

Fig.S1

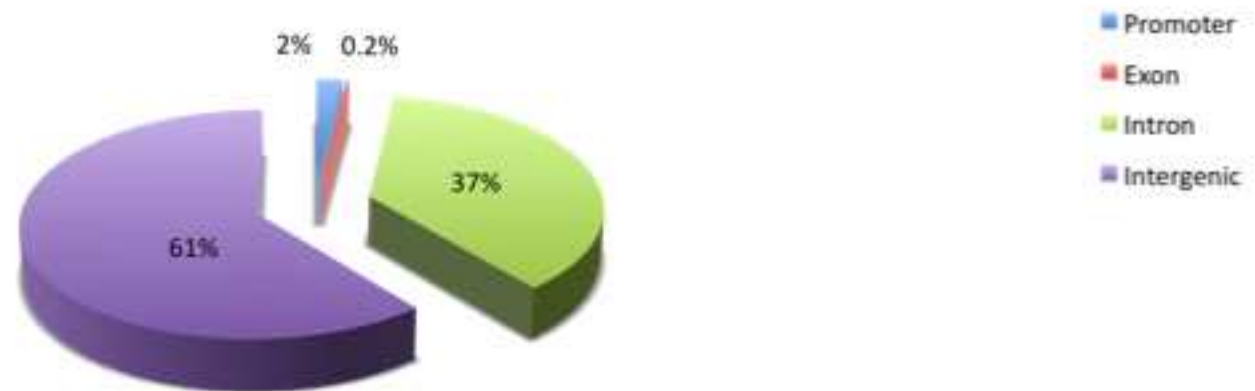


Fig. S2

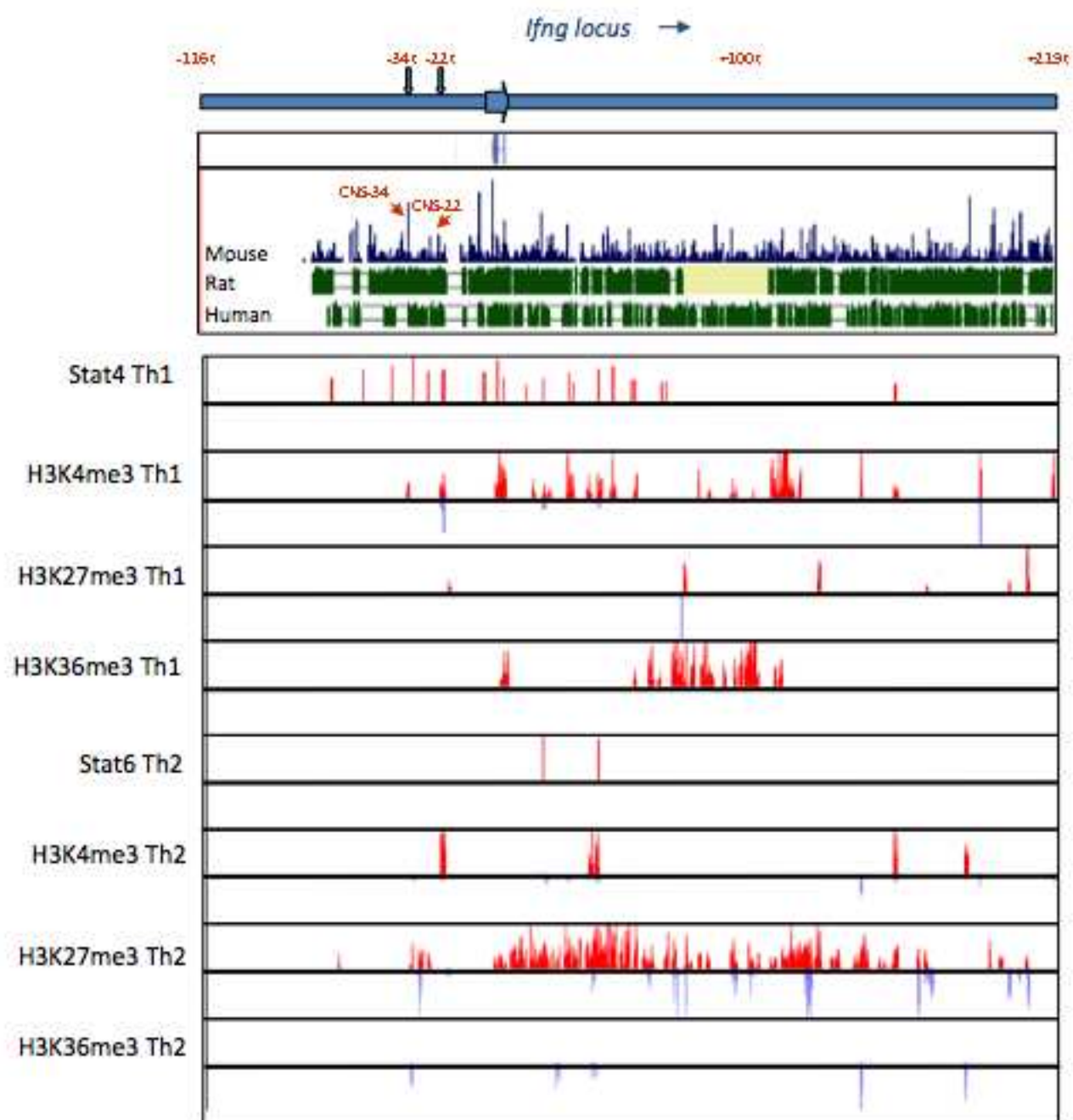


Fig.S3A

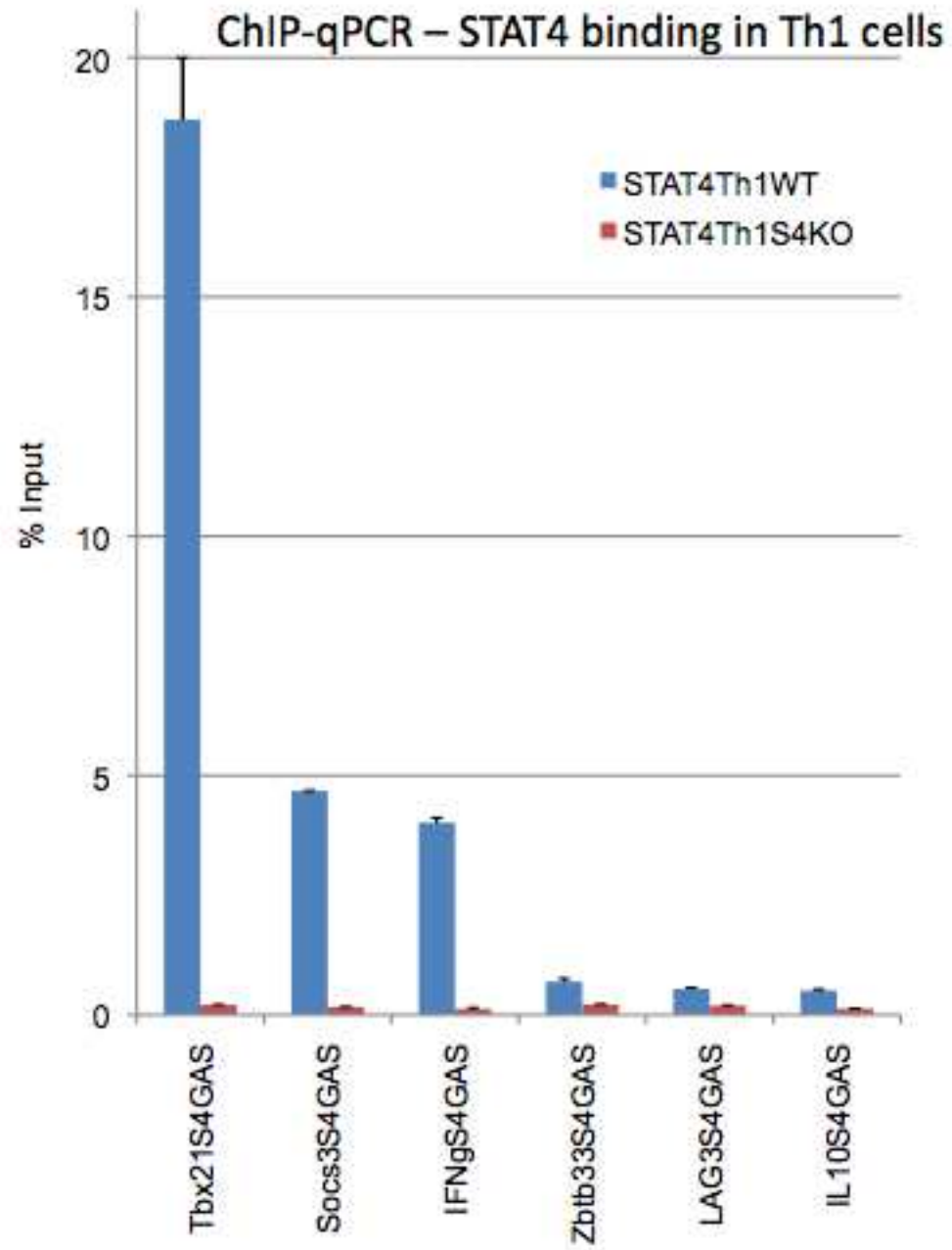


Fig.S3B

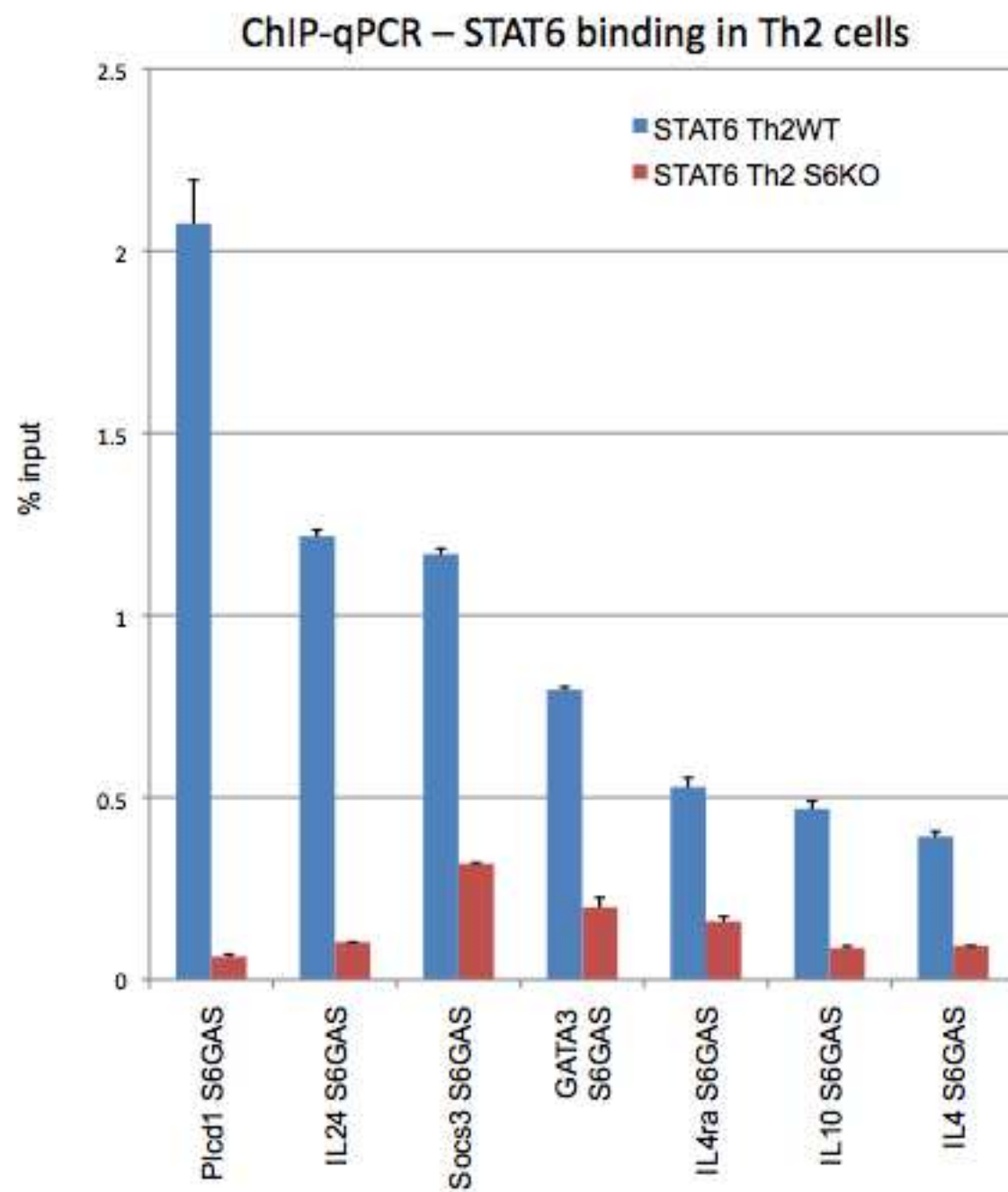


Fig.S4

| | STAT binding | Epigenetic pattern | | | | | Gene expression | | | | | | |
|-------------------------------|-----------------------|--------------------|------------------|--|----------|----------|--------------------------------------|--------------------------------------|---------------|-----------------|---------------|--|-----------|
| | epigenetic cluster | # of genes | Genes in cluster | STAT dependent epigenetic change (WT/KO) | | | STAT induced gene expression (WT/KO) | Th preferential expression (Th1/Th2) | | | | | |
| | | | | H3K4me3 | H3K36me3 | H3K27me3 | | | Up regulation | Down regulation | | | |
| STAT4 bound genes 4486 | K4 high | 257 | Zbtb32 | 251 | 0 | 0 | 2.8 | Up regulation | | Th1 > Th2 | | | |
| | | | Nkg7 | 230 | 0 | 0 | 10.3 | | | | | | |
