Fig. 1

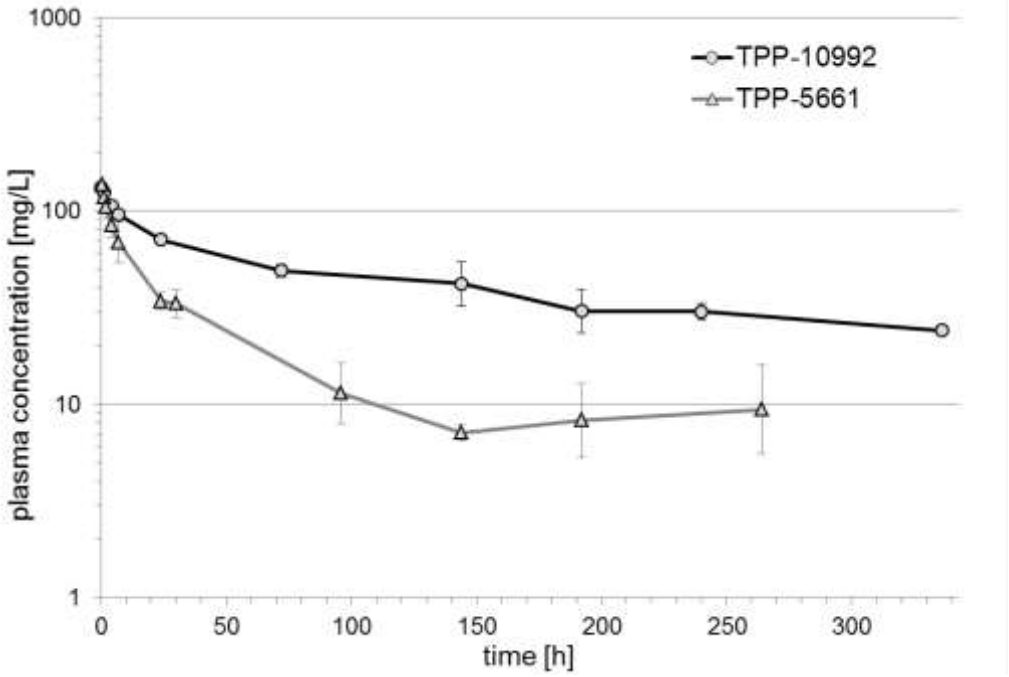

1000
100
10
1
plasma concentration [mg/L]
0
50
100
150
200
250
300
time [h]
TPP-10992
TPP-5661

