# FIG. 1

```
   1 cttgagccag acccagtcca gctctggtgc ctgccctctg gtgcgagctg acctgagatg
  61 cacttccctc ctctgtgagc tgtctcggca cccacttgca gtcactgccg cctgatgttg
 121 ttactcttcc actccaaaag gatgcccgtg gccgaggccc cccaggtggc tggcgggcag
 181 ggggacggag gtgatggcga ggaagcggag ccggagggga tgttcaaggc ctgtgaggac
 241 tccaagagaa aagcccgggg ctacctccgc ctggtgcccc tgtttgtgct gctggccctg
 301 ctcgtgctgg cttcggcggg ggtgctactc tggtatttcc tagggtacaa ggcggaggtg
 361 atggtcagcc aggtgtactc aggcagtctg cgtgtactca atcgccactt ctcccaggat
 421 cttacccgcc gggaatctag tgccttccgc agtgaaaccg ccaaagccca gaagatgctc
 481 aaggagctca tcaccagcac ccgcctggga acttactaca actccagctc cgtctattcc
 541 tttggggagg gacccctcac ctgcttcttc tggttcattc tccaaatccc cgagcaccgc
 601 cggctgatgc tgagccccga ggtggtgcag gcactgctgg tggaggagct gctgtccaca
 661 gtcaacagct cggctgccgt cccctacagg gccgagtacg aagtggaccc cgagggccta
 721 gtgatcctgg aagccagtgt gaaagacata gctgcattga attccacgct gggttgttac
 781 cgctacagct acgtgggcca gggccaggtc ctccggctga aggggcctga ccacctggcc
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 961 aagaggctca tcacctcggt gtacggctgc agccgccagg agcccgtggt ggaggttctg
1021 gcgtcggggg ccatcatggc ggtcgtctgg aagaagggcc tgcacagcta ctacgacccc
1081 ttcgtgctct ccgtgcagcc ggtggtcttc caggcctgtg aagtgaacct gacgctggac
1141 aacaggctcg actcccaggg cgtcctcagc accccgtact tccccagcta ctactcgccc
1201 caaacccact gctcctggca cctcacggtg ccctctctgg actacggctt ggccctctgg
1261 tttgatgcct atgcactgag gaggcagaag tatgatttgc cgtgcaccca gggccagtgg
1321 acgatccaga acaggaggct gtgtggcttg cgcatcctgc agccctacgc cgagaggatc
1381 cccgtggtgg ccacggccgg gatcaccatc aacttcacct cccagatctc cctcaccggg
1441 cccggtgtgc gggtgcacta tggcttgtac aaccagtcgg acccctgccc tggagagttc
1501 ctctgttctg tgaatggact ctgtgtccct gcctgtgatg gggtcaagga ctgccccaac
1561 ggcctggatg agagaaactg cgtttgcaga gccacattcc agtgcaaaga ggacagcaca
1621 tgcatctcac tgcccaaggt ctgtgatggg cagcctgatt gtctcaacgg cagcgacgaa
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1741 tgcgtgaaga agcccaaccc gcagtgtgat gggcggcccg actgcaggga cggctcggat
1801 gaggagcact gtgactgtgg cctccagggc ccctccagcc gcattgttgg tggagctgtg
1861 tcctccgagg gtgagtggcc atggcaggcc agcctccagg ttcggggtcg acacatctgt
1921 gggggggccc tcatcgctga ccgctgggtg ataacagctg cccactgctt ccaggaggac
1981 agcatggcct ccacggtgct gtggaccgtg ttcctgggca aggtgtggca gaactcgcgc
2041 tggcctggag aggtgtcctt caaggtgagc cgcctgctcc tgcacccgta ccacgaagag
2101 gacagccatg actacgacgt ggcgctgctg cagctcgacc acccggtggt gcgctcggcc
2161 gccgtgcgcc ccgtctgcct gcccgcgcgc tcccacttct tcgagcccgg cctgcactgc
2221 tggattacgg gctggggcgc cttgcgcgag ggcggcccca tcagcaacgc tctgcagaaa
2281 gtggatgtgc agttgatccc acaggacctg tgcagcgagg tctatcgcta ccaggtgacg
2341 ccacgcatgc tgtgtgccgg ctaccgcaag ggcaagaagg atgcctgtca gggtgactca
2401 ggtggtccgc tggtgtgcaa ggcactcagt ggccgctggt tcctggcggg gctggtcagc
2461 tggggcctgg gctgtggccg gcctaactac ttcggcgtct acacccgcat cacaggtgtg
2521 atcagctgga tccagcaagt ggtgacctga ggaactgccc ccctgcaaag cagggcccac
2581 ctcctggact cagagagccc agggcaactg ccaagcaggg ggacaagtat tctggcgggg
2641 ggtgggggag agagcaggcc ctgtggtggc aggaggtggc atcttgtctc gtccctgatg
2701 tctgctccag tgatggcagg aggatggaga agtgccagca gctgggggtc aagacgtccc
2761 ctgaggaccc aggcccacac ccagcccttc tgcctcccaa ttctctctcc tccgtccctt
2821 tcctccactg ctgcctaatg caaggcagtg gctcagcagc aagaatgctg gttctacatc
2881 ccgaggagtg tctgaggtgc gccccactct gtacagaggc tgtttgggca gccttgcctc
2941 cagagagcag attccagctt cggaagcccc tggtctaact tgggatctgg gaatggaagg
3001 tgctcccatc ggaggggacc ctcagagccc tggagactgc caggtgggcc tgctgccact
3061 gtaagccaaa aggtggggaa gtcctgactc cagggtcctt gccccacccc tgcctgccac
3121 ctgggccctc acagcccaga ccctcactgg gaggtgagct cagctgccct ttggaataaa
3181 gctgcctgat caaaaaaaaa aaaaaaaaaa aa
```

