Figure 1

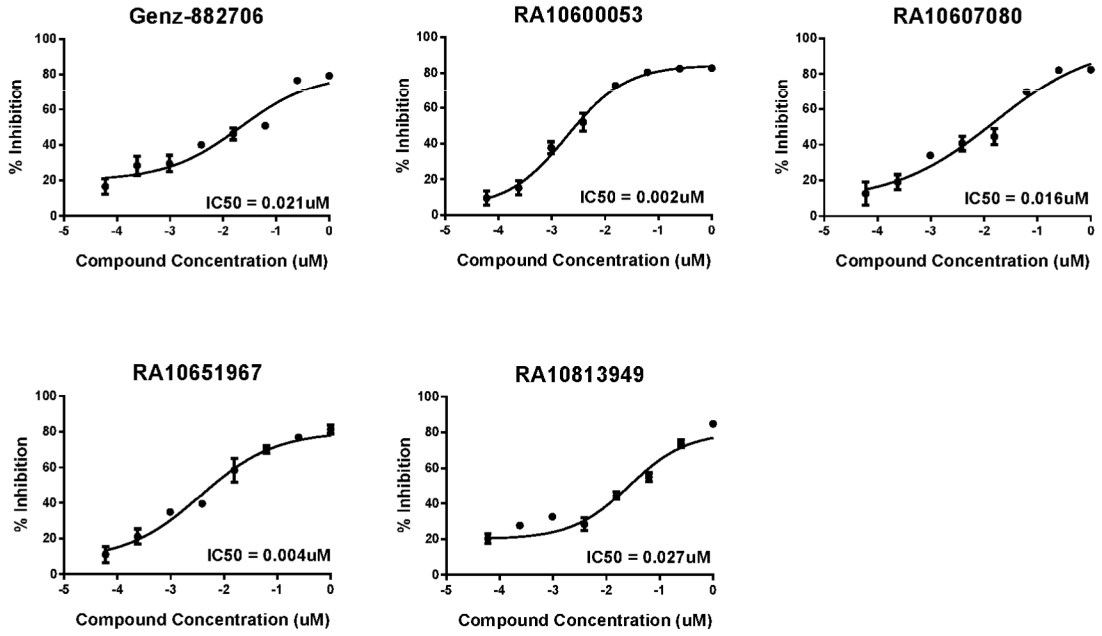

Genz-882706
% Inhibition
IC50 = 0.021uM
Compound Concentration (uM)
RA10600053
% Inhibition
IC50 = 0.002uM
Compound Concentration (uM)
RA10607080
% Inhibition
IC50 = 0.016uM
Compound Concentration (uM)
RA10651967
% Inhibition
IC50 = 0.004uM
Compound Concentration (uM)
RA10813949
% Inhibition
IC50 = 0.027uM
Compound Concentration (uM)

Figure 2

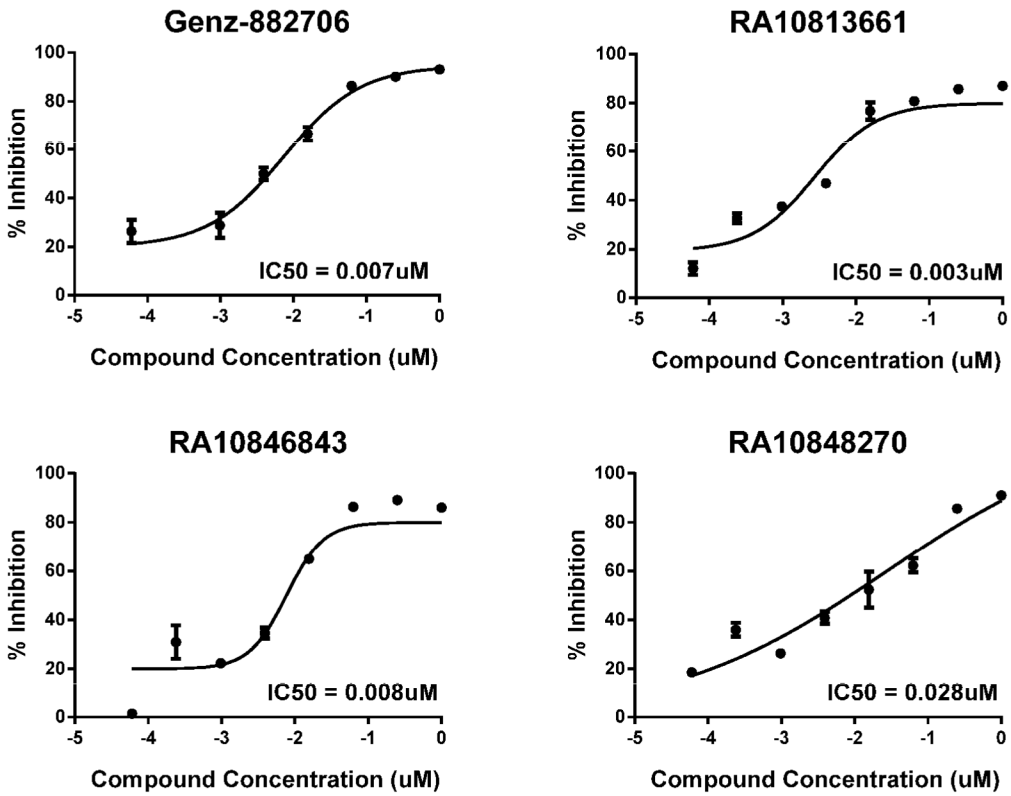

Genz-882706
% Inhibition
IC50 = 0.007uM
Compound Concentration (uM)
RA10813661
% Inhibition
IC50 = 0.003uM
Compound Concentration (uM)
RA10846843
% Inhibition
IC50 = 0.008uM
Compound Concentration (uM)
RA10848270
% Inhibition
IC50 = 0.028uM
Compound Concentration (uM)

