**Supplementary Tables**

**Supplementary Table S1.** Primary antibodies for Western blot, immunohistochemistry and immunofluorescence analysis.

**Supplementary Table S2.** Sequences of primers used in this study.

**Supplementary Table S3.** PanIN 5d ctrl vs 5d NNK (top 100 upregulated).

**Supplementary Table S4.** PanIN 5d ctrl vs 5d NNK (top 100 downregulated genes).

**Supplementary Table S5.** PanIN 50d ctrl vs 50d NNK (top 100 upregulated).

**Supplementary Table S6.** PanIN 50d ctrl vs 50d NNK (top 100 down-regulated genes)**.**

**Supplementary Table S7.** CREB signature genes upregulated by NNK.

**Supplementary Table S8.** Flow cytometry analysis of T cells from PKT mice treated with CREBi.

**Supplementary Table S1.** Primary antibodies for Western blot, immunohistochemistry and immunofluorescence analysis.

|  |  |  |  |
| --- | --- | --- | --- |
| **Primary antibodies** | **Supplier** | **Species** | **Catalog Number** |
| Phospho-CREB | Cell signaling  | Rabbit | 9198 |
| Total-CREB | Cell signaling  | Rabbit | 9197 |
| Actin | Cell signaling  | Mouse | 3700 |
| Phospho-Akt | Cell signaling  | Rabbit | 9198 |
| Total Akt | Cell signaling  | Rabbit | 9272 |
| α7nAChR | Abcam | Rabbit | ab10096 |
| CSF2Rα | Santa Cruz | Rabbit | sc-25472 |
| Ki67 | Abcam | Rabbit | ab15580 |
| Claudin 18 | Invitrogen  | Rabbit | 700178 |
| Cytokeratin 19 | R&Dabcam | MouseRabbit | MAB3506ab133496 |
| αSMA | Abcam | Rabbit | ab32575 |

**Supplementary Table S2.** Sequences of primers used in this study.

|  |  |
| --- | --- |
| **Primers** | **Sequence (5' to 3')** |
| CREB1 (h) | ATACATATCTAGCAAAAAGGTCACG |
|  | ACTAGTGAAAGGAGAGAGATATGGC |
| EGR1 (h) | GGTCAGTGGCCTAGTGAGC |
|  | GTGCCGCTGAGTAAATGGGA |
| FOS (h) | CACTCCAAGCGGAGACAGAC |
|  | AGGTCATCAGGGATCTTGCAG |
| CSF2 (h) | TCCTGAACCTGAGTAGAGACAC |
|  | TGCTGCTTGTAGTGGCTGG |
| CREB1 (m) | ACCCAGGGAGGAGCAATACAG |
|  | TGGGGAGGACGCCATAACA |
| EGR1 (m) | TCGGCTCCTTTCCTCACTCA |
|  | CTCATAGGGTTGTTCGCTCGG |
| FOS (m) | CGGGTTTCAACGCCGACTA |
|  | TGGCACTAGAGACGGACAGAT |
| CDH5 (m) | CACTGCTTTGGGAGCCTTC |
|  | GGGGCAGCGATTCATTTTTCT |
| CSF2 (m) | GGCCTTGGAAGCATGTAGAGG |
|  | GGAGAACTCGTTAGAGACGACTT |
| PRKG1 (m) | ATCCGAGAGGTCGAAGGATCT |
|  | ATTCCACGGGGTACATACAGT |
| SOWAHC (m) | GCGGGACACTCGGAATTGG |
|  | GGCATTGACCAGTTCCTTGAAG |

(h=human; m=mouse)

