Figure 1

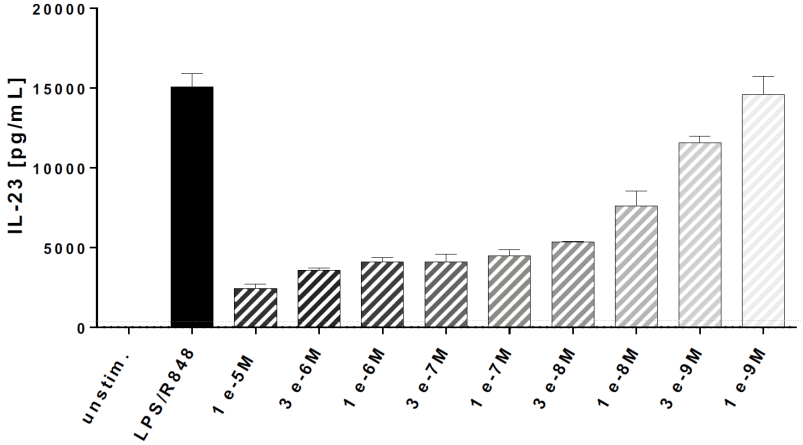
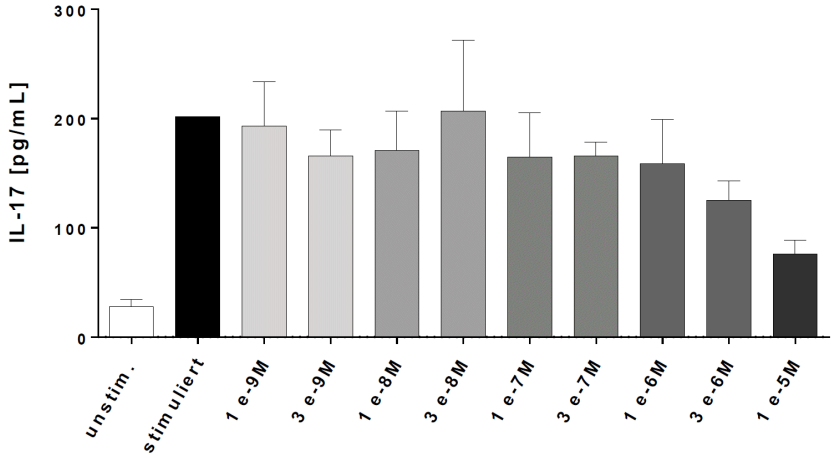


Figure 2

A



B

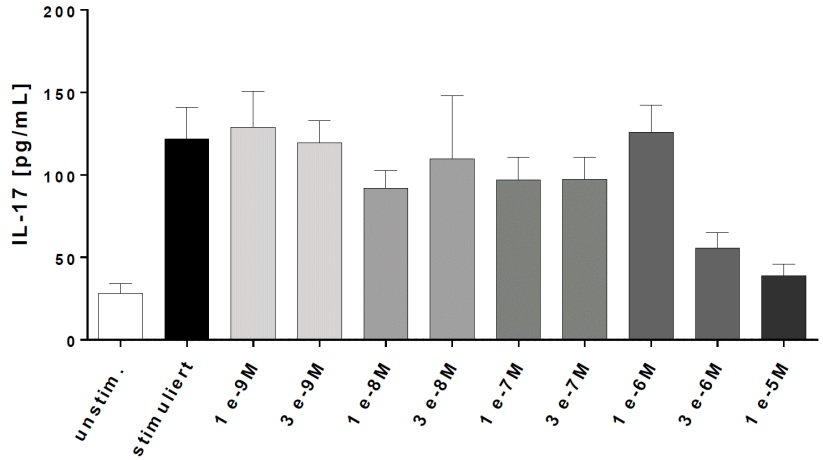
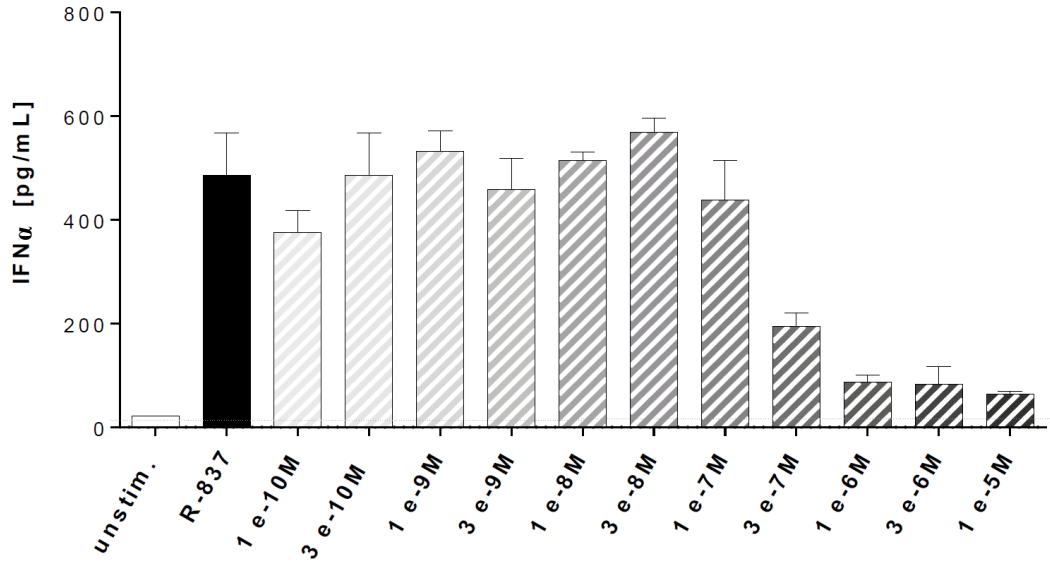


Figure 3

A


IFNα [pg/mL]
800
600
400
200
0
unstim.
R-837
1 e-10M
3 e-10M
1 e-9M
3 e-9M
1 e-8M
3 e-8M
1 e-7M
3 e-7M
1 e-6M
3 e-6M
1 e-5M