Figure 3

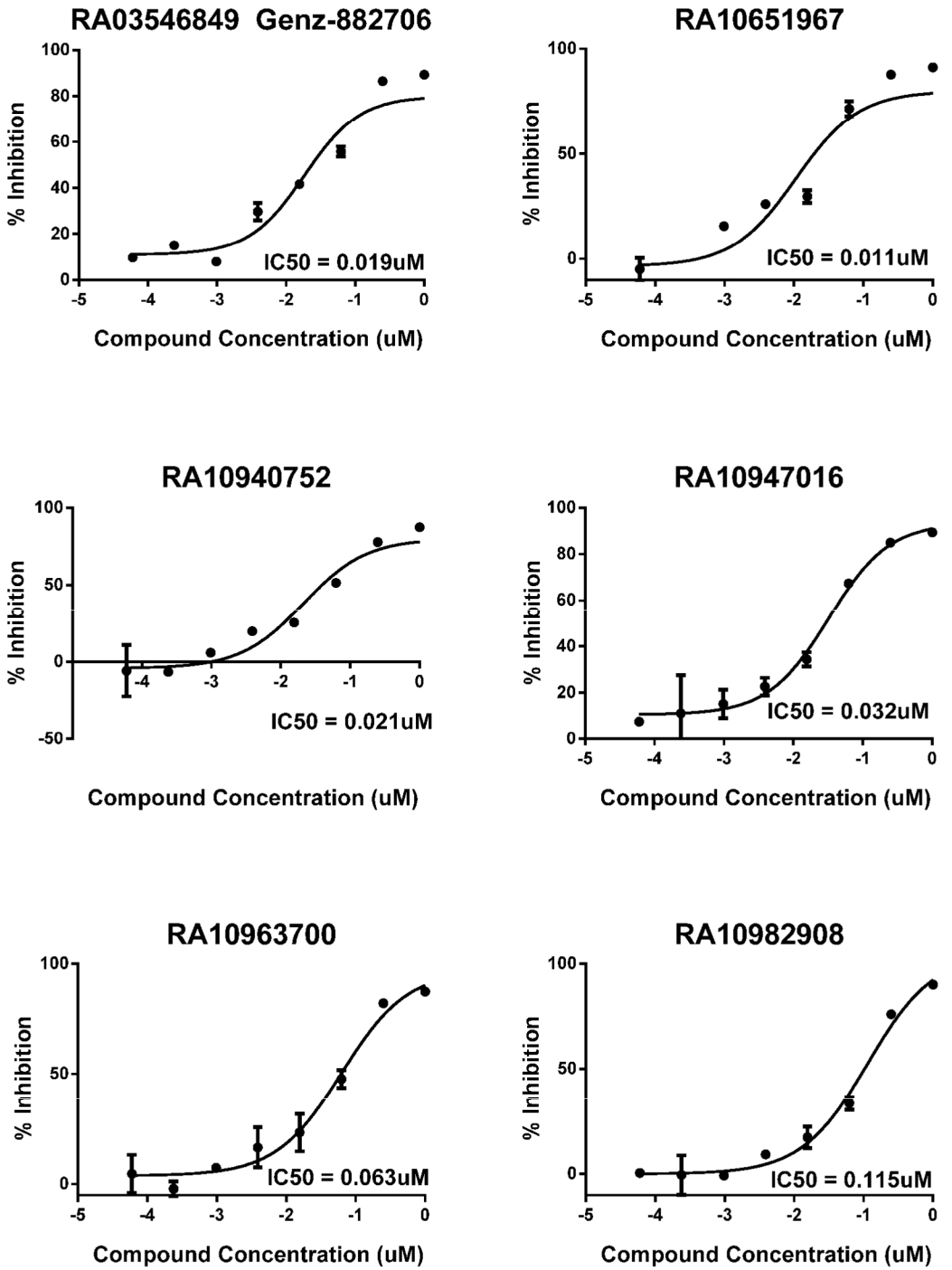
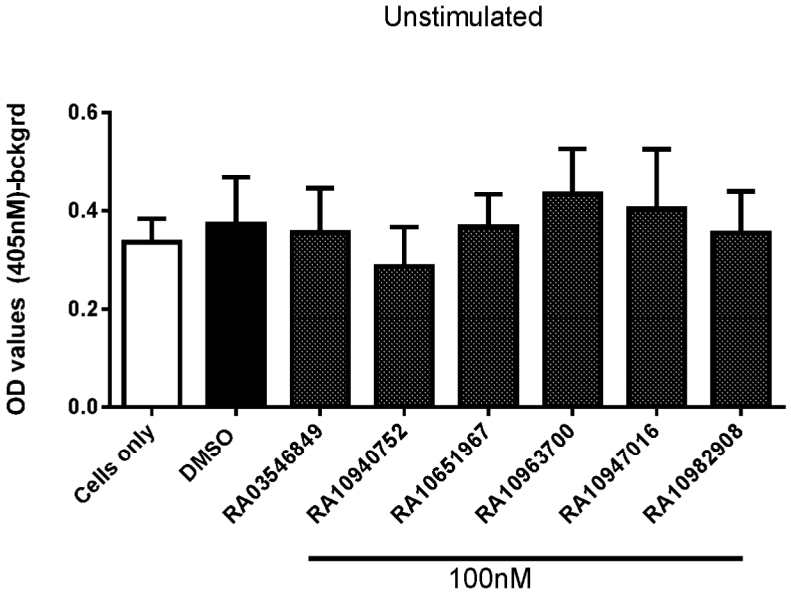

RA03546849 Genz-882706
% Inhibition
Compound Concentration (uM)
IC50 = 0.019uM
RA10651967
IC50 = 0.011uM
RA10940752
IC50 = 0.021uM
RA10947016
IC50 = 0.032uM
RA10963700
IC50 = 0.063uM
RA10982908
IC50 = 0.115uM

Figure 4


Unstimulated
OD values (405nM)-bckgrd
0.6
0.4
0.2
0.0
Cells only
DMSO
RA03546849
RA10940752
RA10651967
RA10963700
RA10947016
RA10982908
100nM

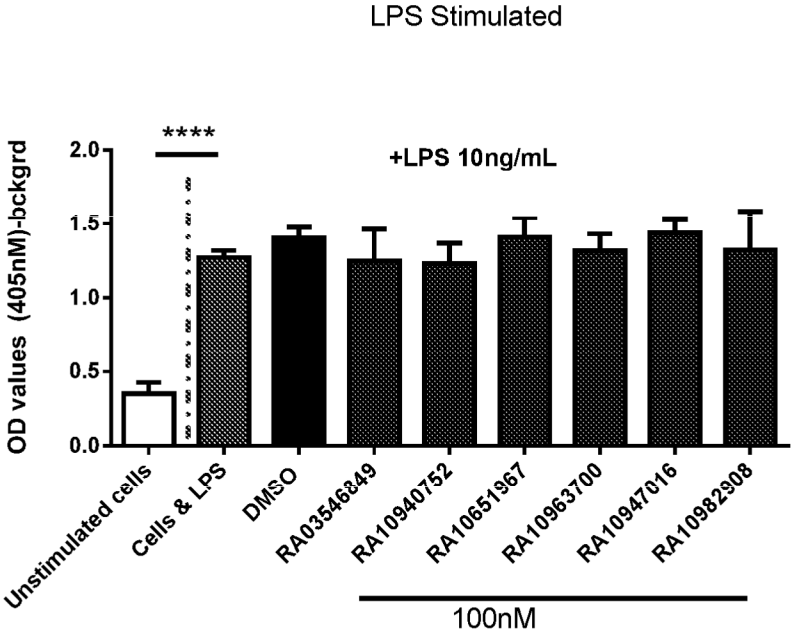

LPS Stimulated
OD values (405nM)-bckgrd
****
+LPS 10ng/mL
2.0
1.5
1.0
0.5
0.0
Unstimulated cells
Cells & LPS
DMSO
RA03546849
RA10940752
RA10651967
RA10963700
RA10947016
RA10982908
100nM