FIG. 2A

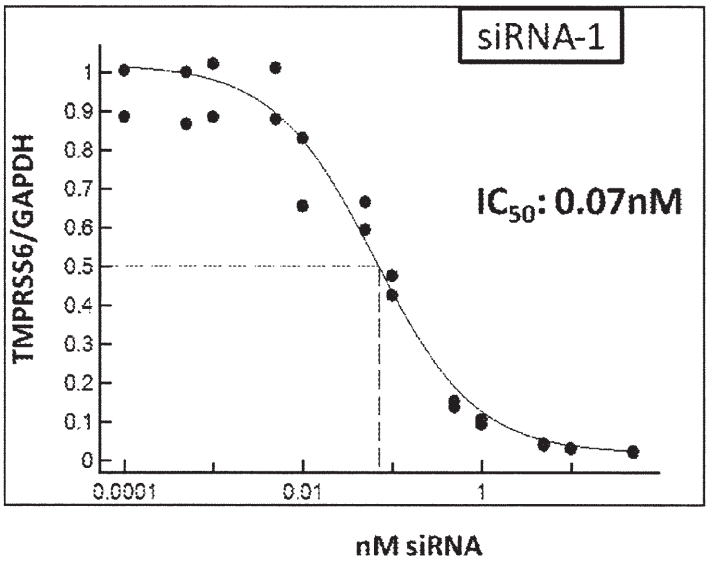

siRNA-1
IC50: 0.07nM
TMPRSS6/GAPDH
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.0001
0.01
1
nM siRNA

