FIG. 1

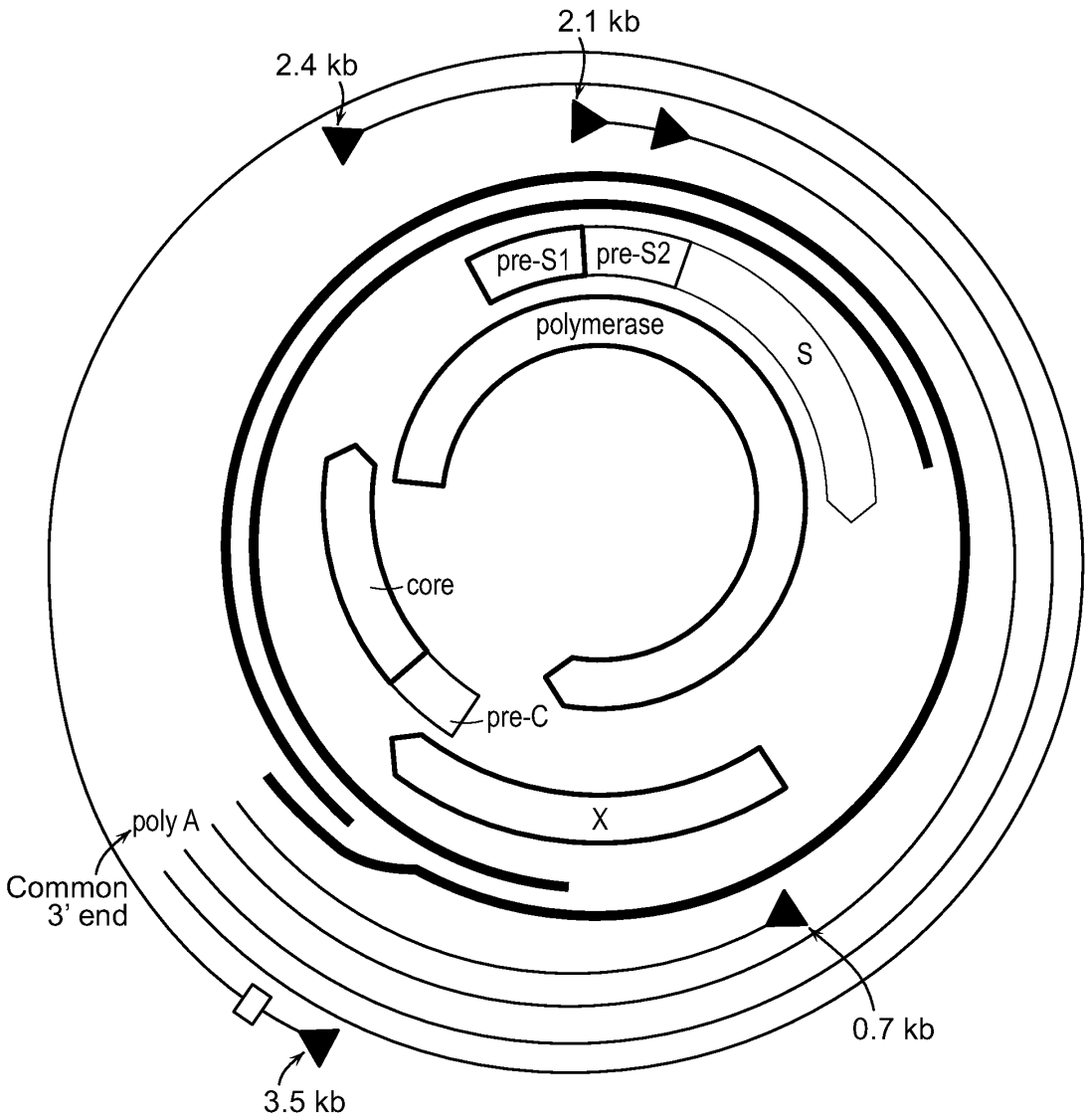

2.1 kb
2.4 kb
pre-S1
pre-S2
polymerase
S
core
pre-C
X
poly A
Common
3' end
0.7 kb
3.5 kb