Figure 5

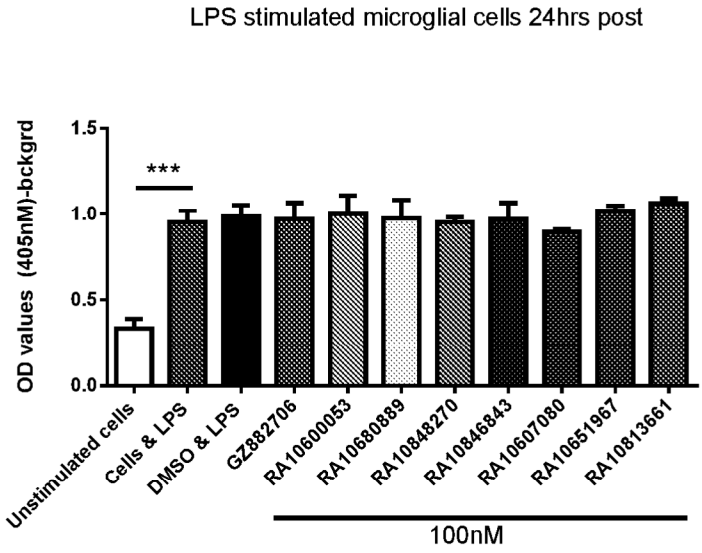

LPS stimulated microglial cells 24hrs post
OD values (405nM)-bckgrd
1.5
1.0
0.5
0.0
***
Unstimulated cells
Cells & LPS
DMSO & LPS
GZ882706
RA10600053
RA10680889
RA10848270
RA10846843
RA10607080
RA10651967
RA10813661
100nM

Figure 6

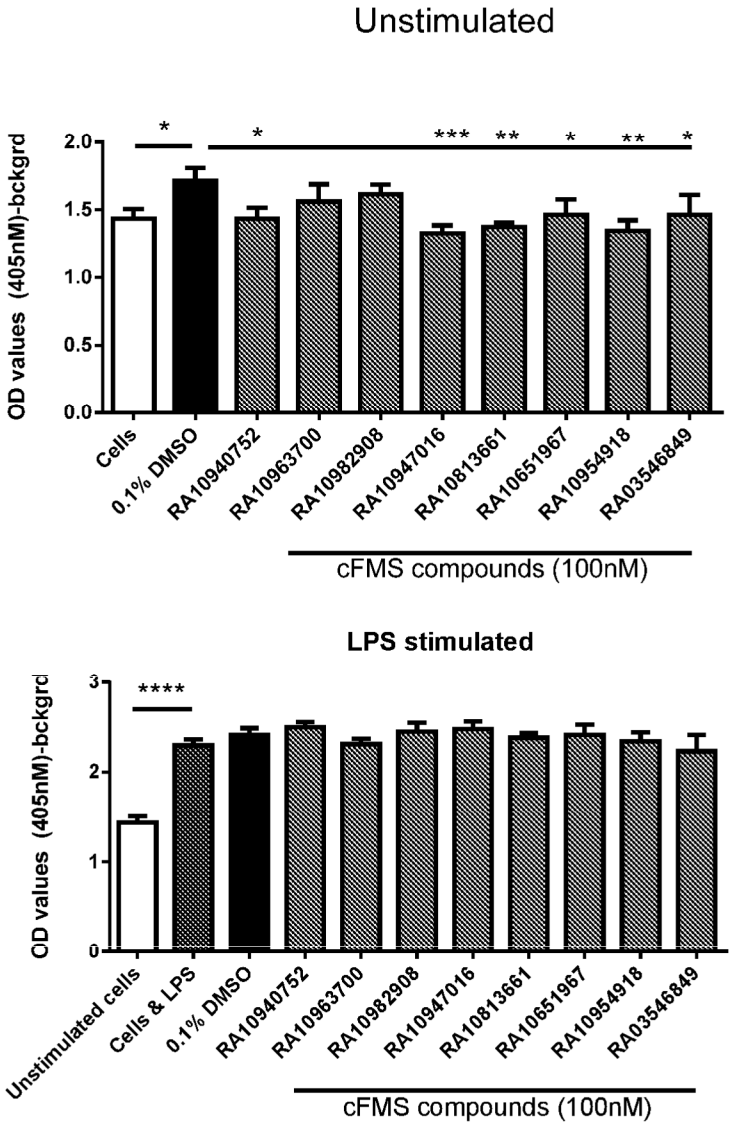

Unstimulated
OD values (405nM)-bckgrd
2.0
1.5
1.0
0.5
0.0
*
*
***
**
*
**
*
Cells
0.1% DMSO
RA10940752
RA10963700
RA10982908
RA10947016
RA10813661
RA10651967
RA10954918
RA03546849
cFMS compounds (100nM)
LPS stimulated
OD values (405nM)-bckgrd
3
2
1
0
****
Unstimulated cells
Cells & LPS
0.1% DMSO
RA10940752
RA10963700
RA10982908
RA10947016
RA10813661
RA10651967
RA10954918
RA03546849
cFMS compounds (100nM)

Figure 7

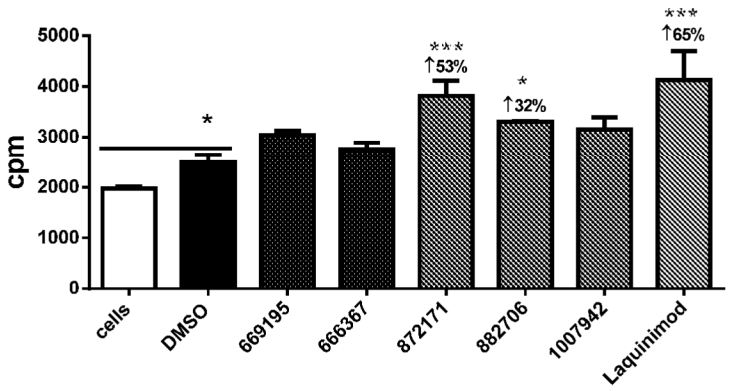

cpm
5000
4000
3000
2000
1000
0
*
***
↑53%
*
↑32%
***
↑65%
cells
DMSO
669195
666367
872171
882706
1007942
Laquinimod

