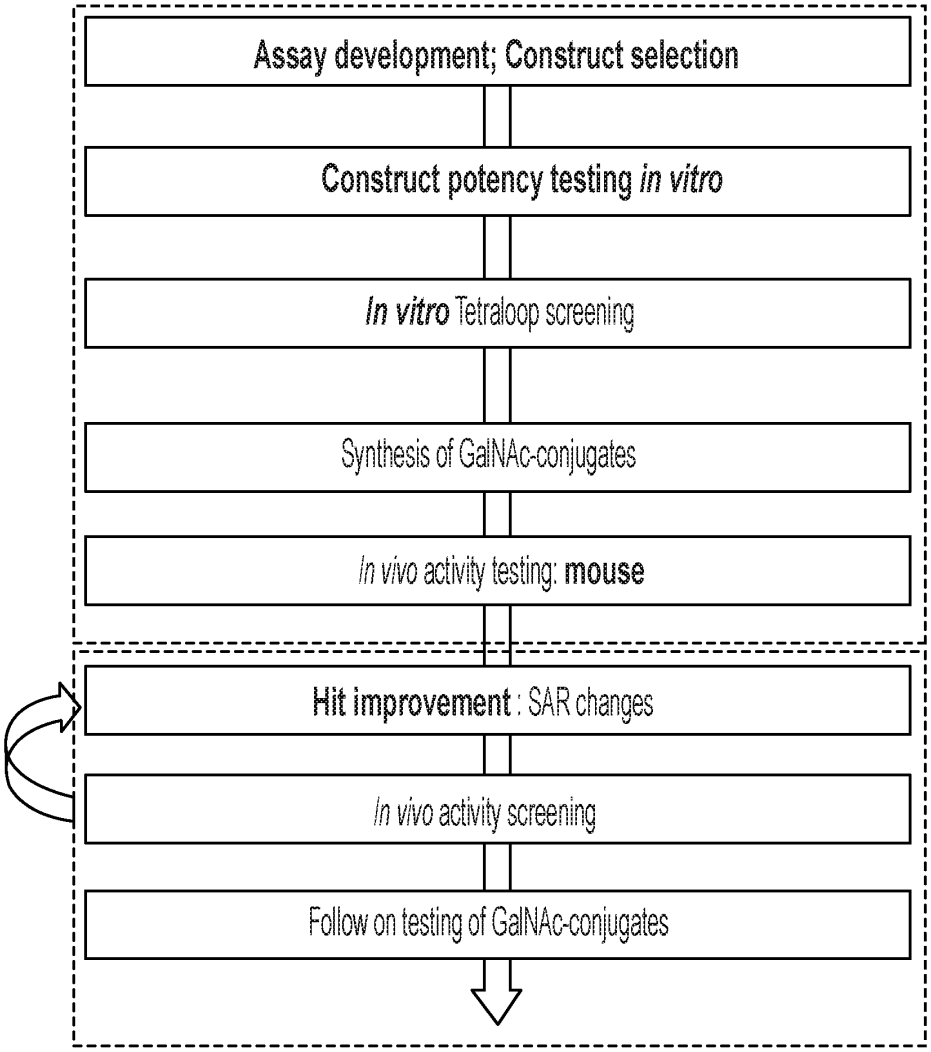

Assay development; Construct selection
Construct potency testing *in vitro*
In vitro Tetraloop screening
Synthesis of GalNAc-conjugates
In vivo activity testing: **mouse**
Hit improvement : SAR changes
In vivo activity screening
Follow on testing of GalNAc-conjugates

