Figures

Figure 1A

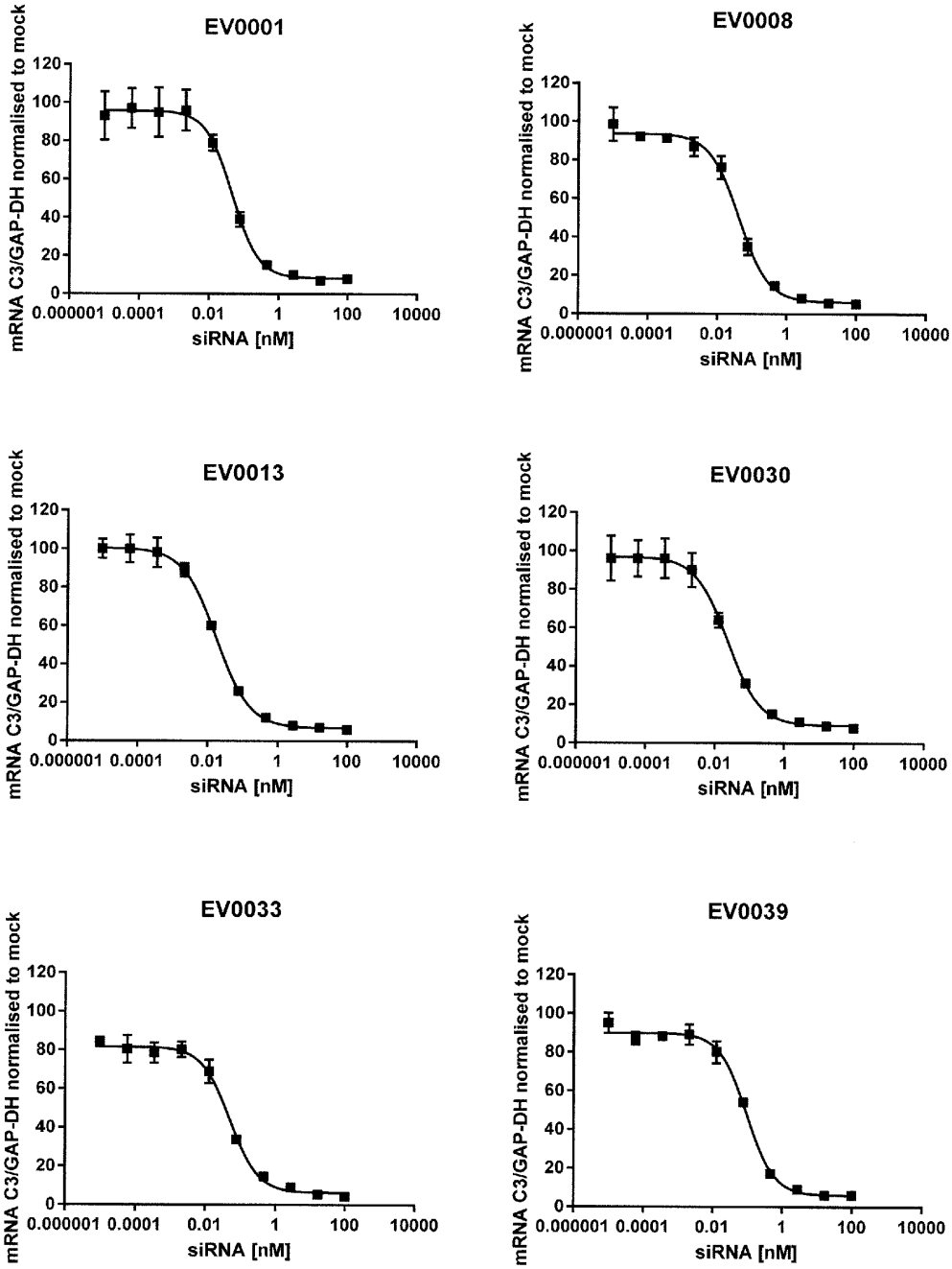


Figure 1B

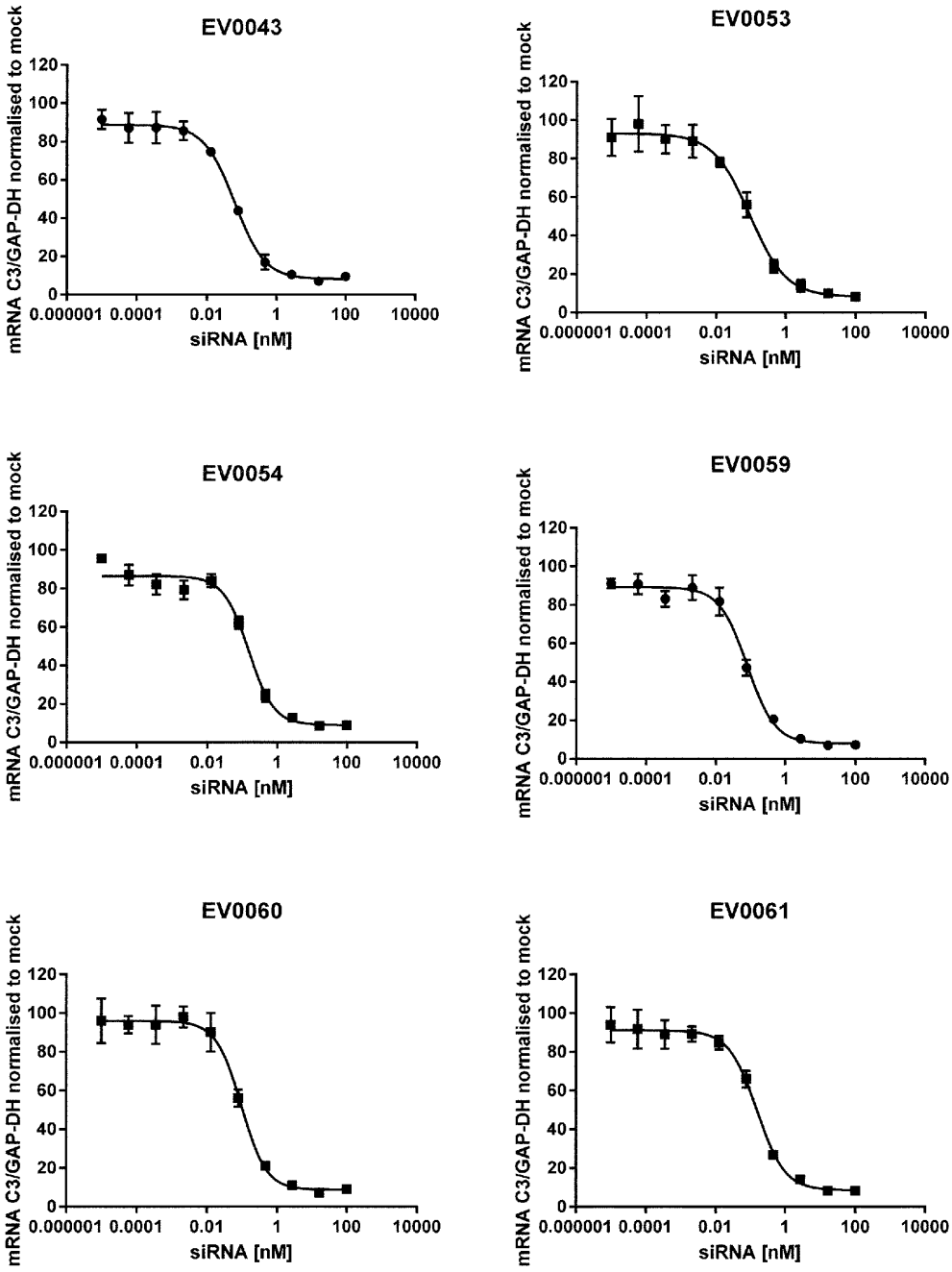

EV0043
EV0053
EV0054
EV0059
EV0060
EV0061
mRNA C3/GAP-DH normalised to mock
siRNA [nM]
0.000001 0.0001 0.01 1 100 10000
0 20 40 60 80 100 120