B

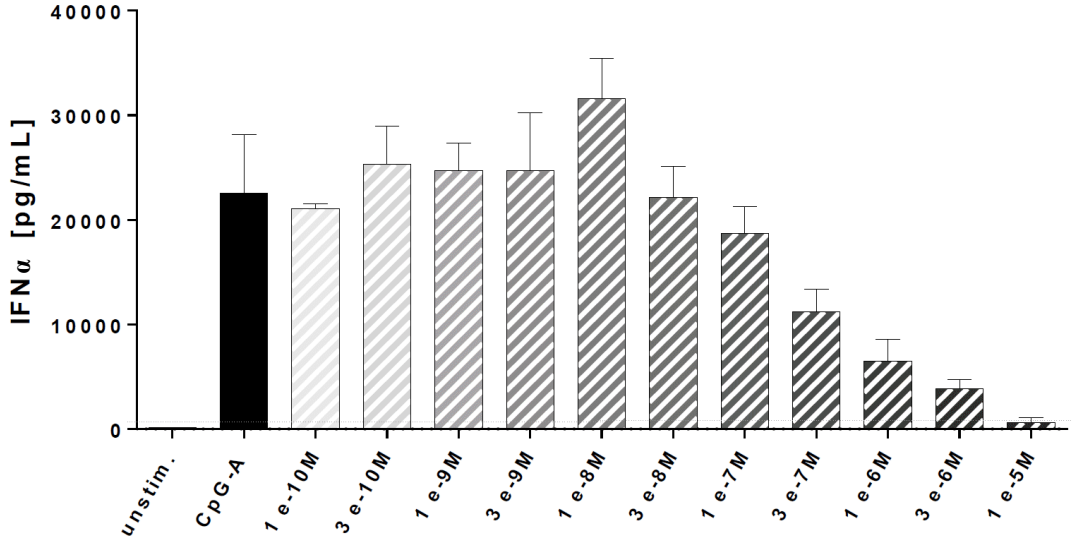
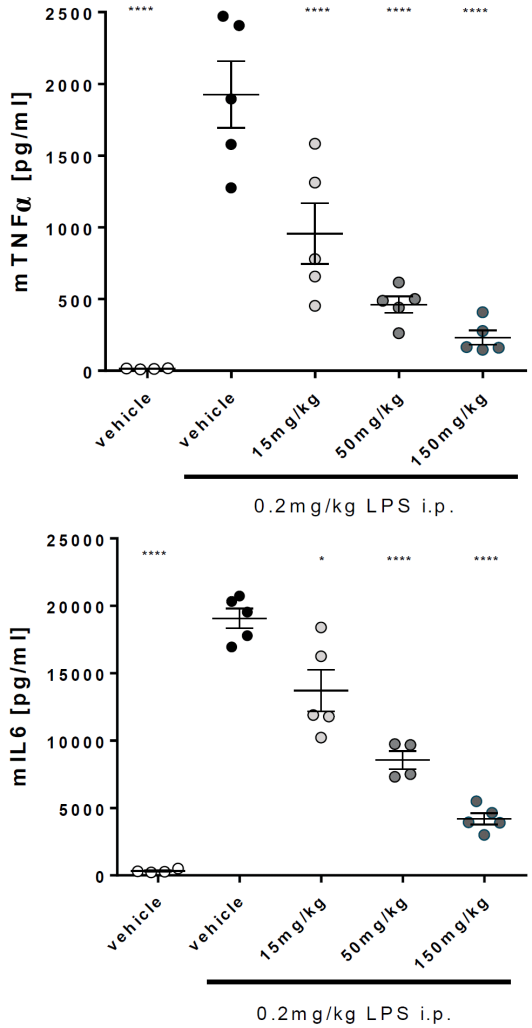

IFNα [pg/mL]
40000
30000
20000
10000
0
unstim.
CpG-A
1 e-10M
3 e-10M
1 e-9M
3 e-9M
1 e-8M
3 e-8M
1 e-7M
3 e-7M
1 e-6M
3 e-6M
1 e-5M

Figure 4

A


mTNFα [pg/ml]
2500
2000
1500
1000
500
0
****
****
****
****
vehicle
vehicle
15mg/kg
50mg/kg
150mg/kg
0.2mg/kg LPS i.p.
mIL6 [pg/ml]
25000
20000
15000
10000
5000
0
****
*
****
****
vehicle
vehicle
15mg/kg
50mg/kg
150mg/kg
0.2mg/kg LPS i.p.

B

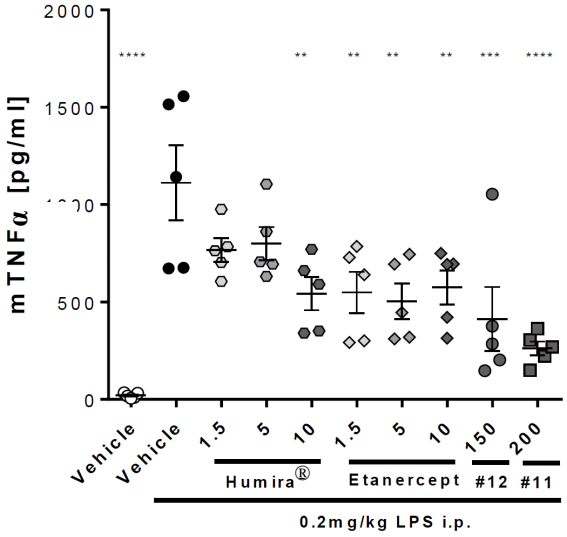
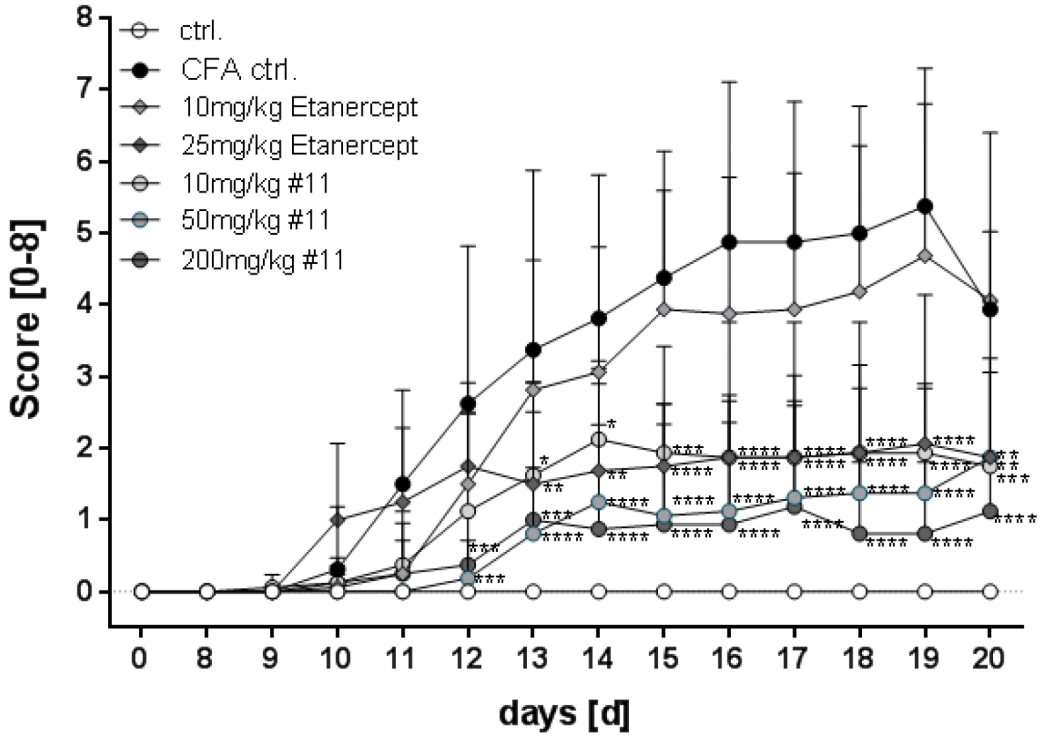
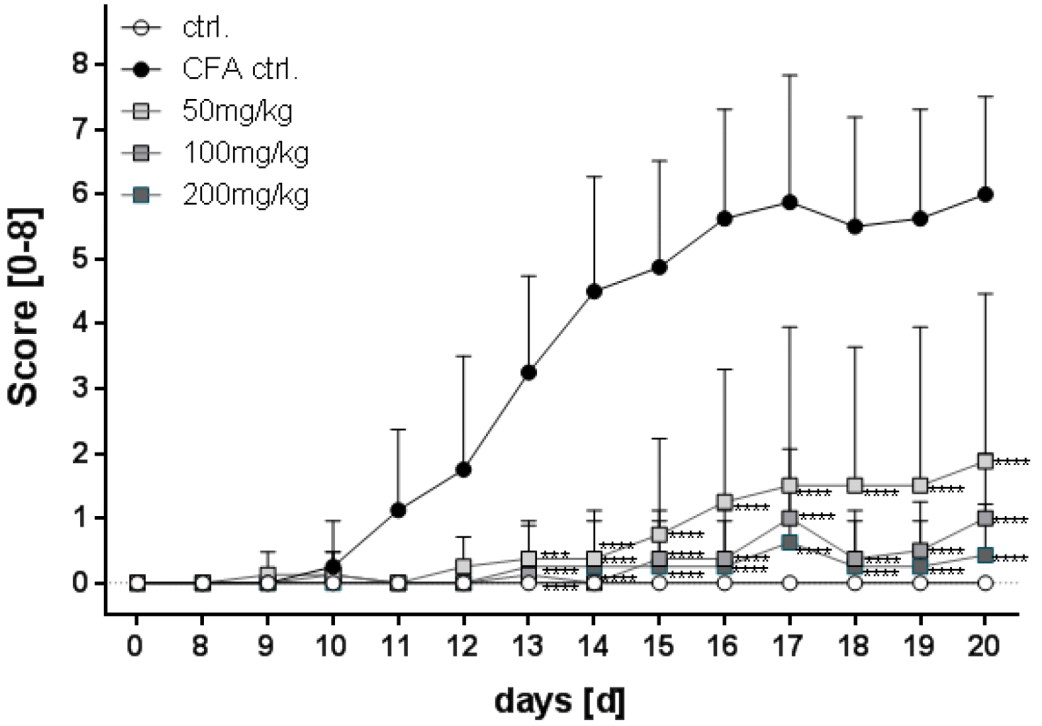