FIG. 1

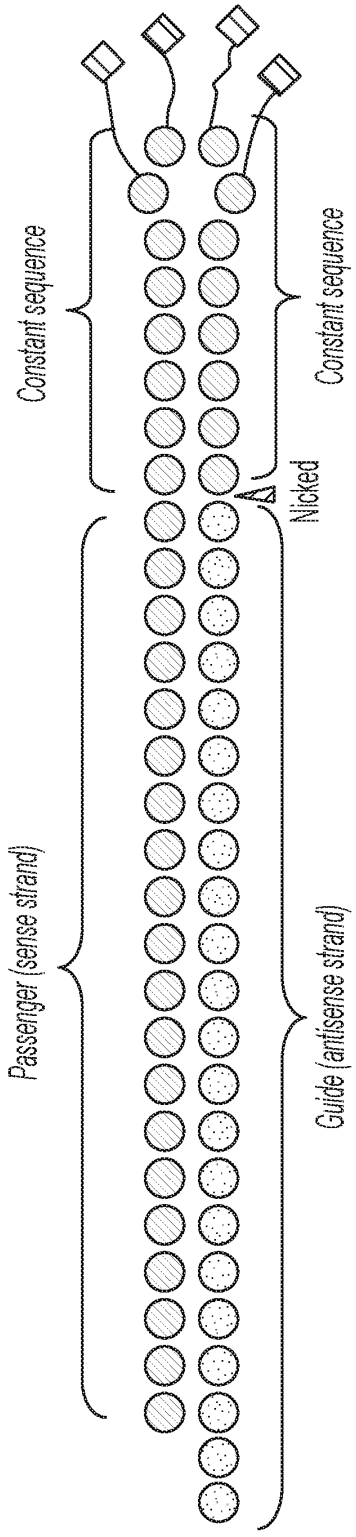

Constant sequence
Constant sequence
Nicked
Passenger (sense strand)
Guide (antisense strand)

