Systematic drug perturbations on cancer cells reveal diverse exit paths from proliferative state

Supplementary Material

Figure S1. The breast cell development tree and the schema of differentiation therapy which induce breast cancer cells MCF7 to differentiated state.

Mammary stem cells differentiate to Basal progenitors, which differentiate to Basal Myoepithelial; They also differentiate to Luminal progenitors, which differentiate to Ductal and milk-secreting Alveolar cells. MCF7 cells derived from breast Luminal cells are induced to Alveola-like mature state through the selected drugs.
Figure S2. 16 drug dose response curves – comparisons between library and repurchased compound.

The horizontal axis is drug concentration (μM) in log scale. The vertical axis is the percentage of positive cells with LipidTOX fluorescent dye. We repeated the experiments twice for the repeatability. Blue, compound from the JHCCCL; Red, repurchased (Sigma)
Figure S3. Error Model: MCF7 Cells Gene Expression levels vs. their standard deviations between untreated and drug-treated samples.

The horizontal axis represents the gene expression level measured by Illumina BeadChip while the vertical axis represents the corresponding standard deviation of gene expression levels across certain samples (both in log scale). The blue dots represent 14 samples of untreated MCF7 Cells while red ones represent 54 drug treated samples. The gene expressions vs. standard deviation curves of the drug-treated samples are significantly higher than those of untreated MCF7 cell samples.
Figure S4. GEDI heatmap of untreated and 15 drug-treated MCF7 Cells Gene Expressions.

The GEDI heatmap project a high-dimensional transcriptome into a 2D self-organizing map to visualize the overall gene expression. Each pixel in the GEDI map (grid element) represents a mini-cluster of highly
similarly behaving genes. The pixel at the same position in each map represents the same genes. The color of each pixel represents the gene expression level. (Both Befemelane and Trimebutine have one transcriptome missed due to the failure to pass the quality control)
Figure S5. Heatmap of the differentially expressed genes identified using SAM.

(A) The heatmap of the differentially expressed genes between the samples untreated (at Day 0), drug treated samples at Day 1 and Day 5 based on SAM multiclass analysis; (B) The differentially expressed genes between the samples at Day 0 and Day 1 based on SAM analysis; (C) The differentially expressed genes between the samples at Day 0 and Day 5 based on SAM analysis.
Figure S6. The modified Pearson correlation coefficients distribution of MCF7 cell samples between Day 0 and Day 1,3,5

From 100-randomly chosen sets of 500 genes out of the entire transcripts of each drug at different time points (indicated by colors), we calculated the distribution of the modified Pearson correlation coefficients.
between the drug-treated and the untreated samples (see details in [1]). Except for Desloratadine, Flunisolide, Guanfacine and Maprotiline, the gene expressions of the drug-treated samples are less correlated between Day 0 and Day 3 than the ones between Day 0 and Day 1 / Day 5. The gene expressions of the drug-treated samples were diverging and converging during the transition.

**Figure S7. The CAP-Net analysis of the transcriptome of drug-treated sample at Day 1**

CAP-Net shows the downstream commonly affected pathways after 1 day drug treatments. Diamonds and circles respectively represent targets and differentially expressed genes. The color of a node shows the average expression level of the corresponding gene. If a gene has a stemness function, it is marked by bold black line.
Supplemental Tables

Table S1-1. List of 16 drugs names, optimal dose, cell differentiation efficiencies

| No. | Full Name     | Indication            | C (μM) | p (%) | Survived Cells (%) |
|-----|---------------|-----------------------|--------|-------|--------------------|
| 1   | Acepromazine  | Sedative              | 10.00  | 45.2  | 73.3               |
| 2   | Amiodarone    | Antiarrhythmic (class III) | 5.00  | 44.8  | 48.3               |
| 3   | Bifemelane    | Nootropic             | 5.00   | 45.2  | 70.1               |
| 4   | Chlorpromazine| Antiemetic            | 5.00   | 46.3  | 70.7               |
| 5   | Clomipramine  | Antidepressant        | 5.00   | 33.7  | 83.6               |
| 6   | Desloratadine | Antihistaminic        | 10.00  | 55.5  | 65.3               |
| 7   | Doxycycline   | Antibiotic            | 5.00   | 38.3  | 86.0               |
| 8   | Fluoxetine    | Antidepressant        | 10.00  | 47.9  | 70.3               |
| 9   | Flunisolide   | Glucocorticoid        | 10.00  | 29.1  | 99.6               |
| 10  | Guanfacine    | Antihypertensive      | 10.00  | 46.3  | 59.6               |
| 11  | Maprotiline   | Antidepressant        | 5.00   | 35.8  | 85.7               |
| 12  | Picrotoxin    | Nootropic             | 10.00  | 19.7  | 100.0              |
| 13  | Raloxifene    | Bone resorption inhibitor | 0.16  | 41.4  | 100.0              |
| 14  | Sertraline    | Antidepressant        | 10.00  | 67.2  | 66.7               |
| 15  | Thiostrepton  | Antibiotic            | 0.08   | 84.9  | 100.0              |
| 16  | Trimebutine   | Antispasmodic         | 10.00  | 22.9  | 75.4               |
Table S1.2. Drug concentrations for transcript profiling

| No. | Drug name       | Concentration (μM) |
|-----|-----------------|--------------------|
| 1   | Acepromazine    | 10                 |
| 2   | Amiodarone      | 5                  |
| 3   | Bifemelane      | 5                  |
| 4   | Chlomipramine   | 5                  |
| 5   | Chlorpromazine  | 10                 |
| 6   | Desloratadine   | 10                 |
| 7   | Doxycycline hyclate | 10         |
| 8   | Fluoxetine      | 10                 |
| 9   | Flunisolide     | 10                 |
| 10  | Guanfacine      | 10                 |
| 11  | Maprotiline     | 10                 |
| 12  | Picrotoxin      | 10                 |
| 13  | Raloxifene HCl  | 5                  |
| 14  | Sertraline HCl  | 5                  |
| 15  | Thiostrepton    | 1                 |
| 16  | Trimebutine     | 10                 |
Table S2. Differentially expressed genes identified by SAM analysis