mTNFα [pg/ml]
2000
1500
500
0
****
**
**
**
**
***
****
Vehicle
Vehicle
1.5
5
10
1.5
5
10
150
200
Humira®
Etanercept
#12
#11
0.2mg/kg LPS i.p.

Figure 5

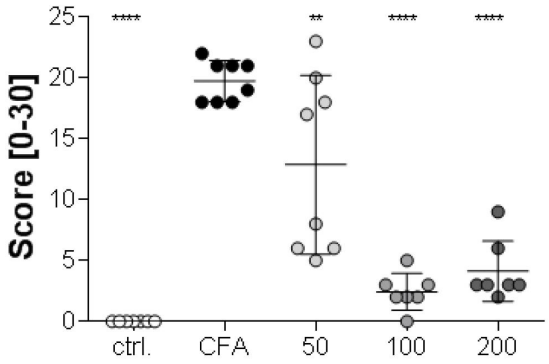
A


ctrl.
CFA ctrl.
10mg/kg Etanercept
25mg/kg Etanercept
10mg/kg #11
50mg/kg #11
200mg/kg #11
Score [0-8]
days [d]
0
8
9
10
11
12
13
14
15
16
17
18
19
20

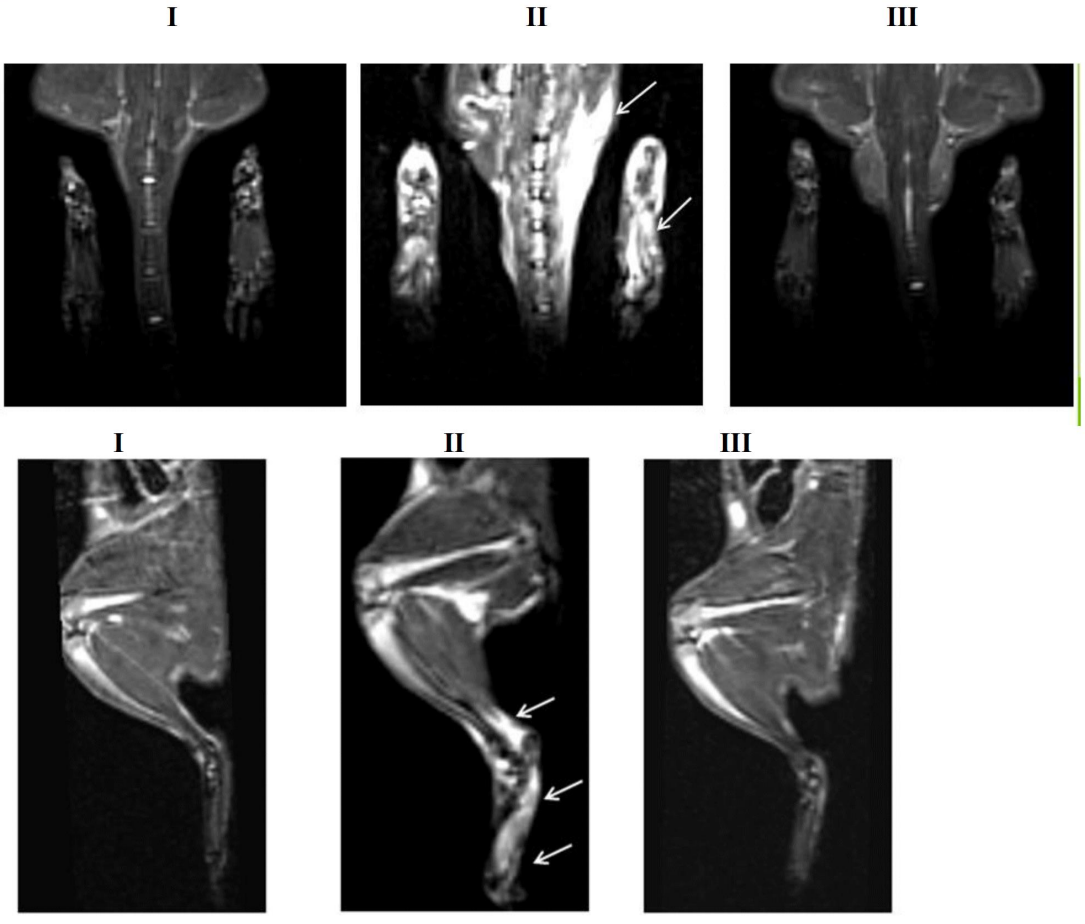
B


ctrl.
CFA ctrl.
50mg/kg
100mg/kg
200mg/kg
Score [0-8]
days [d]
0
8
9
10
11
12
13
14
15
16
17
18
19
20