FIG. 2A

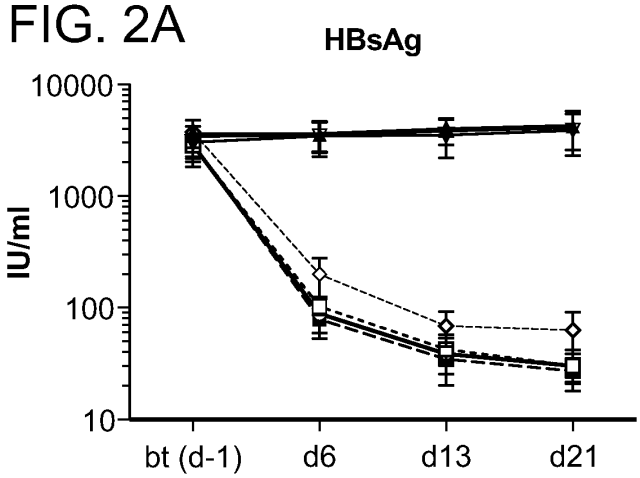


FIG. 2B

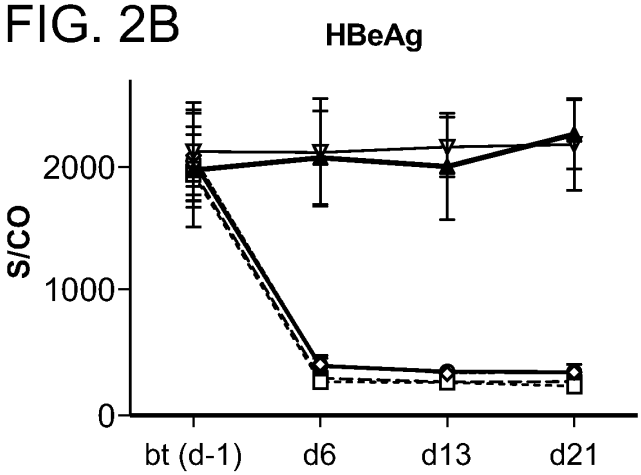


FIG. 2C

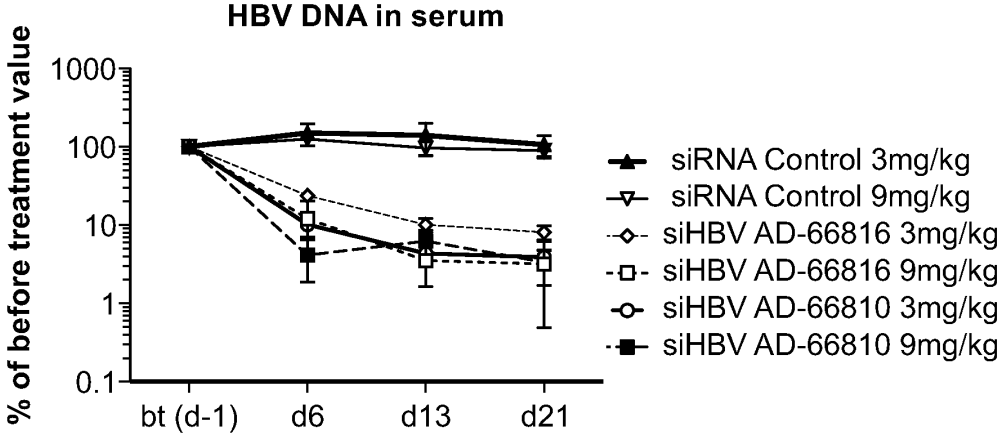


FIG. 2D

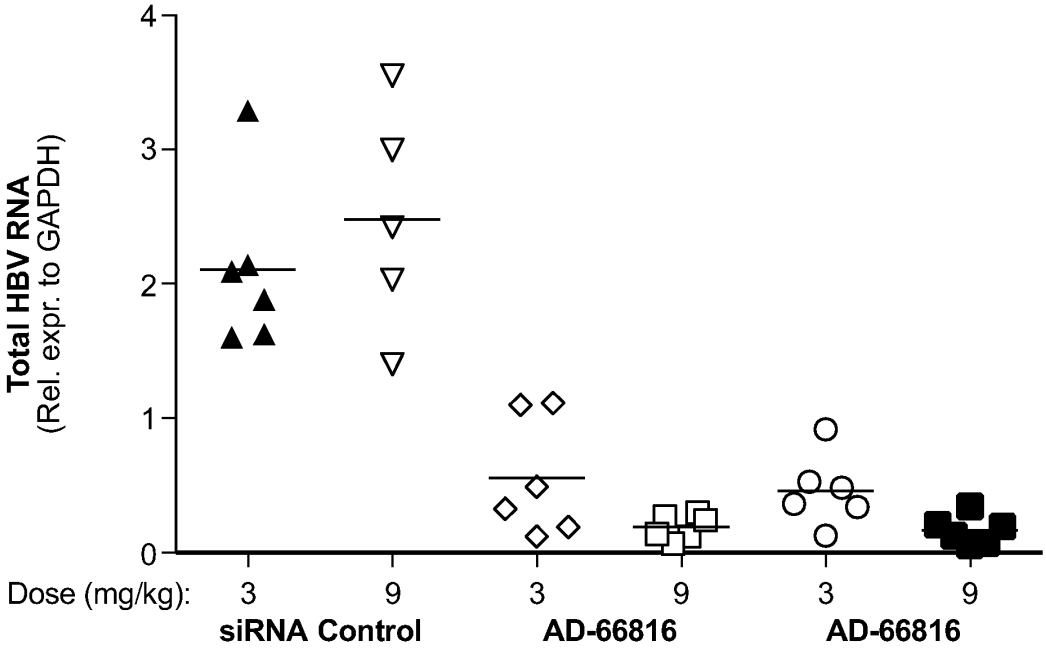

Total HBV RNA
(Rel. expr. to GAPDH)
4
3
2
1
0
Dose (mg/kg):
3
9
3
9
3
9
siRNA Control
AD-66816
AD-66816

FIG. 2E

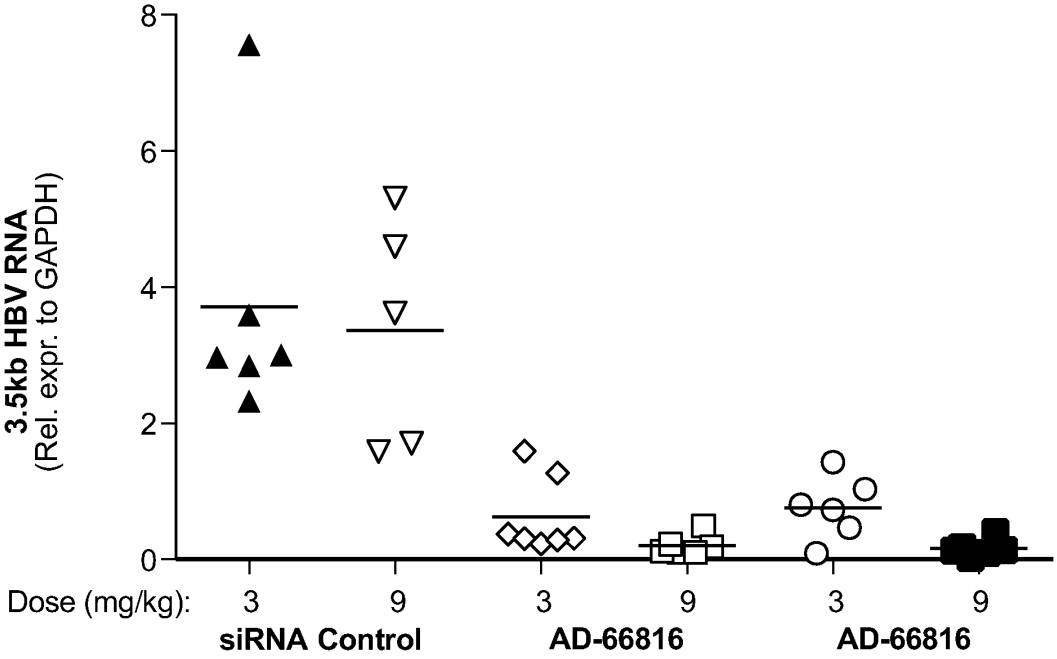
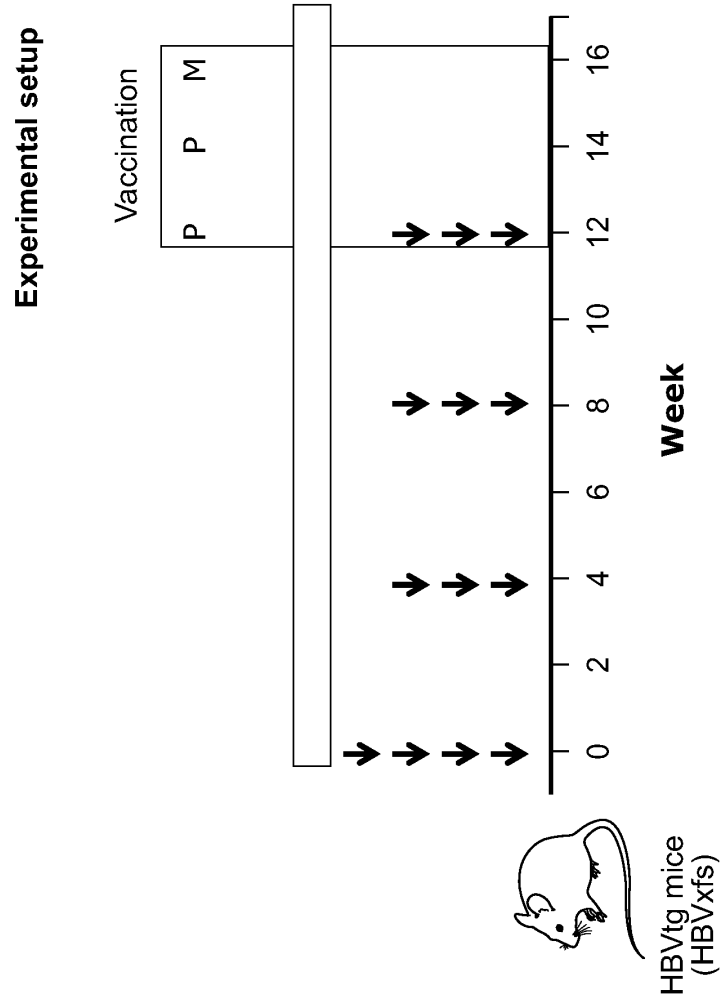

3.5kb HBV RNA
(Rel. expr. to GAPDH)
8
6
4
2
0
Dose (mg/kg):
3
9
3
9
3
9
siRNA Control
AD-66816
AD-66816

FIG. 3


Experimental setup
Vaccination
P P M
P = HBsAg+HBcAg+PCEP+CPG
M= MVA-HBsAg+MVA-HBcAg
MOCK
Entecavir 1 µg/ml drinking water
AAV-shHBV7/TuDHBV7 1x10e11 i.v.
siRNA control 3mg/kg
siHBV AD-66816 3mg/kg
siHBV AD-66810 3mg/kg
s.c.
0 2 4 6 8 10 12 14 16 17
Week
HBVtg mice
(HBVxfs)