Fig. 2

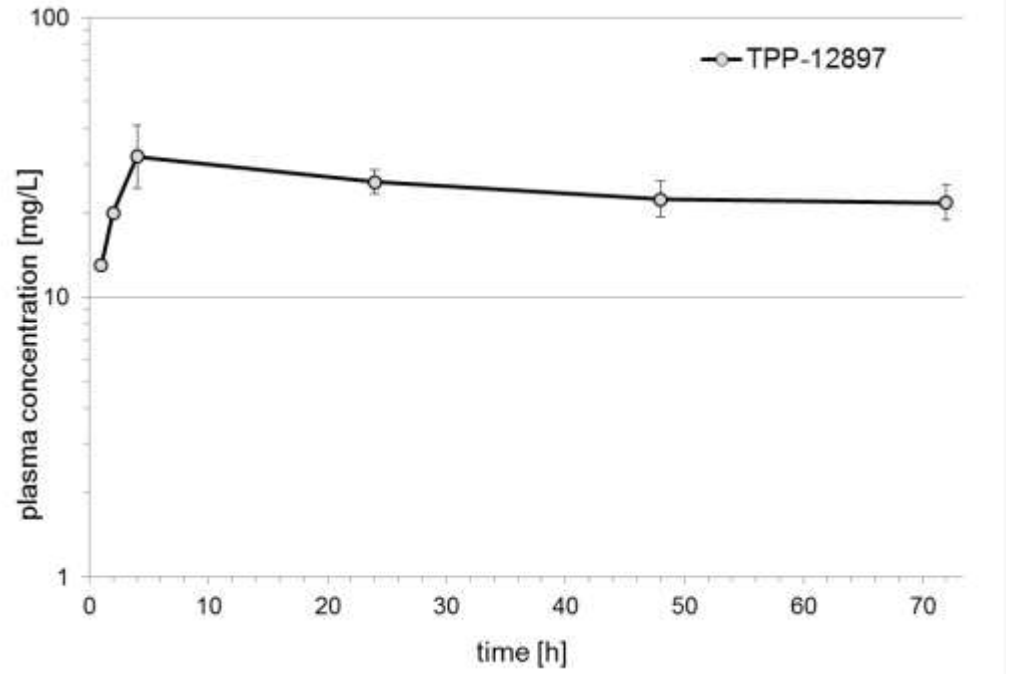

100
10
1
plasma concentration [mg/L]
0
10
20
30
40
50
60
70
time [h]
TPP-12897

Fig. 3

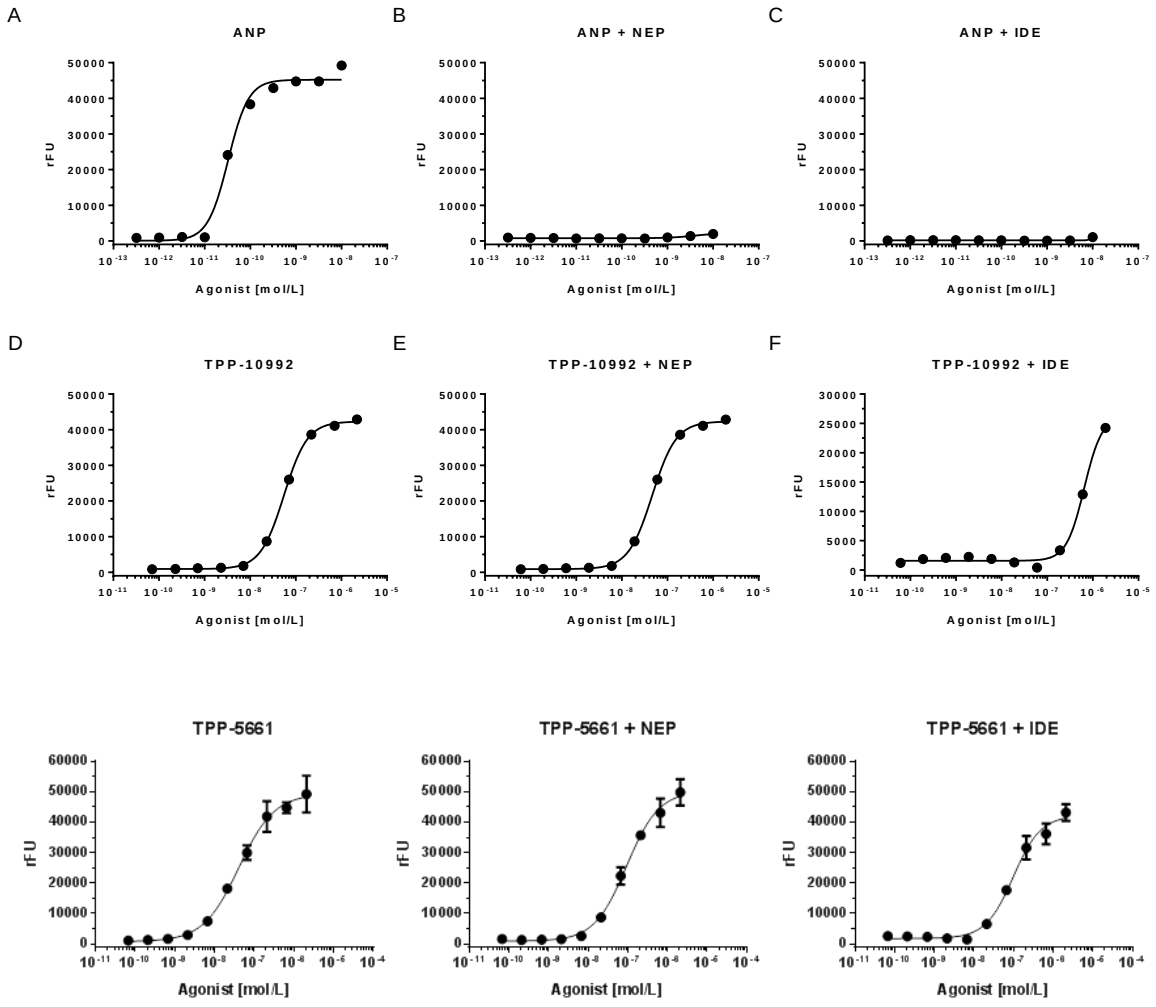

A
ANP
B
ANP + NEP
C
ANP + IDE
D
TPP-10992
E
TPP-10992 + NEP
F
TPP-10992 + IDE
TPP-5661
TPP-5661 + NEP
TPP-5661 + IDE
rFU
Agonist [mol/L]

Fig. 4

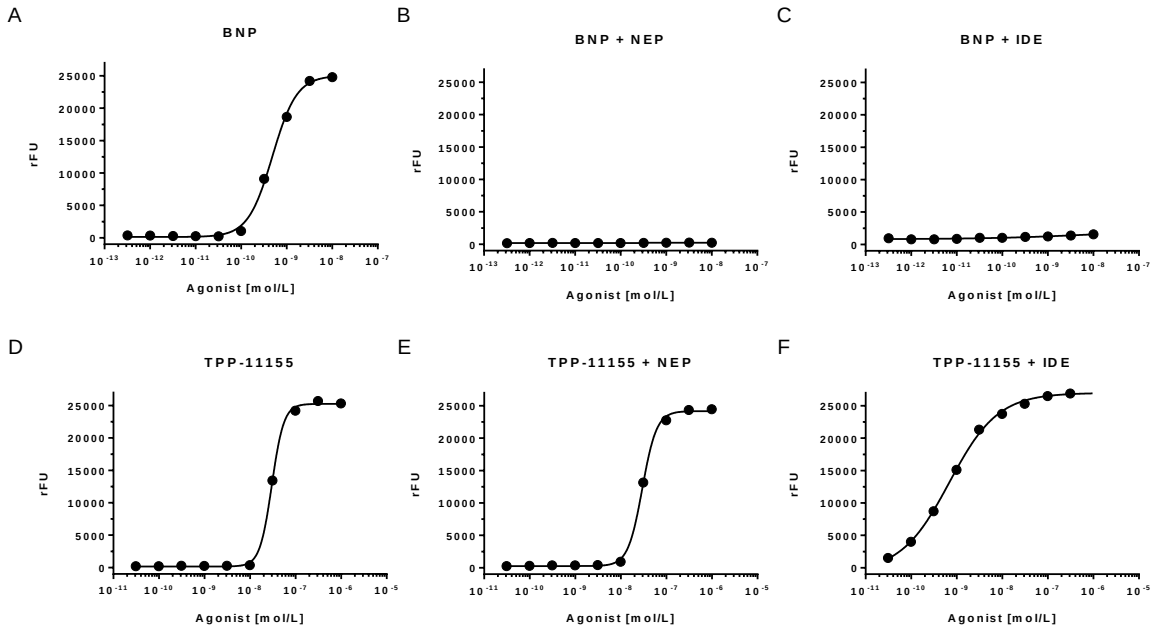

A
BNP
B
BNP + NEP
C
BNP + IDE
D
TPP-11155
E
TPP-11155 + NEP
F
TPP-11155 + IDE
rFU
Agonist [mol/L]

