**Supplementary Information**

**Tables**

Table S1. Top 50 pathways with gene sets showing evidence of enrichment for higher expression in drug-treated rats compared with vehicle treated control rats. (ES = enrichment score, NES = normalised enrichment score, NOM p-val = nominal p-value, FDR q-val = false discovery rate, FWER p-val = family wise error rate, Max rank = position in the ranked list at which the maximum enrichment score occurred).

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Name of Pathway** | **Size** | **ES** | **NES** | **NOM p-val** | **FDR q-val** | **FWER p-val** | **Max rank** |
| Atp synthesis by chemiosmotic coupling and heat production uncoupling proteins | 73 | -0.619 | -2.532 | <0.001 | <0.001 | <0.001 | 3898 |
| Oxidative phosphorylation | 103 | -0.574 | -2.462 | <0.001 | <0.001 | <0.001 | 3907 |
| Respiratory electron transport | 58 | -0.623 | -2.400 | <0.001 | <0.001 | <0.001 | 4198 |
| TCA cycle and respiratory electron transport | 109 | -0.499 | -2.191 | <0.001 | 0.001 | 0.006 | 4040 |
| Ribosome | 84 | -0.495 | -2.022 | <0.001 | 0.013 | 0.062 | 4201 |
| 3 UTR mediated translational regulation | 100 | -0.468 | -1.996 | <0.001 | 0.014 | 0.093 | 4457 |
| Formation of the ternary complex and subsequently the 43s complex | 46 | -0.540 | -2.000 | <0.001 | 0.015 | 0.089 | 4745 |
| Peptide chain elongation | 82 | -0.465 | -1.944 | <0.001 | 0.020 | 0.177 | 3804 |
| Activation of the mRNA upon binding of the cap binding complex and eIFs and subsequent binding to 43s | 53 | -0.521 | -1.949 | <0.001 | 0.021 | 0.162 | 4745 |
| Pyruvate metabolism | 34 | -0.542 | -1.916 | <0.001 | 0.022 | 0.224 | 2783 |
| Nonsense mediated decay enhanced by the exon junction complex | 97 | -0.445 | -1.905 | <0.001 | 0.022 | 0.246 | 3804 |
| Influenza viral RNA transcription and replication | 96 | -0.459 | -1.918 | <0.001 | 0.023 | 0.220 | 3921 |
| SRP dependent co-translational protein targeting to membrane | 104 | -0.438 | -1.880 | <0.001 | 0.026 | 0.307 | 3804 |
| Cdt1 association with the cdc6 orc origin complex | 53 | -0.489 | -1.847 | 0.003 | 0.032 | 0.404 | 4329 |
| Scf beta trcp mediated degradation of Emi1 | 48 | -0.497 | -1.851 | 0.003 | 0.033 | 0.393 | 4329 |
| Parkinsons disease | 102 | -0.433 | -1.834 | <0.001 | 0.034 | 0.443 | 4198 |
| Translation | 139 | -0.403 | -1.827 | <0.001 | 0.035 | 0.468 | 3804 |
| Apc c cdh1 mediated degradation of cdc20 and other apc c cdh1 targeted proteins in late mitosis early g1 | 62 | -0.457 | -1.799 | <0.001 | 0.041 | 0.555 | 4329 |
| **Name of Pathway** | **Size** | **ES** | **NES** | **NOM p-val** | **FDR q-val** | **FWER p-val** | **Max rank** |
| Vif mediated degradation of Apobec3g | 47 | -0.478 | -1.785 | 0.003 | 0.043 | 0.602 | 4329 |
| Proteasome pathway | 28 | -0.547 | -1.790 | <0.001 | 0.043 | 0.583 | 4778 |
| Influenza life cycle | 125 | -0.391 | -1.765 | <0.001 | 0.044 | 0.674 | 4039 |