Figure 1C

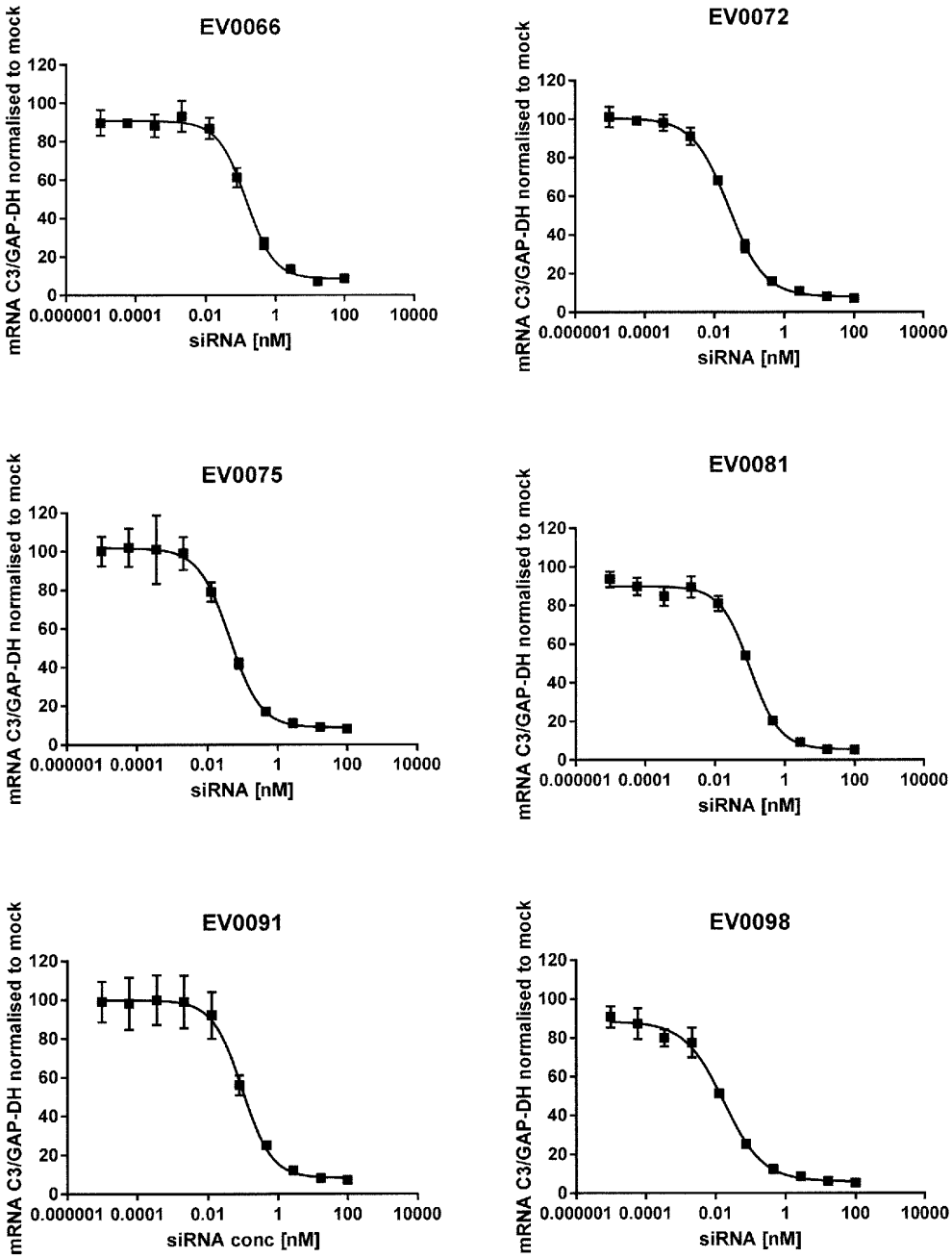
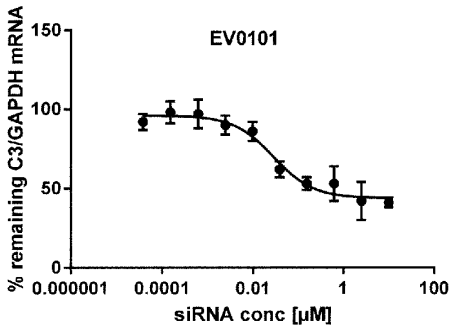
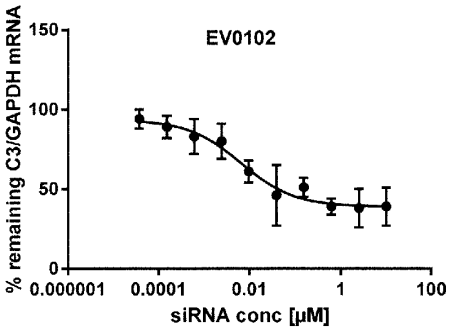
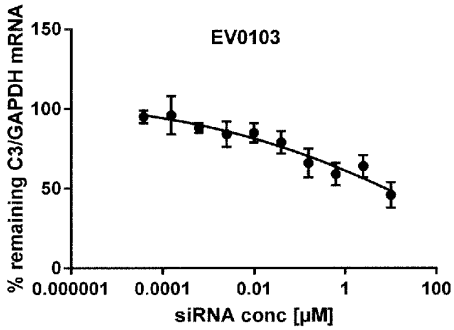
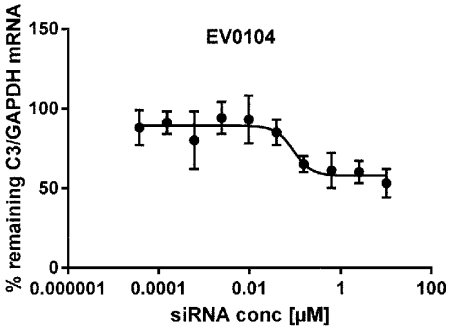

EV0066
EV0072
EV0075
EV0081
EV0091
EV0098
mRNA C3/GAP-DH normalised to mock
siRNA [nM]
siRNA conc [nM]
0.000001 0.0001 0.01 1 100 10000
0 20 40 60 80 100 120

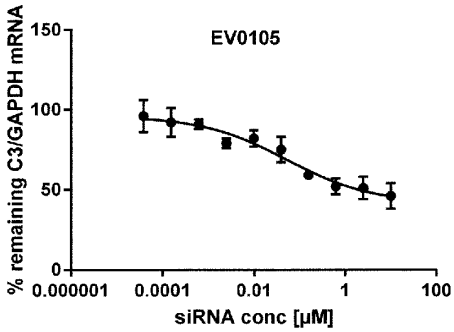
Figure 2A


EV0101
% remaining C3/GAPDH mRNA
150
100
50
0
0.000001
0.0001
0.01
1
100
siRNA conc [µM]


EV0102
% remaining C3/GAPDH mRNA
150
100
50
0
0.000001
0.0001
0.01
1
100
siRNA conc [µM]


EV0103
% remaining C3/GAPDH mRNA
150
100
50
0
0.000001
0.0001
0.01
1
100
siRNA conc [µM]


EV0104
% remaining C3/GAPDH mRNA
150
100
50
0
0.000001
0.0001
0.01
1
100
siRNA conc [µM]


EV0105
% remaining C3/GAPDH mRNA
150
100
50
0
0.000001
0.0001
0.01
1
100
siRNA conc [µM]

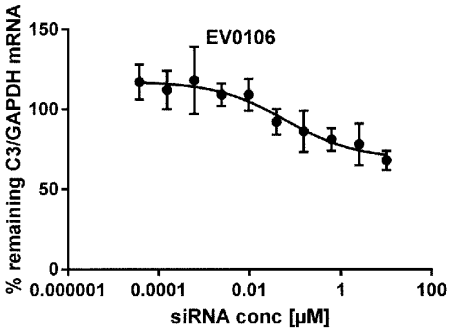
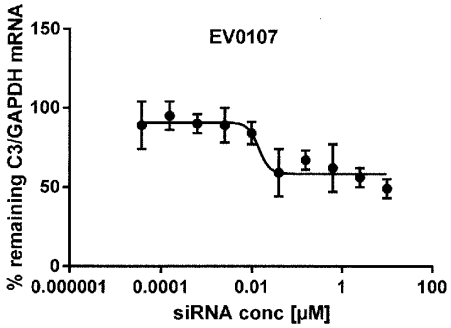
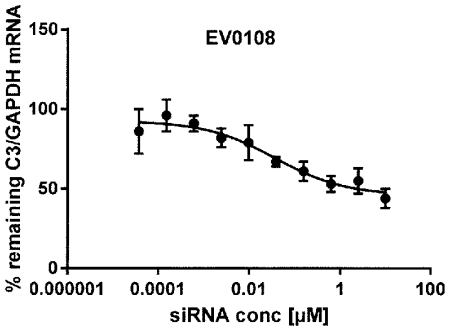
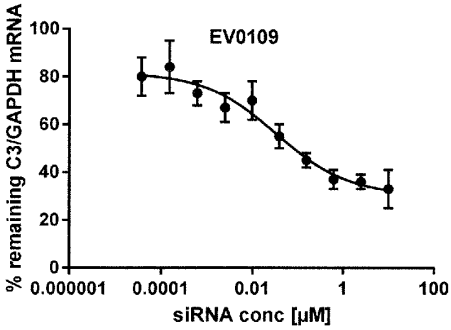
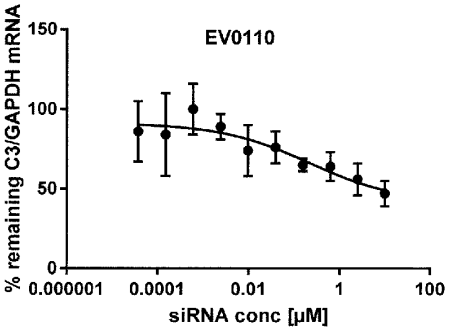