| | | | Lilrb4 | 145 | 0 | 0 | 2.7 | | | | | | |
| | | | Il8rb | 143 | 0 | 0 | 4.8 | | | | | | |
| | K36 high | 191 | Il121 | 113 | 175 | 0 | 198.1 | | | | | | |
| | | | Ifng | 144 | 66 | 0 | 17.6 | | | | | | |
| | | | Skap2 | 2.4 | 48 | 0.89 | 3.6 | | | | | | |
| | | | Tbx21 | 6.1 | 6.3 | 0 | 1.9 | | | | | | |
| | K27 low | 316 | Atf3 | 2 | 5.4 | 0.006 | 4.2 | | | | | | |
| | | | Gbp2 | 3.5 | 1.3 | 0.025 | 2.7 | | | | | | |
| Casp4 | | | 4.6 | 2.8 | 0.031 | 3.3 | | | | | | | |
| Icos | | | 2.6 | 1.5 | 0.05 | 3.6 | | | | | | | |
| indeterminate pattern | 3384 | Il18rap | 6.9 | 4.4 | 0 | 6.2 | | | | | | | |
| | | Il18r1 | 1.8 | 1.9 | 0 | 3.6 | | | | | | | |
| | | Zbtb33 | 2.7 | 0.8 | 0 | 3 | | | | | | | |
| | | Furin | 5.4 | 3.5 | 0 | 2.2 | | | | | | | |
| | | Gata3 | 2.3 | 1 | 0.37 | 0.17 | | | | | | | |
| | | Myo6 | 1.4 | 0 | 0 | 0.11 | | | | | | | |
| | | Tnfrsf10 | 1.9 | 0.77 | 0 | 0.36 | | | | | | | |
| Cpd | 2.4 | 0 | 2.4 | 0.41 | | | | | | | | | |