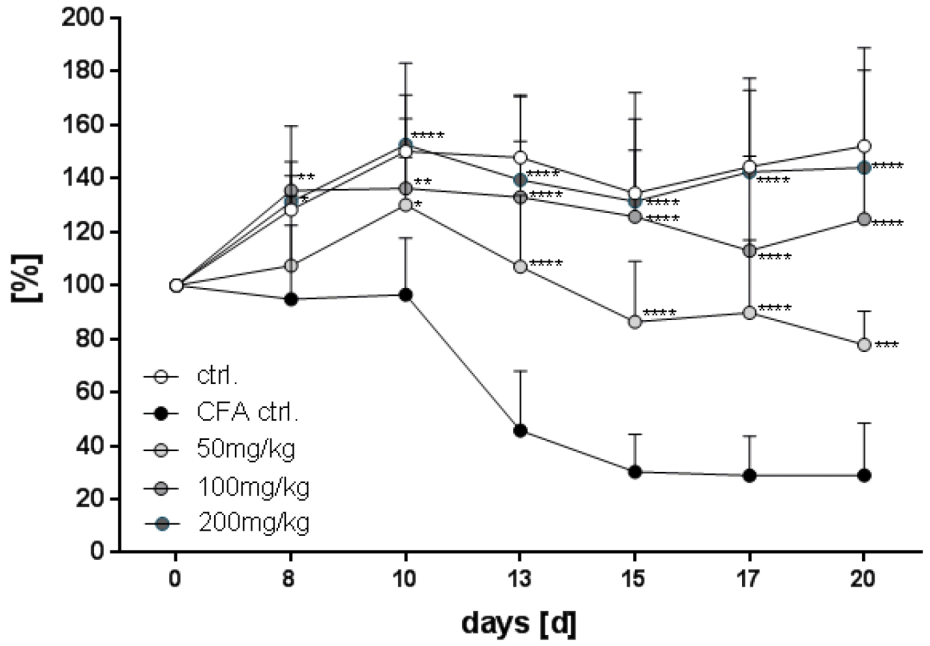
C



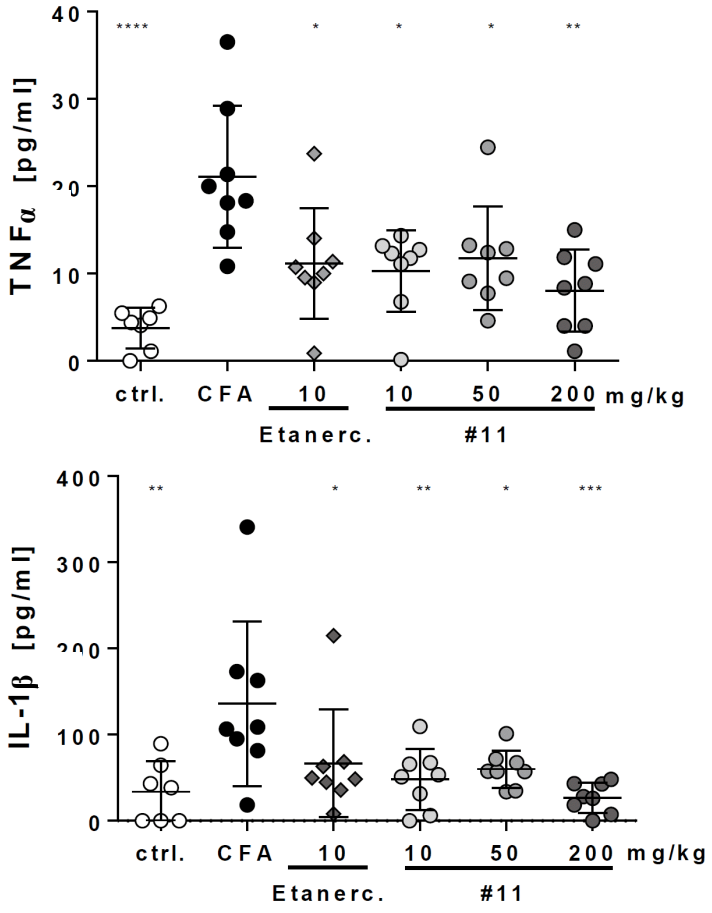
D



E


200
180
160
140
120
100
80
60
40
20
0
[%]
ctrl.
CFA ctrl.
50mg/kg
100mg/kg
200mg/kg
0
8
10
13
15
17
20
days [d]

F


TNFα [pg/ml]
40
30
20
10
0
ctrl.
CFA
10
10
50
200
mg/kg
Etanerc.
#11
IL-1β [pg/ml]
400
300
200
100
0
ctrl.
CFA
10
10
50
200
mg/kg
Etanerc.
#11