EV0106
% remaining C3/GAPDH mRNA
150
100
50
0
0.000001
0.0001
0.01
1
100
siRNA conc [µM]

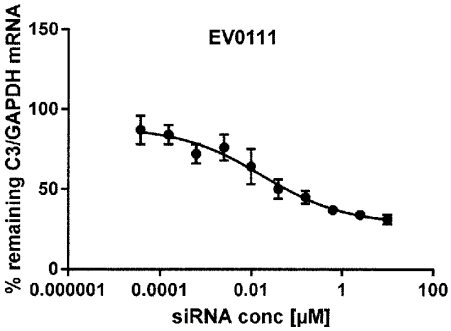
Figure 2B


EV0107
% remaining C3/GAPDH mRNA
150
100
50
0
0.000001
0.0001
0.01
1
100
siRNA conc [µM]


EV0108
% remaining C3/GAPDH mRNA
150
100
50
0
0.000001
0.0001
0.01
1
100
siRNA conc [µM]


EV0109
% remaining C3/GAPDH mRNA
100
80
60
40
20
0
0.000001
0.0001
0.01
1
100
siRNA conc [µM]


EV0110
% remaining C3/GAPDH mRNA
150
100
50
0
0.000001
0.0001
0.01
1
100
siRNA conc [µM]


EV0111
% remaining C3/GAPDH mRNA
150
100
50
0
0.000001
0.0001
0.01
1
100
siRNA conc [µM]

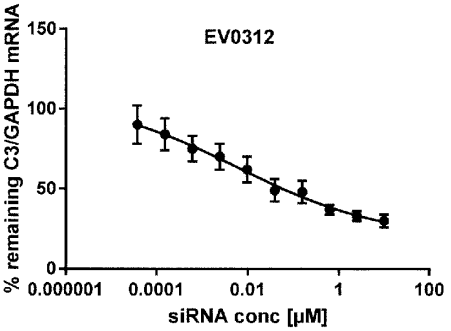
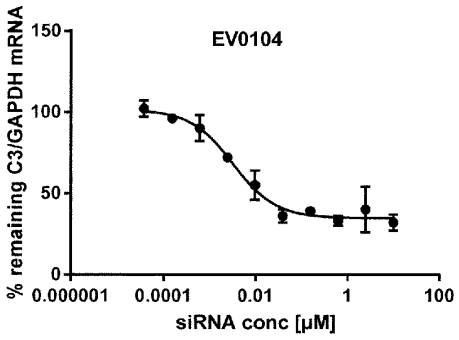
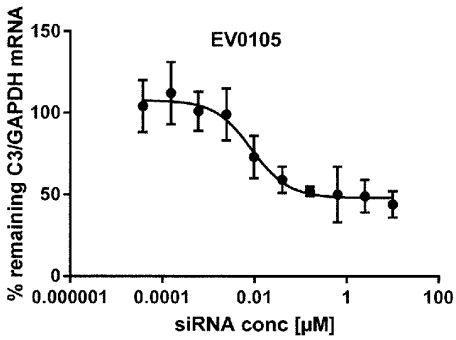
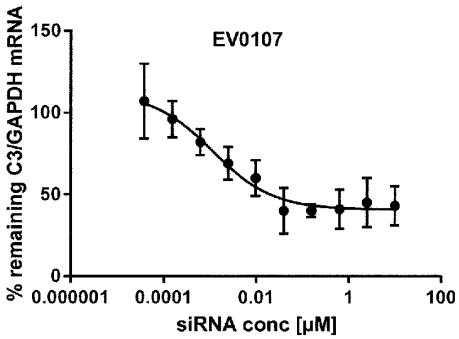
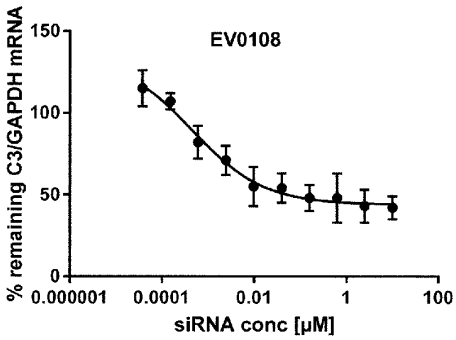

EV0312
% remaining C3/GAPDH mRNA
150
100
50
0
0.000001
0.0001
0.01
1
100
siRNA conc [µM]

Figure 3A


EV0104
% remaining C3/GAPDH mRNA
150
100
50
0
0.000001
0.0001
0.01
1
100
siRNA conc [µM]


EV0105
% remaining C3/GAPDH mRNA
150
100
50
0
0.000001
0.0001
0.01
1
100
siRNA conc [µM]


EV0107
% remaining C3/GAPDH mRNA
150
100
50
0
0.000001
0.0001
0.01
1
100
siRNA conc [µM]


EV0108
% remaining C3/GAPDH mRNA
150
100
50
0
0.000001
0.0001
0.01
1
100
siRNA conc [µM]

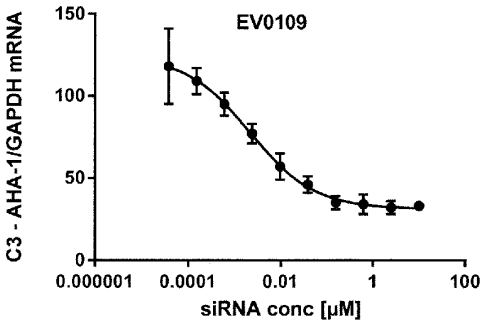
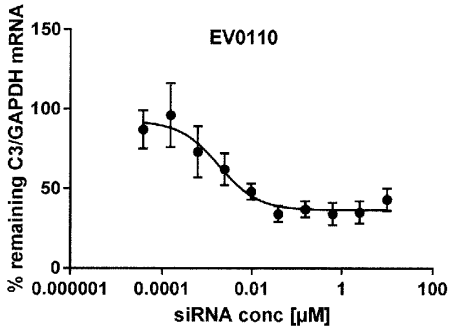
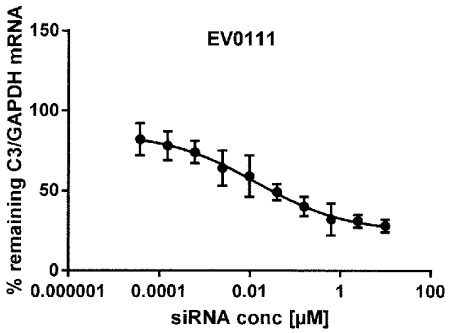

EV0109
C3 - AHA-1/GAPDH mRNA
150
100
50
0
0.000001
0.0001
0.01
1
100
siRNA conc [µM]

Figure 3B


EV0110
% remaining C3/GAPDH mRNA
150
100
50
0
0.000001
0.0001
0.01
1
100
siRNA conc [µM]


EV0111
% remaining C3/GAPDH mRNA
150
100
50
0
0.000001
0.0001
0.01
1
100
siRNA conc [µM]

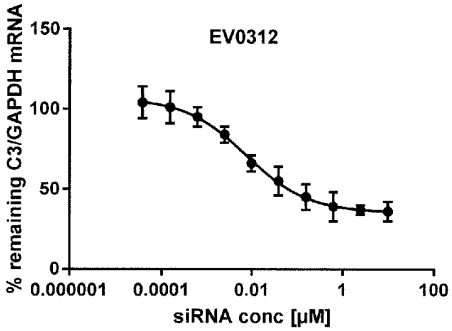

EV0312
% remaining C3/GAPDH mRNA
150
100
50
0
0.000001
0.0001
0.01
1
100
siRNA conc [µM]