**Supplementary Table S3.** PanIN 5d ctrl vs 5d NNK (top 100 upregulated).

|  |  |  |
| --- | --- | --- |
| **gene\_id** | **gene** | **log2(fold\_change)** |
| ENSMUSG00000067161 | Gm5560 | 4.31597 |
| ENSMUSG00000030523 | Trpm1 | 4.18878 |
| ENSMUSG00000097289 | 2010300F17Rik | 3.74605 |
| ENSMUSG00000028782 | Bai2 | 3.13377 |
| ENSMUSG00000040152 | Thbs1 | 2.76103 |
| ENSMUSG00000057722 | Lepr | 2.68274 |
| ENSMUSG00000074766 | Ism1 | 2.60785 |
| ENSMUSG00000031972 | Acta1 | 2.51045 |
| ENSMUSG00000075302 | Erich2 | 2.47847 |
| ENSMUSG00000026420 | Il24 | 2.39673 |
| ENSMUSG00000028195 | Cyr61 | 2.33191 |
| ENSMUSG00000027843 | Ptpn22 | 2.26506 |
| ENSMUSG00000026069 | Il1rl1 | 2.20708 |
| ENSMUSG00000050538 | B230217C12Rik | 2.20385 |
| ENSMUSG00000039376 | Synpo2l | 2.19751 |
| ENSMUSG00000026580 | Selp | 2.15746 |
| ENSMUSG00000026628 | Atf3 | 2.14452 |
| ENSMUSG00000025586 | Cpeb1 | 2.12654 |
| ENSMUSG00000038587 | Akap12 | 2.08336 |
| ENSMUSG00000047562 | Mmp10 | 2.05599 |
| ENSMUSG00000021367 | Edn1 | 2.03245 |
| ENSMUSG00000032487 | Ptgs2 | 1.99902 |
| ENSMUSG00000029019 | Nppb | 1.96955 |
| ENSMUSG00000037411 | Serpine1 | 1.9193 |
| ENSMUSG00000063767 | S100a7a | 1.85333 |
| ENSMUSG00000004791 | Pgf | 1.81302 |
| ENSMUSG00000032315 | Cyp1a1 | 1.76451 |
| ENSMUSG00000091243 | Vgll3 | 1.72686 |
| ENSMUSG00000031880 | Rrad | 1.72482 |
| ENSMUSG00000047428 | Dlk2 | 1.7217 |
| ENSMUSG00000044165 | Bcl2l15 | 1.71002 |
| ENSMUSG00000026177 | Slc11a1 | 1.69367 |
| ENSMUSG00000024803 | Ankrd1 | 1.68139 |
| ENSMUSG00000024512 | Dynap | 1.6688 |
| ENSMUSG00000090362 | Vmn2r79 | 1.64234 |
| ENSMUSG00000030093 | Wnt7a | 1.56286 |
| ENSMUSG00000066749 | Olfr877 | 1.51768 |
| ENSMUSG00000041911 | Dlx1 | 1.51198 |
| ENSMUSG00000032827 | Ppp1r9a | 1.50822 |
| ENSMUSG00000063975 | Slco1a5 | 1.496 |
| ENSMUSG00000070371 | Prss36 | 1.41734 |
| ENSMUSG00000046318 | Ccbe1 | 1.40489 |
| ENSMUSG00000054855 | Rnd1 | 1.39788 |
| ENSMUSG00000071552 | Tigit | 1.39723 |
| ENSMUSG00000029372 | Ppbp | 1.39594 |
| ENSMUSG00000086727 | 4931428L18Rik | 1.37471 |
| ENSMUSG00000062345 | Serpinb2 | 1.35565 |
| ENSMUSG00000019737 | Syne4 | 1.34099 |