| K27 high | 256 | Rreb1 | 7 | 0.5 | 79 | 0.48 | Down regulation | | Th2 > Th1 | | | | |
| | | Ccr8 | 2.8 | 0 | 40 | 0.17 | | | | | | | |
| | | Dhx34 | 1.5 | 0.68 | 27 | 0.49 | | | | | | | |
| | | Dnmt3a | 1.9 | 1.3 | 22 | 0.45 | | | | | | | |
| K36 low | 82 | Osbpl3 | 0.93 | 0.0063 | 0 | 0.098 | | | | | | | |
| | | Socs2 | 2.4 | 0.0078 | 0 | 0.51 | | | | | | | |
| | | Plekha1 | 1.2 | 0.0087 | 95 | 0.28 | | | | | | | |
| | | Mcoln2 | 1.8 | 0.053 | 0 | 0.091 | | | | | | | |
| STAT6 bound genes 4136 | K36 high | 169 | Pparg | 2.1 | 1310 | 1 | | | | 10.6 | Up regulation | | Th2 > Th1 |
| | | | Picd1 | 1.6 | 576 | 0.063 | | | | 16 | | | |
| | | | Pros1 | 1.5 | 46.3 | 0 | 5.4 | | | | | | |
| | | | Hipk2 | 4.7 | 9 | 0.3 | 3.4 | | | | | | |
| | K27 low | 487 | Ikarf3 | 1.3 | 5.4 | 0.0075 | 4.7 | | | | | | |
| | | | Il4ra | 1.4 | 1.1 | 0.013 | 5.2 | | | | | | |
| | | | Il24 | 4 | 8.7 | 0.023 | 191 | | | | | | |
| | | | Il4 | 3.6 | 2 | 0.042 | 6.5 | | | | | | |