Figure 4

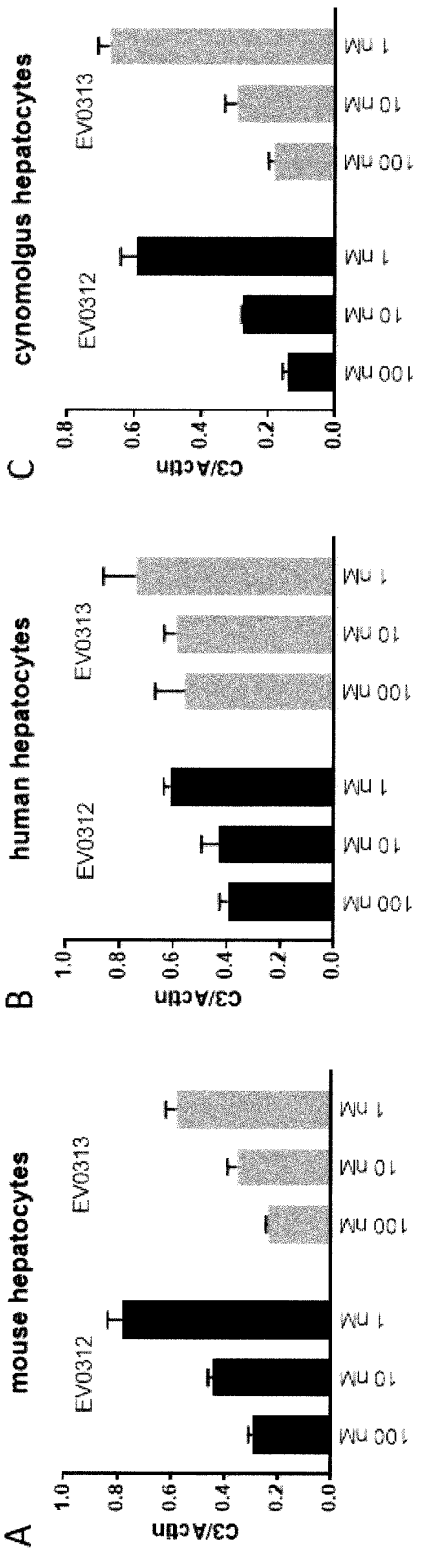
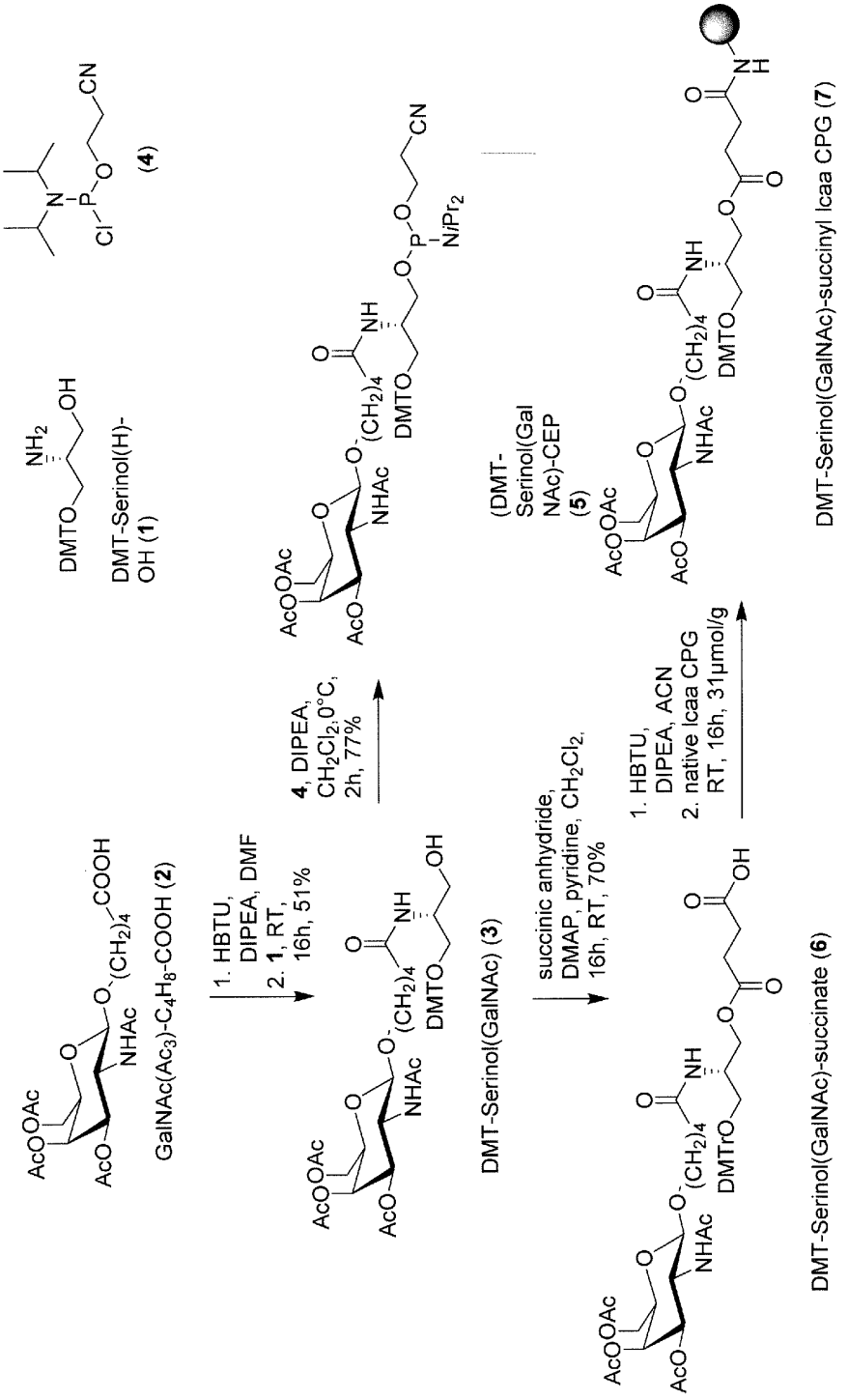

A
mouse hepatocytes
C3/Actin
1.0
0.8
0.6
0.4
0.2
0.0
EV0312
EV0313
100 nM
10 nM
1 nM
100 nM
10 nM
1 nM
B
human hepatocytes
C3/Actin
1.0
0.8
0.6
0.4
0.2
0.0
EV0312
EV0313
100 nM
10 nM
1 nM
100 nM
10 nM
1 nM
C
cynomolgus hepatocytes
C3/Actin
0.8
0.6
0.4
0.2
0.0
EV0312
EV0313
100 nM
10 nM
1 nM
100 nM
10 nM
1 nM

Figure 5


GalNAc(Ac3)-C4H8-COOH (2)
1. HBTU, DIPEA, DMF
2. 1, RT, 16h, 51%
DMT-Serinol(H)-OH (1)
(4)
4, DIPEA, CH2Cl2, 0°C, 2h, 77%
DMT-Serinol(GalNAc) (3)
succinic anhydride, DMAP, pyridine, CH2Cl2, 16h, RT, 70%
(DMT-Serinol(GalNAc)-CEP (5)
1. HBTU, DIPEA, ACN
2. native Icaa CPG RT, 16h, 31µmol/g
DMT-Serinol(GalNAc)-succinate (6)
DMT-Serinol(GalNAc)-succinyl Icaa CPG (7)