G

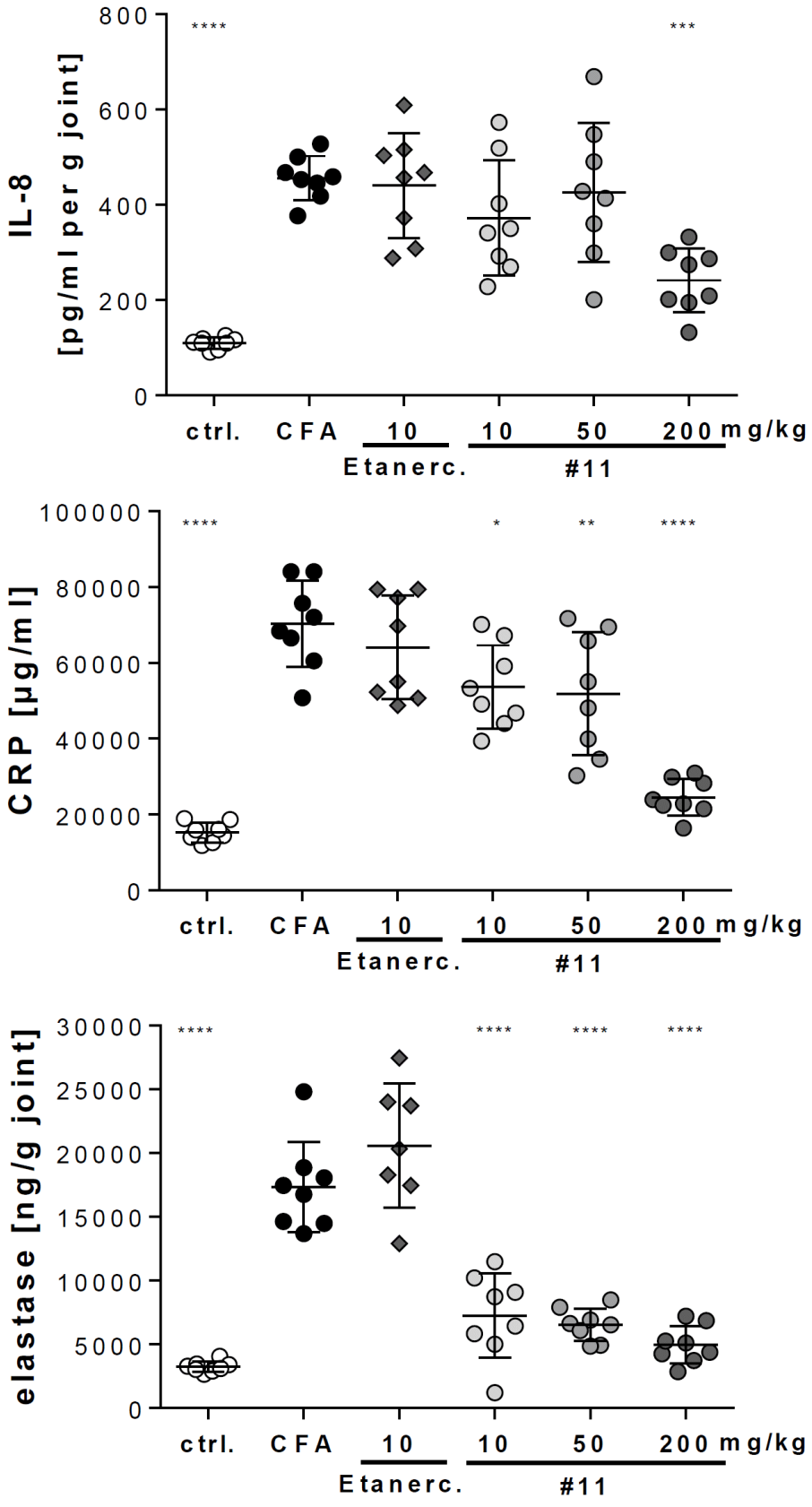
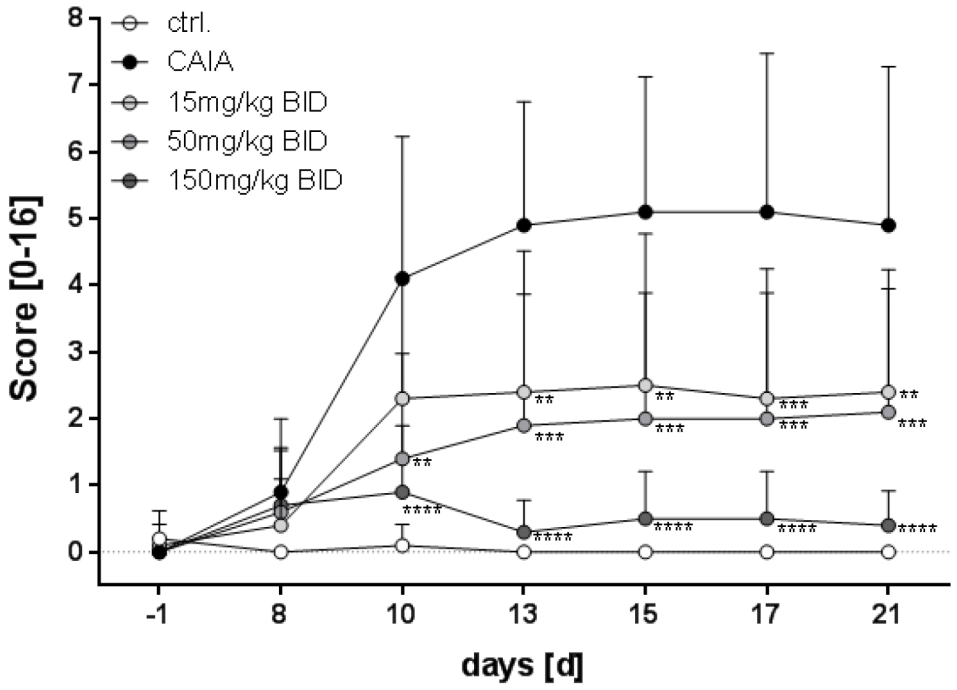
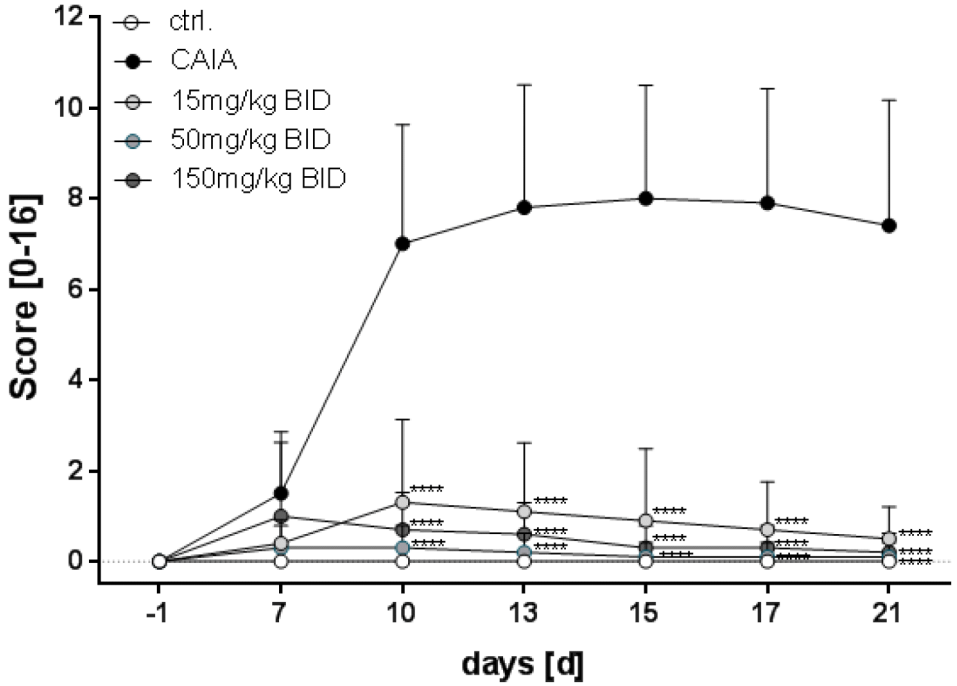

IL-8
[pg/ml per g joint]
800
600
400
200
0
****
***
ctrl.
CFA
10
10
50
200 mg/kg
Etanerc.
#11
CRP [µg/ml]
100000
80000
60000
40000
20000
0
****
*
**
****
ctrl.
CFA
10
10
50
200 mg/kg
Etanerc.
#11
elastase [ng/g joint]
30000
25000
20000
15000
10000
5000
0
****
****
****
****
ctrl.
CFA
10
10
50
200 mg/kg
Etanerc.
#11

Figure 6

A


ctrl.
CAIA
15mg/kg BID
50mg/kg BID
150mg/kg BID
Score [0-16]
days [d]
-1
8
10
13
15
17
21

B


ctrl.
CAIA
15mg/kg BID
50mg/kg BID
150mg/kg BID
Score [0-16]
days [d]
-1
7
10
13
15
17
21