| Apc C Cdc20 mediated degradation of mitotic proteins | 62 | -0.458 | -1.768 | <0.001 | 0.045 | 0.663 | 4329 |
| Proteasome | 42 | -0.486 | -1.759 | 0.003 | 0.046 | 0.695 | 4283 |
| Autodegradation of Cdh1 by Cdh1 Apc C | 55 | -0.451 | -1.744 | 0.004 | 0.050 | 0.739 | 4329 |
| Regulation of Ornithine Decarboxylase Odc | 47 | -0.463 | -1.731 | 0.007 | 0.052 | 0.773 | 4329 |
| Mitochondrial protein import | 42 | -0.478 | -1.731 | 0.003 | 0.054 | 0.770 | 3211 |
| Peroxisome | 70 | -0.415 | -1.700 | <0.001 | 0.062 | 0.866 | 3543 |
| Destabilization of mRNA by Auf1 Hnrnp D0 | 47 | -0.457 | -1.691 | 0.003 | 0.063 | 0.881 | 4329 |
| ER phagosome pathway | 52 | -0.443 | -1.694 | 0.003 | 0.063 | 0.874 | 4329 |
| mRNA capping | 25 | -0.532 | -1.701 | 0.014 | 0.065 | 0.866 | 3879 |
| Prefoldin mediated transfer of substrate to Cct Tric | 21 | -0.542 | -1.677 | 0.011 | 0.068 | 0.911 | 5064 |
| Formation of transcription coupled Ner Tc Ner repair complex | 24 | -0.522 | -1.655 | 0.011 | 0.078 | 0.945 | 4893 |
| Formation of the HIV1 early elongation complex | 25 | -0.505 | -1.631 | 0.011 | 0.085 | 0.967 | 3883 |
| Pentose phosphate pathway | 22 | -0.527 | -1.634 | 0.034 | 0.085 | 0.964 | 2444 |
| Huntingtons disease | 145 | -0.358 | -1.638 | <0.001 | 0.086 | 0.964 | 4147 |
| Orc1 removal from chromatin | 64 | -0.414 | -1.618 | 0.007 | 0.091 | 0.976 | 3063 |
| Autodegradation of the E3 Ubiquitin Ligase Cop1 | 46 | -0.433 | -1.614 | 0.010 | 0.091 | 0.980 | 4329 |
| Tryptophan metabolism | 30 | -0.482 | -1.600 | 0.012 | 0.099 | 0.988 | 1187 |
| Regulation of mitotic cell cycle | 74 | -0.385 | -1.574 | <0.001 | 0.114 | 0.996 | 3063 |
| Signaling by Wnt | 58 | -0.405 | -1.575 | 0.003 | 0.116 | 0.996 | 4698 |
| Cytosolic tRNA aminoacylation | 24 | -0.483 | -1.566 | 0.032 | 0.117 | 0.996 | 4570 |
| Scfskp2 mediated degradation of P27 P21 | 53 | -0.408 | -1.561 | 0.010 | 0.119 | 0.998 | 4396 |
| Cholesterol biosynthesis | 18 | -0.523 | -1.551 | 0.037 | 0.124 | 0.998 | 2958 |
| **Name of Pathway** | **Size** | **ES** | **NES** | **NOM p-val** | **FDR q-val** | **FWER p-val** | **Max rank** |
| Formation of tubulin folding intermediates by Cct Tric | 17 | -0.529 | -1.547 | 0.045 | 0.125 | 0.998 | 5064 |
| Cdk mediated phosphorylation and removal of Cdc6 | 45 | -0.417 | -1.536 | 0.016 | 0.132 | 0.999 | 4329 |
| Host interactions of HIV factors | 107 | -0.350 | -1.526 | 0.004 | 0.134 | 1.000 | 4651 |
| Abortive elongation of HIV1 transcript in the absence of Tat | 17 | -0.526 | -1.522 | 0.034 | 0.135 | 1.000 | 3883 |
| HIV infection | 168 | -0.328 | -1.517 | <0.001 | 0.137 | 1.000 | 4651 |