| Day 0 vs Day 1 vs Day 5 (138) | Day 0 vs Day 1 (49 genes) | Day 0 vs Day 5 (41 genes) |
|-------------------------------|-------------------------|-------------------------|
| ABCC3                         | ALDH1A3                 | ACSL1                   |
| ACSL1                         | ANXA3                   | ACTG2                   |
| ALDH1A3                       | BST2                    | ARCN1                   |
| ANKRK13C                      | CAV1                    | ASAP3                   |
| ARCN1                         | CFB                     | BBS2                    |
| ARL6IP4                       | CKB                     | BST2                    |
| ARMX6                         | CRABP1                  | CDC2L6                  |
| ASAP3                         | CYP1A1                  | CFB                     |
| ASB8                          | CYP1B1                  | COX7A2L                 |
| ATAD1                         | DDX41                   | CTNNB1                  |
| BNI3P                         | DEGS2                   | DAGLA                   |
| BRF1                          | EPS1                    | DCPA6                   |
| BST2                          | GJA1                    | DHR54L2                 |
| C10orf16                      | HG20B                   | DYP19L4                 |
| C17orf90                      | HS3ST3A1                | GAL                     |
| CAV1                          | IDH2                   | GCAT                    |
| CFB                           | IFIT27                  | GRHL3                   |
| CKB                           | IFIT6                   | HMG20B                  |
| CNN2                          | IFIT1                   | IFIT27                  |
| COX7A2L                       | IFITM1                  | MED28                   |
| CRABP2                        | IFITM2                  | MT1A                    |
| CSF1                          | IFITM3                  | MT1X                    |
| CTNNB1                        | IFITM4P                 | PGK1                    |
| CXorf39                       | IFGBP5                  | PGM1                    |
| CYP1B1                        | ILVBL                   | PLD3                    |
| DAGLA                         | IGF9                    | PRRC1                   |
| DDR1                          | ISG15                   | PTPLAD1                 |
| DDT                           | ISG20                   | RHOB1B3                 |
| DDX41                         | KRT13                   | S100A7                  |
| DEGS2                         | LGALS1                  | S100A8                  |
| DNAJ1B14                      | LGALS3BP                | S100A9                  |
| DYP19L4                       | LRR5C8                  | SDCCAG1                 |
| DYNCT1L1                      | MSMB                    | SPRR1A                  |
| EHD1                          | MT1A                    | UGT1A6                  |
| EMD                           | MT1X                    | ZFP90                   |
| ENO1                          | MUC1.1                  |                         |
| EPAS1                         | NDRG1                   |                         |
| FBXL18                        | NQO1                    |                         |
| FIS1                          | PFKFB4                  |                         |
| FLVCR2                        | PPARG                   |                         |
| FOXJ3                         | PRRC1                   |                         |
| GAL                           | PTPN12                  |                         |
| GAPVD1                        | S100A7                  |                         |
| GCAT                          | SELENBP1                |                         |
| GPER                          | S13GAL1                 |                         |
| GPI                           | TGFBI                   |                         |
| GPX2                          | TNS3                    |                         |
| GRHL3                         | UBE2L6                  |                         |
| HGFC1R1                       | UGT1A6                  |                         |
| HERC4                         | UGT1A6                  |                         |
| HIP2                          |                         |                         |
| HLA-DRB5                      |                         |                         |
| HLA-H                         |                         |                         |
| HMG20B                        |                         |                         |
| IDH2                          |                         |                         |
| IFIT27                        |                         |                         |
| IFIT6                         |                         |                         |
| IFIT1                         |                         |                         |
| IFITM1                        |                         |                         |
| Gene Name |
|-----------|
| IFITM2    |
| IFITM3    |
| IFITM4P   |
| IGFBP2    |
| ILVBL     |
| IRF9      |
| ISG15     |
| KLK11     |
| LCN2      |
| LGALS3BP  |
| LIN7C     |
| LMTK3     |
| LOC728037 |
| LPHN1     |
| LRRC58    |
| MAFB      |
| MAPK3     |
| MCOLN2    |
| ME1       |
| MEST      |
| MGA72     |
| MRPL54    |
| MT1A      |
| MT1X      |
| MTE       |
| MUCL1     |
| MYLIP     |
| NCOA6     |
| NDRG1     |
| NFE2L2    |
| OAS1      |
| OBF2C2A   |
| P2RX2     |
| PANX2     |
| PARP12    |
| PAWR      |
| PCP4      |
| PFDN4     |
| PFKFB4    |
| PGK1      |
| PGM1      |
| PHACTR2   |
| PIH1TD1   |
| PLD3      |
| PPARG     |
| PPM1B     |
| PREPL     |
| PRRC1     |
| RHOB1B3   |
| RSRC1     |
| S100A7    |
| S100A8    |
| S100A9    |
| SELENBP1  |
| SERPINA1  |
| SEZ8L2    |
| SIKE      |
| SLC2A1    |
| SPT10     |
| SPRR1A    |
| SQLE      |
| STK3      |
| STRBP     |
| SULF2     |
| SYTL1  | TGFBI  | TMEM1  |
|-------|--------|--------|
|       |        |        |
| TMEM43| TMEM72 | TMEM79 |
|       |        |        |
| TNNT1 | UBE2L6 | UGT1A6 |
|       |        |        |
| VPS35 | WDR54  | YIPF4  |
|       |        |        |
| YTHDC1| ZFP90  | ZNF721 |
| C1 (Const, diverge-converge) | C2 (Const, Concordant) | C3(change, diverge-converge) | C4 (change, concordant) |
|-------------------------------|------------------------|------------------------------|------------------------|
| ACOT11                        | ABCA12                 | ACGL1                        | 7AS                    |
| ACOX2                         | ABCC3                  | ACL3                         | AAAGAB                 |
| ACS52                         | ABHD3                  | AHCFT1                       | AASDHPPPT              |
| ANKRD11                       | ACAP2                  | AHNAP                        | ACO1                   |
| ASPM                          | ACAT2                  | AP1M1                        | ACP1                   |
| BRCA2                         | ACLY                   | ARHGEF16                     | ACTG2                  |
| C1ORF52                       | ACOT4                  | ARL6IP4                      | ACTR3                  |
| COL4A5                        | ACTR1B                 | ASAP3                        | ACVR1                  |
| COMMD7                        | ACTR6                  | ASB8                         | ADAM10                 |
| COX7B                         | ADCY1                  | ATP5B                        | ADNP                   |
| CP110                         | ADM                    | ATP9A                        | AES                    |
| CRIP2                         | AFAP1L2                | BANF1                        | AGTPBP1                |
| CUL5                          | AGL                    | BBS2                         | AHSA1                  |
| CUTA                          | AGR2                   | BCL6                         | AIF1L                  |
| ELF3                          | AHS2A                  | BTG1                         | AKAP9                  |
| EFA                           | AIDA                   | BUB3                         | AKIRIN2                |
| FAM96A                        | AIP                    | C1SORF21                     | ALDH4A1                |
| FDF11                         | AK3L1                  | C1BORF25                     | ALDH5A1                |
| FTHL3                         | AKAP11                 | C1ORF33                      | AAS2                   |
| GDPD3                         | AKR7A2                 | C2ORF64                      | ANAPC5                 |
| GSDM1                         | AKR7A3                 | C3ORF59                      | ANKHD1                 |
| H3F3A                         | ALDOC                  | CCDC124                      | ANKJ1B                 |
| HADH                          | ALG1L                  | CCDC23                       | ANKR13C                |
| HDAC1                         | ALKBH2                 | CCDC72                       | ANKR4D7                |
| HIST1H2BE                     | AMMECR1                | CDC216                       | ANKR6                  |
| HMox1                         | ANLN                   | CFL1                         | ARPT                   |
| IDH2                          | ANP32B                 | CHCHD4                       | ARCN1                  |
| IFT74                         | AP1G2                  | CHMP2B                       | ARHGAP12               |
| IMPA1                         | AP1S3                  | CKS1B                        | ARHGAP18               |
| KBTBD8                        | AP2S1                  | CRY2                         | ARHGEF19               |
| KDM5B                         | APH1A                  | CSNK2B                       | ARHGEF5L               |
| KIAA1033                      | ARF1                   | CTB                          | ARIDS5                 |
| KLCD5                         | ARF5                   | DAPPP1                       | ARL8B                  |
| KRT8                          | ARFGEF2                | DBNDD1                       | ARMCX6                 |
| KRT80                         | ARHGAP21               | DDX41                        | ASF1B                  |
| LAD1                          | ARID1A                 | DHCR7                        | ATAD1                  |
| LOC6353604                    | ARL2                   | DUSP3                        | AFP1                   |
| LOC678635                     | ARL6IP5                | DYRK2                        | ATR5D                  |
| MAP7                          | ARPC5                  | EIF3M                        | ATR5G1                 |
| MGC16703                      | ARRD4C                 | EWSR1                        | ATP6AP2                |
| MGST2                         | ASC1                   | FAM117B                      | ATP6V0E2               |
| MIF                           | ASH1L                  | FAM129B                      | ATP6V1G1               |
| MR6AP1                        | ASS1                   | FAM179B                      | AUT52                  |
| NDUFA1                        | ATG16L1                | FAM43A                       | B3GAT3                 |
| NUBPL                         | ATIC                   | FAM96B                       | B4GALT1                |
| OCIAD2                        | ATOX1                  | FLJ3842                      | BAG3                   |
| PAAFH1B3                      | ATP2B1                 | FLJ44124                     | BAMBI                  |
| PMEPA1                        | ATP2C1                 | FTHL11                       | BAZ2B                  |
| POMP                          | ATP6V0C                | GAK                          | BCR3                   |
| PRDX1                         | ATP6V1B1               | GCA                          | BCL2L1                 |
| RCC2                          | ATP6V1F                | GFMI1                        | BEND6                  |
| RHBD2                         | ATPIF1                 | GLTP                         | BICD2                  |
| RHEB                          | ATR                    | HIST1H4E                     | BIVM                   |
| RNASET2                       | B4GALNT1               | HMNC1                        | BNI1                   |
| RPL11                         | BAIAP2L1               | HMSGCS1                      | BNI3                   |
| RPL15                         | BAT1                   | HSPA1A                       | BNI3P1                 |
| RPS3A                         | BAT5                   | ID2                          | BRF1                   |
| RPS6KB1                       | BAZ1A                  | ID1                          | BRF2                   |
| Gene1   | Gene2       | Gene3 | Gene4 |
|---------|-------------|-------|-------|
| S1PR3   | BBS7        | KIAA0430 | BRPF3 |
| SEMA3E  | BBX         | KLF9   | BRSK1 |
| SH3GLB2 | BCRAP29     | KLHL12 | BRWD3 |
| SHCBP1  | BCKD        | LMTK3  | BSCl2 |
| SIAH2   | BCL2L2      | LSM7   | B5T2  |
| SLC16A12| BCL7C       | MCM2   | BTF3L4|
| SLC36A4 | BIRC5       | MED28  | C12orf24|
| SLTM    | BMS1        | MED30  | C12orf41|
| SQSTM1  | BNIPL       | METAP2 | C13orf23|
| TBC1D8  | BRD3        | MRPL46 | C13orf37|
| TINP1   | BSG         | MRPL51 | C14orf4|
| TMEM165 | BUB1        | MT1A   | C15orf29|
| TMEM205 | C10orf118   | MTX2   | C16orf13|
| TMEM9   | C10orf119   | MYLIP  | C16orf58|
| TMSB10  | C10orf46    | NARS   | C17orf58|
| TTYH3   | C10orf58    | NAT12  | C1orf218|
| UBR3    | C10orf59    | NCOA6  | C10orf63|
| VNR2    | C11orf10    | NDUFA13| C10orf71|
| VPS28   | C11orf60    | NF1B   | C1orf736|
| VPS72   | C11orf61    | NMD3   | C21orf58|
| WDR67   | C12orf10    | NUDT7  | C20orf30|
| XPNPEP1 | C12orf35    | PABPC1 | C20orf54|
| XPNPEP3 | C12orf44    | PDLIM1 | C20orf55|
| ZBTB42  | C12orf57    | PFDN4  | C3orf57|
| ZNF146  | C14orf126   | PPS5   | C6orf23|
| C1orf37 | PP1IC       | C6orf125| C7orf28B|
| C1orf35 | PRGR1       | C7orf42|
| C1orf75 | PSMAS2      | C7orf42|
| C1orf91 | PTPLB       | C9orf127|
| C1orf61 | RAB10       | C9orf142|
| C1orf90 | RAB11A      | CAMSAP1L1|
| C1orf98 | RAB5B       | CAND1  |
| C1orf22 | RBM47       | CAPN5  |
| C1orf30 | RBPM52      | CAPZ2A|
| C1orf43 | REPIN1      | CB25   |
| C1orf123| RF7X        | CBS    |
| C1orf128| RGP2D       | CBX2   |
| C1orf55 | RGS17       | CBX6   |
| C1orf96 | RHDF1       | CBCE1  |
| C2orf199| RHOBTB3     | CCDC128|
| C2orf52 | RNF114      | CCDC132|
| C3orf25 | RNF181      | CCDC22 |
| C5orf33 | RNF216      | CCDC50 |
| C7orf20 | ROCK1       | CCDC83 |
| C7orf30 | RPL26       | CCDC85A|
| C7orf43 | RPL26L1     | CCDC85B|
| C7orf50 | RPL27       | CCDC90A|
| C7orf68 | RPL7L1      | CCDC90B|
| C9orf162| RPS7        | CCDC91 |
| C9orf169| SAFB        | CCDC93 |
| C9orf41 | SEK3A3B     | CCME2  |
| CAB39   | 3-Sep       | CD164  |
| CAB39L  | SLC25A16    | CD46   |
| CABYR   | SLC38A6     | CD96   |
| CAMK2B  | SNORD3D     | CDCI5L |
| CAMTA1  | SNX27       | CDC7   |
| CAPG    | SPAST       | CDKN28 |
| CAPN13  | SPRYD5      | CELSR2 |
| CAPN7   | SRI         | CENPO  |
| CARHPS1 | STAG3       | CEP27  |
| CASA4   | STARD10     | CETN2  |
| CASC5   | STAT6       | CFB    |
| CAT     | STC1        | CFL2   |
| CBX3    | STRA13      | CGGBP1 |
| Gene Symbol | Gene Symbol | Gene Symbol |
|-------------|-------------|-------------|
| CCDC112     | SUCLG2      | CHES1       |
| CCDC120     | SULT1A1     | CHMP4C      |
| CCDC18      | SUMF1       | CHP         |
| CCDC41      | SYPL1       | CHST1       |
| CCDC56      | TACSTD1     | CIDECC      |
| CCNE        | TBL3        | CLDN3       |
| CCNE2       | TCEA3       | CLK4        |
| CCNJ        | TMEM126B    | CMBL        |
| CCNYL1      | TMEM66      | CMTM8       |
| CD63        | TMEM9B      | CNN2        |
| CD97        | TOMM70A     | COBL1       |
| CD99        | TRMT5       | COMT        |
| CDC2        | TUBB2C      | COMT1D1     |
| CDC73       | UBC         | COX10       |
| CDH3        | UBLCP1      | COX6B1      |
| CDK4        | USP38       | CPD         |
| CDKN1A      | YBX1        | CPEB4       |
| CDR2L       | ZC3H3       | COPX        |
| CDS1        | ZNF281      | CRELD2      |
| CEBPZ       | CRIP        |              |
| CENPA       | CTNNB1      |              |
| CEP55       | CTNNBL1     |              |
| CHCHD5      | CTNND2      |              |
| CHKA        | CWF19L1     |              |
| CHML        | CXorf25     |              |
| CHORDC1     | CXorf39     |              |
| CHP1        | CYP1B1      |              |
| CICK0721Q1  | DAGLA       |              |
| CIRBP       | DAZAP2      |              |
| CKB         | DBN1        |              |
| CKMT1A      | DBT         |              |
| CKMT1B      | DCFA6       |              |
| CKS2        | DCTN4       |              |
| CLCN3       | DCCDN1D1    |              |
| CLDN7       | DDF2        |              |
| CLINT1      | DDT         |              |
| CLIP1       | DDX17       |              |
| CLIP4       | DDX6        |              |
| CLK2        | DEGS2       |              |
| COG4        | DHR54       |              |
| COMMD4      | DHR54L2     |              |
| COPS6       | DHR57       |              |
| COX11P      | DIRC2       |              |
| COX5B       | DKC1        |              |
| CRABP2      | Dlg1        |              |
| CRISPLD2    | DMKN        |              |
| CRYZ        | DNAJB14     |              |
| CSNK1G3     | DNAJC9      |              |
| CSRP1       | Dnal4       |              |
| CXXC5       | DNlz        |              |
| CYC1        | DPM3        |              |
| CYHR1       | DPY19L4     |              |
| DAD1        | DR1         |              |
| DARS        | DRAM1       |              |
| DBNL        | DYNC1LI1    |              |
| DC1         | E2F2        |              |
| DCP2        | E2F6        |              |
| DCTN1       | EDF1        |              |
| DCTN2       | EGLN3       |              |
| DCTPP1      | EHD1        |              |
| DDAH2       | EHD4        |              |
| DD8         | EIF2AK3     |              |
| DDHD1       | EIF3C       |              |
| DDR1        | EIF3D       |              |
| DDX24 | ELAVL3 |
|-------|--------|
| DGUOK | ELF5   |
| DHCR24| ELK4   |
| DHFRL1| ELOF1  |
| DHRS3 | EMB    |
| DHX32 | EMD    |
| DHX40 | ENO1   |
| DMXL1 | ENO2   |
| DNAJB4| ENPP4  |
| DNMT3B| ENSA   |
| DNPEP | EPCAM  |
| DOCK6 | ERICH1 |
| DOK4  | ERMP1  |
| DOK7  | ESF1   |
| DPP7  | EXD2   |
| DSC2  | EXO1   |
| DSTN  | EXO4C  |
| DUSP4 | EXOC8  |
| DYNLRB1| EXOSC5|
| ECH1  | FAHD2A |
| ECHDC2| FAM105B|
| EDC3  | FAM107B|
| EDEM3 | FAM120A|
| EEF1D | FAM120B|
| EEF1E1| FAM160B1|
| EEF1G | FAM188A|
| EFCAB2| FAM45A |
| EFHA1 | FAM62B |
| EFHD1 | FAM83A |
| EFNA1 | FAM98A |
| EGFL7 | FAU    |
| EIF3A | FBL    |
| EIF3CL| FBXL18 |
| EIF3G | FBXO18 |
| EIF4E2| FBXO33 |
| EIF4E3| FGD3   |
| EIF4G2| FGF13  |
| ELK1  | FGFR10P|
| ELOVL5| FIS1   |
| ELOVL7| FLAD1  |
| EML1  | FNB    |
| ENTPD8| FLVC2  |
| EPB4I5| FNBP1  |
| EPB4E4| FOXC2  |
| ERFCC1| FOXJ3  |
| ERGIC2| FRAT2  |
| ERGIC3| FSCN1  |
| ERI3  | FTSJ3  |
| ESCO2 | G3BP1  |
| ETNK1 | GAB1   |
| EXOC3 | GAL    |
| EXOSC7| GALK2  |
| FAM104A| GAPVD1|
| FAM108B1| GATS  |
| FAM116A| GCAT   |
| FAM161A| GEMIN4 |
| FAM38A | GK5    |
| FAM57A | GKAP1  |
| FAM65A | GLB1   |
| FAM69A | GLS    |
| FAM72A | GNPT1  |
| FAM80A | GNPD4A |
| FAM84B | GOLT1B |
| FAM91A1| GPI    |
FAT1   GPR137B
FBXL15  GPR89A
FBXL17  GRAMD1A
FBXO30  GRHL3
FBXO32  GRN
FIBP    GSDMC
FKBP9L  GSTO1
FLJ33630 GTF2A2
FLOT1   GTF3C4
FLRT3   GTF3C5
FNBP1   GTE1
FTHL12  GUK1
FTSD1   H19
GABRB3  HARS2
GAN     HBP1
GAPDH   HDHD3
GCH1    HEBP1
GCLC    HERC4
GCLM    HINT2
GCNT1   HIP2
GDI2    HIST1H2AB
GFPT1   HIST1H3E
GNA13   HIST1H4H
GNAI3   HIST1H4J
GNG12   HIST3H3
GON4L   HMGN2
GPER    HMGN4
GPKOW   HNRNPD
GPR65   HNRNPM
GPX2    HOXC6
GPX3    HRASLS3
GRAMD1A HSBP1
GRK6    HSPC111
GSN     HTR3A
GSTO2   IFI6
GTF2F2  IFIT1
GTF2I   IFITM1
GUf1    IFITM3
H2AFV   IFITM4P
H2AFY2  IGFBP4
HAC1    IGF5
HAGH    ILF2
HCFC1R1 ILVBL
HCFC2   INS-IGF2
HDGF    IRF9
HDLBP   IRS1
HES4    ISCU
HHEX    ISG15
HIATL1  ISG20
HIST1H2BC JMJD1C
HIST1H2BH JMY
HIST2H2AC KAT2B
HIST3H2A KCTD7
HLA-A   KIAA0101
HLA-DRB1 KIAA0528
HLA-DRB5 KIAA1267
HLA-DRB6 KIAA1598
HLA-G   KIDINS220
HLA-H   KIF1A
HMGCRC KIF22
HNRNPA1L2 KLC1
HNRNPHE KLHDC10
HNRNPK  KLHDC8B
HNRPH3  KLHL2
| LOC552889 | MID2 |
| LOC606724 | MINPP1 |
| LOC653994 | MIR1185-1 |
| LOC90624 | MITD1 |
| LPIN1 | MNX1 |
| LRPS | MORC3 |
| LRP8 | MPG |
| LRPAP1 | MRGPRF |
| LRRC8B | MRPL12 |
| LSM1 | MRPL2 |
| LYAR | MRPL4 |
| LYN | MRPL42P5 |
| LYPD6 | MRPL54 |
| M6PRBP1 | MRPS15 |
| MACROD1 | MRPS23 |
| MAD2L2 | MRT04 |
| MAN1B1 | MSX2 |
| MANBA1 | MT1G |
| MAP9 | MT1X |
| MAPRE3 | MT2A |
| MAR3 | MTE |
| MAST2 | MTUS1 |
| MAT2B | MXD1 |
| MBNL1 | MYCBP2 |
| MBNL3 | MYH10 |
| MBOAT7 | MYL12A |
| MC1R | MYO1B |
| MCF2L2 | MYO5A |
| ME1 | MYO6 |
| MEIS3 | MYPOP |
| MEIS3P1 | MZF1 |
| METRN | NBEA |
| MFF | NCAM2 |
| MFN1 | NCOA1 |
| MFSD6 | NDRG1 |
| MGC12965 | NDUFA4 |
| MKI67IP | NEDD1 |
| MLS1A | NEK8 |
| MMD | NELL2 |
| MNAT1 | NEURL4 |
| MPHOSPH10 | NFE2L2 |
| MPI | NMB |
| MPP6 | NME1 |
| MPV17 | NNT |
| MRLC2 | NOL10 |
| MRPL1 | NOL3 |
| MRPL22 | NPNT |
| MRPL23 | NR1D1 |
| MRPL34 | NR3C1 |
| MRPL43 | NRB2 |
| MRPS12 | NRCAM |
| MT1F | NSDHL |
| MTERFD1 | NTSE |
| MTFTMT | NUBP2 |
| MTMIR11 | NUCB1 |
| MTMIR9 | NUCB2 |
| MTSS1 | NUP95 |
| MUC1 | OAS1 |
| MXD3 | OMA1 |
| MYL6B | OR1B12 |
| MYO18A | OSBPL8 |
| NAB2 | OSGIN2 |
| NACA2 | P4HA2 |
| NAP1L2 | PA2G4 |
| Gene  | Gene  |
|-------|-------|
| NARF  | PAPD4 |
| NCAPH | PAPSS2|
| NCKAP1| PARP12|
| NDEL1 | PAVR  |
| NDFIP1| PBLD  |
| NDFIP2| PBX3  |
| NDUFA11| PCSK6 |
| NDUFA2 | PDCD2L|
| NDUFAF3| PDLIM7|
| NDUFB11| PDPR  |
| NDUFS5 | PDS5A |
| NETO1 | PDZRN3|
| NHP2  | PERP  |
| NIT1  | PKFB3 |
| NKX3-1| PKFB4 |
| NLRG2 | PGAM1 |
| NME4  | PGK1  |
| NMRA1L| PGM1  |
| NR2C2 | PHACTR2|
| NR2F2 | PHACTR4|
| NRAS  | PHB   |
| NSMCE1| PHYH  |
| NT5C  | PIGK  |
| NT5C2 | PIH1D1|
| NT5C3 | PIK3CA|
| NTN4  | PKD2  |
| NUMA1 | PKMYT1|
| OAS3  | PKP4  |
| OBFC2A| PLCG2 |
| OGF   | PLD3  |
| OIP5  | PLEC1 |
| OKL38 | PLS1  |
| OPA1  | POLD4 |
| ORC2L | POLR1D|
| OTUB2 | PPAP2B|
| OTUD6B| PPIL2 |
| PALLD | PPM1B |
| PAM   | PPM2C |
| PANX2 | PPP2R3A|
| PAPOLA| PPP2R4|
| PAQR3 | PPP2R5D|
| PARK7 | PRED1D|
| PARP10| PREPL |
| PARP4 | PRICKLE2|
| PARP9 | PRICKLE4|
| PBX2  | PRKCSH|
| PCDHB2| PRR15L|
| PCGF5 | PRR7  |
| PCNA  | PRRC1 |
| PCP4  | PSMB1 |
| PDS52 | PSMB10|
| PFKL  | PSMC3 |
| PFN2  | PSM3D |
| PGA3  | PSMF1 |
| PGL5  | PTDSS1|
| PHAX  | PTGER4|
| PHB2  | PTPLAD1|
| PHC3  | PTPN3 |
| PHF11 | PTPN4 |
| PHF2L1| PTPR3 |
| PHOSPHO2| PTPR6 |
| PHPT1 | PTTG1P|
| PHTF2 | PUFG60|
| PI4KB | PURB  |
| Gene 1  | Gene 2  | Gene 3  | Gene 4  |
|--------|--------|--------|--------|
| PIAS3  | PUSL1  | PICALM | PYCRL  |
| PIGC   | QTTR1  | PKM2   | R3HDM2 |
| PKP1   | RAB22A | PLOD3  | RAB2A  |
| POLR2H | RAD21  | POLR2I | RALB   |
| PPB9G1 | RAP1GAP| PPAP2A | RAPGEF2|
| PPIA4A | RASA1  | PPIF   | RELB   |
| PPM1E  | RB1CC1 | PPM1CA | RECQL4 |
| PPP2R1A| RELB   | PPP4C  | RELB   |
| PPP4R1 | REXO2  | PPP4R2 | RFX3   |
| PQBP1  | RHBDF2 | PRD4M  | RHOQ   |
| PRDX5  | RHOU   | PRIM2  | RNA5EL |
| PRKIR  | RNF11  | PRPF19 | RNF34  |
| PRPF31 | RNF40  | PBR14  | RNU4ATAC|
| PSENEN | RNU5A  | PSMA3  | RP11-529I10.4|
| PSMD2  | RPL36A | PSME1  | RPL39L |
| PSMG4  | RPP21  | PTGR1  | RPS21  |
| PTPN11 | RRM2   | PURA   | RRP1   |
| PYGB   | RSR1C  | PYGL   | RUNDC3B|
| PURA   | RTRPL1  | PYNB   | RXRA   |
| RAB8A  | S100A12 | RAB2B  | S100A2 |
| RAB8C  | S100A4  | RAB3B  | S100A7 |
| RAB3GAP2| S100A8 | RAB3JP | SALL1  |
| RAB5C  | SAMD9  | RAB8A  | SASH1  |
| RAB8C  | SCYL2  | RABD1  | SDCCAG1|
| RABGAP2| SF3A2  | RABGAP1| SDCCAG1|
| RAB10A | SF3A3  | RAIF   | SEH2B  |
| RALBP1 | SFD2L1 | RALBP1 | SEC24B |
| RALGDS | SENP6  | RALGDS | SENP7  |
| RAMP1  | SEPT11 | RAP1GDS1| SEPT11 |
| RAP2C  | SERPIN1A| RAP1GDS1| SEPT11 |
| RAPGEF1| SERPINB6| RAP1GDS1| SEPT11 |
| RBM12B | SF3A2  | RBM42  | SF3A3  |
| RBX1   | SFN    | RDH10  | SFMR52 |
| RDH11  | SFMR52 | REEP3  | SFMR52 |
| RFK    | SFMR52 | RFK    | SFMR52 |
| RMNDS5B| SFMR56 | RMNDS5B| SFMR56 |
| Gene1    | Gene2    |
|----------|----------|
| RNASEH2A | SGSH     |
| RNASEK   | SGSM2    |
| RNF19B   | SGTA     |
| RNU4-1   | SH3BP1   |
| ROBLD3   | SH3YL1   |
| ROMO1    | SHRM     |
| RPE      | SIKE     |
| RPL13A   | SKP1     |
| RPL17    | SIAH1N1  |
| RPL3     | SLC25A1  |
| RPL36    | SLC25A12 |
| RPN2     | SLC27A1  |
| RPRD1A   | SLC35F5  |
| RPS15    | SLC38A2  |
| RPS24    | SLC44A1  |
| RPS4X    | SLC44A2  |
| RPS6KB2  | SLC48A1  |
| RPS9     | SLC4A5   |
| RPSA     | SLC9A2   |
| RPSJD3   | SLFN5    |
| RSU1     | SLITRK6  |
| RTCD1    | SMARCA2  |
| RTKN     | SMARCD1  |
| RUFY2    | SMC5     |
| RUNX2    | SNHG9    |
| S100A14  | SNORA40  |
| S100A16  | SNORD3A  |
| SAC5     | SNORD6S  |
| SALL2    | SNRK     |
| SAPS1    | SNRBP    |
| SBF1     | SNRBP2   |
| SNBNO1   | SNRPC    |
| SCP2     | SNRPD2   |
| SCPEP1   | SNX10    |
| SDCBP    | SNX16    |
| SDF2     | SNX3     |
| SDF4     | SORT1    |
| SEC23B   | SOX3     |
| SEC23IP  | SOX4     |
| SEC24A   | SP110    |
| SEC24D   | SPATA7   |
| SEMA4B   | SPG11    |
| SEMA6B   | SPIRE1   |
| SERTAD1  | SPPL2A   |
| SEZ6L2   | SPBP1A   |
| SFRS14   | SS18L2   |
| SFXN5    | SSR1     |
| SH3D19   | SSTR2    |
| SHISA5   | STAG2    |
| SIGIRR   | STK40    |
| SIK3     | STMN3    |
| SIN3A    | STRBP    |
| SIPA1    | STX7     |
| SIX5     | STXBP5   |
| SLC16A6  | STYXL1   |
| SLC22A4  | SUGT1    |
| SLC25A46 | SULF2    |
| SLC29A3  | SUPT16H  |
| SLC2A1   | SVIP     |
| SLC2A6   | SWAP70   |
| SLC30A6  | SYNJ2    |
| SLC31A2  | SYTL1    |
| SLC35A1  | TACC1    |
| SLC35A3  | TAGLN2   |
| SLC35B2 | TAP2 |
| SLC35B3 | TAPT1 |
| SLC35E1 | TCF12 |
| SLC3A2 | TEAD3 |
| SLC7A2 | TERC |
| SLC7A6OS | TGFB2 |
| SLK | TGOLN2 |
| SMARCD2 | THAP10 |
| SNHG11 | THBS3 |
| SNHG6 | THOC2 |
| SNORD16 | TIGD2 |
| SNRNP70 | TIMM9 |
| SNX17 | TIMP2 |
| SOAT1 | TLE1 |
| SPOP | TM9SF4 |
| SPRED2 | TMBIM4 |
| SULF2 | TMC4 |
| SREBF1 | TMEF2 |
| SRP72 | TMEM1 |
| SSR4 | TMEM108 |
| ST13 | TMEM135 |
| ST3GAL1 | TMEM150A |
| STXB3 | TMEM189 |
| SURF1 | TMEM43 |
| SURF6 | TMEM64 |
| SYK | TMEM79 |
| SYNM | TMEM83 |
| TAF10 | TMF1 |
| TAF2 | TMTC2 |
| TAF8 | TNNT1 |
| TATDN1 | TNS3 |
| TBX2 | TOMM6 |
| TC2N | TOP1P1 |
| TCEA2 | TOP1P2 |
| TCEA4 | TOP2B |
| TCF25 | TPD52L2 |
| TEAD2 | TRAK1 |
| THEX1 | TRAPP3 |
| THNSL1 | TRIM24 |
| TIAF1 | TRIM4 |
| TIGA1 | TRIM8 |
| TIMM178 | TRIP12 |
| TJP2 | TRMT61A |
| TM9SF1 | TSC22D1 |
| TMED2 | TTC3 |
| TMED5 | TTC3B |
| TMEM121 | TUBB8 |
| TMEM132A | TUBD1 |
| TMEM134 | TUFT1 |
| TMEM147 | UBE2E2 |
| TMEM159 | UBE2F |
| TMEM170A | UBE2H |
| TMEM170B | UGDH |
| TMEM184C | UGT1A6 |
| TMEM222 | UGT2B7 |
| TMEM33 | UHMK1 |
| TMEM41B | USHP1 |
| TMEM72 | USP42 |
| TMX3 | USP6NL |
| TNS1BP1 | VAMP7 |
| TOP2A | VASN |
| TOR1AIP2 | VDAC3 |
| TRAPP10 | VPS35 |
| TRAPPC10 | VPS54 |
| TRAPPC2L | |
| Left Column | Right Column |
|-------------|--------------|
| TRAPPC5     | WASL         |
| TRAPPC6A    | WBP2         |
| TREML1      | WBSCR22      |
| TRIM33      | WDR54        |
| TRIM59      | WDSUB1       |
| TRIP11      | WHAMM        |
| TRIP6       | WISP2        |
| TROAP       | WNT8A        |
| TSSC1       | WS82         |
| TSTD1       | YES1         |
| TTK         | YIPF4        |
| TUBA4A      | YIPF5        |
| TWF1        | YIPF6        |
| TXNIP       | YTHDC1       |
| UBA1        | YWHAZ        |
| UBE1C       | ZDHHC21      |
| UBE2D1      | ZDHHC20      |
| UBE2L6      | ZDHHC21      |
| UBE3C       | ZFAND28      |
| UBXN1       | ZFHX3        |
| UFC1        | ZFP90        |
| UNKL        | ZFPL1        |
| UPF2        | ZMI22        |
| UPK1A       | ZNF140       |
| USO1        | ZNF16        |
| USP16       | ZNF217       |
| USP3        | ZNF322A      |
| USP5        | ZNF330       |
| UTP14C      | ZNF358       |
| UXT         | ZNF446       |
| VBP1        | ZNF467       |
| VCL         | ZNF529       |
| VEGFA       | ZNF629       |
| VKORC1      | ZNF668       |
| VKORC1L1    | ZNF721       |
| VPS37D      | ZNF771       |
| VPS4A       | ZNF773       |
| WBP1        | ZNF777       |
| WDR44       | ZNF787       |
| WDR61       | ZNF800       |
| WDSOF1      | ZNF816A      |
| WWC3        | ZNF84        |
| XRCC5       | ZPB        |
| YPEL3       | ZWIN         |
| YWHAB       | ZYG11B       |
| ZC3H4       | ZZ3          |
| ZC3H7A      |               |
| ZC3HAV1L    |               |
| ZDHHC4      |               |
| ZDHHC9      |               |
| ZFR         |               |
| ZFYVE16     |               |
| ZFYVE19     |               |
| ZNF142      |               |
| ZNF286C     |               |
| ZNF317      |               |
| ZNF490      |               |
| ZNF503      |               |
| ZNF581      |               |
| ZNF611      |               |
| ZNF621      |               |
| ZNF770      |               |
| ZWILCH      |               |
### Table S4-1. GO Term Enrichment of genes in C1: Constant, diverge-converge