FIG. 2B

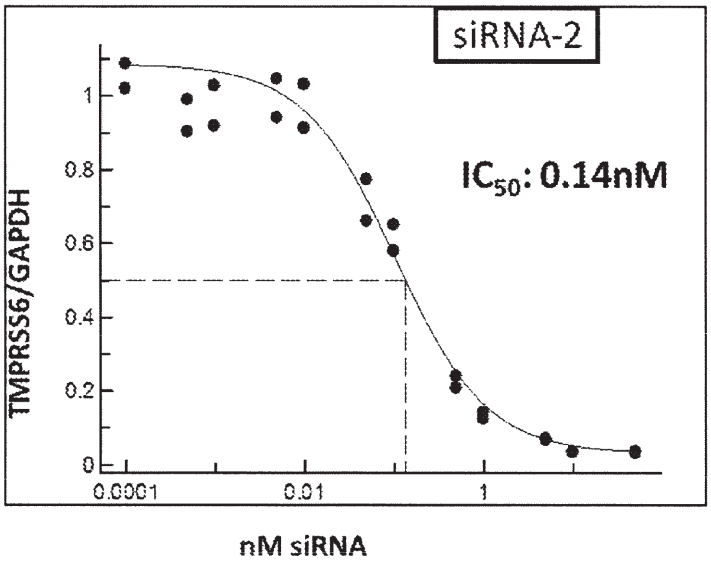

siRNA-2
IC50: 0.14nM
TMPRSS6/GAPDH
1
0.8
0.6
0.4
0.2
0
0.0001
0.01
1
nM siRNA

FIG. 3A

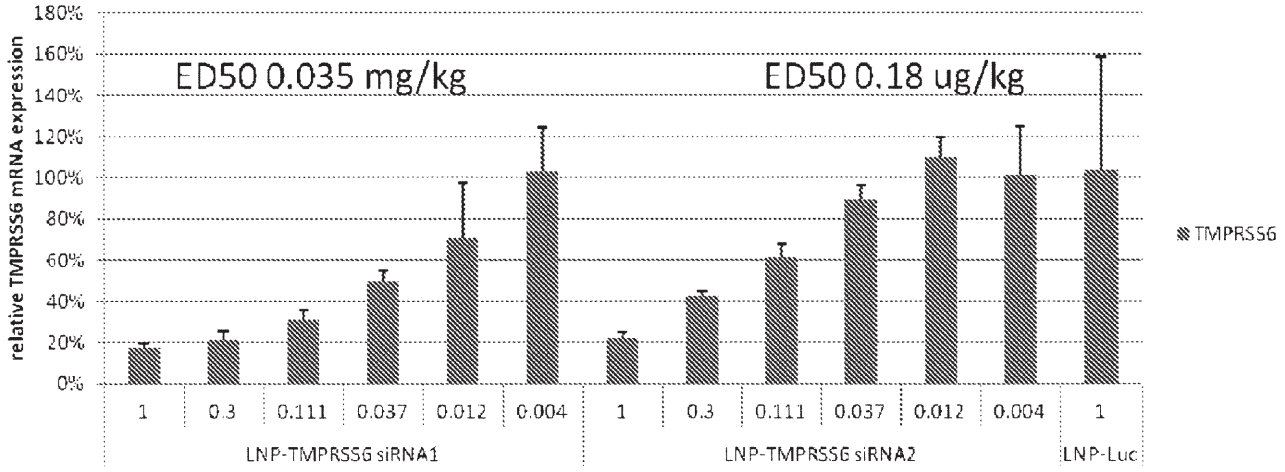

180%
160%
140%
120%
100%
80%
60%
40%
20%
0%
relative TMPRSS6 mRNA expression
ED50 0.035 mg/kg
ED50 0.18 ug/kg
TMPRSS6
1
0.3
0.111
0.037
0.012
0.004
1
0.3
0.111
0.037
0.012
0.004
1
LNP-TMPRSS6 siRNA1
LNP-TMPRSS6 siRNA2
LNP-Luc