| ENSMUSG00000050578 | Mmp13 | 1.33498 |
| ENSMUSG00000034159 | 2310007B03Rik | 1.33277 |
| ENSMUSG00000025921 | Rdh10 | 1.32664 |
| ENSMUSG00000003545 | Fosb | 1.32075 |
| ENSMUSG00000076867 | Trdv4 | 1.31245 |
| ENSMUSG00000013091 | Tmem190 | 1.30104 |
| ENSMUSG00000062991 | Nrg1 | 1.29766 |
| ENSMUSG00000015312 | Gadd45b | 1.29586 |
| ENSMUSG00000068699 | Flnc | 1.29376 |
| ENSMUSG00000097636 | 5830416P10Rik | 1.28046 |
| ENSMUSG00000045545 | Krt14 | 1.25684 |
| ENSMUSG00000032380 | Dapk2 | 1.24482 |
| ENSMUSG00000022799 | Arhgap31 | 1.23704 |
| ENSMUSG00000000627 | Sema4f | 1.22392 |
| ENSMUSG00000032327 | Stra6 | 1.2195 |
| ENSMUSG00000026971 | Itgb6 | 1.21686 |
| ENSMUSG00000055333 | Fat2 | 1.21598 |
| ENSMUSG00000053062 | Jam2 | 1.18673 |
| ENSMUSG00000086779 | Gm13562 | 1.15505 |
| ENSMUSG00000021403 | Serpinb9b | 1.14512 |
| ENSMUSG00000086742 | Gm16201 | 1.12841 |
| ENSMUSG00000021509 | Slc25a48 | 1.11619 |
| ENSMUSG00000002343 | Armc6 | 1.11048 |
| ENSMUSG00000022487 | Gtsf1 | 1.10706 |
| ENSMUSG00000034855 | Cxcl10 | 1.10387 |
| ENSMUSG00000027611 | Procr | 1.09866 |
| ENSMUSG00000040729 | AK129341 | 1.08698 |
| ENSMUSG00000037887 | Dusp8 | 1.08616 |
| ENSMUSG00000002664 | Pspn | 1.08412 |
| ENSMUSG00000090582 | Gm17024 | 1.07923 |
| ENSMUSG00000026166 | Ccl20 | 1.07706 |
| ENSMUSG00000026923 | Notch1 | 1.0662 |
| ENSMUSG00000052485 | Tmem171 | 1.04322 |
| ENSMUSG00000052085 | Dock8 | 1.03656 |
| ENSMUSG00000097928 | Gm26578 | 1.0282 |
| ENSMUSG00000047528 | Als2cr12 | 1.02221 |
| ENSMUSG00000022790 | Igsf11 | 1.02045 |
| ENSMUSG00000001864 | Aif1l | 1.01982 |
| ENSMUSG00000087366 | BC042782 | 1.01885 |
| ENSMUSG00000082593 | Gm11331 | 1.01846 |
| ENSMUSG00000029641 | Rasl11a | 1.00857 |
| ENSMUSG00000050064 | Zfp697 | 1.00416 |
| ENSMUSG00000054555 | Adam12 | 1.00297 |
| ENSMUSG00000027612 | Mmp24 | 1.00033 |
| ENSMUSG00000020469 | Myl7 | 0.99941 |
| ENSMUSG00000032531 | Amotl2 | 0.997574 |
| ENSMUSG00000046259 | Sprr2h | 0.993482 |
| ENSMUSG00000041062 | Mslnl | 0.98668 |
| ENSMUSG00000015451 | C4a | 0.984459 |
| ENSMUSG00000024190 | Dusp1 | 0.984045 |
| ENSMUSG00000021927 | Gm5803 | 0.978127 |