Fig. 5

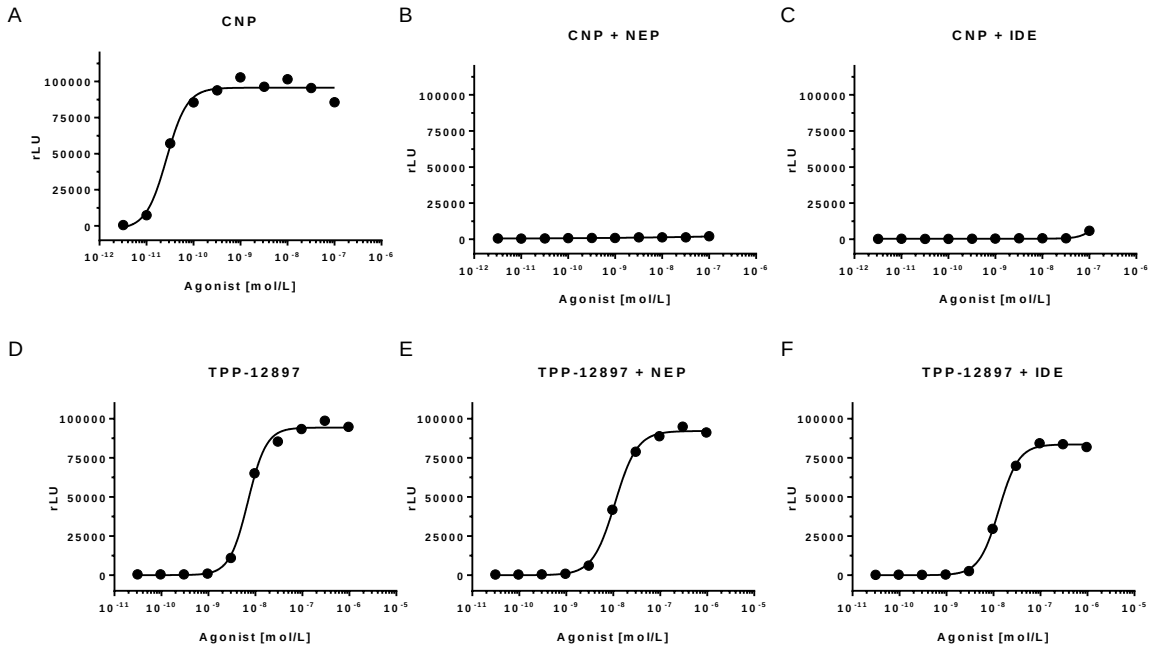

A
CNP
B
CNP + NEP
C
CNP + IDE
D
TPP-12897
E
TPP-12897 + NEP
F
TPP-12897 + IDE
rLU
Agonist [mol/L]

Fig. 6

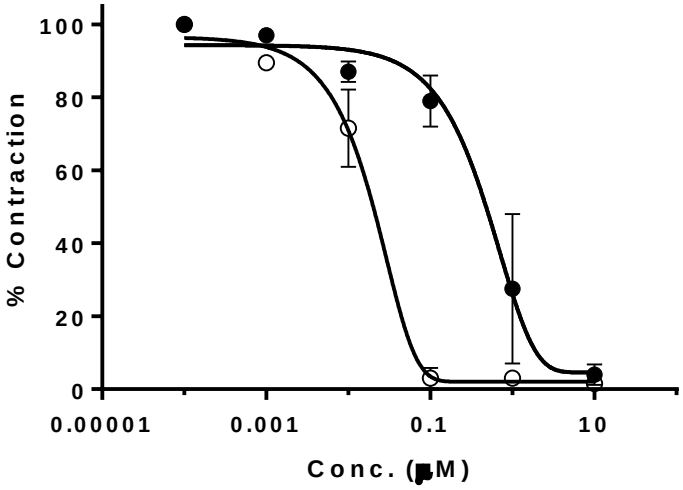

100
80
60
40
20
0
% Contraction
0.00001
0.001
0.1
10
Conc. (μM)

Fig. 7

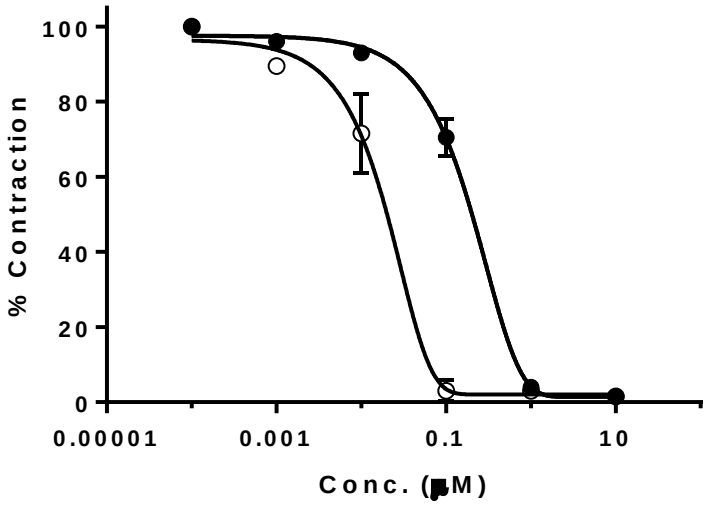

100
80
60
40
20
0
% Contraction
0.00001
0.001
0.1
10
Conc. (μM)

Fig. 8

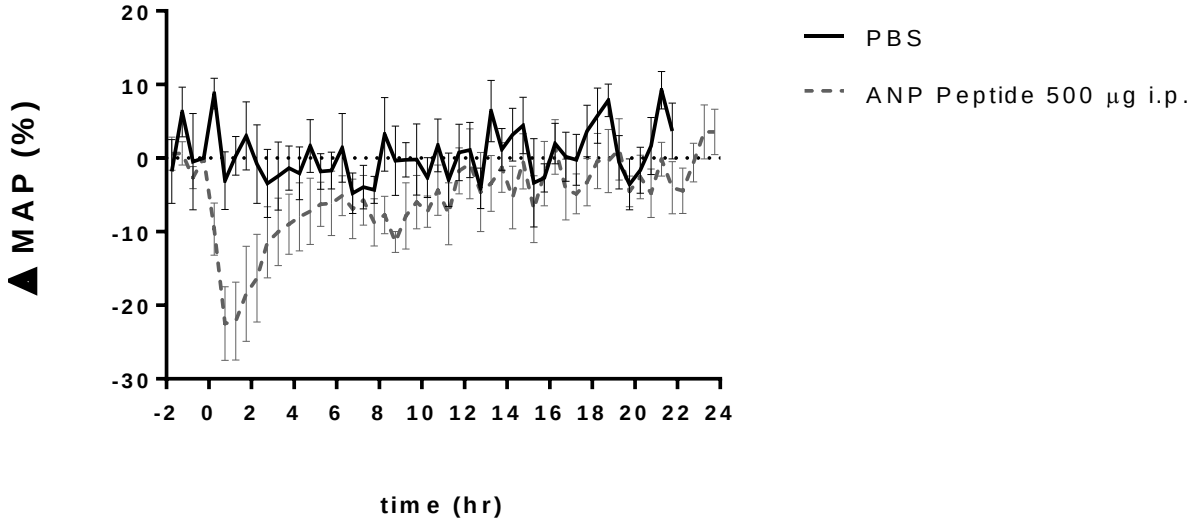

20
10
0
-10
-20
-30
-2 0 2 4 6 8 10 12 14 16 18 20 22 24
▲ MAP (%)
time (hr)
PBS
ANP Peptide 500 µg i.p.