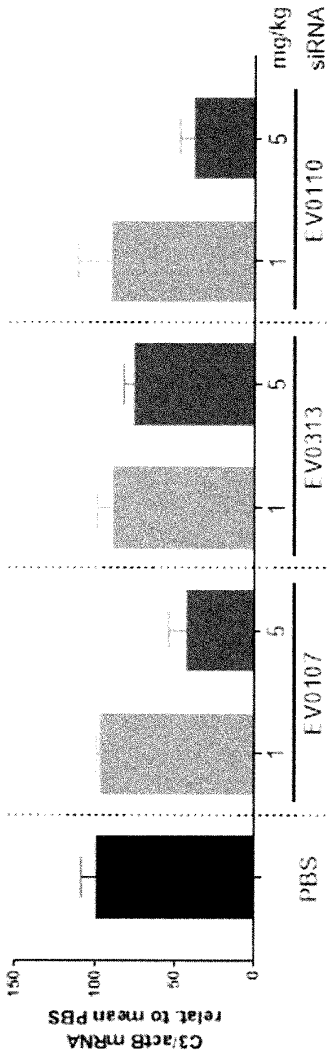


Figure 6A

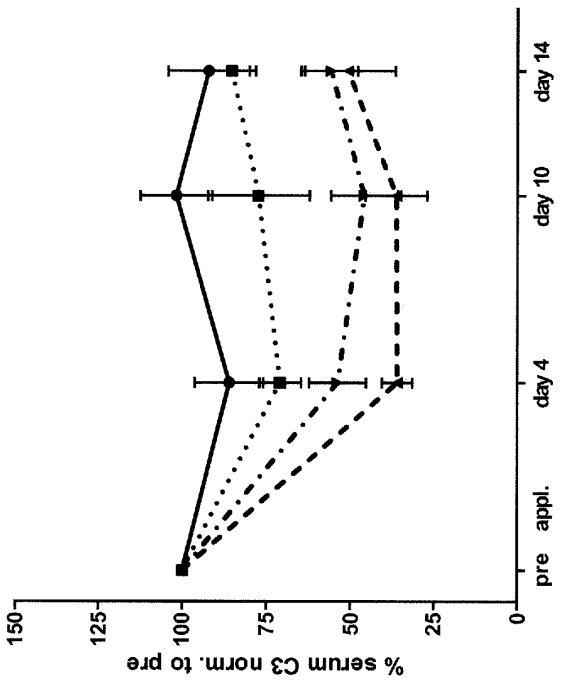


Figure 6B

Figure 7

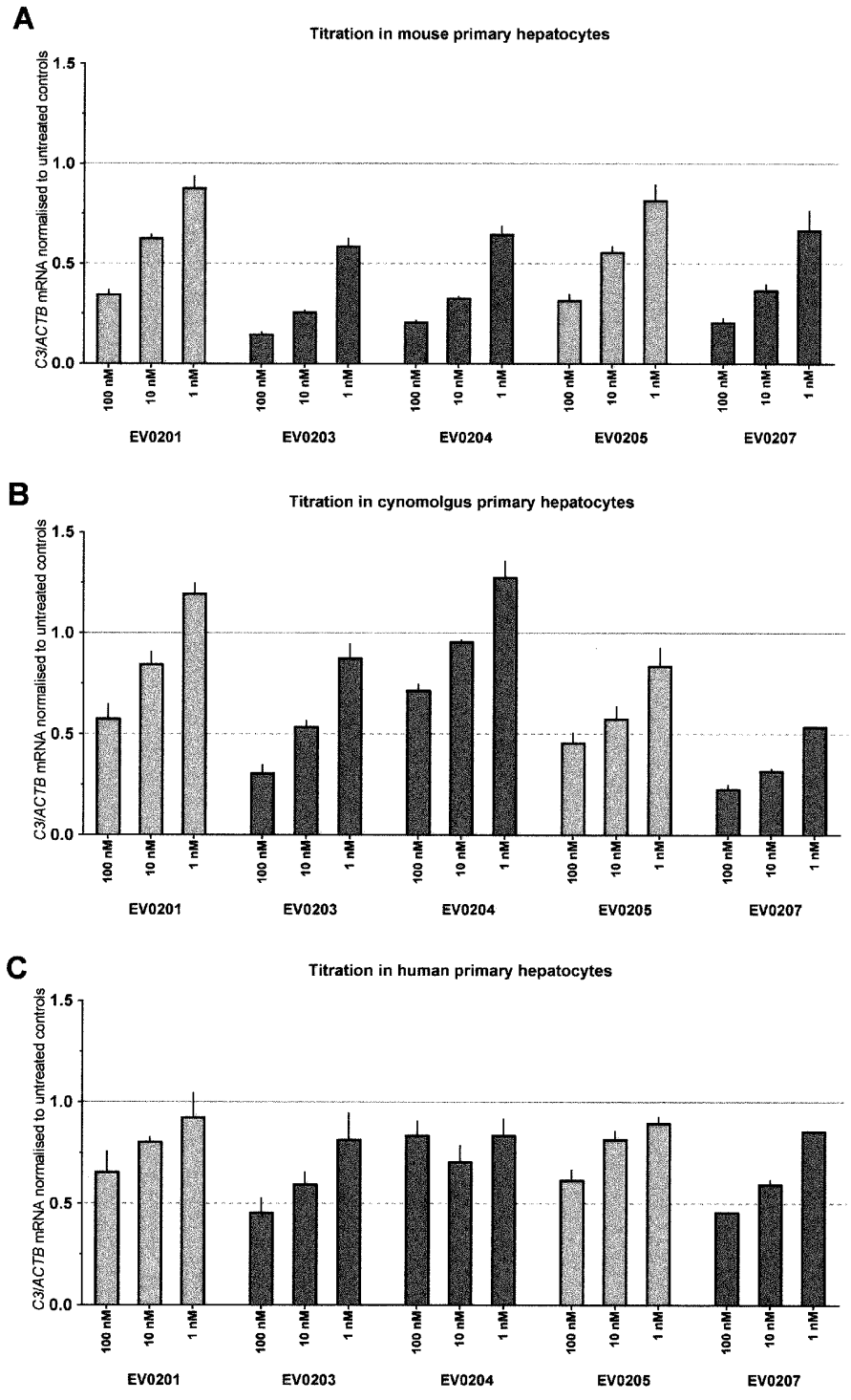

A
Titration in mouse primary hepatocytes
C3/ACTB mRNA normalised to untreated controls
1.5
1.0
0.5
0.0
100 nM
10 nM
1 nM
EV0201
EV0203
EV0204
EV0205
EV0207
B
Titration in cynomolgus primary hepatocytes
C3/ACTB mRNA normalised to untreated controls
EV0201
EV0203
EV0204
EV0205
EV0207
C
Titration in human primary hepatocytes
C3/ACTB mRNA normalised to untreated controls
EV0201
EV0203
EV0204
EV0205
EV0207

Figure 8

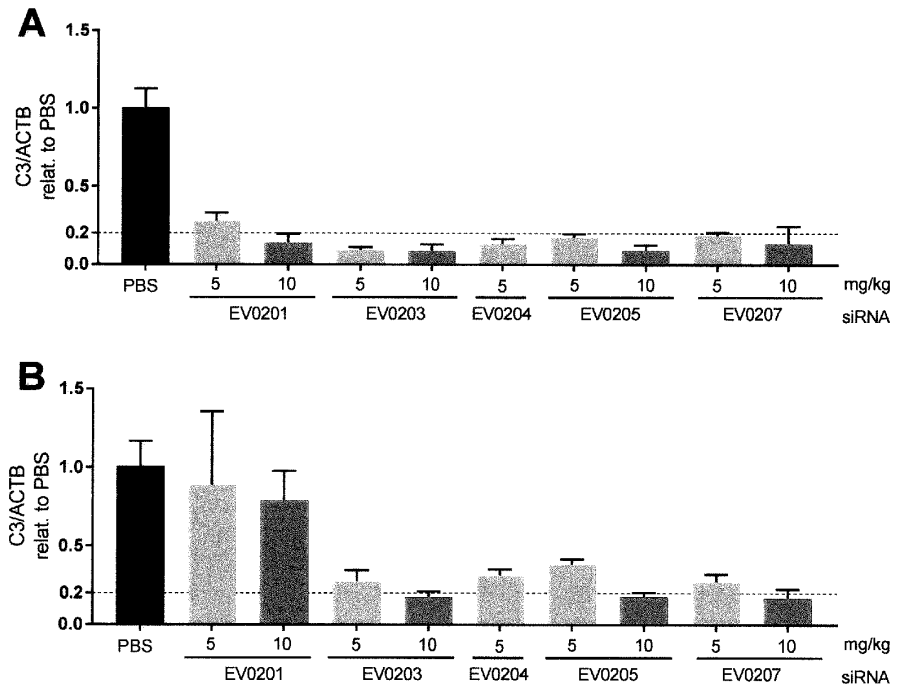

A
C3/ACTB relat. to PBS
1.5
1.0
0.5
0.2
0.0
PBS
5
10
5
10
5
5
10
5
10
mg/kg
EV0201
EV0203
EV0204
EV0205
EV0207
siRNA
B
C3/ACTB relat. to PBS
1.5
1.0
0.5
0.2
0.0
PBS
5
10
5
10
5
5
10
5
10
mg/kg
EV0201
EV0203
EV0204
EV0205
EV0207
siRNA

