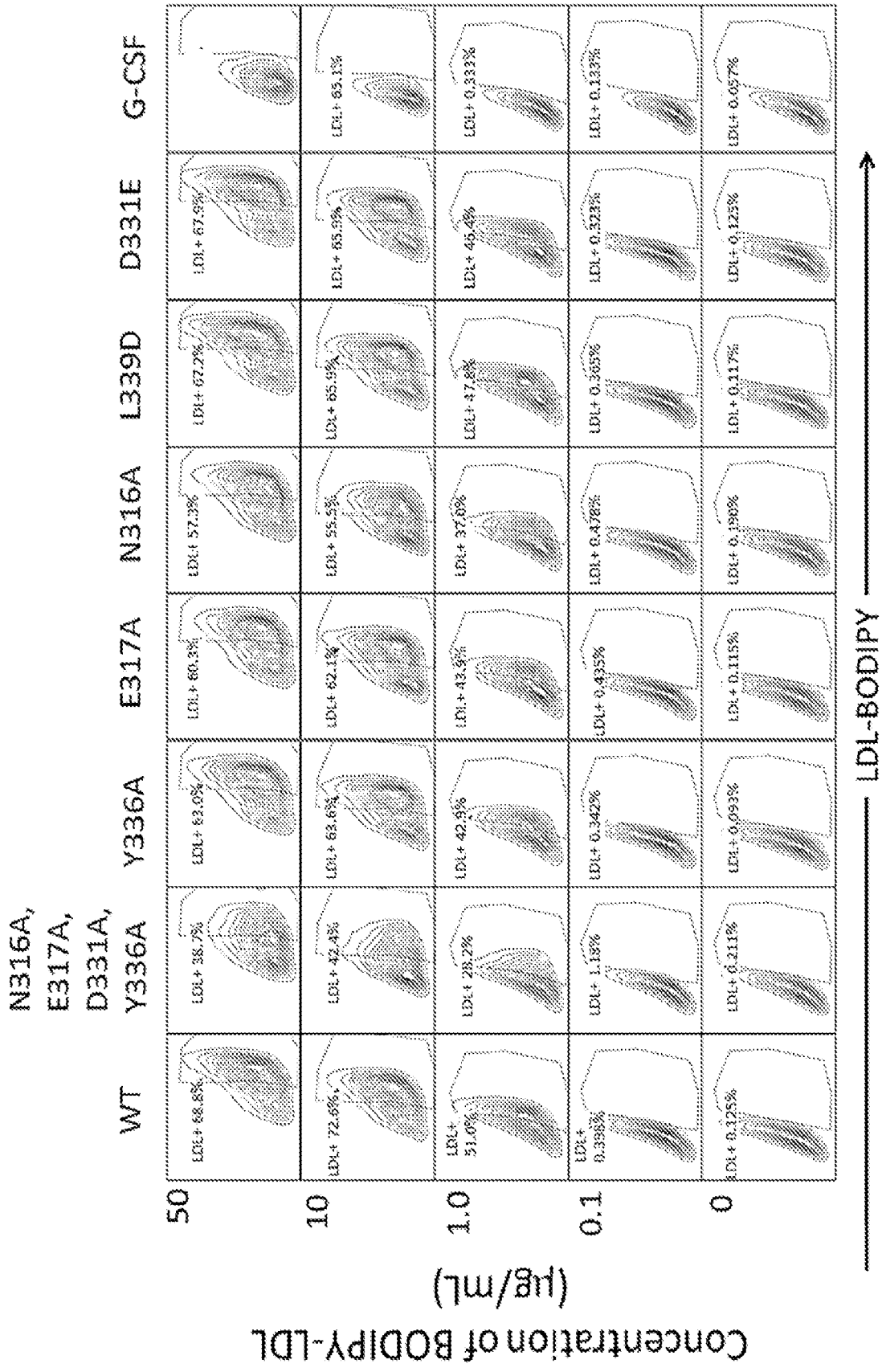

N316A,
E317A,
D331A,
Y336A
WT
Y336A
E317A
N316A
L339D
D331E
G-CSF
Concentration of BODIPY-LDL
(μg/mL)
50
10
1.0
0.1
0
LDL-BODIPY