FIG. 2

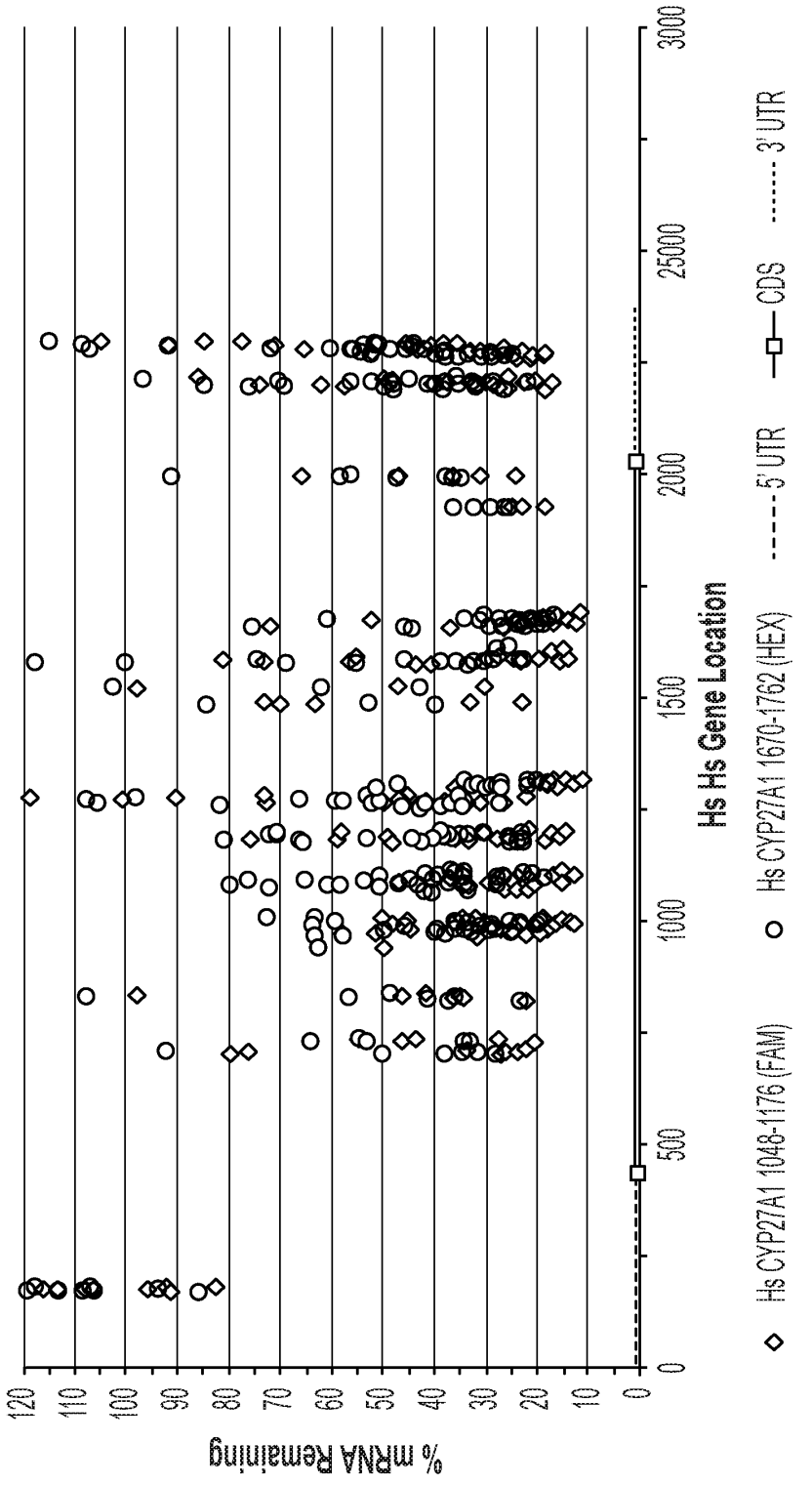

% mRNA Remaining
120
110
100
90
80
70
60
50
40
30
20
10
0
0
500
1000
1500
2000
25000
3000
Hs Hs Gene Location
Hs CYP27A1 1048-1176 (FAM)
Hs CYP27A1 1670-1762 (HEX)
5' UTR
CDS
3' UTR