Fig. 9

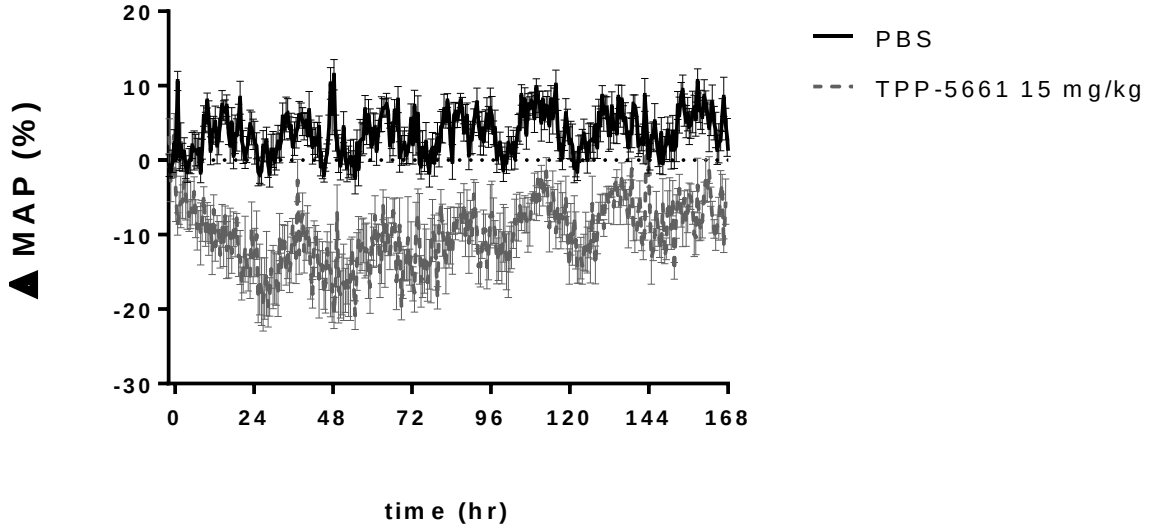

20
10
0
-10
-20
-30
0 24 48 72 96 120 144 168
▲ MAP (%)
time (hr)
PBS
TPP-5661 15 mg/kg

Fig. 10

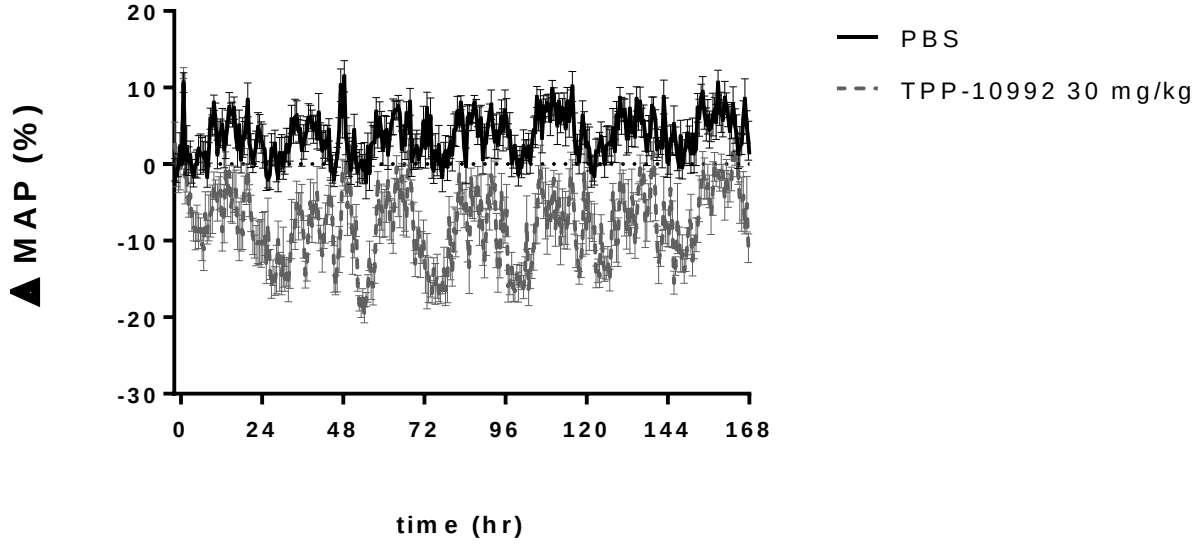
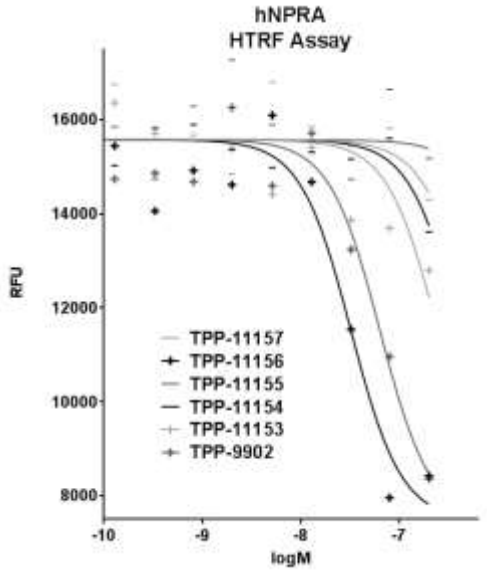