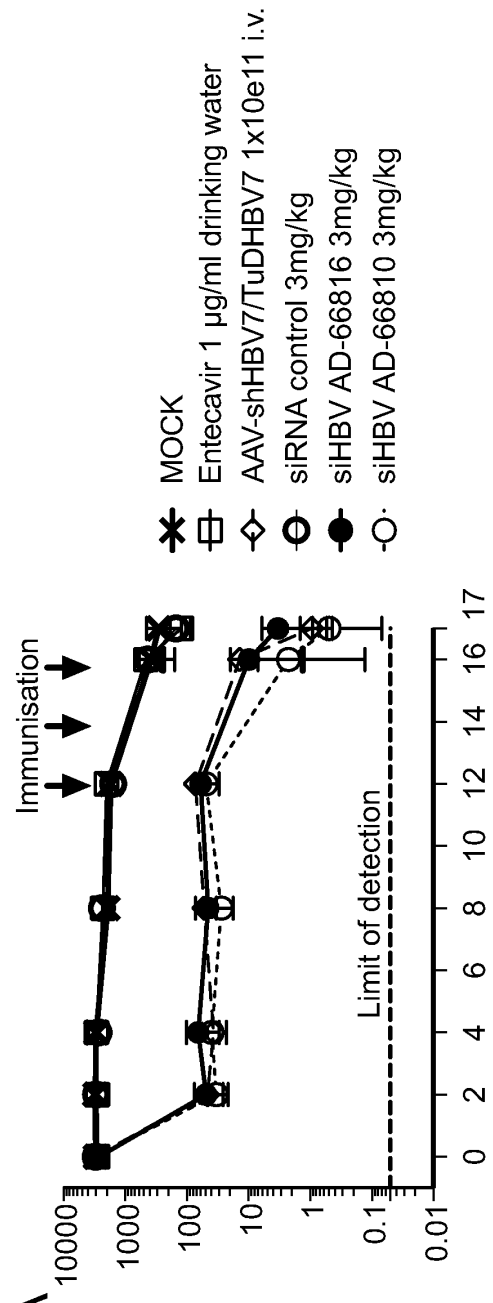


FIG. 4A

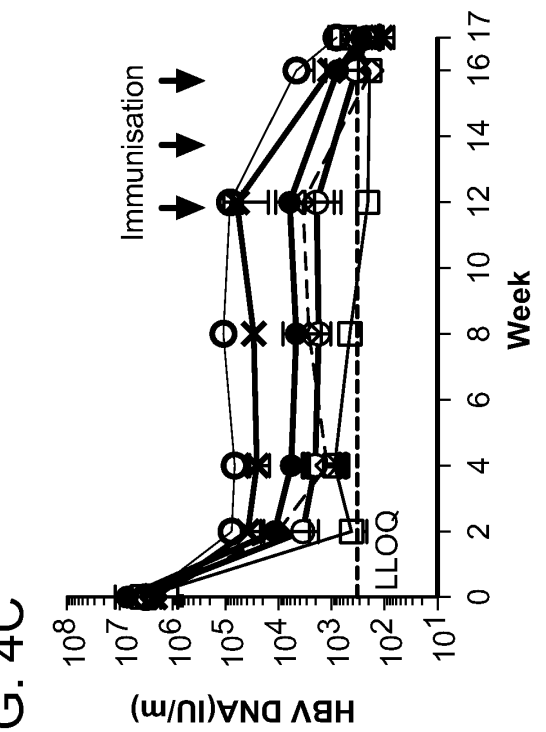


FIG. 4C

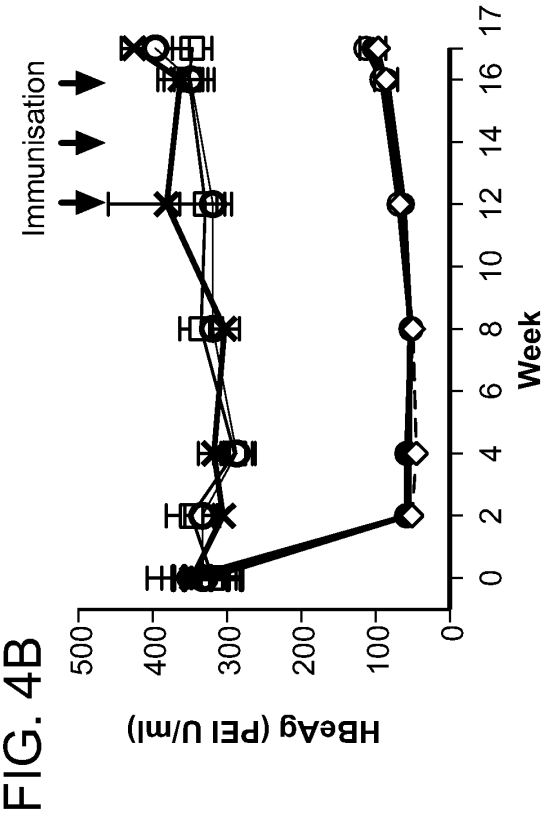


FIG. 4B

FIG. 5A

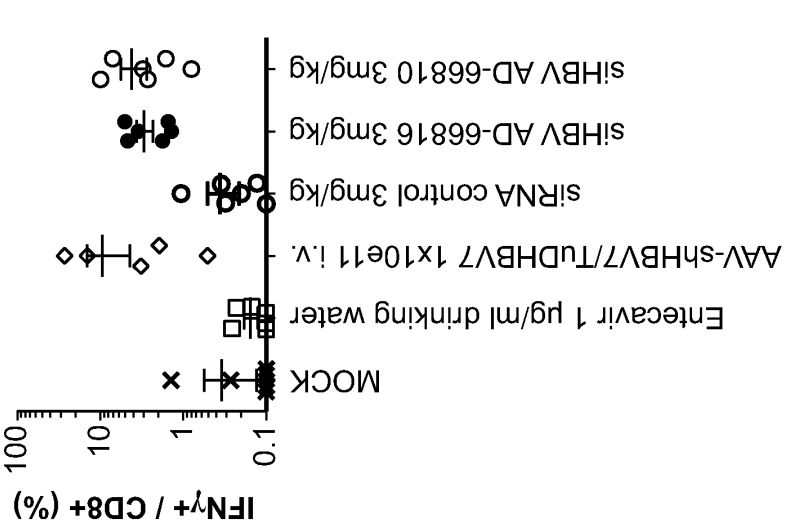


FIG. 5B

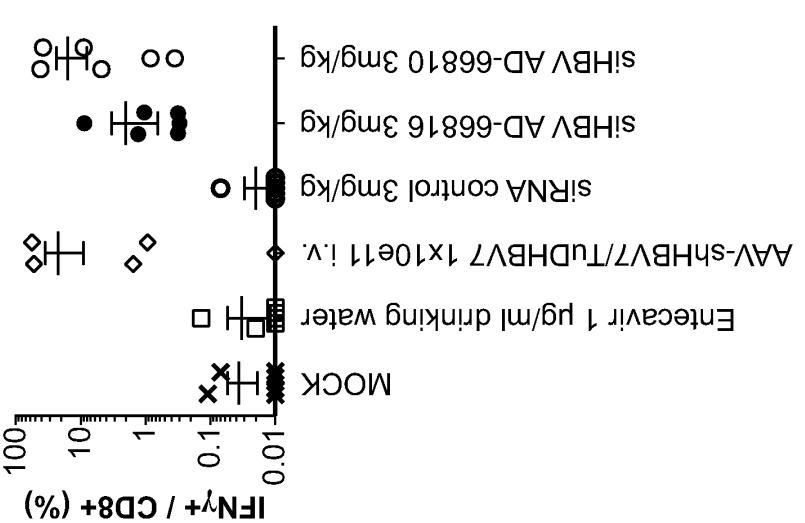


FIG. 5C

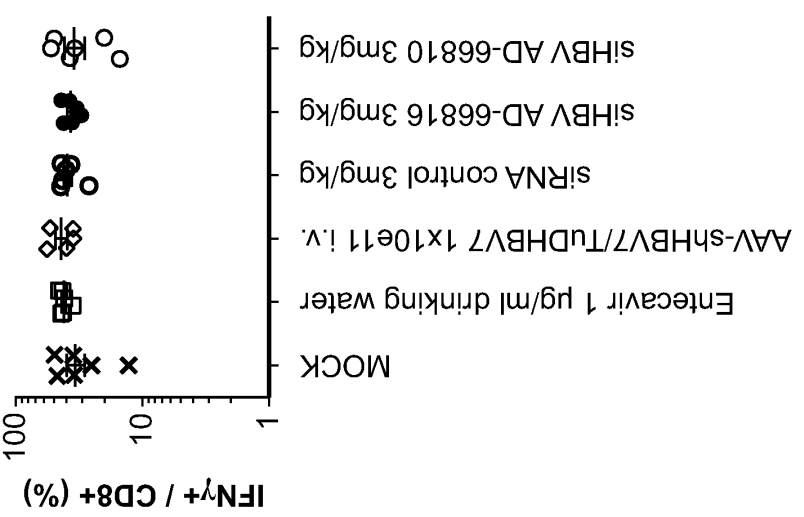


FIG. 5D

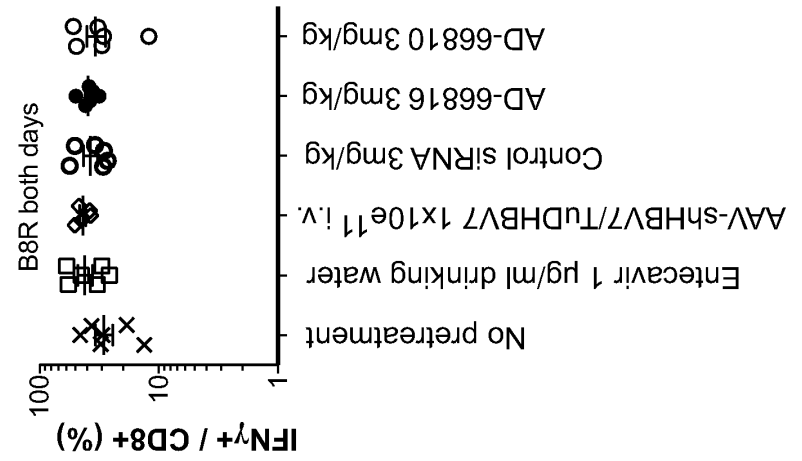


FIG. 5E