FIG. 3

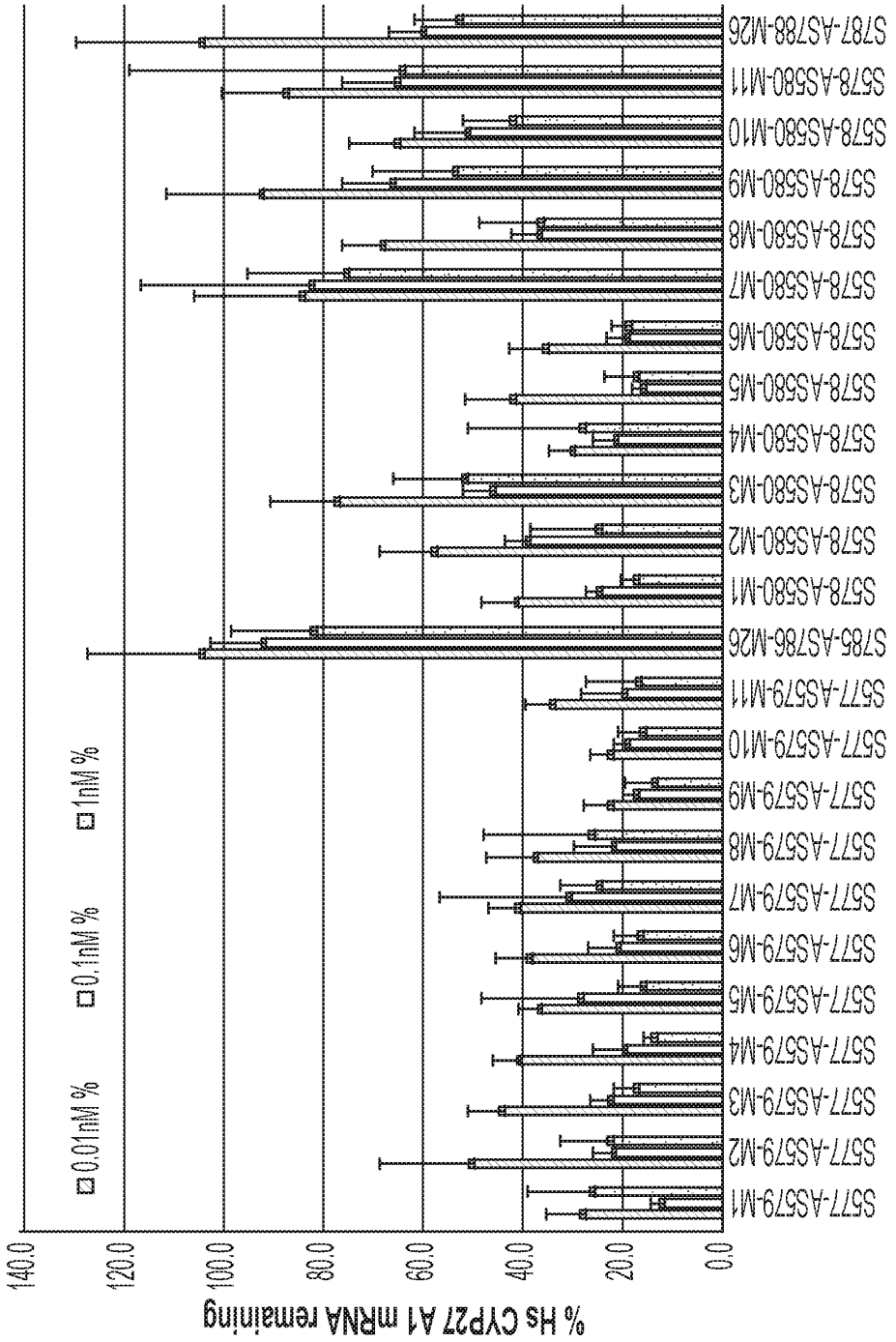

% Hs CYP27 A1 mRNA remaining
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
0.01nM %
0.1nM %
1nM %
S577-AS579-M1
S577-AS579-M2
S577-AS579-M3
S577-AS579-M4
S577-AS579-M5
S577-AS579-M6
S577-AS579-M7
S577-AS579-M8
S577-AS579-M9
S577-AS579-M10
S577-AS579-M11
S786-AS786-M26
S578-AS580-M1
S578-AS580-M2
S578-AS580-M3
S578-AS580-M4
S578-AS580-M5
S578-AS580-M6
S578-AS580-M7
S578-AS580-M8
S578-AS580-M9
S578-AS580-M10
S578-AS580-M11
S787-AS788-M26