| | indeterminate pattern | 3176 | Gata3 | 1.3 | 1.9 | 0.11 | 2.8 | | | | | | |
| | | | Prdm1 | 1.8 | 3.3 | 1.2 | 28.9 | | | | | | |
| | | | Nfil3 | 2.7 | 3.5 | 0 | 13.6 | | | | | | |
| | | | F2rl2 | 1.5 | 2.2 | 0 | 18.4 | | | | | | |
| | | | Asb2 | 1.8 | 7.8 | 0.28 | 19.6 | | | | | | |
| | | | Impa2 | 1.3 | 1.2 | 0 | 5.8 | | | | | | |
| | | | Irf1 | 0.9 | 0.79 | 0 | 0.19 | | | | | | |
| | | | Irf8 | 1.1 | 0.63 | 0.61 | 0.2 | | | | | | |
| K27 high | 185 | Slamf6 | 1.1 | 1.4 | 0 | 0.22 | | | | | | | |
| | | Cd27 | 0.9 | 0.48 | 0 | 0.31 | | | | | | | |
| | | Tcf7 | 0.65 | 0.68 | 782 | 0.24 | | | | | | | |
| | | Il18rap | 0.89 | 0.42 | 252 | 1 | | | | | | | |
| K36 low | 119 | Gfod1 | 1.1 | 0.23 | 49 | 0.65 | Down regulation | | Th1 > Th2 | | | | |
| | | Il18r1 | 0.67 | 0.19 | 23.6 | 0.34 | | | | | | | |
| | | Cnksr3 | 0.78 | 0.0018 | 1.1 | 0.15 | | | | | | | |
| | | Cd9 | 0.69 | 0.003 | 3.9 | 0.13 | | | | | | | |
| Ltb | 1 | 0.017 | 0 | 0.37 | | | | | | | | | |
| Lta | 0.79 | 0.042 | 0 | 0.15 | | | | | | | | | |