Figure 9

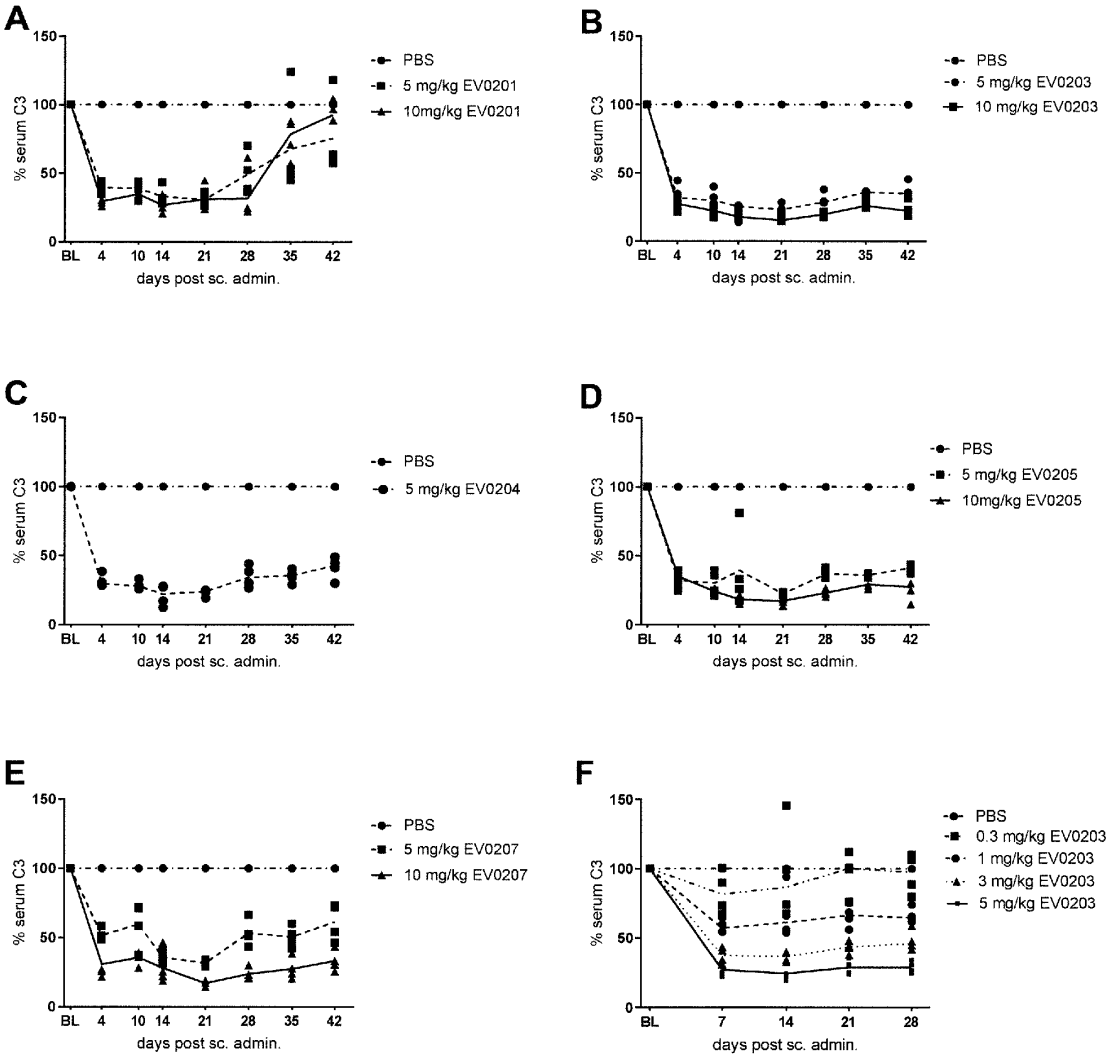

A
% serum C3
150
100
50
0
BL 4 10 14 21 28 35 42
days post sc. admin.
PBS
5 mg/kg EV0201
10mg/kg EV0201
B
% serum C3
BL 4 10 14 21 28 35 42
days post sc. admin.
PBS
5 mg/kg EV0203
10 mg/kg EV0203
C
% serum C3
BL 4 10 14 21 28 35 42
days post sc. admin.
PBS
5 mg/kg EV0204
D
% serum C3
BL 4 10 14 21 28 35 42
days post sc. admin.
PBS
5 mg/kg EV0205
10mg/kg EV0205
E
% serum C3
BL 4 10 14 21 28 35 42
days post sc. admin.
PBS
5 mg/kg EV0207
10 mg/kg EV0207
F
% serum C3
BL 7 14 21 28
days post sc. admin.
PBS
0.3 mg/kg EV0203
1 mg/kg EV0203
3 mg/kg EV0203
5 mg/kg EV0203