**Supplementary Table S4.** PanIN 5d ctrl vs 5d NNK (top 100 downregulated genes).

|  |  |  |
| --- | --- | --- |
| **gene\_id** | **gene** | **log2(fold\_change)** |
| ENSMUSG00000067161 | Gm5560 | -4.20257 |
| ENSMUSG00000030523 | Trpm1 | -3.99189 |
| ENSMUSG00000097289 | 2010300F17Rik | -3.12967 |
| ENSMUSG00000028782 | Bai2 | -3.04404 |
| ENSMUSG00000040152 | Thbs1 | -2.97547 |
| ENSMUSG00000057722 | Lepr | -2.93546 |
| ENSMUSG00000074766 | Ism1 | -2.88039 |
| ENSMUSG00000031972 | Acta1 | -2.80399 |
| ENSMUSG00000075302 | Erich2 | -2.79395 |
| ENSMUSG00000026420 | Il24 | -2.77916 |
| ENSMUSG00000028195 | Cyr61 | -2.70927 |
| ENSMUSG00000027843 | Ptpn22 | -2.63214 |
| ENSMUSG00000026069 | Il1rl1 | -2.61264 |
| ENSMUSG00000050538 | B230217C12Rik | -2.61028 |
| ENSMUSG00000039376 | Synpo2l | -2.578 |
| ENSMUSG00000026580 | Selp | -2.57579 |
| ENSMUSG00000026628 | Atf3 | -2.55756 |
| ENSMUSG00000025586 | Cpeb1 | -2.4704 |
| ENSMUSG00000038587 | Akap12 | -2.45608 |
| ENSMUSG00000047562 | Mmp10 | -2.45131 |
| ENSMUSG00000021367 | Edn1 | -2.44939 |
| ENSMUSG00000032487 | Ptgs2 | -2.44822 |
| ENSMUSG00000029019 | Nppb | -2.40336 |
| ENSMUSG00000037411 | Serpine1 | -2.38241 |
| ENSMUSG00000063767 | S100a7a | -2.37684 |
| ENSMUSG00000004791 | Pgf | -2.37527 |
| ENSMUSG00000032315 | Cyp1a1 | -2.36687 |
| ENSMUSG00000091243 | Vgll3 | -2.36246 |
| ENSMUSG00000031880 | Rrad | -2.34535 |
| ENSMUSG00000047428 | Dlk2 | -2.34102 |
| ENSMUSG00000044165 | Bcl2l15 | -2.3342 |
| ENSMUSG00000026177 | Slc11a1 | -2.28911 |
| ENSMUSG00000024803 | Ankrd1 | -2.26322 |
| ENSMUSG00000024512 | Dynap | -2.25381 |
| ENSMUSG00000090362 | Vmn2r79 | -2.23116 |
| ENSMUSG00000030093 | Wnt7a | -2.22993 |
| ENSMUSG00000066749 | Olfr877 | -2.21363 |
| ENSMUSG00000041911 | Dlx1 | -2.15172 |
| ENSMUSG00000032827 | Ppp1r9a | -2.14801 |
| ENSMUSG00000063975 | Slco1a5 | -2.1439 |
| ENSMUSG00000070371 | Prss36 | -2.12249 |
| ENSMUSG00000046318 | Ccbe1 | -2.10817 |
| ENSMUSG00000054855 | Rnd1 | -2.10609 |
| ENSMUSG00000071552 | Tigit | -2.09887 |
| ENSMUSG00000029372 | Ppbp | -2.09529 |
| ENSMUSG00000086727 | 4931428L18Rik | -2.09175 |
| ENSMUSG00000062345 | Serpinb2 | -2.08991 |
| ENSMUSG00000019737 | Syne4 | -2.08844 |