Fig.S5A

STAT4 negatively regulated genes

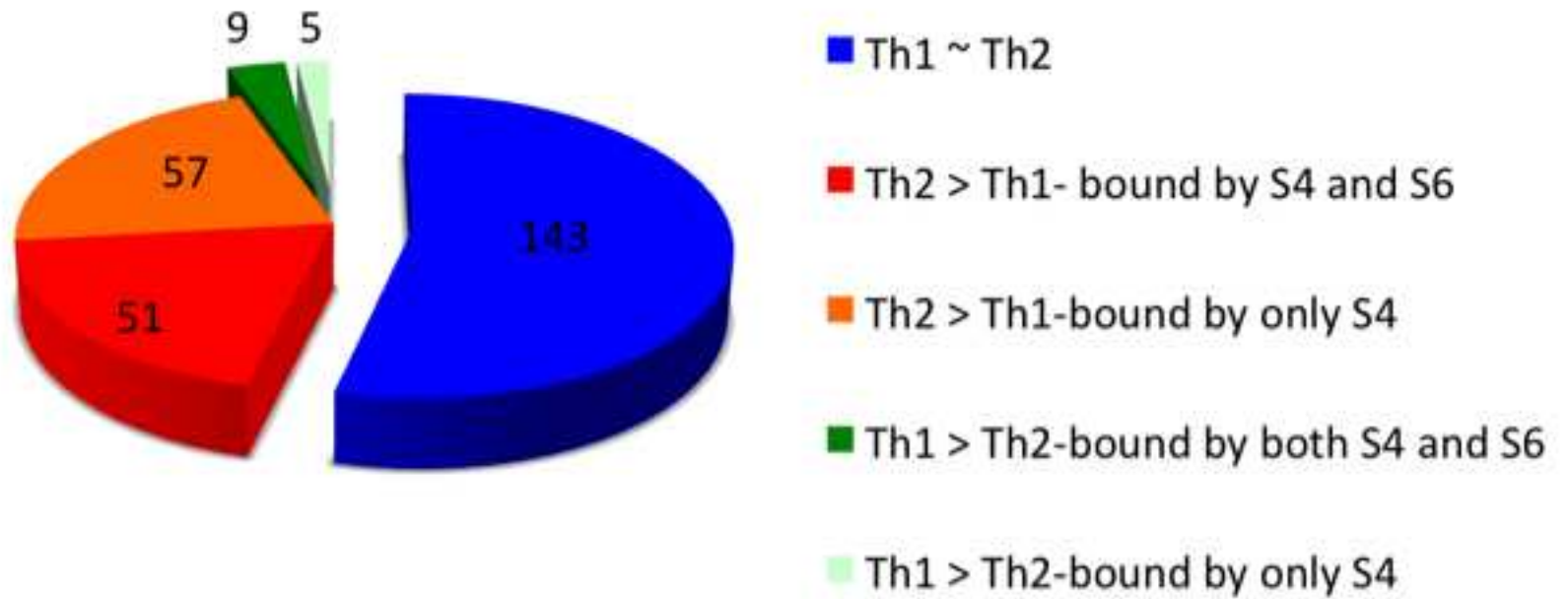


Fig.S5B

STAT6 negatively regulated genes

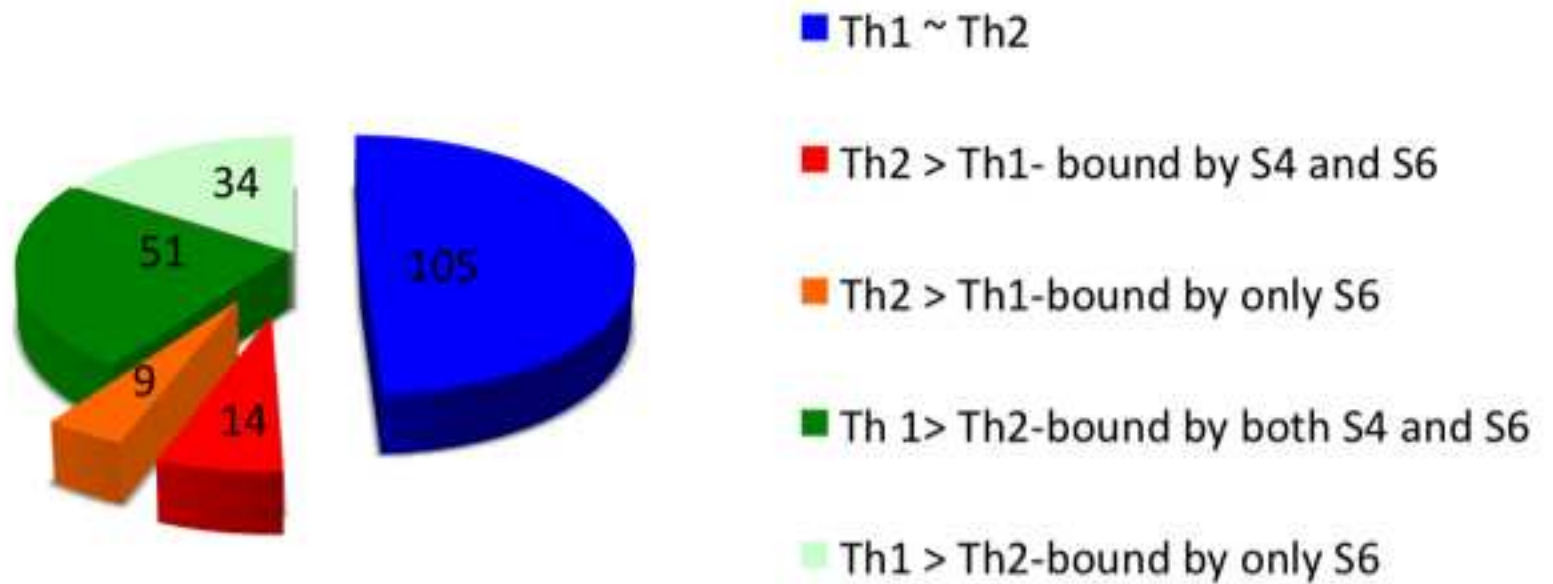


Table S1

| Th1 | STAT4 WT | STAT4 S4KO | H3K4m3 WT | H3K4m3 S4KO | H3K27m3 WT | H3K27m3 S4KO | H3K36m3 WT | H3K36m3 S4KO |
|-------------------------|-------------|---------------|--------------|----------------|---------------|-----------------|---------------|-----------------|
| Total unique tag counts | 8982352 | 7456487 | 6109411 | 5910481 | 11318254 | 11034146 | 6494702 | 6529887 |
| Total peak counts | 10831 | 426 | 28852 | 21353 | 29016 | 21475 | 45784 | 45998 |
| Th2 | STAT6 WT | STAT6 S6KO | H3K4m3 WT | H3K4m3 S6KO | H3K27m3 WT | H3K27m3 S6KO | H3K36m3 WT | H3K36m3 S6KO |
| Total unique tag counts | 7447154 | 8239713 | 10654272 | 10233966 | 11985394 | 12075479 | 10464547 | 8996600 |
| Total peak counts | 8434 | 1002 | 27587 | 28901 | 51057 | 57918 | 49998 | 58197 |

Supplemental Text and Figures

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0 Plekhg2
1 Sorl1
2 Pcx
3 Ebf1
4 Atp13a2
5 Nampt
6 Eif2ak4
7 Tspan3
 8-Sep-07
9 Pknox1
10 Tspan4
11 Tspan5
12 Rybp
13 Ube2d1
14 E130120F12Rik
15 Enthd1
16 Irf8
17 Sos2
18 Sos1
19 Cd5
20 Prph2
21 4930441O14Rik
22 B2m
23 Prm1
24 1500009L16Rik
25 Sult2b1
26 Rhoq
27 Mitf
28 Gpx8
29 Bcl6