FIG. 4A

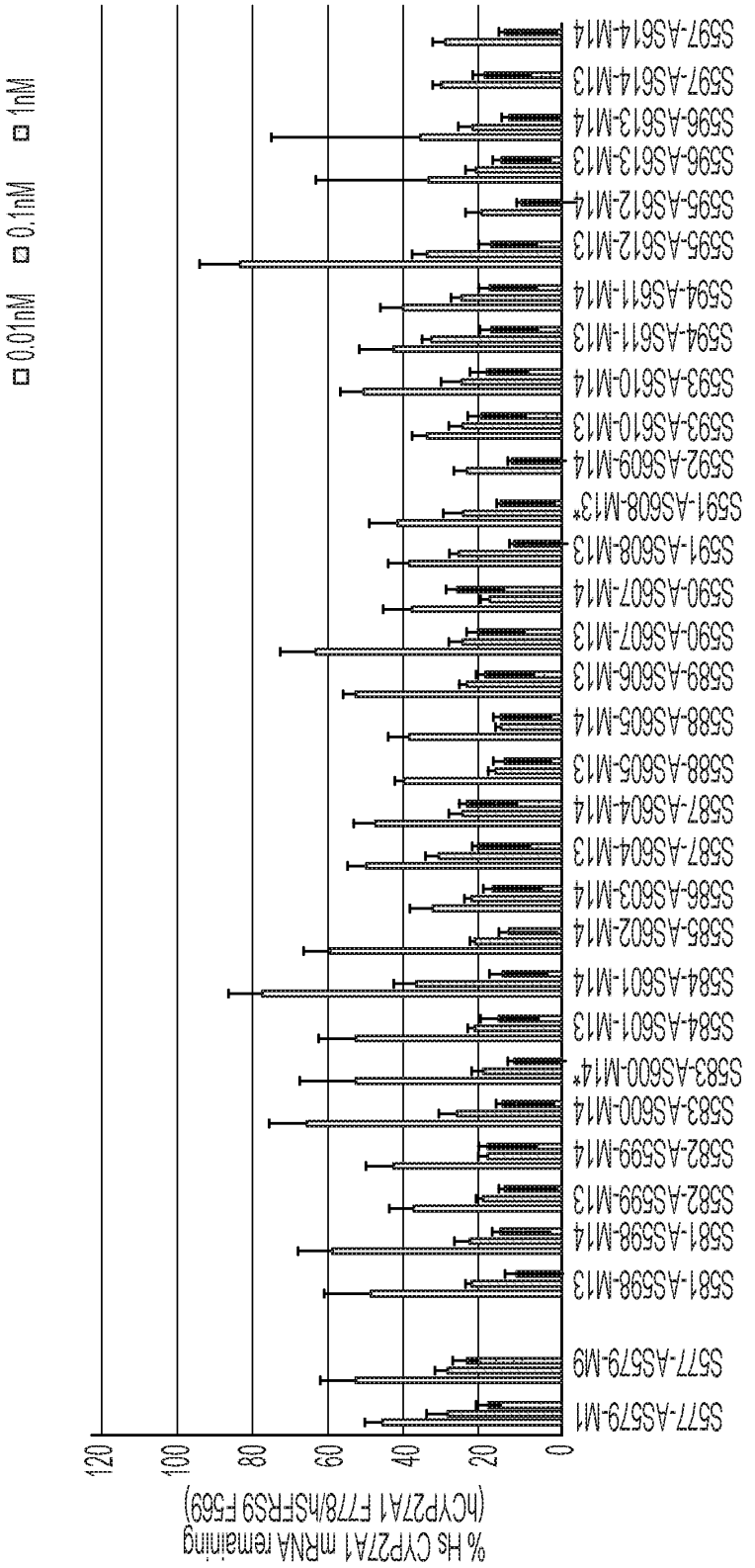

0.01nM
0.1nM
1nM
% hs CYP27A1 mRNA remaining
(hCYP27A1 F778/hSFRS9 F569)
120
100
80
60
40
20
0
S77-AS579-M1
S77-AS579-M9
S81-AS598-M13
S81-AS598-M14
S82-AS599-M13
S82-AS599-M14
S83-AS600-M14
S83-AS600-M14*
S84-AS601-M13
S84-AS601-M14
S85-AS602-M14
S86-AS603-M14
S87-AS604-M13
S87-AS604-M14
S88-AS605-M13
S88-AS605-M14
S89-AS606-M13
S90-AS607-M13
S90-AS607-M14
S91-AS608-M13
S91-AS608-M13*
S92-AS609-M14
S93-AS610-M13
S93-AS610-M14
S94-AS611-M13
S94-AS611-M14
S95-AS612-M13
S95-AS612-M14
S96-AS613-M13
S96-AS613-M14
S97-AS614-M13
S97-AS614-M14

FIG. 4B

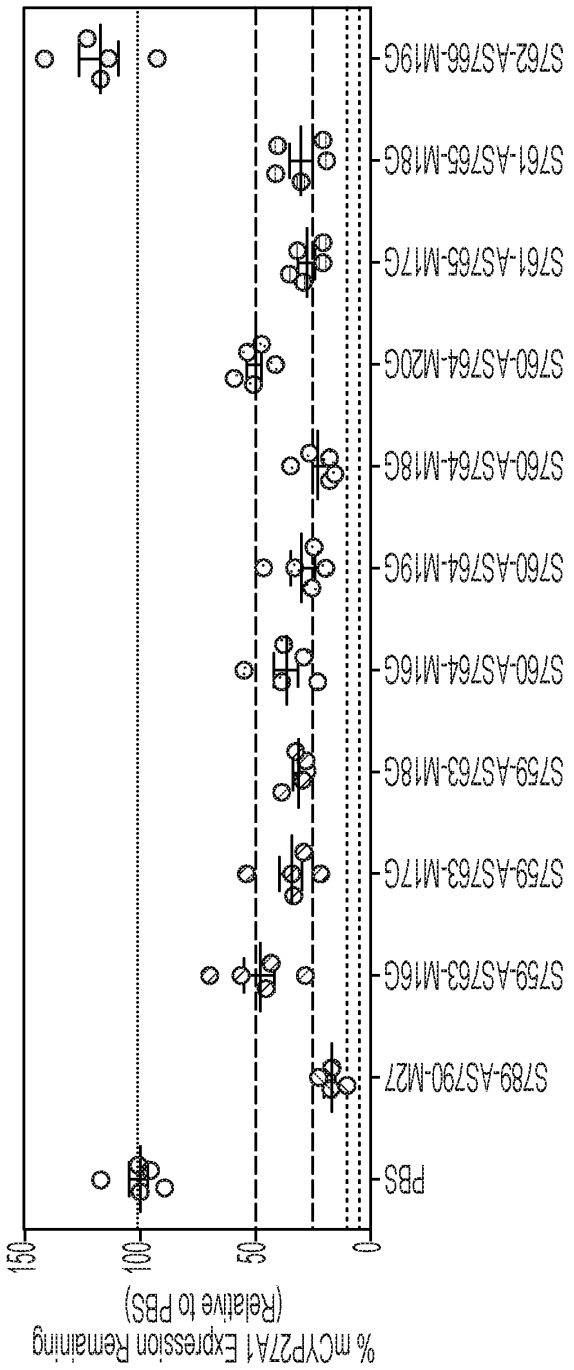

% mCYP27A1 Expression Remaining
(Relative to PBS)
150
100
50
0
PBS
S789-AS790-M27
S759-AS763-M16G
S759-AS763-M17G
S759-AS763-M18G
S760-AS764-M16G
S760-AS764-M19G
S760-AS764-M18G
S760-AS764-M20G
S761-AS765-M17G
S761-AS765-M18G
S762-AS766-M19G