FIG. 3B

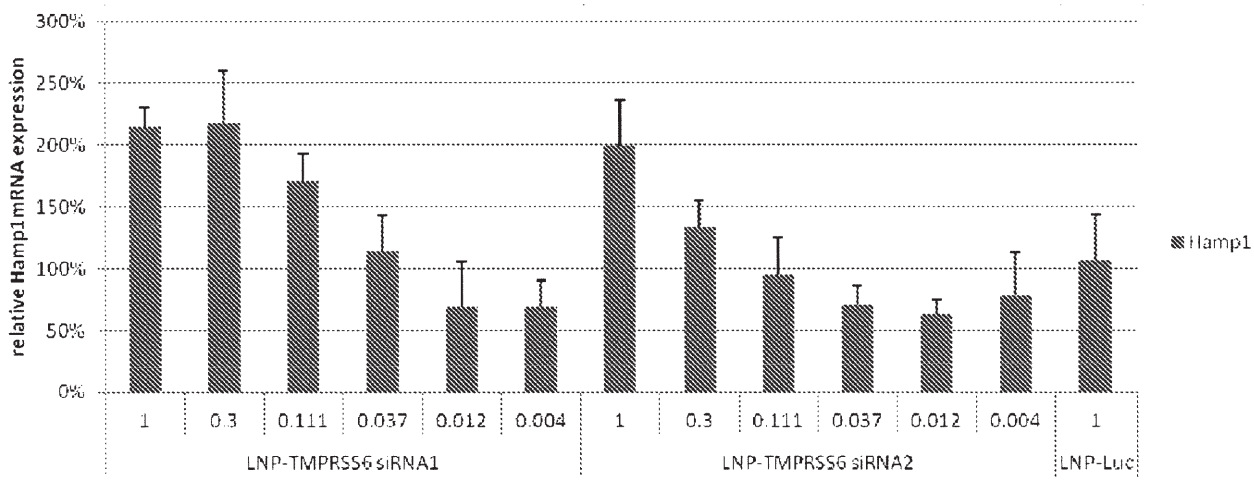

300%
250%
200%
150%
100%
50%
0%
relative Hamp1 mRNA expression
Hamp1
1
0.3
0.111
0.037
0.012
0.004
1
0.3
0.111
0.037
0.012
0.004
1
LNP-TMPRSS6 siRNA1
LNP-TMPRSS6 siRNA2
LNP-Luc

**FIG. 4**

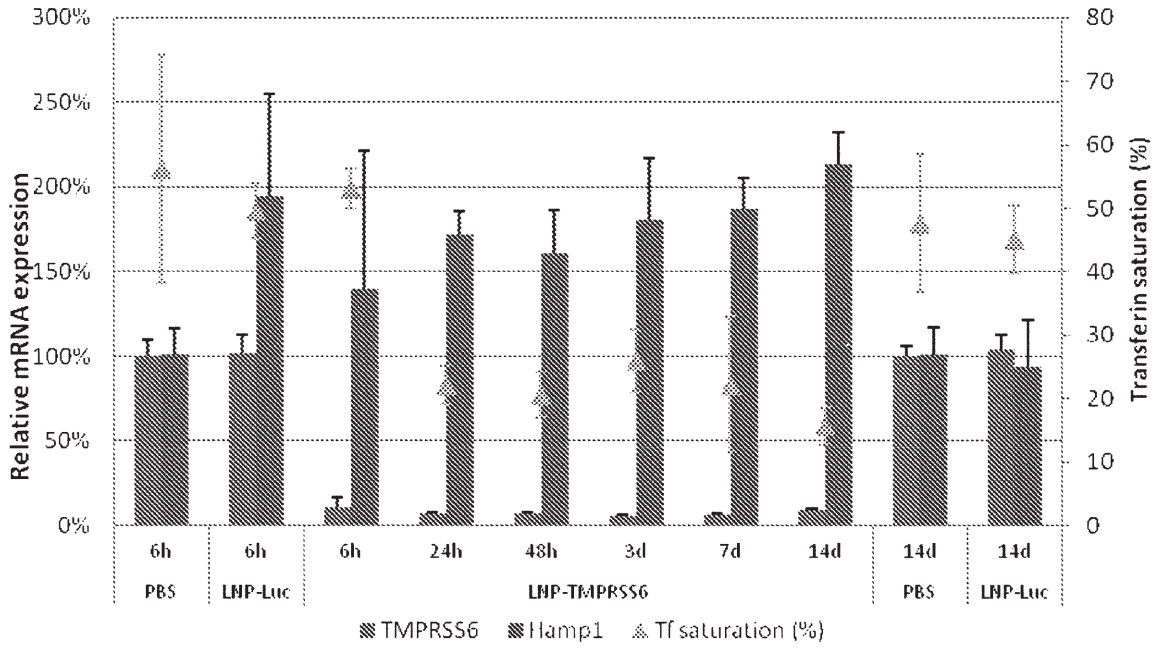

300%
250%
200%
150%
100%
50%
0%
Relative mRNA expression
80
70
60
50
40
30
20
10
0
Transferin saturation (%)
6h
PBS
6h
LNP-Luc
6h
24h
48h
3d
7d
14d
LNP-TMPRSS6
14d
PBS
14d
LNP-Luc
TMPRSS6
Hamp1
Tf saturation (%)