Figure 8

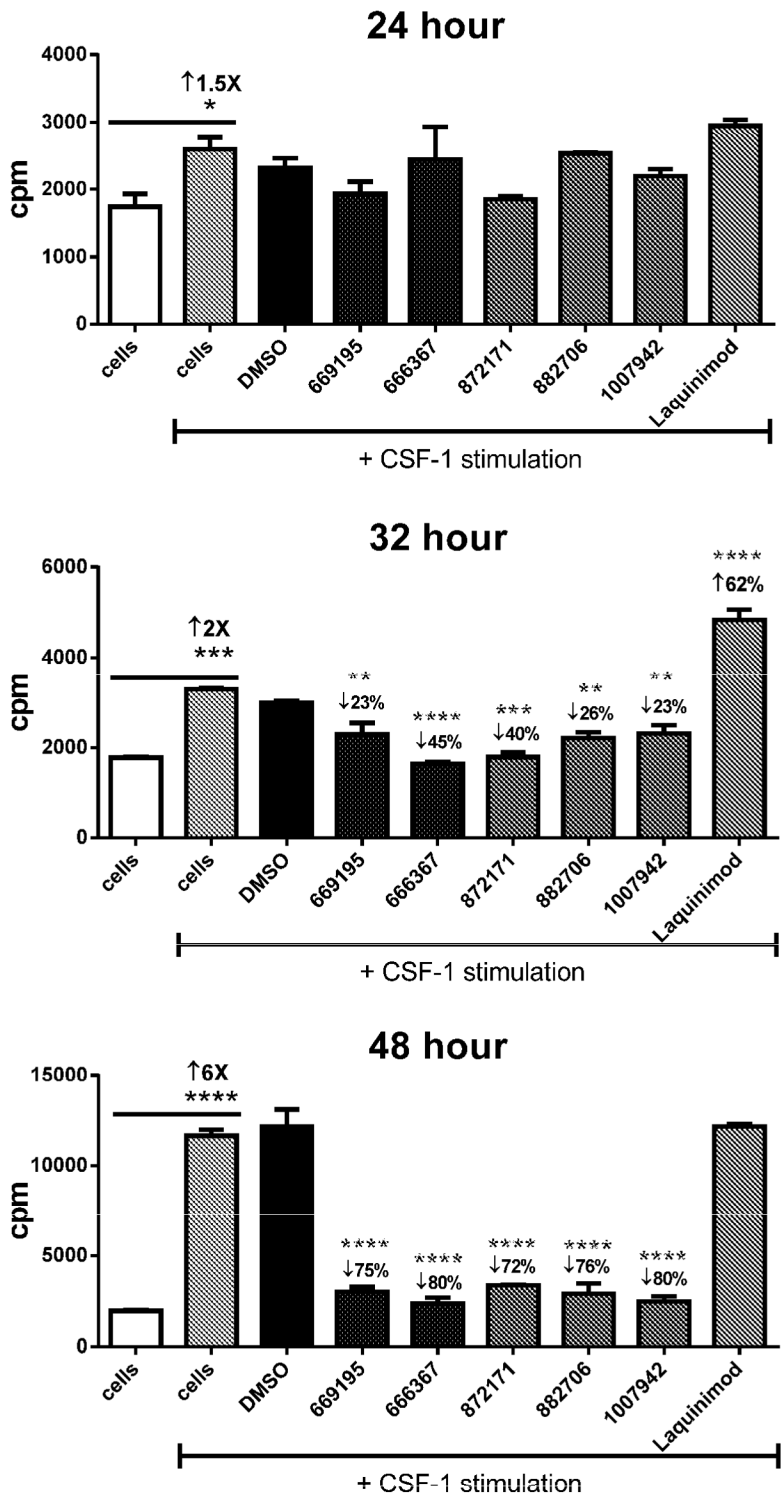

24 hour
cpm
4000
3000
2000
1000
0
↑1.5X
*
cells
cells
DMSO
669195
666367
872171
882706
1007942
Laquinimod
+ CSF-1 stimulation
32 hour
cpm
6000
4000
2000
0
↑2X
***
**
↓23%
****
↓45%
***
↓40%
**
↓26%
**
↓23%
****
↑62%
cells
cells
DMSO
669195
666367
872171
882706
1007942
Laquinimod
+ CSF-1 stimulation
48 hour
cpm
15000
10000
5000
0
↑6X
****
****
↓75%
****
↓80%
****
↓72%
****
↓76%
****
↓80%
cells
cells
DMSO
669195
666367
872171
882706
1007942
Laquinimod
+ CSF-1 stimulation

Figure 9

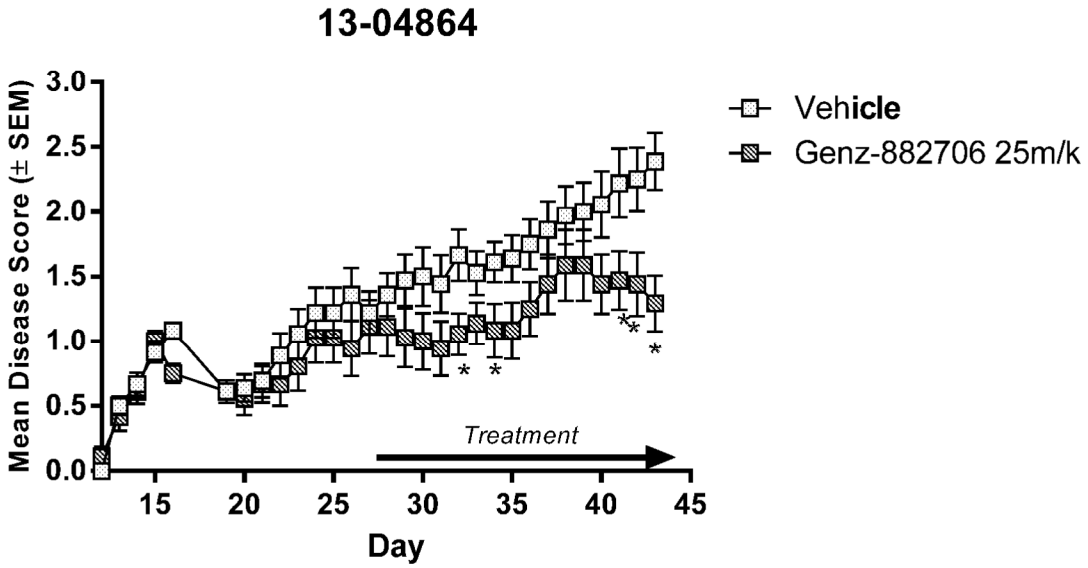

13-04864
Mean Disease Score (± SEM)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
15
20
25
30
35
40
45
Day
Treatment
Vehicle
Genz-882706 25m/k
*
*
*
*