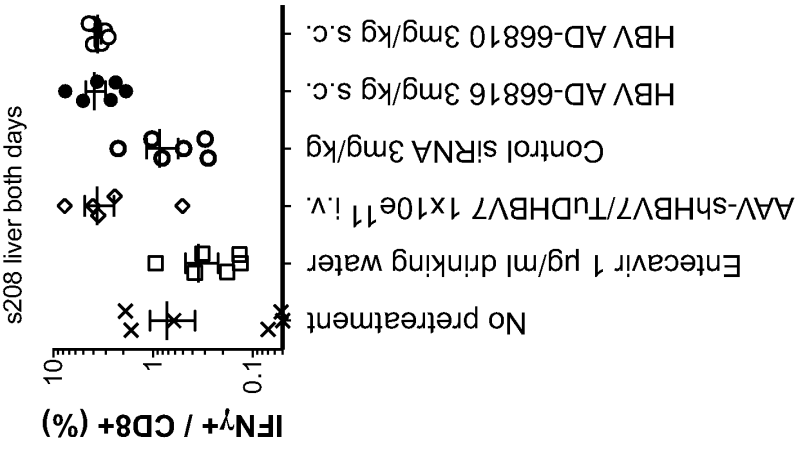


FIG. 5F

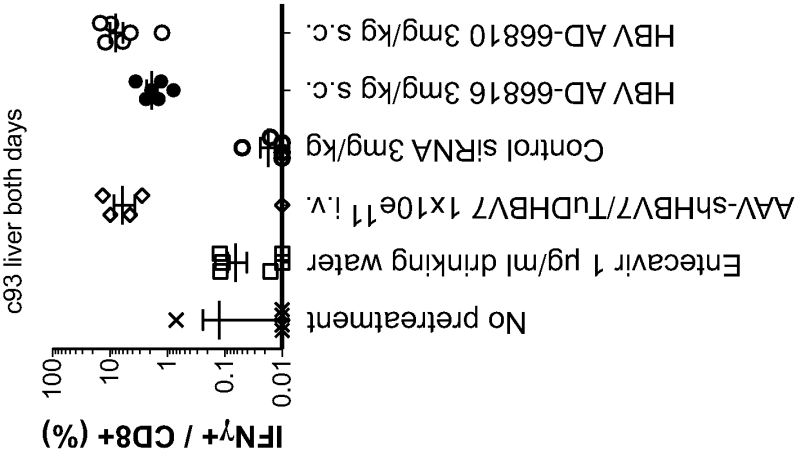


FIG. 6A

FIG. 6B

FIG. 6C

FIG. 7

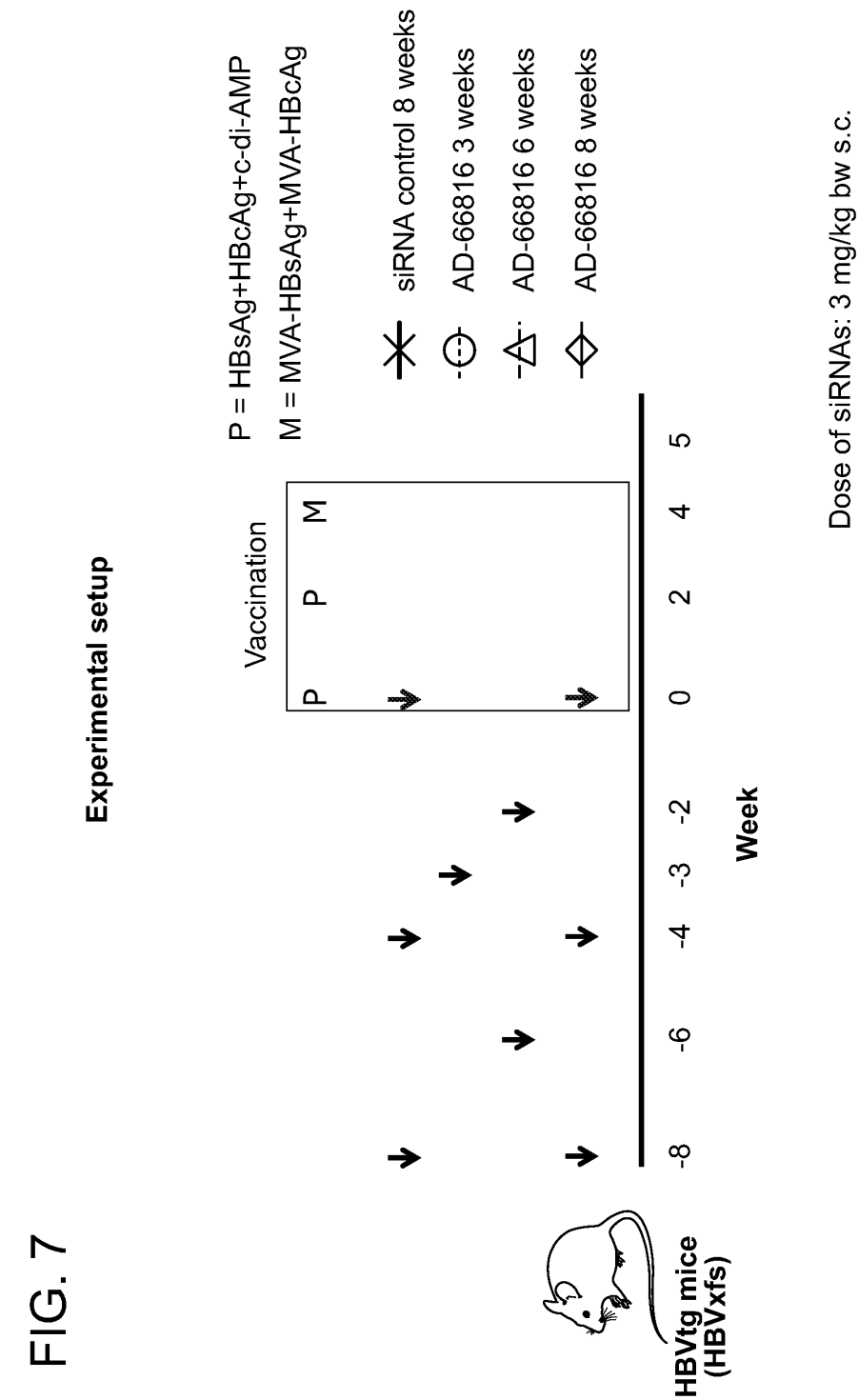

Experimental setup
P = HBsAg+HBcAg+c-di-AMP
M = MVA-HBsAg+MVA-HBcAg
Vaccination
P
P
M
siRNA control 8 weeks
AD-66816 3 weeks
AD-66816 6 weeks
AD-66816 8 weeks
-8
-6
-4
-3
-2
0
2
4
5
Week
HBVtg mice
(HBVxfs)
Dose of siRNAs: 3 mg/kg bw s.c.