FIGURE 18B

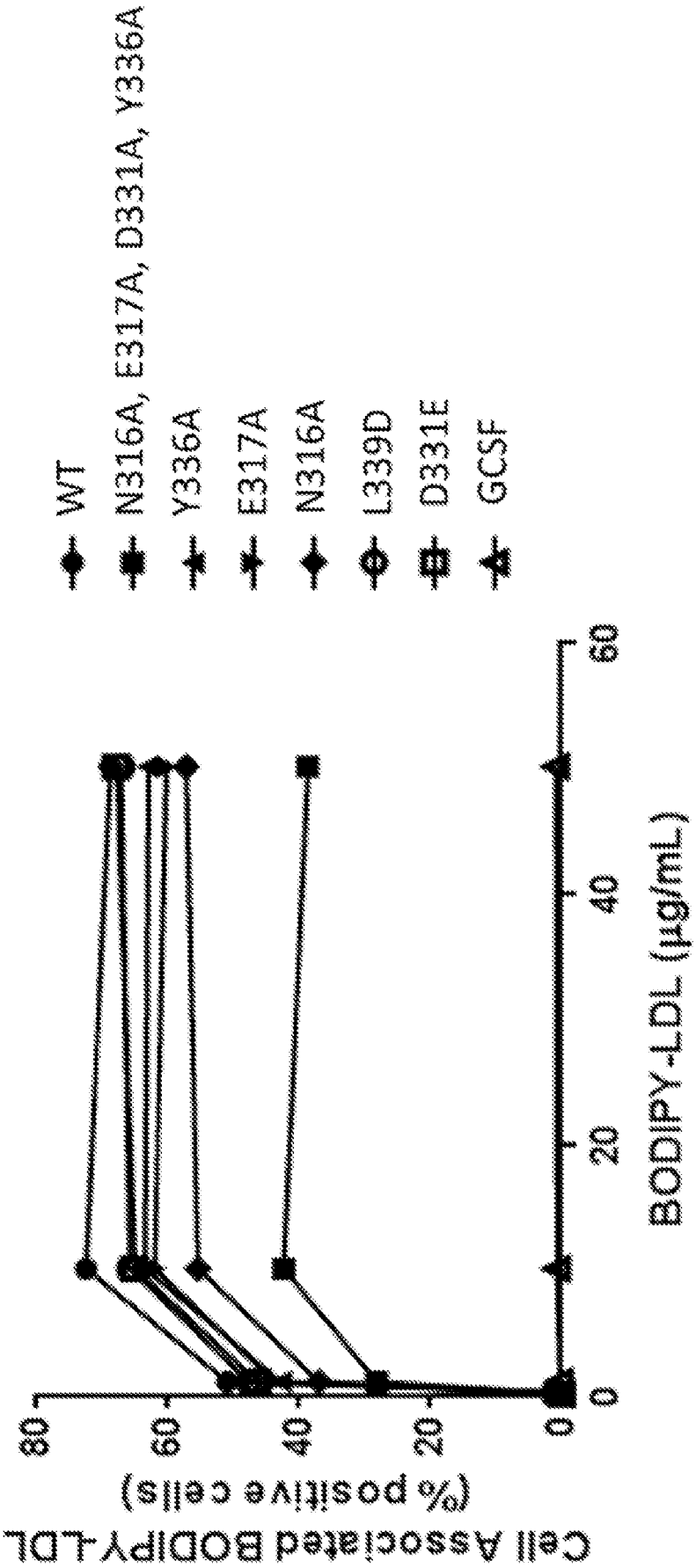

WT
N316A, E317A, D331A, Y336A
Y336A
E317A
N316A
L339D
D331E
GCSF
Cell Associated BODIPY-LDL
(% positive cells)
0
20
40
60
80
0
20
40
60
BODIPY-LDL (µg/mL)