Figure 10

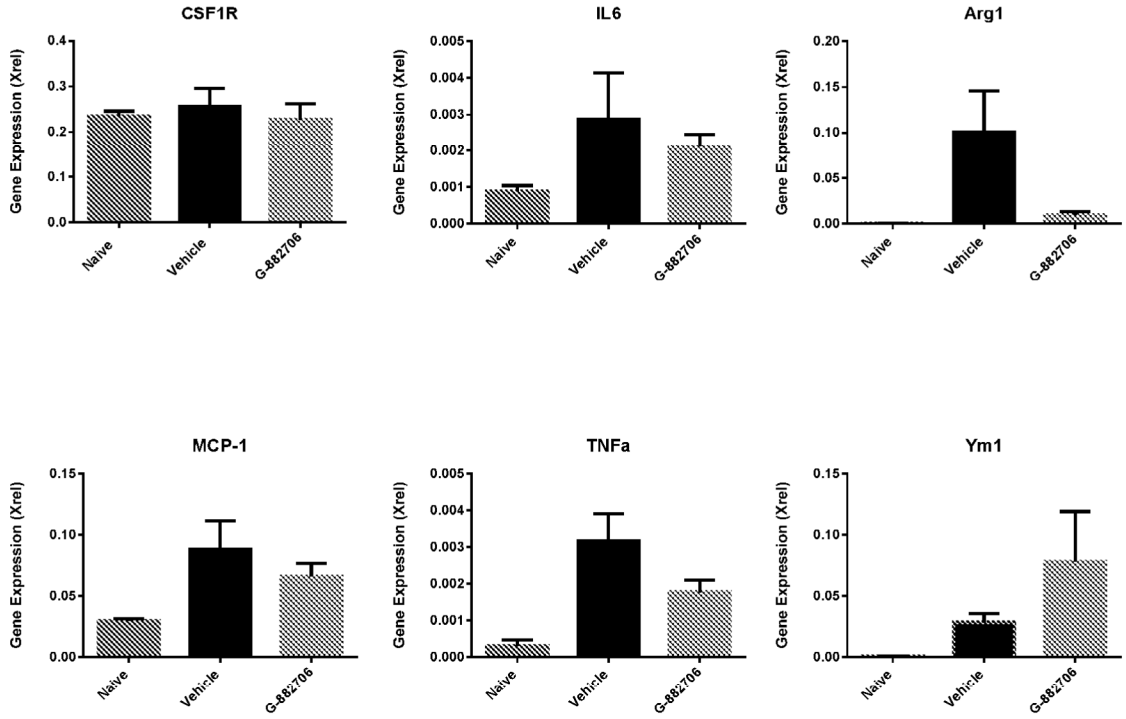

CSF1R
IL6
Arg1
MCP-1
TNFa
Ym1
Gene Expression (Xrel)
Naive
Vehicle
G-882706

Figure 11

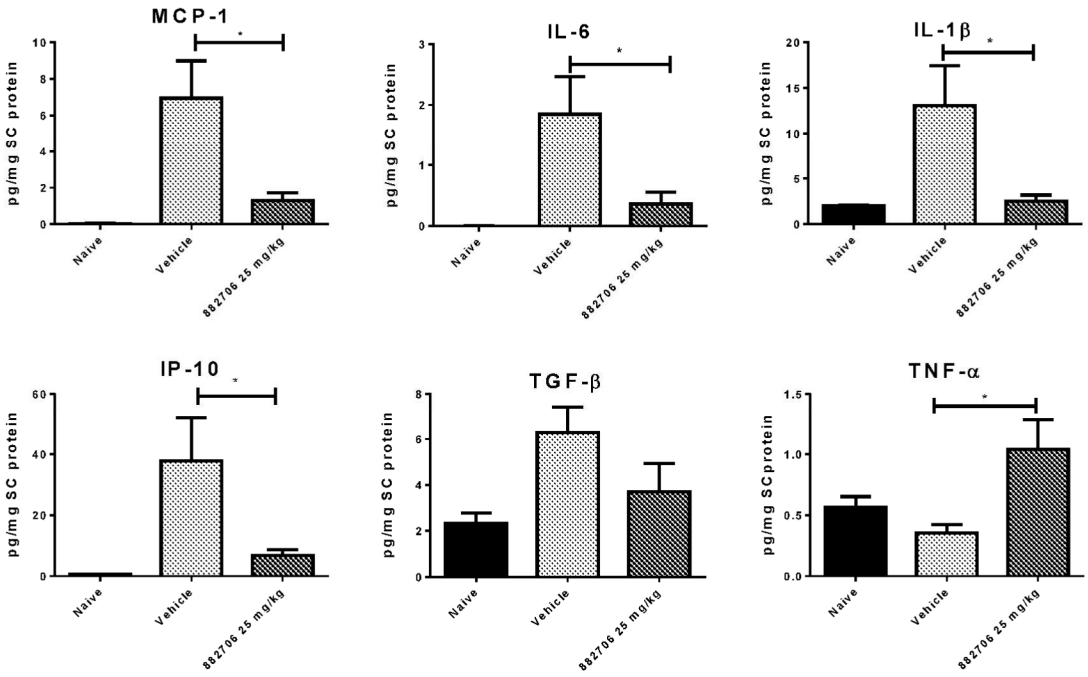


Figure 12

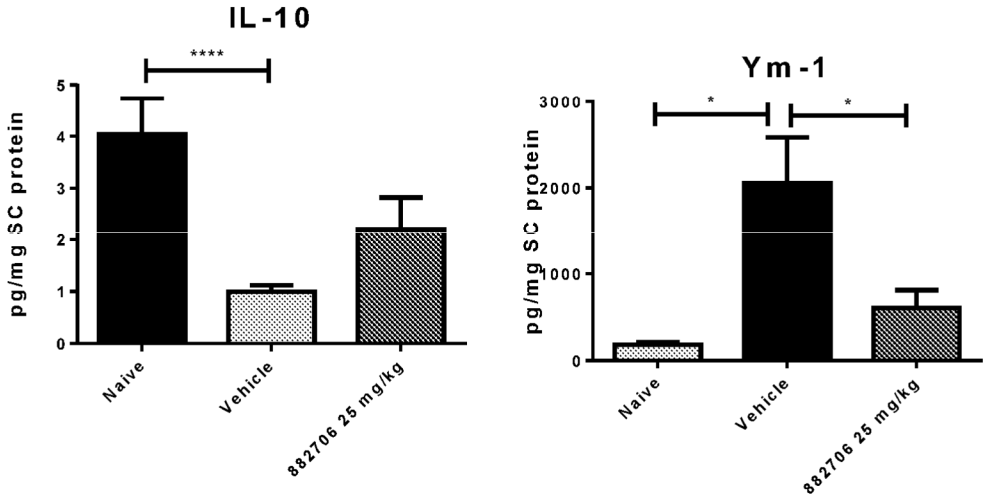


Figure 13

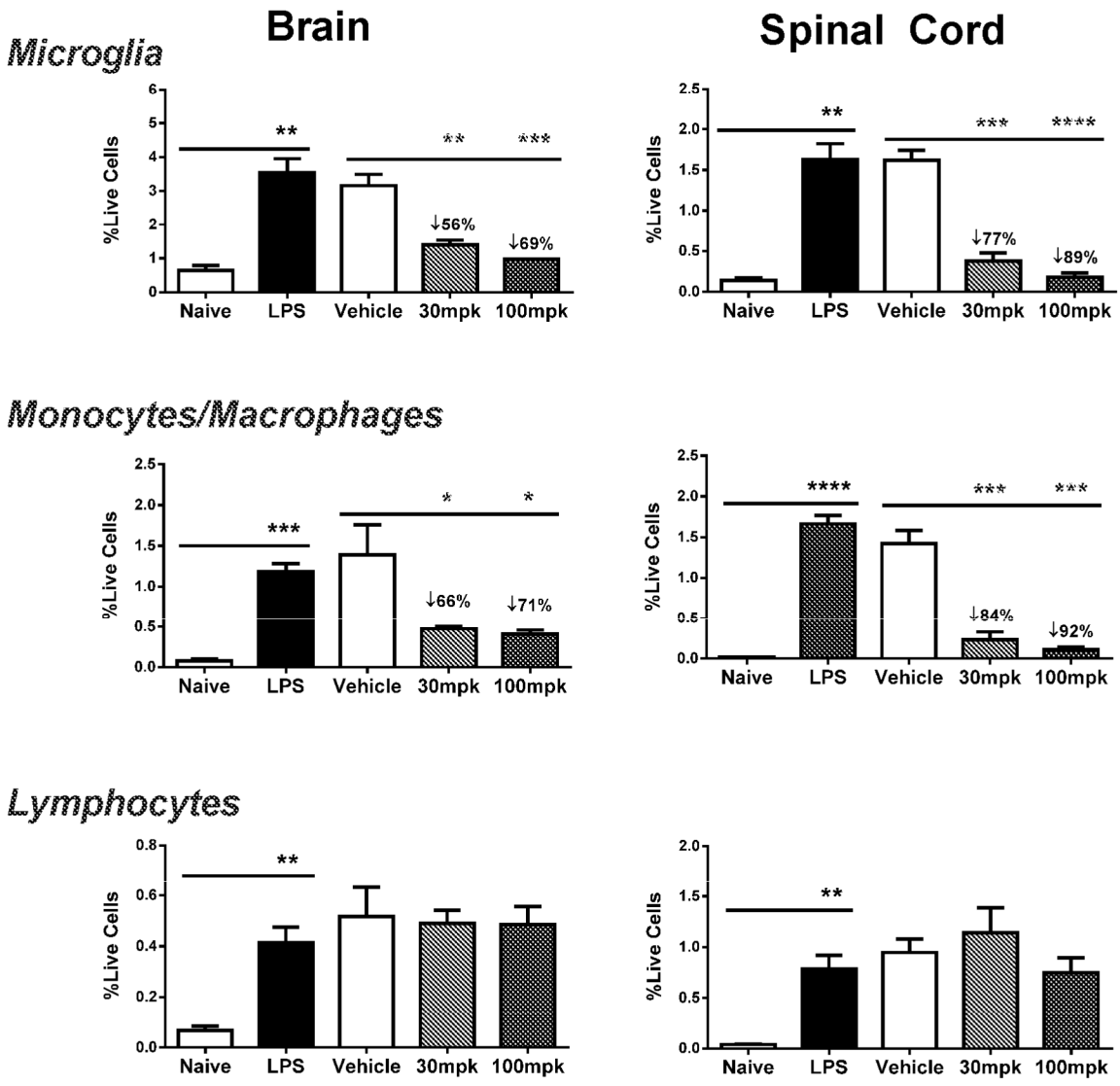

Brain
Spinal Cord
Microglia
Monocytes/Macrophages
Lymphocytes