| GO term                                                                 | \( P_{\text{value}} \)   | # genes |
|------------------------------------------------------------------------|--------------------------|---------|
| GO:0055114~oxidation reduction                                         | 0.001001623              | 10      |
| GO:0005829~cytosol                                                     | 0.001177962              | 15      |
| oxidoreductase                                                         | 0.001811866              | 9       |
| GO:0006917~induction of apoptosis                                      | 0.001827765              | 7       |
| GO:0012502~induction of programmed cell death                         | 0.001856811              | 7       |
| GO:0043065~positive regulation of apoptosis                            | 0.007746022              | 7       |
| GO:0043068~positive regulation of programmed cell death               | 0.008003318              | 7       |
| GO:0010942~positive regulation of cell death                           | 0.008178256              | 7       |
| GO:0008283~cell proliferation                                          | 0.008266675              | 7       |
| GO:0006631~fatty acid metabolic process                                | 0.008486207              | 5       |
| GO:0042127~regulation of cell proliferation                            | 0.013602753              | 9       |
| GO:0042981~regulation of apoptosis                                     | 0.015313907              | 9       |
| GO:0043067~regulation of programmed cell death                         | 0.016171712              | 9       |
| GO:0010941~regulation of cell death                                    | 0.016502291              | 9       |
| GO:0008629~induction of apoptosis by intracellular signals             | 0.020291167              | 3       |
| GO:0043232~intracellular non-membrane-bounded organelle                | 0.020820249              | 19      |
| GO:0043228~non-membrane-bounded organelle                              | 0.020820249              | 19      |
| GO:005198~structural molecule activity                                 | 0.022203014              | 8       |
Table S4-2. GO Term Enrichment of genes in C2: Constant, concordant