Figure 10

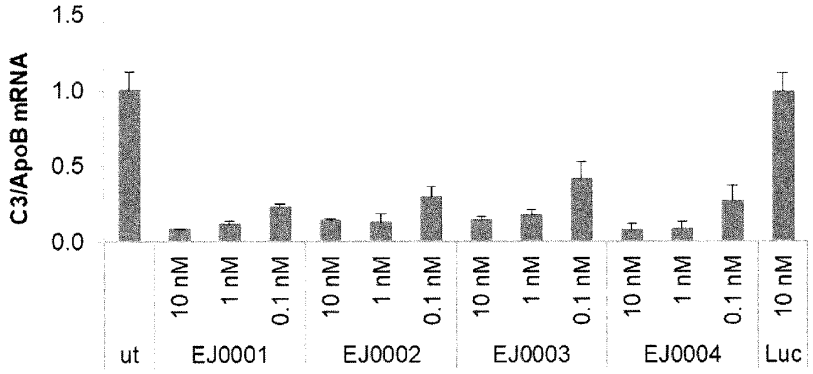


Figure 11

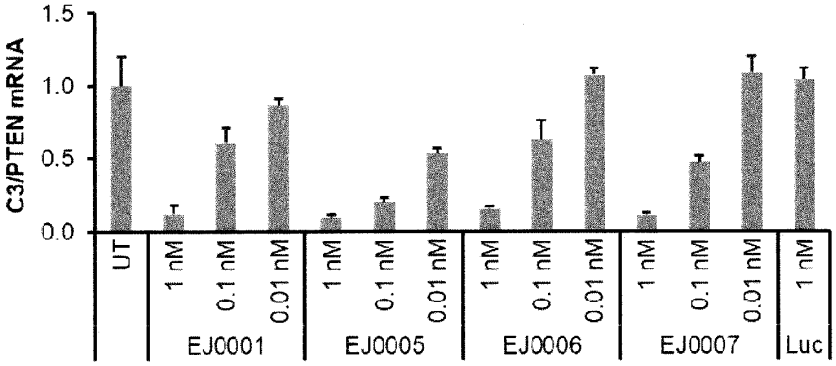


Figure 12

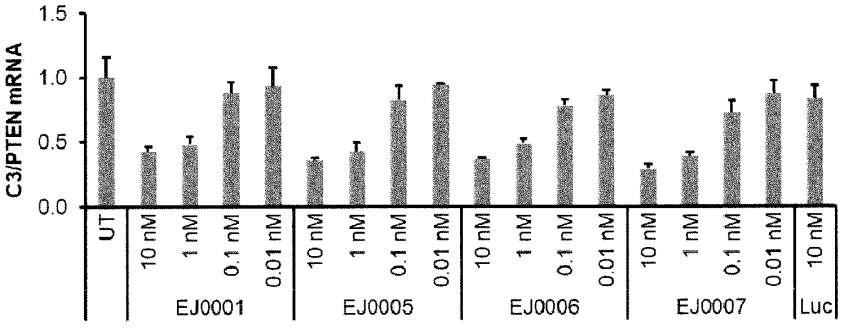


Figure 13

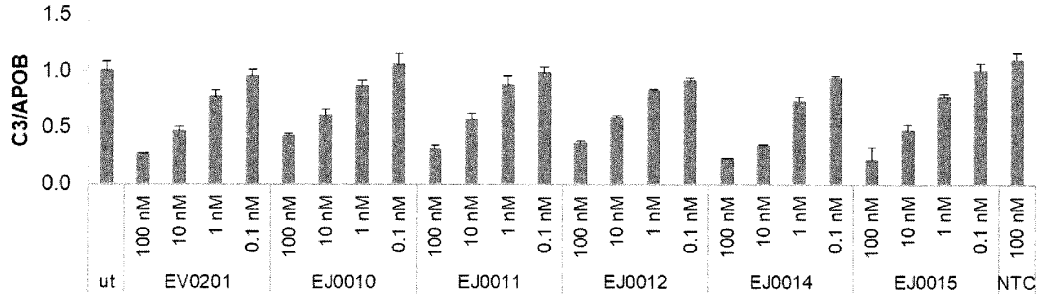


Figure 14

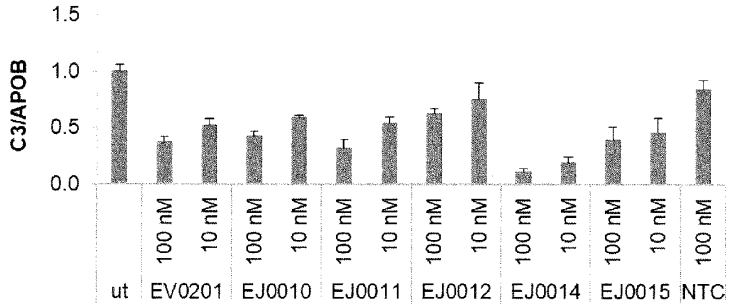


Figure 15

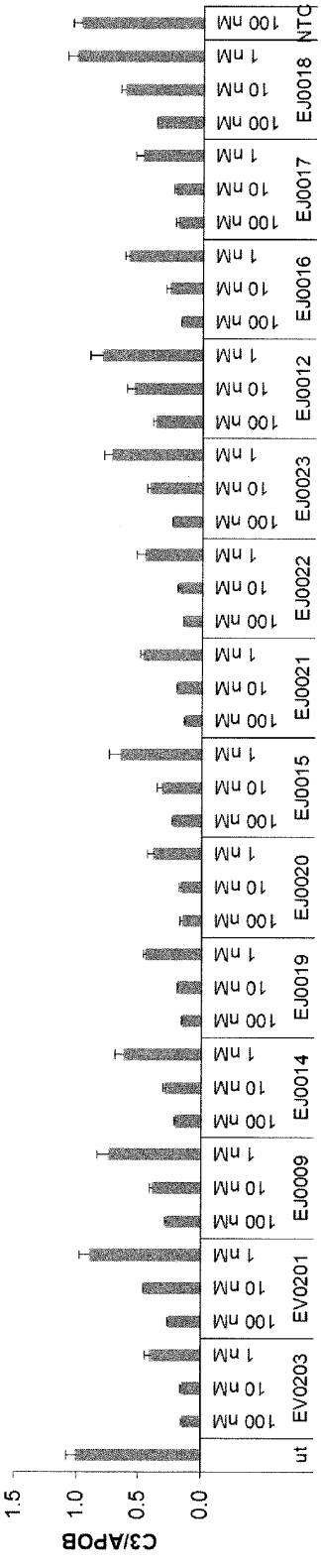


Figure 16

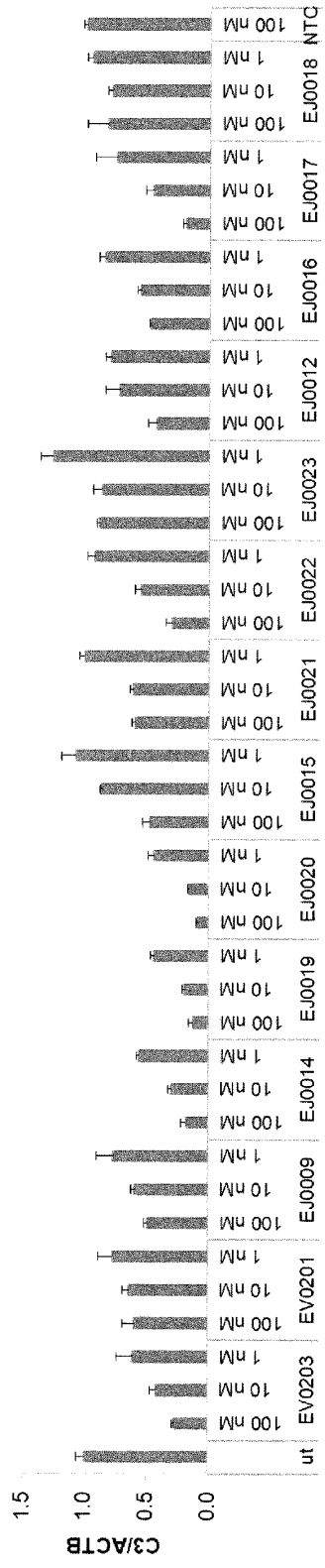


Figure 17

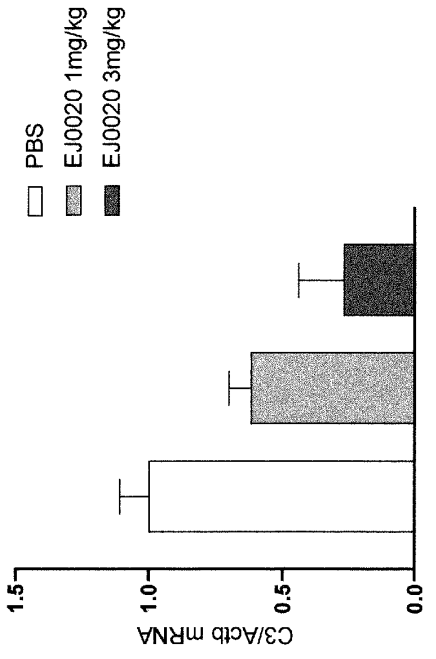


Figure 18

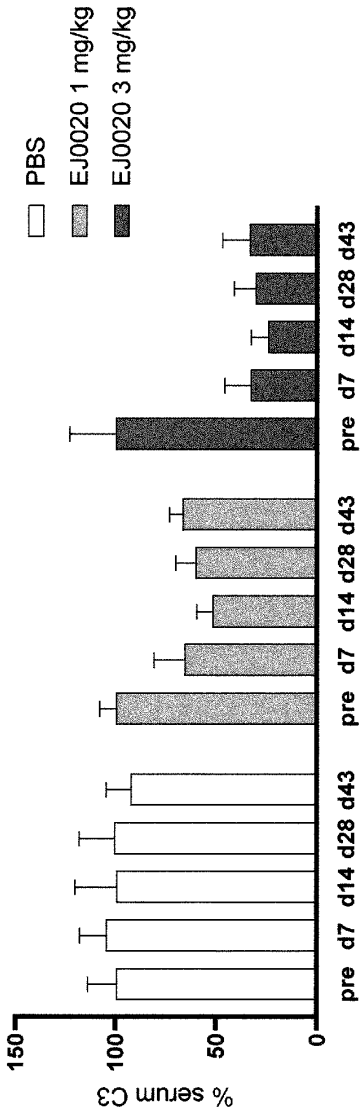


Figure 19

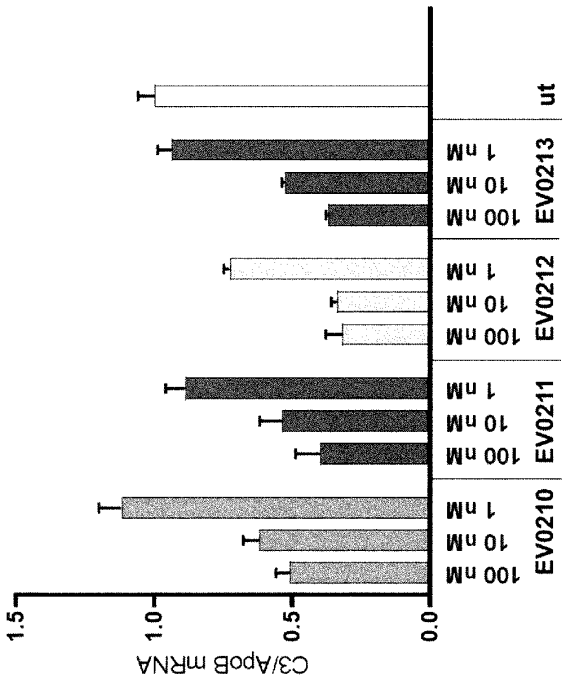
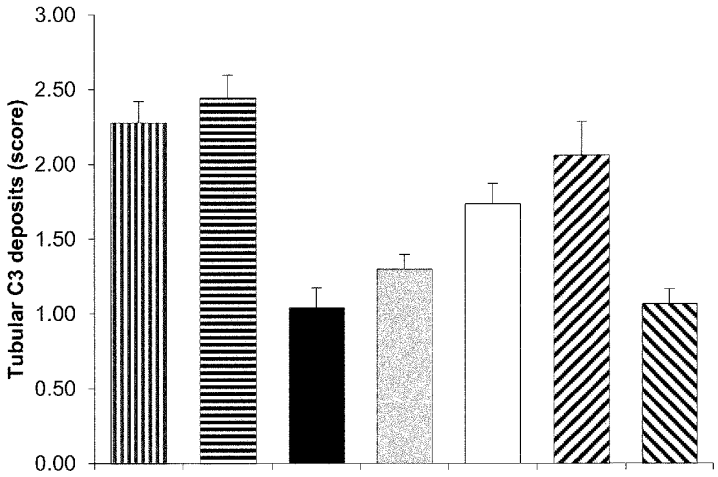
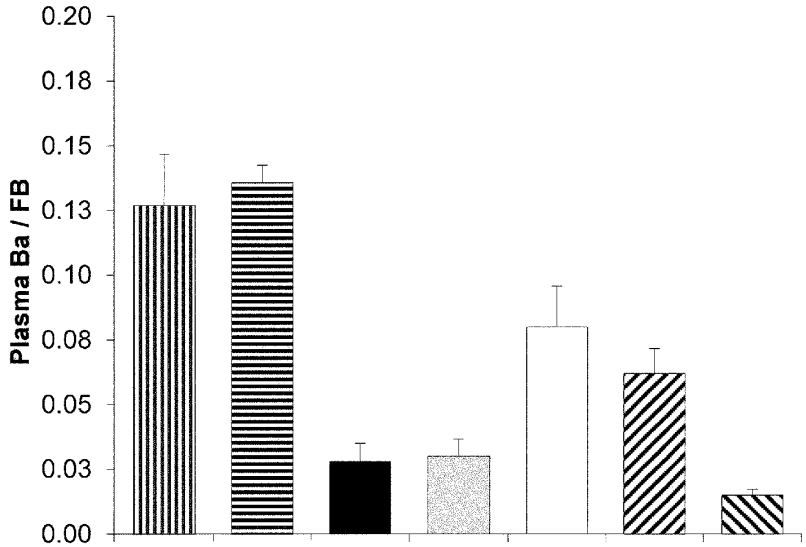

C3/ApoB mRNA
1.5
1.0
0.5
0.0
100 nM
10 nM
1 nM
EV0210
100 nM
10 nM
1 nM
EV0211
100 nM
10 nM
1 nM
EV0212
100 nM
10 nM
1 nM
EV0213
ut

Figure 20



Group A: Cfh def. + PBS
Group B: Cfh def. + Non targeting
Group C: Cfh def. + siRNA C3 (10mg/kg)
Group D: Cfh def. + siRNA C3 (5mg/kg)
Group E: Cfh def. + siRNA C3 (1mg/kg)