%Live Cells
Naive
LPS
Vehicle
30mpk
100mpk
↓56%
↓69%
↓77%
↓89%
↓66%
↓71%
↓84%
↓92%

Figure 14

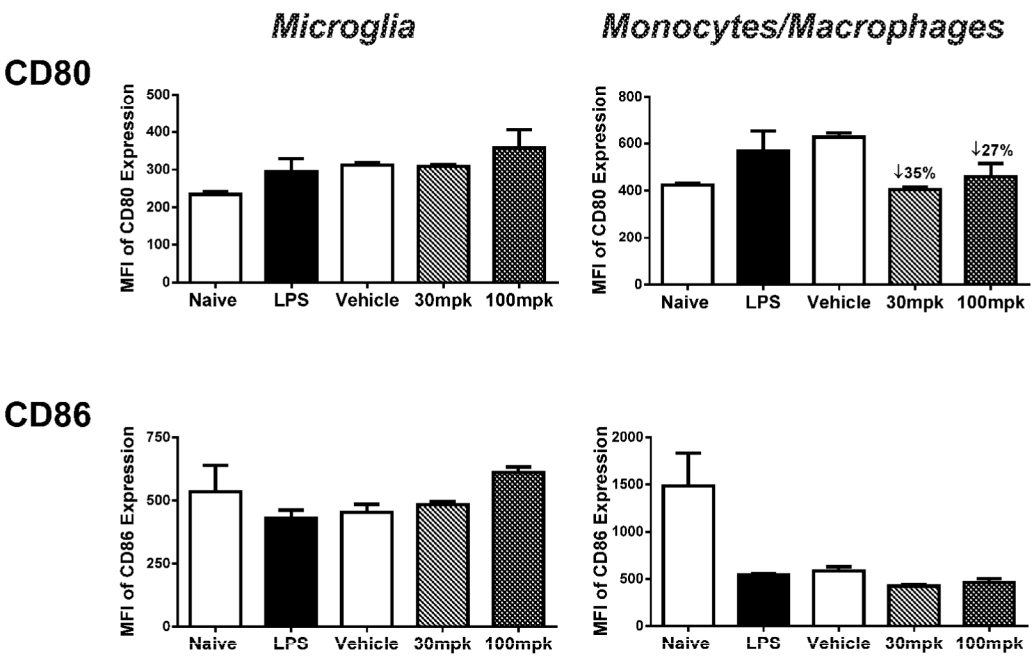

Microglia
Monocytes/Macrophages
CD80
MFI of CD80 Expression
500
400
300
200
100
0
Naive
LPS
Vehicle
30mpk
100mpk
800
600
400
200
0
↓35%
↓27%
CD86
MFI of CD86 Expression
750
500
250
0
2000
1500
1000
500
0