| GO term                                                        | P-value  | # genes |
|----------------------------------------------------------------|----------|---------|
| phosphoprotein                                                | 1.94E-13 | 367     |
| cytoplasm                                                     | 1.10E-07 | 180     |
| GO:0065003~macromolecular complex assembly                    | 1.13E-07 | 57      |
| GO:0043933~macromolecular complex subunit organization         | 1.89E-07 | 59      |
| golgi apparatus                                               | 3.58E-07 | 49      |
| GO:0005829~cytosol                                            | 1.62E-06 | 89      |
| GO:0005794~Golgi apparatus                                    | 3.82E-06 | 64      |
| GO:0031090~organelle membrane                                 | 1.13E-05 | 74      |
| er-golgi transport                                            | 1.18E-05 | 14      |
| GO:0070271~protein complex biogenesis                         | 1.47E-05 | 42      |
| GO:0006461~protein complex assembly                           | 1.47E-05 | 42      |
| ubl conjugation                                               | 2.30E-05 | 44      |
| ribonucleoprotein                                             | 5.21E-05 | 26      |
| protein biosynthesis                                          | 8.38E-05 | 20      |
| GO:0016192~vesicle-mediated transport                         | 1.40E-04 | 43      |
| cross-link:Glycyl lysine isopeptide (Lys-Gly) (interchain with G-Cter in ubiquitin) | 1.93E-04 | 20      |
| GO:0034622~cellular macromolecular complex assembly            | 2.09E-04 | 28      |
| GO:0034621~cellular macromolecular complex subunit organization | 2.63E-04 | 30      |
| nucleus                                                       | 4.24E-04 | 199     |
| endoplasmic reticulum                                         | 4.49E-04 | 46      |
Table S4-3. GO Term Enrichment of genes in C3: net change, diverge-converge