Group F: Wild Type female + PBS
Group G: Wild Type female + siRNA C3 (10mg/kg)

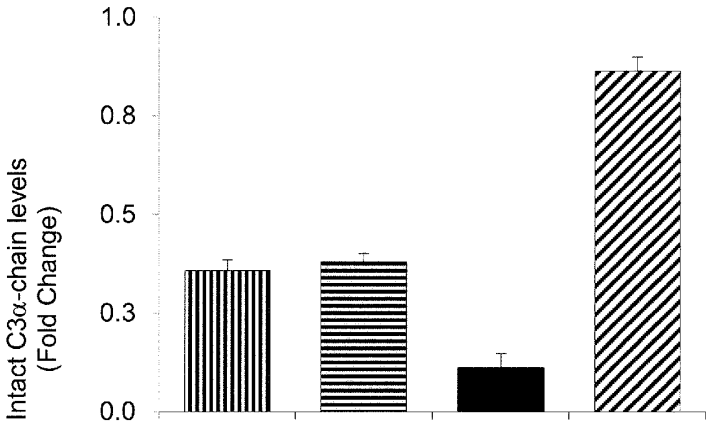
Figure 21



Group A: Cfh def. + PBS
Group B: Cfh def. + Non targeting
Group C: Cfh def. + siRNA C3 (10mg/kg)
Group D: Cfh def. + siRNA C3 (5mg/kg)
Group E: Cfh def. + siRNA C3 (1mg/kg)
Group F: Wild Type female + PBS
Group G: Wild Type female + siRNA C3 (10mg/kg)

Figure 22

A


1.0
0.8
0.5
0.3
0.0
Intact C3α-chain levels
(Fold Change)

B

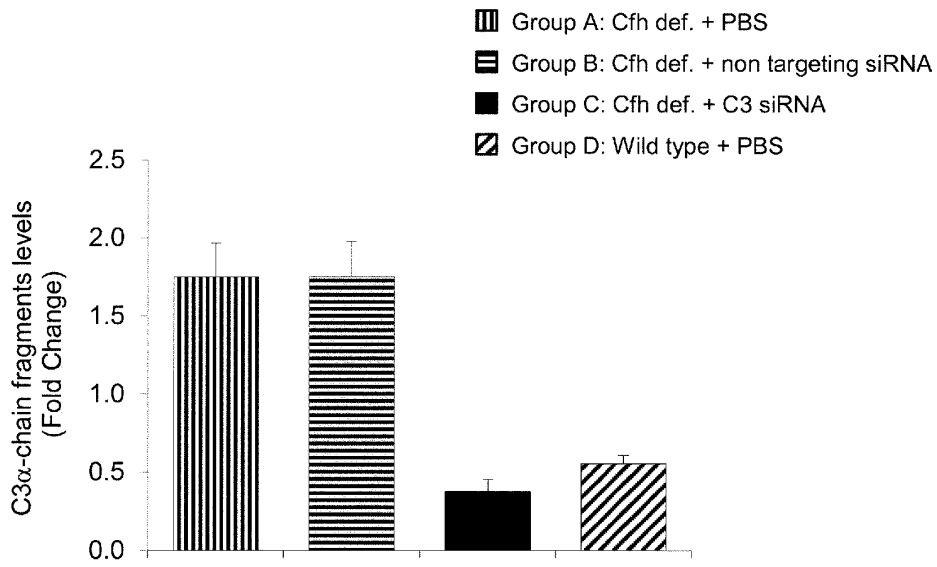
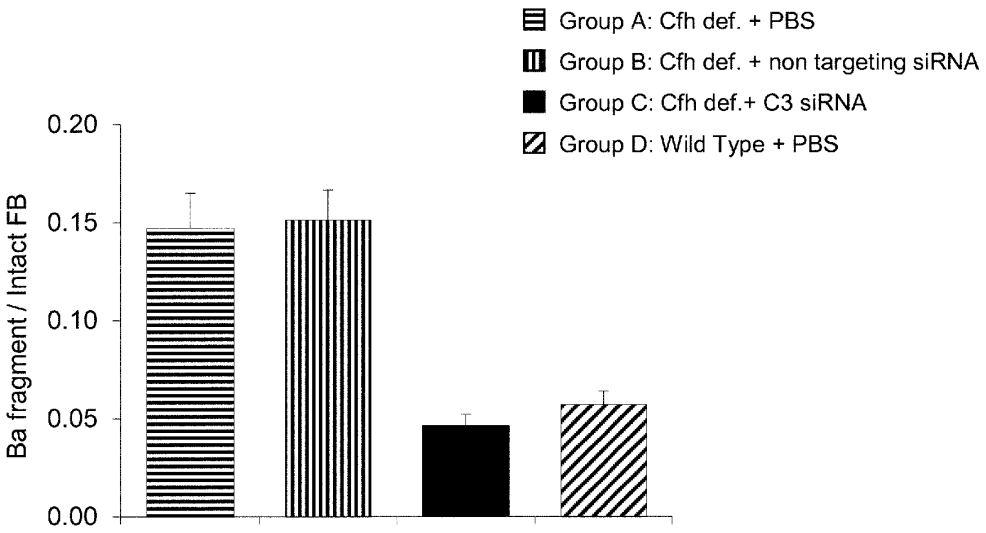

Group A: Cfh def. + PBS
Group B: Cfh def. + non targeting siRNA
Group C: Cfh def. + C3 siRNA
Group D: Wild type + PBS
2.5
2.0
1.5
1.0
0.5
0.0
C3α-chain fragments levels
(Fold Change)

Figure 23


Group A: Cfh def. + PBS
Group B: Cfh def. + non targeting siRNA
Group C: Cfh def.+ C3 siRNA
Group D: Wild Type + PBS
Ba fragment / Intact FB
0.20
0.15
0.10
0.05
0.00