C

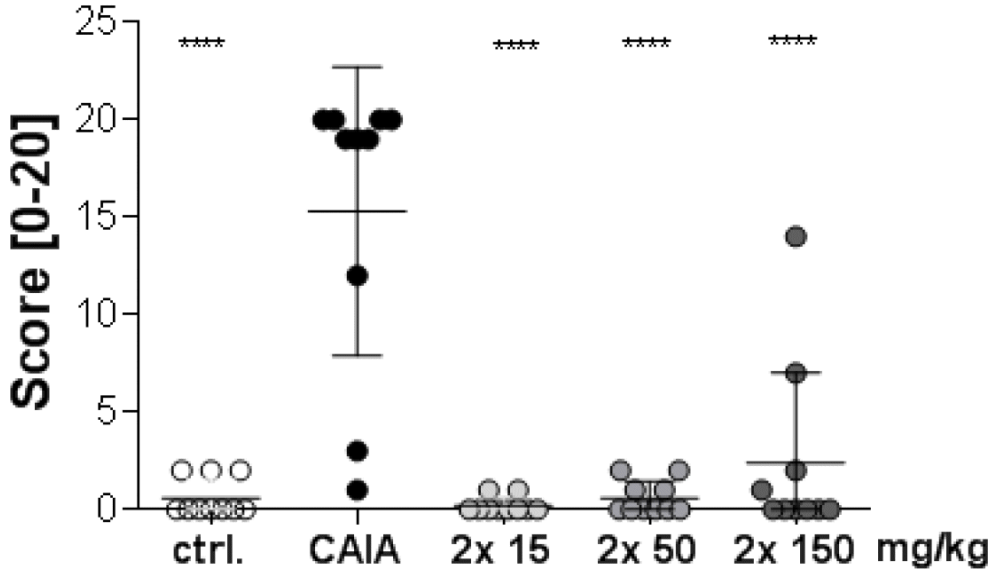
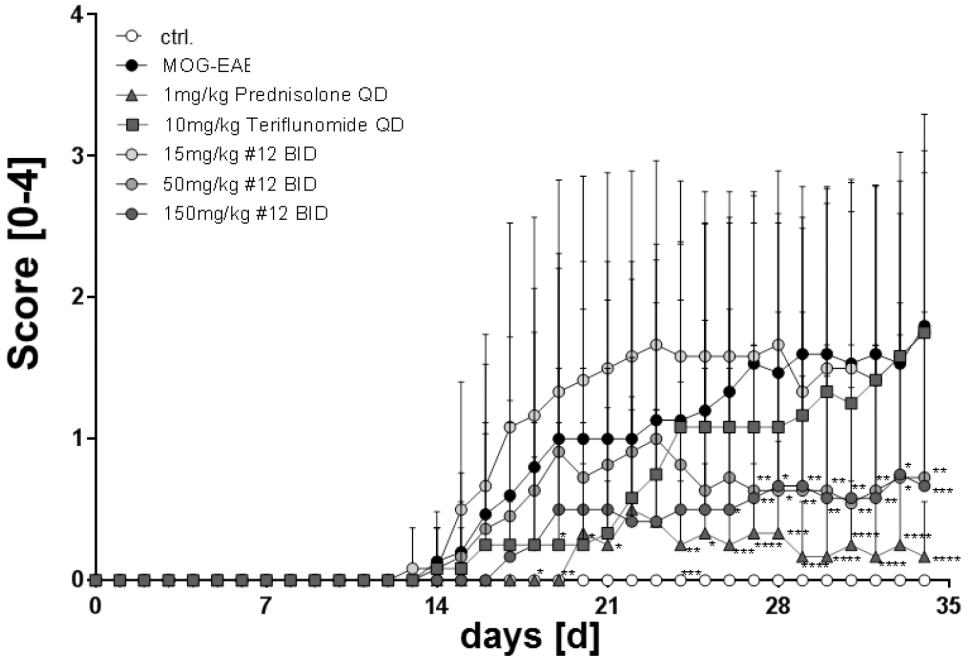
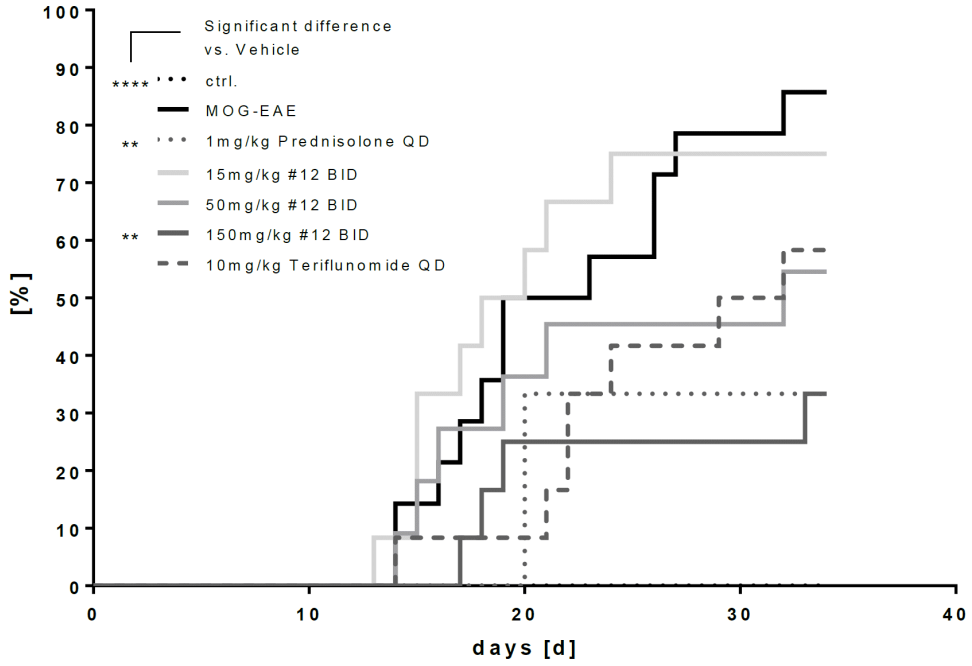


Figure 7

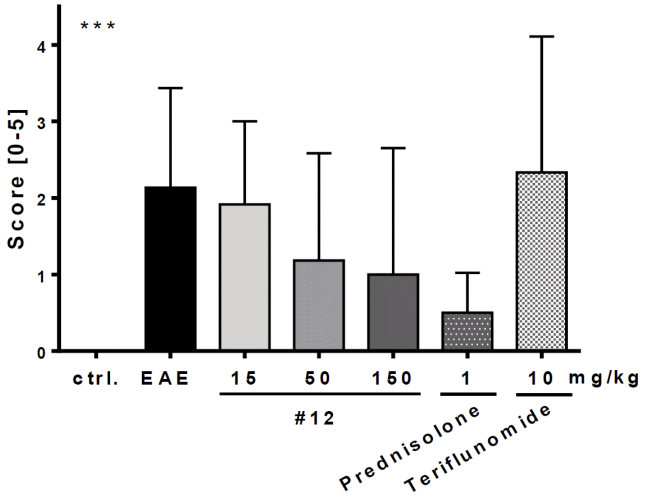
A


ctrl.
MOG-EAE
1mg/kg Prednisolone QD
10mg/kg Teriflunomide QD
15mg/kg #12 BID
50mg/kg #12 BID
150mg/kg #12 BID
Score [0-4]
days [d]