20
10
0
-10
-20
-30
0
24
48
72
96
120
144
168
▲MAP (%)
time (hr)
PBS
TPP-10992 30 mg/kg

Fig. 11


hNPRA
HTRF Assay
RFU
16000
14000
12000
10000
8000
-10
-9
-8
-7
logM
TPP-11157
TPP-11156
TPP-11155
TPP-11154
TPP-11153
TPP-9902

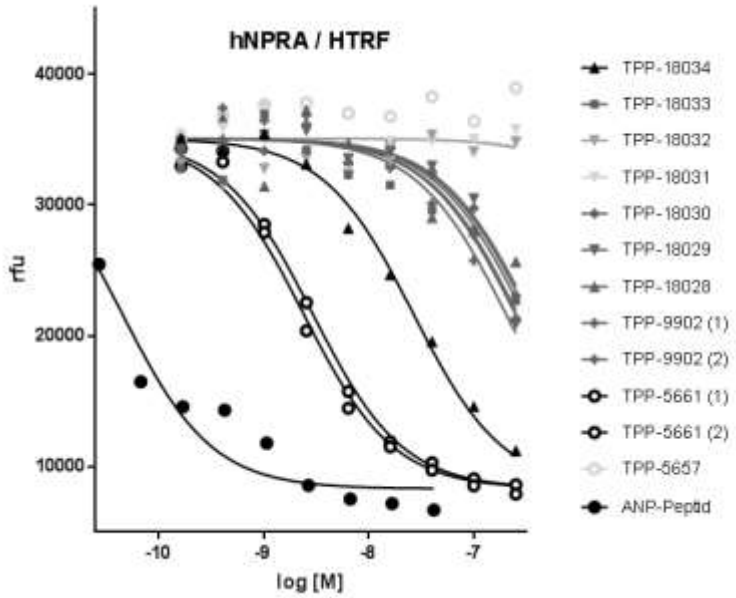

hNPRA / HTRF
rfu
40000
30000
20000
10000
-10
-9
-8
-7
log [M]
TPP-18034
TPP-18033
TPP-18032
TPP-18031
TPP-18030
TPP-18029
TPP-18028
TPP-9902 (1)
TPP-9902 (2)
TPP-5661 (1)
TPP-5661 (2)
TPP-5657
ANP-Peptid

Fig. 12

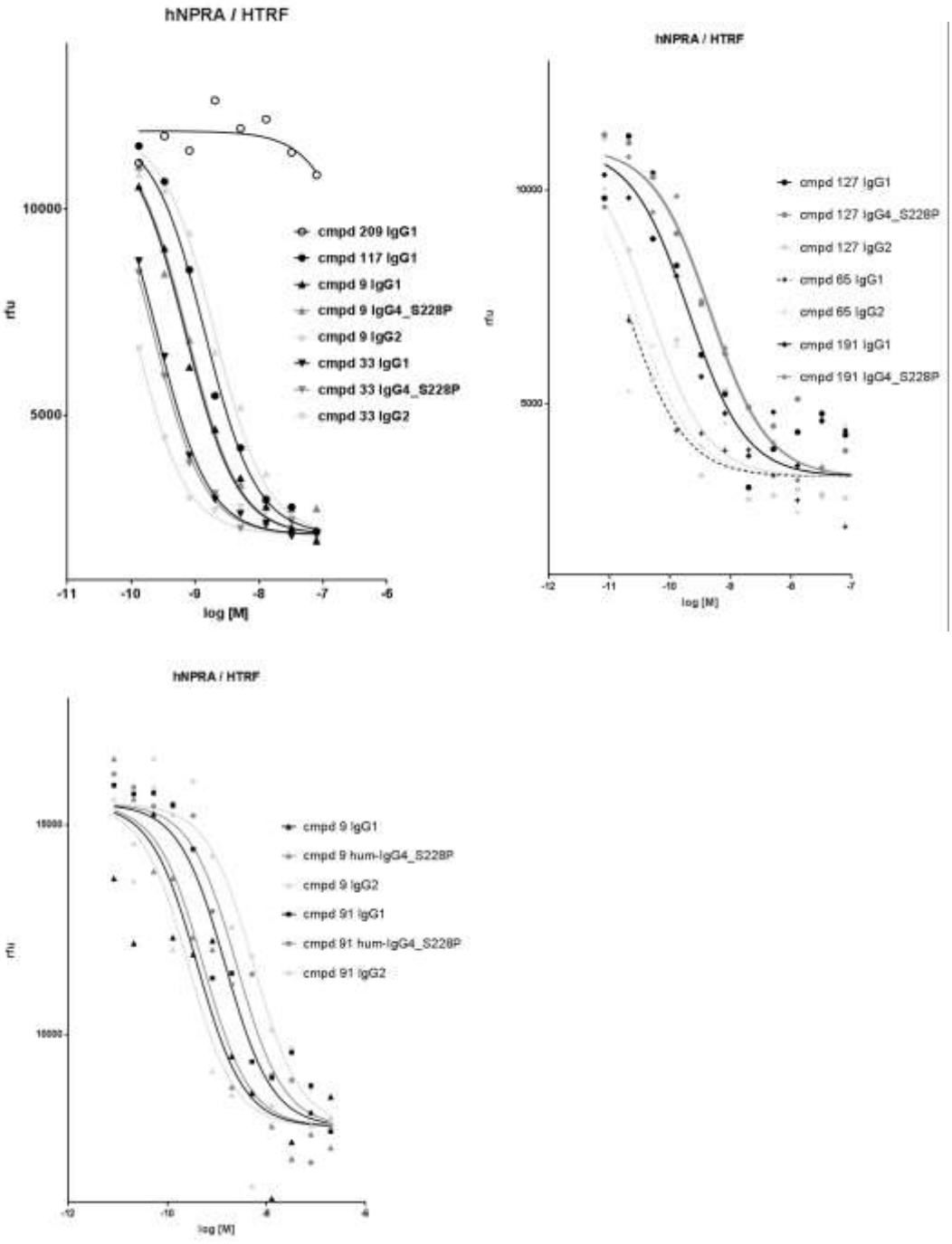
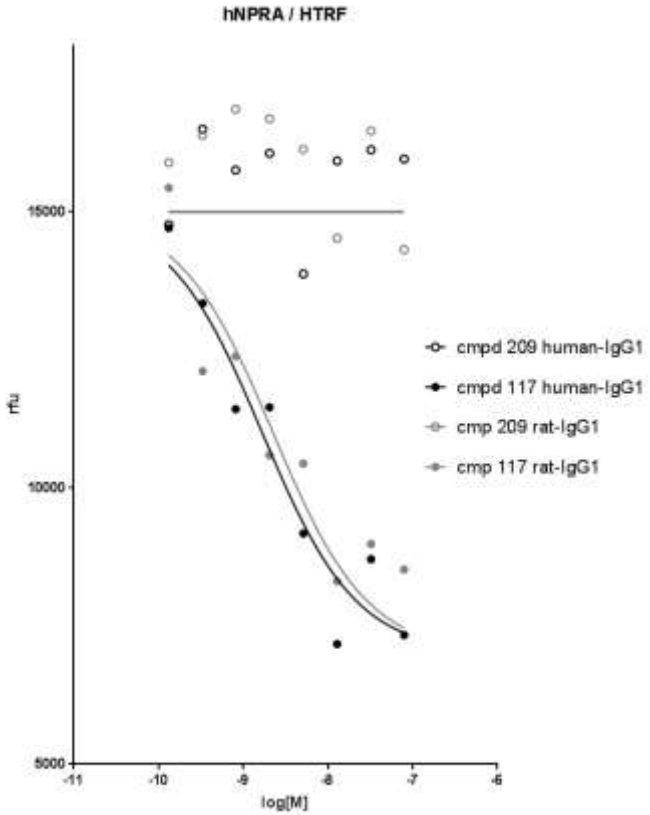