FIG. 5

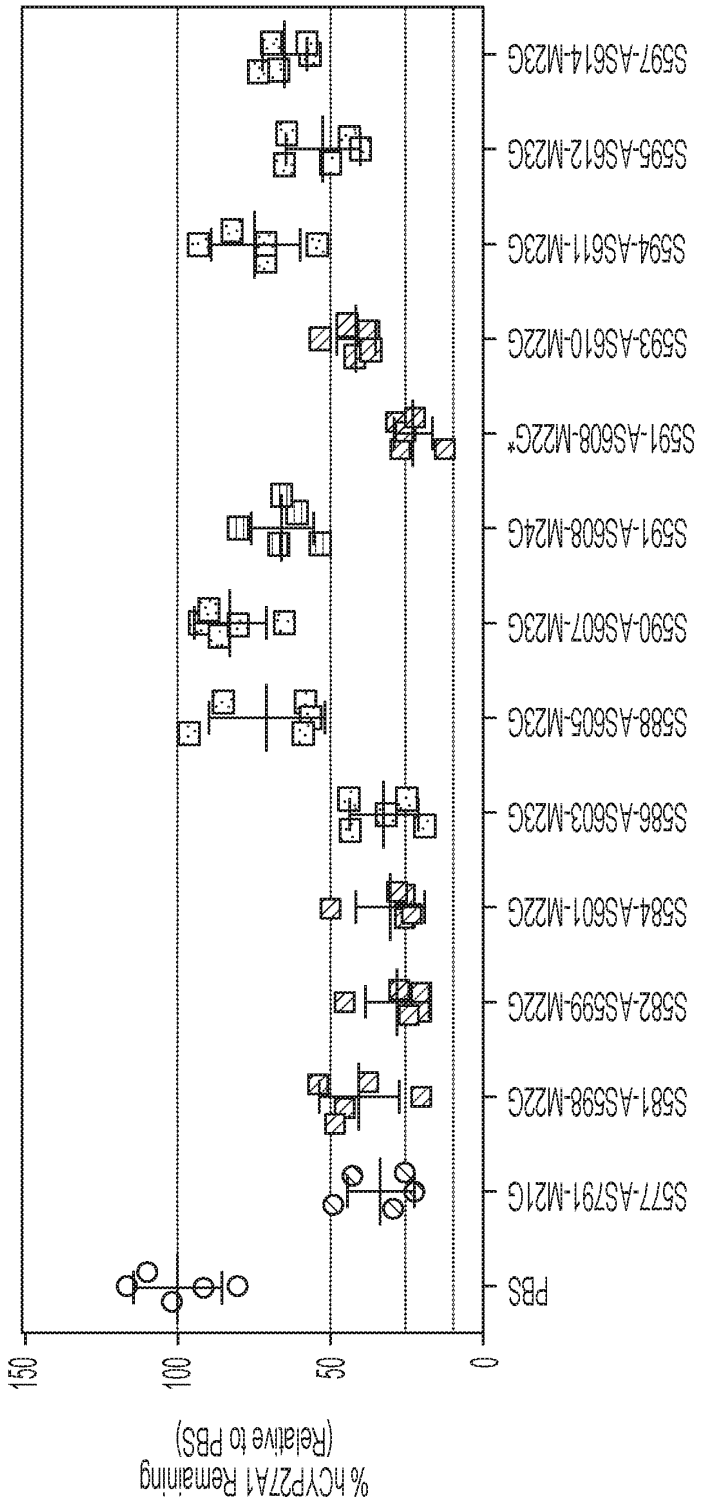

PBS
S577-AS791-M21G
S581-AS598-M22G
S582-AS599-M22G
S584-AS601-M22G
S586-AS603-M23G
S588-AS605-M23G
S590-AS607-M23G
S591-AS608-M24G
S591-AS608-M22G*
S593-AS610-M22G
S594-AS611-M23G
S595-AS612-M23G
S597-AS614-M23G
150
100
50
0
% hCYP27A1 Remaining
(Relative to PBS)