| ENSMUSG00000050578 | Mmp13 | -2.04255 |
| ENSMUSG00000034159 | 2310007B03Rik | -2.03786 |
| ENSMUSG00000025921 | Rdh10 | -2.03525 |
| ENSMUSG00000003545 | Fosb | -2.0294 |
| ENSMUSG00000076867 | Trdv4 | -2.0292 |
| ENSMUSG00000013091 | Tmem190 | -2.01684 |
| ENSMUSG00000062991 | Nrg1 | -2.01496 |
| ENSMUSG00000015312 | Gadd45b | -2.00143 |
| ENSMUSG00000068699 | Flnc | -1.99093 |
| ENSMUSG00000097636 | 5830416P10Rik | -1.98229 |
| ENSMUSG00000045545 | Krt14 | -1.9506 |
| ENSMUSG00000032380 | Dapk2 | -1.94558 |
| ENSMUSG00000022799 | Arhgap31 | -1.94553 |
| ENSMUSG00000000627 | Sema4f | -1.94051 |
| ENSMUSG00000032327 | Stra6 | -1.93955 |
| ENSMUSG00000026971 | Itgb6 | -1.93562 |
| ENSMUSG00000055333 | Fat2 | -1.91556 |
| ENSMUSG00000053062 | Jam2 | -1.90103 |
| ENSMUSG00000086779 | Gm13562 | -1.89468 |
| ENSMUSG00000021403 | Serpinb9b | -1.8906 |
| ENSMUSG00000086742 | Gm16201 | -1.86335 |
| ENSMUSG00000021509 | Slc25a48 | -1.8396 |
| ENSMUSG00000002343 | Armc6 | -1.8352 |
| ENSMUSG00000022487 | Gtsf1 | -1.82956 |
| ENSMUSG00000034855 | Cxcl10 | -1.82888 |
| ENSMUSG00000027611 | Procr | -1.80356 |
| ENSMUSG00000040729 | AK129341 | -1.79676 |
| ENSMUSG00000037887 | Dusp8 | -1.79212 |
| ENSMUSG00000002664 | Pspn | -1.77858 |
| ENSMUSG00000090582 | Gm17024 | -1.76586 |
| ENSMUSG00000026166 | Ccl20 | -1.76265 |
| ENSMUSG00000026923 | Notch1 | -1.75814 |
| ENSMUSG00000052485 | Tmem171 | -1.7546 |
| ENSMUSG00000052085 | Dock8 | -1.75375 |
| ENSMUSG00000097928 | Gm26578 | -1.739 |
| ENSMUSG00000047528 | Als2cr12 | -1.72134 |
| ENSMUSG00000022790 | Igsf11 | -1.71978 |
| ENSMUSG00000001864 | Aif1l | -1.71759 |
| ENSMUSG00000087366 | BC042782 | -1.71449 |
| ENSMUSG00000082593 | Gm11331 | -1.69035 |
| ENSMUSG00000029641 | Rasl11a | -1.68358 |
| ENSMUSG00000050064 | Zfp697 | -1.68135 |
| ENSMUSG00000054555 | Adam12 | -1.66709 |
| ENSMUSG00000027612 | Mmp24 | -1.65847 |
| ENSMUSG00000020469 | Myl7 | -1.65372 |
| ENSMUSG00000032531 | Amotl2 | -1.65034 |
| ENSMUSG00000046259 | Sprr2h | -1.64559 |
| ENSMUSG00000041062 | Mslnl | -1.64507 |
| ENSMUSG00000015451 | C4a | -1.63866 |
| ENSMUSG00000024190 | Dusp1 | -1.63765 |
| ENSMUSG00000021927 | Gm5803 | -1.63617 |