FIGURE 19A

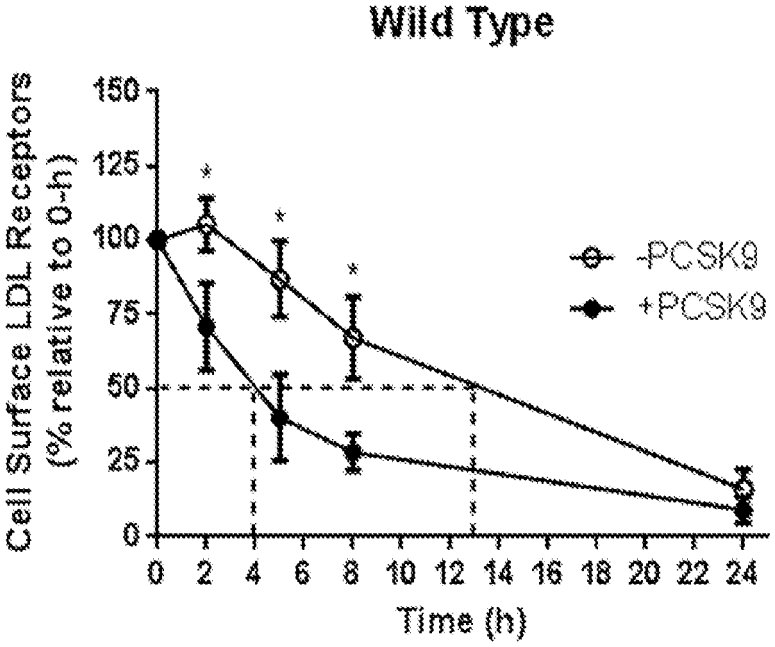


FIGURE 19B

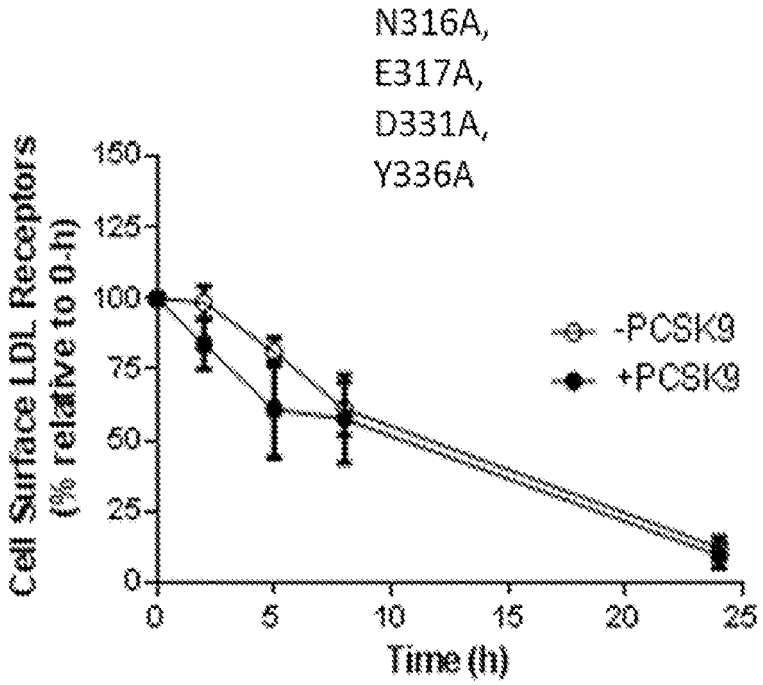


FIGURE 19C

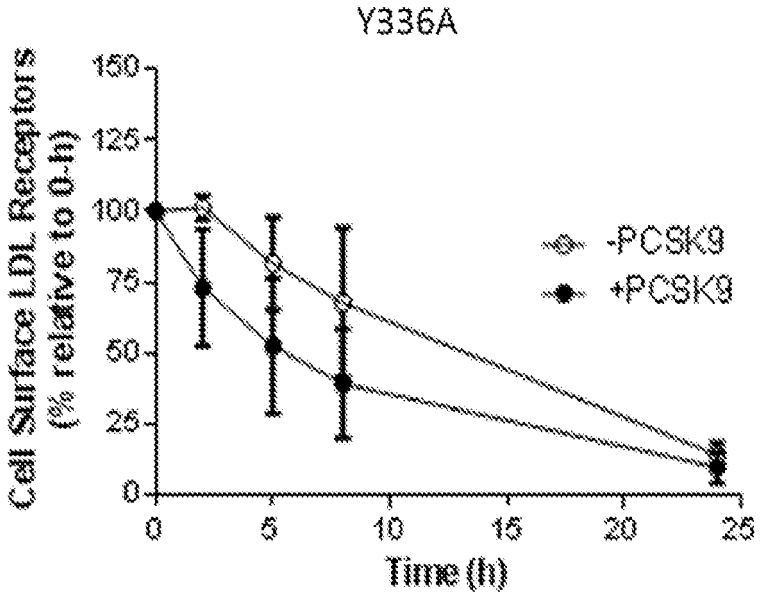