FIG. 8A

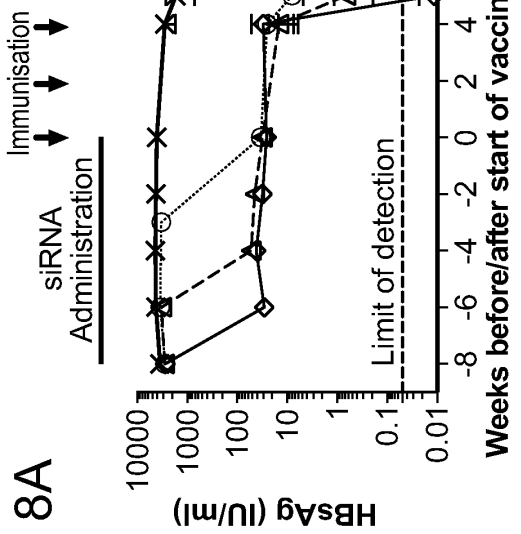
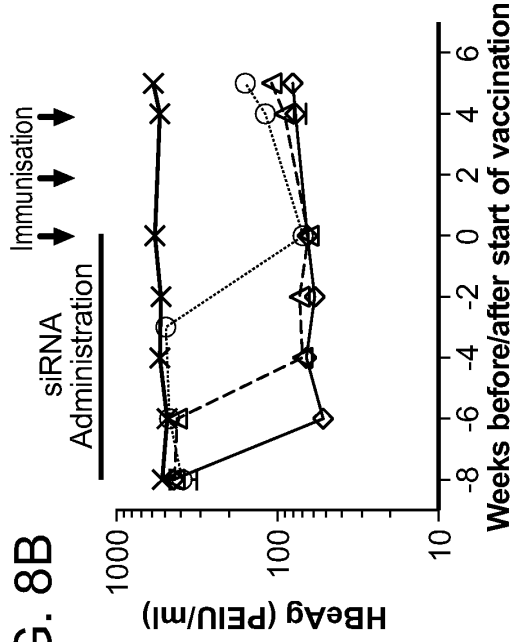


FIG. 8B



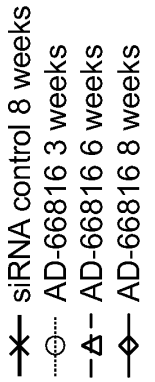


FIG. 8C

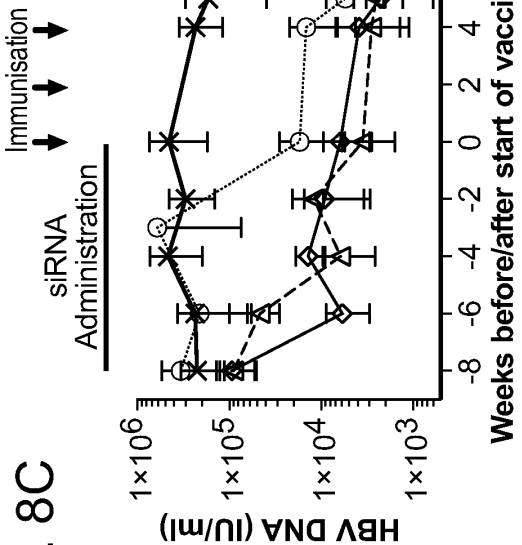


FIG. 9A

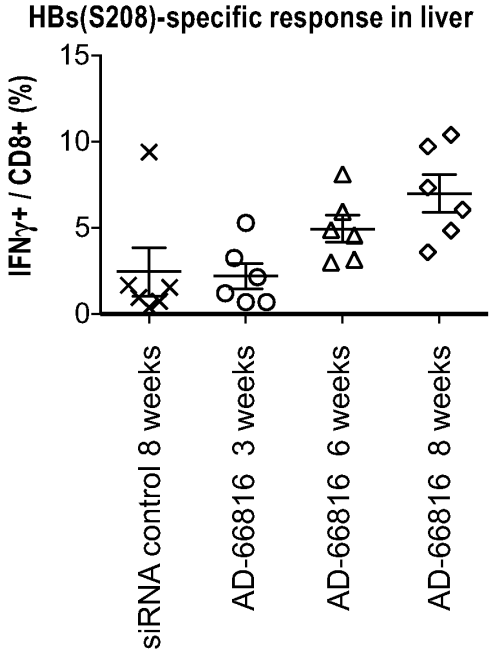


FIG. 9B

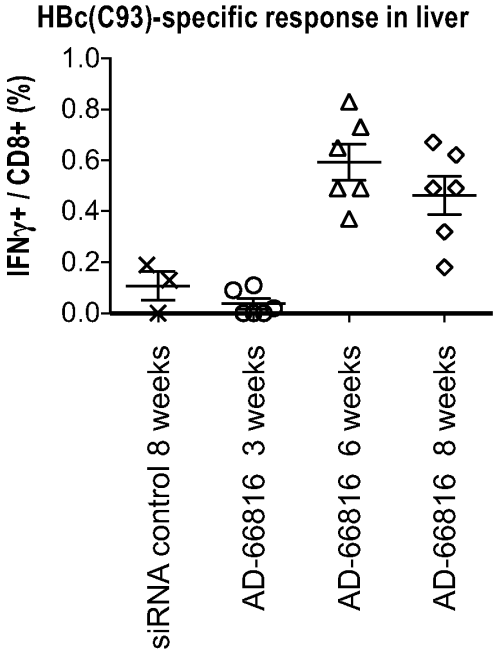


FIG. 9C

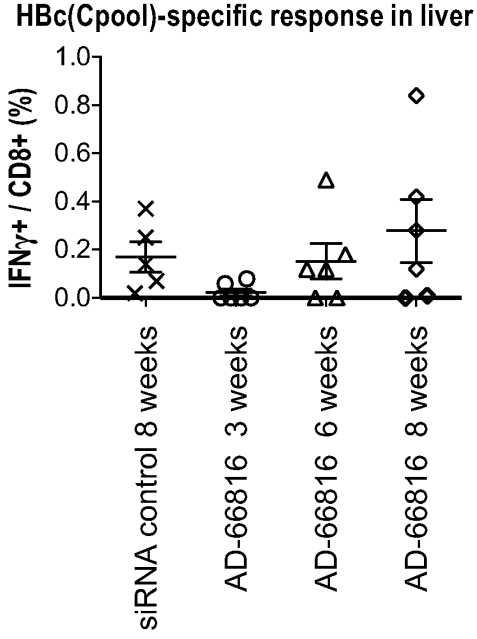


FIG. 9D

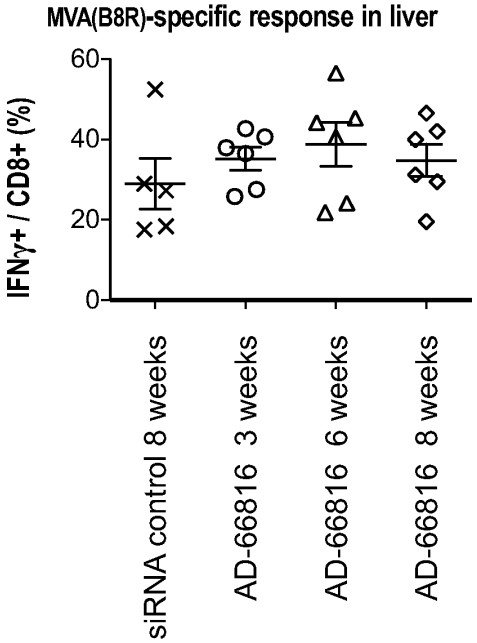


FIG. 10A

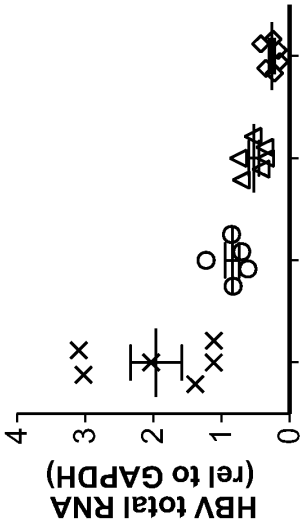


FIG. 10B

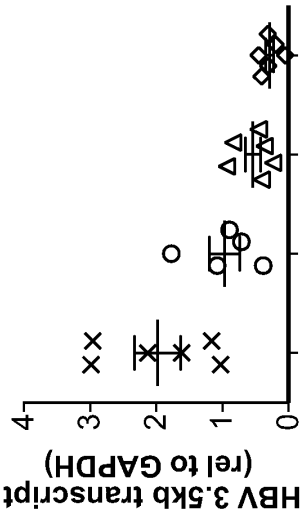
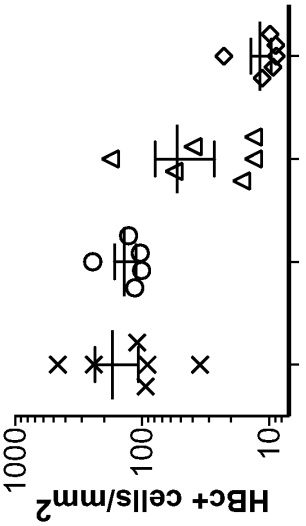