hNPRA / HTRF
rfu
log [M]
cmpd 209 IgG1
cmpd 117 IgG1
cmpd 9 IgG1
cmpd 9 IgG4_S228P
cmpd 9 IgG2
cmpd 33 IgG1
cmpd 33 IgG4_S228P
cmpd 33 IgG2
hNPRA / HTRF
rfu
log [M]
cmpd 127 IgG1
cmpd 127 IgG4_S228P
cmpd 127 IgG2
cmpd 65 IgG1
cmpd 65 IgG2
cmpd 191 IgG1
cmpd 191 IgG4_S228P
hNPRA / HTRF
rfu
log [M]
cmpd 9 IgG1
cmpd 9 hum-IgG4_S228P
cmpd 9 IgG2
cmpd 91 IgG1
cmpd 91 hum-IgG4_S228P
cmpd 91 IgG2

Fig. 13


hNPRA / HTRF
15000
10000
5000
rfu
-11
-10
-9
-8
-7
-6
log[M]
cmpd 209 human-IgG1
cmpd 117 human-IgG1
cmp 209 rat-IgG1
cmp 117 rat-IgG1

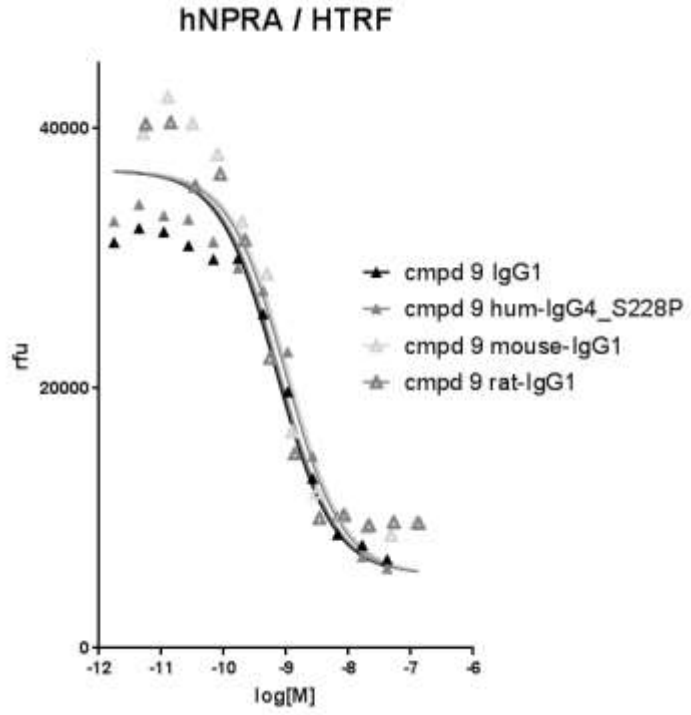

hNPRA / HTRF
40000
20000
0
rfu
-12
-11
-10
-9
-8
-7
-6
log[M]
cmpd 9 IgG1
cmpd 9 hum-IgG4_S228P
cmpd 9 mouse-IgG1
cmpd 9 rat-IgG1