| GO term                                           | P-value   | # genes |
|---------------------------------------------------|-----------|---------|
| GO:0030529~ribonucleoprotein complex               | 6.07E-05  | 14      |
| GO:0043232~intracellular non-membrane-bounded organelle | 9.64E-05  | 35      |
| GO:0043228~non-membrane-bounded organelle          | 9.64E-05  | 35      |
| GO:0005829~cytosol                                 | 1.02E-04  | 23      |
| protein biosynthesis                               | 3.07E-04  | 8       |
| ribosomal protein                                  | 3.07E-04  | 8       |
| phosphoprotein                                     | 3.51E-04  | 70      |
| ribonucleoprotein                                  | 6.58E-04  | 9       |
| GO:0031974~membrane-enclosed lumen                 | 7.87E-04  | 26      |
| GO:0005840~ribosome                                | 7.92E-04  | 8       |
| GO:0006412~translation                             | 8.17E-04  | 10      |
| GO:0031968~organelle outer membrane                | 8.23E-04  | 6       |
| GO:0006414~translational elongation                 | 9.44E-04  | 6       |
| GO:0019867~outer membrane                          | 9.76E-04  | 6       |
| GO:0070013~intracellular organelle lumen           | 0.001014  | 25      |
| GO:0043233~organelle lumen                         | 0.001398  | 25      |
| GO:0003735~structural constituent of ribosome      | 0.001443  | 7       |
**Table S4-4. GO Term Enrichment of genes in C4: net changed, concordant**

| GO term                                                                 | P_value     | # genes |
|-------------------------------------------------------------------------|-------------|---------|
| phosphoprotein                                                          | 6.47E-14    | 357     |
| nucleus                                                                 | 4.84E-08    | 215     |
| GO:0005829~cytosol                                                      | 1.41E-06    | 84      |
| GO:0031974~membrane-enclosed lumen                                      | 3.60E-05    | 102     |
| GO:0043233~organelle lumen                                             | 7.48E-05    | 99      |
| GO:0070013~intracellular organelle lumen                                | 8.50E-05    | 97      |
| GO:0005654~nucleoplasm                                                 | 1.06E-04    | 56      |
| GO:0031981~nuclear lumen                                               | 1.09E-04    | 82      |
| GO:0043232~intracellular non-membrane-bounded organelle                 | 1.14E-04    | 131     |
| GO:0043228~non-membrane-bounded organelle                               | 1.14E-04    | 131     |
| phosphoric monoester hydrolase                                         | 1.70E-04    | 11      |
| GO:0030532~small nuclear ribonucleoprotein complex                      | 1.96E-04    | 7       |
| transcription regulation                                               | 4.15E-04    | 102     |
| GO:0003712~transcription cofactor activity                             | 5.55E-04    | 28      |
| Transcription                                                          | 6.00E-04    | 103     |
| actin-binding                                                          | 6.47E-04    | 21      |
| alternative splicing                                                   | 7.79E-04    | 311     |
| GO:0005794~Golgi apparatus                                             | 8.35E-04    | 52      |
| GO:0005996~monosaccharide metabolic process                            | 8.45E-04    | 20      |
| GO:0008134~transcription factor binding                                 | 8.86E-04    | 35      |
Table S5. Breast basal cell and luminal cell gene signatures