FIG. 10C



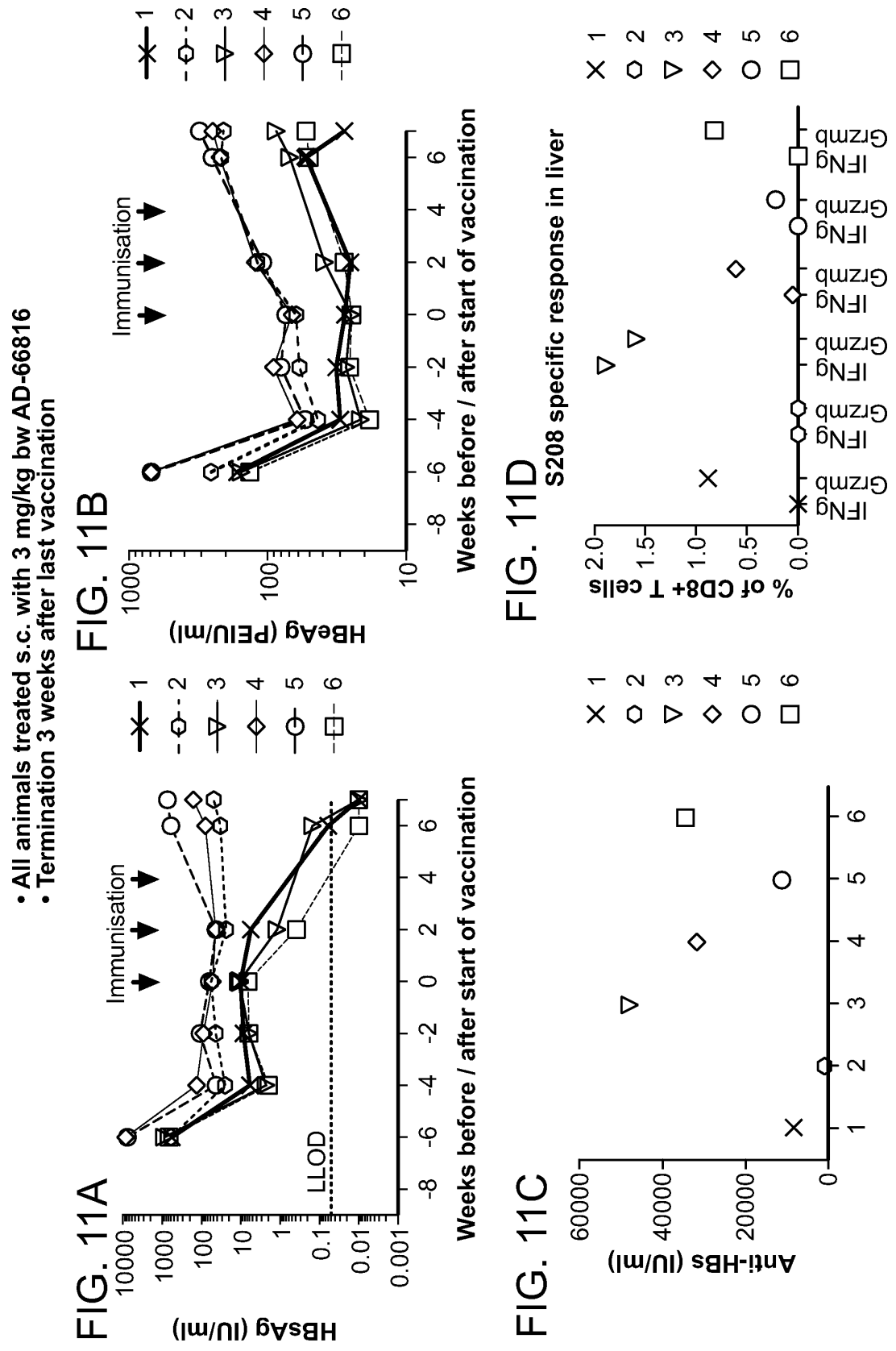

• All animals treated s.c. with 3 mg/kg bw AD-66816
• Termination 3 weeks after last vaccination
FIG. 11A
HBsAg (IU/ml)
10000
1000
100
10
1
0.1
0.01
0.001
LLOD
Immunisation
-8 -6 -4 -2 0 2 4 6
Weeks before / after start of vaccination
1 2 3 4 5 6
FIG. 11B
HBeAg (PEIU/ml)
1000
100
10
Immunisation
-8 -6 -4 -2 0 2 4 6
Weeks before / after start of vaccination
1 2 3 4 5 6
FIG. 11C
Anti-HBs (IU/ml)
60000
40000
20000
0
1 2 3 4 5 6
FIG. 11D
S208 specific response in liver
% of CD8+ T cells
2.0
1.5
1.0
0.5
0.0
IFNg
Grzmb
IFNg
Grzmb
IFNg
Grzmb
IFNg
Grzmb
IFNg
Grzmb
1 2 3 4 5 6

FIG. 12

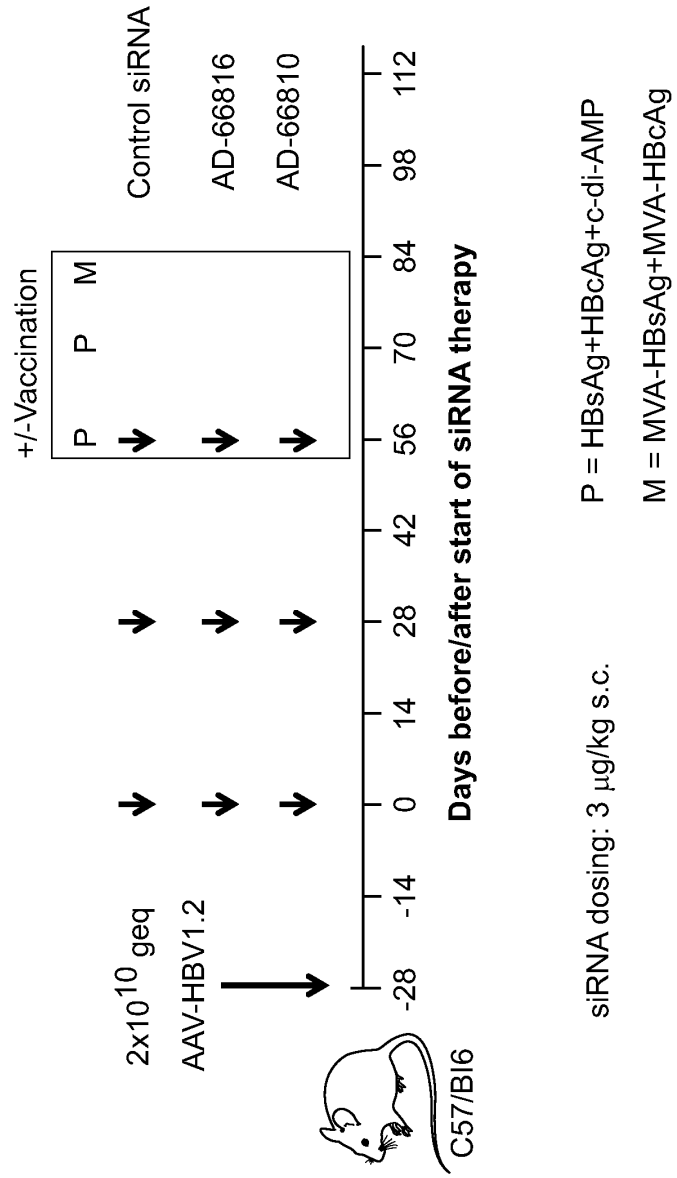

+/-Vaccination
P P M
Control siRNA
AD-66816
AD-66810
2x10^10 geq
AAV-HBV1.2
C57/Bl6
-28 -14 0 14 28 42 56 70 84 98 112
Days before/after start of siRNA therapy
siRNA dosing: 3 µg/kg s.c.
P = HBsAg+HBcAg+c-di-AMP
M = MVA-HBsAg+MVA-HBcAg