Table S2. Top 50 pathways with gene sets showing evidence of enrichment for lower expression in drug-treated rats compared with vehicle treated control rats. (ES = enrichment score, NES = normalised enrichment score, NOM p-val = nominal p-value, FDR q-val = false discovery rate, FWER p-val = family wise error rate, Max rank = position in the ranked list at which the maximum enrichment score occurred).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Name of Pathway** | **Size** | | **ES** | | **NES** | | **NOM p-val** | | **FDR q-val** | | **FWER p-val** | | **Max rank** | |
| Collagen formation | 37 | | 0.675 | | 2.138 | | <0.001 | | 0.001 | | 0.001 | | 2259 | |
| Integrin cell surface interactions | 58 | | 0.605 | | 2.058 | | <0.001 | | 0.008 | | 0.015 | | 1889 | |
| Pathways in cancer | 273 | | 0.482 | | 2.024 | | <0.001 | | 0.008 | | 0.024 | | 3076 | |
| Cell junction organization | 60 | | 0.581 | | 2.004 | | <0.001 | | 0.008 | | 0.031 | | 3510 | |
| Hedgehog signalling pathway | 48 | | 0.606 | | 2.003 | | <0.001 | | 0.006 | | 0.031 | | 1802 | |
| Focal adhesion | 164 | | 0.502 | | 1.995 | | <0.001 | | 0.005 | | 0.032 | | 3131 | |
| Alk pathway | 31 | | 0.650 | | 1.987 | | <0.001 | | 0.005 | | 0.035 | | 3076 | |
| Basal cell carcinoma | 49 | | 0.594 | | 1.977 | | <0.001 | | 0.006 | | 0.045 | | 1802 | |
| Extracellular matrix organization | 54 | | 0.576 | | 1.971 | | <0.001 | | 0.006 | | 0.049 | | 2259 | |
| Nitric oxide stimulates guanylate cyclase | 21 | | 0.703 | | 1.960 | | <0.001 | | 0.006 | | 0.062 | | 2124 | |
| Smooth muscle contraction | 21 | | 0.702 | | 1.958 | | <0.001 | | 0.006 | | 0.063 | | 1841 | |
| Mcalpain pathway | 24 | | 0.645 | | 1.881 | | <0.001 | | 0.018 | | 0.195 | | 2326 | |
| Immunoregulatory interactions between a lymphoid and a non-lymphoid cell | 31 | | 0.610 | | 1.870 | | <0.001 | | 0.019 | | 0.223 | | 2048 | |
| Vascular smooth muscle contraction | 94 | | 0.498 | | 1.835 | | <0.001 | | 0.028 | | 0.330 | | 1967 | |
| ECM receptor interaction | 56 | | 0.538 | | 1.827 | | <0.001 | | 0.029 | | 0.355 | | 2259 | |
| Myosin pathway | 24 | | 0.638 | | 1.820 | | <0.001 | | 0.030 | | 0.388 | | 1860 | |
| Platelet homeostasis | 64 | | 0.512 | | 1.789 | | <0.001 | | 0.043 | | 0.515 | | 2124 | |
| Adherens junction | 62 | | 0.508 | | 1.754 | | <0.001 | | 0.062 | | 0.666 | | 3856 | |
| Cgmp effects | 15 | | 0.679 | | 1.740 | | 0.005 | | 0.069 | | 0.726 | | 2124 | |
| **Name of Pathway** | | **Size** | | **ES** | | **NES** | | **NOM p-val** | | **FDR q-val** | | **FWER**  **p-val** | | **Max rank** | |
| Cell-cell communication | | 97 | | 0.467 | | 1.732 | | 0.001 | | 0.072 | | 0.756 | | 3652 | |
| Drug metabolism cytochrome p450 | | 31 | | 0.576 | | 1.717 | | 0.002 | | 0.081 | | 0.816 | | 1326 | |
| Cell-cell junction organization | | 42 | | 0.523 | | 1.709 | | 0.001 | | 0.085 | | 0.846 | | 3812 | |
| U calpain pathway | | 17 | | 0.645 | | 1.706 | | 0.003 | | 0.085 | | 0.857 | | 2858 | |
| Gap junction | | 77 | | 0.472 | | 1.698 | | 0.001 | | 0.089 | | 0.875 | | 3392 | |
| Tnfr2 pathway | | 16 | | 0.643 | | 1.695 | | 0.005 | | 0.088 | | 0.882 | | 2596 | |