FIGURE 19D

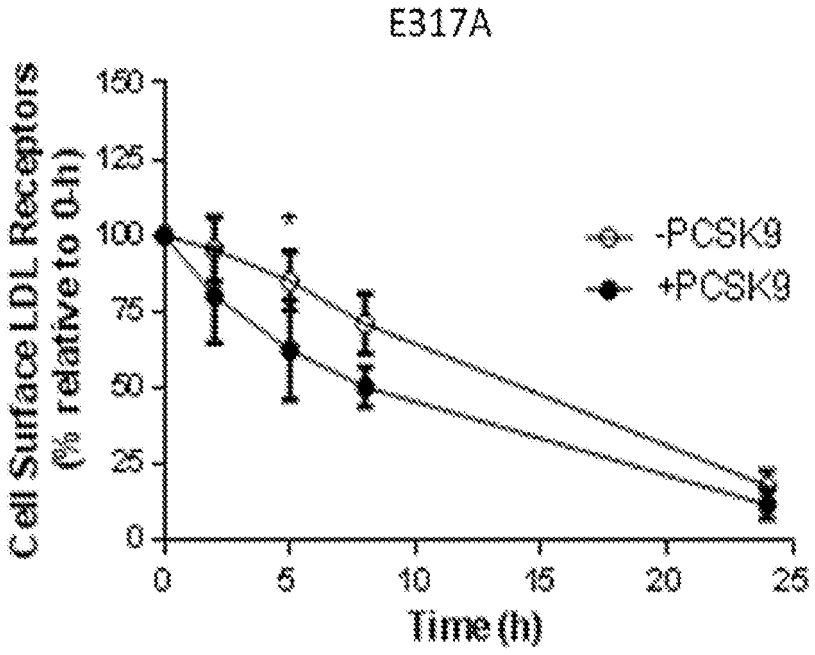


FIGURE 19E

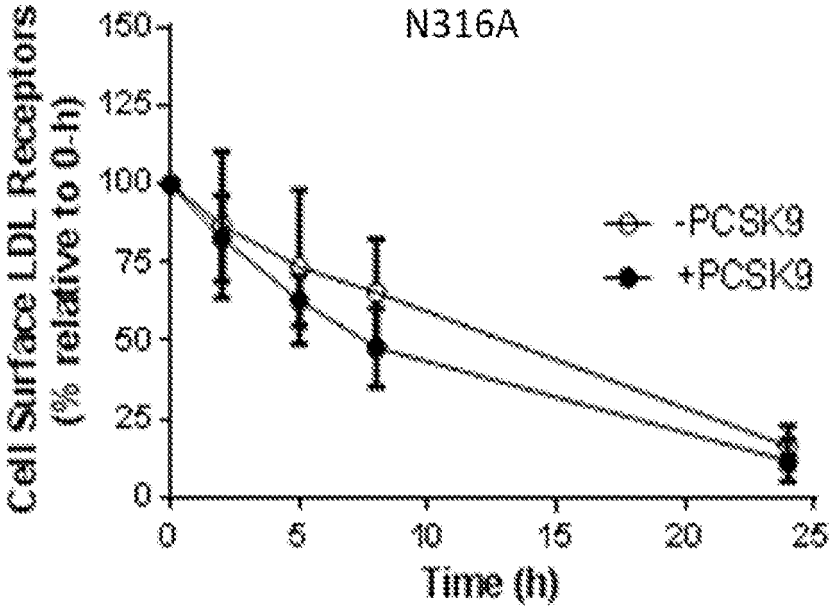


FIGURE 19F

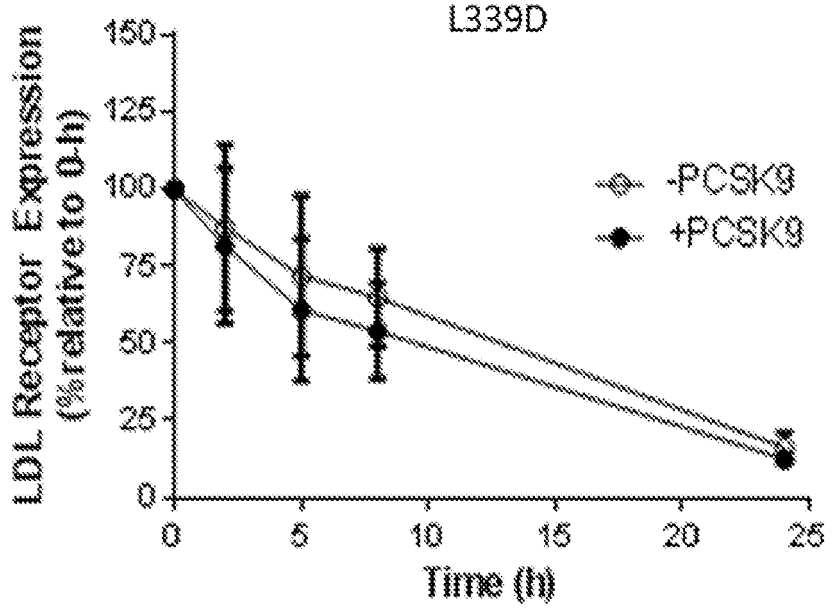