Figure 15

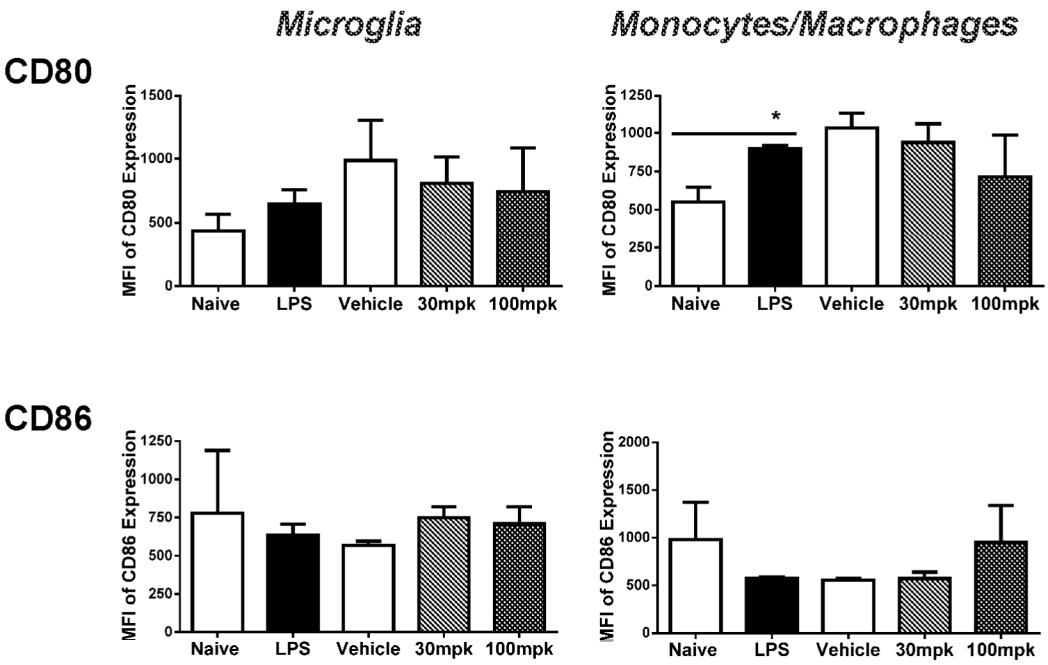


Figure 16

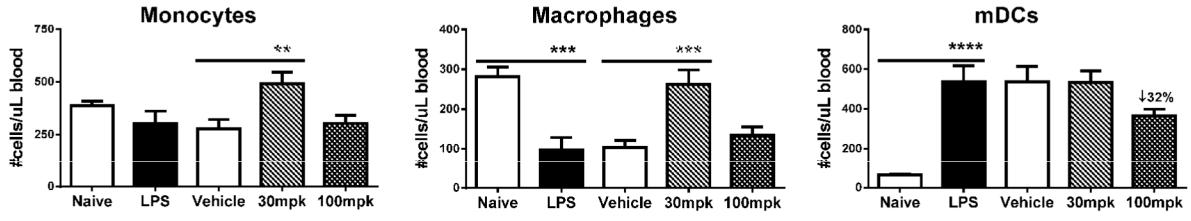


Figure 17

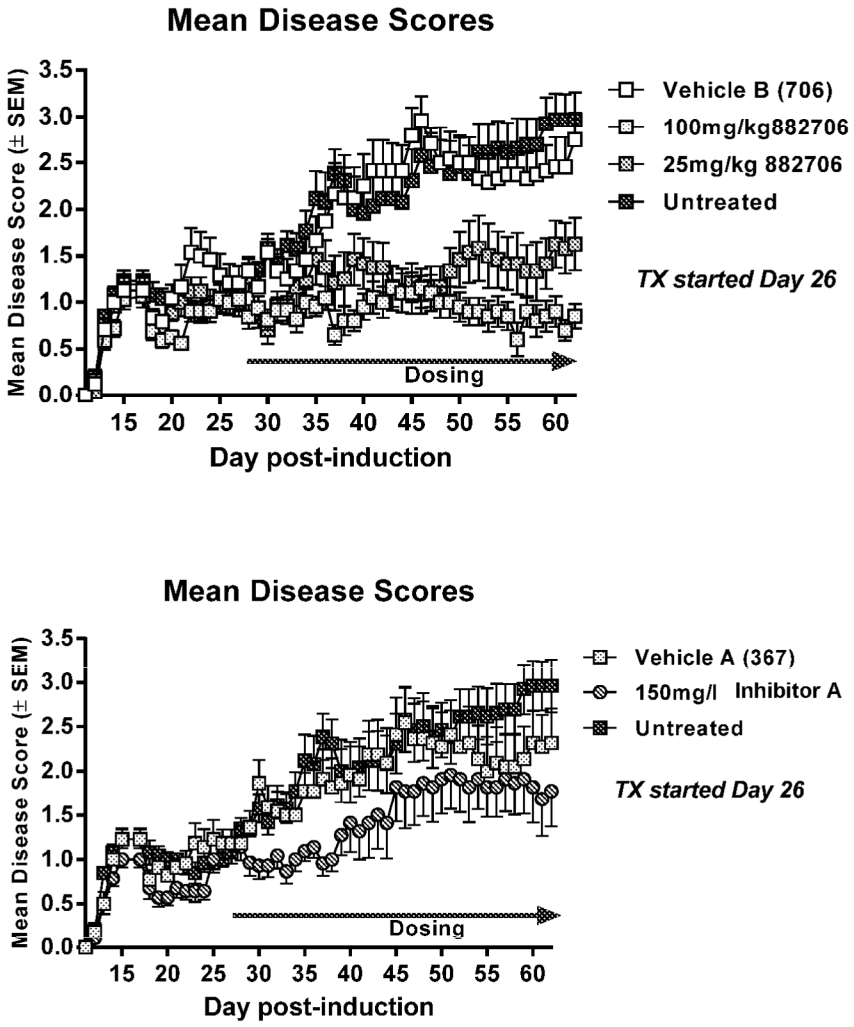

Mean Disease Scores
Mean Disease Score (± SEM)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
15 20 25 30 35 40 45 50 55 60
Day post-induction
Dosing
Vehicle B (706)
100mg/kg882706
25mg/kg 882706
Untreated
TX started Day 26
Mean Disease Scores
Mean Disease Score (± SEM)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
15 20 25 30 35 40 45 50 55 60
Day post-induction
Dosing
Vehicle A (367)
150mg/l Inhibitor A
Untreated
TX started Day 26