| Muscle contraction | | 40 | | 0.536 | | 1.693 | | 0.001 | | 0.084 | | 0.888 | | 1386 | |
| Melanoma | | 58 | | 0.497 | | 1.682 | | 0.001 | | 0.091 | | 0.912 | | 2184 | |
| Cell surface interactions at the vascular wall | | 71 | | 0.477 | | 1.676 | | <0.001 | | 0.094 | | 0.929 | | 2109 | |
| Keratan sulfate biosynthesis | | 22 | | 0.591 | | 1.669 | | 0.008 | | 0.097 | | 0.939 | | 2106 | |
| Tight junction interactions | | 20 | | 0.596 | | 1.658 | | 0.008 | | 0.106 | | 0.957 | | 3812 | |
| Shh pathway | | 15 | | 0.639 | | 1.650 | | 0.015 | | 0.112 | | 0.973 | | 1747 | |
| Bladder cancer | | 36 | | 0.530 | | 1.645 | | 0.003 | | 0.114 | | 0.978 | | 1842 | |
| Yap1 and wwtr1 taz stimulated gene expression | | 19 | | 0.605 | | 1.643 | | 0.014 | | 0.113 | | 0.981 | | 3162 | |
| Signalling by hippo | | 17 | | 0.621 | | 1.635 | | 0.013 | | 0.118 | | 0.986 | | 2848 | |
| Keratan sulfate keratin metabolism | | 26 | | 0.553 | | 1.625 | | 0.017 | | 0.129 | | 0.991 | | 2106 | |
| Transport of glucose and other sugars bile salts and organic acids metal ions and amine compounds | | 66 | | 0.460 | | 1.617 | | 0.003 | | 0.136 | | 0.994 | | 2468 | |
| Par1 pathway | | 28 | | 0.550 | | 1.615 | | 0.012 | | 0.135 | | 0.994 | | 1860 | |
| Primary immunodeficiency | | 23 | | 0.561 | | 1.613 | | 0.012 | | 0.133 | | 0.995 | | 615 | |
| Small cell lung cancer | | 69 | | 0.456 | | 1.613 | | 0.003 | | 0.130 | | 0.995 | | 2945 | |
| Pancreatic cancer | | 65 | | 0.457 | | 1.612 | | 0.006 | | 0.128 | | 0.995 | | 2007 | |
| Amino acid transport across the plasma membrane | | 27 | | 0.545 | | 1.611 | | 0.027 | | 0.126 | | 0.995 | | 888 | |
| Signalling by fgfr1 mutants | | 19 | | 0.593 | | 1.608 | | 0.029 | | 0.127 | | 0.997 | | 4094 | |
| Calcium signalling pathway | | 155 | | 0.403 | | 1.608 | | 0.001 | | 0.124 | | 0.997 | | 3008 | |
| Glycosaminoglycan metabolism | | 92 | | 0.431 | | 1.599 | | 0.001 | | 0.133 | | 0.998 | | 2106 | |
| Regulation of actin cytoskeleton | | 172 | | 0.398 | | 1.595 | | <0.001 | | 0.134 | | 0.998 | | 3796 | |
| Vegf pathway | | 26 | | 0.550 | | 1.593 | | 0.011 | | 0.134 | | 0.998 | | 4207 | |
| Wnt signalling pathway | | 128 | | 0.409 | | 1.589 | | 0.001 | | 0.137 | | 0.999 | | 3156 | |
| Heparan sulfate heparin hs gag metabolism | | 41 | | 0.491 | | 1.586 | | 0.015 | | 0.138 | | 0.999 | | 3777 | |
| Hemostasis | | 346 | | 0.370 | | 1.582 | | <0.001 | | 0.140 | | 1.000 | | 2131 | |

Table S3. Top 50 pathways with gene sets showing evidence of enrichment for higher expression in drug-treated NT2-N cells compared to vehicle treated control NT2-N cells. (ES = enrichment score, NES = normalised enrichment score, NOM p-val = nominal p-value, FDR q-val = false discovery rate, FWER p-val = family wise error rate, Max rank = position in the ranked list at which the maximum enrichment score occurred).