FIGURE 19G

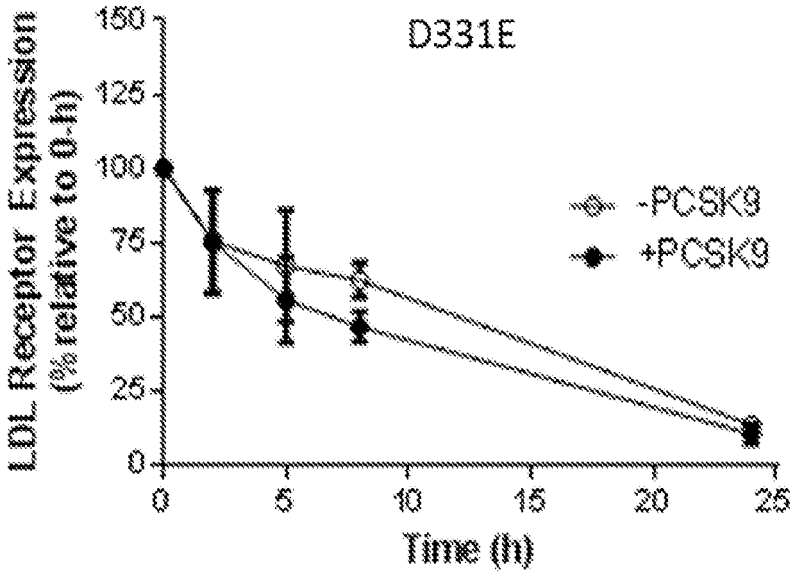

D331E
LDL Receptor Expression
(% relative to 0 h)
150
125
100
75
50
25
0
0
5
10
15
20
25
Time (h)
-PCSK9
+PCSK9