| up-regulated in Luminal cells vs. Basal (455 genes) | down-regulated in Luminal cells vs. Basal (3801 genes) |
|---------------------------------------------------|---------------------------------------------------------|
| ABCD3                                             | ABCA3                                                   |
| ACTN1                                             | ABCG1                                                   |
| ADA                                               | ABHD11                                                  |
| ADD3                                              | ABHD12                                                  |
| ADM                                               | ACVR1B                                                   |
| ADORA2B                                           | ADCY6                                                   |
| ADRB2                                             | AFF3                                                     |
| AGPS                                              | AGR2                                                     |
| AIM1                                              | ANKRD13D                                                 |
| AKR1B1                                            | ANKRD30A                                                  |
| AKR1B10                                           | ANXA6                                                    |
| AKR1C1                                           | ANXA9                                                    |
| AKR1C2                                           | API5                                                     |
| AKR1C3                                           | AR                                                        |
| AKT3                                             | ARF3                                                     |
| ALDH1A3                                           | ARFIP2                                                   |
| ALDH3A2                                           | ARHGEF26                                                  |
| AMD1                                             | ARID2                                                    |
| ANKH                                             | ARR81                                                    |
| ANKRD33B                                          | AS8                                                      |
| ANTXR1                                           | ASH1L                                                    |
| ANXA1                                            | ASTN2                                                    |
| ANXA2                                            | ATP2C2                                                   |
| ANX2AP2                                          | ATP6AP1                                                   |
| ANX3                                             | ATP6VOE2                                                  |
| ANXA4                                            | ATP8B1                                                    |
| APOL6                                            | ATXN7L3B                                                   |
| ARAP3                                            | AVL9                                                      |
| ARHGAP23                                         | BAI2                                                      |
| ARHGAPS                                          | BAZ2A                                                    |
| ARNTL2                                           | BCA51                                                     |
| ARPC2                                            | BCO2                                                      |
| ASXL1                                            | BLNK                                                      |
| ATP1D                                            | BPTF                                                      |
| ATP1A1                                           | CI0orf12                                                   |
| ATP1B3                                           | CI0orf18                                                   |
| AXL                                              | CI0orf51                                                   |
| B2M                                              | CI4orf132                                                   |
| B3GNT5                                           | CI0orf28                                                   |
| BICC1                                            | CI7orf58                                                   |
| BICD2                                            | CI7orf62                                                   |
| BIN1                                             | CI9orf46                                                   |
| BIRC3                                            | C4orf19                                                   |
| BMP1                                             | C7orf26                                                   |
| BNC1                                             | C9orf152                                                   |
| BTG3                                             | C9orf7                                                     |
| BTN3A2                                           | C9orf91                                                   |
| C10orf10                                         | CA12                                                      |
| C12orf39                                         | CACNA1D                                                   |
| C13orf15                                         | CACNA2D2                                                   |
| C15orf52                                         | CACNB3                                                     |
| C1R                                              | CACNG4                                                      |
| Gene  | Gene  |
|-------|-------|
| C1S   | CACYBP |
| C21orf63 | CADM1 |
| C21orf96 | CAMSAP3 |
| C3   | CANT1 |
| C6orf1145 | CAPN9 |
| C9orf5 | CDCDC17 |
| CALD1 | CCND1 |
| CAMTA1 | CDC42SE1 |
| CARD6 | CEP350 |
| CAPS1 | CER52 |
| CAPS4 | CER56 |
| CAV1 | CFD |
| CAV2 | CHN2 |
| CBR1 | CHTOP |
| CCDC28A | CIRBP |
| CCDC80 | CISH |
| CCDC82 | CLSTN2 |
| CCDC88A | CREB3L1 |
| CCNA1 | CREB3L4 |
| CCNYL1 | CRRK1 |
| CD109 | CSNK1D |
| CD14 | CSNK1D |
| CD44 | CTNN2 |
| CD58 | CTXN1 |
| CD59 | CXCR5 |
| CD97 | CYB561 |
| CDC42EP3 | CYHR1 |
| CDCP1 | DAAM1 |
| CDH13 | DACH1 |
| CDH3 | DDAH2 |
| CDK6 | DDX42 |
| CEBP0 | DEGS2 |
| CFB | DENND1A |
| CFI | DENND4B |
| CFL2 | DEPTOR |
| CFLAR | DHR51 |
| CHMP1B | DIP2C |
| CHST3 | DNF2 |
| CLIC4 | DLG3 |
| CLIP4 | DNA1A4 |
| CLMP | DNA1C1 |
| CMKP1 | DNAJ1 |
| COL4A1 | DOPEY2 |
| COL4A2 | DSCAM-AS1 |
| COL8A1 | DUSP8 |
| COP58 | EFR3B |
| COR01C | EIF3B |
| COTL1 | ELOVL2 |
| CRIP1 | EMP2 |
| CRK | ENPP1 |
| CRYAB | EPS8L1 |
| CSA | FAM10B |
| CSNK2A2 | FAM11A |
| CTSC | FAM11A |
| CXCL1 | FAM11A |
| CXCL2 | FAM46C |
| CXCL3 | FAM56C |
| CYB5R3 | FBRSL1 |
| CYB5D | F7 |
| CYLD | F7 |
| DCLD1 | F7 |
| DCLD2 | F7 |
| DCTD | F7 |
| DGKA | F7 |
| Protein   | Gene     |
|-----------|----------|
| DIRC2     | FGFR4    |
| DMD       | FKBP4    |
| DNAI1B4   | FLJ2184  |
| DOCK5     | FLJ3879  |
| DPYD      | FLJ45983 |
| DSC3      | FOXA1    |
| DSE       | FRMD4A   |
| DSG2      | FRS2     |
| DSG3      | FTX      |
| DST       | FUS      |
| DUOX1     | FZD4     |
| EGF       | GALNT6   |
| EHB1      | GAMT     |
| ELK3      | GARNL3   |
| ELL2      | GARS     |
| EMP1      | GART     |
| EMP3      | GATA3    |
| EPHA2     | GGA1     |
| ERAP2     | GGA3     |
| EREG      | GNA12    |
| ESYT2     | GOLTI1A  |
| ETF1      | GP01L    |
| ETS1      | GPR160   |
| ETS2      | GPRSC    |
| EXT1      | GRAMD4   |
| F2RL1     | GSTP1    |
| F3        | GTF3C1   |
| FAM101B   | HEXDC    |
| FAM171A1  | HIP1R    |
| FAM176A   | HK2      |
| FAM69A    | HMG20B   |
| FAM83A    | HMGCS2   |
| FAM83D    | HNRNPA2B |
| FAM92A1   | HPN      |
| FAP       | HPX      |
| FAS       | ICA1     |
| FBLIM1    | INHBB    |
| FDP2T1    | INPP5J   |
| FERM1T1   | INTS3    |
| FG2       | IQCE     |
| GFBP1     | IQSEC1   |
| FH1L1     | IRGQ     |
| FKBP1A    | ISG20    |
| FMNL2     | IVD      |
| FNDC3B    | JHDM1D   |
| FOSL1     | KAT6B    |
| FOXO1     | KCTD15   |
| FRMD6     | KDM4B    |
| FSCN1     | KIAA0040 |
| FST       | KIAA0182 |
| FSTL1     | KIAA0226 |
| FXYD5     | KIAA0232 |
| FZD6      | KIAA0556 |
| GABRE     | KIAA0889 |
| GALNT2    | KIAA0913 |
| GART      | KIAA1211 |
| GAS1      | KIAA1244 |
| GBP1      | KIAA1324 |
| GBP3      | KIAA1467 |
| GFOD1     | KIAA1598 |
| GIP3      | KIF12    |
| GIC1      | KIFC2    |
| GJOR1     | KLF2     |
| GM2A      | KLHDC9   |
| GNA15  | KLHL22 |
|-------|------|
| GNAI1  | KLRG2 |
| GNA1   | KRT19 |
| GNG12  | LARGE |
| GPM6A  | LARP4B |
| GPM6B  | LFNG  |
| GPX1   | LINC00312 |
| GPX8   | LLGL2 |
| GSTP1  | LMCD1 |
| GTF2B  | LNK1 |
| HIF1A  | LOC100130987 |
| HLA-E  | LOC100272216 |
| HMG2A  | LOC100506966 |
| HOXA1  | LOC643837 |
| HOXA3  | LOC692247 |
| HOXA5  | LONRF2 |
| HPBP3  | LR3 |
| HRCT1  | LRRN1 |
| HRH1   | LUC7L3 |
| HSD17B1 | L2TR1 |
| HTRA1  | MAGED2 |
| ICAM1  | MAPK9 |
| IFI16  | MAPT |
| IFI27  | MARS |
| IFI44  | MB21D2 |
| IFIT3  | MCCC2 |
| IFNGR1 | MDM4 |
| IGF2BP2 | MEGF9 |
| IGF2BP3 | MGAT4A |
| IGFBP6 | MGRN1 |
| IGFBP7 | MIF4GD |
| IL15   | MLL2 |
| IL18   | MLPH |
| IL1A   | MTERFD3 |
| IL1RAP | MXRA8 |
| IL20R8 | MY8 |
| IL7R   | MYCN |
| INHBA  | MYEF2 |
| INPP1  | MYO5B |
| IRS2   | MYO6 |
| IRX1   | NACA |
| ITCG3  | NBPF1 |
| ITCG6  | NDUFS8 |
| ITCG8  | NKAIN1 |
| ITCG8B | NLK |
| ITM2C  | NME3 |
| JAG1   | NPDC1 |
| KIF1B  | NUCB2 |
| KIRREL | NUDT4 |
| KLF5   | ONECUT2 |
| KLHL29 | PAHTM |
| KLK10  | PATZ1 |
| KLK5   | PBX1 |
| KPNA1  | PCBP2 |
| KRT14  | PCK2 |
| KRT15  | PCP4 |
| KRT16  | PGT1B |
| KRT17  | PGR |
| KRT5   | PI4KA |
| KRT6A  | PLA2G12A |
| KRT6B  | PLCXD1 |
| LAMA3  | PLEKH1 |
| LAMB3  | PLXNA3 |
| LAMC1  | POGZ |
| Gene  | Description |
|-------|-------------|
| LAMC2 | POLE        |
| LARP6 | PPPM1       |
| LBH   | PPP1R16A    |
| LEPREL1 | PPP2R2C   |
| LPC   | PRKX1       |
| LOC100499467 | PRLR  |
| LOC100505633 | PRR14    |
| LOC100506621 | PRRC2C   |
| LOC285812 | PRRT2    |
| LOC346887 | PRRT3    |
| LOX   | PTPRF       |
| LOXL2 | PVRL2       |
| LUZP1 | PYCR1       |
| LYS   | RAB11FIP3   |
| LYN   | RAB17       |
| MAML2 | RAB3D       |
| MAP4K4 | RAB40C    |
| MAP7D3 | RABEP2    |
| MBNL1 | RALGAPA1    |
| MBNL2 | RALGAP1     |
| MBP   | RBK         |
| MDF1C | RDH13       |
| MDH1  | REEP5       |
| MET   | RGL2        |
| MFGE8 | RHBDF1      |
| MICAL1 | RHOB      |
| MIR100HG | RHOH    |
| MIR22HG | RHPN1     |
| MIR31HG | RIAD1     |
| MMADHC | RND1      |
| MME   | RNF103      |
| MMP14 | RSD1        |
| MPZL1 | RSOP1       |
| MN    | RUSC1       |
| MT1E  | SBK1        |
| MT1F  | SCUBE2      |
| MT1G  | SCYL3       |
| MT1H  | SDCCAG3     |
| MT1P2 | SEC16A      |
| MT1X  | SEC5BP2     |
| MT2A  | SRF2        |
| MTMR2 | SF11       |
| MYL12A | SFMBT2    |
| MYO1B | SH3GLB2     |
| MYO1E | SHANK2      |
| NAB1  | SIDT1       |
| NAMPT | SIDT2       |
| NAV2  | SLC16A6     |
| NCK1  | SLC1A4      |
| NDEL1 | SLC2A4A     |
| NDFIP2 | SLC2A29   |
| NFA1T5 | SLC2A44    |
| NFE2L2 | SLC26A11   |
| NMI   | SLC2A10     |
| NNMNT | SLC3A1      |
| NOB1  | SLC3A1      |
| NR3C1 | SLC3A1      |
| NRP1  | SLC3A10     |
| NSF1C | SLC4A4      |
| NT5E  | SLC4A4      |
| NUDT15 | SLC7A8    |
| NUP50 | SLC9A3R1    |
| NXN   | SMARC2      |
| OBFC2A | SNE1D     |
| Gene 1 | Gene 2 |
|-------|-------|
| OGFR1 | SNX27 |
| ORM1L1| SOX12 |
| OSBP3 | SOX13 |
| OSBP4 | SPATA2L|
| OSMP1 | SPDEF |
| PARP4  | SPTLC2 |
| POGF2  | SRBM2 |
| PDP1   | STARD10|
| PDK1   | STRADA |
| PELO   | STRBP |
| PERP   | SYCP2 |
| PGF2   | SYNGR2 |
| PHLD1A | TADA2B |
| PHLD2B | TAP1 |
| P13    | TBC1D16|
| PIK3CD | TBC1D30|
| PKN2   | TBL1X |
| PKP2   | TBX3 |
| PLA2G4A| TC2N  |
| PLAT   | TESK1 |
| PLA5   | TFF1  |
| PLS5   | TFF3  |
| PLSZ1  | TFGB3 |
| PMLZD2 | TGF2  |
| PNLP1P3| THSD4 |
| PPP1R14C| THUMP1D |
| PPP1R1| TJP3  |
| PRKCDBP| TLE3  |
| PRK3D  | TMBIM6|
| PRTN   | TMEM150C|
| PRTSS1 | TMEM184A|
| PSAT1  | TMEM2298|
| PSMB8  | TMEM57 |
| PSMB9  | TMEM60 |
| PTGS2  | TNIP1 |
| PT7    | TNRC18 |
| PT1N2  | TOB1  |
| PTI2M  | TOMM70A|
| PTYRF  | TRAPP9 |
| RAC2   | TRI1  |
| RALB   | TRIM3 |
| RALBP1 | TRPS1 |
| RBFOX2 | TSPAN13|
| RBM7   | TSPAN15|
| RBMS1  | TTC3  |
| RBMS3  | TTC39A|
| RETSAT | TCC9  |
| RXO2   | UAP1L1 |
| RGL1   | UBN1 |
| RGNF   | ULK1  |
| RGS2   | USP3  |
| RGS20  | USP42 |
| RIOK3  | USP7  |
| RIPK4  | VIPR1 |
| RND3   | VPS37C |
| RNF145 | VPS72 |
| RRRS2  | WFS1 |
| RUNX3  | XBP1 |
| S100A10| ZBTB42 |
| S100A2 | ZDHHC8P1|
| SAMD9  | ZFYVE16|
| SCHIP1 | ZMIZ1 |
| SCPEP1 | ZNF12 |
| SEL113 | ZNF24 |
| Gene  | Symbol |
|-------|--------|
| SEP15 | ZNF296 |
| SEP10 | ZNF398 |
| SERPINB2 | ZNF444 |
| SERPINB5 | ZNF467 |
| SERPINE2 | ZNF703 |
| SFN | ZNF704 |
| SFRP1 | ZNF74 |
| SGK1 | ZNF84 |
| SH3D19 | |
| SH3GLB1 | |
| SH3KBP1 | |
| SIRPA | |
| SKAP2 | |
| SLC16A1 | |
| SLC1A3 | |
| SLC25A37 | |
| SLC6A15 | |
| SLC9A6 | |
| SLP1 | |
| SMAD3 | |
| SMCHD1 | |
| SNAI2 | |
| SNX7 | |
| SOAT1 | |
| SOX7 | |
| SPI100 | |
| SPATS2L | |
| SPRY2 | |
| SPTBN1 | |
| SRI | |
| SRPX | |
| SRPX2 | |
| SSFA2 | |
| STAMBPL1 | |
| STAT3 | |
| STAT4 | |
| STK17A | |
| SVIL | |
| TAP2 | |
| TX1BP3 | |
| TBC1D1 | |
| TBPL1 | |
| TGFA | |
| TGFB1 | |
| TGFBR2 | |
| TKT | |
| TLE4 | |
| TLR2 | |
| TM2D1 | |
| TME05 | |
| TMEM154 | |
| TMEM173 | |
| TMEM30A | |
| TNFAIP3 | |
| TNFAIP8 | |
| TNFRSF10D | |
| TOX2 | |
| TP63 | |
| TRIM22 | |
| TRIM29 | |
| TRIP10 | |
| TRMT6 | |
| TUBA4A | |
| TUBB6 | |
| TWIST2   |
|---------|
| TWSG1   |
| UBASH3B |
| UBE2E3  |
| UPP1    |
| VAMP3   |
| VSNL1   |
| WBFR5   |
| WDR1    |
| WLS     |
| WWTR1   |
| YAP1    |
| YBX1    |
| YES1    |
| ZBTB16  |
| ZBTB38  |
| ZC3H12C |
| ZDHHHC2 |
| ZMYM6   |
## Table S6-1. Gene set enrichment analysis (GSEA) Day 1 up-regulated pathways vs. Day 0