FIG. 13A

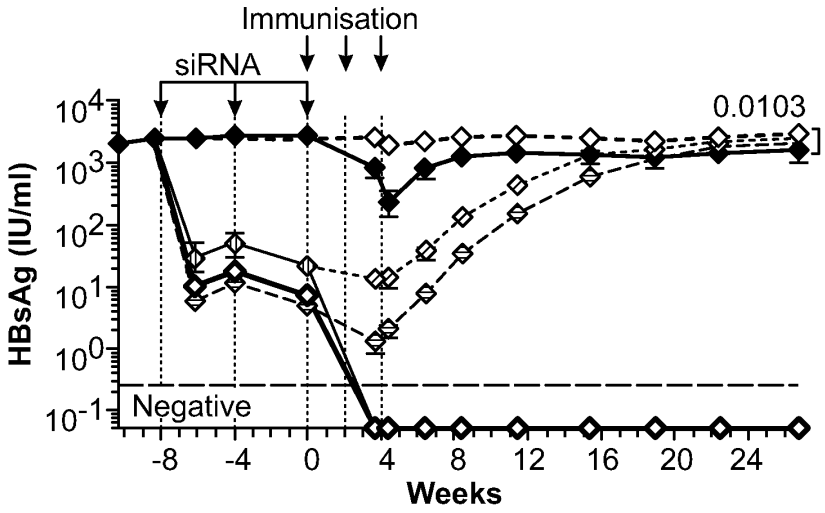
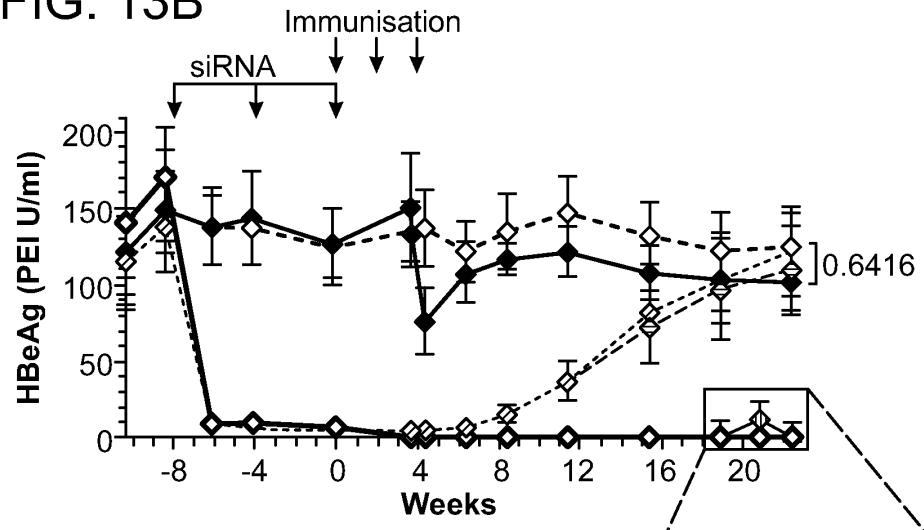


FIG. 13B



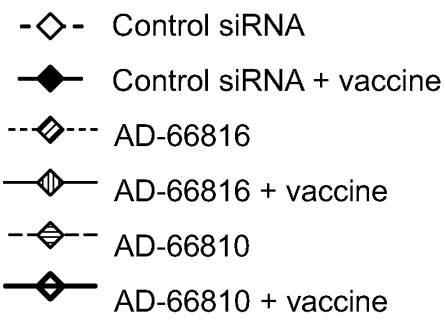
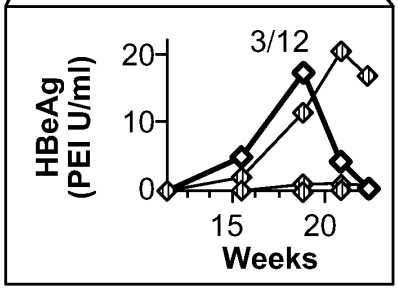