**Supplementary Table S5.** PanIN 50d ctrl vs 50d NNK (top 100 upregulated).

|  |  |  |
| --- | --- | --- |
| **gene\_id** | **gene** | **log2(fold\_change)** |
| ENSMUSG00000031980 | Agt | 5.84648 |
| ENSMUSG00000038418 | Egr1 | 5.65947 |
| ENSMUSG00000031871 | Cdh5 | 5.10432 |
| ENSMUSG00000024593 | Megf10 | 4.94245 |
| ENSMUSG00000047562 | Mmp10 | 4.85996 |
| ENSMUSG00000032511 | Scn5a | 4.81451 |
| ENSMUSG00000048332 | Lhfp | 4.59316 |
| ENSMUSG00000026674 | Ddr2 | 4.43021 |
| ENSMUSG00000037161 | Mgarp | 4.37723 |
| ENSMUSG00000019880 | Rspo3 | 4.28207 |
| ENSMUSG00000043613 | Mmp3 | 4.04492 |
| ENSMUSG00000024302 | Dtna | 3.96203 |
| ENSMUSG00000032271 | Nnmt | 3.94801 |
| ENSMUSG00000026475 | Rgs16 | 3.91579 |
| ENSMUSG00000027313 | Chac1 | 3.75222 |
| ENSMUSG00000048489 | 8430408G22Rik | 3.68108 |
| ENSMUSG00000030220 | Arhgdib | 3.63125 |
| ENSMUSG00000012428 | Steap4 | 3.6306 |
| ENSMUSG00000089672 | Gp49a | 3.59741 |
| ENSMUSG00000043289 | Mei4 | 3.55331 |
| ENSMUSG00000021250 | Fos | 3.49151 |
| ENSMUSG00000032715 | Trib3 | 3.48489 |
| ENSMUSG00000021596 | Mctp1 | 3.44411 |
| ENSMUSG00000040026 | Saa3 | 3.37847 |
| ENSMUSG00000029919 | Hpgds | 3.34882 |
| ENSMUSG00000039936 | Pik3cd | 3.27968 |
| ENSMUSG00000027833 | Shox2 | 3.26776 |
| ENSMUSG00000035385 | Ccl2 | 3.13829 |
| ENSMUSG00000026628 | Atf3 | 3.13752 |
| ENSMUSG00000021070 | Bdkrb2 | 3.11729 |
| ENSMUSG00000004791 | Pgf | 3.10962 |
| ENSMUSG00000028195 | Cyr61 | 3.10544 |
| ENSMUSG00000082082 | Gm13230 | 3.10245 |
| ENSMUSG00000032940 | Rbm11 | 3.09557 |
| ENSMUSG00000019843 | Fyn | 3.09174 |
| ENSMUSG00000025140 | Pycr1 | 3.05525 |
| ENSMUSG00000017390 | Aldoc | 3.01999 |
| ENSMUSG00000032363 | Adamts7 | 3.01773 |
| ENSMUSG00000024084 | Qpct | 2.99985 |
| ENSMUSG00000024232 | Bambi | 2.96729 |
| ENSMUSG00000049709 | Nlrp10 | 2.96546 |
| ENSMUSG00000003545 | Fosb | 2.94673 |
| ENSMUSG00000036390 | Gadd45a | 2.94085 |
| ENSMUSG00000042834 | Nrep | 2.92937 |
| ENSMUSG00000028167 | Bdh2 | 2.89812 |
| ENSMUSG00000028525 | Pde4b | 2.89373 |
| ENSMUSG00000038067 | Csf3 | 2.86537 |
| ENSMUSG00000087231 | E230016M11Rik | 2.86498 |
| ENSMUSG00000044461 | Shisa2 | 2.83943 |
| ENSMUSG00000028179 | Cth | 2.82803 |
| ENSMUSG00000028545 | Bend5 | 2.82721 |
| ENSMUSG00000038539 | Atf5 | 2.822 |
| ENSMUSG00000020034 | Tcp11l2 | 2.80956 |
| ENSMUSG00000029375 | Cxcl15 | 2.7917 |
| ENSMUSG00000057604 | Lmcd1 | 2.75971 |
| ENSMUSG00000025888 | Casp1 | 2.67875 |
| ENSMUSG00000040152 | Thbs1 | 2.66748 |
| ENSMUSG00000041261 | Car8 | 2.64013 |
| ENSMUSG00000085135 | Gm13713 | 2.63007 |
| ENSMUSG00000038587 | Akap12 | 2.62642 |
| ENSMUSG00000038521 | C1s | 2.59245 |
| ENSMUSG00000065999 | Gm13154 | 2.57164 |
| ENSMUSG00000004371 | Il11 | 2.57096 |
| ENSMUSG00000085585 | Gm12223 | 2.56628 |
| ENSMUSG00000022055 | Nefl | 2.5554 |
| ENSMUSG00000024190 | Dusp1 | 2.54658 |
| ENSMUSG00000029752 | Asns | 2.5376 |
| ENSMUSG00000023809 | Rps6ka2 | 2.52666 |
| ENSMUSG00000089961 | Gm16567 | 2.49707 |
| ENSMUSG00000048572 | Tmem252 | 2.46198 |
| ENSMUSG00000073490 | AI607873 | 2.44551 |
| ENSMUSG00000052684 | Jun | 2.44106 |
| ENSMUSG00000028716 | Pdzk1ip1 | 2.43446 |
| ENSMUSG00000020057 | Dram1 | 2.40807 |
| ENSMUSG00000050288 | Fzd2 | 2.39218 |
| ENSMUSG00000026249 | Serpine2 | 2.38793 |
| ENSMUSG00000029092 | 4930435H24Rik | 2.37332 |
| ENSMUSG00000020826 | Nos2 | 2.36566 |
| ENSMUSG00000031125 | 3830403N18Rik | 2.35972 |
| ENSMUSG00000024678 | Ms4a4d | 2.35674 |
| ENSMUSG00000085101 | Gm13227 | 2.35515 |
| ENSMUSG00000020774 | Aspa | 2.35438 |
| ENSMUSG00000063975 | Slco1a5 | 2.3502 |
| ENSMUSG00000038742 | Angptl6 | 2.341 |
| ENSMUSG00000087366 | BC042782 | 2.32677 |
| ENSMUSG00000026193 | Fn1 | 2.31493 |
| ENSMUSG00000056671 | Prelid2 | 2.30325 |
| ENSMUSG00000071324 | Armc2 | 2.30299 |
| ENSMUSG00000046169 | Adamts6 | 2.29672 |
| ENSMUSG00000058656 | Samd12 | 2.2966 |
| ENSMUSG00000028654 | Mycl | 2.2946 |
| ENSMUSG00000037887 | Dusp8 | 2.28225 |
| ENSMUSG00000028132 | Tmem56 | 2.26326 |
| ENSMUSG00000022236 | Ropn1l | 2.25615 |
| ENSMUSG00000054568 | Usp17la | 2.25364 |
| ENSMUSG00000031506 | Ptpn7 | 2.2528 |
| ENSMUSG00000040852 | Plekhh2 | 2.24583 |
| ENSMUSG00000040618 | Pck2 | 2.24428 |
| ENSMUSG00000025089 | Gfra1 | 2.23011 |