**FIG. 5**

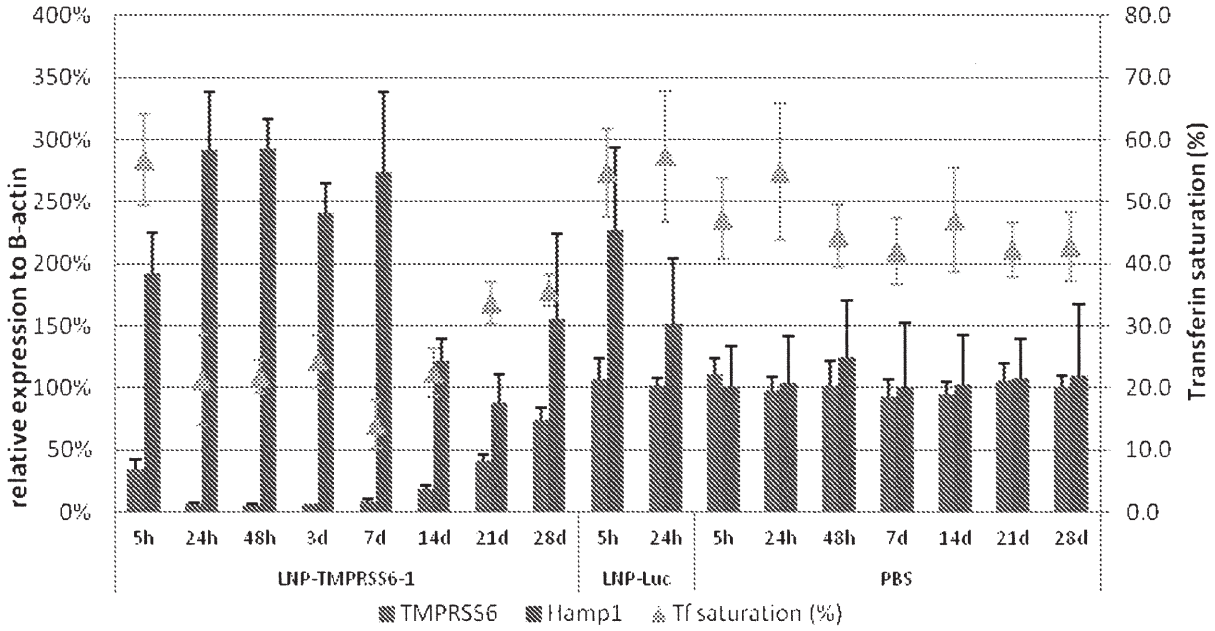

400%
350%
300%
250%
200%
150%
100%
50%
0%
relative expression to B-actin
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
Transferin saturation (%)
5h
24h
48h
3d
7d
14d
21d
28d
5h
24h
5h
24h
48h
7d
14d
21d
28d
LNP-TMPRSS6-1
LNP-Luc
PBS
TMPRSS6
Hamp1
Tf saturation (%)

FIG. 6A

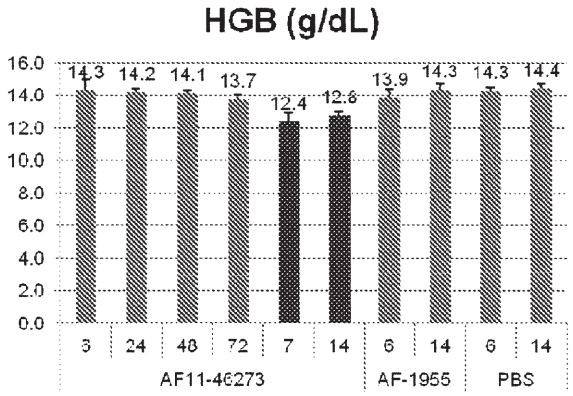

HGB (g/dL)
16.0
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
14.3
14.2
14.1
13.7
12.4
12.8
13.9
14.3
14.3
14.4
6
24
48
72
7
14
6
14
6
14
AF11-46273
AF-1955
PBS