FIG. 13C



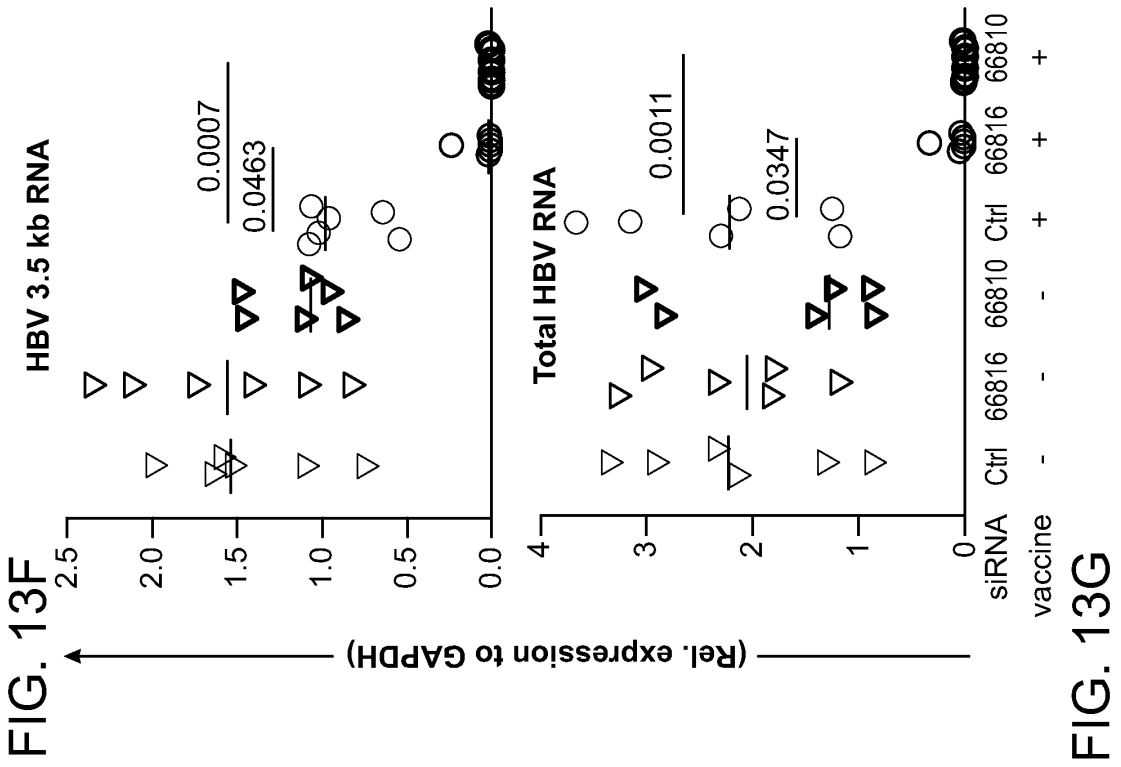


FIG. 13F

FIG. 13G

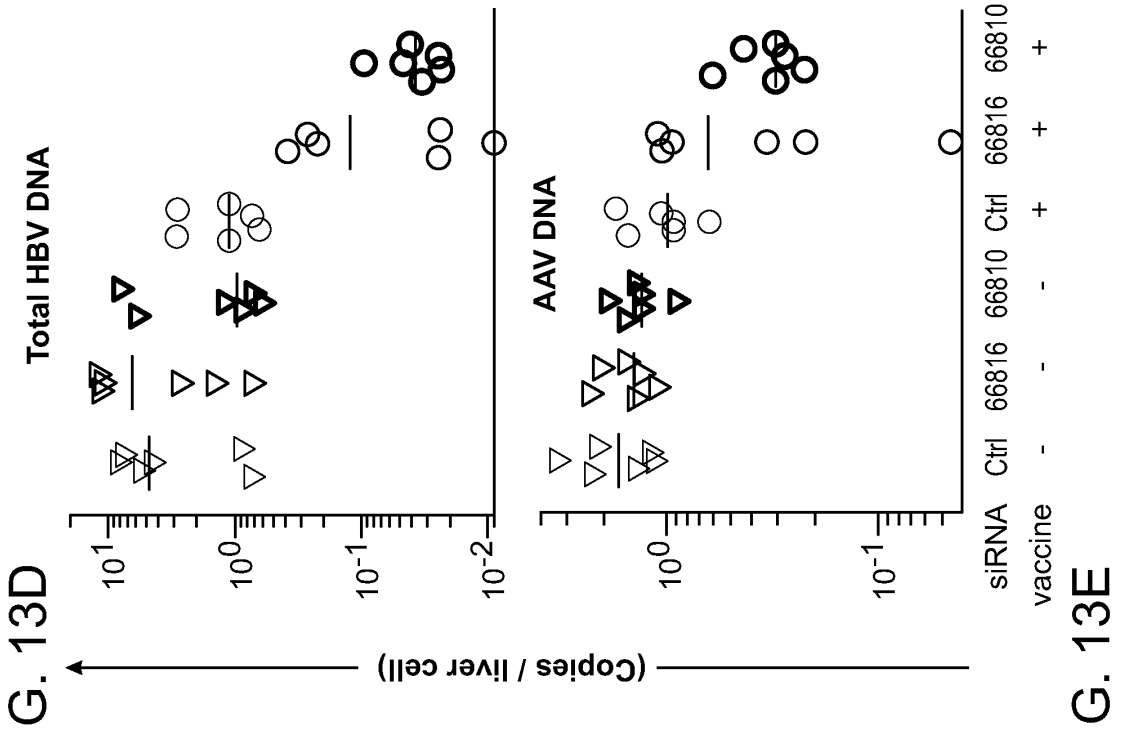


FIG. 13D

FIG. 13E

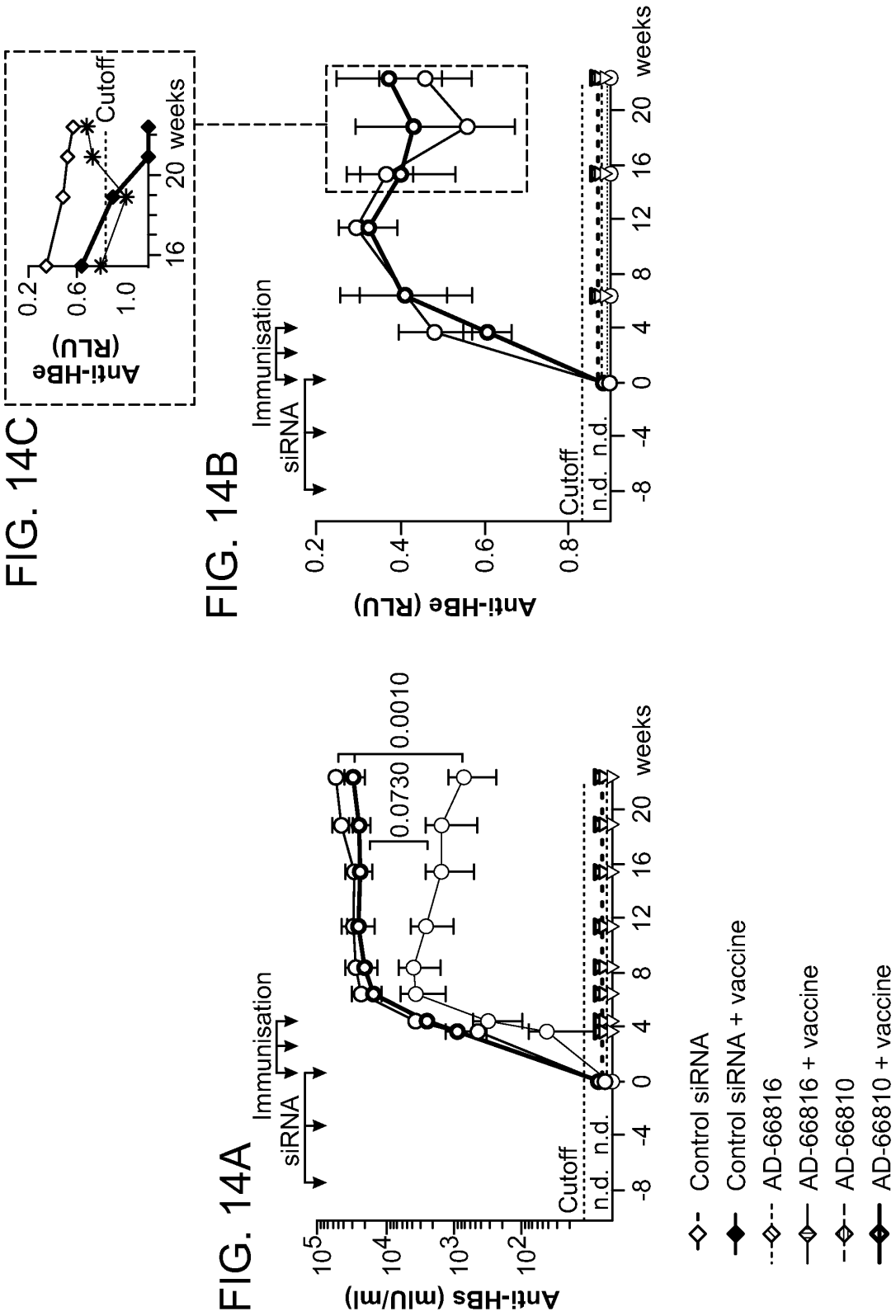

FIG. 14A
Anti-HBs (mIU/ml)
10^5
10^4
10^3
10^2
Cutoff
n.d. n.d.
Immunisation
siRNA
-8 -4 0 4 8 12 16 20 weeks
0.0730
0.0010
Control siRNA
Control siRNA + vaccine
AD-66816
AD-66816 + vaccine
AD-66810
AD-66810 + vaccine
FIG. 14B
Anti-HBe (RLU)
0.2
0.4
0.6
0.8
Cutoff
n.d. n.d.
Immunisation
siRNA
-8 -4 0 4 8 12 16 20 weeks
FIG. 14C
Anti-HBe (RLU)
0.2
0.6
1.0
Cutoff
16 20 weeks

FIG. 15A

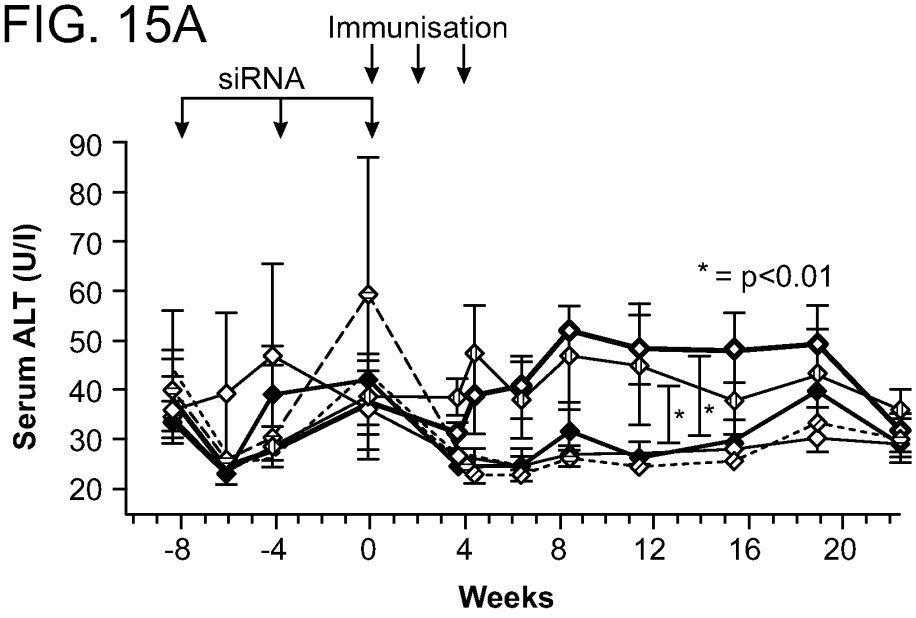


FIG. 15B