30 Sh3gl3
31 Bcl2
32 Map3k11
33 Samd14
34 Orc4l
35 Stk40
36 Unk
37 Kcnj12
38 E2f3
39 Cirbp
40 Ccdc114
41 Tk1
42 Fam78a
43 Uqcrq
44 Gnaq
45 Glg1
46 Akt2
47 Wdr81
48 Wdr82

Table S3

| | | | |
|-----------------------|-----------------------------|-----------------------|-----------------------------|
| mIFN γ forward | AAG GCT CCC TGT GCT GTG C | mIFN γ reverse | GTC TCC CCC TTT TTG CCC T |
| mTbx21 forward | CAC CAT CTC GCT TTC CGC T | mTbx21 reverse | TCC CCC TGG CTG ACT TTT C |
| mLag3 forward | GCA AAC CCA CTG CAG CTA GC | mLag3 reverse | AAG CAG AAG GAC TGG GTC TGG |
| mZbtb33 forward | CTC ACG GAG CCG AGC TCT T | mZbtb33 reverse | CCG TGA CTG CGA AGC ATT TT |
| mSOCS3 forward | GGA GAG ACA GCG GTC GTA AGA | mSOCS3 reverse | TCC GAG GCG GCT CTA ACT C |
| mIL10 forward | AAC CCT AGT TCC CAG AAG CCA | mIL10 reverse | CAG GTG TCT CTG CCT AGC CC |
| mPlcd1 forward | AAC GTC ATG CTC AAG TGC TGA | mPlcd1 reverse | GGG AGA AGA AAG AGG ATG GGA |
| mIL24 forward | GGT CAT GCT TCC CTG GAG AA | mIL24 reverse | ACC CCC CTG TCT AAG AGC AAA |
| mGATA3 forward | TTT AAA CTC GGA GCG CAA ATC | mGATA3 reverse | TGG TGA GGC GGA TAC TGG AT |
| mIL4ra forward | TAA GCC AGC GAT CAG GCA A | mIL4ra reverse | CCC CTC ACC CAG CTC ATT T |
| mIL4 forward | GCA GGC AGA AAG GGA AGA GA | mIL4 reverse | TGG CTG GAG TCT GAC CAT CC |