Figure 18

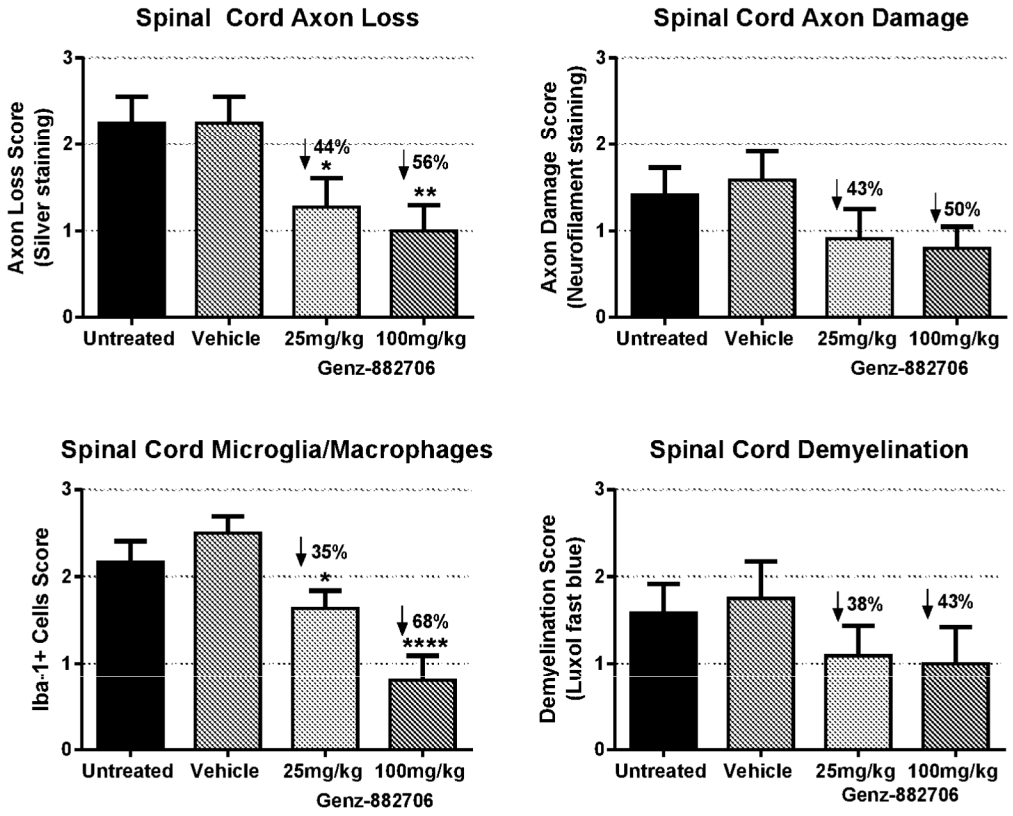


Figure 19

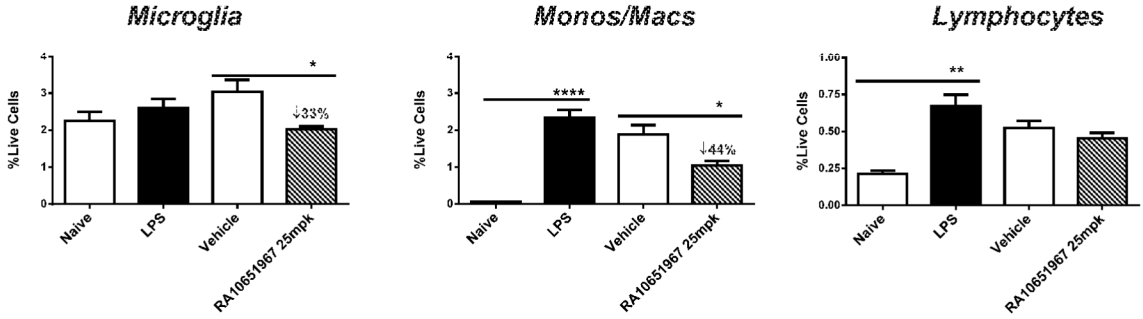


Figure 20

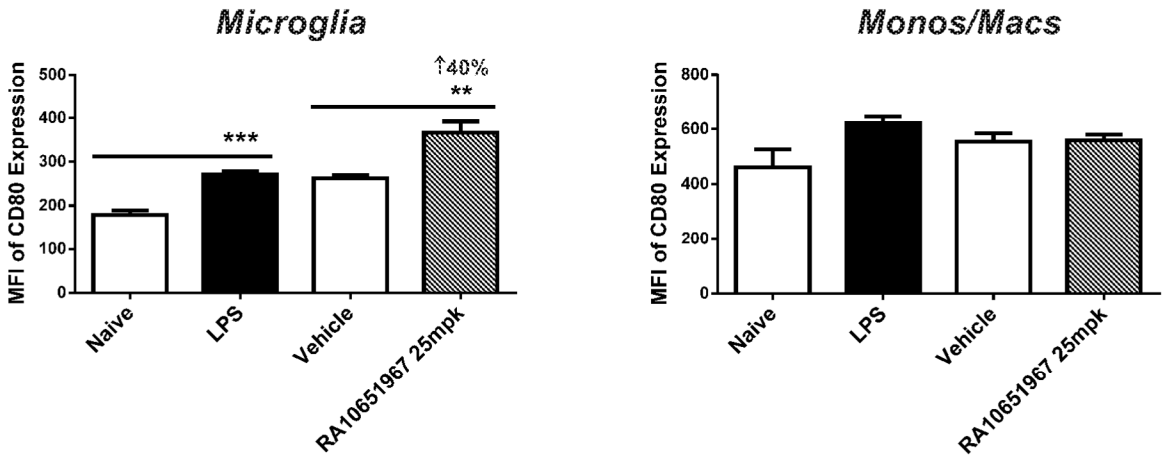


Figure 21