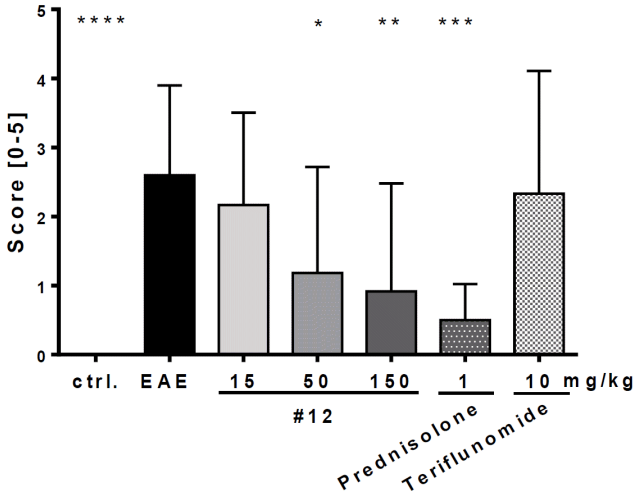
B


Significant difference
vs. Vehicle
ctrl.
MOG-EAE
1mg/kg Prednisolone QD
15mg/kg #12 BID
50mg/kg #12 BID
150mg/kg #12 BID
10mg/kg Teriflunomide QD
[%]
days [d]

C


***
Score [0-5]
0
1
2
3
4
ctrl.
EAE
15
50
150
1
10 mg/kg
#12
Prednisolone
Teriflunomide

D


****
*
**
***
Score [0-5]
0
1
2
3
4
5
ctrl.
EAE
15
50
150
1
10 mg/kg
#12
Prednisolone
Teriflunomide

E

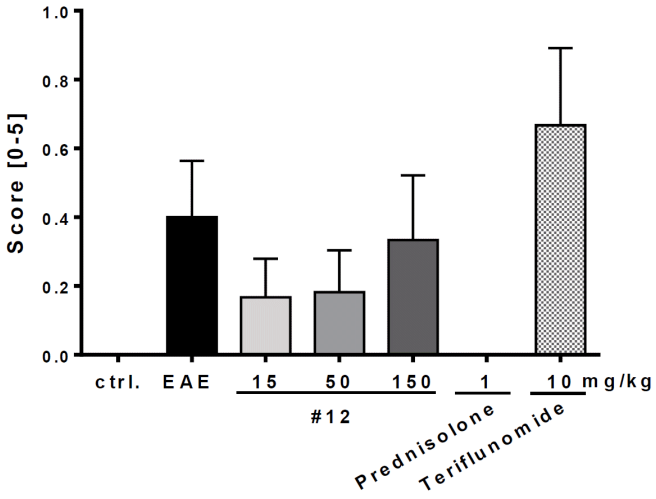
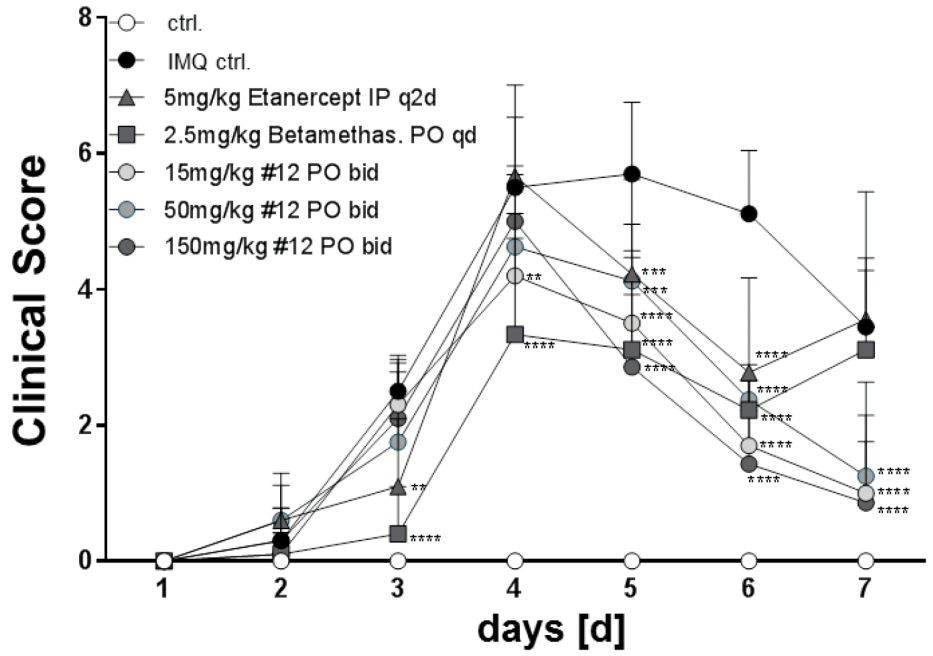
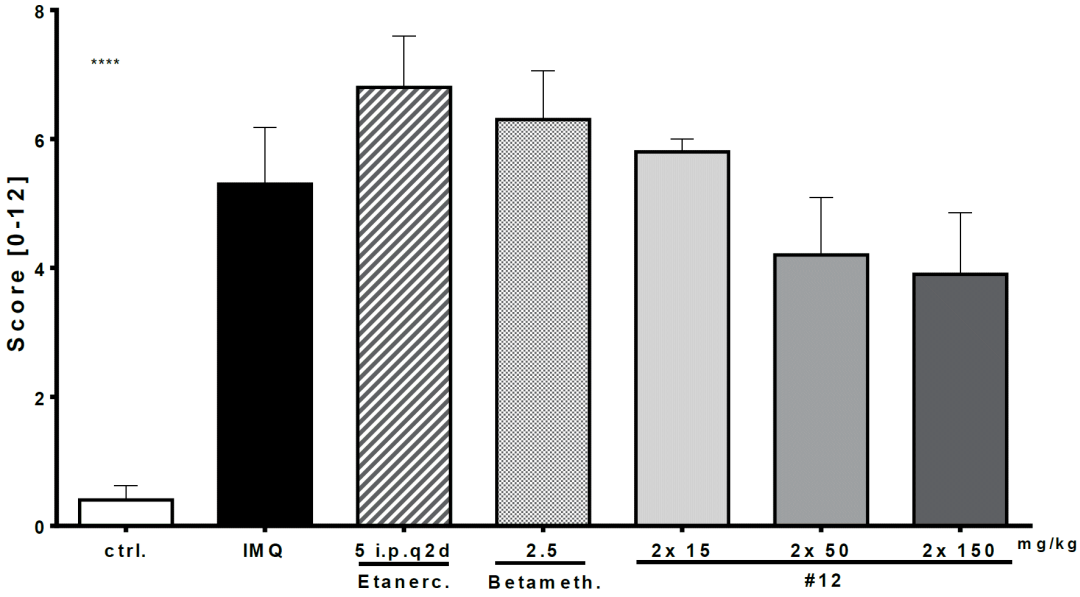

Score [0-5]
0.0
0.2
0.4
0.6
0.8
1.0
ctrl.
EAE
15
50
150
1
10 mg/kg
#12
Prednisolone
Teriflunomide

Figure 8

A


ctrl.
IMQ ctrl.
5mg/kg Etanercept IP q2d
2.5mg/kg Betamethas. PO qd
15mg/kg #12 PO bid
50mg/kg #12 PO bid
150mg/kg #12 PO bid
Clinical Score
days [d]