FIG. 6B

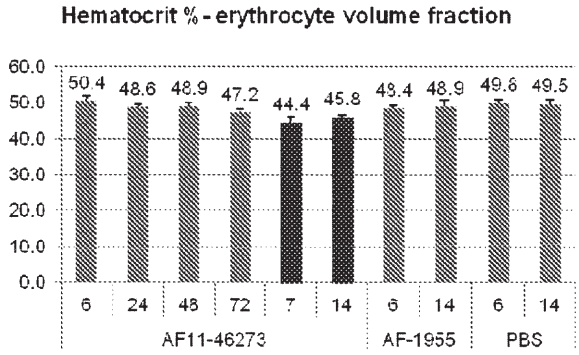
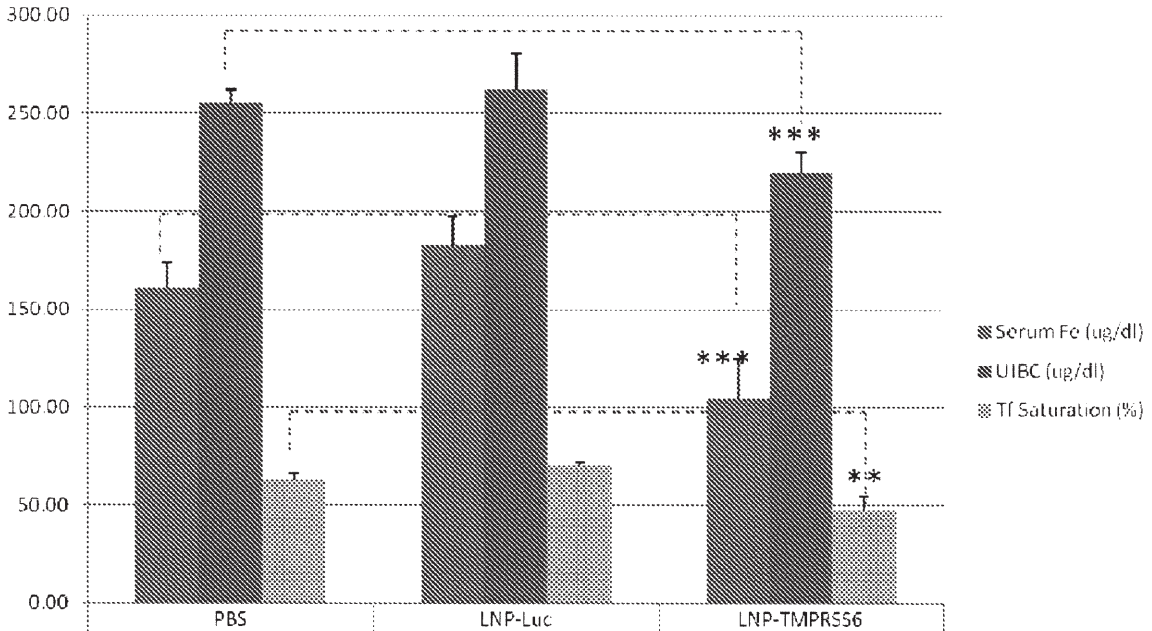

Hematocrit % - erythrocyte volume fraction
60.0
50.0
40.0
30.0
20.0
10.0
0.0
50.4
48.6
48.9
47.2
44.4
45.8
48.4
48.9
49.6
49.5
6
24
48
72
7
14
6
14
6
14
AF11-46273
AF-1955
PBS

**FIG. 7**




| | PBS | LNP-Luc | LNP-TMPRSS6 |
|---|---|---|---|
| Serum Fe (ug/dl) | 160.65 | 183.16 | 104.97 |
| UIBC (ug/dl) | 255.35 | 261.95 | 220.18 |
| Tf Saturation (%) | 62.85 | 69.93 | 47.44 |