FIG. 6

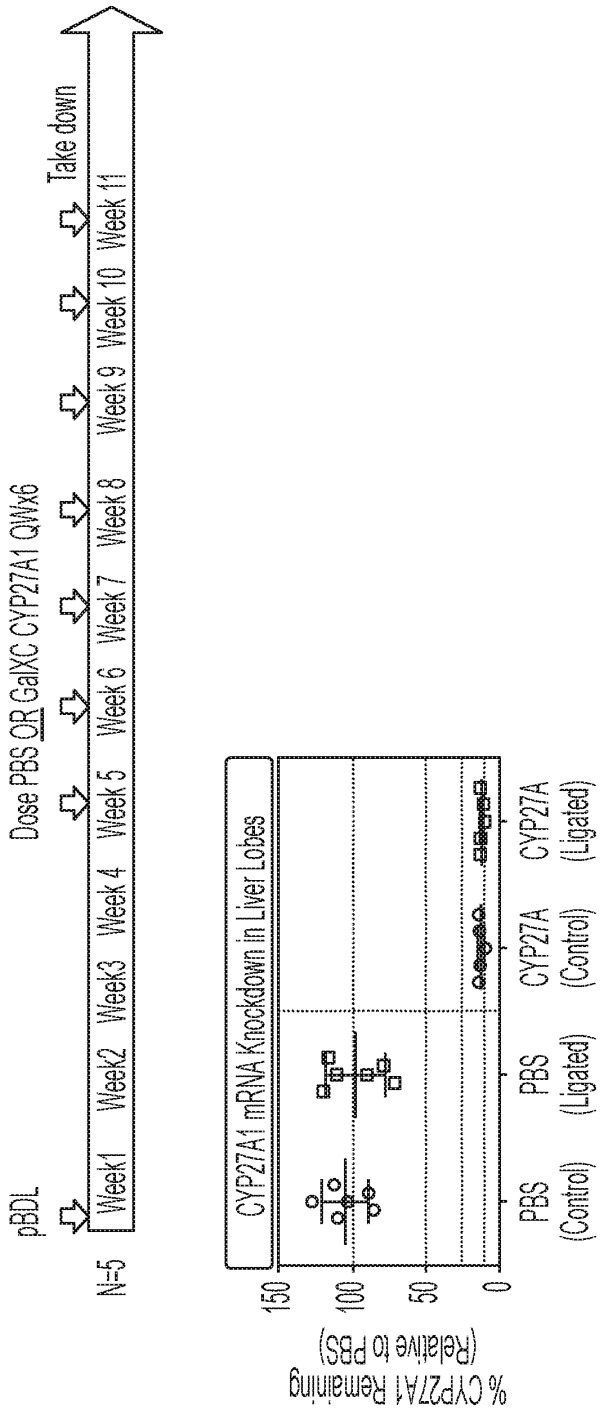

pBDL
Dose PBS OR GalXC CYP27A1 QWx6
Take down
N=5
Week1
Week2
Week3
Week 4
Week 5
Week 6
Week 7
Week 8
Week 9
Week 10
Week 11
CYP27A1 mRNA Knockdown in Liver Lobes
% CYP27A1 Remaining
(Relative to PBS)
150
100
50
0
PBS
(Control)
PBS
(Ligated)
CYP27A
(Control)
CYP27A
(Ligated)