Fig. 14

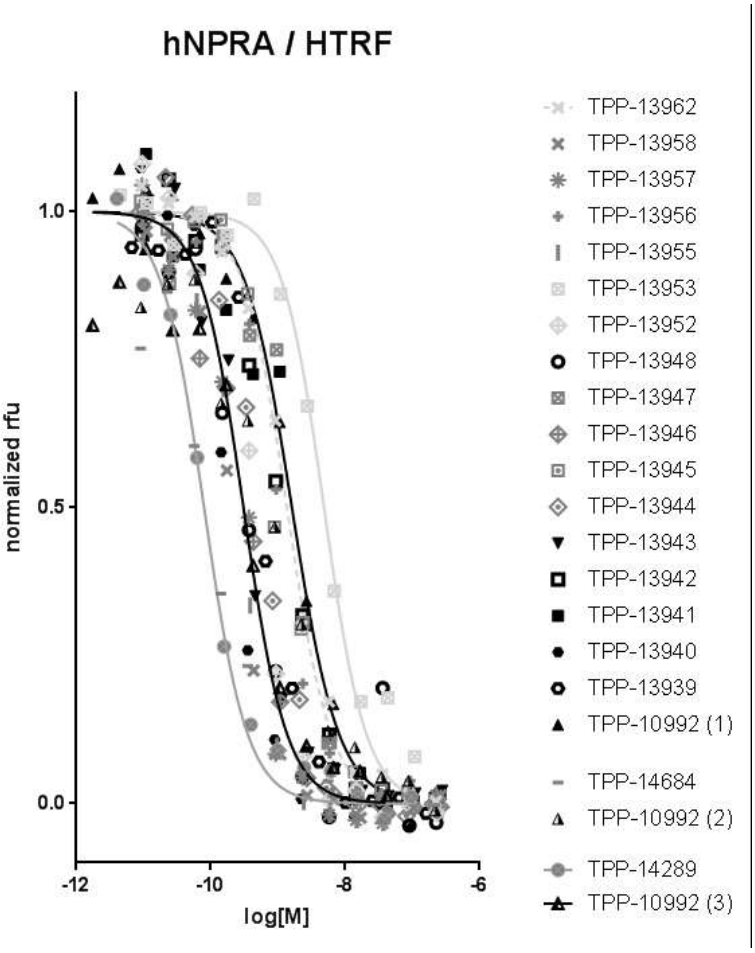

hNPRA / HTRF
normalized rfu
1.0
0.5
0.0
-12
-10
-8
-6
log[M]
TPP-13962
TPP-13958
TPP-13957
TPP-13956
TPP-13955
TPP-13953
TPP-13952
TPP-13948
TPP-13947
TPP-13946
TPP-13945
TPP-13944
TPP-13943
TPP-13942
TPP-13941
TPP-13940
TPP-13939
TPP-10992 (1)
TPP-14684
TPP-10992 (2)
TPP-14289
TPP-10992 (3)

Fig. 15

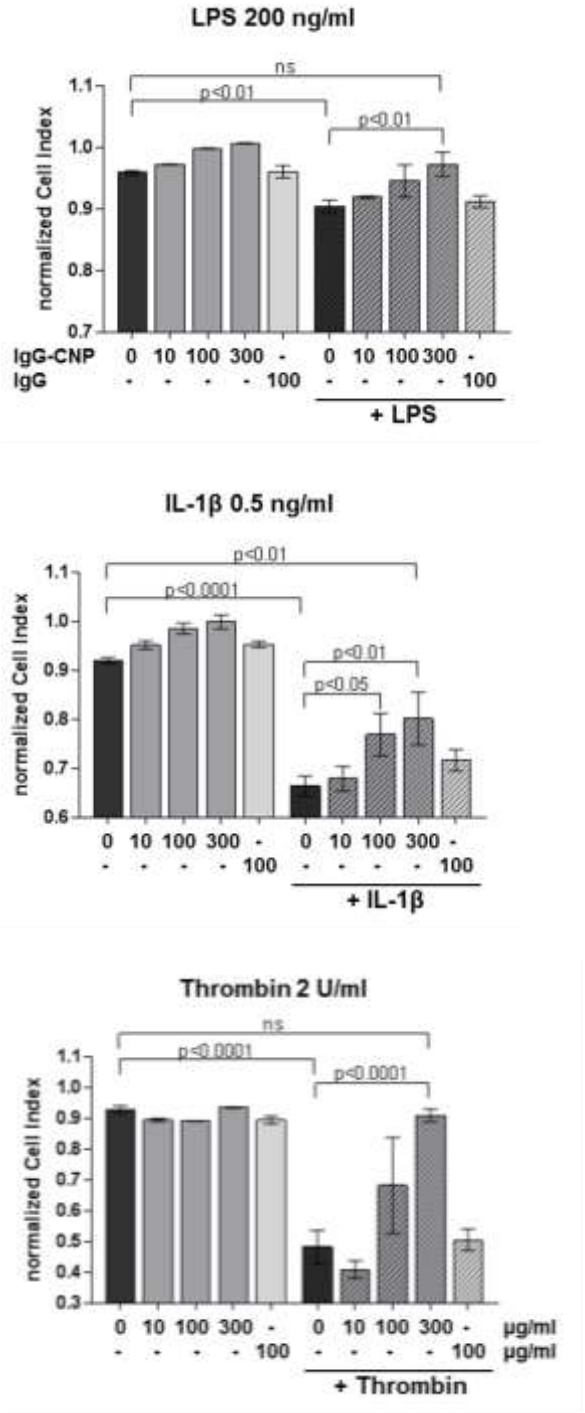

LPS 200 ng/ml
ns
p<0.01
p<0.01
normalized Cell Index
1.1
1.0
0.9
0.8
0.7
IgG-CNP 0 10 100 300 - 0 10 100 300 -
IgG - - - - 100 - - - - 100
+ LPS
IL-1β 0.5 ng/ml
p<0.01
p<0.0001
p<0.01
p<0.05
normalized Cell Index
1.1
1.0
0.9
0.8
0.7
0.6
0 10 100 300 - 0 10 100 300 -
- - - - 100 - - - - 100
+ IL-1β
Thrombin 2 U/ml
ns
p<0.0001
p<0.0001
normalized Cell Index
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0 10 100 300 - 0 10 100 300 - µg/ml
- - - - 100 - - - - 100 µg/ml
+ Thrombin