FIG. 8A

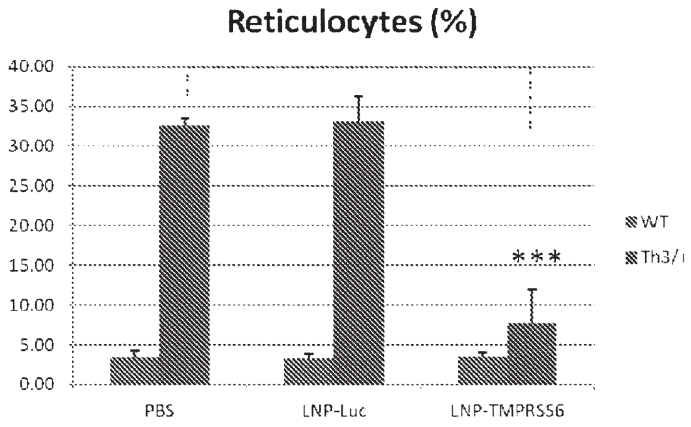



FIG. 8B

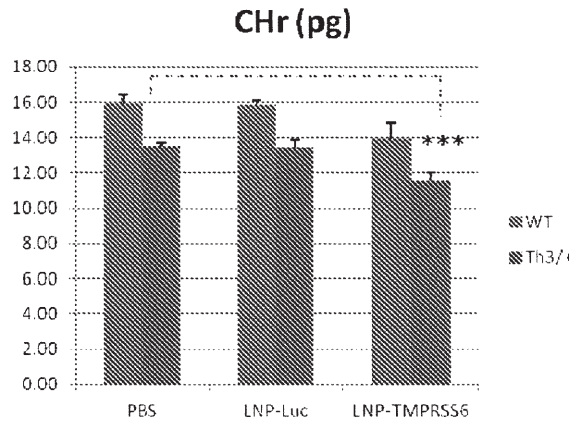



FIG. 8C

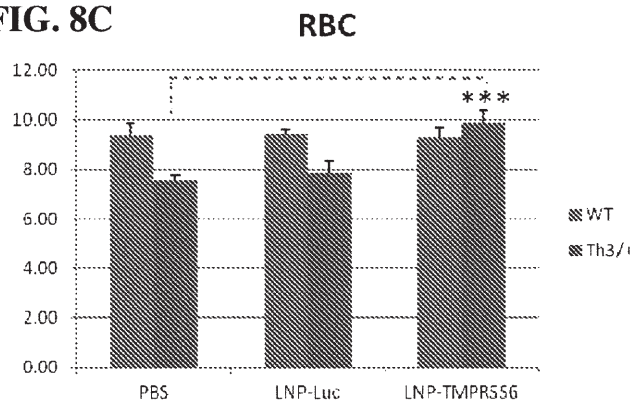


FIG. 9A

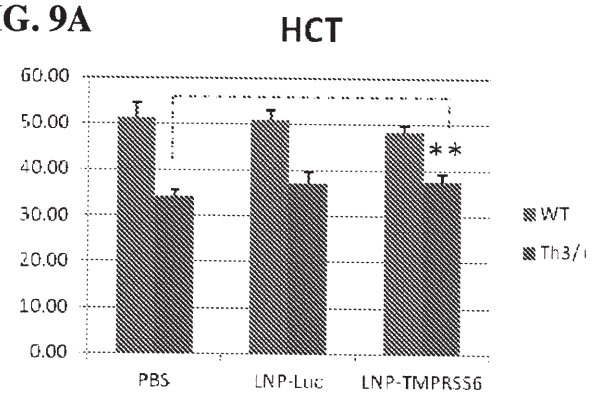



FIG. 9B

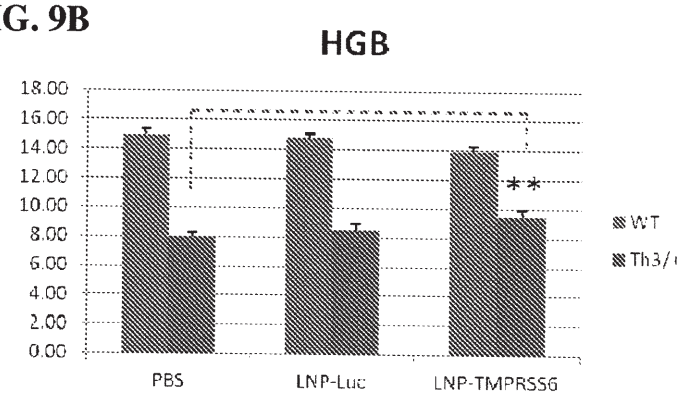