| Gene | Exp WT | Exp KO | Exp WT/KO | K4WT | K4KO | |
|-------------|------------|------------|------------|------|------|----|
| Rybp | 280.591987 | 264.422292 | 1.06115103 | | 64 | 1 |
| Gpx8 | 37.7252878 | 19.1896966 | 1.96591371 | | 34 | 1 |
| Sh3gl3 | 115.592181 | 64.4223775 | 1.79428617 | | 33 | 1 |
| Gnaq | 174.591559 | 142.422177 | 1.2258734 | | 342 | 1 |
| Akt2 | 532.593127 | 273.422849 | 1.94787352 | | 105 | 1 |
| Unc5c | 22.5216403 | 12.3756294 | 1.81983796 | | 31 | 1 |
| 4833422F24F | 29.2426064 | 35.5742146 | 0.82201692 | | 16 | 1 |
| Clcnkb | 45.6151134 | 52.4245257 | 0.87011018 | | 41 | 1 |
| Col16a1 | 104.592094 | 116.422008 | 0.89838765 | | 34 | 1 |
| Slc17a6 | 91.5920198 | 28.9682374 | 3.16180852 | | 31 | 1 |
| P2rx6 | 71.5921748 | 81.4221832 | 0.87927113 | | 27 | 1 |
| Mybph | 55.5937194 | 44.4419434 | 1.25092908 | | 64 | 1 |
| Gm7367 | 240.592857 | 109.422074 | 2.19875979 | | 273 | 21 |
| Ccl3 | 20330.5271 | 4617.416 | 4.40300963 | | 45 | 1 |
| 4930451C15F | 30.1484097 | 30.8113502 | 0.97848389 | | 27 | 1 |
| Klhl5 | 128.59226 | 248.422149 | 0.51763605 | | 19 | 1 |
| Ano7 | 25.753025 | 63.4223751 | 0.40605583 | | 66 | 1 |
| Calr4 | 114.5918 | 94.4219256 | 1.21361431 | | 17 | 1 |
| Rpph1 | 14.761424 | 19.8994962 | 0.74179888 | | 57 | 1 |
| Bcas1 | 45.6151134 | 57.4227294 | 0.79437383 | | 63 | 1 |
| Zbtb12 | 38.7010284 | 65.4222739 | 0.59155737 | | 41 | 1 |
| Fam54a | 82.5919919 | 126.422549 | 0.65330111 | | 87 | 1 |
| Kremen2 | 3027.60232 | 2779.42358 | 1.08929144 | | 189 | 1 |
| Ngef | 73.5921511 | 73.422483 | 1.00231085 | | 30 | 1 |
| 4930519G04F | 15.8432895 | 13.2991303 | 1.19130267 | | 69 | 1 |
| Lim2 | 119.592242 | 111.421976 | 1.07332724 | | 16 | 1 |
| Hfm1 | 81.5922376 | 30.8113502 | 2.64812275 | | 24 | 1 |
| Epb4.1l2 | 887.590244 | 1119.42333 | 0.79289954 | | 40 | 1 |
| Mcm3 | 445.592148 | 579.421738 | 0.76902905 | | 58 | 1 |
| 2200002D01F | 58.5927395 | 48.4290232 | 1.20986829 | | 18 | 1 |
| Cnn3 | 653.593579 | 310.422646 | 2.1054958 | | 90 | 1 |
| Syt16 | 7.30989154 | 7.54829078 | 0.96841679 | | 22 | 1 |
| Ppp4r1 | 583.593498 | 602.42173 | 0.96874576 | | 76 | 1 |
| Ablim3 | 14.761424 | 12.3756294 | 1.19278168 | | 31 | 1 |
| Lonrf3 | 707.590074 | 656.422099 | 1.0779498 | | 76 | 1 |
| Ralgds | 301.591091 | 350.422111 | 0.86065086 | | 64 | 1 |
| Ltbp2 | 17.0091601 | 13.2991303 | 1.27896785 | | 102 | 1 |
| 6330406I15R | 16.4155365 | 17.835503 | 0.9203854 | | 31 | 1 |
| Hao1 | 25.753025 | 22.9474191 | 1.12226237 | | 39 | 1 |
| Mfrp | 179.59209 | 163.422181 | 1.09894562 | | 20 | 1 |
| Cacna1i | 397.5934 | 175.422501 | 2.26649032 | | 35 | 1 |
| Ttll13 | 61.5923812 | 63.4223751 | 0.97114593 | | 113 | 1 |
| Wwp1 | 441.591931 | 217.422887 | 2.03102782 | | 125 | 1 |
| Zbtb20 | 91.5920198 | 130.422593 | 0.70227111 | | 16 | 1 |
| Prune2 | 57.5929374 | 53.4237744 | 1.07803947 | | 101 | 1 |
| Cwh43 | 20.2977794 | 30.8113502 | 0.65877604 | | 21 | 1 |
| Svop | 36.754271 | 41.4632127 | 0.88643085 | | 85 | 1 |
| Nras | 1123.59002 | 726.419943 | 1.54674996 | | 66 | 1 |
| Spns2 | 70.5918634 | 32.6936829 | 2.1591897 | | 42 | 1 |
| Cxcr6 | 1315.59526 | 170.422263 | 7.7196209 | | 496 | 42 |
| Lrp11 | 30.1484097 | 80.4220942 | 0.3748772 | | 55 | 1 |
| Brpf3 | 123.591867 | 98.4220731 | 1.25573322 | | 80 | 1 |