**Supplementary Table S6.** PanIN 50d ctrl vs 50d NNK (top 100 down-regulated genes).

|  |  |  |
| --- | --- | --- |
| **gene\_id** | **gene** | **log2(fold\_change)** |
| ENSMUSG00000031980 | Agt | -6.07577 |
| ENSMUSG00000038418 | Egr1 | -5.02635 |
| ENSMUSG00000031871 | Cdh5 | -4.38698 |
| ENSMUSG00000024593 | Megf10 | -4.16987 |
| ENSMUSG00000047562 | Mmp10 | -3.82788 |
| ENSMUSG00000032511 | Scn5a | -3.75368 |
| ENSMUSG00000048332 | Lhfp | -3.64021 |
| ENSMUSG00000026674 | Ddr2 | -3.53746 |
| ENSMUSG00000037161 | Mgarp | -3.52275 |
| ENSMUSG00000019880 | Rspo3 | -3.38919 |
| ENSMUSG00000043613 | Mmp3 | -3.2199 |
| ENSMUSG00000024302 | Dtna | -3.21776 |
| ENSMUSG00000032271 | Nnmt | -3.19034 |
| ENSMUSG00000026475 | Rgs16 | -3.18819 |
| ENSMUSG00000027313 | Chac1 | -3.17135 |
| ENSMUSG00000048489 | 8430408G22Rik | -3.15095 |
| ENSMUSG00000030220 | Arhgdib | -3.13101 |
| ENSMUSG00000012428 | Steap4 | -3.08341 |
| ENSMUSG00000089672 | Gp49a | -3.03436 |
| ENSMUSG00000043289 | Mei4 | -2.95282 |
| ENSMUSG00000021250 | Fos | -2.94208 |
| ENSMUSG00000032715 | Trib3 | -2.92811 |
| ENSMUSG00000021596 | Mctp1 | -2.92306 |
| ENSMUSG00000040026 | Saa3 | -2.89427 |
| ENSMUSG00000029919 | Hpgds | -2.88455 |
| ENSMUSG00000039936 | Pik3cd | -2.88219 |
| ENSMUSG00000027833 | Shox2 | -2.85545 |
| ENSMUSG00000035385 | Ccl2 | -2.84911 |
| ENSMUSG00000026628 | Atf3 | -2.82484 |
| ENSMUSG00000021070 | Bdkrb2 | -2.76641 |
| ENSMUSG00000004791 | Pgf | -2.69433 |
| ENSMUSG00000028195 | Cyr61 | -2.69062 |
| ENSMUSG00000082082 | Gm13230 | -2.67838 |
| ENSMUSG00000032940 | Rbm11 | -2.66246 |
| ENSMUSG00000019843 | Fyn | -2.6619 |
| ENSMUSG00000025140 | Pycr1 | -2.53316 |
| ENSMUSG00000017390 | Aldoc | -2.4898 |
| ENSMUSG00000032363 | Adamts7 | -2.44318 |
| ENSMUSG00000024084 | Qpct | -2.42948 |
| ENSMUSG00000024232 | Bambi | -2.41568 |
| ENSMUSG00000049709 | Nlrp10 | -2.41326 |
| ENSMUSG00000003545 | Fosb | -2.4072 |
| ENSMUSG00000036390 | Gadd45a | -2.40233 |
| ENSMUSG00000042834 | Nrep | -2.39071 |
| ENSMUSG00000028167 | Bdh2 | -2.38351 |
| ENSMUSG00000028525 | Pde4b | -2.36571 |
| ENSMUSG00000038067 | Csf3 | -2.34837 |
| ENSMUSG00000087231 | E230016M11Rik | -2.34594 |
| ENSMUSG00000044461 | Shisa2 | -2.3291 |
| ENSMUSG00000028179 | Cth | -2.32627 |
| ENSMUSG00000028545 | Bend5 | -2.29263 |
| ENSMUSG00000038539 | Atf5 | -2.27635 |
| ENSMUSG00000020034 | Tcp11l2 | -2.27515 |
| ENSMUSG00000029375 | Cxcl15 | -2.27408 |
| ENSMUSG00000057604 | Lmcd1 | -2.26608 |
| ENSMUSG00000025888 | Casp1 | -2.25257 |
| ENSMUSG00000040152 | Thbs1 | -2.23658 |
| ENSMUSG00000041261 | Car8 | -2.22748 |
| ENSMUSG00000085135 | Gm13713 | -2.20708 |
| ENSMUSG00000038587 | Akap12 | -2.20295 |
| ENSMUSG00000038521 | C1s | -2.16964 |
| ENSMUSG00000065999 | Gm13154 | -2.16204 |
| ENSMUSG00000004371 | Il11 | -2.16031 |
| ENSMUSG00000085585 | Gm12223 | -2.15914 |
| ENSMUSG00000022055 | Nefl | -2.15257 |
| ENSMUSG00000024190 | Dusp1 | -2.15081 |
| ENSMUSG00000029752 | Asns | -2.15055 |
| ENSMUSG00000023809 | Rps6ka2 | -2.13153 |
| ENSMUSG00000089961 | Gm16567 | -2.09078 |
| ENSMUSG00000048572 | Tmem252 | -2.08993 |
| ENSMUSG00000073490 | AI607873 | -2.06712 |
| ENSMUSG00000052684 | Jun | -2.0553 |
| ENSMUSG00000028716 | Pdzk1ip1 | -1.99547 |
| ENSMUSG00000020057 | Dram1 | -1.98983 |
| ENSMUSG00000050288 | Fzd2 | -1.98192 |
| ENSMUSG00000026249 | Serpine2 | -1.97213 |
| ENSMUSG00000029092 | 4930435H24Rik | -1.96293 |
| ENSMUSG00000020826 | Nos2 | -1.95695 |
| ENSMUSG00000031125 | 3830403N18Rik | -1.94929 |
| ENSMUSG00000024678 | Ms4a4d | -1.93985 |
| ENSMUSG00000085101 | Gm13227 | -1.93891 |
| ENSMUSG00000020774 | Aspa | -1.93764 |
| ENSMUSG00000063975 | Slco1a5 | -1.91603 |
| ENSMUSG00000038742 | Angptl6 | -1.90471 |
| ENSMUSG00000087366 | BC042782 | -1.90167 |
| ENSMUSG00000026193 | Fn1 | -1.87924 |
| ENSMUSG00000056671 | Prelid2 | -1.87636 |
| ENSMUSG00000071324 | Armc2 | -1.87015 |
| ENSMUSG00000046169 | Adamts6 | -1.86619 |
| ENSMUSG00000058656 | Samd12 | -1.86278 |
| ENSMUSG00000028654 | Mycl | -1.85932 |
| ENSMUSG00000037887 | Dusp8 | -1.85343 |
| ENSMUSG00000028132 | Tmem56 | -1.83941 |
| ENSMUSG00000022236 | Ropn1l | -1.83552 |
| ENSMUSG00000054568 | Usp17la | -1.82744 |
| ENSMUSG00000031506 | Ptpn7 | -1.81892 |
| ENSMUSG00000040852 | Plekhh2 | -1.80378 |
| ENSMUSG00000040618 | Pck2 | -1.80224 |
| ENSMUSG00000025089 | Gfra1 | -1.79321 |