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Name of Pathway** | **Size** | **ES** | **NES** | **NOM p-val** | **FDR q-val** | **FWER p-val** | **Max rank** |
| Steroid biosynthesis | 17 | -0.85 | -2.10 | <0.001 | <0.001 | <0.001 | 1985 |
| Terpenoid backbone biosynthesis | 12 | -0.86 | -1.97 | <0.001 | 0.004 | 0.009 | 832 |
| Il10 pathway | 16 | -0.75 | -1.86 | <0.001 | 0.022 | 0.072 | 3561 |
| Glycine serine and threonine metabolism | 27 | -0.65 | -1.80 | 0.001 | 0.049 | 0.195 | 1828 |
| Vegf signalling pathway | 66 | -0.55 | -1.76 | <0.001 | 0.070 | 0.317 | 1701 |
| Arachidonic acid metabolism | 44 | -0.58 | -1.75 | 0.002 | 0.075 | 0.391 | 4457 |
| Biosynthesis of unsaturated fatty acids | 22 | -0.64 | -1.70 | 0.004 | 0.134 | 0.629 | 544 |
| Dc pathway | 10 | -0.77 | -1.69 | 0.007 | 0.117 | 0.630 | 3486 |
| Fc epsilon ri signalling pathway | 62 | -0.53 | -1.68 | 0.002 | 0.129 | 0.716 | 2761 |
| Alpha linolenic acid metabolism | 12 | -0.72 | -1.68 | 0.006 | 0.119 | 0.728 | 1701 |
| Tryptophan metabolism | 31 | -0.59 | -1.67 | 0.009 | 0.120 | 0.764 | 2745 |
| Selenoamino acid metabolism | 24 | -0.62 | -1.66 | 0.004 | 0.121 | 0.799 | 3270 |
| Lysosome | 118 | -0.48 | -1.66 | <0.001 | 0.120 | 0.831 | 5293 |
| Long term depression | 63 | -0.52 | -1.64 | 0.002 | 0.129 | 0.876 | 2900 |
| Calcium signalling pathway | 160 | -0.47 | -1.63 | <0.001 | 0.142 | 0.902 | 3224 |
| Glutathione metabolism | 42 | -0.54 | -1.62 | 0.005 | 0.149 | 0.926 | 4881 |
| Arginine and proline metabolism | 51 | -0.52 | -1.62 | 0.003 | 0.141 | 0.926 | 5091 |
| Vascular smooth muscle contraction | 105 | -0.47 | -1.60 | 0.001 | 0.157 | 0.954 | 2505 |
| Nk cells pathway | 17 | -0.63 | -1.59 | 0.023 | 0.170 | 0.971 | 2567 |
| Porphyrin and chlorophyll metabolism | 23 | -0.60 | -1.59 | 0.014 | 0.170 | 0.976 | 3693 |
| B24:b45pentose and glucuronate interconversions | 13 | -0.67 | -1.58 | 0.024 | 0.167 | 0.979 | 3693 |
| **Name of Pathway** | **Size** | **ES** | **NES** | **NOM p-val** | **FDR q-val** | **FWER p-val** | **Max rank** |
| Metabolism of xenobiotics by cytochrome p450 | 43 | -0.53 | -1.58 | 0.011 | 0.172 | 0.985 | 4881 |
| Linoleic acid metabolism | 21 | -0.59 | -1.57 | 0.023 | 0.180 | 0.992 | 2786 |
| Glycosphingolipid biosynthesis globo series | 14 | -0.66 | -1.57 | 0.016 | 0.178 | 0.992 | 1665 |
| Ether lipid metabolism | 25 | -0.58 | -1.56 | 0.019 | 0.174 | 0.993 | 2912 |
| Antigen processing and presentation | 49 | -0.51 | -1.56 | 0.010 | 0.179 | 0.994 | 4900 |
| Neuroactive ligand receptor interaction | 207 | -0.43 | -1.55 | <0.001 | 0.186 | 0.997 | 3036 |
| Fructose and mannose metabolism | 32 | -0.53 | -1.53 | 0.026 | 0.209 | 1.000 | 3222 |
| Gnrh signalling pathway | 91 | -0.46 | -1.53 | 0.003 | 0.220 | 1.000 | 2478 |
| Primary immunodeficiency | 23 | -0.56 | -1.52 | 0.022 | 0.215 | 1.000 | 2651 |