| Gene | ID | Th1WT | Th1S4KO | Th2WT | Th2S6KO |
|-------------|------------|------------|------------|------------|------------|
| Nuak2 | NM_028778 | 143.591844 | 132.42209 | 33.1126369 | 71.6711203 |
| Sntg1 | NM_027671 | 24.1014828 | 38.5032948 | 18.2762731 | 12.7029353 |
| Bai3 | NM_175642 | 9.24395348 | 9.39888749 | 8.01926493 | 6.19056034 |
| Prim2 | NM_008922 | 73.5921511 | 79.4221769 | 229.59382 | 37.6962733 |
| Als2cr12 | NM_175370 | 77.5922147 | 126.422549 | 28.6481486 | 59.6710807 |
| Obsl1 | NM_178884 | 50.5984049 | 64.4223775 | 106.593821 | 38.6900316 |
| Serpib3b | NM_198680 | 9.24395348 | 21.3829649 | 12.3656828 | 15.6638831 |
| Dpp10 | NM_199021 | 11.5925818 | 17.835503 | 20.1860958 | 11.6908668 |
| Capn8 | NM_130890 | 48.6028834 | 47.431382 | 18.2762731 | 24.2766929 |
| Cd247 | NM_0011133 | 248.592679 | 254.422068 | 234.593625 | 136.670683 |
| Spna1 | NM_011465 | 18.9182928 | 23.7584696 | 17.6796769 | 17.0247298 |
| Cd247 | NM_031162 | 248.592679 | 254.422068 | 234.593625 | 136.670683 |
| A830018L16F | NM_177173 | 11.9904176 | 13.2991303 | 14.9905353 | 18.4840629 |
| Lactb2 | NM_145381 | 176.592468 | 158.422122 | 624.591879 | 375.672057 |
| A830018L16F | NM_0011603 | 176.592468 | 158.422122 | 624.591879 | 375.672057 |
| Cpa6 | NM_177834 | 12.4056034 | 11.1326103 | 13.6010865 | 12.1850478 |
| Efhc1 | NM_027974 | 12.4056034 | 11.1326103 | 13.6010865 | 12.1850478 |
| Khdrbs2 | NM_133235 | 66.5921401 | 90.4225062 | 58.5959887 | 63.6708006 |
| Tmem182 | NM_0010811 | 20.2977794 | 25.4333571 | 23.0096957 | 15.6638831 |
| Fam178b | NM_201365 | 76.5919041 | 83.4222316 | 27.794355 | 26.0891855 |
| 2010300C02F | NM_028096 | 76.5919041 | 83.4222316 | 27.794355 | 26.0891855 |
| Dnahc7b | NM_0011603 | 76.5919041 | 83.4222316 | 27.794355 | 26.0891855 |
| Tpp2 | NM_009418 | 332.592079 | 206.421581 | 184.593763 | 182.670518 |
| Plcl1 | NM_0011146 | 8.19281933 | 16.5699805 | 17.1029111 | 13.2451291 |
| Cd28 | NM_007642 | 3168.60037 | 1135.41973 | 2292.60167 | 1545.67362 |
| Pard3b | NM_0010810 | 108.591698 | 64.4223775 | 59.5954383 | 45.6733277 |
| Erbp4 | NM_010154 | 21.7602013 | 10.3917016 | 7.61550654 | 8.50705629 |
| Spag16 | NM_029160 | 12.8387247 | 25.4333571 | 15.4900511 | 17.742286 |
| Abca12 | NM_175210 | 65.5920927 | 62.4223169 | 25.3251692 | 40.6817546 |
| Dock10 | NM_175291 | 3690.60085 | 4030.43545 | 2982.59009 | 5586.65881 |
| Agfg1 | NM_010472 | 1426.59489 | 1425.41866 | 533.594505 | 910.673441 |
| Armc9 | NM_030184 | 16.4155365 | 15.9705268 | 29.5163004 | 11.2198385 |
| Eif4e2 | NM_023314 | 3430.58762 | 2065.42077 | 2918.59841 | 1901.66842 |
| Armc9 | NM_027456 | 16.4155365 | 15.9705268 | 29.5163004 | 11.2198385 |
| Per2 | NM_011066 | 50.5984049 | 62.4223169 | 139.593698 | 105.671316 |
| Hisppd1 | NM_173760 | 369.592072 | 458.421215 | 256.593355 | 691.669965 |
| Farp2 | NM_145519 | 30.1484097 | 47.431382 | 32.1966794 | 27.9522013 |
| St8sia4 | NM_009183 | 760.592551 | 536.424009 | 2956.59312 | 634.668751 |
| Cntnap5b | NM_172851 | 760.592551 | 536.424009 | 2956.59312 | 634.668751 |
| Ptpn4 | NM_019933 | 122.591913 | 48.4290232 | 118.593407 | 41.678747 |
| R3hdm1 | NM_181750 | 687.592501 | 800.423659 | 1237.59195 | 1669.67315 |
| Nckap5 | NM_176957 | 14.2511852 | 20.6308306 | 24.5353509 | 10.7712965 |
| Ikbke | NM_019777 | 630.590664 | 1862.41646 | 570.593697 | 1412.6712 |
| Nckap5 | NM_172484 | 14.2511852 | 20.6308306 | 24.5353509 | 10.7712965 |
| Kif14 | NM_0010812 | 11.2115202 | 11.5287964 | 14.5095412 | 12.1850478 |
| Adipor1 | NM_028320 | 68.5920753 | 73.422483 | 122.593612 | 110.670738 |
| Nav1 | NM_173437 | 14.2511852 | 73.422483 | 106.593821 | 167.671073 |
| Nek7 | NM_021605 | 1061.58929 | 1629.42813 | 2194.59651 | 1505.67011 |
| Etnk2 | NM_175443 | 165.592096 | 112.421955 | 20.1860958 | 81.6708875 |
| Rabgap1l | NM_013862 | 185.591908 | 121.422334 | 143.593835 | 100.670697 |
| Tnr | NM_022312 | 185.591908 | 121.422334 | 143.593835 | 100.670697 |
| Bat2d | NM_0010812 | 98.59209 | 97.4222907 | 146.593772 | 78.6709991 |