**Supplementary Table S7.** CREB signature genes upregulated by NNK.

|  |  |  |  |
| --- | --- | --- | --- |
| **Gene\_ID** | **Gene Name** | **Gene Title** | **Functional Pathway** |
| ENSMUSG00000057722 | Lepr | Leptin Receptor | Adipocyte metabolism |
| ENSMUSG00000074766 | lsm1 | Sm-like proteins (also known as Lm proteins) | RNA binding |
| ENSMUSG00000028195 | Cyr61 | cysteine-rich angiogenic inducer 61 | Cell migration |
| ENSMUSG00000026628 | Atf3 | activating transcription factor | Transcription corepressor activity |
| ENSMUSG00000047562 | Mmp10 | Stromelysin-2 | Stem cell maintainence and metastasis |
| ENSMUSG00000004791 | Pgf | Placental Growth Factor | Cell cycle regulation |
| ENSMUSG00000031880 | Rrad | Ras-related associated with diabetes | Cell growth and maintainence |
| ENSMUSG00000041911 | Dlx1 | Distal-less homeobox-1 | Transcription regulator pathway |
| ENSMUSG00000029372 | Ppbp | pro-platelet basic protein | Cell growth and maintainence |
| ENSMUSG00000003545 | Fosb | FBJ osteosarcoma oncogene B | Cell cycle regulation |
| ENSMUSG00000062991 | Nrg1 | Neuregulin 1 | Invasion |
| ENSMUSG00000015312 | Gadd45b | Growth arrest and DNA-damage inducible protein 45 beta | DNA damage repair response |
| ENSMUSG00000027611 | Procr | Protein C receptor |  |
| ENSMUSG00000037887 | Dusp8 | dual-specificity phosphatase 8 | Cellular metabolism |
| ENSMUSG00000015451 | C4a | Complement-activation fragment | Cell growth and maintainence |
| ENSMUSG00000024190 | Dusp1 | dual specificity phosphatase 1 | Cell growth and maintainence and cellular metabolism |
| ENSMUSG00000038418 | Egr1 | early growth response protein 1 | Nucleic acid binding and transcription regulator activity |
| ENSMUSG00000031871 | Cdh5 | vascular-endothelial–cadherin or CD144 | Metastasis |
| ENSMUSG00000048332 | Lhfp | lipoma HMGIC fusion partner | DNA binding |
| ENSMUSG00000027833 | Shox2 | short stature homeobox 2 | transcription factor activity |
| ENSMUSG00000028525 | Pde4b | cAMP phosphodiesterase | cAMP-specific phosphodiesterase activity |
| ENSMUSG00000038067 | Csf3 | colony-stimulating factor 3 | Cell growth, maintainence and proliferation |
| ENSMUSG00000004371 | Il11 | Interleukin- 11 | Cell growth, maintainence and proliferation |
| ENSMUSG00000022055 | Nefl | neurofilament light | Cell organization and biogenesis |
| ENSMUSG00000052684 | Jun | canonical target JUN(c-JUN) | RNA polymerase II transcription factor activity |
| ENSMUSG00000050288 | Fzd2 | Frizzled 2 | Cell growth , maintainence, organization and biogenesis |
| ENSMUSG00000026193 | Fn1 | fibronectin 1 | Transcription regulator activity |
| ENSMUSG00000025089 | Gfra1 | glycosylphosphatidylinositol-linked GDNF (glial cell derived neurotrophic factor) receptor α 1 | Cell migration |

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**Supplementary Table S8.** Flow cytometry analysis of T cells from PKT mice treated with CREBi.