| Gene set                                                                 | Size | NES    | NOM p-val |
|--------------------------------------------------------------------------|------|--------|-----------|
| KEGG_METABOLISM_OF_XENOBIOTICS_BY_CYTOCHROME_P450                        | 30   | 1.9015 | 0         |
| KEGG_RETINOL_METABOLISM                                                 | 19   | 1.7918 | 0.001862  |
| KEGG_STEROID_HORMONE_BIOSYNTHESIS                                       | 16   | 1.758  | 0         |
| Stress Response                                                          | 33   | 1.6812 | 0         |
| Stemness Markers                                                         | 22   | 1.6572 | 0.003759  |
| REACTOME BIOLOGICAL_OXIDATIONS                                           | 54   | 1.5728 | 0.001901  |
| TURASHVILI_BREAST_DUCTAL_CARCINOMA_VS LOBULAR_NORMAL_UP                  | 49   | 1.5493 | 0.005435  |
| PID_INTEGRIN3_PATHWAY                                                    | 21   | 1.5448 | 0.01495   |
| KEGG_TRYPTOPHAN_METABOLISM                                              | 24   | 1.5363 | 0.01132   |
| REACTOME_PPARA_ACTIVATES_GENE_EXPRESSION                                 | 74   | 1.5246 | 0.007722  |
| PID_WNT_NONCANONICAL_PATHWAY                                            | 24   | 1.4902 | 0.01845   |
| REACTOME_FATTY_ACID_TRIACYLGLYCEROL_METABOLISM                          | 124  | 1.4818 | 0.01512   |
| TURASHVILI_BREAST_NORMAL_DUCTAL_VS LOBULAR_UP                            | 45   | 1.4769 | 0.02239   |
| KEGG_PORPHYRIN_AND_CHLOROPHYLL_METABOLISM                               | 24   | 1.4691 | 0.04656   |
| PID_ERBB4_PATHWAY                                                       | 27   | 1.4494 | 0.04934   |
| TURASHVILI_BREAST_LOBULAR_CARCINOMA_VS LOBULAR_NORMAL_UP                 | 51   | 1.4255 | 0.02186   |
| KEGG_OGLYCAN_BIOSYNTHESIS                                               | 15   | 1.4137 | 0.06814   |
| BIOCARTA_Igf1_PATHWAY                                                   | 15   | 1.4104 | 0.05311   |
| BIOCARTA_INSULIN_PATHWAY                                                | 16   | 1.3738 | 0.06897   |
| Prolactin signaling pathway                                             | 43   | 0.62659| 0.9497    |
Table S6-2. Gene set enrichment analysis (GSEA) Day 1 down-regulated pathways vs. Day 0