| Ppar signalling pathway | 58 | -0.49 | -1.52 | 0.013 | 0.210 | 1.000 | 3415 |
| Sppa pathway | 20 | -0.58 | -1.52 | 0.022 | 0.210 | 1.000 | 2478 |
| Thelper pathway | 5 | -0.82 | -1.52 | 0.024 | 0.205 | 1.000 | 1450 |
| Folate biosynthesis | 8 | -0.73 | -1.52 | 0.044 | 0.203 | 1.000 | 3153 |
| Lym pathway | 9 | -0.70 | -1.50 | 0.031 | 0.220 | 1.000 | 1280 |
| Tight junction | 122 | -0.44 | -1.50 | 0.002 | 0.218 | 1.000 | 1818 |
| Nicotinate and nicotinamide metabolism | 23 | -0.57 | -1.50 | 0.040 | 0.221 | 1.000 | 998 |
| Pgc1a pathway | 22 | -0.56 | -1.50 | 0.037 | 0.216 | 1.000 | 2991 |
| Toll like receptor signalling pathway | 79 | -0.46 | -1.50 | 0.012 | 0.213 | 1.000 | 3490 |
| Cytokine pathway | 10 | -0.67 | -1.49 | 0.044 | 0.217 | 1.000 | 1591 |
| Asthma | 9 | -0.68 | -1.49 | 0.047 | 0.211 | 1.000 | 746 |
| Pyruvate metabolism | 35 | -0.52 | -1.49 | 0.027 | 0.212 | 1.000 | 4129 |
| Glycerolipid metabolism | 43 | -0.49 | -1.47 | 0.025 | 0.249 | 1.000 | 3332 |
| Natural killer cell mediated cytotoxicity | 86 | -0.45 | -1.46 | 0.022 | 0.263 | 1.000 | 4067 |
| Cell adhesion molecules cams | 103 | -0.43 | -1.46 | 0.005 | 0.259 | 1.000 | 2272 |
| Amino sugar and nucleotide sugar metabolism | 42 | -0.49 | -1.45 | 0.039 | 0.258 | 1.000 | 5146 |
| Hematopoietic cell lineage | 51 | -0.47 | -1.45 | 0.043 | 0.258 | 1.000 | 4013 |
| Glycosaminoglycan biosynthesis keratan sulfate | 15 | -0.59 | -1.45 | 0.068 | 0.253 | 1.000 | 2779 |
| Glycerophospholipid metabolism | 69 | -0.45 | -1.45 | 0.024 | 0.251 | 1.000 | 3332 |
| Phosphatidylinositol signalling system | 72 | -0.44 | -1.45 | 0.027 | 0.247 | 1.000 | 3490 |

Table S4. Top 50 pathways with gene sets showing evidence of enrichment for lower expression in drug-treated NT2-N cells compared to vehicle treated control NT2-N cells. (ES = enrichment score, NES = normalised enrichment score, NOM p-val = nominal p-value, FDR q-val = false discovery rate, FWER p-val = family wise error rate, Max rank = position in the ranked list at which the maximum enrichment score occurred).

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Name of Pathway** | **Size** | | | **ES** | | **NES** | | **NOM p-val** | | **FDR q-val** | | **FWER p-val** | | **Max rank** |
| Systemic lupus erythematosus | 96 | | | 0.550 | | 2.520 | | <0.001 | | <0.001 | | <0.001 | | 2443 |
| Tel pathway | 17 | | | 0.580 | | 1.800 | | 0.008 | | 0.309 | | 0.378 | | 4996 |
| Mcalpain pathway | 24 | | | 0.530 | | 1.780 | | 0.004 | | 0.254 | | 0.442 | | 2242 |
| Wnt pathway | 25 | | | 0.520 | | 1.740 | | <0.001 | | 0.277 | | 0.579 | | 1730 |
| Tgf beta signaling pathway | 79 | | | 0.400 | | 1.730 | | <0.001 | | 0.245 | | 0.614 | | 2742 |
| Carm er pathway | 34 | | | 0.470 | | 1.720 | | 0.005 | | 0.218 | | 0.633 | | 1776 |
| Spliceosome | 125 | | | 0.360 | | 1.710 | | <0.001 | | 0.204 | | 0.663 | | 4341 |