Fig. 16

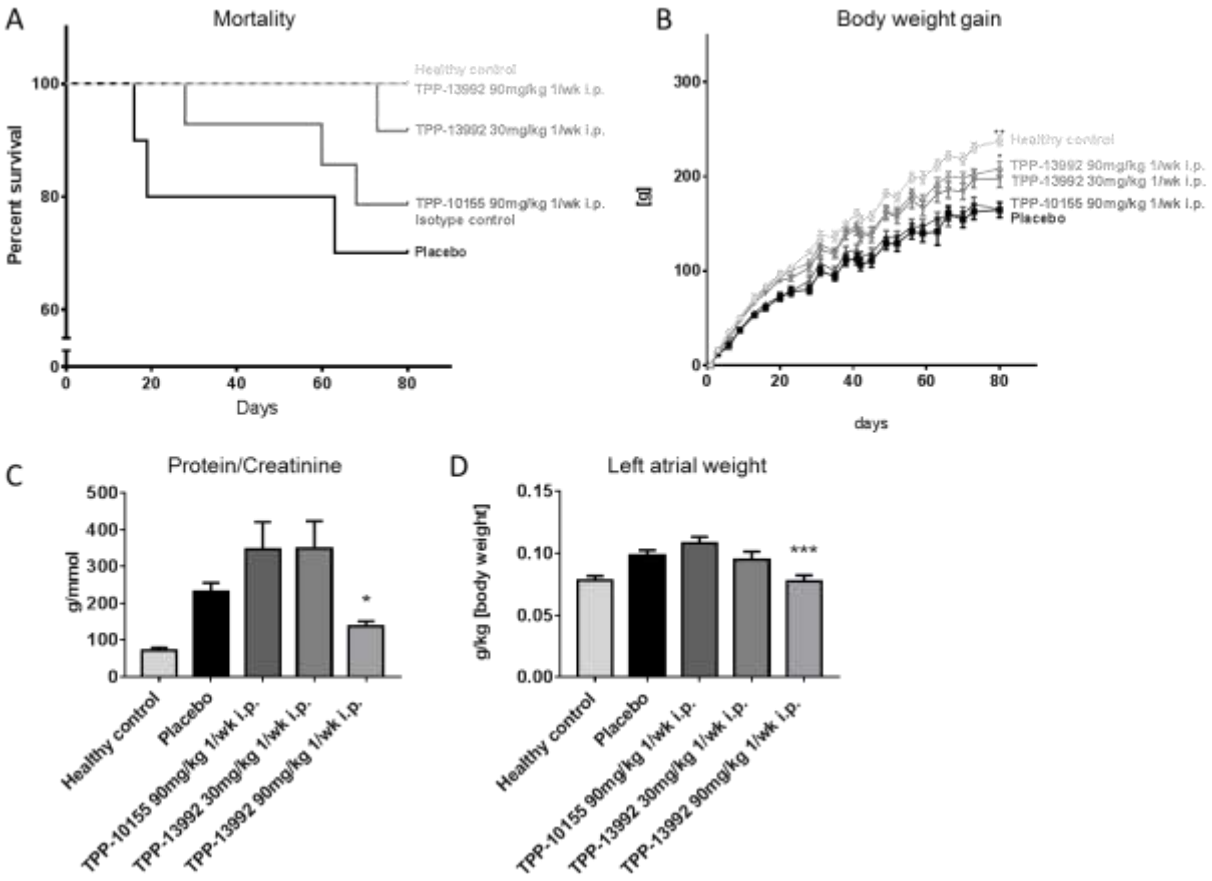
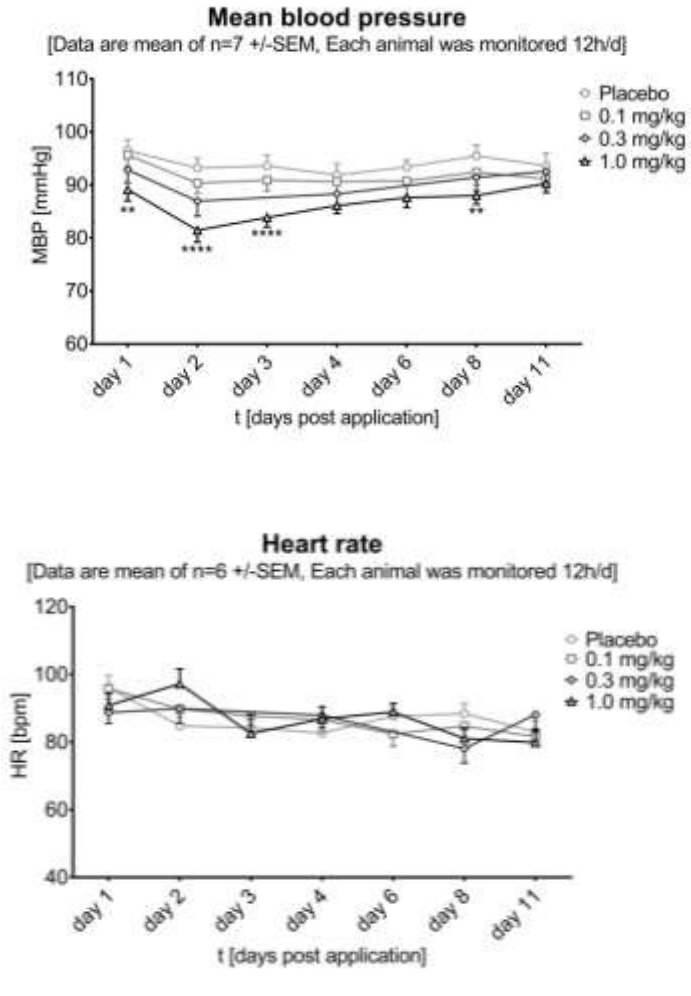

A
Mortality
Percent survival
Days
Healthy control
TPP-13992 90mg/kg 1/wk i.p.
TPP-13992 30mg/kg 1/wk i.p.
TPP-10155 90mg/kg 1/wk i.p.
Isotype control
Placebo
B
Body weight gain
[g]
days
Healthy control
TPP-13992 90mg/kg 1/wk i.p.
TPP-13992 30mg/kg 1/wk i.p.
TPP-10155 90mg/kg 1/wk i.p.
Placebo
C
Protein/Creatinine
g/mmol
*
D
Left atrial weight
g/kg [body weight]
***
Healthy control
Placebo
TPP-10155 90mg/kg 1/wk i.p.
TPP-13992 30mg/kg 1/wk i.p.
TPP-13992 90mg/kg 1/wk i.p.

Fig. 17


Mean blood pressure
[Data are mean of n=7 +/-SEM, Each animal was monitored 12h/d]
MBP [mmHg]
110
100
90
80
70
60
Placebo
0.1 mg/kg
0.3 mg/kg
1.0 mg/kg
**
****
****
**
day 1
day 2
day 3
day 4
day 6
day 8
day 11
t [days post application]

Heart rate
[Data are mean of n=6 +/-SEM, Each animal was monitored 12h/d]
HR [bpm]
120
100
80
60
40
Placebo
0.1 mg/kg
0.3 mg/kg
1.0 mg/kg
day 1
day 2
day 3
day 4
day 6
day 8
day 11
t [days post application]