| Gene set                                               | Size | NES    | NOM p-val |
|--------------------------------------------------------|------|--------|-----------|
| REACTOME_INTERFERON_GAMMA_SIGNALING                     | 37   | 1.7986 | 0.001984  |
| REACTOME_INTERFERON_SIGNALING                          | 111  | 1.7965 | 0         |
| REACTOME_CYTOKINE_SIGNALING_IN_IMMUNE_SYSTEM           | 179  | 1.7637 | 0         |
| REACTOME_INTERFERON_ALPHA_BETA_SIGNALING               | 41   | 1.7234 | 0.001972  |
| KEGG_FRUCTOSE_AND_MANNOSE_METABOLISM                   | 28   | 1.5556 | 0.01359   |
| REACTOME_GLUCOSE_METABOLISM                            | 52   | 1.5539 | 0.009766  |
| REACTOME_METABOLISM_OF_CARBOHYDRATES                   | 152  | 1.5428 | 0.001942  |
| REACTOME_IMMUNOREGULATORY_INTERACTIONS_LYMPHOID_NON_LYMPHOID_CELL | 23   | 1.5419 | 0.02299   |
| REACTOME_GLYCOLYSIS                                    | 22   | 1.5296 | 0.01357   |
| REACTOME_NEGATIVE_REGULATORS_OF_RIG_I_MDAS_SIGNALING  | 23   | 1.5176 | 0.04016   |
| BIOCARTA_MCALPAIN_PATHWAY                              | 17   | 1.512  | 0.02806   |
| PID_MYC_REPRESSPATHWAY                                 | 51   | 1.5075 | 0.01461   |
| HUPER_BREAST_BASAL_VS_LUMINAL_UP                       | 29   | 1.4952 | 0.01047   |
| PID_IL12_2PATHWAY                                      | 30   | 1.4814 | 0.03346   |
| KEGG_SPLICEOSOME                                       | 104  | 1.4716 | 0.01553   |
| REACTOME_GLUCONEOGENESIS                               | 24   | 1.4512 | 0.03536   |
| REACTOME_RESPIRATORY_ELECTRON_TRANSPORT               | 61   | 1.4106 | 0.1008    |
| REACTOME_RNA_POL_I_TRANSCRIPTION                       | 60   | 1.4082 | 0.03929   |
Table S6-3. Gene set enrichment analysis (GSEA) Day 5 up-regulated pathways vs. Day 0

| Gene set                                      | Size | NES  | NOM p-val |
|------------------------------------------------|------|------|-----------|
| KEGGTRYPTOPHANMETABOLISM                       | 24   | -1.6197 | 0.005859 |
| BIOCARTAALKPATHWAY                             | 21   | -1.5426 | 0.01613  |
| PIDERBB4PATHWAY                                | 27   | -1.5418 | 0.008264 |
| REACTOMESYNTHESIS_OF_PIPS_AT_THE_PLASMA_MEMBRANE | 24   | -1.5    | 0.0409   |
| REACTOMESIGNALINGBYHIPPO                       | 15   | -1.4979 | 0.06962  |
| BIOCARTARASPATHWAY                             | 22   | -1.4779 | 0.04065  |
| KEGGPORPHRYINANDCHLOROPHYLLMETABOLISM          | 24   | -1.4294 | 0.06751  |
| TURASHVILI_BREAST_NORMAL_DUCTAL_VS_LOBULAR_UP  | 45   | 1.421   | 0.04286  |
| PIDPSI1PATHWAY                                 | 35   | -1.4208 | 0.04732  |
| BIOCARTAWNTPATHWAY                             | 21   | -1.4131 | 0.04277  |
| REACTOMESIGNALINGBYRHOGTPASES                  | 66   | -1.4082 | 0.04848  |
| KEGGPHOSPHATIDYLINSOLIGNALINGSYSTEM            | 52   | -1.3904 | 0.04878  |
| KEGGSTEROIDHORMONEBIOSYNTHESIS                | 16   | -1.3848 | 0.0846   |
| StressResponse                                 | 33   | -1.3769 | 0.1175   |
| BIOCARTAIGF1PATHWAY                            | 15   | -1.3701 | 0.08299  |
| BIOCARTAINSULINPATHWAY                         | 16   | -1.358  | 0.07724  |
| REACTOMETRANSCRIPTIONAL_REGULATIONOFWHITEADIPOCYTEDIFFERENTIATION | 54   | 1.2819  | 0.1223   |
| Prolactin signaling pathway                    | 43   | -1.207  | 0.233    |
Table S6-4. Gene set enrichment analysis (GSEA) Day 5 down-regulated pathways vs. Day 0

| Gene set                                         | Size | NES      | NOM p-val |
|--------------------------------------------------|------|----------|-----------|
| HUPER_BREAST_BASAL_VS_LUMINAL_UP                 | 29   | -1.5767  | 0.001992  |
| Epithelial Signature Genes                       | 31   | 1.5497   | 0.02505   |
| REACTOME_INTERFERON_ALPHA_BETA_SIGNALING         | 41   | 1.5494   | 0.025     |
| PID_MYC_REPRESSPATHWAY                           | 51   | 1.5226   | 0.01663   |
| REACTOME_S_PHASE                                 | 93   | 1.5045   | 0.0121    |
| REACTOME_INTERFERON_SIGNALING                    | 111  | 1.4954   | 0.05979   |
| KEGG_DNA_REPLICATION                             | 35   | 1.4902   | 0.02434   |
| REACTOME_DNA_STRAND_ELONGATION                   | 29   | 1.4734   | 0.02899   |
| REACTOME_ASSEMBLY_OF_THE_PRE_REPLICATIVE_COMPLEX | 52   | 1.4701   | 0.04546   |
| REACTOME_ORC1_REMOVAL_FROM_CHROMATIN             | 53   | 1.4698   | 0.03666   |
| KEGG_COMPLEMENT_AND_COAGULATION_CASCADES         | 16   | 1.4689   | 0.02053   |
| REACTOME_SYNTHESIS_OF_DNA                        | 77   | 1.4655   | 0.03106   |
| REACTOME_G1_S_TRANSITION                         | 89   | 1.4653   | 0.03279   |
| REACTOME_GLUCOSE_METABOLISM                      | 52   | 1.4652   | 0.02245   |
| REACTOME_METABOLISM_OF_MRNA                      | 191  | 1.4567   | 0.0167    |
| REACTOME_M_G1_TRANSITION                         | 64   | 1.4558   | 0.05405   |
| REACTOME_SCFSKP2_MEDIATED_DEGRADATION_OF_P27_P21 | 49   | 1.4545   | 0.04481   |
| REACTOME_ER_PHAGOSOME_PATHWAY                    | 52   | 1.453    | 0.05955   |
| REACTOME_G2_M_CHECKPOINTS                        | 30   | 1.4457   | 0.064     |
| KEGG_MISMATCH_REPAIR                             | 22   | 1.4447   | 0.04508   |
| REACTOME_CYTOKINE_SIGNALING_IN_IMMUNE_SYSTEM     | 179  | 1.4424   | 0.05589   |
Table S7. Candidate genes identified from CAP-Net analysis which cause MCF7 cell to differentiate

| Gene   | Biological functions                                                                                                                                                                                                 | Effects | Reference |
|--------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-----------|
| IFI27  | A protein that promotes cell death and mediates IFN-induced apoptosis, characterized by a rapid and robust release of cytochrome C from the mitochondrial membrane. | Inhibition | [2,3]    |
| VEGFA  | A growth factor that regulates angiogenesis. The CAP-Net shows a low expression of VEGFA, which indicates a reduction in the angiogenesis and tumor growth.     | Inhibition | [4–6]   |
| CSF1   | A cytokine that enhances the tumor growth via tumor-associated macrophages. It is highly expressed in several subtypes of breast cancer and causes the M2 macrophage differentiation by stimulating VEGFA. The down-regulation of CSF1 in the CAP-Net supports previous findings as a positive effect on breast cancer treatment. | Inhibition | [7–9]   |
| AKT1   | A Serine-Threonine protein kinase that regulates metabolism, proliferation, cell survival, growth and angiogenesis.                                                                                              | -       | [10]    |
| IL8    | A chemotactic factor that attracts neutrophils, basophils and T-cells. It activates neutrophils. It is released from several cell types in response to an inflammatory stimulus. | inhibition | [11]   |
| CYP1B1 | An enzyme that metabolizes drugs, involved in electron transport pathway.                                                                                                                                          | activation | [12]    |
| DHCR24 | An enzyme that protects cells from apoptosis induced by oxidative stress.                                                                                                                                           | activation | [13,14]|  |
| EDN1   | A protein that is used to produce vasoconstrictive peptides.                                                                                                                                                     | activation | [15]    |
| HMOX1  | An enzyme that cleaves the heme ring at the alpha methene bridge to form biliverdin, and exhibits cytoprotective effect since excess of heme sensitizes cells to apoptosis.                                               | activation | [16]    |
| MAOA   | A mitochondrial enzyme that degrades monoamines neuron transmitters and dietary amines, induces EMT through activation of VEGF.                                                                                      | Inhibition | [17,18]|  |
| MUC1   | A membrane protein that activated T-cells, influences the Ras/MAPK pathway, promotes tumor progression, regulates TP53-mediated transcription, determines cell fate in the genotoxic stress response and represses TP53 activity. | Inhibition | [19–21]|  |
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