| Carm1 pathway | 13 | | | 0.600 | | 1.660 | | 0.024 | | 0.247 | | 0.777 | | 2242 |
| Mcm pathway | 18 | | | 0.530 | | 1.610 | | 0.008 | | 0.309 | | 0.860 | | 1405 |
| Dna replication | 35 | | | 0.430 | | 1.580 | | 0.015 | | 0.336 | | 0.913 | | 1127 |
| Alk pathway | 34 | | | 0.430 | | 1.540 | | 0.017 | | 0.401 | | 0.961 | | 1674 |
| Ctcf pathway | 22 | | | 0.470 | | 1.540 | | 0.045 | | 0.372 | | 0.963 | | 2742 |
| P53 signaling pathway | 65 | | | 0.350 | | 1.510 | | <0.001 | | 0.400 | | 0.984 | | 2522 |
| Ranms pathway | 10 | | | 0.590 | | 1.490 | | 0.095 | | 0.407 | | 0.988 | | 3977 |
| Vip pathway | 26 | | | 0.450 | | 1.490 | | 0.025 | | 0.382 | | 0.988 | | 2893 |
| Thyroid cancer | 29 | | | 0.430 | | 1.490 | | 0.045 | | 0.368 | | 0.989 | | 1550 |
| Akapcentrosome pathway | 15 | | | 0.500 | | 1.440 | | 0.061 | | 0.454 | | 0.998 | | 2242 |
| Tgfb pathway | 19 | | | 0.470 | | 1.440 | | 0.079 | | 0.432 | | 0.999 | | 3812 |
| P35alzheimers pathway | 11 | | | 0.540 | | 1.400 | | 0.096 | | 0.507 | | 1.000 | | 6086 |
| Plce pathway | 12 | | | 0.520 | | 1.390 | | 0.121 | | 0.494 | | 1.000 | | 2242 |
| Shh pathway | 16 | | | 0.480 | | 1.380 | | 0.104 | | 0.488 | | 1.000 | | 2242 |
| **Name of Pathway** | | **Size** | **ES** | | **NES** | | **NOM p-val** | | **FDR q-val** | | **FWER p-val** | | **Max rank** | | |
| Gata3 pathway | | 13 | 0.490 | | 1.380 | | 0.117 | | 0.474 | | 1.000 | | 2242 | | |
| Akap95 pathway | | 12 | 0.510 | | 1.380 | | 0.117 | | 0.460 | | 1.000 | | 2390 | | |
| Arap pathway | | 15 | 0.480 | | 1.360 | | 0.098 | | 0.474 | | 1.000 | | 2931 | | |
| P53hypoxia pathway | | 22 | 0.420 | | 1.360 | | 0.077 | | 0.458 | | 1.000 | | 2051 | | |
| Cell cycle | | 121 | 0.300 | | 1.360 | | 0.016 | | 0.441 | | 1.000 | | 2355 | | |
| Pitx2 pathway | | 14 | 0.450 | | 1.310 | | 0.179 | | 0.536 | | 1.000 | | 1611 | | |
| Cftr pathway | | 12 | 0.470 | | 1.300 | | 0.135 | | 0.555 | | 1.000 | | 2242 | | |
| G1 pathway | | 28 | 0.370 | | 1.300 | | 0.120 | | 0.537 | | 1.000 | | 1145 | | |
| No1 pathway | | 28 | 0.360 | | 1.270 | | 0.134 | | 0.590 | | 1.000 | | 1585 | | |
| Ribosome | | 84 | 0.280 | | 1.270 | | 0.048 | | 0.574 | | 1.000 | | 13172 | | |
| Cardiacegf pathway | | 18 | 0.400 | | 1.240 | | 0.169 | | 0.618 | | 1.000 | | 1571 | | |
| Tob1 pathway | | 11 | 0.470 | | 1.240 | | 0.203 | | 0.616 | | 1.000 | | 3717 | | |
| Csk pathway | | 14 | 0.420 | | 1.230 | | 0.171 | | 0.617 | | 1.000 | | 2242 | | |
| Colorectal cancer | | 61 | 0.300 | | 1.220 | | 0.132 | | 0.614 | | 1.000 | | 1796 | | |
| Base excision repair | | 33 | 0.330 | | 1.210 | | 0.158 | | 0.630 | | 1.000 | | 2850 | | |
| Eif pathway | | 16 | 0.400 | | 1.200 | | 0.222 | | 0.650 | | 1.000 | | 1617 | | |
| Ubiquitin mediated proteolysis | | 129 | 0.250 | | 1.200 | | 0.063 | | 0.639 | | 1.000 | | 4128 | | |
| Lysine degradation | | 44 | 0.310 | | 1.190 | | 0.174 | | 0.626 | | 1.000 | | 2513 | | |