FIG. 9C

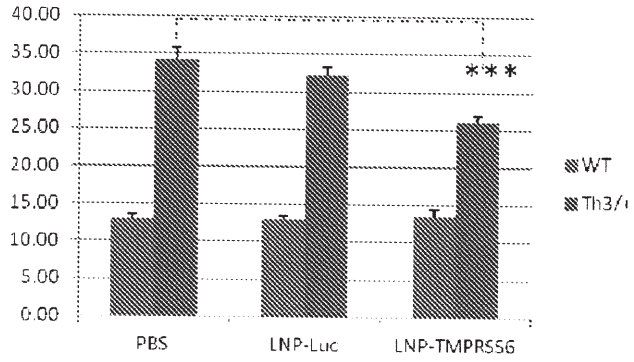



FIG. 9D

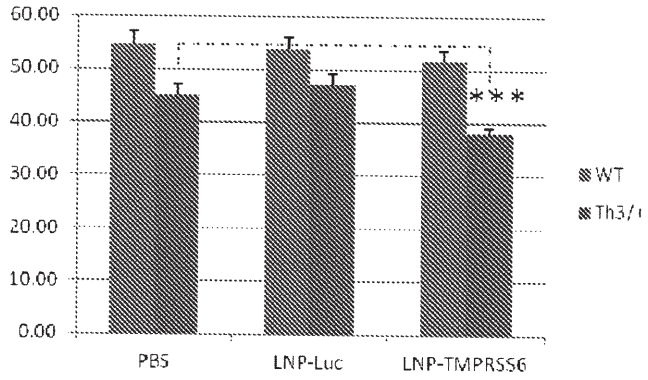


FIG. 10A

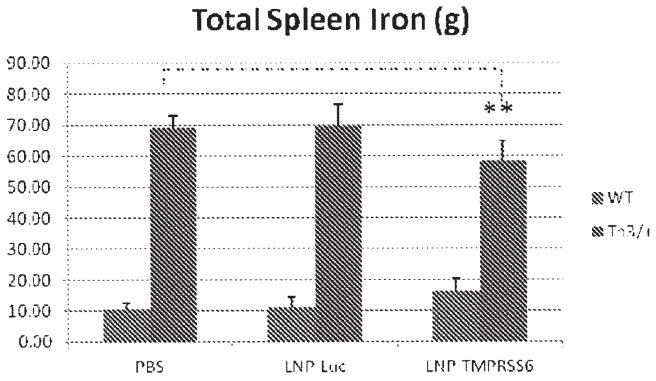



FIG. 10B

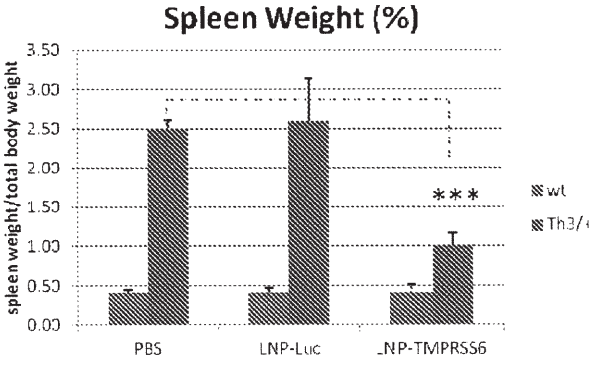



FIG. 10C