FIG. 7

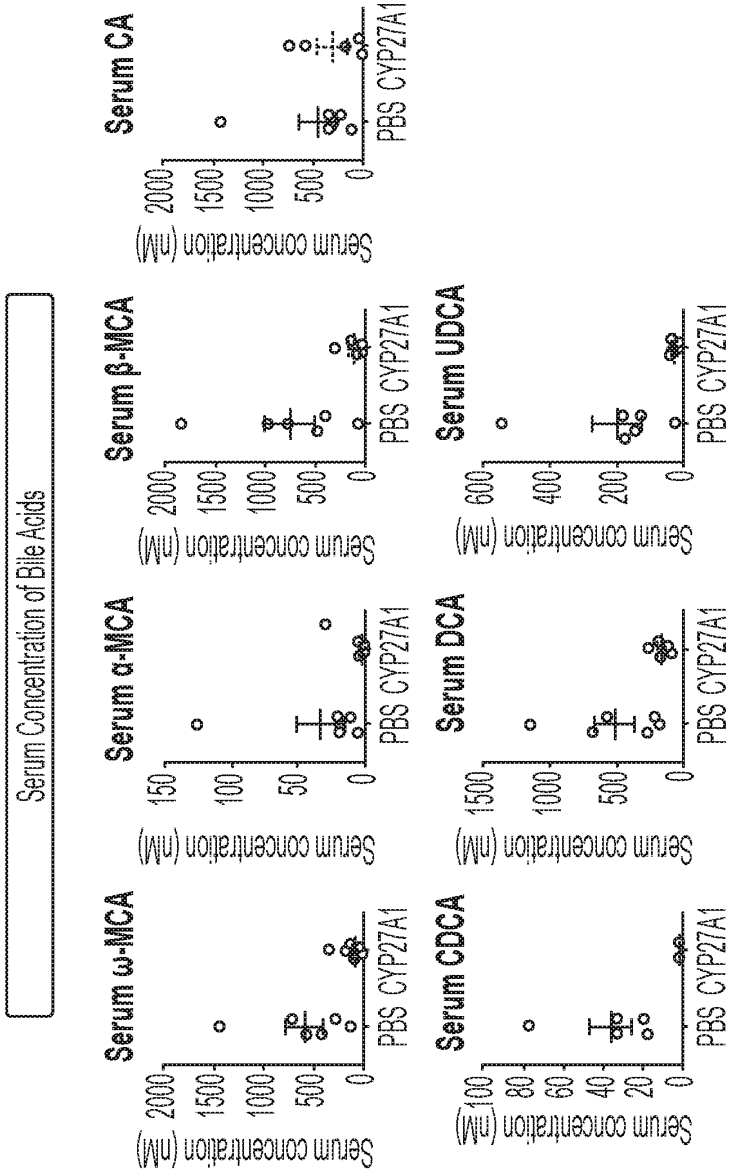


FIG. 7
CONTINUED

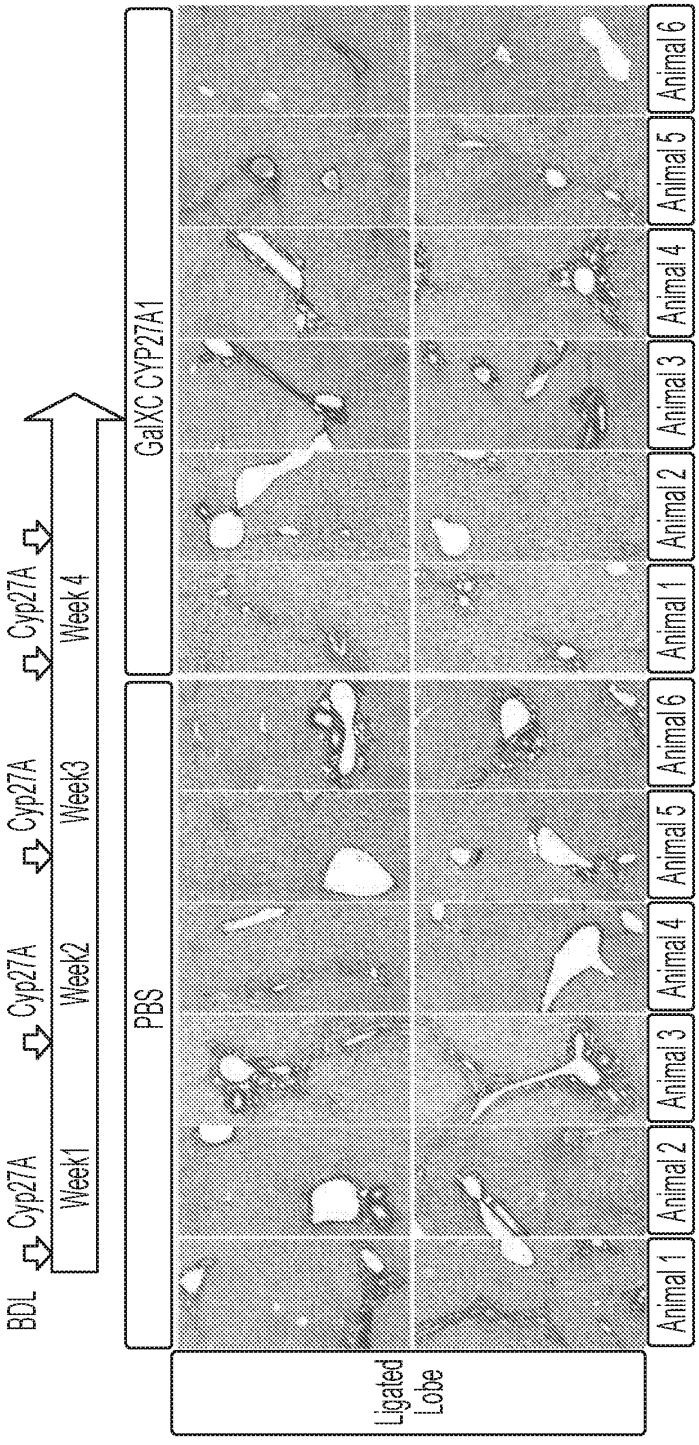

BDL
Cyp27A
Week1
Cyp27A
Week2
Cyp27A
Week3
Cyp27A
Week 4
PBS
GalXC CYP27A1
Ligated Lobe
Animal 1
Animal 2
Animal 3
Animal 4
Animal 5
Animal 6
Animal 1
Animal 2
Animal 3
Animal 4
Animal 5
Animal 6

FIG. 8