B


Score [0-12]
ctrl.
IMQ
5 i.p.q2d
Etanerc.
2.5
Betameth.
2x 15
2x 50
2x 150
#12
mg/kg

C

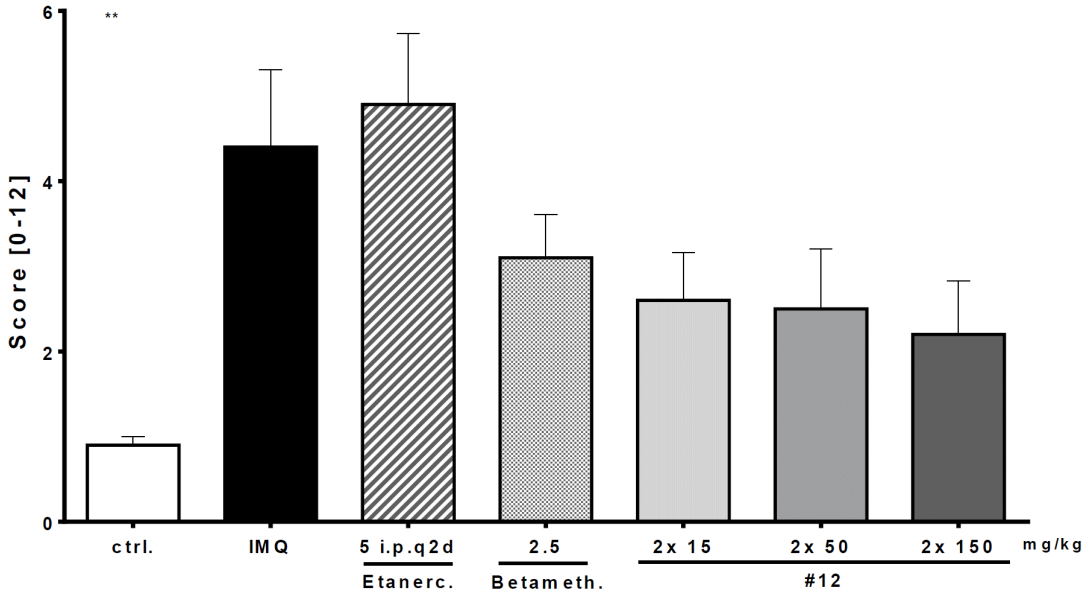

**
Score [0-12]
6
4
2
0
ctrl.
IMQ
5 i.p.q2d
Etanerc.
2.5
Betameth.
2x 15
2x 50
2x 150
mg/kg
#12

Figure 9

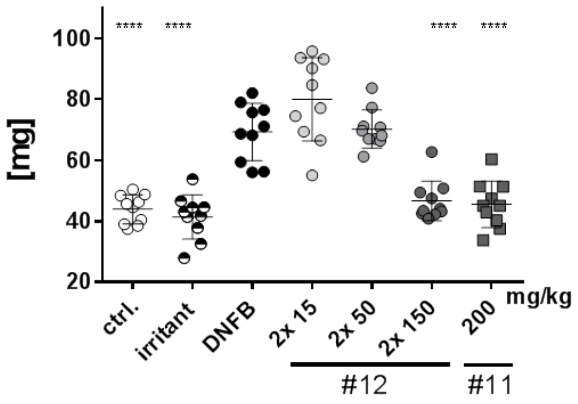


Figure 10

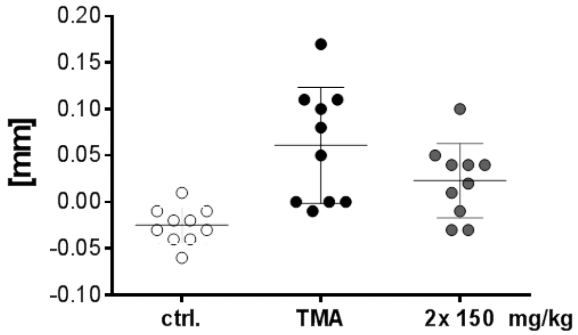


Figure 11

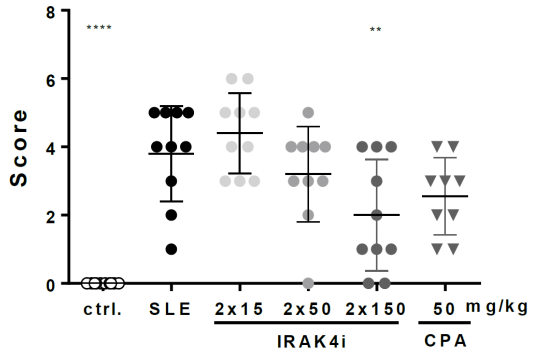
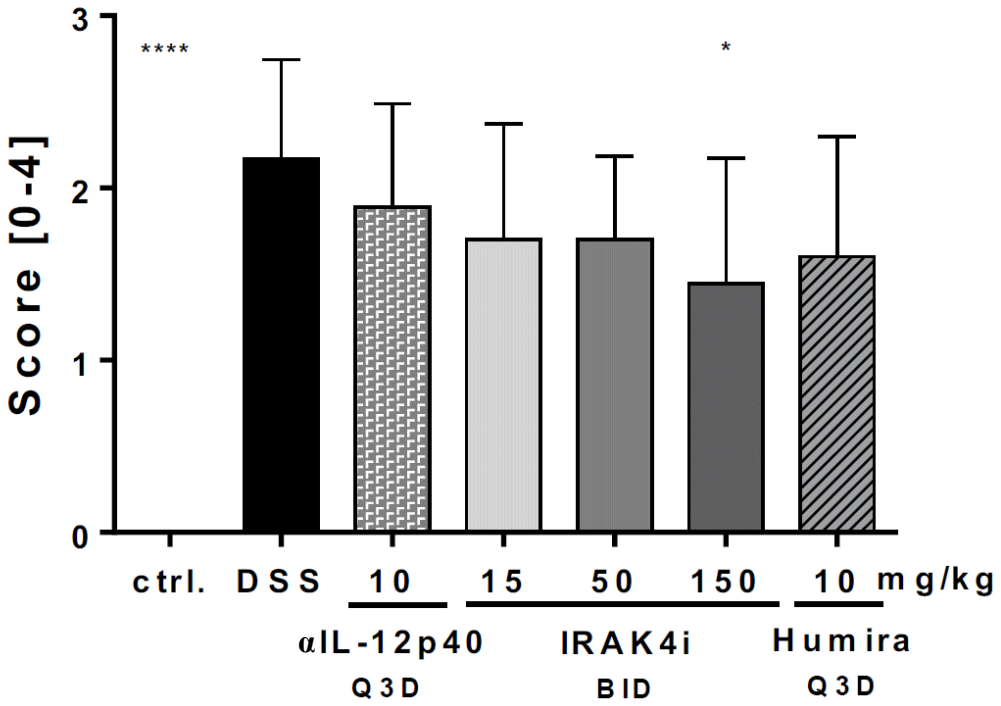


Figure 12


Score [0-4]
3
2
1
0
****
*
ctrl.
DSS
10
15
50
150
10 mg/kg
αIL-12p40
Q3D
IRAK4i
BID
Humira
Q3D