| Mtor pathway | | 23 | 0.360 | | 1.190 | | 0.204 | | 0.611 | | 1.000 | | 3177 | | |
| Salmonella pathway | | 13 | 0.430 | | 1.190 | | 0.222 | | 0.599 | | 1.000 | | 3579 | | |
| Vdr pathway | | 12 | 0.430 | | 1.190 | | 0.239 | | 0.605 | | 1.000 | | 3989 | | |
| Chronic myeloid leukemia | | 71 | 0.270 | | 1.170 | | 0.178 | | 0.636 | | 1.000 | | 2766 | | |
| Prostate cancer | | 82 | 0.270 | | 1.170 | | 0.143 | | 0.627 | | 1.000 | | 1915 | | |
| **Name of Pathway** | | **Size** | **ES** | | **NES** | | **NOM p-val** | | **FDR q-val** | | **FWER p-val** | | **Max rank** | | |
| Wnt signaling pathway | | 145 | 0.240 | | 1.150 | | 0.121 | | 0.652 | | 1.000 | | 1683 | | |
| Nfat pathway | | 50 | 0.280 | | 1.130 | | 0.240 | | 0.689 | | 1.000 | | 1585 | | |
| Gcr pathway | | 16 | 0.370 | | 1.130 | | 0.295 | | 0.689 | | 1.000 | | 4803 | | |
| Il2rb pathway | | 34 | 0.310 | | 1.130 | | 0.244 | | 0.678 | | 1.000 | | 1937 | | |
| Dream pathway | | 14 | 0.380 | | 1.120 | | 0.302 | | 0.689 | | 1.000 | | 2242 | | |
| Ps1 pathway | | 13 | 0.400 | | 1.110 | | 0.346 | | 0.708 | | 1.000 | | 1047 | | |

Table S5. The Oxidative Phosphorylation (OXPHOS) pathway is upregulated by the combination of bipolar drugs in rat frontal cortex (GSEA – FDR q<0.001, FWER p<0.001), particularly genes in Complexes I and V. The majority of the OXPHOS genes are also upregulated by the drug combination in the NT2-N cells, especially in Complex IV (data derived from next generation sequencing) (n.s-not significant)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | NT2-N Cells | | | | Rat Brains | | | |
|  | Total Number of Genes | Number of genes higher in drug treated NT2-N cells | Number of genes lower in drug treated NT2-N cells | p-value | Total Number of Genes | Number of genes higher in drug treated rats | Number of genes lower in drug treated rats | p-value |
| OXPHOS Pathway | 100 | 70 | 30 | <0.005 | 103 | 90 | 13 | <0.001 |
| Complex I | 32 | 18 | 14 | n.s. | 33 | 30 | 3 | <0.001 |
| Complex II | 4 | 3 | 1 | n.s. | 4 | 3 | 1 | n.s. |
| Complex III | 9 | 6 | 3 | n.s. | 9 | 7 | 2 | <0.005 |
| Complex IV | 15 | 13 | 2 | <0.05 | 16 | 13 | 3 | <0.05 |
| Complex V | 15 | 8 | 7 | n.s. | 15 | 14 | 1 | <0.001 |
| Other | 25 | 22 | 3 | <0.05 | 26 | 22 | 4 | n.s |

**Figures**



Figure S1. Increased OXPHOS gene expression in the frontal cortex of rats by complex in the mitochondrial electron transport chain (fold change compared to vehicle) following treatment with BD drugs. \*p<0.05, \*\*p<0.005, \*\*\*p<0.001.



Figure S2. Increased OXPHOS gene expression in the NT2-N cells by complex in the mitochondrial electron transport chain (fold change compared to vehicle) following treatment with BD drugs. \*p<0.05, \*\*p<0.005.

Figure S3. Gene expression of *SIRT3* and *SIRT4* in drug-treated frontal cortex of rats relative to vehicle. \*p<0.05