FIGURE 20

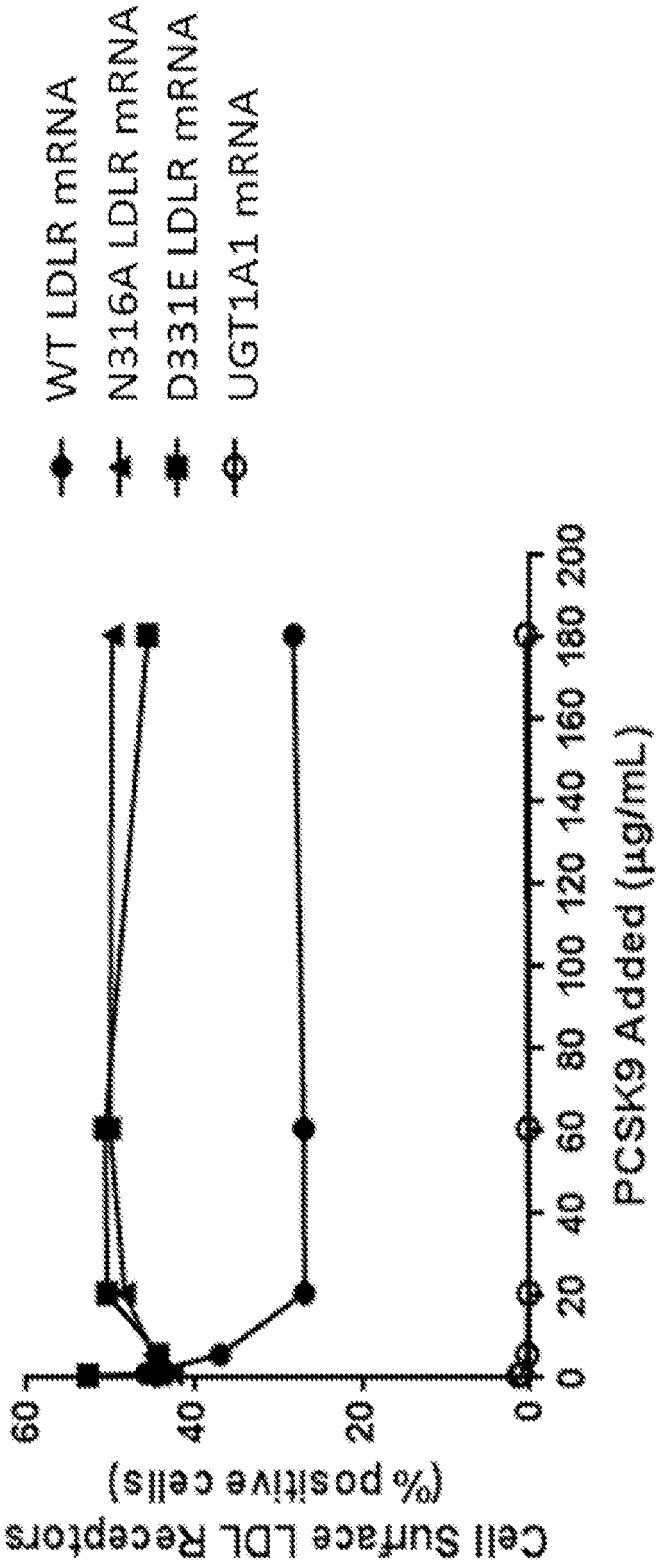
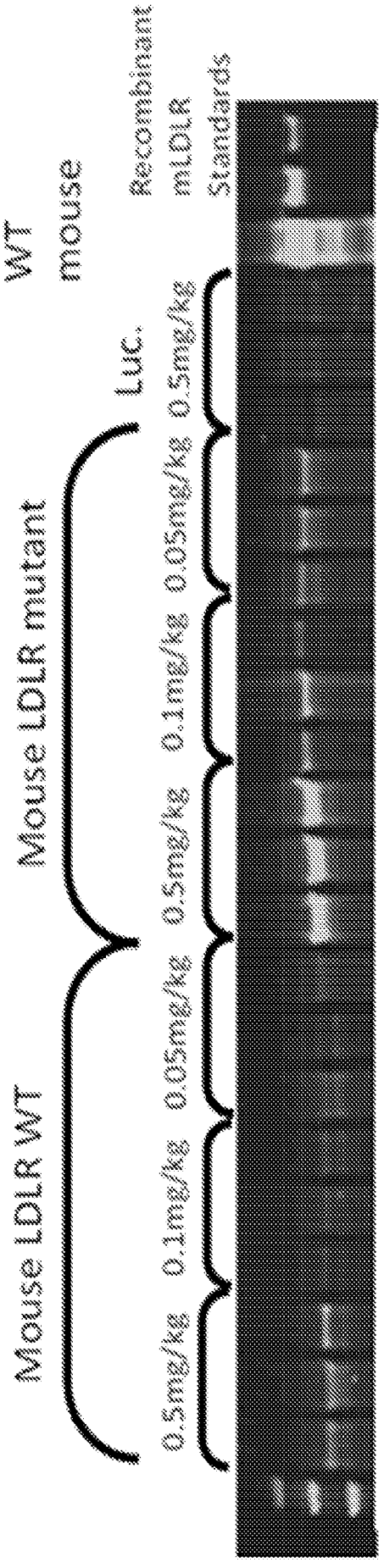

WT LDLR mRNA
N316A LDLR mRNA
D331E LDLR mRNA
UGT1A1 mRNA
Cell Surface LDL Receptors
(% positive cells)
0
20
40
60
PCSK9 Added (µg/mL)
0
20
40
60
80
100
120
140
160
180
200

FIGURE 21


Mouse LDLR WT
Mouse LDLR mutant
Luc.
WT mouse
Recombinant mLDLR
Standards
0.5mg/kg
0.1mg/kg
0.05mg/kg
0.5mg/kg
0.1mg/kg
0.05mg/kg
0.5mg/kg